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NOTE

From:	General Secretariat of the Council
To:	Delegations
Subject:	Directive on the Union code relating to medicinal product for human use - Annexes to the four-column table

Delegations will find enclosed the annexes to the four-column table on the above-mentioned Directive. This document contains in Annex A the explanations on the layout of the table used in this document and in Annex B the text of the Commission proposal, the amendments voted by the European Parliament on 10 April 2024 and changes to the proposal approved by the Council on 4 June 2025.

ANNEX A

	Commission proposal	EP amendments voted on 10 April 2024	Text agreed by the Council on 4 June 2025	Draft agreement
		Plain text in this column is text from the Commission proposal that the European Parliament proposes to maintain. ***Text in blue underlined bold italics in this column is text that the EP proposes to add to the Commission proposal.*** ***Text in red italics ~~strikethrough~~ in this column is text that the EP proposes to delete.***	Plain text in this column is text from the Commission proposal that Council wishes to maintain. **Text in bold** in this column is text that Council has agreed to add. Text in ~~strikethrough~~ in this column is text that Council has agreed to delete.	

ANNEX B

Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (Text with EEA relevance)

2023/0132(COD)

Annexes

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex I				
1999	Annex I	Annex I	Annex I	
Annex I, first paragraph				
2000	INFORMATION REFERRED TO IN THE APPLICATION	INFORMATION REFERRED TO IN THE APPLICATION	INFORMATION REFERRED TO IN THE APPLICATION	
Annex I, second paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2001	(1) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.	(1) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.	(1) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.	
Annex I, 2 paragraph				
2002	(2) Name of the medicinal product.	(2) Name of the medicinal product.	(2) Name of the medicinal product.	
Annex I, 3 paragraph				
2003	(3) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the World Health Organization, where an INN for the medicinal product	(3) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the World Health Organization, where an INN for the medicinal product	(3) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the World Health Organization, where an INN for the medicinal product	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	exists, or a reference to the relevant chemical name.	exists, or a reference to the relevant chemical name.	exists, or a reference to the relevant chemical name.	
Annex I, 4 paragraph				
2004	(4) An environmental risk assessment (ERA) in accordance with the requirements laid down in Articles 22 and 23.	(4) An environmental risk assessment (ERA) in accordance with the requirements laid down in Articles 22 and 23.	(4) An environmental risk assessment (ERA) in accordance with the requirements laid down in Articles 22 and 23.	
Annex I, 5 paragraph				
2005	(5) For medicinal product for human use containing or consisting of genetically modified organisms, an environmental risk assessment identifying and characterising possible hazards for human health, animals and the environment. The assessment shall be conducted in accordance with	(5) For medicinal product for human use containing or consisting of genetically modified organisms, an environmental risk assessment identifying and characterising possible hazards for human health, animals and the environment. The assessment shall be conducted in accordance with	(5) For medicinal product for human use containing or consisting of genetically modified organisms, an environmental risk assessment identifying and characterising possible hazards for human health, animals and the environment. The assessment shall be conducted in accordance with	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	the elements described in Article 8 of [revised Regulation (EC) No 726/2004] and the requirements of Annex II to this Directive, based on the principles set out in Annex II to Directive 2001/18/EC of the European Parliament and of the Council[1] taking into account the specificities of medicinal products. __________ 1. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration (OJ L 106, 17.4.2001, p. 1)	the elements described in Article 8 of [revised Regulation (EC) No 726/2004] and the requirements of Annex II to this Directive, based on the principles set out in Annex II to Directive 2001/18/EC of the European Parliament and of the Council[1] taking into account the specificities of medicinal products. __________ 1. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration (OJ L 106, 17.4.2001, p. 1)	the elements described in Article 8 of [revised Regulation (EC) No 726/2004] and the requirements of Annex II to this Directive, based on the principles set out in Annex II to Directive 2001/18/EC of the European Parliament and of the Council[1] taking into account the specificities of medicinal products. __________ 1. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration (OJ L 106, 17.4.2001, p. 1)	
Annex I, 6 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2006	(6) Description of the manufacturing method.	(6) Description of the manufacturing method.	(6) Description of the manufacturing method.	
Annex I, 7 paragraph				
2007	(7) Therapeutic indications, contra-indications and adverse reactions.	(7) Therapeutic indications, contra-indications and adverse reactions.	(7) Therapeutic indications, contra-indications and adverse reactions.	
Annex I, 8 paragraph				
2008	(8) Posology, pharmaceutical form, method and route of administration and expected shelf life.	(8) Posology, pharmaceutical form, method and route of administration and expected shelf life.	(8) Posology, pharmaceutical form, method and route of administration and expected shelf life.	
Annex I, 9 paragraph				
2009	(9) Reasons for any precautionary and safety measures to be taken for the storage of the	(9) Reasons for any precautionary and safety measures to be taken for the storage of the	(9) Reasons for any precautionary and safety measures to be taken for the storage of the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.	medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.	medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.	
Annex I, 10 paragraph				
2010	(10) Description of the control methods employed by the manufacturer.	(10) Description of the control methods employed by the manufacturer.	(10) Description of the control methods employed by the manufacturer.	
Annex I, 11 paragraph				
2011	(11) A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with	(11) A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with	(11) A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	principles of good manufacturing practice by conducting audits, in accordance with Article 160. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles of good manufacturing practice.	principles of good manufacturing practice by conducting audits, in accordance with Article 160. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles of good manufacturing practice.	principles of good manufacturing practice by conducting audits, in accordance with Article 160. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles of good manufacturing practice.	
Annex I, 12 paragraph				
2012	(12) Results of:	(12) Results of:	(12) Results of:	
Annex I, 12 paragraph, point (a)				
2013	(a) pharmaceutical (physico-chemical, biological or micro biological) tests,	(a) pharmaceutical (physico-chemical, biological or micro biological) tests,	(a) pharmaceutical (physico-chemical, biological or micro biological) tests,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex I, 12 paragraph, point (b)				
2014	(b) non-clinical (toxicological and pharmacological) tests,	(b) non-clinical (toxicological and pharmacological) tests,	(b) non-clinical (toxicological and pharmacological) tests,	
Annex I, 12 paragraph, point (c)				
2015	(c) clinical trials.	(c) clinical trials.	(c) clinical trials.	
Annex I, 13 paragraph				
2016	(13) Where relevant, evidence from other sources of clinical data (non-interventional clinical studies, registries).	(13) Where relevant, evidence from other sources of clinical data (non-interventional clinical studies, registries).	(13) Where relevant, evidence from other sources of clinical data (non-interventional clinical studies, registries).	
Annex I, 14 paragraph				
2017	(14) A summary of the applicant's pharmacovigilance	(14) A summary of the applicant's pharmacovigilance	(14) A summary of the applicant's pharmacovigilance	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	system which shall include the following elements:	system which shall include the following elements:	system which shall include the following elements:	
Annex I, 14 paragraph, point (a)				
2018	(a) proof that the applicant has at their disposal a qualified person responsible for pharmacovigilance,	(a) proof that the applicant has at their disposal a qualified person responsible for pharmacovigilance,	(a) proof that the applicant has at their disposal a qualified person responsible for pharmacovigilance,	
Annex I, 14 paragraph, point (b)				
2019	(b) the Member States in which the qualified person resides and carries out their tasks,	(b) the Member States in which the qualified person resides and carries out their tasks,	(b) the Member States in which the qualified person resides and carries out their tasks,	
Annex I, 14 paragraph, point (c)				
2020	(c) the contact details of the qualified person,	(c) the contact details of the qualified person,	(c) the contact details of the qualified person,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex I, 14 paragraph, point (d)				
2021	(d) a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Chapter VI,	(d) a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Chapter VI,	(d) a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Chapter VI,	
Annex I, 14 paragraph, point (e)				
2022	(e) a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.	(e) a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.	(e) a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.	
Annex I, 15 paragraph				
2023	(15) The risk management plan describing the risk management system which the applicant will	(15) The risk management plan describing the risk management system which the applicant will	(15) The risk management plan describing the risk management system which the applicant will	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	introduce for the medicinal product concerned, together with a summary thereof.	introduce for the medicinal product concerned, together with a summary thereof.	introduce for the medicinal product concerned, together with a summary thereof.	
Annex I, 16 paragraph				
2024	(16) A statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Regulation (EU) No 536/2014.	(16) A statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Regulation (EU) No 536/2014.	(16) A statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Regulation (EU) No 536/2014.	
Annex I, 17 paragraph				
2025	(17) A summary of product characteristics in accordance with Article 62, a mock-up of the outer packaging, containing the details provided for in Annex IV, and of the immediate packaging of the medicinal product, containing the	(17) A summary of product characteristics in accordance with Article 62, a mock-up of the outer packaging, containing the details provided for in Annex IV, and of the immediate packaging of the medicinal product, containing the	(17) A summary of product characteristics in accordance with Article 62, a mock-up of the outer packaging, containing the details provided for in Annex IV, and of the immediate packaging of the medicinal product, containing the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	details provided for in Article 66, together with a package leaflet in accordance with Article 64.	details provided for in Article 66, together with a package leaflet in accordance with Article 64.	details provided for in Article 66, together with a package leaflet in accordance with Article 64.	
Annex I, 18 paragraph				
2026	(18) A document showing that the manufacturer is authorised in their own country to produce medicinal products.	(18) A document showing that the manufacturer is authorised in their own country to produce medicinal products.	(18) A document showing that the manufacturer is authorised in their own country to produce medicinal products.	
Annex I, 19 paragraph				
2027	(19) Copies of the following:	(19) Copies of the following:	(19) Copies of the following:	
Annex I, 19 paragraph, point (a)				
2028	(a) any marketing authorisation, obtained in another Member State or in a third country, to place the medicinal	(a) any marketing authorisation, obtained in another Member State or in a third country, to place the medicinal	(a) any marketing authorisation, obtained in another Member State or in a third country, to place the medicinal	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for marketing authorisation submitted in accordance with this Directive is under examination;	product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for marketing authorisation submitted in accordance with this Directive is under examination;	product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for marketing authorisation submitted in accordance with this Directive is under examination;	
Annex I, 19 paragraph, point (b)				
2029	(b) the summary of product characteristics proposed by the applicant in accordance with Article 62 or approved by the competent authorities of the Member State in accordance with Article 43 and the package leaflet	(b) the summary of product characteristics proposed by the applicant in accordance with Article 62 or approved by the competent authorities of the Member State in accordance with Article 43 and the package leaflet	(b) the summary of product characteristics proposed by the applicant in accordance with Article 62 or approved by the competent authorities of the Member State in accordance with Article 43 and the package leaflet	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	proposed in accordance with Article 64 or approved by the competent authorities of the Member State in accordance with Article 76;	proposed in accordance with Article 64 or approved by the competent authorities of the Member State in accordance with Article 76;	proposed in accordance with Article 64 or approved by the competent authorities of the Member State in accordance with Article 76;	
Annex I, 19 paragraph, point (c)				
2030	(c) details of any decision to refuse marketing authorisation, whether in the Union or in a third country, and the reasons for such a decision.	(c) details of any decision to refuse marketing authorisation, whether in the Union or in a third country, and the reasons for such a decision.	(c) details of any decision to refuse marketing authorisation, whether in the Union or in a third country, and the reasons for such a decision.	
Annex I, 20 paragraph				
2031	(20) A copy of any designation of the medicinal product as an orphan medicinal product as defined in Article 63 of [revised Regulation (EC) No 726/2004],	(20) A copy of any designation of the medicinal product as an orphan medicinal product as defined in Article 63 of [revised Regulation (EC) No 726/2004],	(20) A copy of any designation of the medicinal product as an orphan medicinal product as defined in Article 63 of [revised Regulation (EC) No 726/2004],	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	accompanied by a copy of the relevant Agency opinion.	accompanied by a copy of the relevant Agency opinion.	accompanied by a copy of the relevant Agency opinion.	
Annex I, 21 paragraph				
2032	(21) Where the application concerns an antimicrobial medicinal product, the application shall also contain:	(21) Where the application concerns an antimicrobial medicinal product, the application shall also contain:	(21) Where the application concerns an antimicrobial medicinal product, the application shall also contain:	
Annex I, 21 paragraph, point (a)				
2033	a) an antimicrobial stewardship plan which shall in particular outline:	a) an antimicrobial stewardship ***and access*** plan which shall in particular outline:	a) an antimicrobial stewardship plan which shall in particular outline:	
Annex I, 21 paragraph, point (a)(i)				
2034	(i) information about risk mitigation measures to limit antimicrobial resistance	(i) information about risk mitigation measures to limit antimicrobial resistance	(i) information about risk mitigation measures to limit antimicrobial resistance	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	development related to the use, prescription and administration of the medicinal product;	development related to the use, prescription and administration of the medicinal product;	development related to the use, prescription and administration of the medicinal product;	
Annex I, 21 paragraph, point (a)(ii)				
2035	(ii) how the marketing authorisation holder intends to monitor and report to the competent authority the resistance to the antimicrobial medicinal product.	(ii) how the marketing authorisation holder intends to monitor and report to the competent authority the resistance to the antimicrobial medicinal product.	(ii) how the marketing authorisation holder intends to monitor and report to the competent authority the resistance to the antimicrobial medicinal product.	
Annex I, 21 paragraph, point (a)(iia)				
2035a		***(iia) information about measures for a strategy to promote access, including proposed production chain capacity;***		

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex I, 21 paragraph, point (a)(iib)				
2035b		***(iib) information about measures to ensure marketing approvals are received for key territories in a timely manner; and***		
Annex I, 21 paragraph, point (a)(iic)				
2035c		***(iic) information about measures to monitor effectiveness of stewardship and access.***		
Annex I, 21 paragraph, point (b)				
2036	b) a description of the special information requirements outlined in Article 58	b) a description of the special information requirements outlined in Article 58	b) a description of the special information requirements outlined in Article 58	
Annex I, 21 paragraph, point (c)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2037	c) details on the pack size which shall correspond to the usual posology and duration of treatment.	c) details on the pack size which shall correspond to the usual posology and duration of treatment.	c) details on the pack size which shall correspond to the usual posology and duration of treatment.	
Annex I, 22 paragraph				
2038	(22) Where an application concerns the marketing authorisation to market a radionuclide generator, in addition to the requirements set out in Articles 6 and 9, it shall also contain:	(22) Where an application concerns the marketing authorisation to market a radionuclide generator, in addition to the requirements set out in Articles 6 and 9, it shall also contain:	(22) Where an application concerns the marketing authorisation to market a radionuclide generator, in addition to the requirements set out in Articles 6 and 9, it shall also contain:	
Annex I, 22 paragraph, point (a)				
2039	(a) a general description of the system together with a detailed description of the components of the system that may affect the	(a) a general description of the system together with a detailed description of the components of the system that may affect the	(a) a general description of the system together with a detailed description of the components of the system that may affect the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	composition or quality of the daughter nucleid preparation; and	composition or quality of the daughter nucleid preparation; and	composition or quality of the daughter nucleid preparation; and	
Annex I, 22 paragraph, point (b)				
2040	(b) qualitative and quantitative particulars of the eluate or the sublimate.	(b) qualitative and quantitative particulars of the eluate or the sublimate.	(b) qualitative and quantitative particulars of the eluate or the sublimate.	
Annex I, 23 paragraph				
2041	(23) Good manufacturing practices certificates.	(23) Good manufacturing practices certificates.	(23) Good manufacturing practices certificates.	
Annex II				
2042	Annex II	Annex II The table of contents of annex II is missing in TTE.	Annex II	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, first paragraph				
2043	ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLININCAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS	ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLININCAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS	ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLININCAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS	
Annex II, second paragraph				
2044	Introduction and general principles	Introduction and general principles	Introduction and general principles	
Annex II, third paragraph				
2045	(1) The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 8 and 10(1) shall be presented in	(1) The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 8 and 10(1) shall be presented in	(1) The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 8 and 10(1) shall be presented in	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	accordance with the requirements set out in this Annex and shall follow the guidance published by the Commission in The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD).	accordance with the requirements set out in this Annex and shall follow the guidance published by the Commission in The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD).	accordance with the requirements set out in this Annex and shall follow the guidance published by the Commission in The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD).	
Annex II, 2 paragraph				
2046	(2) The particulars and documents shall be presented as five modules: Module 1 provides European Community specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3	(2) The particulars and documents shall be presented as five modules: Module 1 provides European Community specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3	(2) The particulars and documents shall be presented as five modules: Module 1 provides European Community specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH ([1]) regions (European Community, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to above. __________ 1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH ([1]) regions (European Community, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to above. __________ 1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH ([1]) regions (European Community, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to above. __________ 1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 3 paragraph				
2047	(3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.	(3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.	(3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.	
Annex II, 4 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2048	(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.	(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.	(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.	
Annex II, 5 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2049	(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.	(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.	(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.	
Annex II, 6 paragraph				
2050	(6) The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use ([1]) and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal	(6) The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use ([1]) and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal	(6) The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use ([1]) and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	products in the European Community, Volume 4. __________ 1. OJ L 193, 17.7.1991, p. 30	products in the European Community, Volume 4. __________ 1. OJ L 193, 17.7.1991, p. 30	products in the European Community, Volume 4. __________ 1. OJ L 193, 17.7.1991, p. 30	
Annex II, 7 paragraph				
2051	(7) All information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials	(7) All information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials	(7) All information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	concerning therapeutic indications not covered by the application.	concerning therapeutic indications not covered by the application.	concerning therapeutic indications not covered by the application.	
Annex II, 8 paragraph				
2052	(8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use ([1]). To be taken into account during the assessment of an application, clinical trials,	(8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use ([1]). To be taken into account during the assessment of an application, clinical trials,	(8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use ([1]). To be taken into account during the assessment of an application, clinical trials,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki. __________ 1. OJ L 121, 1.5.2001, p. 34	conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki. __________ 1. OJ L 121, 1.5.2001, p. 34	conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki. __________ 1. OJ L 121, 1.5.2001, p. 34	
Annex II, 9 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2053	(9) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests in chemical substances ([1]) and 88/320/EEC on the inspection and verification of good laboratory practice (GLP) ([2]). __________ 1. OJ L 15, 17.1.1987, p. 29 2. OJ L 145, 11.6.1988, p. 35	(9) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests in chemical substances ([1]) and 88/320/EEC on the inspection and verification of good laboratory practice (GLP) ([2]). __________ 1. OJ L 15, 17.1.1987, p. 29 2. OJ L 145, 11.6.1988, p. 35	(9) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests in chemical substances ([1]) and 88/320/EEC on the inspection and verification of good laboratory practice (GLP) ([2]). __________ 1. OJ L 15, 17.1.1987, p. 29 2. OJ L 145, 11.6.1988, p. 35	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 10 paragraph				
2054	(10) Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes.	(10) Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes.	(10) Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes.	
Annex II, 11 paragraph				
2055	(11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmaco-vigilance information shall be	(11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmaco-vigilance information shall be	(11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmaco-vigilance information shall be	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	submitted to the competent authority. After marketing authorisation has been granted, any change to the data in the dossier shall be submitted to the competent authorities in accordance with the requirements of Commission Regulations (EC) No 1084/2003 ([1]) and (EC) No 1085/2003 ([2]) of the Commission or, if relevant, in accordance with national provisions, as well as the requirements in Volume 9 of Commission publication The rules governing medicinal products in the European Community. __________ 1. See p. 1 of this Official Journal 2. See p. 1 of this Official Journal	submitted to the competent authority. After marketing authorisation has been granted, any change to the data in the dossier shall be submitted to the competent authorities in accordance with the requirements of Commission Regulations (EC) No 1084/2003 ([1]) and (EC) No 1085/2003 ([2]) of the Commission or, if relevant, in accordance with national provisions, as well as the requirements in Volume 9 of Commission publication The rules governing medicinal products in the European Community. __________ 1. See p. 1 of this Official Journal 2. See p. 1 of this Official Journal	submitted to the competent authority. After marketing authorisation has been granted, any change to the data in the dossier shall be submitted to the competent authorities in accordance with the requirements of Commission Regulations (EC) No 1084/2003 ([1]) and (EC) No 1085/2003 ([2]) of the Commission or, if relevant, in accordance with national provisions, as well as the requirements in Volume 9 of Commission publication The rules governing medicinal products in the European Community. __________ 1. See p. 1 of this Official Journal 2. See p. 1 of this Official Journal	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 12 paragraph				
2056	This Annex is divided in four different parts:	This Annex is divided in four different parts:	This Annex is divided in four different parts:	
Annex II, 13 paragraph				
2057	- Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for standard applications (Modules 1 to 5).	- Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for standard applications (Modules 1 to 5).	- Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for standard applications (Modules 1 to 5).	
Annex II, -a paragraph				
2058	- Part II provides derogation for 'Specific applications', i.e. well-established medicinal use, essentially similar products, fixed	- Part II provides derogation for 'Specific applications', i.e. well-established medicinal use, essentially similar products, fixed	- Part II provides derogation for 'Specific applications', i.e. well-established medicinal use, essentially similar products, fixed	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).	combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).	combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).	
Annex II, -a paragraph				
2059	- Part III deals with 'Particular application requirements' for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.	- Part III deals with 'Particular application requirements' for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.	- Part III deals with 'Particular application requirements' for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2060	- Part IV deals with ‘Advanced therapy medicinal products’ and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.	- Part IV deals with ‘Advanced therapy medicinal products’ and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.	- Part IV deals with ‘Advanced therapy medicinal products’ and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.	
Annex II, Part I				
2061	Part I PART I	Part I PART I	Part I PART I	
Annex II, -a paragraph				
2062	STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS	STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS	STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, point 1.				
2063	1. MODULE 1: ADMINISTRATIVE INFORMATION	1. MODULE 1: ADMINISTRATIVE INFORMATION	1. MODULE 1: ADMINISTRATIVE INFORMATION	
Annex II, -b paragraph, point				
2064	Table of contents	Table of contents	Table of contents	
Annex II, 2 paragraph				
2065	A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorisation application shall be presented.	A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorisation application shall be presented.	A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorisation application shall be presented.	
Annex II, 3 paragraph, point				
2066	Application form	Application form	Application form	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 3 paragraph				
2067	The medicinal product, which is the subject of the application, shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the route of administration, the strength and the final presentation, including packaging.	The medicinal product, which is the subject of the application, shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the route of administration, the strength and the final presentation, including packaging.	The medicinal product, which is the subject of the application, shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the route of administration, the strength and the final presentation, including packaging.	
Annex II, 4 paragraph				
2068	The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished	The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished	The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished	

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	product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the importer.	product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the importer.	product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the importer.	
Annex II, 5 paragraph				
2069	The applicant shall identify the type of application and indicate what samples, if any, are also provided.	The applicant shall identify the type of application and indicate what samples, if any, are also provided.	The applicant shall identify the type of application and indicate what samples, if any, are also provided.	
Annex II, 6 paragraph				
2070	Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in Article 40, together with a list of countries in which authorisation has been granted, copies of all the summaries of	Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in Article 40, together with a list of countries in which authorisation has been granted, copies of all the summaries of	Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in Article 40, together with a list of countries in which authorisation has been granted, copies of all the summaries of	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	product characteristics in accordance with Article 11 as approved by Member States and a list of countries in which an application has been submitted.	product characteristics in accordance with Article 11 as approved by Member States and a list of countries in which an application has been submitted.	product characteristics in accordance with Article 11 as approved by Member States and a list of countries in which an application has been submitted.	
Annex II, 7 paragraph				
2071	As outlined in the application form, the applicants shall provide, inter alia, details of the medicinal product subject of the application, the legal basis of the application, the proposed marketing authorisation holder and manufacture(s), information on orphan medicinal product status, scientific advice and paediatric development program.	As outlined in the application form, the applicants shall provide, inter alia, details of the medicinal product subject of the application, the legal basis of the application, the proposed marketing authorisation holder and manufacture(s), information on orphan medicinal product status, scientific advice and paediatric development program.	As outlined in the application form, the applicants shall provide, inter alia, details of the medicinal product subject of the application, the legal basis of the application, the proposed marketing authorisation holder and manufacture(s), information on orphan medicinal product status, scientific advice and paediatric development program.	
Annex II, 8 paragraph				

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2072	1.3. Summary of product characteristics, labelling and package leaflet	1.3. Summary of product characteristics, labelling and package leaflet	1.3. Summary of product characteristics, labelling and package leaflet	
Annex II, 4 paragraph				
2073	Summary of product characteristics	Summary of product characteristics	Summary of product characteristics	
Annex II, 5 paragraph				
2074	The applicant shall propose a summary of the product characteristics, in accordance with Article 11.	The applicant shall propose a summary of the product characteristics, in accordance with Article 11.	The applicant shall propose a summary of the product characteristics, in accordance with Article 11.	
Annex II, 6 paragraph,				
2075	Labelling and package leaflet	Labelling and package leaflet	Labelling and package leaflet	
Annex II, 3 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2076	A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with all mandatory items listed in Title V on the labelling of medicinal products for human use (Article 63) and on package leaflet (Article 59).	A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with all mandatory items listed in Title V on the labelling of medicinal products for human use (Article 63) and on package leaflet (Article 59).	A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with all mandatory items listed in Title V on the labelling of medicinal products for human use (Article 63) and on package leaflet (Article 59).	
Annex II, 4 paragraph,				
2077	Mock-ups and specimens	Mock-ups and specimens	Mock-ups and specimens	
Annex II, 4 paragraph				
2078	The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product concerned.	The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product concerned.	The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product concerned.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 5 paragraph,				
2079	Summaries of product characteristics already approved in the Member States	Summaries of product characteristics already approved in the Member States	Summaries of product characteristics already approved in the Member States	
Annex II, 5 paragraph				
2080	Annexed to the administrative data of the application form shall be copies of all the summaries of product characteristics in accordance with Articles 11 and 21 as approved by Member States, where applicable and a list of countries in which an application has been submitted.	Annexed to the administrative data of the application form shall be copies of all the summaries of product characteristics in accordance with Articles 11 and 21 as approved by Member States, where applicable and a list of countries in which an application has been submitted.	Annexed to the administrative data of the application form shall be copies of all the summaries of product characteristics in accordance with Articles 11 and 21 as approved by Member States, where applicable and a list of countries in which an application has been submitted.	
Annex II, 6 paragraph, point				
2081	Information about the experts	Information about the experts	Information about the experts	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 5 paragraph				
2082	In accordance with Article 12 (2) experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.	In accordance with Article 12 (2) experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.	In accordance with Article 12 (2) experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 6 paragraph				
2083	These requirements shall be met by providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.	These requirements shall be met by providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.	These requirements shall be met by providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 7 paragraph, point				
2084	Specific requirements for different types of applications	Specific requirements for different types of applications	Specific requirements for different types of applications	
Annex II, 6 paragraph				
2085	Specific requirements for different types of applications are addressed in Part II of the present Annex.	Specific requirements for different types of applications are addressed in Part II of the present Annex.	Specific requirements for different types of applications are addressed in Part II of the present Annex.	
Annex II, 7 paragraph, point				
2086	Environmental risk assessment	Environmental risk assessment	Environmental risk assessment	
Annex II, 7 paragraph				
2087	Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the	Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the	Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products containing or consisting of GMOs (Genetically Modified Organisms) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of modified organisms and repealing Council Directive 90/220/EEC ([1]) shall be addressed. 1. OJ L 106, 17.4.2001, p. 1	environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products containing or consisting of GMOs (Genetically Modified Organisms) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of modified organisms and repealing Council Directive 90/220/EEC ([1]) shall be addressed. 1. OJ L 106, 17.4.2001, p. 1	environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products containing or consisting of GMOs (Genetically Modified Organisms) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of modified organisms and repealing Council Directive 90/220/EEC ([1]) shall be addressed. 1. OJ L 106, 17.4.2001, p. 1	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 8 paragraph				
2088	Information pertaining to the environmental risk shall appear as an appendix to Module 1.	Information pertaining to the environmental risk shall appear as an appendix to Module 1.	Information pertaining to the environmental risk shall appear as an appendix to Module 1.	
Annex II, 9 paragraph				
2089	The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.	The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.	The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.	
Annex II, 10 paragraph				
2090	The information shall consist of:	The information shall consist of:	The information shall consist of:	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 11 paragraph				
2091	- an introduction;	- an introduction;	- an introduction;	
Annex II, -a paragraph				
2092	- a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;	- a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;	- a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;	
Annex II, -a paragraph				
2093	- the information requested in Annexes II to IV of the Directive 2001/18/EC, including detection and identification methods as well as unique code of	- the information requested in Annexes II to IV of the Directive 2001/18/EC, including detection and identification methods as well as unique code of	- the information requested in Annexes II to IV of the Directive 2001/18/EC, including detection and identification methods as well as unique code of	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	the GMO, plus any additional information on the GMO or the product of relevance to evaluating the environmental risk;	the GMO, plus any additional information on the GMO or the product of relevance to evaluating the environmental risk;	the GMO, plus any additional information on the GMO or the product of relevance to evaluating the environmental risk;	
Annex II, -a paragraph				
2094	- an environment risk assessment (ERA) report prepared on basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of Directive 2001/18/EC;	- an environment risk assessment (ERA) report prepared on basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of Directive 2001/18/EC;	- an environment risk assessment (ERA) report prepared on basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of Directive 2001/18/EC;	
Annex II, -a paragraph				
2095	- taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management	- taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management	- taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management	

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	strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;	strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;	strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;	
Annex II, -a paragraph				
2096	- appropriate measures in order to inform the public.	- appropriate measures in order to inform the public.	- appropriate measures in order to inform the public.	
Annex II, -a paragraph				
2097	A dated signature of the author, information on the author's educational, training and occupational experience, and a	A dated signature of the author, information on the author's educational, training and occupational experience, and a	A dated signature of the author, information on the author's educational, training and occupational experience, and a	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	statement of the author's relationship with the applicant, shall be included.	statement of the author's relationship with the applicant, shall be included.	statement of the author's relationship with the applicant, shall be included.	
Annex II, point 2., first subparagraph				
2098	2. MODULE 2: SUMMARIES	2. MODULE 2: SUMMARIES	2. MODULE 2: SUMMARIES	
Annex II, point 2., second subparagraph				
2099	This Module aims to summarise the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation, and to provide the reports/overviews described in Article 12 of this Directive.	This Module aims to summarise the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation, and to provide the reports/overviews described in Article 12 of this Directive.	This Module aims to summarise the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation, and to provide the reports/overviews described in Article 12 of this Directive.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, point 2., third subparagraph				
2100	Critical points shall be addressed and analysed. Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).	Critical points shall be addressed and analysed. Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).	Critical points shall be addressed and analysed. Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).	
Annex II, point 2., fourth subparagraph				
2101	Information contained in Module 2 shall be presented in accordance	Information contained in Module 2 shall be presented in accordance	Information contained in Module 2 shall be presented in accordance	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	with the format, content and numbering system delineated in the Volume 2 of the Notice to Applicants. The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:	with the format, content and numbering system delineated in the Volume 2 of the Notice to Applicants. The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:	with the format, content and numbering system delineated in the Volume 2 of the Notice to Applicants. The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:	
Annex II, -b paragraph, point				
2102	Overall table of contents	Overall table of contents	Overall table of contents	
Annex II, 2 paragraph				
2103	Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.	Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.	Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.	
Annex II, 3 paragraph, point				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2104	Introduction	Introduction	Introduction	
Annex II, 3 paragraph				
2105	Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be supplied.	Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be supplied.	Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be supplied.	
Annex II, 4 paragraph, point				
2106	Quality overall summary	Quality overall summary	Quality overall summary	
Annex II, 4 paragraph				
2107	A review of the information related to the chemical, pharmaceutical and biological data	A review of the information related to the chemical, pharmaceutical and biological data	A review of the information related to the chemical, pharmaceutical and biological data	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	shall be provided in a quality overall summary.	shall be provided in a quality overall summary.	shall be provided in a quality overall summary.	
Annex II, 5 paragraph				
2108	Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.	Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.	Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.	
Annex II, 6 paragraph, point				
2109	Non-clinical overview	Non-clinical overview	Non-clinical overview	
Annex II, 5 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2110	An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animals/in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.	An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animals/in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.	An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animals/in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.	
Annex II, 6 paragraph				
2111	Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound	Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound	Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	used in the non-clinical studies and the product to be marketed shall be discussed.	used in the non-clinical studies and the product to be marketed shall be discussed.	used in the non-clinical studies and the product to be marketed shall be discussed.	
Annex II, 7 paragraph				
2112	For biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.	For biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.	For biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.	
Annex II, 8 paragraph				
2113	Any novel excipient shall be the subject of a specific safety assessment.	Any novel excipient shall be the subject of a specific safety assessment.	Any novel excipient shall be the subject of a specific safety assessment.	
Annex II, 9 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2114	The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.	The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.	The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.	
Annex II, 10 paragraph, point				
2115	Clinical overview	Clinical overview	Clinical overview	
Annex II, 6 paragraph				
2116	The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal	The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal	The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	product, including critical study design, decisions related to and performance of the studies shall be provided.	product, including critical study design, decisions related to and performance of the studies shall be provided.	product, including critical study design, decisions related to and performance of the studies shall be provided.	
Annex II, 7 paragraph				
2117	A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the	A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the	A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	benefits and manage the risks is required.	benefits and manage the risks is required.	benefits and manage the risks is required.	
Annex II, 8 paragraph				
2118	Efficacy or safety issues encountered in development and unresolved issues shall be explained.	Efficacy or safety issues encountered in development and unresolved issues shall be explained.	Efficacy or safety issues encountered in development and unresolved issues shall be explained.	
Annex II, 9 paragraph, point				
2119	Non-clinical summary	Non-clinical summary	Non-clinical summary	
Annex II, 7 paragraph				
2120	The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals/in vitro shall be provided as factual written and tabulated summaries	The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals/in vitro shall be provided as factual written and tabulated summaries	The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals/in vitro shall be provided as factual written and tabulated summaries	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	which shall be presented in the following order:	which shall be presented in the following order:	which shall be presented in the following order:	
Annex II, 8 paragraph				
2121	- Introduction	- Introduction	- Introduction	
Annex II, -a paragraph				
2122	- Pharmacology Written Summary	- Pharmacology Written Summary	- Pharmacology Written Summary	
Annex II, -a paragraph				
2123	- Pharmacology Tabulated Summary	- Pharmacology Tabulated Summary	- Pharmacology Tabulated Summary	
Annex II, -a paragraph				
2124	- Pharmaco-kinetics Written Summary	- Pharmaco-kinetics Written Summary	- Pharmaco-kinetics Written Summary	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2125	- Pharmaco-kinetics Tabulated Summary	- Pharmaco-kinetics Tabulated Summary	- Pharmaco-kinetics Tabulated Summary	
Annex II, -a paragraph				
2126	- Toxicology Written Summary	- Toxicology Written Summary	- Toxicology Written Summary	
Annex II, -a paragraph				
2127	- Toxicology Tabulated Summary.	- Toxicology Tabulated Summary.	- Toxicology Tabulated Summary.	
Annex II, -a paragraph, point				
2128	Clinical Summary	Clinical Summary	Clinical Summary	
Annex II, 8 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2129	A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.	A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.	A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.	
Annex II, 9 paragraph				
2130	Summarised clinical information shall be presented in the following order:	Summarised clinical information shall be presented in the following order:	Summarised clinical information shall be presented in the following order:	
Annex II, 10 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2131	- Summary of Bio-pharmaceutics and Associated Analytical Methods	- Summary of Bio-pharmaceutics and Associated Analytical Methods	- Summary of Bio-pharmaceutics and Associated Analytical Methods	
Annex II, -a paragraph				
2132	- Summary of Clinical Pharmacology Studies	- Summary of Clinical Pharmacology Studies	- Summary of Clinical Pharmacology Studies	
Annex II, -a paragraph				
2133	- Summary of Clinical Efficacy	- Summary of Clinical Efficacy	- Summary of Clinical Efficacy	
Annex II, -a paragraph				
2134	- Summary of Clinical Safety	- Summary of Clinical Safety	- Summary of Clinical Safety	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2135	- Synopses of Individual Studies	- Synopses of Individual Studies	- Synopses of Individual Studies	
Annex II, point 3.				
2136	3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES	3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES	3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES	
Annex II, -a paragraph, point				
2137	Format and presentation	Format and presentation	Format and presentation	
Annex II, 2 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2138	The general outline of Module 3 is as follows:	The general outline of Module 3 is as follows:	The general outline of Module 3 is as follows:	
Annex II, 3 paragraph				
2139	- Table of contents	- Table of contents	- Table of contents	
Annex II, -a paragraph				
2140	- Body of data	- Body of data	- Body of data	
Annex II, -a paragraph				
2141	- Active substance	- Active substance	- Active substance	
Annex II, -a paragraph				
2142	General Information	General Information	General Information	
Annex II, -b paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2143	- Nomenclature	- Nomenclature	- Nomenclature	
Annex II, -a paragraph				
2144	- Structure	- Structure	- Structure	
Annex II, -a paragraph				
2145	- General Properties	- General Properties	- General Properties	
Annex II, -a paragraph				
2146	Manufacture	Manufacture	Manufacture	
Annex II, -b paragraph				
2147	- Manufacturer(s)	- Manufacturer(s)	- Manufacturer(s)	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2148	- Description of Manufacturing Process and Process Controls	- Description of Manufacturing Process and Process Controls	- Description of Manufacturing Process and Process Controls	
Annex II, -a paragraph				
2149	- Control of Materials	- Control of Materials	- Control of Materials	
Annex II, -a paragraph				
2150	- Controls of Critical Steps and Intermediates	- Controls of Critical Steps and Intermediates	- Controls of Critical Steps and Intermediates	
Annex II, -a paragraph				
2151	- Process Validation and/or Evaluation	- Process Validation and/or Evaluation	- Process Validation and/or Evaluation	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2152	- Manufacturing Process Development	- Manufacturing Process Development	- Manufacturing Process Development	
Annex II, -a paragraph				
2153	Characterisation	Characterisation	Characterisation	
Annex II, -b paragraph				
2154	- Elucidation of Structure and other Characteristics	- Elucidation of Structure and other Characteristics	- Elucidation of Structure and other Characteristics	
Annex II, -a paragraph				
2155	- Impurities	- Impurities	- Impurities	
Annex II, -a paragraph				
2156	Control of Active Substance	Control of Active Substance	Control of Active Substance	
Annex II, -b paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2157	- Specification	- Specification	- Specification	
Annex II, -a paragraph				
2158	- Analytical Procedures	- Analytical Procedures	- Analytical Procedures	
Annex II, -a paragraph				
2159	- Validation of Analytical Procedures	- Validation of Analytical Procedures	- Validation of Analytical Procedures	
Annex II, -a paragraph				
2160	- Batch Analyses	- Batch Analyses	- Batch Analyses	
Annex II, -a paragraph				
2161	- Justification of Specification	- Justification of Specification	- Justification of Specification	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2162	Reference Standards or Materials	Reference Standards or Materials	Reference Standards or Materials	
Annex II, -b paragraph				
2163	Container Closure System	Container Closure System	Container Closure System	
Annex II, -c paragraph				
2164	Stability	Stability	Stability	
Annex II, -Ca paragraph				
2165	- Stability Summary and Conclusions	- Stability Summary and Conclusions	- Stability Summary and Conclusions	
Annex II, -a paragraph				
2166	- Post-approval Stability Protocol and Stability Commitment	- Post-approval Stability Protocol and Stability Commitment	- Post-approval Stability Protocol and Stability Commitment	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2167	- Stability Data	- Stability Data	- Stability Data	
Annex II, -a paragraph				
2168	- Finished Medicinal Product	- Finished Medicinal Product	- Finished Medicinal Product	
Annex II, -a paragraph				
2169	Description and Composition of the Medicinal Product	Description and Composition of the Medicinal Product	Description and Composition of the Medicinal Product	
Annex II, -b paragraph				
2170	Pharmaceutical Development	Pharmaceutical Development	Pharmaceutical Development	
Annex II, -c paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2171	- Components of the Medicinal Product	- Components of the Medicinal Product	- Components of the Medicinal Product	
Annex II, -a paragraph				
2172	- Active Substance	- Active Substance	- Active Substance	
Annex II, -a paragraph				
2173	- Excipients	- Excipients	- Excipients	
Annex II, -a paragraph				
2174	- Medicinal Product	- Medicinal Product	- Medicinal Product	
Annex II, -a paragraph				
2175	- Formulation Development	- Formulation Development	- Formulation Development	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2176	- Overages	- Overages	- Overages	
Annex II, -a paragraph				
2177	- Physicochemical and Biological Properties	- Physicochemical and Biological Properties	- Physicochemical and Biological Properties	
Annex II, -a paragraph				
2178	- Manufacturing Process Development	- Manufacturing Process Development	- Manufacturing Process Development	
Annex II, -a paragraph				
2179	- Container Closure System	- Container Closure System	- Container Closure System	
Annex II, -a paragraph				
2180	- Microbiological Attributes	- Microbiological Attributes	- Microbiological Attributes	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2181	- Compatibility	- Compatibility	- Compatibility	
Annex II, -a paragraph				
2182	Manufacture	Manufacture	Manufacture	
Annex II, -b paragraph				
2183	- Manufacturer(s)	- Manufacturer(s)	- Manufacturer(s)	
Annex II, -a paragraph				
2184	- Batch Formula	- Batch Formula	- Batch Formula	
Annex II, -a paragraph				
2185	- Description of Manufacturing Process and Process Controls	- Description of Manufacturing Process and Process Controls	- Description of Manufacturing Process and Process Controls	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2186	- Controls of Critical Steps and Intermediates	- Controls of Critical Steps and Intermediates	- Controls of Critical Steps and Intermediates	
Annex II, -a paragraph				
2187	- Process Validation and/or Evaluation	- Process Validation and/or Evaluation	- Process Validation and/or Evaluation	
Annex II, -a paragraph				
2188	Control of Excipients	Control of Excipients	Control of Excipients	
Annex II, -b paragraph				
2189	- Specifications	- Specifications	- Specifications	
Annex II, -a paragraph				
2190	- Analytical Procedures	- Analytical Procedures	- Analytical Procedures	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2191	- Validation of Analytical Procedures	- Validation of Analytical Procedures	- Validation of Analytical Procedures	
Annex II, -a paragraph				
2192	- Justification of Specifications	- Justification of Specifications	- Justification of Specifications	
Annex II, -a paragraph				
2193	- Excipients of Human or Animal Origin	- Excipients of Human or Animal Origin	- Excipients of Human or Animal Origin	
Annex II, -a paragraph				
2194	- Novel Excipients	- Novel Excipients	- Novel Excipients	
Annex II, -a paragraph				
2195	Control of Finished Medicinal Product	Control of Finished Medicinal Product	Control of Finished Medicinal Product	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -b paragraph				
2196	- Specification(s)	- Specification(s)	- Specification(s)	
Annex II, -a paragraph				
2197	- Analytical Procedures	- Analytical Procedures	- Analytical Procedures	
Annex II, -a paragraph				
2198	- Validation of Analytical Procedures	- Validation of Analytical Procedures	- Validation of Analytical Procedures	
Annex II, -a paragraph				
2199	- Batch Analyses	- Batch Analyses	- Batch Analyses	
Annex II, -a paragraph				
2200	- Characterisation of Impurities	- Characterisation of Impurities	- Characterisation of Impurities	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2201	- Justification of Specification(s)	- Justification of Specification(s)	- Justification of Specification(s)	
Annex II, -a paragraph				
2202	Reference Standards or Materials	Reference Standards or Materials	Reference Standards or Materials	
Annex II, -b paragraph				
2203	Container Closure System	Container Closure System	Container Closure System	
Annex II, -c paragraph				
2204	Stability	Stability	Stability	
Annex II, -Ca paragraph				
2205	- Stability Summary and Conclusion	- Stability Summary and Conclusion	- Stability Summary and Conclusion	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2206	- Post-approval Stability Protocol and Stability Commitment	- Post-approval Stability Protocol and Stability Commitment	- Post-approval Stability Protocol and Stability Commitment	
Annex II, -a paragraph				
2207	- Stability Data	- Stability Data	- Stability Data	
Annex II, -a paragraph				
2208	- Appendices	- Appendices	- Appendices	
Annex II, -a paragraph				
2209	- Facilities and Equipment (Biological Medicinal Products only)	- Facilities and Equipment (Biological Medicinal Products only)	- Facilities and Equipment (Biological Medicinal Products only)	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2210	- Adventitious Agents Safety Evaluation	- Adventitious Agents Safety Evaluation	- Adventitious Agents Safety Evaluation	
Annex II, -a paragraph				
2211	- Excipients	- Excipients	- Excipients	
Annex II, -a paragraph				
2212	- European Community Additional Information — Process Validation Scheme for the Medicinal Product	- European Community Additional Information — Process Validation Scheme for the Medicinal Product	- European Community Additional Information — Process Validation Scheme for the Medicinal Product	
Annex II, -a paragraph				
2213	- Medical Device	- Medical Device	- Medical Device	
Annex II, -a paragraph				
2214	- Certificate(s) of Suitability	- Certificate(s) of Suitability	- Certificate(s) of Suitability	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2215	- Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)	- Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)	- Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)	
Annex II, -a paragraph				
2216	- Literature References	- Literature References	- Literature References	
Annex II, -a paragraph				
2217	- THIS INDENT IS MISSING. THANK YOU FOR USING ANOTHER LANGUAGE.	- THIS INDENT IS MISSING. THANK YOU FOR USING ANOTHER LANGUAGE.	- THIS INDENT IS MISSING. THANK YOU FOR USING ANOTHER LANGUAGE.	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2218	3.2. Content: basic principles and requirements	3.2. Content: basic principles and requirements	3.2. Content: basic principles and requirements	
Annex II, 3 paragraph				
2219	(1) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.	(1) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.	(1) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.	
Annex II, 2 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2220	(2) Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.	(2) Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.	(2) Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.	
Annex II, 3 paragraph				
2221	(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.	(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.	(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.	
Annex II, 4 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2222	(4) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).	(4) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).	(4) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 5 paragraph				
2223	(5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.	(5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.	(5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.	
Annex II, 6 paragraph				
2224	However, where a material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and	However, where a material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and	However, where a material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency	their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency	their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	and the additional specifications applied.	and the additional specifications applied.	and the additional specifications applied.	
Annex II, 7 paragraph				
2225	In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).	In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).	In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).	
Annex II, 8 paragraph				
2226	(6) In case where starting and raw materials, active substance(s) or excipient(s) are described neither in the European Pharmacopoeia nor in the	(6) In case where starting and raw materials, active substance(s) or excipient(s) are described neither in the European Pharmacopoeia nor in the	(6) In case where starting and raw materials, active substance(s) or excipient(s) are described neither in the European Pharmacopoeia nor in the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.	pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.	pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.	
Annex II, 7 paragraph				
2227	(7) Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European	(7) Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European	(7) Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines.	Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines.	Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines.	
Annex II, 8 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2228	(8) For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the	(8) For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the	(8) For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the	
Annex II, 9 paragraph				
2229	(i) detailed description of the manufacturing process,	(i) detailed description of the manufacturing process,	(i) detailed description of the manufacturing process,	
Annex II, II paragraph				
2230	(ii) quality control during manufacture, and	(ii) quality control during manufacture, and	(ii) quality control during manufacture, and	
Annex II, III paragraph				
2231	(iii) process validation	(iii) process validation	(iii) process validation	
Annex II, IV paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2232	to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File.	to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File.	to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File.	
Annex II, V paragraph				
2233	In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing	In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing	In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.	the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.	the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.	
Annex II, VI paragraph				
2234	(9) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on	(9) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on	(9) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance.	Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance.	Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance.	
Annex II, 10 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2235	(10) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided.	(10) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided.	(10) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided.	
Annex II, 11 paragraph				
2236	(11) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.	(11) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.	(11) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.	
Annex II, 12 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2237	(12) Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council ([1]), a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.	(12) Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council ([1]), a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.	(12) Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council ([1]), a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	___________ 1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1)	___________ 1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1)	___________ 1. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1)	
Annex II, 13 paragraph				
2238	If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall	If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall	If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.	require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.	require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.	
Annex II, 14 paragraph				
2239	3.2.1 Active substance(s)	3.2.1 Active substance(s)	3.2.1 Active substance(s)	
Annex II, 2 paragraph				
2240	General information and information related to the	General information and information related to the	General information and information related to the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 3 paragraph				
2241	starting and raw materials	starting and raw materials	starting and raw materials	
Annex II, 3 paragraph, point (a), first subparagraph				
2242	a) Information on the nomenclature of the active substance shall be provided, including recommended International Non-proprietary Name (INN), European Pharmacopoeia name if relevant, chemical name(s).	a) Information on the nomenclature of the active substance shall be provided, including recommended International Non-proprietary Name (INN), European Pharmacopoeia name if relevant, chemical name(s).	a) Information on the nomenclature of the active substance shall be provided, including recommended International Non-proprietary Name (INN), European Pharmacopoeia name if relevant, chemical name(s).	
Annex II, 3 paragraph, point (a), second subparagraph				
2243	The structural formula, including relative and absolute stereo-chemistry, the molecular formula,	The structural formula, including relative and absolute stereo-chemistry, the molecular formula,	The structural formula, including relative and absolute stereo-chemistry, the molecular formula,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	and the relative molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.	and the relative molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.	and the relative molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.	
Annex II, 3 paragraph, point (a), third subparagraph				
2244	A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.	A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.	A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.	
Annex II, 3 paragraph, point (b), first subparagraph				
2245	b) For the purposes of this Annex, starting materials shall	b) For the purposes of this Annex, starting materials shall	b) For the purposes of this Annex, starting materials shall	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	mean all the materials from which the active substance is manufactured or extracted.	mean all the materials from which the active substance is manufactured or extracted.	mean all the materials from which the active substance is manufactured or extracted.	
Annex II, 3 paragraph, point (b), second subparagraph				
2246	For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).	For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).	For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).	
Annex II, 3 paragraph, point (b), third subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2247	A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex	A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex	A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	to Regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex.	to Regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex.	to Regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex.	
Annex II, 3 paragraph, point (b), fourth subparagraph				
2248	Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.	Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.	Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.	
Annex II, 4 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2249	3.2.1.2. Manufacturing process of the active substance(s)	3.2.1.2. Manufacturing process of the active substance(s)	3.2.1.2. Manufacturing process of the active substance(s)	
Annex II, 4 paragraph(a)				
2250	a) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines published by the Agency shall be provided.	a) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines published by the Agency shall be provided.	a) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines published by the Agency shall be provided.	
Annex II, 4 paragraph(b), first subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2251	b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.	b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.	b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.	
Annex II, 4 paragraph(b), second subparagraph				
2252	Raw materials shall be listed and their quality and controls shall also be documented.	Raw materials shall be listed and their quality and controls shall also be documented.	Raw materials shall be listed and their quality and controls shall also be documented.	
Annex II, 4 paragraph(b), third subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2253	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.	
Annex II, 4 paragraph(c), first subparagraph				
2254	c) For biological medicinal products, the following additional requirements shall apply.	c) For biological medicinal products, the following additional requirements shall apply.	c) For biological medicinal products, the following additional requirements shall apply.	
Annex II, 4 paragraph(c), second subparagraph				
2255	The origin and history of starting materials shall be described and documented.	The origin and history of starting materials shall be described and documented.	The origin and history of starting materials shall be described and documented.	
Annex II, 4 paragraph(c), third subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2256	Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.	Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.	Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.	
Annex II, 4 paragraph(c), fourth subparagraph				
2257	When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the	When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the	When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	passage level used for the production and beyond.	passage level used for the production and beyond.	passage level used for the production and beyond.	
Annex II, 4 paragraph(c), fifth subparagraph				
2258	Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.	Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.	Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.	
Annex II, 4 paragraph(c), sixth subparagraph				
2259	If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.	If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.	If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph(c), seventh subparagraph				
2260	Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.	Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.	Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.	
Annex II, 4 paragraph(c), eighth subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2261	For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.	For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.	For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.	
Annex II, 4 paragraph(c), ninth subparagraph				
2262	The manufacturing facilities and equipment shall be described.	The manufacturing facilities and equipment shall be described.	The manufacturing facilities and equipment shall be described.	
Annex II, 4 paragraph(d)				
2263	d) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and	d) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and	d) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	process validation and/or evaluation studies shall be provided as appropriate.	process validation and/or evaluation studies shall be provided as appropriate.	process validation and/or evaluation studies shall be provided as appropriate.	
Annex II, 4 paragraph(e)				
2264	e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.	e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.	e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.	
Annex II, 4 paragraph(f)				
2265	f) A description and discussion of the significant changes made to the	f) A description and discussion of the significant changes made to the	f) A description and discussion of the significant changes made to the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	manufacturing process during development and/or manufacturing site of the active substance shall be provided.	manufacturing process during development and/or manufacturing site of the active substance shall be provided.	manufacturing process during development and/or manufacturing site of the active substance shall be provided.	
Annex II, 3 paragraph,				
2266	Characterisation of the active substance(s)	Characterisation of the active substance(s)	Characterisation of the active substance(s)	
Annex II, 4 paragraph				
2267	Data highlighting the structure and other characteristics of the active substance(s) shall be provided.	Data highlighting the structure and other characteristics of the active substance(s) shall be provided.	Data highlighting the structure and other characteristics of the active substance(s) shall be provided.	
Annex II, 5 paragraph				
2268	Confirmation of the structure of the active substance(s) based on	Confirmation of the structure of the active substance(s) based on	Confirmation of the structure of the active substance(s) based on	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.	any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.	any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.	
Annex II, 6 paragraph,				
2269	Control of activesubstance(s)	Control of activesubstance(s)	Control of activesubstance(s)	
Annex II, 5 paragraph				
2270	Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.	Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.	Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 6 paragraph				
2271	The results of control carried out on individual batches manufactured during development shall be presented.	The results of control carried out on individual batches manufactured during development shall be presented.	The results of control carried out on individual batches manufactured during development shall be presented.	
Annex II, 7 paragraph,				
2272	Reference standards or materials	Reference standards or materials	Reference standards or materials	
Annex II, 6 paragraph				
2273	Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used.	Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used.	Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 7 paragraph,				
2274	Container and closure system of the active substance	Container and closure system of the active substance	Container and closure system of the active substance	
Annex II, 7 paragraph				
2275	A description of the container and the closure system(s) and their specifications shall be provided.	A description of the container and the closure system(s) and their specifications shall be provided.	A description of the container and the closure system(s) and their specifications shall be provided.	
Annex II, 8 paragraph				
2276	3.2.1.7. Stability of the active substance(s)	3.2.1.7. Stability of the active substance(s)	3.2.1.7. Stability of the active substance(s)	
Annex II, 8 paragraph(a)				
2277	a) The type s of studies conducted, protocols used, and the	a) The type s of studies conducted, protocols used, and the	a) The type s of studies conducted, protocols used, and the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	results of the studies shall be summarised	results of the studies shall be summarised	results of the studies shall be summarised	
Annex II, 8 paragraph(b)				
2278	b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format	b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format	b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format	
Annex II, 8 paragraph(c)				
2279	c) The post authorisation stability protocol and stability commitment shall be provided	c) The post authorisation stability protocol and stability commitment shall be provided	c) The post authorisation stability protocol and stability commitment shall be provided	
Annex II, 8 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2280	3.2.2 Finished medicinal product	3.2.2 Finished medicinal product	3.2.2 Finished medicinal product	
Annex II, 3 paragraph				
2281	Description and composition of the finished	Description and composition of the finished	Description and composition of the finished	
Annex II, 4 paragraph				
2282	medicinal product	medicinal product	medicinal product	
Annex II, 5 paragraph				
2283	A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished	A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished	A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	medicinal product, their amount on a per-unit basis, the function of the constituents of:	medicinal product, their amount on a per-unit basis, the function of the constituents of:	medicinal product, their amount on a per-unit basis, the function of the constituents of:	
Annex II, 6 paragraph				
2284	- the active substance(s),	- the active substance(s),	- the active substance(s),	
Annex II, -a paragraph				
2285	- the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,	- the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,	- the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2286	- the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),	- the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),	- the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),	
Annex II, -a paragraph				
2287	- these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.	- these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.	- these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2288	The ‘usual terminology’, to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in Article 8 (3) (c):	The ‘usual terminology’, to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in Article 8 (3) (c):	The ‘usual terminology’, to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in Article 8 (3) (c):	
Annex II, -b paragraph				
2289	- in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,	- in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,	- in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2290	- in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,	- in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,	- in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,	
Annex II, -a paragraph				
2291	- in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12	- in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12	- in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorised for use in medicinal products ([1]) and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs ([2]). __________ 1. OJ L 11, 14.1.1978, p. 18 2. OJ L 237, 10.9.1994, p. 13	December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorised for use in medicinal products ([1]) and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs ([2]). __________ 1. OJ L 11, 14.1.1978, p. 18 2. OJ L 237, 10.9.1994, p. 13	December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorised for use in medicinal products ([1]) and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs ([2]). __________ 1. OJ L 11, 14.1.1978, p. 18 2. OJ L 237, 10.9.1994, p. 13	
Annex II, -a paragraph				
2292	In order to give the 'quantitative composition' of the active substance(s) of the finished medicinal products, it is necessary, depending on the pharmaceutical	In order to give the 'quantitative composition' of the active substance(s) of the finished medicinal products, it is necessary, depending on the pharmaceutical	In order to give the 'quantitative composition' of the active substance(s) of the finished medicinal products, it is necessary, depending on the pharmaceutical	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.	form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.	form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.	
Annex II, -b paragraph				
2293	Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.	Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.	Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.	
Annex II, -c paragraph				
2294	For medicinal products containing an active substance, which is the subject of an application for	For medicinal products containing an active substance, which is the subject of an application for	For medicinal products containing an active substance, which is the subject of an application for	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	marketing authorisation in any Member State for the first time, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.	marketing authorisation in any Member State for the first time, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.	marketing authorisation in any Member State for the first time, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.	
Annex II, -Ca paragraph				
2295	Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological activity has been	Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological activity has been	Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological activity has been	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.	defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.	defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.	
Annex II, -Cb paragraph,				
2296	P h a r m a c e u t i c a l d e v e l o p m e n t	P h a r m a c e u t i c a l d e v e l o p m e n t	P h a r m a c e u t i c a l d e v e l o p m e n t	
Annex II, 3 paragraph				
2297	This chapter shall be devoted to information on the development studies conducted to establish that	This chapter shall be devoted to information on the development studies conducted to establish that	This chapter shall be devoted to information on the development studies conducted to establish that	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier.	the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier.	the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier.	
Annex II, 4 paragraph				
2298	The studies described in this chapter are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where	The studies described in this chapter are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where	The studies described in this chapter are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	appropriate, shall be referenced to the relevant chapters of Module 4 (Non Clinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorisation application dossier.	appropriate, shall be referenced to the relevant chapters of Module 4 (Non Clinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorisation application dossier.	appropriate, shall be referenced to the relevant chapters of Module 4 (Non Clinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorisation application dossier.	
Annex II, 4 paragraph, point (a)				
2299	a) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.	a) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.	a) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph, point (b)				
2300	b) The choice of excipients, in particular relative to their respective functions and concentration shall be documented.	b) The choice of excipients, in particular relative to their respective functions and concentration shall be documented.	b) The choice of excipients, in particular relative to their respective functions and concentration shall be documented.	
Annex II, 4 paragraph, point (c)				
2301	c) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.	c) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.	c) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.	
Annex II, 4 paragraph, point (d)				
2302	d) Any overages in the formulation(s) shall be warranted.	d) Any overages in the formulation(s) shall be warranted.	d) Any overages in the formulation(s) shall be warranted.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph, point (e)				
2303	e) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.	e) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.	e) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.	
Annex II, 4 paragraph, point (f)				
2304	f) The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.	f) The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.	f) The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph, point (g)				
2305	g) The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.	g) The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.	g) The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.	
Annex II, 4 paragraph, point (h)				
2306	h) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the European Pharmacopoeia.	h) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the European Pharmacopoeia.	h) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the European Pharmacopoeia.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph, point (i)				
2307	i) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented	i) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented	i) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented	
Annex II, 5 paragraph				
2308	3.2.2.3. Manufacturing process of the finished medicinal product	3.2.2.3. Manufacturing process of the finished medicinal product	3.2.2.3. Manufacturing process of the finished medicinal product	
Annex II, 5 paragraph(a), first subparagraph				
2309	a) The description of the manufacturing method accompanying the application for	a) The description of the manufacturing method accompanying the application for	a) The description of the manufacturing method accompanying the application for	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	Marketing Authorisation pursuant to Article 8 (3) (d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.	Marketing Authorisation pursuant to Article 8 (3) (d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.	Marketing Authorisation pursuant to Article 8 (3) (d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.	
Annex II, 5 paragraph(a), second subparagraph				
2310	For this purpose it shall include at least:	For this purpose it shall include at least:	For this purpose it shall include at least:	
Annex II, 4 paragraph				
2311	- mention of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes employed in producing the pharmaceutical	- mention of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes employed in producing the pharmaceutical	- mention of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes employed in producing the pharmaceutical	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	form might have produced an adverse change in the constituents,	form might have produced an adverse change in the constituents,	form might have produced an adverse change in the constituents,	
Annex II, -a paragraph				
2312	- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,	- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,	- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,	
Annex II, -a paragraph				
2313	- experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,	- experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,	- experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2314	- for sterile medicinal products, details of the sterilisation processes and/or aseptic procedures used,	- for sterile medicinal products, details of the sterilisation processes and/or aseptic procedures used,	- for sterile medicinal products, details of the sterilisation processes and/or aseptic procedures used,	
Annex II, -a paragraph				
2315	- a detailed batch formula.	- a detailed batch formula.	- a detailed batch formula.	
Annex II, -a paragraph				
2316	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.	
Annex II, -b paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2317	b) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.	b) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.	b) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.	
Annex II, c paragraph				
2318	These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).	These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).	These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, CI paragraph				
2319	The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method of preparation.	The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method of preparation.	The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method of preparation.	
Annex II, CII paragraph				
2320	c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.	c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.	c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.	
Annex II, CI paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2321	3.2.2.4. Control of excipients	3.2.2.4. Control of excipients	3.2.2.4. Control of excipients	
Annex II, CI paragraph(a), first subparagraph				
2322	a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.	a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.	a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.	
Annex II, CI paragraph(a), second subparagraph				
2323	Colouring matter shall, in all cases, satisfy the requirements of	Colouring matter shall, in all cases, satisfy the requirements of	Colouring matter shall, in all cases, satisfy the requirements of	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	Directives 78/25/EEC and/or 94/36/EC. In addition, colouring matter shall meet purity criteria as laid down in Directive 95/45/EC, as amended.	Directives 78/25/EEC and/or 94/36/EC. In addition, colouring matter shall meet purity criteria as laid down in Directive 95/45/EC, as amended.	Directives 78/25/EEC and/or 94/36/EC. In addition, colouring matter shall meet purity criteria as laid down in Directive 95/45/EC, as amended.	
Annex II, CI paragraph(b)				
2324	b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.	b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.	b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.	
Annex II, CI paragraph(c), first subparagraph				
2325	c) Specific attention shall be paid to excipients of human or animal origin.	c) Specific attention shall be paid to excipients of human or animal origin.	c) Specific attention shall be paid to excipients of human or animal origin.	
Annex II, CI paragraph(c), second subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2326	Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.	Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.	Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.	
Annex II, CI paragraph(c), third subparagraph				
2327	Demonstration of compliance with the aforementioned Note for Guidance can be done by	Demonstration of compliance with the aforementioned Note for Guidance can be done by	Demonstration of compliance with the aforementioned Note for Guidance can be done by	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.	submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.	submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.	
Annex II, CI paragraph(d), first subparagraph				
2328	d) Novel excipients:	d) Novel excipients:	d) Novel excipients:	
Annex II, CI paragraph(d), second subparagraph				
2329	For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting	For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting	For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting	

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	safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.	safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.	safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.	
Annex II, CI paragraph(d), third subparagraph				
2330	A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.	A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.	A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.	
Annex II, CI paragraph(d), fourth subparagraph				
2331	Information on novel excipient(s) may be presented as a stand-alone document following the format described in the former	Information on novel excipient(s) may be presented as a stand-alone document following the format described in the former	Information on novel excipient(s) may be presented as a stand-alone document following the format described in the former	

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	paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the competent authority.	paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the competent authority.	paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the competent authority.	
Annex II, CI paragraph(d), fifth subparagraph				
2332	Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.	Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.	Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.	
Annex II, CI paragraph(d), sixth subparagraph				
2333	Clinical studies shall be provided in Module 5.	Clinical studies shall be provided in Module 5.	Clinical studies shall be provided in Module 5.	
Annex II, 5 paragraph,				

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2334	C o n t r o l o f t h e f i n i s h e d m e d i c i n a l p r o d u c t	C o n t r o l o f t h e f i n i s h e d m e d i c i n a l p r o d u c t	C o n t r o l o f t h e f i n i s h e d m e d i c i n a l p r o d u c t	
Annex II, 6 paragraph				
2335	For the control of the finished medicinal product, a batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.	For the control of the finished medicinal product, a batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.	For the control of the finished medicinal product, a batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.	
Annex II, 7 paragraph				

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2336	Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.	Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.	Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.	
Annex II, 8 paragraph				
2337	Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.	Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.	Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.	
Annex II, 9 paragraph,				
2338	Reference standards or materials	Reference standards or materials	Reference standards or materials	
Annex II, 7 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2339	Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.	Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.	Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.	
Annex II, 8 paragraph,				
2340	Container and closure of the finished medicinal product	Container and closure of the finished medicinal product	Container and closure of the finished medicinal product	
Annex II, 8 paragraph				
2341	A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided.	A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided.	A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.	The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.	The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.	
Annex II, 9 paragraph				
2342	For non-functional outer packaging materials only a brief description shall be provided. For functional outer packaging materials additional information shall be provided.	For non-functional outer packaging materials only a brief description shall be provided. For functional outer packaging materials additional information shall be provided.	For non-functional outer packaging materials only a brief description shall be provided. For functional outer packaging materials additional information shall be provided.	
Annex II, 10 paragraph				
2343	3.2.2.8. Stability of the finished medicinal product	3.2.2.8. Stability of the finished medicinal product	3.2.2.8. Stability of the finished medicinal product	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 10 paragraph(a)				
2344	a) The types of studies conducted, protocols used, and the results of the studies shall be summarised;	a) The types of studies conducted, protocols used, and the results of the studies shall be summarised;	a) The types of studies conducted, protocols used, and the results of the studies shall be summarised;	
Annex II, 10 paragraph(b)				
2345	b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format; in case of vaccines, information on cumulative stability shall be provided where appropriate;	b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format; in case of vaccines, information on cumulative stability shall be provided where appropriate;	b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format; in case of vaccines, information on cumulative stability shall be provided where appropriate;	
Annex II, 10 paragraph(c)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2346	c) The post authorisation stability protocol and stability commitment shall be provided.	c) The post authorisation stability protocol and stability commitment shall be provided.	c) The post authorisation stability protocol and stability commitment shall be provided.	
Annex II, point 4.				
2347	4. MODULE 4: NON-CLINICAL REPORTS	4. MODULE 4: NON-CLINICAL REPORTS	4. MODULE 4: NON-CLINICAL REPORTS	
Annex II, 9 paragraph				
2348	4.1. The general outline of Module 4 is as follows:	4.1. The general outline of Module 4 is as follows:	4.1. The general outline of Module 4 is as follows:	
Annex II, 2 paragraph				
2349	- Table of contents	- Table of contents	- Table of contents	
Annex II, -a paragraph				
2350	- Study reports	- Study reports	- Study reports	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2351	- Pharmacology	- Pharmacology	- Pharmacology	
Annex II, -a paragraph				
2352	- Primary Pharmaco-dynamics	- Primary Pharmaco-dynamics	- Primary Pharmaco-dynamics	
Annex II, -a paragraph				
2353	- Secondary Pharmaco-dynamics	- Secondary Pharmaco-dynamics	- Secondary Pharmaco-dynamics	
Annex II, -a paragraph				
2354	- Safety Pharmacology	- Safety Pharmacology	- Safety Pharmacology	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2355	- Pharmaco-dynamic Interactions	- Pharmaco-dynamic Interactions	- Pharmaco-dynamic Interactions	
Annex II, -a paragraph				
2356	- Pharmaco-kinetics	- Pharmaco-kinetics	- Pharmaco-kinetics	
Annex II, -a paragraph				
2357	- Analytical Methods and Validation Reports	- Analytical Methods and Validation Reports	- Analytical Methods and Validation Reports	
Annex II, -a paragraph				
2358	- Absorption	- Absorption	- Absorption	
Annex II, -a paragraph				
2359	- Distribution	- Distribution	- Distribution	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2360	- Metabolism	- Metabolism	- Metabolism	
Annex II, -a paragraph				
2361	- Excretion	- Excretion	- Excretion	
Annex II, -a paragraph				
2362	- Pharmaco-kinetic Interactions (non-clinical)	- Pharmaco-kinetic Interactions (non-clinical)	- Pharmaco-kinetic Interactions (non-clinical)	
Annex II, -a paragraph				
2363	- Other Pharmaco-kinetic Studies Interactions	- Other Pharmaco-kinetic Studies Interactions	- Other Pharmaco-kinetic Studies Interactions	
Annex II, -a paragraph				
2364	- Toxicology	- Toxicology	- Toxicology	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2365	- Single-Dose Toxicity	- Single-Dose Toxicity	- Single-Dose Toxicity	
Annex II, -a paragraph				
2366	- Repeat-Dose Toxicity Interactions	- Repeat-Dose Toxicity Interactions	- Repeat-Dose Toxicity Interactions	
Annex II, -a paragraph				
2367	- Genotoxicity	- Genotoxicity	- Genotoxicity	
Annex II, -a paragraph				
2368	- In vitro	- In vitro	- In vitro	
Annex II, -a paragraph				
2369	- In vivo (including supportive toxico-kinetics evaluations) Interactions	- In vivo (including supportive toxico-kinetics evaluations) Interactions	- In vivo (including supportive toxico-kinetics evaluations) Interactions	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2370	- Carcinogenicity	- Carcinogenicity	- Carcinogenicity	
Annex II, -a paragraph				
2371	- Long-term studies	- Long-term studies	- Long-term studies	
Annex II, -a paragraph				
2372	- Short- or medium-term studies	- Short- or medium-term studies	- Short- or medium-term studies	
Annex II, -a paragraph				
2373	- Other studies Interactions	- Other studies Interactions	- Other studies Interactions	
Annex II, -a paragraph				
2374	- Reproductive and Developmental Toxicity	- Reproductive and Developmental Toxicity	- Reproductive and Developmental Toxicity	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2375	- Fertility and early embryonic development	- Fertility and early embryonic development	- Fertility and early embryonic development	
Annex II, -a paragraph				
2376	- Embryo-fetal development	- Embryo-fetal development	- Embryo-fetal development	
Annex II, -a paragraph				
2377	- Prenatal and postnatal development	- Prenatal and postnatal development	- Prenatal and postnatal development	
Annex II, -a paragraph				
2378	- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated	- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated	- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2379	- Local Tolerance Interactions	- Local Tolerance Interactions	- Local Tolerance Interactions	
Annex II, -a paragraph				
2380	- Other Toxicity Studies	- Other Toxicity Studies	- Other Toxicity Studies	
Annex II, -a paragraph				
2381	- Antigenicity	- Antigenicity	- Antigenicity	
Annex II, -a paragraph				
2382	- Immuno-toxicity	- Immuno-toxicity	- Immuno-toxicity	
Annex II, -a paragraph				
2383	- Mechanistic studies	- Mechanistic studies	- Mechanistic studies	
Annex II, -a paragraph				

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2384	- Dependence	- Dependence	- Dependence	
Annex II, -a paragraph				
2385	- Metabolites	- Metabolites	- Metabolites	
Annex II, -a paragraph				
2386	- Impurities	- Impurities	- Impurities	
Annex II, -a paragraph				
2387	- Other	- Other	- Other	
Annex II, -a paragraph				
2388	- Literature references	- Literature references	- Literature references	
Annex II, -a paragraph				

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2389	- THIS INDENT IS MISSING. THANK YOU FOR USING ANOTHER LANGUAGE.	- THIS INDENT IS MISSING. THANK YOU FOR USING ANOTHER LANGUAGE.	- THIS INDENT IS MISSING. THANK YOU FOR USING ANOTHER LANGUAGE.	
Annex II, -a paragraph				
2390	4.2. Content: basic principles and requirements	4.2. Content: basic principles and requirements	4.2. Content: basic principles and requirements	
Annex II, 3 paragraph				
2391	Special attention shall be paid to the following selected elements.	Special attention shall be paid to the following selected elements.	Special attention shall be paid to the following selected elements.	
Annex II, 4 paragraph				
2392	(1) The pharmacological and toxicological tests must show:	(1) The pharmacological and toxicological tests must show:	(1) The pharmacological and toxicological tests must show:	
Annex II, 4 paragraph, point (a)				

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2393	a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;	a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;	a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;	
Annex II, 4 paragraph, point (b), first subparagraph				
2394	b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental	b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental	b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	methods and in evaluating the results.	methods and in evaluating the results.	methods and in evaluating the results.	
Annex II, 4 paragraph, point (b), second subparagraph				
2395	Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.	Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.	Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.	
Annex II, 2 paragraph				
2396	(2) For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program	(2) For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program	(2) For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	carried out shall be justified by the applicant.	carried out shall be justified by the applicant.	carried out shall be justified by the applicant.	
Annex II, 3 paragraph				
2397	In establishing the testing program, the following shall be taken into consideration:	In establishing the testing program, the following shall be taken into consideration:	In establishing the testing program, the following shall be taken into consideration:	
Annex II, 4 paragraph				
2398	all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;	all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;	all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;	
Annex II, 5 paragraph				
2399	examination of reproductive function, of embryo/foetal and	examination of reproductive function, of embryo/foetal and	examination of reproductive function, of embryo/foetal and	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	peri-natal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.	peri-natal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.	peri-natal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.	
Annex II, 6 paragraph				
2400	(3) The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.	(3) The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.	(3) The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.	
Annex II, 4 paragraph				
2401	(4) Where there is a possibility of significant degradation during storage of the	(4) Where there is a possibility of significant degradation during storage of the	(4) Where there is a possibility of significant degradation during storage of the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	medicinal product, the toxicology of degradation products must be considered.	medicinal product, the toxicology of degradation products must be considered.	medicinal product, the toxicology of degradation products must be considered.	
Annex II, 5 paragraph,				
2402	Pharmacology	Pharmacology	Pharmacology	
Annex II, 2 paragraph				
2403	Pharmacology study shall follow two distinct lines of approach.	Pharmacology study shall follow two distinct lines of approach.	Pharmacology study shall follow two distinct lines of approach.	
Annex II, 3 paragraph				
2404	- Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both in vivo and in vitro, shall be	- Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both in vivo and in vitro, shall be	- Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both in vivo and in vitro, shall be	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.	used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.	used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.	
Annex II, -a paragraph				
2405	- Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated	- Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated	- Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated	

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	therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.	therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.	therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.	
Annex II, -a paragraph				
2406	For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-	For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-	For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	dynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.	dynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.	dynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.	
Annex II, -b paragraph,				
2407	Pharmaco-kinetics	Pharmaco-kinetics	Pharmaco-kinetics	
Annex II, 3 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2408	Pharmaco-kinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.	Pharmaco-kinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.	Pharmaco-kinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.	
Annex II, 4 paragraph				
2409	The study of these different phases may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmaco-dynamic activity of the substance itself.	The study of these different phases may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmaco-dynamic activity of the substance itself.	The study of these different phases may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmaco-dynamic activity of the substance itself.	
Annex II, 5 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2410	Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemo-therapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmaco-dynamic effects (e.g. numerous diagnostic agents, etc.).	Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemo-therapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmaco-dynamic effects (e.g. numerous diagnostic agents, etc.).	Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemo-therapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmaco-dynamic effects (e.g. numerous diagnostic agents, etc.).	
Annex II, 6 paragraph				
2411	In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).	In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).	In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).	
Annex II, 7 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2412	Pharmaco-kinetic investigation of all pharmacologically active substances is necessary. In the case of new combinations of known substances, which have been investigated in accordance with the provisions of this Directive, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.	Pharmaco-kinetic investigation of all pharmacologically active substances is necessary. In the case of new combinations of known substances, which have been investigated in accordance with the provisions of this Directive, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.	Pharmaco-kinetic investigation of all pharmacologically active substances is necessary. In the case of new combinations of known substances, which have been investigated in accordance with the provisions of this Directive, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.	
Annex II, 8 paragraph				
2413	The pharmaco-kinetic program shall be design to allow comparison and extrapolation between animal and human.	The pharmaco-kinetic program shall be design to allow comparison and extrapolation between animal and human.	The pharmaco-kinetic program shall be design to allow comparison and extrapolation between animal and human.	
Annex II, 9 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2414	4.2.3. Toxicology	4.2.3. Toxicology	4.2.3. Toxicology	
Annex II, 9 paragraph(a), first subparagraph				
2415	a) Single-dose toxicity	a) Single-dose toxicity	a) Single-dose toxicity	
Annex II, 9 paragraph(a), second subparagraph				
2416	A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.	A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.	A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.	
Annex II, 9 paragraph(a), third subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2417	The single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Agency.	The single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Agency.	The single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Agency.	
Annex II, 9 paragraph(b), first subparagraph				
2418	b) Repeat-dose toxicity	b) Repeat-dose toxicity	b) Repeat-dose toxicity	
Annex II, 9 paragraph(b), second subparagraph				
2419	Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.	Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.	Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 9 paragraph(b), third subparagraph				
2420	Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies. The duration is defined in the relevant guidelines published by the Agency.	Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies. The duration is defined in the relevant guidelines published by the Agency.	Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies. The duration is defined in the relevant guidelines published by the Agency.	
Annex II, 9 paragraph(c), first subparagraph				
2421	c) Geno-toxicity	c) Geno-toxicity	c) Geno-toxicity	
Annex II, 9 paragraph(c), second subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2422	The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.	The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.	The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.	
Annex II, 9 paragraph(d), first subparagraph				
2423	d) Carcino-genicity	d) Carcino-genicity	d) Carcino-genicity	
Annex II, 9 paragraph(d), second subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2424	Tests to reveal carcinogenic effects shall normally be required:	Tests to reveal carcinogenic effects shall normally be required:	Tests to reveal carcinogenic effects shall normally be required:	
Annex II, 4 paragraph				
2425	1. These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.	1. These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.	1. These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.	
Annex II, 2 paragraph				
2426	2. These studies are recommended for some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or	2. These studies are recommended for some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or	2. These studies are recommended for some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	similar structure, or from evidence in repeated dose toxicity studies.	similar structure, or from evidence in repeated dose toxicity studies.	similar structure, or from evidence in repeated dose toxicity studies.	
Annex II, 3 paragraph				
2427	3. Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.	3. Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.	3. Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.	
Annex II, 4 paragraph				
2428	e) Reproductive and developmental toxicity	e) Reproductive and developmental toxicity	e) Reproductive and developmental toxicity	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, f paragraph				
2429	Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.	Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.	Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.	
Annex II, g paragraph				
2430	These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.	These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.	These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, h paragraph				
2431	Omission of these tests must be adequately justified.	Omission of these tests must be adequately justified.	Omission of these tests must be adequately justified.	
Annex II, i paragraph				
2432	Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.	Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.	Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.	
Annex II, II paragraph				
2433	Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal studies shall be	Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal studies shall be	Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal studies shall be	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies.	conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies.	conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies.	
Annex II, III paragraph				
2434	The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.	The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.	The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.	
Annex II, IV paragraph				
2435	f) Local tolerance	f) Local tolerance	f) Local tolerance	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, g paragraph				
2436	The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmaco-dynamic ones.	The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmaco-dynamic ones.	The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmaco-dynamic ones.	
Annex II, h paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2437	Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/reference substances shall be included where necessary.	Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/reference substances shall be included where necessary.	Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/reference substances shall be included where necessary.	
Annex II, i paragraph				
2438	The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.	The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.	The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, II paragraph				
2439	Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.	Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.	Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.	
Annex II, III paragraph				
2440	For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitising potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).	For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitising potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).	For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitising potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).	
Annex II, point 5.				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2441	5. MODULE 5: CLINICAL STUDY REPORTS	5. MODULE 5: CLINICAL STUDY REPORTS	5. MODULE 5: CLINICAL STUDY REPORTS	
Annex II, IV paragraph				
2442	5.1. Format and Presentation	5.1. Format and Presentation	5.1. Format and Presentation	
Annex II, 2 paragraph				
2443	The general outline of Module 5 is as follows:	The general outline of Module 5 is as follows:	The general outline of Module 5 is as follows:	
Annex II, 3 paragraph				
2444	- Table of contents for clinical study reports	- Table of contents for clinical study reports	- Table of contents for clinical study reports	
Annex II, -a paragraph				
2445	- Tabular listing of all clinical studies	- Tabular listing of all clinical studies	- Tabular listing of all clinical studies	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2446	- Clinical study reports	- Clinical study reports	- Clinical study reports	
Annex II, -a paragraph				
2447	- Reports of Bio-pharmaceutical Studies	- Reports of Bio-pharmaceutical Studies	- Reports of Bio-pharmaceutical Studies	
Annex II, -a paragraph				
2448	- Bio-availability Study Reports	- Bio-availability Study Reports	- Bio-availability Study Reports	
Annex II, -a paragraph				
2449	- Comparative Bio-availability and Bio-equivalence Study Reports	- Comparative Bio-availability and Bio-equivalence Study Reports	- Comparative Bio-availability and Bio-equivalence Study Reports	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2450	- In vitro — In vivo Correlation Study Report	- In vitro — In vivo Correlation Study Report	- In vitro — In vivo Correlation Study Report	
Annex II, -a paragraph				
2451	- Reports of Bio-analytical and Analytical Methods	- Reports of Bio-analytical and Analytical Methods	- Reports of Bio-analytical and Analytical Methods	
Annex II, -a paragraph				
2452	- Reports of Studies Pertinent to Pharmaco-kinetics Using Human Bio-materials	- Reports of Studies Pertinent to Pharmaco-kinetics Using Human Bio-materials	- Reports of Studies Pertinent to Pharmaco-kinetics Using Human Bio-materials	
Annex II, -a paragraph				
2453	- Plasma Protein Binding Study Reports	- Plasma Protein Binding Study Reports	- Plasma Protein Binding Study Reports	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2454	- Reports of Hepatic Metabolism and Interaction Studies	- Reports of Hepatic Metabolism and Interaction Studies	- Reports of Hepatic Metabolism and Interaction Studies	
Annex II, -a paragraph				
2455	- Reports of Studies Using Other Human Bio-materials Methods	- Reports of Studies Using Other Human Bio-materials Methods	- Reports of Studies Using Other Human Bio-materials Methods	
Annex II, -a paragraph				
2456	- Reports of Human Pharmaco-kinetic Studies	- Reports of Human Pharmaco-kinetic Studies	- Reports of Human Pharmaco-kinetic Studies	
Annex II, -a paragraph				
2457	- Healthy subjects Pharmaco-kinetics and Initial Tolerability Study Reports	- Healthy subjects Pharmaco-kinetics and Initial Tolerability Study Reports	- Healthy subjects Pharmaco-kinetics and Initial Tolerability Study Reports	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2458	- Patient Pharmaco-kinetics and Initial Tolerability Study Reports	- Patient Pharmaco-kinetics and Initial Tolerability Study Reports	- Patient Pharmaco-kinetics and Initial Tolerability Study Reports	
Annex II, -a paragraph				
2459	- Intrinsic Factor Pharmaco-kinetics Study Reports	- Intrinsic Factor Pharmaco-kinetics Study Reports	- Intrinsic Factor Pharmaco-kinetics Study Reports	
Annex II, -a paragraph				
2460	- Extrinsic Factor Pharmaco-kinetics Study Reports	- Extrinsic Factor Pharmaco-kinetics Study Reports	- Extrinsic Factor Pharmaco-kinetics Study Reports	
Annex II, -a paragraph				
2461	- Population Pharmaco-kinetics Study Reports Methods	- Population Pharmaco-kinetics Study Reports Methods	- Population Pharmaco-kinetics Study Reports Methods	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2462	- Reports of Human Pharmaco-dynamic Studies	- Reports of Human Pharmaco-dynamic Studies	- Reports of Human Pharmaco-dynamic Studies	
Annex II, -a paragraph				
2463	- Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports	- Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports	- Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports	
Annex II, -a paragraph				
2464	- Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Studies Study Reports Methods	- Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Studies Study Reports Methods	- Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Studies Study Reports Methods	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2465	- Reports of Efficacy and Safety Studies	- Reports of Efficacy and Safety Studies	- Reports of Efficacy and Safety Studies	
Annex II, -a paragraph				
2466	- Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	- Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	- Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	
Annex II, -a paragraph				
2467	- Study Reports of Uncontrolled Clinical Studies	- Study Reports of Uncontrolled Clinical Studies	- Study Reports of Uncontrolled Clinical Studies	
Annex II, -a paragraph				
2468	- Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses	- Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses	- Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2469	- Other Study Reports Methods	- Other Study Reports Methods	- Other Study Reports Methods	
Annex II, -a paragraph				
2470	- Reports of Post-marketing Experience	- Reports of Post-marketing Experience	- Reports of Post-marketing Experience	
Annex II, -a paragraph				
2471	- Literature references Methods	- Literature references Methods	- Literature references Methods	
Annex II, -a paragraph				
2472	5.2 Content: basic principles and requirements	5.2 Content: basic principles and requirements	5.2 Content: basic principles and requirements	
Annex II, 3 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2473	Special attention shall be paid to the following selected elements.	Special attention shall be paid to the following selected elements.	Special attention shall be paid to the following selected elements.	
Annex II, 3 paragraph, point (a)				
2474	a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.	a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.	a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.	
Annex II, 3 paragraph, point (b)				

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2475	b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmaco-kinetic and pharmaco-dynamic data in animals and the results of earlier clinical trials, with adequate data to justify the	b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmaco-kinetic and pharmaco-dynamic data in animals and the results of earlier clinical trials, with adequate data to justify the	b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmaco-kinetic and pharmaco-dynamic data in animals and the results of earlier clinical trials, with adequate data to justify the	

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	nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.	nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.	nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.	
Annex II, 3 paragraph, point (c), first subparagraph				
2476	c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:	c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:	c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:	
Annex II, 4 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2477	- for at least 15 years after completion or discontinuation of the trial,	- for at least 15 years after completion or discontinuation of the trial,	- for at least 15 years after completion or discontinuation of the trial,	
Annex II, -a paragraph				
2478	- or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,	- or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,	- or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,	
Annex II, -a paragraph				
2479	- or for at least two years after formal discontinuation of clinical development of the investigational product.	- or for at least two years after formal discontinuation of clinical development of the investigational product.	- or for at least two years after formal discontinuation of clinical development of the investigational product.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2480	Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.	Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.	Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.	
Annex II, -b paragraph				
2481	The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these	The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these	The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	documents no longer need to be retained.	documents no longer need to be retained.	documents no longer need to be retained.	
Annex II, -c paragraph				
2482	The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol	The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol	The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.	and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.	and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.	
Annex II, -Ca paragraph				
2483	In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.	In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.	In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -Cb paragraph				
2484	Any change of ownership of the data shall be documented.	Any change of ownership of the data shall be documented.	Any change of ownership of the data shall be documented.	
Annex II, -Cc paragraph				
2485	All data and documents shall be made available if requested by relevant authorities.	All data and documents shall be made available if requested by relevant authorities.	All data and documents shall be made available if requested by relevant authorities.	
Annex II, -CCa paragraph				
2486	d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:	d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:	d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:	
Annex II, DI paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2487	- the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used	- the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used	- the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used	
Annex II, -a paragraph				
2488	- audit certificate(s), if available	- audit certificate(s), if available	- audit certificate(s), if available	
Annex II, -a paragraph				
2489	- the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information	- the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information	- the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	in respect of each patient individually, including case report forms on each trial subject	in respect of each patient individually, including case report forms on each trial subject	in respect of each patient individually, including case report forms on each trial subject	
Annex II, -a paragraph				
2490	- final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.	- final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.	- final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.	
Annex II, -a paragraph				
2491	e) The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete	e) The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete	e) The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	documentation shall be provided forthwith upon request.	documentation shall be provided forthwith upon request.	documentation shall be provided forthwith upon request.	
Annex II, f paragraph				
2492	The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his	The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his	The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.	conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.	conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.	
Annex II, g paragraph				
2493	f) The clinical observations shall be summarised for each trial indicating:	f) The clinical observations shall be summarised for each trial indicating:	f) The clinical observations shall be summarised for each trial indicating:	
Annex II, g paragraph				
2494	1) the number and sex of subjects treated;	1) the number and sex of subjects treated;	1) the number and sex of subjects treated;	
Annex II, 2 paragraph				
2495	2) the selection and age-distribution of the groups of	2) the selection and age-distribution of the groups of	2) the selection and age-distribution of the groups of	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	patients being investigated and the comparative tests;	patients being investigated and the comparative tests;	patients being investigated and the comparative tests;	
Annex II, 3 paragraph				
2496	3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;	3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;	3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;	
Annex II, 4 paragraph				
2497	4) where controlled trials were carried out under the above conditions, whether the control group:	4) where controlled trials were carried out under the above conditions, whether the control group:	4) where controlled trials were carried out under the above conditions, whether the control group:	
Annex II, 5 paragraph				
2498	- received no treatment	- received no treatment	- received no treatment	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2499	- received a placebo	- received a placebo	- received a placebo	
Annex II, -a paragraph				
2500	- received another medicinal product of known effect	- received another medicinal product of known effect	- received another medicinal product of known effect	
Annex II, -a paragraph				
2501	- received treatment other than therapy using medicinal products	- received treatment other than therapy using medicinal products	- received treatment other than therapy using medicinal products	
Annex II, -a paragraph				
2502	5) the frequency of observed adverse reactions;	5) the frequency of observed adverse reactions;	5) the frequency of observed adverse reactions;	
Annex II, 6 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2503	6) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;	6) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;	6) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;	
Annex II, 7 paragraph				
2504	7) parameters or evaluation criteria of efficacy and the results in terms of these parameters;	7) parameters or evaluation criteria of efficacy and the results in terms of these parameters;	7) parameters or evaluation criteria of efficacy and the results in terms of these parameters;	
Annex II, 8 paragraph				
2505	8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.	8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.	8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 9 paragraph				
2506	g) In addition, the investigator shall always indicate his observations on:	g) In addition, the investigator shall always indicate his observations on:	g) In addition, the investigator shall always indicate his observations on:	
Annex II, h paragraph				
2507	1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;	1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;	1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;	
Annex II, 2 paragraph				
2508	2) any interactions that have been observed with other medicinal products administered concomitantly;	2) any interactions that have been observed with other medicinal products administered concomitantly;	2) any interactions that have been observed with other medicinal products administered concomitantly;	
Annex II, 3 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2509	3) the criteria determining exclusion of certain patients from the trials;	3) the criteria determining exclusion of certain patients from the trials;	3) the criteria determining exclusion of certain patients from the trials;	
Annex II, 4 paragraph				
2510	4) any deaths which occurred during the trial or within the follow-up period.	4) any deaths which occurred during the trial or within the follow-up period.	4) any deaths which occurred during the trial or within the follow-up period.	
Annex II, 5 paragraph				
2511	h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.	h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.	h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.	
Annex II, i paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2512	i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.	i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.	i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.	
Annex II, II paragraph				
2513	j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.	j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.	j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.	
Annex II, k paragraph,				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2514	Reports of bio-pharmaceutics studies	Reports of bio-pharmaceutics studies	Reports of bio-pharmaceutics studies	
Annex II, 2 paragraph				
2515	Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on in vitro and in vivo correlation study, and bio-analytical and analytical methods shall be provided.	Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on in vitro and in vivo correlation study, and bio-analytical and analytical methods shall be provided.	Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on in vitro and in vivo correlation study, and bio-analytical and analytical methods shall be provided.	
Annex II, 3 paragraph				
2516	In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 10 (1) (a).	In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 10 (1) (a).	In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 10 (1) (a).	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph,				
2517	Reports of studies pertinent to pharmaco-kinetics using human bio-materials	Reports of studies pertinent to pharmaco-kinetics using human bio-materials	Reports of studies pertinent to pharmaco-kinetics using human bio-materials	
Annex II, 3 paragraph				
2518	For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of drug substances.	For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of drug substances.	For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of drug substances.	
Annex II, 4 paragraph				
2519	In this respect, reports of plasma protein binding study, hepatic	In this respect, reports of plasma protein binding study, hepatic	In this respect, reports of plasma protein binding study, hepatic	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.	metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.	metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.	
Annex II, 5 paragraph				
2520	5.2.3. Reports of human pharmaco-kinetic studies	5.2.3. Reports of human pharmaco-kinetic studies	5.2.3. Reports of human pharmaco-kinetic studies	
Annex II, 5 paragraph(a), first subparagraph				
2521	a) The following pharmaco-kinetic characteristics shall be described:	a) The following pharmaco-kinetic characteristics shall be described:	a) The following pharmaco-kinetic characteristics shall be described:	
Annex II, 4 paragraph				
2522	- absorption (rate and extent),	- absorption (rate and extent),	- absorption (rate and extent),	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2523	- distribution,	- distribution,	- distribution,	
Annex II, -a paragraph				
2524	- metabolism,	- metabolism,	- metabolism,	
Annex II, -a paragraph				
2525	- excretion.	- excretion.	- excretion.	
Annex II, -a paragraph				
2526	Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the pre clinical studies, shall be described.	Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the pre clinical studies, shall be described.	Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the pre clinical studies, shall be described.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -b paragraph				
2527	In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose- pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.	In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose- pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.	In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose- pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -c paragraph				
2528	b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.	b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.	b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.	
Annex II, c paragraph				
2529	Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.	Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.	Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.	
Annex II, CI paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2530	5.2.4. Reports of human pharmaco-dynamic studies	5.2.4. Reports of human pharmaco-dynamic studies	5.2.4. Reports of human pharmaco-dynamic studies	
Annex II, CI paragraph(a), first subparagraph				
2531	a) The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including:	a) The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including:	a) The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including:	
Annex II, 5 paragraph				
2532	- the dose-response relationship and its time course,	- the dose-response relationship and its time course,	- the dose-response relationship and its time course,	
Annex II, -a paragraph				
2533	- justification for the dosage and conditions of administration,	- justification for the dosage and conditions of administration,	- justification for the dosage and conditions of administration,	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2534	- the mode of action, if possible.	- the mode of action, if possible.	- the mode of action, if possible.	
Annex II, -a paragraph				
2535	The pharmaco-dynamic action not related to efficacy shall be described.	The pharmaco-dynamic action not related to efficacy shall be described.	The pharmaco-dynamic action not related to efficacy shall be described.	
Annex II, -b paragraph				
2536	The demonstration of pharmaco-dynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.	The demonstration of pharmaco-dynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.	The demonstration of pharmaco-dynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.	
Annex II, -c paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2537	b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.	b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.	b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.	
Annex II, c paragraph				
2538	Pharmaco-dynamic interactions between the active substance and other medicinal products or substances shall be investigated.	Pharmaco-dynamic interactions between the active substance and other medicinal products or substances shall be investigated.	Pharmaco-dynamic interactions between the active substance and other medicinal products or substances shall be investigated.	
Annex II, CI paragraph				
2539	5.2.5. Reports of efficacy and safety studies	5.2.5. Reports of efficacy and safety studies	5.2.5. Reports of efficacy and safety studies	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 6 paragraph				
2540	S t u d y R e p o r t s o f C o n t r o l l e d C l i n i c a l S t u d i e s P e r t i n e n t t o t h e C l a i m e d i n d i c a t i o n	S t u d y R e p o r t s o f C o n t r o l l e d C l i n i c a l S t u d i e s P e r t i n e n t t o t h e C l a i m e d i n d i c a t i o n	S t u d y R e p o r t s o f C o n t r o l l e d C l i n i c a l S t u d i e s P e r t i n e n t t o t h e C l a i m e d i n d i c a t i o n	
Annex II, 7 paragraph				
2541	In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in	In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in	In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.	some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.	some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.	
Annex II, 8 paragraph				
2542	(1) As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.	(1) As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.	(1) As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.	
Annex II, 2 paragraph				
2543	(2) The protocol of the trial must include a thorough	(2) The protocol of the trial must include a thorough	(2) The protocol of the trial must include a thorough	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.	description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.	description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.	
Annex II, 3 paragraph				
2544	The safety data shall be reviewed taking into account guidelines published by the Commission,	The safety data shall be reviewed taking into account guidelines published by the Commission,	The safety data shall be reviewed taking into account guidelines published by the Commission,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.	with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.	with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.	
Annex II, 4 paragraph,				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2545	Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports	Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports	Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports	
Annex II, 3 paragraph				
2546	These reports shall be provided.	These reports shall be provided.	These reports shall be provided.	
Annex II, 4 paragraph,				
2547	Reports of post-marketing experience	Reports of post-marketing experience	Reports of post-marketing experience	
Annex II, 7 paragraph				
2548	If the medicinal product is already authorised in third countries,	If the medicinal product is already authorised in third countries,	If the medicinal product is already authorised in third countries,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.	information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.	information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.	
Annex II, 8 paragraph,				
2549	Case reports forms and individual patient listings	Case reports forms and individual patient listings	Case reports forms and individual patient listings	
Annex II, 8 paragraph				
2550	When submitted in accordance with the relevant Guideline published by the Agency, case report forms and individual patient data listings shall be provided and presented in the same order as the	When submitted in accordance with the relevant Guideline published by the Agency, case report forms and individual patient data listings shall be provided and presented in the same order as the	When submitted in accordance with the relevant Guideline published by the Agency, case report forms and individual patient data listings shall be provided and presented in the same order as the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	clinical study reports and indexed by study.	clinical study reports and indexed by study.	clinical study reports and indexed by study.	
Annex II, Part II				
2551	Part II PART II	Part II PART II	Part II PART II	
Annex II, 9 paragraph				
2552	SPECIFIC MARKETING AUTHORISATION DOSSIERS AND REQUIREMENTS	SPECIFIC MARKETING AUTHORISATION DOSSIERS AND REQUIREMENTS	SPECIFIC MARKETING AUTHORISATION DOSSIERS AND REQUIREMENTS	
Annex II, 10 paragraph				
2553	Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Annex need to be	Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Annex need to be	Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Annex need to be	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	adapted. To take account of these particular situations, an appropriate and adapted presentation of the dossier shall be followed by applicants.	adapted. To take account of these particular situations, an appropriate and adapted presentation of the dossier shall be followed by applicants.	adapted. To take account of these particular situations, an appropriate and adapted presentation of the dossier shall be followed by applicants.	
Annex II, point 6., first subparagraph				
2554	1. WELL-ESTABLISHED MEDICINAL USE	1. WELL-ESTABLISHED MEDICINAL USE	1. WELL-ESTABLISHED MEDICINAL USE	
Annex II, point 6., second subparagraph				
2555	For medicinal products the active substance(s) of which has/have a ‘well-established medicinal use’ as referred to Article 10(1)(a)(ii), with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.	For medicinal products the active substance(s) of which has/have a ‘well-established medicinal use’ as referred to Article 10(1)(a)(ii), with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.	For medicinal products the active substance(s) of which has/have a ‘well-established medicinal use’ as referred to Article 10(1)(a)(ii), with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, point 6., third subparagraph				
2556	The applicant shall submit Modules 1, 2 and 3 as described in part I of this Annex.	The applicant shall submit Modules 1, 2 and 3 as described in part I of this Annex.	The applicant shall submit Modules 1, 2 and 3 as described in part I of this Annex.	
Annex II, point 6., fourth subparagraph				
2557	For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.	For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.	For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.	
Annex II, point 6., fifth subparagraph				
2558	The following specific rules shall apply in order to demonstrate the well-established medicinal use:	The following specific rules shall apply in order to demonstrate the well-established medicinal use:	The following specific rules shall apply in order to demonstrate the well-established medicinal use:	
Annex II, point 6., fifth subparagraph, point (a), first subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2559	a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:	a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:	a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:	
Annex II, 11 paragraph				
2560	- the time over which a substance has been used,	- the time over which a substance has been used,	- the time over which a substance has been used,	
Annex II, -a paragraph				
2561	- quantitative aspects of the use of the substance,	- quantitative aspects of the use of the substance,	- quantitative aspects of the use of the substance,	
Annex II, -a paragraph				
2562	- the degree of scientific interest in the use of the substance	- the degree of scientific interest in the use of the substance	- the degree of scientific interest in the use of the substance	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	(reflected in the published scientific literature) and	(reflected in the published scientific literature) and	(reflected in the published scientific literature) and	
Annex II, -a paragraph				
2563	- the coherence of scientific assessments.	- the coherence of scientific assessments.	- the coherence of scientific assessments.	
Annex II, -a paragraph				
2564	Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of	Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of	Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	that substance as a medicinal product in the Community.	that substance as a medicinal product in the Community.	that substance as a medicinal product in the Community.	
Annex II, -b paragraph				
2565	b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated. With respect to the	b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated. With respect to the	b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated. With respect to the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	provisions on ‘well-established medicinal use’ it is in particular necessary to clarify that ‘bibliographic reference’ to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.	provisions on ‘well-established medicinal use’ it is in particular necessary to clarify that ‘bibliographic reference’ to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.	provisions on ‘well-established medicinal use’ it is in particular necessary to clarify that ‘bibliographic reference’ to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.	
Annex II, c paragraph				
2566	c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or	c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or	c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	efficacy can be supported although some studies are lacking.	efficacy can be supported although some studies are lacking.	efficacy can be supported although some studies are lacking.	
Annex II, CI paragraph				
2567	d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.	d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.	d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.	
Annex II, DI paragraph				

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2568	e) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.	e) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.	e) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.	
Annex II, point 7.				
2569	7. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS	7. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS	7. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS	
Annex II, point 7.(a)				
2570	a) Applications based upon Article 10(1) (a) (i) (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided the applicant has been granted the	a) Applications based upon Article 10(1) (a) (i) (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided the applicant has been granted the	a) Applications based upon Article 10(1) (a) (i) (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided the applicant has been granted the	

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	consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.	consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.	consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.	
Annex II, point 7.(b), first subparagraph				
2571	b) Applications based upon Article 10(1) (a) (iii) (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bio-availability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).	b) Applications based upon Article 10(1) (a) (iii) (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bio-availability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).	b) Applications based upon Article 10(1) (a) (iii) (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bio-availability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).	
Annex II, point 7.(b), second subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2572	For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:	For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:	For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:	
Annex II, f paragraph				
2573	- the grounds for claiming essential similarity;	- the grounds for claiming essential similarity;	- the grounds for claiming essential similarity;	
Annex II, -a paragraph				
2574	- a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to	- a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to	- a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to	

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	be marketed together with an evaluation of these impurities;	be marketed together with an evaluation of these impurities;	be marketed together with an evaluation of these impurities;	
Annex II, -a paragraph				
2575	- an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';	- an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';	- an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';	
Annex II, -a paragraph				
2576	- an update of published literature relevant to the substance and the present application. It may be acceptable for articles in 'peer review' journals to be annotated for this purpose;	- an update of published literature relevant to the substance and the present application. It may be acceptable for articles in 'peer review' journals to be annotated for this purpose;	- an update of published literature relevant to the substance and the present application. It may be acceptable for articles in 'peer review' journals to be annotated for this purpose;	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2577	- every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.	- every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.	- every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.	
Annex II, -a paragraph				
2578	- if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives	- if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives	- if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	of an authorised active substance should be provided by the applicant when he claims essential similarity.	of an authorised active substance should be provided by the applicant when he claims essential similarity.	of an authorised active substance should be provided by the applicant when he claims essential similarity.	
Annex II, point 8., first subparagraph				
2579	3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS	3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS	3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS	
Annex II, point 8., second subparagraph				
2580	Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the	Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the	Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance.	pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance.	pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance.	
Annex II, point 8., third subparagraph				
2581	Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.	Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.	Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.	

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Annex II, point 9., first subparagraph				
2582	4. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS	4. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS	4. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS	
Annex II, point 9., second subparagraph				
2583	The provisions of Article 10(1)(a)(iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.	The provisions of Article 10(1)(a)(iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.	The provisions of Article 10(1)(a)(iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.	
Annex II, point 9., third subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2584	When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.	When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.	When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.	
Annex II, -a paragraph				
2585	- Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and	- Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and	- Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.	amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.	amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.	
Annex II, -a paragraph				
2586	- Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.	- Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.	- Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2587	The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.	The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.	The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.	
Annex II, point 10., first subparagraph				
2588	5. FIXED COMBINATION MEDICINAL PRODUCTS	5. FIXED COMBINATION MEDICINAL PRODUCTS	5. FIXED COMBINATION MEDICINAL PRODUCTS	
Annex II, point 10., second subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2589	Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.	Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.	Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.	
Annex II, point 10., third subparagraph				
2590	For those applications a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.	For those applications a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.	For those applications a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.	
Annex II, point 11., first subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2591	6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES	6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES	6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES	
Annex II, point 11., second subparagraph				
2592	When, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:	When, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:	When, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:	
Annex II, -b paragraph				
2593	- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be	- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be	- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be	

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	expected to provide comprehensive evidence, or	expected to provide comprehensive evidence, or	expected to provide comprehensive evidence, or	
Annex II, -a paragraph				
2594	- in the present state of scientific knowledge, comprehensive information cannot be provided, or	- in the present state of scientific knowledge, comprehensive information cannot be provided, or	- in the present state of scientific knowledge, comprehensive information cannot be provided, or	
Annex II, -a paragraph				
2595	- it would be contrary to generally accepted principles of medical ethics to collect such information,	- it would be contrary to generally accepted principles of medical ethics to collect such information,	- it would be contrary to generally accepted principles of medical ethics to collect such information,	
Annex II, -a paragraph				

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2596	marketing authorisation may be granted subject to certain specific obligations.	marketing authorisation may be granted subject to certain specific obligations.	marketing authorisation may be granted subject to certain specific obligations.	
Annex II, -b paragraph				
2597	These obligations may include the following:	These obligations may include the following:	These obligations may include the following:	
Annex II, -c paragraph				
2598	- the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,	- the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,	- the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2599	- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,	- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,	- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,	
Annex II, -a paragraph				
2600	- the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.	- the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.	- the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.	

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Annex II, point 12., first subparagraph				
2601	7. MIXED MARKETING AUTHORISATION APPLICATIONS	7. MIXED MARKETING AUTHORISATION APPLICATIONS	7. MIXED MARKETING AUTHORISATION APPLICATIONS	
Annex II, point 12., second subparagraph				
2602	Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format	Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format	Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format	

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	presented by the applicant on a case by case basis.	presented by the applicant on a case by case basis.	presented by the applicant on a case by case basis.	
Annex II, Part III				
2603	Part III PART III	Part III PART III	Part III PART III	
Annex II, -a paragraph				
2604	PARTICULAR MEDICINAL PRODUCTS	PARTICULAR MEDICINAL PRODUCTS	PARTICULAR MEDICINAL PRODUCTS	
Annex II, -b paragraph				
2605	This Part lays down specific requirements related to the nature of identified medicinal products.	This Part lays down specific requirements related to the nature of identified medicinal products.	This Part lays down specific requirements related to the nature of identified medicinal products.	
Annex II, point 13.				

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2606	13. BIOLOGICAL MEDICINAL PRODUCTS	13. BIOLOGICAL MEDICINAL PRODUCTS	13. BIOLOGICAL MEDICINAL PRODUCTS	
Annex II, -c paragraph, point				
2607	Plasma-derived medicinal product	Plasma-derived medicinal product	Plasma-derived medicinal product	
Annex II, 2 paragraph				
2608	For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in 'Information related to the starting and raw materials', for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.	For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in 'Information related to the starting and raw materials', for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.	For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in 'Information related to the starting and raw materials', for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.	

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Annex II, 2 paragraph, point (a), first subparagraph				
2609	a) Principles	a) Principles	a) Principles	
Annex II, 2 paragraph, point (a), second subparagraph				
2610	For the purposes of this Annex:	For the purposes of this Annex:	For the purposes of this Annex:	
Annex II, 3 paragraph				
2611	- Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions,	- Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions,	- Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma ([1]). __________ 1. OJ L 313, 13.12.2000, p. 22	constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma ([1]). __________ 1. OJ L 313, 13.12.2000, p. 22	constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma ([1]). __________ 1. OJ L 313, 13.12.2000, p. 22	
Annex II, -a paragraph				
2612	- Every centre or establishment for fractionation/processing of human plasma shall prepare and keep	- Every centre or establishment for fractionation/processing of human plasma shall prepare and keep	- Every centre or establishment for fractionation/processing of human plasma shall prepare and keep	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	updated the set of detailed relevant information referred to in the Plasma Master File.	updated the set of detailed relevant information referred to in the Plasma Master File.	updated the set of detailed relevant information referred to in the Plasma Master File.	
Annex II, -a paragraph				
2613	- The Plasma Master File shall be submitted to the Agency or to the competent authority by the applicant for a marketing authorisation or the holder of the marketing authorisation. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the	- The Plasma Master File shall be submitted to the Agency or to the competent authority by the applicant for a marketing authorisation or the holder of the marketing authorisation. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the	- The Plasma Master File shall be submitted to the Agency or to the competent authority by the applicant for a marketing authorisation or the holder of the marketing authorisation. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	applicant or marketing authorisation holder shall take responsibility for the medicinal product.	applicant or marketing authorisation holder shall take responsibility for the medicinal product.	applicant or marketing authorisation holder shall take responsibility for the medicinal product.	
Annex II, -a paragraph				
2614	- The competent authority that is evaluating the marketing authorisation shall await for the Agency to issue the certificate before deciding on the application.	- The competent authority that is evaluating the marketing authorisation shall await for the Agency to issue the certificate before deciding on the application.	- The competent authority that is evaluating the marketing authorisation shall await for the Agency to issue the certificate before deciding on the application.	
Annex II, -a paragraph				
2615	- Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.	- Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.	- Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -a paragraph				
2616	b) Content	b) Content	b) Content	
Annex II, c paragraph				
2617	In accordance with the provisions of Article 109, as amended by Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:	In accordance with the provisions of Article 109, as amended by Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:	In accordance with the provisions of Article 109, as amended by Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:	
Annex II, CI paragraph				
2618	(1) Plasma origin	(1) Plasma origin	(1) Plasma origin	
Annex II, 2 paragraph				

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2619	(i) information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.	(i) information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.	(i) information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.	
Annex II, II paragraph				
2620	(ii) information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.	(ii) information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.	(ii) information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.	
Annex II, III paragraph				
2621	(iii) selection/exclusion criteria for blood/plasma donors.	(iii) selection/exclusion criteria for blood/plasma donors.	(iii) selection/exclusion criteria for blood/plasma donors.	
Annex II, IV paragraph				

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2622	(iv) system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.	(iv) system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.	(iv) system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.	
Annex II, V paragraph				
2623	(2) Plasma quality and safety	(2) Plasma quality and safety	(2) Plasma quality and safety	
Annex II, 3 paragraph				
2624	(i) compliance with European Pharmacopoeia Monographs.	(i) compliance with European Pharmacopoeia Monographs.	(i) compliance with European Pharmacopoeia Monographs.	
Annex II, II paragraph				
2625	(ii) testing of blood/plasma donations and pools for infectious agents, including information on	(ii) testing of blood/plasma donations and pools for infectious agents, including information on	(ii) testing of blood/plasma donations and pools for infectious agents, including information on	

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	test methods and, in the case of plasma pools, validation data on the tests used.	test methods and, in the case of plasma pools, validation data on the tests used.	test methods and, in the case of plasma pools, validation data on the tests used.	
Annex II, III paragraph				
2626	(iii) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.	(iii) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.	(iii) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.	
Annex II, IV paragraph				
2627	(iv) conditions of storage and transport of plasma.	(iv) conditions of storage and transport of plasma.	(iv) conditions of storage and transport of plasma.	
Annex II, V paragraph				
2628	(v) procedures for any inventory hold and/or quarantine period.	(v) procedures for any inventory hold and/or quarantine period.	(v) procedures for any inventory hold and/or quarantine period.	

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Annex II, VI paragraph				
2629	(vi) characterisation of the plasma pool.	(vi) characterisation of the plasma pool.	(vi) characterisation of the plasma pool.	
Annex II, VII paragraph				
2630	(3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.	(3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.	(3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.	
Annex II, 4 paragraph				

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2631	In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Directive 2001/20/EC of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.	In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Directive 2001/20/EC of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.	In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Directive 2001/20/EC of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.	
Annex II, 5 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2632	c) Evaluation and Certification	c) Evaluation and Certification	c) Evaluation and Certification	
Annex II, CI paragraph				
2633	- For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.	- For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.	- For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.	
Annex II, -a paragraph				
2634	- The Plasma Master File is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of	- The Plasma Master File is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of	- The Plasma Master File is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	compliance with Community legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Community.	compliance with Community legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Community.	compliance with Community legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Community.	
Annex II, -a paragraph				
2635	- The Plasma Master File shall be updated and re-certified on an annual basis.	- The Plasma Master File shall be updated and re-certified on an annual basis.	- The Plasma Master File shall be updated and re-certified on an annual basis.	
Annex II, -a paragraph				
2636	- Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation procedure laid down by Commission Regulation (EC) No 542/95 ([1]) concerning the	- Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation procedure laid down by Commission Regulation (EC) No 542/95 ([1]) concerning the	- Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation procedure laid down by Commission Regulation (EC) No 542/95 ([1]) concerning the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	examination of variations to the terms of a marketing authorisation falling within the scope of Council regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (2). Conditions for the assessment of these changes are laid down by Regulation (EC) No 1085/2003. __________ 1. OJ L 55, 11.3.1995, p. 15 2. OJ L 214, 24.8.1993, p. 1	examination of variations to the terms of a marketing authorisation falling within the scope of Council regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (2). Conditions for the assessment of these changes are laid down by Regulation (EC) No 1085/2003. __________ 1. OJ L 55, 11.3.1995, p. 15 2. OJ L 214, 24.8.1993, p. 1	examination of variations to the terms of a marketing authorisation falling within the scope of Council regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (2). Conditions for the assessment of these changes are laid down by Regulation (EC) No 1085/2003. __________ 1. OJ L 55, 11.3.1995, p. 15 2. OJ L 214, 24.8.1993, p. 1	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2637	- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).	- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).	- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).	
Annex II, -a paragraph				
2638	- By derogation from the provisions of the second indent of the present point (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted	- By derogation from the provisions of the second indent of the present point (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted	- By derogation from the provisions of the second indent of the present point (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.	to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.	to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.	
Annex II, -a paragraph, point				
2639	Vaccines	Vaccines	Vaccines	
Annex II, 3 paragraph				
2640	For vaccines for human use and by derogation from the provisions of Module 3 on ‘Active substance(s)’, the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.	For vaccines for human use and by derogation from the provisions of Module 3 on ‘Active substance(s)’, the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.	For vaccines for human use and by derogation from the provisions of Module 3 on ‘Active substance(s)’, the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph				
2641	The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.	The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.	The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.	
Annex II, 4 paragraph, point (a), first subparagraph				
2642	a) P r i n c i p l e s	a) P r i n c i p l e s	a) P r i n c i p l e s	
Annex II, 4 paragraph, point (a), second subparagraph				
2643	For the purposes of this Annex:	For the purposes of this Annex:	For the purposes of this Annex:	
Annex II, 5 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2644	- Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.	- Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.	- Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.	
Annex II, -a paragraph				
2645	- A vaccine may contain one or several distinct vaccine antigens. There are as many active	- A vaccine may contain one or several distinct vaccine antigens. There are as many active	- A vaccine may contain one or several distinct vaccine antigens. There are as many active	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	substance(s) as vaccine antigen(s) present in a vaccine.	substance(s) as vaccine antigen(s) present in a vaccine.	substance(s) as vaccine antigen(s) present in a vaccine.	
Annex II, -a paragraph				
2646	- A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.	- A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.	- A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.	
Annex II, -a paragraph				
2647	- A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.	- A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.	- A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.	
Annex II, -a paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2648	b) Content	b) Content	b) Content	
Annex II, c paragraph				
2649	The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on 'Quality Data' as delineated in Part I of this Annex:	The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on 'Quality Data' as delineated in Part I of this Annex:	The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on 'Quality Data' as delineated in Part I of this Annex:	
Annex II, CI paragraph				
2650	Active Substance	Active Substance	Active Substance	
Annex II, CII paragraph				
2651	1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.	1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.	1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 2 paragraph				
2652	2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and adventitious agents safety evaluation and facilities and equipment.	2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and adventitious agents safety evaluation and facilities and equipment.	2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and adventitious agents safety evaluation and facilities and equipment.	
Annex II, 3 paragraph				
2653	3. Characterisation of the active substance	3. Characterisation of the active substance	3. Characterisation of the active substance	
Annex II, 4 paragraph				
2654	4. Quality control of the active substance	4. Quality control of the active substance	4. Quality control of the active substance	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 5 paragraph				
2655	5. Reference standard and materials	5. Reference standard and materials	5. Reference standard and materials	
Annex II, 6 paragraph				
2656	6. Container and closure system of the active substance	6. Container and closure system of the active substance	6. Container and closure system of the active substance	
Annex II, 7 paragraph				
2657	7. Stability of the active substance.	7. Stability of the active substance.	7. Stability of the active substance.	
Annex II, 8 paragraph				
2658	c) Evaluation and Certification	c) Evaluation and Certification	c) Evaluation and Certification	
Annex II, CI paragraph				

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2659	- For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate	- For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate	- For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	shall apply throughout the Community.	shall apply throughout the Community.	shall apply throughout the Community.	
Annex II, -a paragraph				
2660	- The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Community.	- The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Community.	- The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Community.	
Annex II, -a paragraph				
2661	- Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Community shall be subject to a scientific and technical evaluation	- Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Community shall be subject to a scientific and technical evaluation	- Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Community shall be subject to a scientific and technical evaluation	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	carried out by the Agency in accordance with the procedure laid down in Commission Regulation (EC) No 1085/2003. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Community legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Community.	carried out by the Agency in accordance with the procedure laid down in Commission Regulation (EC) No 1085/2003. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Community legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Community.	carried out by the Agency in accordance with the procedure laid down in Commission Regulation (EC) No 1085/2003. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Community legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Community.	
Annex II, -a paragraph				
2662	- By derogation from the provisions of the first, second and third indents of the present point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing	- By derogation from the provisions of the first, second and third indents of the present point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing	- By derogation from the provisions of the first, second and third indents of the present point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	authorisation which has not been/will not be granted according to a Community procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Community procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.	authorisation which has not been/will not be granted according to a Community procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Community procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.	authorisation which has not been/will not be granted according to a Community procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Community procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.	
Annex II, -a paragraph				
2663	- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant	- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant	- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).	or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).	or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).	
Annex II, point 14.				
2664	14. RADIO-PHARMACEUTICALS AND PRECURSORS	14. RADIO-PHARMACEUTICALS AND PRECURSORS	14. RADIO-PHARMACEUTICALS AND PRECURSORS	
Annex II, -a paragraph, point				
2665	Radio-pharmaceuticals	Radio-pharmaceuticals	Radio-pharmaceuticals	
Annex II, 2 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2666	For the purposes of this chapter, applications based upon Articles 6 (2) and 9 shall provide a full dossier in which the following specific details shall be included:	For the purposes of this chapter, applications based upon Articles 6 (2) and 9 shall provide a full dossier in which the following specific details shall be included:	For the purposes of this chapter, applications based upon Articles 6 (2) and 9 shall provide a full dossier in which the following specific details shall be included:	
Annex II, 3 paragraph				
2667	Module 3	Module 3	Module 3	
Annex II, 4 paragraph				
2668	a) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-	a) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-	a) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia. In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.	pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia. In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.	pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia. In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.	
Annex II, b paragraph				
2669	For radio-nuclides, the nuclear reactions involved shall be discussed.	For radio-nuclides, the nuclear reactions involved shall be discussed.	For radio-nuclides, the nuclear reactions involved shall be discussed.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, c paragraph				
2670	In a generator, both mother and daughter radio-nuclides shall be considered as active substances.	In a generator, both mother and daughter radio-nuclides shall be considered as active substances.	In a generator, both mother and daughter radio-nuclides shall be considered as active substances.	
Annex II, CI paragraph				
2671	b) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.	b) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.	b) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.	
Annex II, c paragraph				
2672	c) Starting materials include irradiation target materials.	c) Starting materials include irradiation target materials.	c) Starting materials include irradiation target materials.	
Annex II, CI paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2673	d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.	d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.	d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.	
Annex II, DI paragraph				
2674	e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.	e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.	e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.	
Annex II, f paragraph				
2675	f) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.	f) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.	f) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, g paragraph				
2676	g) The requirement to express the content of active substances in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.	g) The requirement to express the content of active substances in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.	g) The requirement to express the content of active substances in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.	
Annex II, h paragraph				
2677	h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on	h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on	h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.	radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.	radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.	
Annex II, i paragraph				
2678	i) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.	i) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.	i) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.	
Annex II, II paragraph				
2679	Module 4	Module 4	Module 4	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, III paragraph				
2680	It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.	It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.	It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, IV paragraph				
2681	Module 5	Module 5	Module 5	
Annex II, V paragraph				
2682	The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.	The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.	The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.	
Annex II, VI paragraph, point				
2683	Radio-pharmaceutical precursors for radio-labelling purposes	Radio-pharmaceutical precursors for radio-labelling purposes	Radio-pharmaceutical precursors for radio-labelling purposes	
Annex II, 3 paragraph				
2684	In the specific case of a radio-pharmaceutical precursor intended	In the specific case of a radio-pharmaceutical precursor intended	In the specific case of a radio-pharmaceutical precursor intended	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.	solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.	solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.	
Annex II, 4 paragraph				
2685	In particular, the following information where applicable shall be provided:	In particular, the following information where applicable shall be provided:	In particular, the following information where applicable shall be provided:	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 5 paragraph				
2686	Module 3	Module 3	Module 3	
Annex II, 6 paragraph				
2687	The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as define above (indents a) to i)), where applicable.	The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as define above (indents a) to i)), where applicable.	The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as define above (indents a) to i)), where applicable.	
Annex II, 7 paragraph				
2688	Module 4	Module 4	Module 4	
Annex II, 8 paragraph				
2689	Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the	Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the	Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	provisions related to good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC shall be provided, unless otherwise justified.	provisions related to good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC shall be provided, unless otherwise justified.	provisions related to good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC shall be provided, unless otherwise justified.	
Annex II, 9 paragraph				
2690	Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.	Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.	Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.	
Annex II, 10 paragraph				
2691	Information relating to the chemical toxicity and disposition of the relevant ‘cold’ nuclide shall be presented.	Information relating to the chemical toxicity and disposition of the relevant ‘cold’ nuclide shall be presented.	Information relating to the chemical toxicity and disposition of the relevant ‘cold’ nuclide shall be presented.	
Annex II, 11 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2692	Module 5	Module 5	Module 5	
Annex II, 12 paragraph				
2693	Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.	Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.	Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.	
Annex II, 13 paragraph				
2694	However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.	However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.	However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, point 15., first subparagraph				
2695	3. HOMEOPATHIC MEDICINAL PRODUCTS	3. HOMEOPATHIC MEDICINAL PRODUCTS	3. HOMEOPATHIC MEDICINAL PRODUCTS	
Annex II, point 15., second subparagraph				
2696	This section sets out specific provisions on the application of Modules 3 and 4 to homeopathic medicinal products as defined in Article 1(5).	This section sets out specific provisions on the application of Modules 3 and 4 to homeopathic medicinal products as defined in Article 1(5).	This section sets out specific provisions on the application of Modules 3 and 4 to homeopathic medicinal products as defined in Article 1(5).	
Annex II, 14 paragraph				
2697	Module 3	Module 3	Module 3	
Annex II, 15 paragraph				
2698	The provisions of Module 3 shall apply to the documents submitted	The provisions of Module 3 shall apply to the documents submitted	The provisions of Module 3 shall apply to the documents submitted	

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	in accordance with Article 15 in the simplified registration of homeopathic medicinal products referred to in Article 14(1) as well as to the documents for authorisation of other homeopathic medicinal products referred to in Article 16(1) with the following modifications.	in accordance with Article 15 in the simplified registration of homeopathic medicinal products referred to in Article 14(1) as well as to the documents for authorisation of other homeopathic medicinal products referred to in Article 16(1) with the following modifications.	in accordance with Article 15 in the simplified registration of homeopathic medicinal products referred to in Article 14(1) as well as to the documents for authorisation of other homeopathic medicinal products referred to in Article 16(1) with the following modifications.	
Annex II, 15 paragraph, point (a), first subparagraph				
2699	a) Terminology	a) Terminology	a) Terminology	
Annex II, 15 paragraph, point (a), second subparagraph				
2700	The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of	The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of	The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of	

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	the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.	the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.	the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.	
Annex II, 15 paragraph, point (b), first subparagraph				
2701	b) Control of starting materials	b) Control of starting materials	b) Control of starting materials	
Annex II, 15 paragraph, point (b), second subparagraph				
2702	The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product, accompanying	The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product, accompanying	The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product, accompanying	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	the application shall be supplemented by additional data on the homeopathic stock.	the application shall be supplemented by additional data on the homeopathic stock.	the application shall be supplemented by additional data on the homeopathic stock.	
Annex II, 15 paragraph, point (b), third subparagraph				
2703	The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final	The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final	The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	dilution to be incorporated into the finished medicinal product must be fully described.	dilution to be incorporated into the finished medicinal product must be fully described.	dilution to be incorporated into the finished medicinal product must be fully described.	
Annex II, 15 paragraph, point (b), fourth subparagraph				
2704	In case dilutions are involved, these dilution steps should be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State.	In case dilutions are involved, these dilution steps should be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State.	In case dilutions are involved, these dilution steps should be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State.	
Annex II, 15 paragraph, point (c), first subparagraph				
2705	c) Control tests on the finished medicinal product	c) Control tests on the finished medicinal product	c) Control tests on the finished medicinal product	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 15 paragraph, point (c), second subparagraph				
2706	The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.	The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.	The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.	
Annex II, 15 paragraph, point (c), third subparagraph				
2707	Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete	Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete	Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	validation of the manufacturing and dilution process.	validation of the manufacturing and dilution process.	validation of the manufacturing and dilution process.	
Annex II, 15 paragraph, point (d), first subparagraph				
2708	d) Stability tests	d) Stability tests	d) Stability tests	
Annex II, 15 paragraph, point (d), second subparagraph				
2709	The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.	The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.	The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 16 paragraph				
2710	Module 4	Module 4	Module 4	
Annex II, 17 paragraph				
2711	The provisions of Module 4 shall apply to the simplified registration of homeopathic medicinal products referred to in Article 14(1) with the following specifications.	The provisions of Module 4 shall apply to the simplified registration of homeopathic medicinal products referred to in Article 14(1) with the following specifications.	The provisions of Module 4 shall apply to the simplified registration of homeopathic medicinal products referred to in Article 14(1) with the following specifications.	
Annex II, 18 paragraph				
2712	Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.	Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.	Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, point 16., first subparagraph				
2713	4. HERBAL MEDICINAL PRODUCTS	4. HERBAL MEDICINAL PRODUCTS	4. HERBAL MEDICINAL PRODUCTS	
Annex II, point 16., second subparagraph				
2714	Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.	Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.	Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.	
Annex II, 19 paragraph				
2715	Module 3	Module 3	Module 3	
Annex II, 20 paragraph				
2716	The provisions of Module 3, including compliance with monograph(s) of the European	The provisions of Module 3, including compliance with monograph(s) of the European	The provisions of Module 3, including compliance with monograph(s) of the European	

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	Pharmacopoeia, shall apply to the authorisation of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.	Pharmacopoeia, shall apply to the authorisation of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.	Pharmacopoeia, shall apply to the authorisation of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.	
Annex II, 21 paragraph				
2717	The following aspects specific to herbal medicinal products shall be considered:	The following aspects specific to herbal medicinal products shall be considered:	The following aspects specific to herbal medicinal products shall be considered:	
Annex II, 22 paragraph				
2718	(1) Herbal substances and herbal preparations	(1) Herbal substances and herbal preparations	(1) Herbal substances and herbal preparations	
Annex II, 2 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2719	For the purposes of this Annex the terms 'herbal substances and preparations' shall be considered equivalent to the terms 'herbal drugs and herbal drug preparations', as defined in the European Pharmacopoeia.	For the purposes of this Annex the terms 'herbal substances and preparations' shall be considered equivalent to the terms 'herbal drugs and herbal drug preparations', as defined in the European Pharmacopoeia.	For the purposes of this Annex the terms 'herbal substances and preparations' shall be considered equivalent to the terms 'herbal drugs and herbal drug preparations', as defined in the European Pharmacopoeia.	
Annex II, 3 paragraph				
2720	With respect to the nomenclature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.	With respect to the nomenclature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.	With respect to the nomenclature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph				
2721	With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.	With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.	With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.	
Annex II, 5 paragraph				
2722	To document the section of the structure for herbal substance(s)	To document the section of the structure for herbal substance(s)	To document the section of the structure for herbal substance(s)	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass) as well as other constituent(s) shall be provided.	and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass) as well as other constituent(s) shall be provided.	and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass) as well as other constituent(s) shall be provided.	
Annex II, 6 paragraph				
2723	To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved	To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved	To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	in production/collection and testing of the herbal substance shall be provided, where appropriate.	in production/collection and testing of the herbal substance shall be provided, where appropriate.	in production/collection and testing of the herbal substance shall be provided, where appropriate.	
Annex II, 7 paragraph				
2724	To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.	To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.	To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.	
Annex II, 8 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2725	With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.	With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.	With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.	
Annex II, 9 paragraph				
2726	With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing,	With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing,	With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing,	

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	solvents and reagents, purification stages and standardisation.	solvents and reagents, purification stages and standardisation.	solvents and reagents, purification stages and standardisation.	
Annex II, 10 paragraph				
2727	With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where	With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where	With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.	applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.	applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.	
Annex II, 11 paragraph				
2728	With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.	With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.	With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.	
Annex II, 12 paragraph				
2729	With respect to the elucidation of the structure and other	With respect to the elucidation of the structure and other	With respect to the elucidation of the structure and other	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.	characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.	characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.	
Annex II, 13 paragraph				
2730	The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	
Annex II, 14 paragraph				
2731	The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	

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Annex II, 15 paragraph				
2732	With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	
Annex II, 16 paragraph				
2733	With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.	With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.	With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.	

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Annex II, 17 paragraph				
2734	Justification for the specifications of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	Justification for the specifications of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	Justification for the specifications of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	
Annex II, 18 paragraph				
2735	Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.	
Annex II, 19 paragraph				
2736	Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can	Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can	Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.	apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.	apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.	
Annex II, 20 paragraph				
2737	(2) Herbal Medicinal Products	(2) Herbal Medicinal Products	(2) Herbal Medicinal Products	
Annex II, 3 paragraph				
2738	With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the	With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the	With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.	products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.	products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.	
Annex II, point 17.				
2739	17. ORPHAN MEDICINAL PRODUCTS	17. ORPHAN MEDICINAL PRODUCTS	17. ORPHAN MEDICINAL PRODUCTS	
Annex II, 4 paragraph				
2740	- In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide	- In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide	- In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.	the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.	the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.	
Annex II, -a paragraph				
2741	- When an applicant for an marketing authorisation for an orphan medicinal product invokes the provisions of Article 10 (1)(a)(ii) and Part II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer — as way of derogation — to the use of that substance in accordance with the provisions of Article 5 of this Directive.	- When an applicant for an marketing authorisation for an orphan medicinal product invokes the provisions of Article 10 (1)(a)(ii) and Part II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer — as way of derogation — to the use of that substance in accordance with the provisions of Article 5 of this Directive.	- When an applicant for an marketing authorisation for an orphan medicinal product invokes the provisions of Article 10 (1)(a)(ii) and Part II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer — as way of derogation — to the use of that substance in accordance with the provisions of Article 5 of this Directive.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, Part IV				
2742	Part IV PART IV	Part IV PART IV	Part IV PART IV	
Annex II, -a paragraph				
2743	ADVANCED THERAPY MEDICINAL PRODUCTS	ADVANCED THERAPY MEDICINAL PRODUCTS	ADVANCED THERAPY MEDICINAL PRODUCTS	
Annex II, point 18., first subparagraph				
2744	1. INTRODUCTION	1. INTRODUCTION	1. INTRODUCTION	
Annex II, point 18., second subparagraph				
2745	Marketing authorisation applications for advanced therapy medicinal products, as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007, shall follow the format	Marketing authorisation applications for advanced therapy medicinal products, as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007, shall follow the format	Marketing authorisation applications for advanced therapy medicinal products, as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007, shall follow the format	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	requirements (Modules 1, 2, 3, 4 and 5) described in Part I of this Annex.	requirements (Modules 1, 2, 3, 4 and 5) described in Part I of this Annex.	requirements (Modules 1, 2, 3, 4 and 5) described in Part I of this Annex.	
Annex II, point 18., third subparagraph				
2746	The technical requirements for Modules 3, 4 and 5 for biological medicinal products, as described in Part I of this Annex, shall apply. The specific requirements for advanced therapy medicinal products described in sections 3, 4 and 5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products. In addition, where appropriate and taking into account the specificities of advanced therapy medicinal	The technical requirements for Modules 3, 4 and 5 for biological medicinal products, as described in Part I of this Annex, shall apply. The specific requirements for advanced therapy medicinal products described in sections 3, 4 and 5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products. In addition, where appropriate and taking into account the specificities of advanced therapy medicinal	The technical requirements for Modules 3, 4 and 5 for biological medicinal products, as described in Part I of this Annex, shall apply. The specific requirements for advanced therapy medicinal products described in sections 3, 4 and 5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products. In addition, where appropriate and taking into account the specificities of advanced therapy medicinal	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	products, additional requirements have been set.	products, additional requirements have been set.	products, additional requirements have been set.	
Annex II, point 18., fourth subparagraph				
2747	Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in point 4 of the 'Introduction and general principles'.	Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in point 4 of the 'Introduction and general principles'.	Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in point 4 of the 'Introduction and general principles'.	
Annex II, point 18., fifth subparagraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2748	The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used in vivo, the level of integration of nucleic acids sequences or genes into the genome, the long time functionality, the risk of oncogenicity and the mode of administration or use.	The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used in vivo, the level of integration of nucleic acids sequences or genes into the genome, the long time functionality, the risk of oncogenicity and the mode of administration or use.	The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used in vivo, the level of integration of nucleic acids sequences or genes into the genome, the long time functionality, the risk of oncogenicity and the mode of administration or use.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, point 18., sixth subparagraph				
2749	Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.	Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.	Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.	
Annex II, point 18., seventh subparagraph				
2750	Any deviation from the requirements of this Annex shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks	Any deviation from the requirements of this Annex shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks	Any deviation from the requirements of this Annex shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	and the implications of the risk based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Annex resulting from the risk analysis shall be described.	and the implications of the risk based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Annex resulting from the risk analysis shall be described.	and the implications of the risk based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Annex resulting from the risk analysis shall be described.	
Annex II, point 19., first subparagraph				
2751	2. DEFINITIONS	2. DEFINITIONS	2. DEFINITIONS	
Annex II, point 19., second subparagraph				
2752	For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.	For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.	For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, -b paragraph, point				
2753	Gene therapy medicinal product	Gene therapy medicinal product	Gene therapy medicinal product	
Annex II, 2 paragraph				
2754	Gene therapy medicinal product means a biological medicinal product which has the following characteristics:	Gene therapy medicinal product means a biological medicinal product which has the following characteristics:	Gene therapy medicinal product means a biological medicinal product which has the following characteristics:	
Annex II, 2 paragraph, point (a)				
2755	(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;	(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;	(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 2 paragraph, point (b)				
2756	(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.	(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.	(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.	
Annex II, 3 paragraph				
2757	Gene therapy medicinal products shall not include vaccines against infectious diseases.	Gene therapy medicinal products shall not include vaccines against infectious diseases.	Gene therapy medicinal products shall not include vaccines against infectious diseases.	
Annex II, 4 paragraph, point				
2758	Somatic cell therapy medicinal product	Somatic cell therapy medicinal product	Somatic cell therapy medicinal product	
Annex II, 3 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2759	Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:	Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:	Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:	
Annex II, 3 paragraph, point (a)				
2760	(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;	(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;	(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;	
Annex II, 3 paragraph, point (b)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2761	(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.	(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.	(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.	
Annex II, 4 paragraph				
2762	For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.	For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.	For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.	
Annex II, point 20.				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2763	20. SPECIFIC REQUIREMENTS REGARDING MODULE 3	20. SPECIFIC REQUIREMENTS REGARDING MODULE 3	20. SPECIFIC REQUIREMENTS REGARDING MODULE 3	
Annex II, 5 paragraph, point				
2764	Specific requirements for all advanced therapy medicinal products	Specific requirements for all advanced therapy medicinal products	Specific requirements for all advanced therapy medicinal products	
Annex II, 2 paragraph				
2765	A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be	A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be	A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.	traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.	traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.	
Annex II, 3 paragraph				
2766	The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council ([1]), as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells. __________ 1. OJ L 102, 7.4.2004, p. 48	The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council ([1]), as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells. __________ 1. OJ L 102, 7.4.2004, p. 48	The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council ([1]), as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells. __________ 1. OJ L 102, 7.4.2004, p. 48	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph				
2767	3.2. Specific requirements for gene therapy medicinal products	3.2. Specific requirements for gene therapy medicinal products	3.2. Specific requirements for gene therapy medicinal products	
Annex II, 4 paragraph, point (3.2.1)				
2768	3.2.1. Introduction: finished product, active substance and starting materials	3.2.1. Introduction: finished product, active substance and starting materials	3.2.1. Introduction: finished product, active substance and starting materials	
Annex II, 3 paragraph,				
2769	Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)	Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)	Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)	
Annex II, 2 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2770	The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.	The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.	The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.	
Annex II, 3 paragraph				
2771	The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).	The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).	The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).	
Annex II, 4 paragraph,				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2772	Gene therapy medicinal product containing genetically modified cells	Gene therapy medicinal product containing genetically modified cells	Gene therapy medicinal product containing genetically modified cells	
Annex II, 3 paragraph				
2773	The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.	The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.	The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.	
Annex II, 4 paragraph				
2774	The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.	The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.	The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 5 paragraph				
2775	3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.	3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.	3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.	
Annex II, 4 paragraph				
2776	3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the	3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the	3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.	producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.	producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.	
Annex II, 5 paragraph				
2777	3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.	3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.	3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.	
Annex II, 6 paragraph,				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2778	Specific requirements	Specific requirements	Specific requirements	
Annex II, 3 paragraph				
2779	In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:	In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:	In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:	
Annex II, 3 paragraph, point (a)				
2780	(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into	(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into	(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	consideration the possible absence of purification steps;	consideration the possible absence of purification steps;	consideration the possible absence of purification steps;	
Annex II, 3 paragraph, point (b)				
2781	(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;	(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;	(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;	
Annex II, 3 paragraph, point (c)				
2782	(c) process-related impurities and product-related impurities shall be described in the relevant	(c) process-related impurities and product-related impurities shall be described in the relevant	(c) process-related impurities and product-related impurities shall be described in the relevant	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;	sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;	sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;	
Annex II, 3 paragraph, point (d)				
2783	(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;	(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;	(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;	
Annex II, 3 paragraph, point (e)				
2784	(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent	(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent	(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	freezing/storage procedures, shall be tested.	freezing/storage procedures, shall be tested.	freezing/storage procedures, shall be tested.	
Annex II, 4 paragraph				
2785	For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.	For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.	For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.	
Annex II, 5 paragraph				
2786	3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph				
2787	Introduction: finished product, active substance and starting materials	Introduction: finished product, active substance and starting materials	Introduction: finished product, active substance and starting materials	
Annex II, 5 paragraph				
2788	The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.	The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.	The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.	
Annex II, 6 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2789	The active substance shall be composed of the engineered cells and/or tissues.	The active substance shall be composed of the engineered cells and/or tissues.	The active substance shall be composed of the engineered cells and/or tissues.	
Annex II, 7 paragraph				
2790	Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.	Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.	Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.	
Annex II, 8 paragraph				
2791	Materials used during the manufacture of the active substance (e.g. culture media,	Materials used during the manufacture of the active substance (e.g. culture media,	Materials used during the manufacture of the active substance (e.g. culture media,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.	growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.	growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.	
Annex II, 9 paragraph,				
2792	Specific requirements	Specific requirements	Specific requirements	
Annex II, 3 paragraph				
2793	In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:	In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:	In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:	
Annex II, 3 paragraph, point (3.3.2.1)				
2794	3.3.2.1. Starting materials	3.3.2.1. Starting materials	3.3.2.1. Starting materials	
Annex II, 4 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2795	(a) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Directive 2004/23/EC. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.	(a) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Directive 2004/23/EC. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.	(a) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Directive 2004/23/EC. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.	
Annex II, b paragraph				
2796	(b) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.	(b) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.	(b) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.	
Annex II, c paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2797	(c) The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.	(c) The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.	(c) The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.	
Annex II, CI paragraph				
2798	(d) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing	(d) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing	(d) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing	

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	of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.	of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.	of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.	
Annex II, DI paragraph				
2799	(e) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.	(e) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.	(e) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.	
Annex II, f paragraph				

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2800	(f) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.	(f) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.	(f) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.	
Annex II, g paragraph				
2801	(g) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.	(g) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.	(g) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.	
Annex II, h paragraph				
2802	(h) For scaffolds, matrices and devices that fall under the definition of a medical device or	(h) For scaffolds, matrices and devices that fall under the definition of a medical device or	(h) For scaffolds, matrices and devices that fall under the definition of a medical device or	

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	active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.	active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.	active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.	
Annex II, i paragraph				
2803	3.3.2.2. Manufacturing process	3.3.2.2. Manufacturing process	3.3.2.2. Manufacturing process	
Annex II, i paragraph(a)				
2804	(a) The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.	(a) The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.	(a) The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.	

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Annex II, i paragraph(b)				
2805	(b) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.	(b) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.	(b) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.	
Annex II, 3 paragraph				
2806	3.3.2.3. Characterisation and control strategy	3.3.2.3. Characterisation and control strategy	3.3.2.3. Characterisation and control strategy	
Annex II, 3 paragraph(a)				
2807	(a) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity	(a) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity	(a) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity	

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	(e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.	(e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.	(e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.	
Annex II, 3 paragraph(b)				
2808	(b) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.	(b) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.	(b) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.	
Annex II, 3 paragraph(c)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2809	(c) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.	(c) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.	(c) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.	
Annex II, 3 paragraph(d)				
2810	(d) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised.	(d) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised.	(d) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised.	
Annex II, 3 paragraph(e)				

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2811	(e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.	(e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.	(e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.	
Annex II, 4 paragraph,				
2812	Excipients	Excipients	Excipients	
Annex II, 5 paragraph				

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2813	For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Annex, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.	For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Annex, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.	For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Annex, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.	
Annex II, 6 paragraph,				
2814	Developmental studies	Developmental studies	Developmental studies	
Annex II, 6 paragraph				
2815	The description of the development program shall address the choice of materials and processes. In particular, the	The description of the development program shall address the choice of materials and processes. In particular, the	The description of the development program shall address the choice of materials and processes. In particular, the	

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	integrity of the cell population as in the final formulation shall be discussed.	integrity of the cell population as in the final formulation shall be discussed.	integrity of the cell population as in the final formulation shall be discussed.	
Annex II, 7 paragraph,				
2816	Reference materials	Reference materials	Reference materials	
Annex II, 7 paragraph				
2817	A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.	A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.	A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.	
Annex II, 8 paragraph				
2818	3.4. Specific requirements for advanced therapy medicinal products containing devices	3.4. Specific requirements for advanced therapy medicinal products containing devices	3.4. Specific requirements for advanced therapy medicinal products containing devices	

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Annex II, 5 paragraph				
2819	Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007	Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007	Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007	
Annex II, 6 paragraph				
2820	A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.	A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.	A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.	
Annex II, 7 paragraph				
2821	The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.	The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.	The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.	

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Annex II, 8 paragraph,				
2822	Combined advanced therapy medicinal products as defined in Article 2(1)(d) of Regulation (EC) No 1394/2007	Combined advanced therapy medicinal products as defined in Article 2(1)(d) of Regulation (EC) No 1394/2007	Combined advanced therapy medicinal products as defined in Article 2(1)(d) of Regulation (EC) No 1394/2007	
Annex II, 3 paragraph				
2823	For the cellular or tissue part of the combined advanced therapy medicinal product, the specific requirements for somatic cell therapy medicinal products and tissue engineered products set out in section 3.3 shall apply and, in the case of genetically modified cells, the specific requirements for gene therapy medicinal products set out in section 3.2 shall apply.	For the cellular or tissue part of the combined advanced therapy medicinal product, the specific requirements for somatic cell therapy medicinal products and tissue engineered products set out in section 3.3 shall apply and, in the case of genetically modified cells, the specific requirements for gene therapy medicinal products set out in section 3.2 shall apply.	For the cellular or tissue part of the combined advanced therapy medicinal product, the specific requirements for somatic cell therapy medicinal products and tissue engineered products set out in section 3.3 shall apply and, in the case of genetically modified cells, the specific requirements for gene therapy medicinal products set out in section 3.2 shall apply.	

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Annex II, 4 paragraph				
2824	The medical device or the active implantable medical device may be an integral part of the active substance. Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or application or administration of the finished products, they shall be considered as an integral part of the finished product.	The medical device or the active implantable medical device may be an integral part of the active substance. Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or application or administration of the finished products, they shall be considered as an integral part of the finished product.	The medical device or the active implantable medical device may be an integral part of the active substance. Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or application or administration of the finished products, they shall be considered as an integral part of the finished product.	
Annex II, 5 paragraph				
2825	Information related to the medical device or the active implantable medical device (which is an integral part of the active	Information related to the medical device or the active implantable medical device (which is an integral part of the active	Information related to the medical device or the active implantable medical device (which is an integral part of the active	

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	substance or of the finished product) which is relevant for the evaluation of the combined advanced therapy medicinal product shall be provided. This information shall include:	substance or of the finished product) which is relevant for the evaluation of the combined advanced therapy medicinal product shall be provided. This information shall include:	substance or of the finished product) which is relevant for the evaluation of the combined advanced therapy medicinal product shall be provided. This information shall include:	
Annex II, 5 paragraph, point (a)				
2826	(a) information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;	(a) information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;	(a) information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;	
Annex II, 5 paragraph, point (b)				
2827	(b) evidence of conformity of the medical device part with the essential requirements laid down	(b) evidence of conformity of the medical device part with the essential requirements laid down	(b) evidence of conformity of the medical device part with the essential requirements laid down	

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	in Annex I to Council Directive 93/42/EEC ([1]), or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC ([2]); __________ 1. OJ L 169, 12.7.1993, p. 1 2. OJ L 189, 20.7.1990, p. 17	in Annex I to Council Directive 93/42/EEC ([1]), or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC ([2]); __________ 1. OJ L 169, 12.7.1993, p. 1 2. OJ L 189, 20.7.1990, p. 17	in Annex I to Council Directive 93/42/EEC ([1]), or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC ([2]); __________ 1. OJ L 169, 12.7.1993, p. 1 2. OJ L 189, 20.7.1990, p. 17	
Annex II, 5 paragraph, point (c)				
2828	(c) where applicable, evidence of compliance of the medical device or implantable medical device with the BSE/TSE requirements laid down in Commission Directive 2003/32/EC ([1]);	(c) where applicable, evidence of compliance of the medical device or implantable medical device with the BSE/TSE requirements laid down in Commission Directive 2003/32/EC ([1]);	(c) where applicable, evidence of compliance of the medical device or implantable medical device with the BSE/TSE requirements laid down in Commission Directive 2003/32/EC ([1]);	

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	_____ 1. OJ L 105, 26.4.2003, p. 18	_____ 1. OJ L 105, 26.4.2003, p. 18	_____ 1. OJ L 105, 26.4.2003, p. 18	
Annex II, 5 paragraph, point (d)				
2829	(d) where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC.	(d) where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC.	(d) where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC.	
Annex II, 6 paragraph				
2830	The notified body which has carried out the assessment referred to in point (d) of this section shall make available on request of the competent authority assessing the application, any information	The notified body which has carried out the assessment referred to in point (d) of this section shall make available on request of the competent authority assessing the application, any information	The notified body which has carried out the assessment referred to in point (d) of this section shall make available on request of the competent authority assessing the application, any information	

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	related to the results of the assessment in accordance with Directive 93/42/EEC or Directive 90/385/EEC. This may include information and documents contained in the conformity assessment application concerned, where necessary for the evaluation of the combined advanced therapy medicinal product as a whole.	related to the results of the assessment in accordance with Directive 93/42/EEC or Directive 90/385/EEC. This may include information and documents contained in the conformity assessment application concerned, where necessary for the evaluation of the combined advanced therapy medicinal product as a whole.	related to the results of the assessment in accordance with Directive 93/42/EEC or Directive 90/385/EEC. This may include information and documents contained in the conformity assessment application concerned, where necessary for the evaluation of the combined advanced therapy medicinal product as a whole.	
Annex II, point 21.				
2831	21. SPECIFIC REQUIREMENTS REGARDING MODULE 4	21. SPECIFIC REQUIREMENTS REGARDING MODULE 4	21. SPECIFIC REQUIREMENTS REGARDING MODULE 4	
Annex II, 7 paragraph, point				

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2832	Specific requirements for all advanced therapy medicinal products	Specific requirements for all advanced therapy medicinal products	Specific requirements for all advanced therapy medicinal products	
Annex II, 2 paragraph				
2833	The requirements of Part I, Module 4 of this Annex on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 4.1, 4.2 and 4.3 below explain how the requirements in Part I of this Annex apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of	The requirements of Part I, Module 4 of this Annex on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 4.1, 4.2 and 4.3 below explain how the requirements in Part I of this Annex apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of	The requirements of Part I, Module 4 of this Annex on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 4.1, 4.2 and 4.3 below explain how the requirements in Part I of this Annex apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of	

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	advanced therapy medicinal products, additional requirements have been set.	advanced therapy medicinal products, additional requirements have been set.	advanced therapy medicinal products, additional requirements have been set.	
Annex II, 3 paragraph				
2834	The rationale for the non-clinical development and the criteria used to choose the relevant species and models (in vitro and in vivo) shall be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanised or transgenic animals. The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies.	The rationale for the non-clinical development and the criteria used to choose the relevant species and models (in vitro and in vivo) shall be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanised or transgenic animals. The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies.	The rationale for the non-clinical development and the criteria used to choose the relevant species and models (in vitro and in vivo) shall be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanised or transgenic animals. The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies.	

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Annex II, 4 paragraph				
2835	In addition to the requirements of Part I, the safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product, shall be provided. Their physical, mechanical, chemical and biological properties shall be taken into account.	In addition to the requirements of Part I, the safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product, shall be provided. Their physical, mechanical, chemical and biological properties shall be taken into account.	In addition to the requirements of Part I, the safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product, shall be provided. Their physical, mechanical, chemical and biological properties shall be taken into account.	
Annex II, 5 paragraph, point				
2836	Specific requirements for gene therapy medicinal products	Specific requirements for gene therapy medicinal products	Specific requirements for gene therapy medicinal products	

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Annex II, 3 paragraph				
2837	In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.	In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.	In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.	
Annex II, 3 paragraph, point (4.2.1)				
2838	4.2.1. Pharmacology	4.2.1. Pharmacology	4.2.1. Pharmacology	
Annex II, 4 paragraph				
2839	(a) In vitro and in vivo studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic 'proof of	(a) In vitro and in vivo studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic 'proof of	(a) In vitro and in vivo studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic 'proof of	

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	concept' studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.	concept' studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.	concept' studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.	
Annex II, b paragraph				
2840	(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of	(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of	(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of	

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	functionality and activity in target cells and tissues shall be provided.	functionality and activity in target cells and tissues shall be provided.	functionality and activity in target cells and tissues shall be provided.	
Annex II, c paragraph				
2841	4.2.2. Pharmacokinetics	4.2.2. Pharmacokinetics	4.2.2. Pharmacokinetics	
Annex II, c paragraph(a)				
2842	(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.	(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.	(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.	
Annex II, c paragraph(b)				
2843	(b) Investigations of shedding and risk of transmission to third parties shall be provided with the	(b) Investigations of shedding and risk of transmission to third parties shall be provided with the	(b) Investigations of shedding and risk of transmission to third parties shall be provided with the	

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	environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.	environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.	environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.	
Annex II, 3 paragraph				
2844	4.2.3. Toxicology	4.2.3. Toxicology	4.2.3. Toxicology	
Annex II, 3 paragraph(a)				
2845	(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the in vivo effect of expressed nucleic acid sequence-related products which are not intended for the	(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the in vivo effect of expressed nucleic acid sequence-related products which are not intended for the	(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the in vivo effect of expressed nucleic acid sequence-related products which are not intended for the	

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	physiological function shall be evaluated.	physiological function shall be evaluated.	physiological function shall be evaluated.	
Annex II, 3 paragraph(b)				
2846	(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.	(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.	(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.	
Annex II, 3 paragraph(c)				
2847	(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged	(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged	(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged	

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	functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.	functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.	functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.	
Annex II, 3 paragraph(d)				
2848	(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.	(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.	(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.	

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Annex II, 3 paragraph(e)				
2849	(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant in vivo/in vitro models.	(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant in vivo/in vitro models.	(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant in vivo/in vitro models.	
Annex II, 3 paragraph(f)				
2850	(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly	(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly	(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	justified in the application on the basis of the type of product concerned.	justified in the application on the basis of the type of product concerned.	justified in the application on the basis of the type of product concerned.	
Annex II, 3 paragraph(g)				
2851	(g) Additional toxicity studies	(g) Additional toxicity studies	(g) Additional toxicity studies	
Annex II, 4 paragraph				
2852	- Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be	- Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be	- Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	performed, if biodistribution data indicate a risk for germline transmission.	performed, if biodistribution data indicate a risk for germline transmission.	performed, if biodistribution data indicate a risk for germline transmission.	
Annex II, -a paragraph				
2853	- Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.	- Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.	- Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.	
Annex II, -a paragraph				
2854	4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	
Annex II, -a paragraph, point (4.3.1)				
2855	4.3.1. Pharmacology	4.3.1. Pharmacology	4.3.1. Pharmacology	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex II, 4 paragraph				
2856	(a) The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.	(a) The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.	(a) The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.	
Annex II, b paragraph				
2857	(b) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.	(b) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.	(b) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.	
Annex II, c paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2858	(c) Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.	(c) Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.	(c) Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.	
Annex II, CI paragraph				
2859	4.3.2. Pharmacokinetics	4.3.2. Pharmacokinetics	4.3.2. Pharmacokinetics	
Annex II, CI paragraph(a)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2860	(a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.	(a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.	(a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.	
Annex II, CI paragraph(b)				
2861	(b) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and	(b) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and	(b) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	amount of expression of these molecules shall be studied.	amount of expression of these molecules shall be studied.	amount of expression of these molecules shall be studied.	
Annex II, 3 paragraph				
2862	4.3.3. Toxicology	4.3.3. Toxicology	4.3.3. Toxicology	
Annex II, 3 paragraph(a)				
2863	(a) The toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities shall be taken into consideration.	(a) The toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities shall be taken into consideration.	(a) The toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities shall be taken into consideration.	
Annex II, 3 paragraph(b)				
2864	(b) The duration of observations may be longer than in	(b) The duration of observations may be longer than in	(b) The duration of observations may be longer than in	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.	standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.	standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.	
Annex II, 3 paragraph(c)				
2865	(c) Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.	(c) Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.	(c) Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.	
Annex II, 3 paragraph(d)				

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2866	(d) Potential immunogenic and immunotoxic effects shall be studied.	(d) Potential immunogenic and immunotoxic effects shall be studied.	(d) Potential immunogenic and immunotoxic effects shall be studied.	
Annex II, 3 paragraph(e)				
2867	(e) In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.	(e) In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.	(e) In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.	
Annex II, point 22.				
2868	22. SPECIFIC REQUIREMENTS REGARDING MODULE 5	22. SPECIFIC REQUIREMENTS REGARDING MODULE 5	22. SPECIFIC REQUIREMENTS REGARDING MODULE 5	
Annex II, 4 paragraph				

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2869	5.1. Specific requirements for all advanced therapy medicinal products	5.1. Specific requirements for all advanced therapy medicinal products	5.1. Specific requirements for all advanced therapy medicinal products	
Annex II, 4 paragraph, point (5.1.1)				
2870	5.1.1. The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Annex.	5.1.1. The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Annex.	5.1.1. The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Annex.	
Annex II, 4 paragraph, point (5.1.2), first subparagraph				
2871	5.1.2. Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and	5.1.2. Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and	5.1.2. Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.	described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.	described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.	
Annex II, 4 paragraph, point (5.1.2), second subparagraph				
2872	Where medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.	Where medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.	Where medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.	
Annex II, 4 paragraph, point (5.1.2), third subparagraph				
2873	Specific expertise required to carry out the application, implantation,	Specific expertise required to carry out the application, implantation,	Specific expertise required to carry out the application, implantation,	

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	administration or follow-up activities shall be defined. Where necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.	administration or follow-up activities shall be defined. Where necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.	administration or follow-up activities shall be defined. Where necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.	
Annex II, 4 paragraph, point (5.1.3)				
2874	5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.	5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.	5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.	
Annex II, 4 paragraph, point (5.1.4)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2875	5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.	5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.	5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.	
Annex II, 4 paragraph, point (5.1.5)				
2876	5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.	5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.	5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.	
Annex II, 4 paragraph, point (5.1.6)				
2877	5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the	5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the	5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.	intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.	intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.	
Annex II, 4 paragraph, point (5.1.7)				
2878	5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.	5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.	5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.	
Annex II, 4 paragraph, point (5.1.8)				
2879	5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.	5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.	5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.	

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Annex II, 2 paragraph				
2880	5.2. Specific requirements for gene therapy medicinal products	5.2. Specific requirements for gene therapy medicinal products	5.2. Specific requirements for gene therapy medicinal products	
Annex II, 3 paragraph				
2881	Human pharmacokinetic studies	Human pharmacokinetic studies	Human pharmacokinetic studies	
Annex II, 4 paragraph				
2882	Human pharmacokinetic studies shall include the following aspects:	Human pharmacokinetic studies shall include the following aspects:	Human pharmacokinetic studies shall include the following aspects:	
Annex II, 4 paragraph, point (a)				
2883	(a) shedding studies to address the excretion of the gene therapy medicinal products;	(a) shedding studies to address the excretion of the gene therapy medicinal products;	(a) shedding studies to address the excretion of the gene therapy medicinal products;	

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Annex II, 4 paragraph, point (b)				
2884	(b) biodistribution studies;	(b) biodistribution studies;	(b) biodistribution studies;	
Annex II, 4 paragraph, point (c)				
2885	(c) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).	(c) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).	(c) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).	
Annex II, 5 paragraph,				
2886	Human pharmacodynamic studies	Human pharmacodynamic studies	Human pharmacodynamic studies	
Annex II, 3 paragraph				
2887	Human pharmacodynamic studies shall address the expression and function of the nucleic acid	Human pharmacodynamic studies shall address the expression and function of the nucleic acid	Human pharmacodynamic studies shall address the expression and function of the nucleic acid	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	sequence following administration of the gene therapy medicinal product.	sequence following administration of the gene therapy medicinal product.	sequence following administration of the gene therapy medicinal product.	
Annex II, 4 paragraph,				
2888	Safety studies	Safety studies	Safety studies	
Annex II, 4 paragraph				
2889	Safety studies shall address the following aspects:	Safety studies shall address the following aspects:	Safety studies shall address the following aspects:	
Annex II, 4 paragraph, point (a)				
2890	(a) emergence of replication competent vector;	(a) emergence of replication competent vector;	(a) emergence of replication competent vector;	
Annex II, 4 paragraph, point (b)				
2891	(b) emergence of new strains;	(b) emergence of new strains;	(b) emergence of new strains;	

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Annex II, 4 paragraph, point (c)				
2892	(c) reassortment of existing genomic sequences;	(c) reassortment of existing genomic sequences;	(c) reassortment of existing genomic sequences;	
Annex II, 4 paragraph, point (d)				
2893	(d) neoplastic proliferation due to insertional mutagenicity.	(d) neoplastic proliferation due to insertional mutagenicity.	(d) neoplastic proliferation due to insertional mutagenicity.	
Annex II, 5 paragraph				
2894	5.3. Specific requirements for somatic cell therapy medicinal products	5.3. Specific requirements for somatic cell therapy medicinal products	5.3. Specific requirements for somatic cell therapy medicinal products	
Annex II, 4 paragraph				
2895	Somatic cell therapy medicinal products where the mode of action	Somatic cell therapy medicinal products where the mode of action	Somatic cell therapy medicinal products where the mode of action	

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	is based on the production of defined active biomolecule(s)	is based on the production of defined active biomolecule(s)	is based on the production of defined active biomolecule(s)	
Annex II, 5 paragraph				
2896	For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules shall be addressed, if feasible.	For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules shall be addressed, if feasible.	For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules shall be addressed, if feasible.	
Annex II, 6 paragraph,				
2897	Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components	Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components	Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components	

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Annex II, 3 paragraph				
2898	The biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development.	The biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development.	The biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development.	
Annex II, 4 paragraph,				
2899	Safety studies	Safety studies	Safety studies	
Annex II, 4 paragraph				
2900	Safety studies shall address the following aspects:	Safety studies shall address the following aspects:	Safety studies shall address the following aspects:	
Annex II, 4 paragraph, point (a)				

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2901	(a) distribution and engrafting following administration;	(a) distribution and engrafting following administration;	(a) distribution and engrafting following administration;	
Annex II, 4 paragraph, point (b)				
2902	(b) ectopic engraftment;	(b) ectopic engraftment;	(b) ectopic engraftment;	
Annex II, 4 paragraph, point (c)				
2903	(c) oncogenic transformation and cell/tissue lineage fidelity.	(c) oncogenic transformation and cell/tissue lineage fidelity.	(c) oncogenic transformation and cell/tissue lineage fidelity.	
Annex II, 5 paragraph				
2904	5.4. Specific requirements for tissue engineered products	5.4. Specific requirements for tissue engineered products	5.4. Specific requirements for tissue engineered products	
Annex II, 5 paragraph				
2905	Pharmacokinetic studies	Pharmacokinetic studies	Pharmacokinetic studies	

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Annex II, 6 paragraph				
2906	Where conventional pharmacokinetic studies are not relevant for tissue engineered products, the biodistribution, persistence and degradation of the tissue engineered product components shall be addressed during the clinical development.	Where conventional pharmacokinetic studies are not relevant for tissue engineered products, the biodistribution, persistence and degradation of the tissue engineered product components shall be addressed during the clinical development.	Where conventional pharmacokinetic studies are not relevant for tissue engineered products, the biodistribution, persistence and degradation of the tissue engineered product components shall be addressed during the clinical development.	
Annex II, 7 paragraph,				
2907	Pharmacodynamic studies	Pharmacodynamic studies	Pharmacodynamic studies	
Annex II, 3 paragraph				
2908	Pharmacodynamic studies shall be designed and tailored to the specificities of tissue engineered products. The evidence for the	Pharmacodynamic studies shall be designed and tailored to the specificities of tissue engineered products. The evidence for the	Pharmacodynamic studies shall be designed and tailored to the specificities of tissue engineered products. The evidence for the	

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	‘proof of concept’ and the kinetics of the product to obtain the intended regeneration, repairing or replacement shall be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure shall be taken into account.	‘proof of concept’ and the kinetics of the product to obtain the intended regeneration, repairing or replacement shall be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure shall be taken into account.	‘proof of concept’ and the kinetics of the product to obtain the intended regeneration, repairing or replacement shall be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure shall be taken into account.	
Annex II, 4 paragraph,				
2909	Safety studies	Safety studies	Safety studies	
Annex II, 4 paragraph				
2910	Section 5.3.3 shall apply.	Section 5.3.3 shall apply.	Section 5.3.3 shall apply.	
Annex III				
2911	Annex III	Annex III	Annex III	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex III, first paragraph				
2912	CONDITIONS FOR QUALIFICATION OF A QUALIFIED PERSON	CONDITIONS FOR QUALIFICATION OF A QUALIFIED PERSON	CONDITIONS FOR QUALIFICATION OF A QUALIFIED PERSON	
Annex III, point 1., first subparagraph				
2913	1. The qualified person shall hold a university degree in one or more of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.	1. The qualified person shall hold a university degree in one or more of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.	1. The qualified person shall ~~hold~~**be in possession of evidence of formal qualifications awarded on completion of** a university ~~degree~~**course of study, or a course recognised as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study,** in one or more of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry,	

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			pharmaceutical chemistry and technology, biology**, biomedical engineering and biotechnology, chemical engineering**.	
Annex III, point 1., second subparagraph				
2913a			**However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.**	
Annex III, point 1., third subparagraph				

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2913b			**Where two university courses or two courses recognised by the Member State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to evidence of formal qualifications awarded on completion of a university course or its recognised equivalent shall be considered to fulfil the condition of duration referred to in the second subparagraph in so far as evidence of formal qualifications awarded on completion of both courses are recognised as equivalent by the Member State in question.**	

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Annex III, point 1., fourth subparagraph				
2913c			**The course shall include theoretical and practical study bearing upon at least the following basic subjects:**	
Annex III, point 1., fourth subparagraph, point (a)				
2913d			**(a) Physics**	
Annex III, point 1., fourth subparagraph, point (b)				
2913e			**(b) General and inorganic Chemistry**	
Annex III, point 1., fourth subparagraph, point (c)				
2913f			**(c) Organic chemistry**	
Annex III, point 1., fourth subparagraph, point (d)				

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2913g			**(d) Analytical chemistry**	
Annex III, point 1., fourth subparagraph, point (e)				
2913h			**(e) Pharmaceutical chemistry, including analysis of medicinal products**	
Annex III, point 1., fourth subparagraph, point (f)				
2913i			**(f) Biochemistry**	
Annex III, point 1., fourth subparagraph, point (g)				
2913j			**(g) Physiology**	
Annex III, point 1., fourth subparagraph, point (h)				
2913k			**(h) Microbiology**	
Annex III, point 1., fourth subparagraph, point (i)				

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2913l			**(i) Pharmacology**	
Annex III, point 1., fourth subparagraph, point (j)				
2913m			**(j) Pharmaceutical technology**	
Annex III, point 1., fourth subparagraph, point (k)				
2913n			**(k) Toxicology.**	
Annex III, point 1., fifth subparagraph				
2913o			**Studies in these subjects shall be so balanced as to enable the person concerned to fulfil the obligations specified in Article 153.**	
Annex III, point 1., sixth subparagraph				

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2913p			**In so far as evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.**	
Annex III, point 2.				
2914	2. The qualified person shall have acquired practical full-time experience over at least two years, in one or more undertakings that are authorised manufacturers, obtaining sufficient knowledge of manufacture, testing, supply chains, good manufacturing	2. The qualified person shall have acquired practical full-time experience over at least two years, in one or more undertakings that are authorised manufacturers, obtaining sufficient knowledge of manufacture, testing, supply chains, good manufacturing	2. The qualified person shall have acquired practical full-time experience over at least two years **or equivalent experience acquired over proportionally longer period of time**, in one or more undertakings **or entities not engaged in an economic activity**	

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	practice and pharmaceutical quality systems as well as regulatory processes and dossier content for ensuring the quality of medicinal products.	practice and pharmaceutical quality systems as well as regulatory processes and dossier content for ensuring the quality of medicinal products.	that are authorised manufacturers, obtaining sufficient knowledge of manufacture, testing, supply chains, good manufacturing practice and pharmaceutical quality systems as well as regulatory processes and dossier content for ensuring the quality of medicinal products. **The duration of practical experience may be reduced by one year by the competent authority of the Member State where a university course lasts for at least five years.**	
Annex III, point 3., first subparagraph				
2915	3. A qualified person shall be in possession of a diploma, certificate or other evidence of	3. A qualified person shall be in possession of a diploma, certificate or other evidence of	3. ~~A qualified person shall be in possession of a diploma, certificate or other evidence of~~	

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	formal qualifications awarded on completion of a university course of study, or a course recognised as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.	formal qualifications awarded on completion of a university course of study, or a course recognised as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.	~~formal qualifications awarded on completion of a university course of study, or a course recognised as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.~~	
Annex III, point 3., second subparagraph				
2916	However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year	However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year	~~However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year~~	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.	and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.	~~and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.~~	
Annex III, point 3., third subparagraph				
2917	Where two university courses or two courses recognised by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognised equivalent shall be considered to fulfil the condition of duration referred to in the second	Where two university courses or two courses recognised by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognised equivalent shall be considered to fulfil the condition of duration referred to in the second	~~Where two university courses or two courses recognised by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognised equivalent shall be considered to fulfil the condition of duration referred to in the second~~	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognised as equivalent by the Member State in question.	subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognised as equivalent by the Member State in question.	~~subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognised as equivalent by the Member State in question.~~	
Annex III, point 3., fourth subparagraph				
2918	The course shall include theoretical and practical study bearing upon at least the following basic subjects:	The course shall include theoretical and practical study bearing upon at least the following basic subjects:	~~The course shall include theoretical and practical study bearing upon at least the following basic subjects:~~	
Annex III, point 3., fourth subparagraph, point (a)				
2919	(a) Experimental physics	(a) Experimental physics	(a) ~~Experimental physics~~	
Annex III, point 3., fourth subparagraph, point (b)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2920	(b) General and inorganic chemistry	(b) General and inorganic chemistry	(b) ~~General and inorganic chemistry~~	
Annex III, point 3., fourth subparagraph, point (c)				
2921	(c) Organic chemistry	(c) Organic chemistry	(c) ~~Organic chemistry~~	
Annex III, point 3., fourth subparagraph, point (d)				
2922	(d) Analytical chemistry	(d) Analytical chemistry	(d) ~~Analytical chemistry~~	
Annex III, point 3., fourth subparagraph, point (e)				
2923	(e) Pharmaceutical chemistry, including analysis of medicinal products	(e) Pharmaceutical chemistry, including analysis of medicinal products	(e) ~~Pharmaceutical chemistry, including analysis of medicinal products~~	
Annex III, point 3., fourth subparagraph, point (f)				
2924	(f) General and applied biochemistry (medical)	(f) General and applied biochemistry (medical)	(f) ~~General and applied biochemistry (medical)~~	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex III, point 3., fourth subparagraph, point (g)				
2925	(g) Physiology	(g) Physiology	(g) ~~Physiology~~	
Annex III, point 3., fourth subparagraph, point (h)				
2926	(h) Micro biology	(h) Micro biology	(h) ~~Micro biology~~	
Annex III, point 3., fourth subparagraph, point (i)				
2927	(i) Pharmacology	(i) Pharmacology	(i) ~~Pharmacology~~	
Annex III, point 3., fourth subparagraph, point (j)				
2928	(j) Pharmaceutical technology	(j) Pharmaceutical technology	(j) ~~Pharmaceutical technology~~	
Annex III, point 3., fourth subparagraph, point (k)				
2929	(k) Toxicology	(k) Toxicology	(k) ~~Toxicology~~	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex III, point 3., fourth subparagraph, point (l)				
2930	(l) Pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).	(l) Pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).	(l) ~~Pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).~~	
Annex III, point 3., fifth subparagraph				
2931	Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 153.	Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 153.	~~Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 153.~~	
Annex III, point 3., sixth subparagraph				
2932	In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this	In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this	~~In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this~~	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.	paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.	~~paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.~~	
Annex III, point 4.				
2933	4. The qualified person shall have acquired practical experience over at least two years, in one or more undertakings or not-for-profit entities that are authorised to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.	4. The qualified person shall have acquired practical experience over at least two years, in one or more undertakings or not-for-profit entities that are authorised to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.	4. ~~The qualified person shall have acquired practical experience over at least two years, in one or more undertakings or not-for-profit entities that are authorised to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.~~	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex III, point 5.				
2934	5. A person engaging in the activities of the person referred to in Article 152 from the time of the application of Second Council Directive 75/319/EEC[1], in a Member State without complying with the provisions of this Annex shall be eligible to continue to engage in those activities within the Union. __________ 1. Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products (OJ L 147, 9.6.1975, p. 13). Directive is not in force anymore.	5. A person engaging in the activities of the person referred to in Article 152 from the time of the application of Second Council Directive 75/319/EEC[1], in a Member State without complying with the provisions of this Annex shall be eligible to continue to engage in those activities within the Union. __________ 1. Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products (OJ L 147, 9.6.1975, p. 13). Directive is not in force anymore.	5. A person engaging in the activities of the person referred to in Article 152 from the time of the application of Second Council Directive 75/319/EEC[1], in a Member State without complying with the provisions of this Annex shall be eligible to continue to engage in those activities within the Union. __________ 1. Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products (OJ L 147, 9.6.1975, p. 13). Directive is not in force anymore.	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex III, point 6.				
2935	6. The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course — or a course recognised as equivalent by the Member State concerned — in a scientific discipline allowing them to engage in the activities of the person referred to in Article 48 in accordance with the laws of that Member State may — if they began their course prior to 21 May 1975 — be considered as qualified to carry out in that Member State the duties of the person referred to in Article 152 provided that they have previously engaged in the following activities for at least two	6. The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course — or a course recognised as equivalent by the Member State concerned — in a scientific discipline allowing them to engage in the activities of the person referred to in Article 48 in accordance with the laws of that Member State may — if they began their course prior to 21 May 1975 — be considered as qualified to carry out in that Member State the duties of the person referred to in Article 152 provided that they have previously engaged in the following activities for at least two	6. The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course — or a course recognised as equivalent by the Member State concerned — in a scientific discipline allowing them to engage in the activities of the person referred to in Article 48 in accordance with the laws of that Member State may — if they began their course prior to 21 May 1975 — be considered as qualified to carry out in that Member State the duties of the person referred to in Article 152 provided that they have previously engaged in the following activities for at least two	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	years before 21 May 1985 following notification of this directive in one or more undertakings or not-for-profit entities authorised to manufacture: production supervision or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 152 to ensure the quality of the medicinal products.	years before 21 May 1985 following notification of this directive in one or more undertakings or not-for-profit entities authorised to manufacture: production supervision or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 152 to ensure the quality of the medicinal products.	years before 21 May 1985 following notification of this directive in one or more undertakings or ~~not-for-profit~~ entities **not engaged in an economic activity** authorised to manufacture: production supervision or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 152 to ensure the quality of the medicinal products.	
Annex IV				
2936	Annex IV	Annex IV	Annex IV	
Annex IV, first paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2937	LABELLING PARTICULARS	LABELLING PARTICULARS	LABELLING PARTICULARS	
Annex IV, second paragraph				
2938	The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:	The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:	The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:	
Annex IV, second paragraph, point (a)				
2939	(a) the name of the medicinal product, including in Braille, followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults; where the medicinal product contains up to three active substances, the international non-	(a) the name of the medicinal product, including in Braille, followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults; where the medicinal product contains up to three active substances, the international non-	(a) the name of the medicinal product, **(**including in Braille**)**, followed by its strength**, if appropriate (including in Braille),** and pharmaceutical form **(including in Braille, if appropriate)**, and, if appropriate, whether it is intended for babies, children or adults; where the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	proprietary name (INN) shall be included, or, if one does not exist, the common name;	proprietary name (INN) shall be included, ***unless it is already part of the name of the medicinal product,*** or, if one does not exist, the common name;	medicinal product contains up to three active substances, the international non-proprietary name (INN) shall be included, or, if one does not exist, the common name;	
Annex IV, second paragraph, point (b)				
2940	(b) a statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight, using their common names;	(b) a statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight, using their common names;	(b) a statement of the active substances expressed qualitatively and quantitatively per ~~dosage~~**dose or** unit or according to the form of administration for a given volume or weight, using their common names;	
Annex IV, second paragraph, point (c)				
2941	(c) the pharmaceutical form and the contents by weight, by	(c) the pharmaceutical form and the contents by weight, by	(c) the pharmaceutical form and the contents by weight, by	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	volume or by number of doses of the medicinal product;	volume or by number of doses of the medicinal product;	volume or by number of doses of the medicinal product;	
Annex IV, second paragraph, point (d)				
2942	(d) a list of those excipients known to have a recognised action or effect and included in the detailed guidance published pursuant to Article 68;	(d) a list of those excipients known to have a recognised action or effect and included in the detailed guidance published pursuant to Article 68;	(d) a list of those excipients**, expressed qualitatively,** known to have a recognised action or effect ~~and included~~**;** in the ~~detailed guidance published pursuant to Article 68;~~**case of injectable medicinal products, topical preparations or eye drops, all excipients shall be listed**	
Annex IV, second paragraph, point (e)				
2943	(e) the method of administration and, if necessary, the route of administration. Space	(e) the method of administration and, if necessary, the route of administration. Space	(e) the method of administration and, if necessary, the route of administration. Space	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	shall be provided for the prescribed dose to be indicated;	shall be provided for the prescribed dose to be indicated;	shall be provided for the prescribed dose to be indicated;	
Annex IV, second paragraph, point (f)				
2944	(f) a special warning that the medicinal product must be stored out of the reach and sight of children;	(f) a special warning that the medicinal product must be stored out of the reach and sight of children;	(f) **if appropriate,** a special warning that the medicinal product must be stored out of the reach and sight of children;	
Annex IV, second paragraph, point (g)				
2945	(g) a special warning, if this is necessary for the medicinal product;	(g) a special warning, if this is necessary for the medicinal product;	(g) ~~a~~ special warning, if ~~this is~~ necessary for the medicinal product;	
Annex IV, second paragraph, point (ga)				
2945a		***(ga) for antimicrobials, a warning that improper use and unsafe disposal of the medicinal***		

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
		product contributes to antimicrobial resistance;		
Annex IV, second paragraph, point (h)				
2946	(h) the expiry date in clear terms (month/year);	(h) the expiry date in clear terms (month/year);	(h) the expiry date in clear terms (month/year);	
Annex IV, second paragraph, point (i)				
2947	(i) special storage precautions, if any;	(i) special storage precautions, if any;	(i) special storage precautions, if any;	
Annex IV, second paragraph, point (j)				
2948	(j) specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as	(j) specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products~~,~~ ~~*where appropriate,*~~ as well as	(j) specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	reference to any appropriate collection system in place;	reference to any appropriate collection system in place;	reference to any appropriate collection system in place;	
Annex IV, second paragraph, point (k)				
2949	(k) the name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent them;	(k) the name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent them;	(k) the name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent them;	
Annex IV, second paragraph, point (l)				
2950	(l) the number of the marketing authorisation for placing the medicinal product on the market;	(l) the number of the marketing authorisation for placing the medicinal product on the market;	(l) the number of the marketing authorisation for placing the medicinal product on the market;	
Annex IV, second paragraph, point (m)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2951	(m) the manufacturer's batch number;	(m) the manufacturer's batch number;	(m) the manufacturer's batch number;	
Annex IV, second paragraph, point (n)				
2952	(n) in the case of non-prescription medicinal products, instructions for use;	(n) in the case of non-prescription medicinal products, instructions for use;	(n) in the case of non-prescription medicinal products, instructions for use;	
Annex IV, second paragraph, point (o)				
2953	(o) for medicinal products other than radiopharmaceuticals referred to in Article 67(1), safety features enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:	(o) for medicinal products other than radiopharmaceuticals referred to in Article 67(1), safety features enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:	(o) for medicinal products other than radiopharmaceuticals referred to in Article 67(1), safety features enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:	
Annex IV, second paragraph, point (o)(i)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2954	(i) verify the authenticity of the medicinal product, and	(i) verify the authenticity of the medicinal product, and	(i) verify the authenticity of the medicinal product, and	
Annex IV, second paragraph, point (o)(ii)				
2955	(ii) identify individual packs,	(ii) identify individual packs,	(ii) identify individual packs,	
Annex IV, third paragraph				
2956	- as well as a device allowing verification of whether the outer packaging has been tampered with.	- as well as a device allowing verification of whether the outer packaging has been tampered with.	- as well as a device allowing verification of whether the outer packaging has been tampered with.	
Annex V				
2957	Annex V	Annex V	Annex V	
Annex V, first paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2958	CONTENTS OF SUMMMARY PRODUCT CHARACTERISTICS	CONTENTS OF SUMMMARY PRODUCT CHARACTERISTICS	CONTENTS OF SUMMMARY PRODUCT CHARACTERISTICS	
Annex V, second paragraph				
2959	The summary of product characteristics shall contain, in the order indicated below, the following information:	The summary of product characteristics shall contain, in the order indicated below, the following information:	The summary of product characteristics shall contain, in the order indicated below, the following information:	
Annex V, third paragraph				
2960	(1) name of the medicinal product followed by the strength and the pharmaceutical form.	(1) name of the medicinal product followed by the strength and the pharmaceutical form.	(1) name of the medicinal product followed by the strength**, if appropriate,** and the pharmaceutical form.	
Annex V, 2 paragraph				
2961	(2) qualitative and quantitative composition in terms	(2) qualitative and quantitative composition in terms	(2) qualitative and quantitative composition in terms	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	of the active substances and of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.	of the active substances and of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.	of the active substances and of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.	
Annex V, 3 paragraph				
2962	(3) pharmaceutical form.	(3) pharmaceutical form.	(3) pharmaceutical form.	
Annex V, 4 paragraph				
2963	(4) clinical particulars:	(4) clinical particulars:	(4) clinical particulars:	
Annex V, 4 paragraph, point (a)				
2964	(a) therapeutic indications,	(a) therapeutic indications,	(a) therapeutic indications,	
Annex V, 4 paragraph, point (b)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2965	(b) posology and method of administration for adults and, where necessary for children,	(b) posology and method of administration for adults and, where necessary for children,	(b) posology and method of administration for adults and, where necessary for children,	
Annex V, 4 paragraph, point (c)				
2966	(c) contra-indications,	(c) contra-indications,	(c) contra-indications,	
Annex V, 4 paragraph, point (d)				
2967	(d) special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such medicinal products and administering them to patients, together with any precautions to be taken by the patient,	(d) special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such medicinal products and administering them to patients, together with any precautions to be taken by the patient,	(d) special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such medicinal products and administering them to patients, together with any precautions to be taken by the patient,	
Annex V, 4 paragraph, point (e)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2968	(e) interaction with other medicinal products and other forms of interactions,	(e) interaction with other medicinal products and other forms of interactions,	(e) interaction with other medicinal products and other forms of interactions,	
Annex V, 4 paragraph, point (f)				
2969	(f) use during pregnancy and lactation,	(f) use during pregnancy and lactation,	(f) use during pregnancy**, breastfeeding, and information on influence on fertility** ~~and lactation,~~	
Annex V, 4 paragraph, point (g)				
2970	(g) effects on ability to drive and to use machines,	(g) effects on ability to drive and to use machines,	(g) effects on ability to drive and to use machines,	
Annex V, 4 paragraph, point (h)				
2971	(h) undesirable effects,	(h) undesirable effects,	(h) undesirable effects **including standardised text expressly asking healthcare**	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
			professionals to report any suspected adverse reaction in accordance with the national reporting system referred to in Article 106(1) and specifying the different ways of reporting available (electronic reporting, postal address or others) in compliance with Article 106(1), second subparagraph;	
Annex V, 4 paragraph, point (i)				
2972	(i) overdose (symptoms, emergency procedures, antidotes).	(i) overdose (symptoms, emergency procedures, antidotes).	(i) overdose (symptoms, emergency procedures, antidotes).	
Annex V, 5 paragraph				
2973	(5) pharmacological properties:	(5) pharmacological properties:	(5) pharmacological properties:	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex V, 5 paragraph, point (a)				
2974	(a) pharmacodynamic properties,	(a) pharmacodynamic properties,	(a) pharmacodynamic properties,	
Annex V, 5 paragraph, point (b)				
2975	(b) pharmacokinetic properties,	(b) pharmacokinetic properties,	(b) pharmacokinetic properties,	
Annex V, 5 paragraph, point (c)				
2976	(c) non-clinical safety data.	(c) non-clinical safety data.	(c) non-clinical safety data.	
Annex V, 6 paragraph				
2977	(6) pharmaceutical particulars:	(6) pharmaceutical particulars:	(6) pharmaceutical particulars:	
Annex V, 6 paragraph, point (a)				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2978	(a) list of excipients,	(a) list of excipients,	(a) list of excipients,	
Annex V, 6 paragraph, point (b)				
2979	(b) major incompatibilities,	(b) major incompatibilities,	(b) major incompatibilities,	
Annex V, 6 paragraph, point (c)				
2980	(c) shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,	(c) shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,	(c) shelf life **and**, when necessary**, shelf life** after reconstitution **or dilution** of the medicinal product or when the immediate packaging is opened for the first time,	
Annex V, 6 paragraph, point (d)				
2981	(d) special precautions for storage,	(d) special precautions for storage,	(d) ~~special~~ precautions for storage,	
Annex V, 6 paragraph, point (e)				

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2982	(e) nature and contents of container,	(e) nature and contents of container,	(e) nature and contents of container,	
Annex V, 6 paragraph, point (f)				
2983	(f) special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate. In case of antimicrobial medicinal products in addition to the precautions a warning that inappropriate disposal of the medicinal product contributes to antimicrobial resistance.	(f) special precautions for disposal of a ~~used~~ medicinal product or waste materials derived from such medicinal product~~, if appropriate~~ ***as well as any designated collection system in place***. In case of antimicrobial medicinal products in addition to the precautions a warning that inappropriate disposal of the medicinal product contributes to antimicrobial resistance~~.~~**;**	(f) ~~special~~ precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate. In case of antimicrobial medicinal products in addition to the precautions a warning that inappropriate disposal of the medicinal product contributes to antimicrobial resistance.	
Annex V, 7 paragraph				

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
2984	(7) marketing authorisation holder.	(7) marketing authorisation holder.	(7) marketing authorisation holder.	
Annex V, 8 paragraph				
2985	(8) marketing authorisation numbers.	(8) marketing authorisation numbers.	(8) marketing authorisation numbers.	
Annex V, 9 paragraph				
2986	(9) date of the first marketing authorisation or renewal of the marketing authorisation.	(9) date of the first marketing authorisation or renewal of the marketing authorisation.	(9) date of the first marketing authorisation or renewal of the marketing authorisation.	
Annex V, 10 paragraph				
2987	(10) date of revision of the text.	(10) date of revision of the text.	(10) date of revision of the text.	
Annex V, 11 paragraph				

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2988	(11) for radiopharmaceuticals, full details of internal radiation dosimetry.	(11) for radiopharmaceuticals, full details of internal radiation dosimetry.	(11) for radiopharmaceuticals, full details of internal radiation dosimetry.	
Annex V, 12 paragraph				
2989	(12) for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.	(12) for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.	(12) for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.	
Annex V, 13 paragraph				
2990	For marketing authorisations under Articles 9 to 12 and	For marketing authorisations under Articles 9 to 12 and	~~For marketing authorisations under Articles 9 to 12 and~~	

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	subsequent variations, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms that are still covered by patent law at the time when a generic or biosimilar medicinal product is placed on the market need not be included.	subsequent variations, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms that are still covered by patent law at the time when a generic or biosimilar medicinal product is placed on the market need not be included.	~~subsequent variations, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms that are still covered by patent law at the time when a generic or biosimilar medicinal product is placed on the market need not be included.~~	
Annex VI				
2991	Annex VI	Annex VI	Annex VI	
Annex VI, first paragraph				
2992	CONTENTS OF PACKAGE LEAFLET	CONTENTS OF PACKAGE LEAFLET	CONTENTS OF PACKAGE LEAFLET	
Annex VI, second paragraph				

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2993	The package leaflet shall contain, in the order indicated below, the following information:	The package leaflet shall contain, in the order indicated below, the following information:	The package leaflet shall contain, in the order indicated below, the following information:	
Annex VI, third paragraph				
2994	(1) for the identification of the medicinal product:	(1) for the identification of the medicinal product:	(1) for the identification of the medicinal product:	
Annex VI, third paragraph, point (a)				
2995	(a) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common name shall be included where the medicinal product contains only one active substance and if its name is an invented name;	(a) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common name shall be included where the medicinal product contains only one active substance and if its name is an invented name;	(a) the name of the medicinal product followed by its strength**, if appropriate,** and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. ~~The common name shall be included~~ Where the medicinal product contains ~~only one~~**up to three** active ~~substance and if its name is an invented~~**substances,**	

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			the international non-proprietary name (INN) shall be included, or, if one does not exist, the common name;	
Annex VI, third paragraph, point (b)				
2996	(b) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;	(b) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;	(b) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;	
Annex VI, 2 paragraph				
2997	(2) the therapeutic indications;	(2) the therapeutic indications;	(2) the therapeutic indications;	
Annex VI, 2 paragraph a				
2997a		***(2a) a key information section reflecting the results of***		

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		consultations with patients' organisations to ensure that the leaflet is legible, clear and easy to use;		
Annex VI, 3 paragraph				
2998	(3) a list of information that is necessary before the medicinal product is taken:	(3) a list of information that is necessary before the medicinal product is taken:	(3) a list of information that is necessary before the medicinal product is taken:	
Annex VI, 3 paragraph, point (a)				
2999	(a) contra-indications;	(a) contra-indications;	(a) contra-indications;	
Annex VI, 3 paragraph, point (b)				
3000	(b) appropriate precautions for use;	(b) appropriate precautions for use;	(b) appropriate precautions for use;	
Annex VI, 3 paragraph, point (c)				

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3001	(c) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, food) that may affect the action of the medicinal product;	(c) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, food) that may affect the action of the medicinal product;	(c) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, food **and herbal products**) that may affect the action of the medicinal product;	
Annex VI, 3 paragraph, point (d)				
3002	(d) special warnings;	(d) special warnings;	(d) special warnings;	
Annex VI, 4 paragraph				
3003	(4) the necessary and usual instructions for proper use, and in particular:	(4) the necessary and usual instructions for proper use, and in particular:	(4) the necessary and usual instructions for proper use, and in particular:	
Annex VI, 4 paragraph, point (a)				
3004	(a) the dosage,	(a) the dosage,	(a) the ~~dosage~~**dose/posology**,	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
Annex VI, 4 paragraph, point (b)				
3005	(b) the method and, if necessary, route of administration;	(b) the method and, if necessary, route of administration, ***and where relevant a description of the measuring or delivery device, as well as the relevant individual steps of medicine preparation and administration***;	(b) the method and, if necessary, route of administration;	
Annex VI, 4 paragraph, point (c)				
3006	(c) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;	(c) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;	(c) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;	
Annex VI, 5 paragraph				

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3007	- and, as appropriate, depending on the nature of the medicinal product:	- and, as appropriate, depending on the nature of the medicinal product:	- ~~and, as appropriate, depending on the nature of the medicinal product:~~	
Annex VI, -a paragraph				
3008	(d) the duration of treatment, where it should be limited;	(d) the duration of treatment, where it should be limited;	(d) the duration of treatment, where it should be limited;	
Annex VI, DI paragraph				
3009	(e) the action to be taken in case of an overdose (such as symptoms, emergency procedures);	(e) the action to be taken in case of an overdose (such as symptoms, emergency procedures);	(e) the action to be taken in case of an overdose (such as symptoms, emergency procedures)**, if applicable**;	
Annex VI, f paragraph				
3010	(f) what to do when one or more doses have not been taken;	(f) what to do when one or more doses have not been taken;	(f) what to do when one or more doses have not been taken;	

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Annex VI, g paragraph				
3011	(g) indication, if necessary, of the risk of withdrawal effects;	(g) indication, if necessary, of the risk of withdrawal effects;	(g) indication, if necessary, of the risk of withdrawal effects;	
Annex VI, h paragraph				
3012	(h) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the medicinal product;	(h) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the medicinal product;	(h) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the medicinal product;	
Annex VI, i paragraph				
3013	(5) a description of the adverse reactions that may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case;	(5) a description of the adverse reactions that may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case;	(5) a description of the adverse reactions that may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case – **including standardised text**	

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			expressly asking patients to communicate any suspected adverse reaction to their doctor, pharmacist, healthcare professional or directly to the national reporting system referred to in Article 106(1), and specifying the different ways of reporting available (electronic reporting, postal address or others) in compliance with Article 106(1), second subparagraph;	
Annex VI, 6 paragraph				
3014	(6) references to the following:	(6) references to the following:	(6) references to the following:	
Annex VI, 6 paragraph, point (a)				

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3015	(a) the expiry date indicated on the label, with a warning against using the medicinal product after that date;	(a) the expiry date indicated on the label, with a warning against using the medicinal product after that date;	(a) the expiry date indicated on the label, with a warning against using the medicinal product after that date;	
Annex VI, 6 paragraph, point (b)				
3016	(b) where appropriate, special storage precautions;	(b) where appropriate, special storage precautions;	(b) where appropriate, ~~special~~ storage precautions;	
Annex VI, 6 paragraph, point (c)				
3017	(c) if necessary, a warning concerning certain visible signs of deterioration;	(c) if necessary, a warning concerning certain visible signs of deterioration;	(c) if necessary, a warning concerning certain visible signs of deterioration;	
Annex VI, 6 paragraph, point (d)				
3018	(d) the full qualitative composition (in active substances and excipients) and the	(d) the full qualitative composition (in active substances and excipients) and the	(d) the full qualitative composition (in active substances and excipients) and the	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	quantitative composition in active substances, using common names, for each presentation of the medicinal product;	quantitative composition in active substances, using common names, for each presentation of the medicinal product;	quantitative composition in active substances, using common names, for each presentation of the medicinal product;	
Annex VI, 6 paragraph, point (e)				
3019	(e) for each presentation of the medicinal product, the pharmaceutical form and content in weight, volume or units of dosage;	(e) for each presentation of the medicinal product, the pharmaceutical form and content in weight, volume or units of dosage;	(e) for each presentation of the medicinal product, the pharmaceutical form and content in weight, volume or units of dosage;	
Annex VI, 6 paragraph, point (f)				
3020	(f) information on where the leaflet is available in formats accessible for persons with disabilities;	(f) information on where the leaflet is available in formats accessible for persons with disabilities;	(f) information on where the leaflet is available in formats accessible for persons with disabilities;	
Annex VI, 6 paragraph, point (g)				

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3021	(g) the name and address of the marketing authorisation holder and, where applicable, the name of their appointed representatives in the Member States;	(g) the name and address of the marketing authorisation holder and, where applicable, the name of their appointed representatives in the Member States;	(g) ~~-~~the name**, address and e-mail** ~~and~~ address of the marketing authorisation holder and, where applicable, the name of their appointed representatives in the Member States;	
Annex VI, 6 paragraph, point (h)				
3022	(h) the name and address of the manufacturer.	(h) the name and address of the manufacturer.	(h) the name and address of the manufacturer.	
Annex VI, 7 paragraph				
3023	(7) the date on which the package leaflet was last revised;	(7) the date on which the package leaflet was last revised;	(7) the date on which the package leaflet was last revised;	
Annex VI, 8 paragraph				
3024	(8) for antimicrobials, a warning that improper use and	(8) for antimicrobials, a warning that improper use and	(8) for antimicrobials, a ~~warning that improper use and~~	

	Commission Proposal	EP Mandate	Council Mandate	Draft Agreement
	disposal of the medicinal product contributes to antimicrobial resistance.	disposal of the medicinal product contributes to antimicrobial resistance.	~~disposal of~~**section that contains the global antimicrobial resistance symbol, specific information about** the medicinal product ~~contributes to~~**concerned and information on** antimicrobial resistance **and the importance of appropriate use and disposal of antimicrobials referred to in Article 69 paragraph 2** .	
Annex VI, 9 paragraph				
3025	The list set out in point (3) shall:	The list set out in point (3) shall:	The list set out in point (3) shall:	
Annex VI, 9 paragraph, point (a)				
3026	(a) take into account the particular condition of certain categories of users (children, pregnant or breastfeeding women,	(a) take into account the particular condition of certain categories of users (children, pregnant or breastfeeding women,	(a) take into account the particular condition of certain categories of users (children, pregnant or breastfeeding women,	

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	older adults, persons with specific pathological conditions and persons with disabilities);	older adults, persons with specific pathological conditions and persons with disabilities);	~~older adults~~**elderly**, persons with specific pathological conditions and persons with disabilities);	
Annex VI, 9 paragraph, point (b)				
3027	(b) mention, if appropriate, possible effects on the ability to drive vehicles or to operate machinery;	(b) mention, if appropriate, possible effects on the ability to drive vehicles or to operate machinery;	(b) mention, if appropriate, possible effects on the ability to drive vehicles or to operate machinery;	
Annex VI, 9 paragraph, point (c)				
3028	(c) list those excipients the knowledge of which is important for the safe and effective use of the medicinal product and that are included in the detailed guidance referred to in Article 77.	(c) list those excipients the knowledge of which is important for the safe and effective use of the medicinal product and that are included in the detailed guidance referred to in Article 77.	(c) list those excipients the knowledge of which is important for the safe and effective use of the medicinal product ~~and that are included in the detailed guidance referred to in Article 77~~.	
Annex VI, 9 paragraph a				

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3028a		***The package leaflet may also contain information on the importance of therapeutic adherence and available support for adherence in the Member State.***		
Annex VII				
3029	Annex VII	Annex VII	Annex VII	
Annex VII, first paragraph				
3030	AREAS FOR ADAPTED FRAMEWORKS REFERRED TO IN ARTICLE 28	AREAS FOR ADAPTED FRAMEWORKS REFERRED TO IN ARTICLE 28	AREAS FOR ADAPTED FRAMEWORKS REFERRED TO IN ARTICLE 28	
Annex VII, second paragraph				
3031	Phage-containing medicinal products, in cases where the	Phage-containing medicinal products, in cases where the	Phage-containing medicinal products, in cases where the	

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	medicinal product has a variable composition depending on the specific clinical context.	medicinal product has a variable composition depending on the specific clinical context.	medicinal product has a variable composition depending on the specific clinical context.	
Annex VIII				
3032	Annex VIII	Annex VIII	Annex VIII	
Annex VIII, first paragraph				
3033	CORRELATION TABLE	CORRELATION TABLE	CORRELATION TABLE	