Written contributions from delegations

AUSTRIA

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	See Annex; based on medium hourly rates/procedures

Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure
Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	See Annex; based on medium hourly rates/procedure
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	See Annex; based on medium hourly rates/procedure
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration	No data provided.	No data provided.

Annex – Justification of Fee adjustments:

I. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

II. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

1. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[1],[2]. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation, expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

2. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

3. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

[1] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[2] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

4. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

5. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

6. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to provide that service. With staff turnover this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can

fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

7. **NCAs and value for money**

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

1. Increase in complexity/innovative developments or methodologies.
2. Subsequently need to involve senior assessor and external experts to cover the requested expertise.
3. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
4. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.
5. Sustainability of the network.
6. Current limitation of human resources in NCA.
7. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.
8. Increase number of experts by SA level.
9. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice

The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.
The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.
There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice
Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).
Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.
In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:
a)

The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations addition of a new therapeutic indication or modification of an approved indication.
- For type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of renumeration for type II addition of therapeutic indication or modification.
- Decrease of renumeration for type II other.
- The Rapp no longer receives the renumeration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher renumeration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less then for type II addition of therapeutic indication or modification.
- Introducing an in-between level for “complex” type II variations (including complex quality variations) would require a definition of “complex”. It is doubtful whether a sufficiently distinct definition can be drawn up. For example a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCA expenses.
- The proposed lower renumeration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in renumeration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.

- No renumeration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the renumeration should be the same as the renumeration of the Rapp (and not dividing the renumeration between Rapp and Co-Rapp).
- The additional renumeration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced renumeration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same renumeration for each individual type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCA. Therefore no additional renumeration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more then one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the renumeration.
- Equal renumeration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching renumeration proposal.

Proposal for new fee proposal and data collection**:**

To keep the renumeration for type II variations simple and cost effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			**Sustainability factor**	**Proposal – adjusted**
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:
Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:
Targeted type of referrals : art. 20, art 31 and art. 107
In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.
This decrease is of public health concern because the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage adequate assessment, based on robust expertise?
The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:
The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).
Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.
MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs
The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20% that includes adjustment by inflation (for 2023 and 2024).

PSURs:
Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.
EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10 fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the propose update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC	Fee proposal- adjusted

Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.

The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).

The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(a) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.

Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).

Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the

fee is awarded per inspected product.

(b) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.

Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).

A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.

Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees

Hard data in relation to the proposal

See **appendix 1.1**

The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

1. Evidence of increased hours from the data gathering exercise.
2. Evidence that the fee does not cover the costs; costs estimation does not account for :
   A) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.
   B) Need to create/support inspection teams, frequently with more than one inspector per NCAs.
   C) Need to spend more time on site/extend inspection duration.
   D) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	**Fees as proposed by the EC 13/12/22 (in EUR)**						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65

GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3

		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

Addendum to

Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council

- *Request for data for the targeted approach*

Following agreement in the policy debate at the meeting of the EPSCO Council (Health) of 14 March 2023 on a targeted approach and further to delegations' comments on the text of draft request, Member States have submitted further data collection in a targeted approach for adjustments of fees and renumeration for specific procedures, as well as a general adjustment.

Update fee codes

Referrals	Annex I, point 6	Was: 27 326 euro **Proposed: 85.000 EUR**	See Annex; based on medium hourly rates/procedure and realistic hourly rate

Data calculations - referrals:

The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).
Time data was collected from 13 NCAs on 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report. MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs.
Proposal to adjust the hourly rate: In the proposal of the EC an hourly rate of € 38,50 is used. The current hourly rate falls considerably short for the NCA to carry out the necessary tasks. A more feasible rate would be €120 per hour. To achieve the PhV referrals target proposal, the mean time would need to be increased by 30%, and the final rate would be calculated by multiplying the hourly rate of €120 with a sustainability-factor of 20%.

Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	**Annual fee** New fee and remuneration required	10% of suggested annual fee of CHMP-Rapp for PRAC-Rapp and 10% of suggested annual fee of CHMP-co-Rapp for PRAC-Rapp; Remains 90% of annual fee for CHMP-Rapp and 90% for the co-Rapp.	Covering PRAC Rapp activities such as signal assessments and assessment of RMP for variations
	New applications New fee and remuneration required	5% of suggested fee for new applications of CHMP-Rapp for PRAC-Rapp and 5% of suggested fee for new applications of CHMP-co-Rapp for PRAC-Rapp; Remains 95% of annual fee for CHMP-Rapp and 95% for the co-Rapp.	Covering PRAC Rapp activities such as assessment of RMP and PhV Plan for new applications

BELGIUM

We decided to share with you proposals that are the result of a coordinated re-calculation effort of the National Competent Authorities, in which Belgium took part.

The sustainability of our network fully depends on securing an agreement that benefits all. And the continued sustainable access to effective and safe medicines to all Europeans depends on it. To ensure this, a sustainability and inflation adjustment has been applied to our joint numbers across the categories. The sustainability adjustment reflects the tasks that are costly to the NCAs and necessary to perform each category task, yet are not a direct cost to the fee category. Actual cost of procedures are based on data that have been provided by a significant number of national competent authorities. NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate. This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- *Increase in complexity/innovative developments or methodologies.*
- *Increased involvement of senior assessor and external experts to cover the requested expertise.*
- *Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.*
- *Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts*
- *Increase burden of work subsequent to European priority actions*

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**

Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	See Annex; based on medium hourly rates/procedures
Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure
Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	See Annex; based on medium hourly rates/procedure

Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	See Annex; based on medium hourly rates/procedure
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration	No data provided.	No data provided.

Annex – Justification of Fee adjustments:

III. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

IV. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

8. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[3],[4]. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation, expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

9. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

10. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

[3] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[4] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

11. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

12. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

13. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to provide that service. With staff turnover this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can

fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

14. NCAs and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

10. Increase in complexity/innovative developments or methodologies.
11. Subsequently need to involve senior assessor and external experts to cover the requested expertise.
12. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
13. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.
14. Sustainability of the network.
15. Current limitation of human resources in NCA.
16. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.
17. Increase number of experts by SA level.
18. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice

The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.
The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.
There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice
Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).
Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.
In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:
a)

The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations addition of a new therapeutic indication or modification of an approved indication.
- For type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of renumeration for type II addition of therapeutic indication or modification.
- Decrease of renumeration for type II other.
- The Rapp no longer receives the renumeration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher renumeration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less then for type II addition of therapeutic indication or modification.
- Introducing an in-between level for “complex” type II variations (including complex quality variations) would require a definition of “complex”. It is doubtful whether a sufficiently distinct definition can be drawn up. For example a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCA expenses.
- The proposed lower renumeration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in renumeration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.

- No renumeration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the renumeration should be the same as the renumeration of the Rapp (and not dividing the renumeration between Rapp and Co-Rapp).
- The additional renumeration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced renumeration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same renumeration for each individual type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCA. Therefore no additional renumeration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more then one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the renumeration.
- Equal renumeration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching renumeration proposal.

Proposal for new fee proposal and data collection**:**

To keep the renumeration for type II variations simple and cost effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			**Sustainability factor**	**Proposal – adjusted**
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:
Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:
Targeted type of referrals : art. 20, art 31 and art. 107
In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.
This decrease is of public health concern because the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage adequate assessment, based on robust expertise?
The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:
The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).
Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.
MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs
The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20% that includes adjustment by inflation (for 2023 and 2024).

PSURs:
Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.
EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10 fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the propose update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC	Fee proposal- adjusted

Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.

The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).

The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(c) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.

Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).

Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the

fee is awarded per inspected product.

(d) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.

Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).

A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.

Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees

Hard data in relation to the proposal

See **appendix 1.1**

The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

3. Evidence of increased hours from the data gathering exercise.
4. Evidence that the fee does not cover the costs; costs estimation does not account for :
   E) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.
   F) Need to create/support inspection teams, frequently with more than one inspector per NCAs.
   G) Need to spend more time on site/extend inspection duration.
   H) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	**Fees as proposed by the EC 13/12/22 (in EUR)**						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65

GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3		**Fees as proposed by the EC 13/12/22**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

BE written comment on rolling review and on annexes

We would like to draw your attention to the following issue regarding the EMA fee regulation proposal: In annex 1 point 2.1.(b) a fee and renumeration are foreseen for 'an assessment on an ongoing basis', which, as the commission confirmed, is equivalent to a rolling review. The issue is that in the current proposal, there is no fee or renumeration for such a rolling review when it is followed by a market authorization application. Point 2.3 of annex 1 states the amounts of the fees and renumerations for the rolling review will be deducted from the respective fee and renumeration to NCAs for a marketing authorization application for the same product. This de facto means in case after a rolling review a marketing authorization application is submitted, the rolling review will be free of charge and without renumeration for the NCAs.

Given the extensive work, time investment and lever of expertise needed for these rolling reviews, we believe this is not acceptable. We are not opposed to the concept of rolling review; but to not have this procedure renumerated would be a threat to the sustainability of the network.

We will submit a written comment to the SE presidency and invite you to support this point during the next working party.

Written comments on 'Rolling review' - EMA Fee regulation proposal

Annex 1, point 2

2. Scientific opinions and assessments prior to potential submission of an application for a marketing authorisation

2.1. A fee of EUR 549 800 shall apply to any of the following:

(a) an opinion on a medicinal product for compassionate use pursuant to Article 83 of Regulation (EC) No 726/2004;

(b) a **rolling review of** ~~an assessment on an on-going basis of~~ data packages of particulars and documents submitted to the Agency by a prospective applicant prior to a formal submission of an application for a marketing authorisation falling within the scope of Regulation (EC) No 726/2004.

That fee shall cover all strengths, all pharmaceutical forms and all presentations submitted in the same application. The remuneration shall be EUR 153 000 for the rapporteur and EUR 143 300 for the co-rapporteur.

2.2. In the event of multiple submissions of data packages submitted by the same prospective applicant for the same product, the fee set out in point 2.1 (b) shall only be charged once.

2.3. The amounts set out in point 2.1 shall be **charged and payed on top of** ~~deducted from~~ the respective fee and ~~from~~ the remuneration to competent authorities of the Member States payable for a marketing authorisation application for the same product, where such application is submitted by the same applicant.

Argumentation

In annex 1 point 2.1.(b) a fee and renumeration are foreseen for 'an assessment on an ongoing basis', which, as the commission confirmed, is equivalent to a rolling review. The issue however is that in the current proposal, there is no fee or renumeration for such a rolling review in when it is followed by a market authorization application:

- Point 2.3 of annex 1 states the amounts of the fees and renumerations for the rolling review will be deducted from the respective fee and renumeration to NCAs for a marketing authorization application for the same product. This de facto means in case after a rolling review a marketing authorization application is submitted, the rolling review will be free of charge.

  In concrete terms this means the following: the rolling review fee for a company is €549800; when the company applies for a market authorization after this rolling review, the company will only pay the difference amount between the rolling review fee and the market application fee. In case of a market application for a new product with new active substance (3.1) which costs 684900 euros, the company pays a fee of (684900 minus 549800 euros) the residual amount of 135100 euro. The total fee for the company is always the market application fee. This seems to suggest an incentive through a fee waiver. Why is this incentive not covered by the EMA budget like the other reductions?

- The text seems to suggest that the same applies to renumerations for NCAs. In our reading the NCAs will not be renumerated for a rolling review in case the rolling review is followed by a market authorization application.

  In concrete terms, this means the following: the renumerations for a rolling review are 153000 euro and 143300 euro for the respective rapporteurs. The renumerations for a market authorization application (3.1) are 217300 euro and 189300 euro for the respective rapporteurs. When a market authorization application follows a rolling review, the renumeration for the respective rapporteurs will be (217300 euro minus 153000 euro) and (189300 euro minus 143300 euro). The total renumeration for the respective rapporteurs for a rolling review and a marketing authorization application for that same product will always be the market authorization application renumeration. This is very troublesome, as rolling reviews are very labour, time and expert intensive. It is not sustainable to not have this work renumerated.

Both the fee charged and the renumeration paid to an NCA for a rolling review should be charged and paid on top of the respective fee and renumeration for a marketing authorization application for the same product.

We also want to call for coherence with the upcoming pharma review. In the leaked document, more specifically in the draft regulation art. 6§2, a "phased review for medicinal products that are likely to offer an exceptional therapeutic advancement in the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Union with major contribution to patient care" is mentioned. Does this refer the concept of rolling review? And if so, is the this the procedure that the commission means to refer to in the fee regulation proposal?

Written comments on annexes - EMA Fee regulation proposal

Comment on Annex 3

We believe that the repartition of the annual fees should take into account rapporteurship for both CHMP rapporteur and PRAC rapporteur, and include a share for the HMA/network for the financing of the HMA network activities.

Proposal to amend annex 3

4 (new). Annual fee for non-procedure related activities at EU level conducted by Competent Authorities

4.1. **For medicinal products for human use authorised in accordance with Directive 2001/83/EC, a fee of EUR XX per chargeable unit-human, shall apply once per**

year to cover non-procedure related activities at EU level conducted by Competent Authorities.

4.2. **For veterinary medicinal products authorised by competent authorities of the Member States in accordance with Chapter III, Sections 2 to 5 of Regulation (EU) 2019/6, a fee of EUR XX per chargeable unit-veterinary shall apply once per year to cover non-procedure related activities at EU level conducted by Competent Authorities.**

4.3. **The total payable amount of the annual fees referred to in points 4.1 and 4.2 for each marketing authorisation holder shall be calculated by the Agency on the basis of the number of chargeable units-human and chargeable units-veterinary, respectively, which correspond to the information recorded on 1 July of each year.**

4.4. **The annual fees referred to in points 4.1 and 4.2 shall be due on 1 July of every year and shall cover the period from 1 January to 31 December of that calendar year.**

4.5. **The remuneration shall be calculated on a yearly basis based on the participation of the receiving national competent authorities in non-procedure related activities in the context of EU level activities.**

Rationale

In the current proposal, non-procedure related activities on EU level such as active participation in and member ship of committees, working parties, projects and other, are not renumerated. We therefore propose a separate annual fee to renumerate these activities, based on the chargeable units.

Proposal to amend annex 5

5. Applications relating to core dossier medicinal products to be used in a human pandemic situation

The payment of the fee for an application for a marketing authorisation of a medicinal product to be used in a human pandemic situation shall be deferred until the pandemic situation is duly recognised, either by the World Health Organisation or by the Union in accordance with **Regulation (EU) 2022/2371** ~~Decision No 1082/2013/EU~~.

Such deferral shall not exceed 5 years.

In addition to the deferral provided for in point 2.1, for regulatory activities within the framework of the submission of a core dossier for a **pandemic** **treatments and vaccines** ~~influenza vaccine~~ and the follow-up submission of a pandemic variation, a fee reduction of 100 % shall apply in the following cases:

(a) pre-submission activities pursuant to section 9 of Annex IV;

(b) scientific advice pursuant to section 1 of Annex I;

(c) extension of marketing authorisation pursuant to section 4 of Annex I;

(d) major type-II variation pursuant to section 5 of Annex I;

(e) annual fee pursuant to section 1 of Annex III.

Those reductions shall apply until the human pandemic situation is duly recognised.

Where reductions apply pursuant to point 2.2, no remuneration shall be paid to the national competent authorities for the annual fees referred to in point 2.2(e).

Rationale

In §1.1, the relevant legislation should be the regulation on cross-border health treats that repeals the decision that was mentioned

In §1.2, there is no reason to limit to 'influenza' or to vaccines.

Proposal for adding a point in annex 5

9 (New). Fee reduction for products addressing unmet medical needs according to [article 73 of revised directive 2001/83/EC] and antimicrobial resistance as referred to in [article 40 of revised regulation 726/2004].

A 50 % fee reduction shall apply to products adressing a unmet medical need according to [revised directive 2001/83/EC (article 73)] for the following services:

a) initial marketing authorisation application pursuant to section 3 of Annex I, to this Regulation;
b) pre-authorisation inspection pursuant to section 1 of Annex IV, to this Regulation;
c) extension of a marketing authorisation pursuant to section 4 of Annex I, to this Regulation, in the first year from granting of the marketing authorisation;
d) major type-II variation pursuant to section 5 of Annex I, to this Regulation, in the first year from granting of a marketing authorisation;
e) annual fee pursuant to section 1 of Annex III, to this Regulation, in the first year from granting of a marketing authorisation;
f) post-authorisation inspection pursuant to section 1 of Annex IV, to this Regulation, in the first year from granting of a marketing authorisation.

Rationale

We support incentives that are needs-based, rather than product based, producer based, or technology based.

CROATIA

Contribution by Croatian Delegation on the Annexes of the

Proposal for a Regulation of the European Parliament and of the Council on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council

At the outset Croatia welcomes, and in principle supports, the adoption of the *Regulation of the European Parliament and of the Council on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council (Proposal for EMA Fees Regulation),* which aims to ensure a comprehensive list of all fees that are charged to the marketing authorization holders for centralized procedure and remuneration for MS for their contribution in this activity.

Following the agreement in the policy debate at the meeting of the EPSCO Council (Health) of 14 March 2023 on a targeted approach, and the formal request from the Presidency set in the document ST 7501/23 from 16 March 2023 regarding the data collection for the targeted approach in adjusting fees and remuneration, please find Croatian contribution below.

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	See Annex; based on medium hourly rates/procedures
Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure
Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure

Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	See Annex; based on medium hourly rates/procedure
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	See Annex; based on medium hourly rates/procedure
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration	No data provided.	No data provided.

Annex – Justification of Fee adjustments:

V. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

VI. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

15. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[5],[6]. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation, expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

16. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

17. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

[5] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[6] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

18. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

19. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

20. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to provide that service. With staff turnover this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can

fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

21. NCAs and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

19. Increase in complexity/innovative developments or methodologies.
20. Subsequently need to involve senior assessor and external experts to cover the requested expertise.
21. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
22. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.
23. Sustainability of the network.
24. Current limitation of human resources in NCA.
25. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.
26. Increase number of experts by SA level.
27. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice

The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.
The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.
There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice
Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).
Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.
In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:
a)

The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations addition of a new therapeutic indication or modification of an approved indication.
- For type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of renumeration for type II addition of therapeutic indication or modification.
- Decrease of renumeration for type II other.
- The Rapp no longer receives the renumeration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher renumeration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less then for type II addition of therapeutic indication or modification.
- Introducing an in-between level for “complex” type II variations (including complex quality variations) would require a definition of “complex”. It is doubtful whether a sufficiently distinct definition can be drawn up. For example a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCA expenses.
- The proposed lower renumeration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in renumeration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.

- No renumeration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the renumeration should be the same as the renumeration of the Rapp (and not dividing the renumeration between Rapp and Co-Rapp).
- The additional renumeration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced renumeration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same renumeration for each individual type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCA. Therefore no additional renumeration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more then one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the renumeration.
- Equal renumeration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching renumeration proposal.

Proposal for new fee proposal and data collection**:**

To keep the renumeration for type II variations simple and cost effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			**Sustainability factor**	**Proposal – adjusted**
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:
Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:
Targeted type of referrals : art. 20, art 31 and art. 107
In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.
This decrease is of public health concern because the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage adequate assessment, based on robust expertise?
The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:
The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).
Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.
MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs
The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20% that includes adjustment by inflation (for 2023 and 2024).

PSURs:
Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.
EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10 fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the propose update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC	Fee proposal- adjusted

Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.

The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).

The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(e) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.

Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).

Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the

fee is awarded per inspected product.

(f) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.

Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).

A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.

Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees

Hard data in relation to the proposal

See **appendix 1.1**

The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

5. Evidence of increased hours from the data gathering exercise.
6. Evidence that the fee does not cover the costs; costs estimation does not account for :
   I) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.
   J) Need to create/support inspection teams, frequently with more than one inspector per NCAs.
   K) Need to spend more time on site/extend inspection duration.
   L) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	**Fees as proposed by the EC 13/12/22 (in EUR)**						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65
GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)

Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

CZECHIA

Request for data for the targeted approach - Czechia			
General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration			CZ does not propose any general adjustment for the NCA remuneration, however CZ requests wording in the Regulation with fixed scale of fees in remuneration of the services of rapporteurs, co-rapporteurs and experts within the main text of the Regulation (e.g., **half** of the fees paid to the Agency is allocated to the assessment teams)
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	As CZ has limited experience with full SA assessment, no adjustment is suggested.	Average time spent: 64 hours (*Note: CZ does not have full SAWP member and provides only limited assessment – for quality part of Scientific Advice only, since 2022*)
Generics	Annex I, point 3.6 & 3.8	70 600 EUR	Average time spent: Quality part: 320 hours Clinical, non-clinical: 130 hours In total: 450 hours
Type II variations	Annex I, point 5	No need for adjustment	Average time spent: 120 hours (time may differ depending on whether it is a Quality Variation

			or Clinical Variation), also involvement in case of PRAC lead type II variation (45 hours)
Referrals	Annex I, point 6	63 575 EUR	Average time spent: 576 hours
Periodic Safety Update Reports (PSURs)	Annex I, point 14	No need for adjustment	No need for adjustment in case of new fee and remuneration PRAC Rapporteurship.
Inspections	Annex IV, point 1	No need for adjustment	Only GMP inspections outside the Union are considered as CZ has limited or no experience with other types of inspections.
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration required	There is need to clarify, what activities should be covered by this new fee	There is need to distinguish between initial involvement of PRAC Rapp into Marketing Authorisation Application and post-authorisation involvement 222h/1 PRAC Rapp CAP Marketing Authorisation assessment 35h/ PRAC Rapp assessments of 1 CAP/1 year - other than initial MA (MEA (Additional pharmacovigilance activity in the risk-management plan), PAM (Post-authorisation measures), signal, ESI (Emerging safety issue), summary safety reports...)

CYPRUS

Procedure	Article	General adjustment for all procedures (%)	Total remuneration to NCAs (incl. general adjustment)	Justification
Scientific Advice	Annex I, point 1	20%	1.1.:12480 1.2.: 7800 1.3.: 6360	The euro had an average inflation rate of 2.60% per year between 2016 and today, producing a cumulative price increase of 19.69%. Therefore, it should be considered that a round up to 20% on the fees levied by EMA is logical across the board.
Generics	Annex I, point 3.6 & 3.8	20%	3.6.: 48240 3.8.: 8160 & 1200	See above
Type II variations	Annex I, point 5		5.1.: 35280 & 35280 5.2.: 8160 5.3.: See 5.1. & 5.2. 5.4.: See 5.1. & 5.2.	See above
Referrals	Annex I, point 6	20%	6.1.: 14880 & 14880 6.2.: 18360 & 18360 6.3.: 3360 &3360 6.4.: 8160 & 8160 6.5.: 14880 & 14880 6.6: 21000 & 21000 6.7.1.: 21000 & 21000 6.7.2.: 31560 & 31560 6.7.3.: 38400 & 38400	See above

			6.7.4.: 52080 & 52080	
Periodic Safety Update Reports (PSURs)	Annex I, point 14	20%	14.1.: 15480	See above
Inspections	Annex IV, point 1	20%	1.1.1.: 10320 & 6240 1.1.2.: 18720 & 11280 1.1.3.: 17640 & 10920 1.1.4.: 23520 & 12480 1.1.5.: 16080 & 9840 1.1.6.: 16080 & 9840 1.1.7.: 15840 & 10440 1.1.8: 19440 & 12120	See above
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration required		200000 (EMA) & 30000 (Rap) & 20000 (Co-Rap)	It is suggested that the fees and renumerations levied is proportional to Section 6.7 of Annex I

DENMARK

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	See Annex; based on medium hourly rates/procedures

Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure
Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	See Annex; based on medium hourly rates/procedure
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	See Annex; based on medium hourly rates/procedure
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration	No data provided.	No data provided.

Annex – Justification of Fee adjustments:

VII. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

VIII. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

22. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[7],[8]. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation, expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

23. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

24. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

[7] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[8] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

25. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

26. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

27. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to provide that service. With staff turnover this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can

fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

28. NCAs and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

28. Increase in complexity/innovative developments or methodologies.
29. Subsequently need to involve senior assessor and external experts to cover the requested expertise.
30. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
31. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.
32. Sustainability of the network.
33. Current limitation of human resources in NCA.
34. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.
35. Increase number of experts by SA level.
36. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice

The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.
The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.
There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice
Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).
Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.
In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:
a)

The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations addition of a new therapeutic indication or modification of an approved indication.
- For type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of renumeration for type II addition of therapeutic indication or modification.
- Decrease of renumeration for type II other.
- The Rapp no longer receives the renumeration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher renumeration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less then for type II addition of therapeutic indication or modification.
- Introducing an in-between level for “complex” type II variations (including complex quality variations) would require a definition of “complex”. It is doubtful whether a sufficiently distinct definition can be drawn up. For example a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCA expenses.
- The proposed lower renumeration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in renumeration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.

- No renumeration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the renumeration should be the same as the renumeration of the Rapp (and not dividing the renumeration between Rapp and Co-Rapp).
- The additional renumeration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced renumeration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same renumeration for each individual type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCA. Therefore no additional renumeration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more then one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the renumeration.
- Equal renumeration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching renumeration proposal.

Proposal for new fee proposal and data collection**:**

To keep the renumeration for type II variations simple and cost effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			**Sustainability factor**	**Proposal – adjusted**
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:
Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:
Targeted type of referrals : art. 20, art 31 and art. 107
In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.
This decrease is of public health concern because the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage adequate assessment, based on robust expertise?
The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:
The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).
Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.
MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs
The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20% that includes adjustment by inflation (for 2023 and 2024).

PSURs:
Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.
EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10 fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the propose update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC	Fee proposal- adjusted

Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.

The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).

The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(g) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.

Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).

Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the

fee is awarded per inspected product.

(h) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.

Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).

A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.

Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees

Hard data in relation to the proposal

See **appendix 1.1**

The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

7. Evidence of increased hours from the data gathering exercise.
8. Evidence that the fee does not cover the costs; costs estimation does not account for :
   M) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.
   N) Need to create/support inspection teams, frequently with more than one inspector per NCAs.
   O) Need to spend more time on site/extend inspection duration.
   P) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	**Fees as proposed by the EC 13/12/22 (in EUR)**						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51

GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65
GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3

		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

FINLAND

FINLAND'S COMMENTS ON EMA FEES PROPOSAL

Inflation adjustment
In 2022, European inflation was 9.1%, which also has an impact on the increase in the salary level of the personnel and thus also on the costs arising of the work. For this reason, it is desirable that changes in the cost level should be taken into account in the pricing often enough so the costs arising of the work correspond to the reality.

The seven procedures identified for the targeted approach (and confirmed at the meeting of the Working Party on 20 February 2023) are as follows:
- Scientific Advice (Annex I, point 1)
With the new proposed fees, the cost recovery rate of scientific advice would fall significantly below 100%, in which case the expenses arising from scientific advice would be almost EUR 0.5 million higher than the income if we use data of year 2021. In the proposal, the new annual fees improve the cost recovery, but not enough and the cost recovery remains below 50%. Revenues of scientific advice and annul fees are important for the agency because they make up almost half of the income of the centralized procedure.
The tailored scientific advice procedure (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance#scientific-advice-on-biosimilars-section) is based on a detailed review of the quality, analytical and functional data followed by multidisciplinary considerations on the impact of the quality data on the (non-)clinical program. Due to the more extensive and detailed regulatory review conducted as part of the tailored scientific advice, an extra month has been added into the timetable as compared to a standard scientific advice. The higher resource demand for the tailored scientific advice procedure should be acknowledged and consequently the fee should be higher than for standard scientific advices.

- Generics (Annex I, point 3.6 & 3.8)
NA
- Type II variations (Annex I, point 5)
For indication extensions (major type II variation) the renumeration should be split 60% for the Rapp and 40% for the Co-Rapp (reflecting the actual amount of work).
Some of the type II variations may be very laborious. Suggestion: the fee should be higher for MAHs, and thereafter the renumeration should be higher for the Rapporteur in the following cases (details to be formulated): **major complex quality variation, clinical variation affecting posology section of the SmPC**. *The fee could be e.g. 40% of the current fee (currently EUR 70 600; revision into EUR 28000, out of which 21 000 for the Rapp, and 7000 for EMA (EMA-part as currently suggested).*

- Referrals (Annex I, point 6)
The work for Art 5(3) referral may be very laborious for Rapporteurs (various topics, like hypothesis of Pandemrix and narcolepsy. The fee proposal for Rapporteurs seems very small related to workload.
Art 30-31: Article 30 and 31 on referrals fees have been reduced by 68% and 36% respectively, notwithstanding an increase to overall fee of 65% and 132%. This means that the NCA fees are only between 10% and 13% of the total fee. Referrals are hugely resource and time intensive and were always a "loss making activity". These reduced fees will discourage triggering / acting as a Rapp on a referral which could undermine the supervision of products on the EU market.
Art 20: This may be very laborious task as well and also in this case NCA-fee seems very low.

- Periodic safety update reports (PSURS) (Annex I, point 14)
NA
- Inspections (Annex IV, point 1)
The inspection fee increases in the proposed Regulation are welcome and crucial for NCAs to ascertain necessary inspection resources at NCAs. In addition to the inspection fee increase, it is crucial to ascertain that the basis of inspection fees remain the same as currently. This is not visible in the proposed regulation.
Currently, the GMP inspection fees for leading and supporting NCA is based on number of activities performed by the inspected pharmaceutical company i.e. how complex manufacturing or analyses the site performs, and how many CAP medicines of active substances the site manufactures. Therefore, more complex GMP inspections result typically 4- or 6-times of the basic inspection fees. For NCAs, and to ascertain sufficient GMP inspection resources in NCAs, this difference in fees is crucial. The current basis of CAP inspection fees is included in the following link:
https://www.ema.europa.eu/en/documents/win/work-instructions-calculation-fees-good-manufacturing-practice-product-related-inspections_en.pdf

- Pharmacovigilance Risk Assessment Committee (PRAC) rapporteur ship (new fee and remuneration required)
New fee proposal can be supported as long as it does not negatively change / impact current rapporteur/co rapp. fee structure.

Finland supports the result of a coordinated re-calculation effort of the National Competent Authorities, in which Finland took part also.

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	See Annex; based on medium hourly rates/procedures

Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure
Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	See Annex; based on medium hourly rates/procedure
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	See Annex; based on medium hourly rates/procedure
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration	No data provided.	No data provided.

Annex – Justification of Fee adjustments:

IX. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

X. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

29. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[9],[10]. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation, expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

30. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

31. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

[9] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[10] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

32. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

33. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

34. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to provide that service. With staff turnover this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can

fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

35. NCAs and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

37. Increase in complexity/innovative developments or methodologies.

38. Subsequently need to involve senior assessor and external experts to cover the requested expertise.

39. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.

40. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.

41. Sustainability of the network.

42. Current limitation of human resources in NCA.

43. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.

44. Increase number of experts by SA level.

45. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice

The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.
The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.
There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice
Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).
Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.
In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:
a)

The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations addition of a new therapeutic indication or modification of an approved indication.
- For type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of renumeration for type II addition of therapeutic indication or modification.
- Decrease of renumeration for type II other.
- The Rapp no longer receives the renumeration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher renumeration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less then for type II addition of therapeutic indication or modification.
- Introducing an in-between level for “complex” type II variations (including complex quality variations) would require a definition of “complex”. It is doubtful whether a sufficiently distinct definition can be drawn up. For example a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCA expenses.
- The proposed lower renumeration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in renumeration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.

- No renumeration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the renumeration should be the same as the renumeration of the Rapp (and not dividing the renumeration between Rapp and Co-Rapp).
- The additional renumeration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced renumeration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same renumeration for each individual type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCA. Therefore no additional renumeration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more then one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the renumeration.
- Equal renumeration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching renumeration proposal.

Proposal for new fee proposal and data collection**:**

To keep the renumeration for type II variations simple and cost effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			**Sustainability factor**	**Proposal – adjusted**
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:
Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:
Targeted type of referrals : art. 20, art 31 and art. 107
In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.
This decrease is of public health concern because the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage adequate assessment, based on robust expertise?
The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:
The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).
Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.
MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs
The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20% that includes adjustment by inflation (for 2023 and 2024).

PSURs:
Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.
EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10 fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the propose update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC	Fee proposal- adjusted

Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.

The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).

The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(i) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.

Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).

Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the

fee is awarded per inspected product.

(j) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.

Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).

A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.

Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees

Hard data in relation to the proposal

See **appendix 1.1**

The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

9. Evidence of increased hours from the data gathering exercise.

10. Evidence that the fee does not cover the costs; costs estimation does not account for :

Q) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.

R) Need to create/support inspection teams, frequently with more than one inspector per NCAs.

S) Need to spend more time on site/extend inspection duration.

T) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	**Fees as proposed by the EC 13/12/22 (in EUR)**						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65

GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3

		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

FRANCE

General adjustment for all procedures			
		Adjustment (%)	
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR) Network average proposal**	**Coûts estimés FR (incl. general adjustment) (EUR)**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	Level I: 9300 EUR Level II: 11 400 EUR Level III: 18 240 EUR
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 97 244 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	Pas de données FR disponibles
Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	Indic ext: 26 310 EUR Other: 6 790 EUR

Referrals	Annex I, point 6	27330 EUR	Pas de données FR disponibles
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	12 120 EUR
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	GMP : Leading/supporting 7 920 EUR GCP : Leading : 48 240 EUR/ Supporting : 25 990 EUR Pas de données disponibles
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration required		?

Annex – Justification of Fee adjustments:

XI. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

XII. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

36. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[11],[12]. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation, expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

37. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

38. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

[11] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[12] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

39. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

40. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

41. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to provide that service. With staff turnover this is an ongoing investment required by the NCAs

to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

42. NCAs and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

46. Increase in complexity/innovative developments or methodologies.

47. Subsequently need to involve senior assessor and external experts to cover the requested expertise.

48. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.

49. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.

50. Sustainability of the network.

51. Current limitation of human resources in NCA.

52. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.

53. Increase number of experts by SA level.

54. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the

ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice
The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.
The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.
There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice
Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).
Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.
In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **97 244 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:
a)

The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed.

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR

Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations addition of a new therapeutic indication or modification of an approved indication.
- For type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of renumeration for type II addition of therapeutic indication or modification.
- Decrease of renumeration for type II other.
- The Rapp no longer receives the renumeration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher renumeration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less then for type II addition of therapeutic indication or modification.
- Introducing an in-between level for “complex” type II variations (including complex quality variations) would require a definition of “complex”. It is doubtful whether a sufficiently distinct definition can be drawn up. For example a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCA expenses.

- The proposed lower renumeration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in renumeration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.
- No renumeration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the renumeration should be the same as the renumeration of the Rapp (and not dividing the renumeration between Rapp and Co-Rapp).
- The additional renumeration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced renumeration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same renumeration for each individual type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCA. Therefore no additional renumeration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more then one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the renumeration.
- Equal renumeration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching renumeration proposal.

Proposal for new fee proposal and data collection**:**

To keep the renumeration for type II variations simple and cost effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			**Sustainability factor**	**Proposal – adjusted**
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:

Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27.330 EUR**

Background and Justification:
The proposal is based on the average of time data (hours) representing 48 referrals between 2017 and 2022.

PSURs:

Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.

EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10 fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the propose update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC			**Fee proposal- adjusted**		
Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.
The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).
The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(k) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.
Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.
Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).
Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the fee is awarded per inspected product.

(l) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.
Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction

of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).
A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network
There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.
Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.
It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees
Hard data in relation to the proposal
See **appendix 1.1**
The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

11. Evidence of increased hours from the data gathering exercise.
12. Evidence that the fee does not cover the costs; costs estimation does not account for :
   U) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.
   V) Need to create/support inspection teams, frequently with more than one inspector per NCAs.
   W) Need to spend more time on site/extend inspection duration.
   X) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	Fees as proposed by the EC 13/12/22 (in EUR)						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65

GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3

		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

GERMANY

Current costs of the NCA procedures - DE

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	See Annex; based on medium hourly rates/procedures
Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure

Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	See Annex; based on medium hourly rates/procedure
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	See Annex; based on medium hourly rates/procedure
Pharmacovigilance Risk Assessment Committee	New fee and remuneration		

These data are equivalent to the data and calculations shared and performed by NCA experts in the HMA.

Annex – Justification of Fee adjustments:

XIII. General adjustment for the NCA remuneration – for all procedures:

The costs submitted for the general adjustment represent the situation in 2022. The increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when this regulation will come into force probably in 2024, an adjustment for inflation for the years 2023 and 2024 will be necessary.

The following factors have led to an increase in the average cost of procedures since 2016 for DE:

1. Increase in complexity/innovative developments or methodologies.
2. Increased involvement of senior assessors and external experts to cover the requested expertise.
3. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
4. Current limitation of human resources and involvement of external experts.
5. Increase burden of work subsequent to European priority actions.

XIV. Targeted approach for the chosen procedures:

II.1. Procedure Scientific Advice - Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully pass the regulatory process. Statistics show a higher success rate for marketing authorization applications (MAAs) where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients. Furthermore, SA benefits industry and may save unnecessary expenditure by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered and the importance of that service. The reduced fees in the EC proposal would put the sustainability of the network at risk. EFPIA in its response to the published proposed fee regulation expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

The following factors have led to an increase in the average cost of SA procedures for DE since

2016:

55. Increase in complexity/innovative developments or methodologies (Advanced Therapy Medicinal Products (ATMP), personalised medicine, orphan diseases, mRNA technology, therapeutic allergens, novel application forms, use of AI in product research & development etc.).
56. Subsequent need to involve senior assessors and external experts to cover the requested expertise, to increase number of experts by SA level.
57. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advice involving upcoming scientific developments.
58. Increase burden of work subsequent to European priority actions aiming at reinforcing the scientific advice system also in coordination with clinical trials approval/design.
59. Current limitation of human resources.

II.2. Procedure Generics - Annex I, point 3.6 & 3.8:

Fee proposal by EC	Fee proposal - adjusted
141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

The following factors have led to an increase in the average cost of procedures for DE since 2016:

1. Stronger focus on new market trends and innovation of generica manufacturers.
2. Subsequently need to involve senior assessor and external experts to cover the requested expertise.
3. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees.

II.3. Type II variations - Annex I, point 5:

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the EC proposal. Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the EC proposal.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

To keep the renumeration for type II variations simple and cost effective, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (5.1 and 5.2 of Annex I to the EC proposal) should both be increased in order to cover expenses. Based on the average hours spent and the average hourly rate, the renumeration should be increased as stated above. The general adjustment of 1.2 (+20 %) is included.

II.4. Pharmacovigilance: Referrals - Annex I, point 6 // PSURs - Annex I, point 14:

Referrals:

Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:

In the EC proposal the fee for NCAs will strongly decrease: more than 3-fold from 67 145 euros today to 17 500 euros. This decrease is of public health concern owing to the risk that EMA will not find rapporteurs among Member States since the work is not sufficiently paid.

The following factors have led to an increase in the average cost of procedures for DE since 2016:

1. Increase in complexity/innovative developments or methodologies.
2. Subsequent need to involve senior assessor and external experts to cover the requested expertise.
3. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees.

PSURs:

Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products with new technology implies that assessment capacity needs to be developed and updated. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available with different areas of expertise depending on the nature of a certain risk.

Various activities are required and need to be compensated for, for example:

- Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC
  -> CMDh or PRAC -> CHMP.
- EMA funded studies regarding the impact of PhV measures requiring Rapporteur assessment and preparation of the presentation at PRAC.
- costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h).

II.5. Inspections (GMP, GCP and PMF inspections outside EU) - Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Fee proposal by EC:

	Fee proposal by EC		
Inspection	EMA fee (total)	Leading	Supporting
GMP	37 800 EUR	15 600	9 400
GCP	44 200 EUR	19 600	10 400
PMF	36 100 EUR	13 400	8 200

Fee proposal – adjusted:

	Fee proposal- adjusted		
Inspection	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

Costs of providing the service

(m)Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials. Inspections are labour intensive. The actual inspection is performed by an inspection team traveling to one or several sites and includes a range of activities from planning, travel to various stages of elaboration of the report. In case of a negative outcome, the process becomes more complex and the inspectors' work increases significantly.

Inspections of particular complexity (in terms of products or dosage forms and/or large sites) regularely require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time has not been considered in the current proposal.

(n) Indirect costs

Building a qualified inspection workforce is costly in terms of time and resources. As per EU requirements inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme on scientific or regulatory developments is in place.

Some particular products such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training.

An increase in inspection fees is needed due to increased hours from the data gathering exercise. The fee in the EC proposal does not cover the costs; costs estimation does not account for:

1. Need to create/support (larger) inspection teams, frequently with more than one inspector per NCA.
2. Senior inspection costs versus average scientific salaried.
3. Need to spend more time on site/extend inspection duration.
4. Inspector mentoring, training and qualification.
5. Increased inflation rate.

HUNGARY

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	See Annex; based on medium hourly rates/procedures
Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure

Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	See Annex; based on medium hourly rates/procedure
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	See Annex; based on medium hourly rates/procedure
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration		

Annex – Justification of Fee adjustments:

XV. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

XVI. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

43. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[13],[14]. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation, expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

44. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

45. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- additionally, the amount of information covered by briefing books and attached

[13] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[14] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

documents also significantly increased over time.

46. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

47. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

48. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to

provide that service. With staff turnover this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

49. NCAs and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

60. Increase in complexity/innovative developments or methodologies.
61. Subsequently need to involve senior assessor and external experts to cover the requested expertise.
62. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
63. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.
64. Sustainability of the network.
65. Current limitation of human resources in NCA.
66. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.
67. Increase number of experts by SA level.
68. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice
The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.
The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.
There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice
Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).
Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.
In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:
a)

The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations addition of a new therapeutic indication or modification of an approved indication.
- For type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of renumeration for type II addition of therapeutic indication or modification.
- Decrease of renumeration for type II other.
- The Rapp no longer receives the renumeration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher renumeration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less then for type II addition of therapeutic indication or modification.
- Introducing an in-between level for “complex” type II variations (including complex quality variations) would require a definition of “complex”. It is doubtful whether a sufficiently distinct definition can be drawn up. For example a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCA expenses.
- The proposed lower renumeration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in renumeration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.

- No renumeration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the renumeration should be the same as the renumeration of the Rapp (and not dividing the renumeration between Rapp and Co-Rapp).
- The additional renumeration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced renumeration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same renumeration for each individual type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCA. Therefore no additional renumeration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more then one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the renumeration.
- Equal renumeration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching renumeration proposal.

Proposal for new fee proposal and data collection**:**

To keep the renumeration for type II variations simple and cost effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			Sustainability factor	Proposal – adjusted
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:

Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:
Targeted type of referrals : art. 20, art 31 and art. 107
In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.
This decrease is of public health concern because the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage adequate assessment, based on robust expertise?
The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:
The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).
Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.
MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs
The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20% that includes adjustment by inflation (for 2023 and 2024).

PSURs:
Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise.

Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.
EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10 fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the propose update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC	Fee proposal- adjusted

Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.

The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).

The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(o) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.

Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).

Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the

fee is awarded per inspected product.

(p) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.

Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).

A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.

Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees

Hard data in relation to the proposal

See **appendix 1.1**

The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

13. Evidence of increased hours from the data gathering exercise.

14. Evidence that the fee does not cover the costs; costs estimation does not account for :

Y) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.

Z) Need to create/support inspection teams, frequently with more than one inspector per NCAs.

AA) Need to spend more time on site/extend inspection duration.

BB) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	**Fees as proposed by the EC 13/12/22 (in EUR)**						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65
GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

IRELAND

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	See Annex; based on medium hourly rates/procedures
Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure

Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	See Annex; based on medium hourly rates/procedure
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	See Annex; based on medium hourly rates/procedure
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration	No data provided.	No data provided.

Annex – Justification of Fee adjustments:

XVII. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

XVIII. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

50. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[15],[16]. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation, expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

51. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

52. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

[15] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[16] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

53. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

54. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

55. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to provide that service. With staff turnover this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can

fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

56. NCAs and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

69. Increase in complexity/innovative developments or methodologies.

70. Subsequently need to involve senior assessor and external experts to cover the requested expertise.

71. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.

72. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.

73. Sustainability of the network.

74. Current limitation of human resources in NCA.

75. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.

76. Increase number of experts by SA level.

77. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice

The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.
The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.
There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice
Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).
Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.
In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

View of EFPIA

It should be noticed that the innovator industry recognize the importance of Scientific advice and the need for the NCAs to be properly remunerated.

Extract from EFPIA response to the new Regulation

"EFPIA members are concerned that NCA remuneration for the SA procedure will significantly decrease in real terms. This decrease is being implemented at a time when the resources and capacity of the EU Network are under significant strain, and at a time when companies are experiencing delays and other challenges (such as obtaining in a timely manner further or additional clarification of scientific advice, especially when it is received in writing only) in SA procedures. The proposed reduction is significant, with fees for a single SA procedure reduced by 20 to 40%. The distribution to an NCA for its participation in an SA procedure will also decrease proportionally compared to some other NCA supported activities (e.g., serving as MAA Rapporteur). This could function as an unintentional deterrent for NCAs' contributions to SA, and thus could exacerbate an already significant challenge, lessen opportunities for continued development of cutting-edge scientific expertise within NCAs, and ultimately have a chilling effect on the support for R&D in Europe. As such, we strongly urge the EC to confirm that the fee and remuneration genuinely reflect the actual costs for NCA participation. "

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:

a)

While the EC proposal does not apply a county co-efficient to fees at the point of payment, the initial calculations of the fees embedded a country co-efficient into the proposed fee by weighting the cost of the procedure with the countries that predominantly carried out the procedure. . This therefore does not reflect the reality where countries with high costs carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations addition of a new therapeutic indication or modification of an approved indication.
- For type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of renumeration for type II addition of therapeutic indication or modification.
- Decrease of renumeration for type II other.

- The Rapp no longer receives the renumeration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher renumeration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less then for type II addition of therapeutic indication or modification.
- Introducing an in-between level for "complex" type II variations (including complex quality variations) would require a definition of "complex". It is doubtful whether a sufficiently distinct definition can be drawn up. For example a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCA expenses.
- The proposed lower renumeration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in renumeration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.
- No renumeration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the renumeration should be the same as the renumeration of the Rapp (and not dividing the renumeration between Rapp and Co-Rapp).
- The additional renumeration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced renumeration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same renumeration for each individual type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCA. Therefore no additional renumeration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more then one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the renumeration.
- Equal renumeration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching renumeration proposal.

Proposal for new fee proposal and data collection**:**

To keep the renumeration for type II variations simple and cost effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the renumeration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			Sustainability factor	Proposal – adjusted
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

An alternative compromise proposal (IE)

The fees as proposed by the Commission are maintained (or substantially maintained), but the definition of the fee attracting the higher fee is extended beyond new indications to include other complex type II variations. By reference to the variation's regulation, the following variations could be considered "complex" type II variations and attract the higher fee:

APPENDIX I LIST OF COMPLEX VARIATIONS The following are classified as complex variations: Quality Changes – I Active Substance B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier b) Introduction of a new manufacturer of the active substance that is supported by an ASMF. c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability. d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk. B.I.a.2 Changes in the manufacturing process of the active substance b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product. B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning: a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures. b) Test procedures for starting materials/reagents/intermediates and/or the active substance. B.I.e.2 Introduction of a post approval change management protocol related to the active substance HPRA Guide to Fees for Human Products FIN-G0002-30 33/34 Quality Changes – II Finished Product B.II.a.3 Changes in the composition (excipients) of the finished product b) Other excipients. 2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product. 4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk. 5. Change that is supported by a bioequivalence study. B.II.a.5 Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product. B.II.c.3 Change in source of an excipient or reagent with TSE risk b) Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability. B.II.d.3 Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.e.1 Change in immediate packaging of the finished product b) Type of container or addition of a new container. 2. Sterile medicinal products and biological/immunological medicinal products. B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, excluding biologicals, concerning: a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures. b) Test procedures for

excipients/intermediates and/or the finished product. B.II.g.2 Introduction of a post approval change management protocol related to the finished product HPRA Guide to Fees for Human Products FIN-G0002-30 34/34 Safety, Efficacy and Pharmacovigilance changes C.I.4 Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data – SmPC sections 4.2, 4.3 or 5.1. One complex fee is charged if the additional changes applied for are consequential to the main change. C.I.6 Change(s) to therapeutic indication(s) a) Addition of a new therapeutic indication or modification of an approved one. (Note: complex fee not charged for a modification)

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:

Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:

Targeted type of referrals : art. 20, art 31 and art. 107

In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.

This decrease is of public health concern because the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage adequate assessment, based on robust expertise?

The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:

The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).

Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.

MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs

The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20% that includes adjustment by inflation (for 2023 and 2024).

PSURs:
Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.
EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10 fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the propose update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third

countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC			**Fee proposal- adjusted**		
Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal
It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.
The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).
The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(q) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.
Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases

significantly.
Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).
Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the fee is awarded per inspected product.

(r) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.
Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).
A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.
Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees
Hard data in relation to the proposal
See **appendix 1.1**
The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

15. Evidence of increased hours from the data gathering exercise.
16. Evidence that the fee does not cover the costs; costs estimation does not account for :
CC) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.
DD) Need to create/support inspection teams, frequently with more than one inspector per NCAs.
EE) Need to spend more time on site/extend inspection duration.
FF) Increased inflation versus those used in the Rand modelling.
Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	**Fees as proposed by the EC 13/12/22 (in EUR)**						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39

GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65
GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3

		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

ITALY

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		+20%	See Annex; including sustainability aspects - inflation, increased complexity since data gathering in 2016
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	Exercise not performed
Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	See Annex; based on medium hours & hourly rates/procedure

Referrals	Annex I, point 6	27 326 EUR	Exercise not performed
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	Exercise not performed
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	Exercise not performed
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration	No data provided.	Exercise not performed

Annex – Justification of Fee adjustments:

XIX. General adjustment for the NCA remuneration – for all procedures:

The actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% in the following years. These rates would need an uplift.
There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.
NCAs participating in the targeted approach agreed to apply a so-called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessors and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advice involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

Italy contributed to the joint work at the level of the NCA respecting the cost-based principle and is aware that the European Commission could carry out a consistency test of the new data proposed by the NCAs.
In the event that critical issues should arise with respect to the proposal made by the NCAs, Italy suggests simplifying the process, in agreement with the Commission which is the owner of the calculation process, as follow. Maintain the general adjustment and work directly on the average time of each procedure (known value displayed in the "time data" of Annex_COMM), instead of on the average hourly cost (unknown value, characterised by strong variability according to the country of reference).

XX. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

57. Background

Scientific Advice (SA) supports innovation in the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients[17],[18]. Furthermore, SA benefits the industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. EFPIA in its response to the published proposed fee regulation expressed concerns that the fees for the NCAs were too low to ensure the continuity of service required.

58. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

59. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMPs and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous

[17] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.

[18] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

manufacturing became available. Above that, qualification advice turned out to be the most challenging based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.

- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- the number of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- Additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

60. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7-year-old time audit that was already criticised at that time. If agencies can not contribute to the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high-level experts could resign since they cannot use those experts in other assignments. Therefore, those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

61. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up their expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies to small agencies.

It may be presumed that it will also be more costly for the pharmaceutical companies to get a SA since there will be much more difficult to develop and have available the expertise in the

field needed for the SA.

62. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour-intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to provide that service. With staff turnover, this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and scientifically appropriate service to the EMA and the patients of Europe.

63. NCAs and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by the European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

78. Increase in complexity/innovative developments or methodologies.

79. Subsequently need to involve senior assessor and external experts to cover the

requested expertise.

80. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.

81. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.

82. Sustainability of the network.

83. Current limitation of human resources in NCA.

84. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.

85. Increase number of experts by SA level.

86. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice

The new Fee Regulation needs to ensure that the EU network reinforces and increases the level of response to scientific procedures.

The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.

Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.

There is also a need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes wita h clear impact in public health.

The reduction of the fee to the NCA is not adequate to maintain the level of response needed at the EU level.

Remarks on the proposed fees for Scientific advice

Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well-trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.

Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT is adopted fhe several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, the definition of the population to be included in CT, use of RWE and registries).

Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, and CTCG are required which also implies further interactions and coordination at national level.

In a time when new procedures are arising, where NCAs need to cope with innovation and

highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand for the procedures and complexity of products. This also includes making significant investments in the training of new experts, that need to have a comprehensive knowledge of scientific, technical, and regulatory domains.
The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the remuneration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of the EU to innovation. The proposed new fee must reflect the real cost of the work performed.

Italy has contributed to the work with the following data

Italian Fee proposal – adjusted:

	Proposal – adjusted
Level I	5.100 EUR
Level II	9.300 EUR
Level III	15.8000 EUR

II.2 Procedure: Generics, Article: Annex I, point 3.6 & 3.8

	Fee proposal by EC	**Fee proposal - adjusted**
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

Background and justification:
a)

The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This, therefore, does not reflect the reality where countries with high country-weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted at 19.4 %.

The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees, therefore, have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

Since one of the aims of the multinational team assessment is to enable the involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

b) A separate fee for informed consent MAAs is warranted for legal clarity.

II.3: Type II variations, Article: Annex I, point 5

Current fee:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	23 500 EUR	23 500 EUR
Type II variation other	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

If there is no Co-Rapp involved, the Rapp also gets the renumeration of the Co-Rapp.

Fee proposal by EC:

	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For type II grouped variations:
For each type II that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I to the Regulation of the EC on fees (Link to EC website). Example: for a grouped type II variation consisting of 3 type II variations (no indication) the renumeration will be 3 x 6.800.

For Worksharing (WS) variations:
No additional renumeration for Rapp / Co-Rapp. See 5.4 of Annex I to the Regulation of the EC on fees.

Fee proposal – adjusted:

		Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:		**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for type II variations supported by clinical and non-clinical data, but only for type II variations in addition to a new therapeutic indication or modification of an approved indication.

- Type II variations supported by clinical and non-clinical data and type II quality variations only involvement of Rapp by default.
- Increase (25%) of remuneration for type II addition of therapeutic indication or modification.
- Decrease of remuneration for type II others.
- The Rapp no longer receives the remuneration of the Co-Rapp, when there is no Co-Rapp involved.

Remarks on the new fee proposal:

- The proposal to have a higher remuneration for type II addition of therapeutic indication or modification than for all other kind of type II variations is considered acceptable. All other kind of type II variations should be considered the same, as average NCA time spent on type II safety, type II quality and type II other are largely comparable and considerably less than for type II addition of therapeutic indication or modification.
- Introducing an in-between level for "complex" type II variations (including complex quality variations) would require a definition of "complex". It is doubtful whether a sufficiently distinct definition can be drawn up. For example, a type II posology change cannot be considered complex by default. More levels will make the fee regulation complicated and the goal is the opposite.
- However, both the higher and especially the lower remuneration are considered not sufficient to cover the NCA expenses.
- The proposed lower remuneration does not adequately reflect to the complexity of some type II variations (e.g. change in posology or reformulation supported by bioequivalence study).
- No differentiation in remuneration between Rapp and Co-Rapp for type II addition of therapeutic indication or modification is considered acceptable.
- No remuneration for Co-Rapp for type II other is considered acceptable. However, if EMA asks involvement of the Co-Rapp the remuneration should be the same as the renumeration of the Rapp (and not remuneration renumeration between Rapp and Co-Rapp).
- The additional remuneration for grouped type II variations seems plausible. In the current fee regulation the NCA receives for the 1st and for the 2nd type II variation the normal renumeration and a reduced remuneration for the 3rd and subsequent type II variation. As each type II variation in a grouped variation requires an assessment it is considered plausible to have the same remuneration for each individual type II in a grouped variation.
- WS-type variations do not require additonal assessment time by NCA. Therefore no additional remuneration for a WS type compared to a single type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more than one type II each type II variation should be renumerated as mentioned in section 5.3 of Annex I to the Regulation of the EC on fees. Section 5.4 of Annex I to the Regulation of the EC on fees could be clarified to indicate this.
- If the PRAC Rapp instead of CHMP Rapp performs the assessment then the PRAC-Rapp should receive the remuneration.
- Equal remuneration for both the Rapp and Co-Rapp for type II addition of therapeutic indication or modification asssumes that both perform a full assessment. However, this does not take into account the possibility of the "Co-Rapp critique" approach. It is suggested the new fee proposal might take into account the possibility of the "Co-Rapp critique" approach including a matching remuneration proposal.

Proposal for new fee proposal and data collection**:**

To keep the remuneration for type II variations simple and cost-effective for the NCAs, it is proposed to maintain the principles of the EC proposal. However, the remuneration for Type II variation indication and for Type II variation other (§5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses. Based on the average hours spent and the average hourly rate, the remuneration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

Supporting data:
From a number of NCA's is new data collected. Based on the data the average hours en average hourly rate is calculated. The make the proposal also acceptable for the more expensive NCA's a sustainability factor of 20% is added.

		Average			Sustainability factor	Proposal – adjusted
		hours	**rate**	**costs**		
Add. indication	**Rapp**	347	154,75	53 698 EUR	1,2	**64 400 EUR**
	Co-Rapp	347	154,75	53 698 EUR	1,2	**64 400 EUR**
Quality and Safety	**Rapp**	58	145	8 410 EUR	1,2	**10 100 EUR**

II.4: Pharmacovigilance: Referrals, Article: Annex I, point 6 // PSURs, Article: Annex I point 14

Referrals:

Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:
Targeted type of referrals : art. 20, art 31 and art. 107
In the EC proposal, the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.
This decrease is of public health concern because of the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage in adequate assessment, based on robust expertise?
The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:
The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).
Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.
MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs
The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20%, which includes adjustment by inflation (for 2023 and 2024).

PSURs:
Current fee:

PSURs	14 750 EUR

Fee proposal by EC:

PSURs	12 900 EUR

Fee proposal – adjusted:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, implies that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise.
Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP.
EMA funded studies regarding the impact of PhV measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC.
The work in Pharmacovigilance relies on the maintenance and updates of the national database as well as the maintenance and updates of other supportive national database (ex. Product's Information database, SATS, GRCM, SGA, Cloud, GiMed)
Also, the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h) have to be considered and assured.

Hard data calculations:

Table 117. Periodic Safety Update Reports (PSURs)

MBDG	EMA AD	EMA AST	EMA TOT	NCA AD	NCA AST	NCA TOT
Mean	4.68	9.74	***14.42***	9.54	0.61	***10.15***

Hours declared by the EMA secretariat and NCAs for a sample size of 46 procedures.

Time declared by NCA every year since 2017 is at least 10-fold (fees were never adjusted).

Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the proposed update (16 560 EUR).

II.5: Inspections (GMP, GCP and PMF inspections outside EU), Article: Annex IV, point 1:

Background

Inspection is the lynchpin of the regulatory system. It is particularly important in third countries where inspections area key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Proposal adjustment
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee proposal by the EC			**Fee proposal- adjusted**		
Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 EUR	15 600	9 400	70,800 (↑87%)	**34 000 EUR**	**24 000 EUR**
GCP	44 200 EUR	19 600	10 400	65,200 (↑48%)	**32 000 EUR**	**19 000 EUR**
PMF	36 100 EUR	13 400	8 200	54,500 (↑51%)	**20 000 EUR**	**20 000 EUR**

High level Explanation of the Proposal
It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This is also vital with regard to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remains inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.
The data indicate that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, the coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).
The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(s) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on-site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process becomes more complex and the inspectors' work increases significantly.
Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is the lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors into the team and/or extend the inspection time has not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).
The current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the fee is awarded per inspected product.

(t) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.
Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of the scope of inspections to include environmental matters (currently under discussion).
A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.
Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation

(although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees
Hard data in relation to the proposal
See **appendix 1.1**
The points made above illustrates the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

17. Evidence of increased hours from the data gathering exercise.
18. Evidence that the fee does not cover the costs; costs estimation does not account for :
GG) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.
HH) Need to create/support inspection teams, frequently with more than one inspector per NCAs.
II) Need to spend more time on site/extend inspection duration.
JJ) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.
Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.
Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	**Fees as proposed by the EC 13/12/22 (in EUR)**						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Appendix 1.1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided, and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Country 1		**Fees as proposed by the EC 13/12/22 (EUR)**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Country 2		**Fees as proposed by the EC 13/12/22 (EUR)**						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65

GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Country 3

		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Appendix 1.2: Hours and remuneration per type procedure, EMA vs NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

LATVIA

CONTRIBUTION OF LATVIA

Proposed amended remuneration amounts in tabular format

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		20%	This adjustment includes inflation rate and increased scientific complexity of procedures.
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	**Level I (point 1.3 of Annex I):** 9 720 EUR for each of the two scientific coordinators **Level II (point 1.2 of Annex I):** 13 440 EUR for each of the two scientific coordinators **Level III (point 1.1 in Annex I):** 20 160 EUR for each of the two scientific coordinators	See Annex I, based on medium hours & hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs: EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs: EUR 40 200 for rapporteur.	See Annex I; based on medium hourly rates/procedures
Type II variations	Annex I, point 5	**Single type II variation –extension indication:** 64 400 EUR for the rapporteur 64 400 EUR for the co-rapporteur **Single type II variation – other:** 10 100 EUR for the rapporteur	See Annex I, based on medium hours & hourly rates/procedure
Referrals	Annex I, point 6.7	No data provided	
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR for the rapporteur	See Annex I, based on medium hours & hourly rates/procedure
Inspections	Annex IV, point 1	No data provided	
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration required	No data provided	

1. General adjustment

A general adjustment of 20% is proposed. Latvia proposes to apply a so called "Sustainability factor" that would include the uplifted inflation rate.
This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts

Increase burden of work subsequent to European priority actions

2. Scientific advice

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients. Furthermore, SA benefits industry and may save unnecessary expenditure, by focusing the company on key regulatory requirements. The current level of SA fees are considered to reflect the service delivered, and the importance of that service. Fees for the NCAs for providing this service should reflect the actual amount of work and ensure the continuity of service required. There is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and from increased remuneration amounts for NCA experts (considering that specific scientific background, knowledge and skills are required).

The complexity of topics covered by the advice has significantly increased over time.

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues.

3. Generics

	Fee proposal by EC	Fee proposal - adjusted
	141 200 EUR	a) **198 244 EUR** Remuneration to NCAs: **99 122 EUR** for rapporteur. b) **A fee of 141 200 EUR shall apply to an application**. Remuneration to NCAs: **40 200 EUR** for rapporteur.

4.

5. Background and justification:

6. a)

7.

8. The EC proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %.

9.

10. The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split).

11.

12. The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee.

13.

14. Since one of the aims of the multinational team assessment is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.

15.

16. The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market).

17.

18. b) A separate fee for informed consent MAAs is warranted for legal clarity.

19.Type II variations

Current remuneration amount:

Procedure	Rapp renumeration	Co-Rapp renumeration
Type II variation indication + other	23 500 EUR	23 500 EUR
Type II variation quality (not containing non-clinical or clinical data)	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

Currently, if there is no co-rapporteur involved, the rapporteur also gets the renumeration of the co-rapporteur.

Remuneration proposed by the Commission:

Procedure	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For Type II grouped variations:
For each Type II variation that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I of the Commission proposal for a Regulation on fees (Link to EC website). Example: for a grouped Type II variation consisting of 3 Type II variations (no indication) the renumeration will be 3 x €6.800.

For Worksharing (WS) variations:
No additional renumeration for rapporteur / co-rapporteur. See 5.4 of Annex I of the Commission proposal.

Remuneration proposed by LV:

Procedure	Role	Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:	Rapp	**10 100 EUR**

Main changes compared to the current fee legislation:

- The higher remuneration is no longer applicable for Type II variations supported by clinical and non-clinical data, but only for Type II variations - addition of a new therapeutic indication or modification of an approved indication.
- For Type II variations supported by clinical and non-clinical data and Type II quality variations only involvement of the rapporteur by default.
- Increase (25%) of renumeration for Type II - addition of therapeutic indication or modification.
- Decrease of renumeration for Type II other.
- The rapporteur no longer receives the renumeration of the co-rapporteur, when there is no co-rapporteur involved.

Remarks on the new proposal:

- The proposal to have a higher renumeration for Type II addition of therapeutic indication or modification than for all other kind of Type II variations is considered acceptable. All other kind of Type II variations should be considered the same in regards costs incurred, as average NCA time spent on Type II safety, Type II quality and Type II other is largely comparable and considerably less than for Type II addition of therapeutic indication or modification.
- Introducing an in-between level for "complex" Type II variations (including complex quality variations) is not desirable, as this would require a definition of "complex". It is doubtful whether a sufficiently distinct definition can be drawn up. For example, a Type II posology change cannot be considered complex by default. In addition, more levels will make the fee regulation complicated, and the goal of this revision is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCAs' expenses.
- The proposed lower renumeration does not adequately reflect the complexity of some Type II variations (e.g. change in posology or reformulation supported by a bioequivalence study).
- It is considered acceptable to have no differentiation in renumeration between rapporteur and co-rapporteur for Type II addition of therapeutic indication or modification.
- It is considered acceptable to have no renumeration for the co-rapporteur for Type II other. However, if EMA asks involvement of the co-rapporteur, the renumeration should be the same as the renumeration for the rapporteur (i.e., the remuneration for the rapporteur should not be divided by 2).
- The additional renumeration for grouped Type II variations seems plausible. In the current Fee Regulation the rapporteur receives for the 1st and for the 2nd Type II variation the normal renumeration amount and a reduced renumeration amount for the 3rd and subsequent Type II variations. As each Type II variation in a grouped variation requires an assessment, it is considered plausible to have the same renumeration amount for each individual Type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCAs. Therefore, no additional renumeration for a WS type compared to a single Type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more than one Type II variation, each Type II variation should be renumerated as mentioned in section 5.3 of Annex I of the proposed regulation. The relevant clarification should be added to point 5.4 of Annex I.
- If the PRAC rapporteur instead of CHMP rapporteur performs the assessment, then the PRAC rapporteur should receive the renumeration.
- Equal renumeration for both the rapporteur and co-rapporteur for Type II addition of therapeutic indication or modification is based on the assumption that both perform a full assessment. However, this does not take into account the possibility of the "co-rapporteur critique" approach. It is proposed that the new fee proposal takes into account the possibility of the "co-rapporteur critique" approach, including a matching renumeration proposal.

Proposal for new remuneration amounts and data collection:

To keep the renumeration for Type II variations simple and cost effective, it is proposed to maintain the main principles of the Commission proposal. However, the renumeration for Type II variation indication and for Type II variation other (point 5.1 and 5.1 of Annex I) should both be increased in order to cover NCA's expenses. Based on the average hours spent and the average hourly rate, the renumeration should be increased as stated above.

Supporting data for the targeted approach:
New data were collected from a number of NCAs. Based on these data, the average hours and average hourly rate were calculated. Numbers are shown in the table below.

		Average		Proposal – adjusted remuneration amount
		hours	**Rate (this includes the general adjustment of 20%)**	
Add. indication	**Rapp**	347	185.60 EUR	**64 400 EUR**
	Co-Rapp	347	185.60 EUR	**64 400 EUR**
Quality and Safety	**Rapp**	58	174,15	**10 100 EUR**

20.Pharmacovigilance referrals (point 6.7 of Annex I)

21.Periodic Safety Update Report (PSUR)

Current remuneration amount:

PSURs	14 750 EUR

Remuneration amount proposed by the Commission:

PSURs	12 900 EUR

Proposal NL for adjusted remuneration amount:

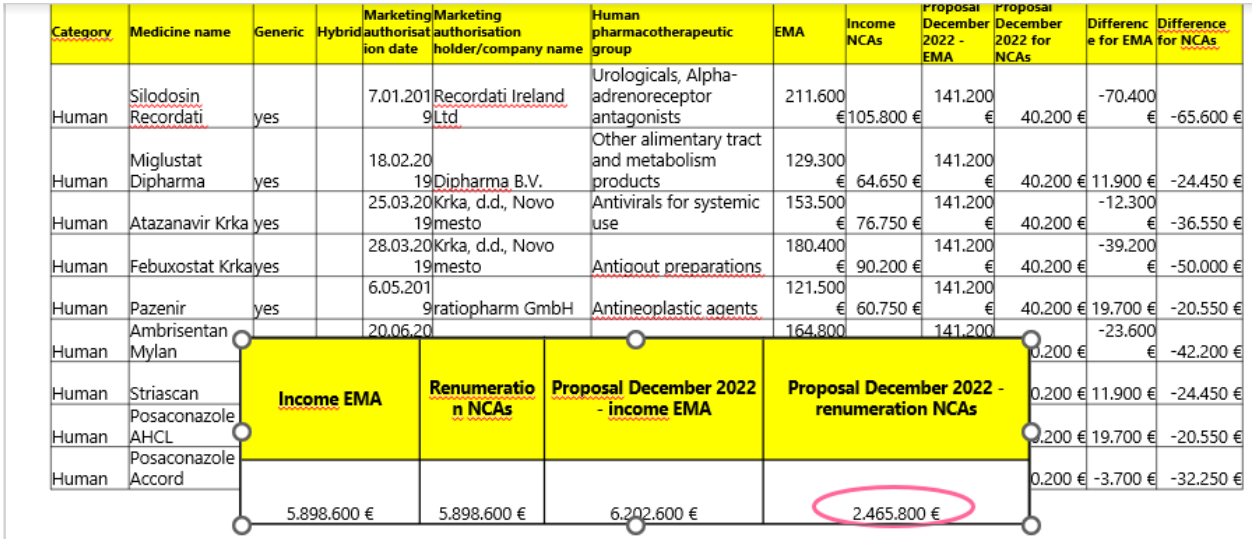
PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure may require a multidisciplinary evaluation. The development of innovative products with new technology implies that assessment capacity needs to be developed and updated. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available with different areas of expertise depending on the nature of a certain risk.

Various activities are required and need to be compensated for, for example:

- PSUR procedures need to be presented frequently at the respective regulatory committee; PRAC → CMDh or PRAC → CHMP.
- EMA funded studies regarding the impact of pharmacovigilance measures requiring rapporteur assessment and preparation of the presentation at PRAC.
- Costs for resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h).
- Taking an average time estimation and average hourly costs, we have got 13 800 €; the Sustainability factor of 1.2 was applied to get the proposed update (16 560 EUR).

MALTA

Current (2022 numbers) fee in Euro*)	Proposed fee in Euro	MT Justification / proposal
Annex I **3.6.** A fee of EUR 141 200 shall apply to any of the following: (a) an application for a marketing authorisation for a generic medicinal product pursuant to Article 10(1) of Directive 2001/83/EC, (b) an application based on informed consent for a marketing authorisation for a medicinal product pursuant to Article 10c of	**Annex I** 3.6 A fee of EUR 198 244 shall apply to any of the following: (a) an application for a marketing authorisation for a generic medicinal product pursuant to Article 10(1) of Directive 2001/83/EC, That fee shall cover all strengths, all pharmaceutical forms and all presentations submitted in the same application. The remuneration shall be EUR 97 244 for the rapporteur. A fee of EUR 141 200 shall apply to any of the following: (b) an application based on informed consent for a marketing authorisation for a medicinal product pursuant to Article 10c of	**Having regard to the agreed principle the NCAs having to be adequately reimbursed for their costs (including soft skills) in providing the scientific service to the European Medicines Agency.** **Whereas the new commission proposal results in a shortfall income for NCAs by 58% based on all the fees paid to the EMA for the period 2019-2022 (reference table below). Where the reduction in fee arising in pharmaceutical forms and strengths has made an imapct in the NCA income to maintain their sustainability.**  **Wheras the European Commission has also adjusted the EMA human medicines fees upwards by 14% (proposed fee in 2021 vs 2022 commission proposal) to cover the shortfall in income in waivers and**

Category	Medicine name	Generic	Hybrid	Marketing authorisation date	Marketing authorisation holder/company name	Human pharmacotherapeutic group	EMA	Income NCAs	Proposal December 2022 - EMA	Proposal December 2022 for NCAs	Difference for EMA	Difference for NCAs
Human	Silodosin Recordati	yes		7.01.2019	Recordati Ireland Ltd	Urologicals, Alpha-adrenoreceptor antagonists	211.600 €	105.800 €	141.200 €	40.200 €	-70.400 €	-65.600 €
Human	Miglustat Dipharma	yes		18.02.2019	Dipharma B.V.	Other alimentary tract and metabolism products	129.300 €	64.650 €	141.200 €	40.200 €	11.900 €	-24.450 €
Human	Atazanavir Krka	yes		25.03.2019	Krka, d.d., Novo mesto	Antivirals for systemic use	153.500 €	76.750 €	141.200 €	40.200 €	-12.300 €	-36.550 €
Human	Febuxostat Krka	yes		28.03.2019	Krka, d.d., Novo mesto	Antigout preparations	180.400 €	90.200 €	141.200 €	40.200 €	-39.200 €	-50.000 €
Human	Pazenir	yes		6.05.2019	ratiopharm GmbH	Antineoplastic agents	121.500 €	60.750 €	141.200 €	40.200 €	19.700 €	-20.550 €
Human	Ambrisentan Mylan			20.06.20			164.800		141.200	0.200 €	-23.600 €	-42.200 €
Human	Striascan									0.200 €	11.900 €	-24.450 €
Human	Posaconazole AHCL									0.200 €	19.700 €	-20.550 €
Human	Posaconazole Accord									0.200 €	-3.700 €	-32.250 €

Income EMA	Renumeration NCAs	Proposal December 2022 - income EMA	Proposal December 2022 - renumeration NCAs
5.898.600 €	5.898.600 €	6.202.600 €	2.465.800 €

Directive 2001/83/EC. That fee shall cover all strengths, all pharmaceutical forms and all presentations submitted in the same application. The remuneration shall be EUR 40 200 for the rapporteur.	Directive 2001/83/EC. That fee shall cover all strengths, all pharmaceutical forms and all presentations submitted in the same application. The remuneration shall be EUR 40 200 for the rapporteur.	**incentives offered by the EMA (incl for veterinary fees) and therefore a similar financial adjustment is acceptable if used by any member state proposal.** **It is noted that the time data that the EU Commission used in the Model (excel sheet presented at the Council Working Party of Pharmaceuticals and Medical devices of 2/February/2023) to calculate the fees proposal is not the one adopted by the EMA MB 2017 data gatthering exercise. The time used by the commission in its model for generics is 401.37 hours (sheet 2; CION model excel sheet). The time adopted by the EMA MB 2017 data of 507.19 hours. A descrepancy of 21% in time is to be adjusted to the proposed fee.** **It is further noted that the Commission proposal methodology has given no consideration of current practise at the EMA establishing Multi National Teams for the assessment of medicinal products. The CION proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment for the rapporteur as a multi national team which has a low country weighted co-efficient. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since, this calculation does not consider the setting up of Multi National teams it is proposed to used the average country co-efficient of 109% as assigned to the netherlands since this is the seat of the EMA which in itself constitutes a multi national working environment. Therefore an adjustment in fees for generic medicines is warranted of 19.4 %.** **Since one of the aims of the multi national team assessment, is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted.** **Therefore a proposed fee of 198,244 is recommended whereby the remuneration shall be EUR 97 244 000 for the rapporteur.** **Furthermore, a separate fee for informed conset is warranted for legal clarity.** **The proposed new fee is also more appropriate when considereing the fees chaged by the USA for the evaluation of a generic medicinal product.**

HIGH LEVEL EXPLANATION

The fee, as proposed, results in a significant decrease in NCA income by 30 to 40% and therefore is totally inadequate to cover the costs, and will reduce the ability of the network to support public health in Europe through the regulation of medicines.

MT comments as per Presidency table

Procedure	Article	General adjustment for all procedures (%)	Total remuneration to NCAs (incl. general adjustment)	Justification
Scientific Advice	Annex I, point 1.1, 1.2 & 1.3	1.1: 42% 1.2: 49% 1.3: 34.5%	1.1 A fee of EUR 78 900 shall apply to any of the following requests: The remuneration shall be EUR 22 250 for each of the two scientific advice co-ordinators. 1.2 A fee of EUR 67 000 shall apply to any of the following requests: The remuneration shall be EUR 17 650 for each of the two scientific advice co-ordinators.	The methodology used by the EC to calculate these fees is challanged and does not even consider the hours appropriately that each NCAs contribute to such high level expertise being delivered. The EMA mean hours for a Scientific advice is recorded at: 73.58 hours while EACH NCA mean average is 101.17 hours the % is therefore 42% vs 58%.[1] The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed . For this procedure 2 NCAs carryout the service and therefore the mean hours are 202.14 when all types of advices are grouped together. The commission proposal as it stands undermines the sustainability of the EU medicines regulatory network reimbursing scientific work by the a to the NCAs to deliver this service. Experts are engaged by NCAs and the costs should be appropriately reimbursed.

			1.3 A fee of EUR 50,050 shall apply to any of the following requests The remuneration shall be EUR 11,725 for each of the two scientific advice co-ordinators.	
Generics	Annex I, point 3.6 & 3.8	3.6.(a): 40,4 % 3.6.(b): /	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 97 244 for rapporteur. b) A fee of EUR 141 200 shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	a) Whereas, the European Commission has adjusted the EMA human medicines fees upwards by 14% (proposed fee in 2021 vs 2022 commission proposal) due to inflation rate, therefore a similar financial adjustment is acceptable if used by any member state proposal. The proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since, this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %. The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed.

				The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee. Since one of the aims of the multinational team assessment, is to enable the involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted. The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market). b) A separate fee for informed consent MAAs is warranted for legal clarity.
Type II variations	Annex I, point 5	5.1: 40% 5.2: 76%	5.1 A fee of EUR 139 800 shall apply to an application for a major variation of type II for an addition of a new therapeutic indication or modification of an approved indication. The remuneration shall be EUR 49 400 for the rapporteur and EUR 49 400 for the	The proposal envisages a higher fee only for new therapeutic indications or changes to an approved indication (under 5.1). A single fee is provided for all other type II changes (covered under 5.2), which does not adequately reflect to the possible complexity of some variations (e.g. change in posology). Similarly, a very low fee is provided for quality changes of type II, which may also include some very complex ones,

			co-rapporteur. 5.2 A fee of EUR 80 500 shall apply to an application for a major variation of type II, complex clinical/non-clinical/quality variation of type II, not covered by point 5.1. The remuneration shall be EUR 56 350 for the rapporteur. 5.3 A fee of EUR 23 000 shall apply to an application for a variation of type II, not covered by points 5.1 and 5.2. The remuneration shall be EUR 16 800 for the rapporteur.	e.g. assessment of BE studies (in relation to changed formulation of MP). Even in this case, both the amount and the distribution of the fee for the services provided are not appropriate and are insufficient for the work done by the NCAs.[1] As per EMA Management Board data gathereing document the hours to evaluate variations is documented to be 76-82% (NCA) vs 18-24 % (EMA). The commission proposal as it stands undermines the sustainability of the EU medicines regulatory network and therefore in this respect three levels of variations are proposed.
Referrals	Annex I, point 6	Fees for rapporteur and co-rapporteur: 6.1 42% 6.2 96% 6.3 14% 6.4 14% 6.5 61% 6.6 14%	6.1 A fee of EUR 136 700 shall apply to the assessment carried out in the context of a procedure initiated under Article 5(3) of Regulation (EC) No 726/2004. Such fee	The methodology used by the EC to calculate these fees is challanged and does not even consider the hours appropriately that each NCAs contribute to such high level expertise being delivered. As per the ECs own document: **evaluation_ema_fee_frep_en.pdf (europa.eu) https://ec.europa.eu/health/sites/default/files/files/fees/evaluation_ema_fee_frep_en.pdf**. [1] The commission proposal as it stands undermines the

			shall be waived in full. The remuneration shall be EUR 42 400 for the rapporteur and EUR 42 400 for the co-rapporteur. 6.2 A fee of EUR 262 400 shall apply to the assessment carried out in the context of a procedure initiated under Article 13 of Regulation (EC) No 1234/2008. Such fee shall be waived in full. The remuneration shall be EUR 45 300 for the rapporteur and EUR 45 300 for the co-rapporteur. 6.3 A fee of EUR 83 000 shall apply to the assessment carried out in the context of a procedure initiated under Article 29(4)	sustainability of the EU medicines regulatory network reimbursing a not sustainable ammountto the NCAs to deliver this service. Experts are engaged by NCAs and the costs should be appropriately reimbursed.

			of Directive 2001/83/EC. Such fee shall be waived in full. The remuneration shall be EUR 22 800 for the rapporteur and EUR 22 800 for the co-rapporteur. 6.4 A fee of EUR 128 200 shall apply to the assessment carried out in the context of a procedure initiated under Article 30 of Directive 2001/83/EC. The remuneration shall be EUR 36 800 for the rapporteur and EUR 36 800 for the co-rapporteur. 6.5 A fee of EUR 180 700 shall apply to the assessment carried out in the context of a procedure initiated	

			under Article 31 of Directive 2001/83/EC where the procedure is initiated as a result of the evaluation of data other than data relating to pharmacovigilance. The remuneration shall be EUR 32 400 for the rapporteur and EUR 32 400 for the co-rapporteur. 6.6 A fee of EUR 172 100 shall apply to the assessment carried out in accordance with a procedure initiated under Article 20 of Regulation (EC) No 726/2004 where that procedure is initiated as a result of the evaluation of data other than data relating to pharmacovigilance. The remuneration	

			shall be EUR 37 500 for the rapporteur and EUR 37 500 for the co-rapporteur	
Periodic Safety Update Reports (PSURs)	Annex I, point 14	No changes	No changes	No changes
Inspections	Annex IV, point 1	No changes	No changes	No changes
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration required	No changes	No changes	No changes

Marketing Authorisation	Annex I, 4.3	4.3 68%	4.3 Without prejudice to points 4.1 and 4.2, a fee of EUR 46 600 shall apply to each application for extension of a marketing authorisation on the basis of an application submitted under Article 10(1), (3) or (4) of Directive 2001/83/EC on usage patent grounds as referred to in point 3.8 of this Annex. The remuneration shall be EUR 16 800 for the rapporteur and EUR 10 000 for the co-rapporteur.	The methodology used by the EC to calculate these fees is challanged and does not even consider the hours appropriately thaet each NCAs contribute to such high level expertise being delivered. As per the ECs own document: **evaluation_ema_fee_frep_en.pdf (europa.eu) https://ec.europa.eu/health/sites/default/files/files/fees/evaluation_ema_fee_frep_en.pdf**. [1] The commission proposal as it stands undermines the sustainability of the EU medicines regulatory network reimbursing a non sustainable ammount to the NCAs to deliver this service. Experts are engaged by NCAs and the costs should be appropriately reimbursed.

Notes:

1. **Reference:** [evaluation_ema_fee_frep_en.pdf (europa.eu) https://ec.europa.eu/health/sites/default/files/files/fees/evaluation_ema_fee_frep_en.pdf](https://ec.europa.eu/health/sites/default/files/files/fees/evaluation_ema_fee_frep_en.pdf).

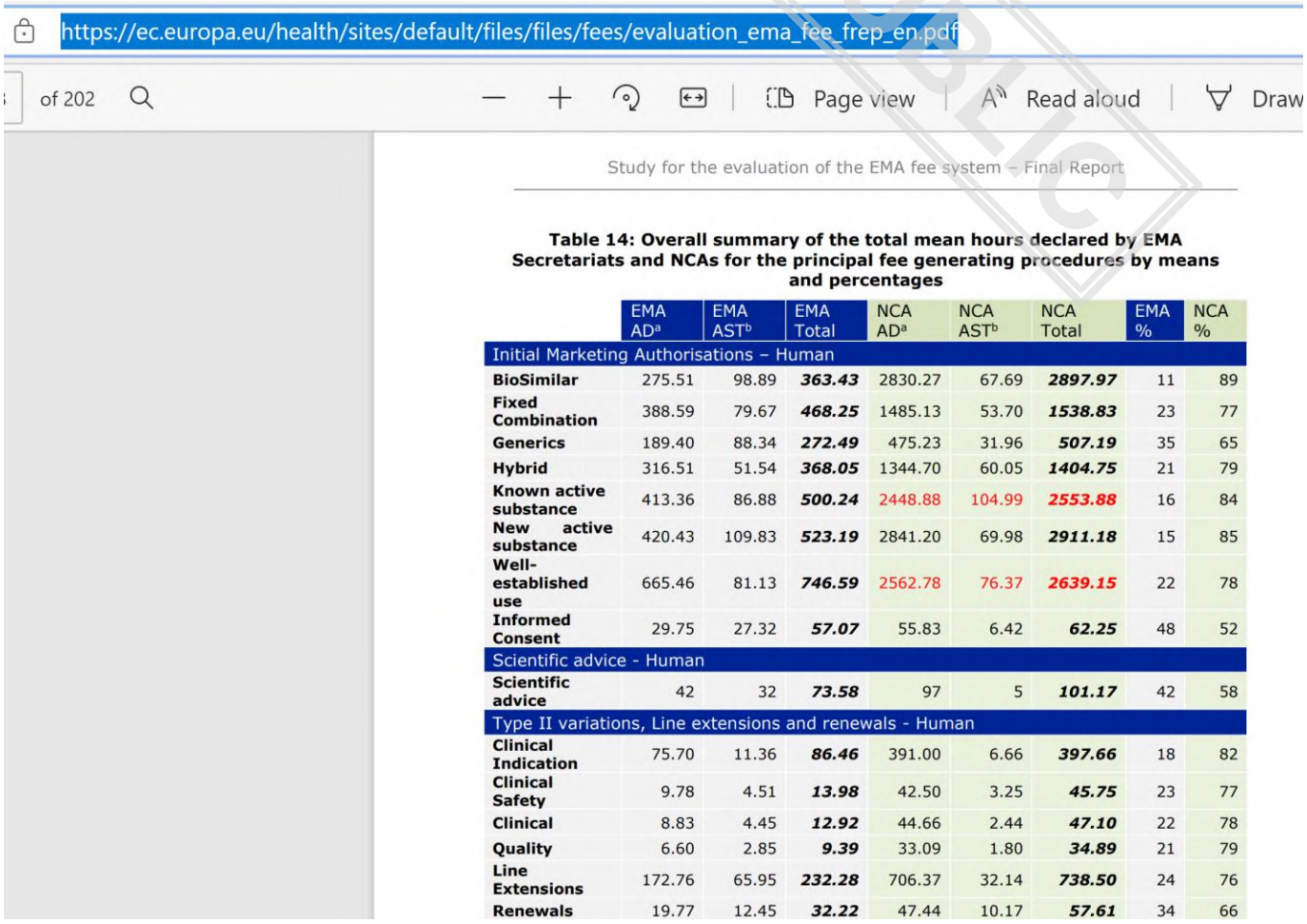


Table 14: Overall summary of the total mean hours declared by EMA Secretariats and NCAs for the principal fee generating procedures by means and percentages

	EMA AD[a]	EMA AST[b]	EMA Total	NCA AD[a]	NCA AST[b]	NCA Total	EMA %	NCA %
Initial Marketing Authorisations – Human								
BioSimilar	275.51	98.89	***363.43***	2830.27	67.69	***2897.97***	11	89
Fixed Combination	388.59	79.67	***468.25***	1485.13	53.70	***1538.83***	23	77
Generics	189.40	88.34	***272.49***	475.23	31.96	***507.19***	35	65
Hybrid	316.51	51.54	***368.05***	1344.70	60.05	***1404.75***	21	79
Known active substance	413.36	86.88	***500.24***	2448.88	104.99	***2553.88***	16	84
New active substance	420.43	109.83	***523.19***	2841.20	69.98	***2911.18***	15	85
Well-established use	665.46	81.13	***746.59***	2562.78	76.37	***2639.15***	22	78
Informed Consent	29.75	27.32	***57.07***	55.83	6.42	***62.25***	48	52
Scientific advice - Human								
Scientific advice	42	32	***73.58***	97	5	***101.17***	42	58
Type II variations, Line extensions and renewals - Human								
Clinical Indication	75.70	11.36	***86.46***	391.00	6.66	***397.66***	18	82
Clinical Safety	9.78	4.51	***13.98***	42.50	3.25	***45.75***	23	77
Clinical	8.83	4.45	***12.92***	44.66	2.44	***47.10***	22	78
Quality	6.60	2.85	***9.39***	33.09	1.80	***34.89***	21	79
Line Extensions	172.76	65.95	***232.28***	706.37	32.14	***738.50***	24	76
Renewals	19.77	12.45	***32.22***	47.44	10.17	***57.61***	34	66

THE NETHERLANDS

CONTRIBUTION OF THE NETHERLANDS

Proposed amended remuneration amounts in tabular format

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		20%	This adjustment includes inflation rate and increased hourly costs for more expensive NCAs.
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	**Level I (point 1.3 of Annex I):** 9 720 EUR for each of the two scientific coordinators **Level II (point 1.2 of Annex I):** 13 440 EUR for each of the two scientific coordinators **Level III (point 1.1 in Annex I):** 20 160 EUR for each of the two scientific coordinators	See annex I, based on medium hours & hourly rates/procedure
Generics	Annex I, point 3.6 & 3.8	N/A	The Netherlands does not take on the role of rapporteur for generic applications. For proposed fees and remuneration amounts, reference is made to the proposals of other Member States.
Type II variations	Annex I, point 5	**Single type II variation –extension indication:** 64 400 EUR for the rapporteur 64 400 EUR for the co-rapporteur **Single type II variation – other:** 10 100 EUR for the rapporteur	See annex I, based on medium hours & hourly rates/procedure
Referrals	Annex I, point 6.7	85 000 EUR for the rapporteur 85 000 EUR for the co-rapporteur	See annex I, based on medium hours & hourly rates/procedure
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR for the rapporteur	See annex I, based on medium hours & hourly rates/procedure
Inspections	Annex IV, point 1	**GMP:** Leading: 34 000 EUR Supporting: 24 000 EUR **GCP:**	See annex I, based on medium hours & hourly rates/procedure

		Leading: 32 000 EUR Supporting: 19 000 EUR **PMF:** Leading: 20 000 EUR Supporting: 20 000 EUR	
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration required	**Annual fee:** PRAC rapporteur to receive 10% of the proposed remuneration amount of the CHMP rapporteur **PLUS** 10% of the proposed remuneration amount of the CHMP co-rapporteur. Remains: CHMP rapporteur receives 90% of the remuneration amount initially proposed for this role. Similarly, CHMP co-rapporteur receives 90% of the remuneration amount initially proposed for this role. Translated into numbers: <u>Annual fee under point 1.1 of Annex III:</u> PRAC rap: 1 356 EUR CHMP rap: 5 695 EUR CHMP co-rap: 5040 EUR <u>Annual fee under point 1.2 of Annex III:</u> PRAC rap: 2 746 EUR CHMP rap: 13 119 EUR CHMP co-rap: 11 594 EUR <u>Annual fee under point 1.3 of Annex III:</u> PRAC rap: 5 469 EUR CHMP rap: 26 137 EUR CHMP co-rap: 23 086 EUR **New applications for marketing authorisation (MAAs):** PRAC rapporteur to receive 5% of proposed remuneration amount of CHMP rapporteur **PLUS** 5% of proposed remuneration amount of CHMP co-rapporteur. Remains: CHMP rapporteur receives 95% of the remuneration amount initially proposed for this role. Similarly, CHMP co-	<u>Note:</u> This proposal does not lead to amendment of the total fee to be paid by industry or to amendment of the fee share for EMA, it only leads to amended remuneration amounts for the CHMP rapporteurs and new remuneration amounts for the PRAC rapporteur. Proposed amounts are based on medium hours & hourly rates/activity. See annex I for further explanation. **Annual fee:** To cover PRAC rapporteur activities such as signal assessments as well as assessment of RMP for variations. **New MAAs:** To cover PRAC rapporteur activities such as assessment of RMP and PhV Plan for new applications. For generic applications, no actual numbers have been included, since a new remuneration amount will be put forward by other Member States based on their data. We propose however, to apply the same 5% rule as described here.

		rapporteur receives 95% of the remuneration amount initially proposed for this role. Translated into numbers: <u>Procedural fee under point 3.1 of Annex I:</u> PRAC rap: 22 973 EUR CHMP rap: 233 272 EUR CHMP co-rap: 203 214 EUR <u>Procedural fee under point 3.2 of Annex I:</u> PRAC rap: 164 246 EUR CHMP rap: 153 833 EUR CHMP co-rap: 16 741 EUR <u>Procedural fee under point 3.3 of Annex I:</u> PRAC rap: 12 684 EUR CHMP rap: 151 900 EUR CHMP co-rap: 89 101 EUR <u>Procedural fee under point 3.4 of Annex I:</u> PRAC rap: 21 933 EUR CHMP rap: 253 883 EUR CHMP co-rap: 162 850 EUR <u>Procedural fee under point 3.5 of Annex I:</u> PRAC rap: 17 515 EUR CHMP rap: 172 404 EUR CHMP co-rap: 160 381 EUR <u>Procedural fee under point 3.7 of Annex I:</u> PRAC rap: 10 068 EUR CHMP rap: 95 649 EUR CHMP co-rap: 95 649 EUR	

Annex I – justification to the above table

22.General adjustment

A general adjustment of 20% is proposed. For the Netherlands, this general adjustment is mainly based on the following two factors:

- The Commission has based their proposal on a weighted average. This may lead to issues for some NCAs in regards their ability to carry out their work. The use of a weighted average means that more expensive NCAs (i.e., due to higher staff and non-staff costs and/or more time spent on a certain procedure) will face difficulties covering their costs. This will be detrimental for the sustainability of the network as a whole.

- In addition, the amounts proposed by the Commission are based on an inflation rate of 1.2% per year, instead of actual inflation rates (inflation rates used by Eurostat: 5.3% for 2021 and 10.4% for 2022). The amounts proposed by the Netherlands below automatically include a correction for the inflation rates for 2022, as they are based on current costs. However, the regulation will become applicable at the earliest in Q3 of 2024 and it is expected that an inflation rate of 1.2% will not suffice for 2023 and 2024 either. The general adjustment of 20% therefore also includes the prospected inflation for those years.

The general adjustment of 20% has already been included in the proposed amounts below. The proposed amounts are based on hard data of actual costs per procedure provided by a significant number of NCAs in a very short time. In other words, the proposed amounts apply to all NCAs and not just to the Dutch Medicines Agency and Dutch Inspectorate.

23.Scientific advice

23.1 Remuneration amounts

The amounts below apply to both initial scientific advice and follow-up scientific advice.

Current remuneration amounts for each of the co-ordinators:

Level I (point 1.3 of Annex I)	11 725 EUR
Level II (point 1.2 of Annex I)	17 650 EUR
Level III (point 1.1 of Annex I)	23 500 EUR

Remuneration amounts proposed by the Commission for each of the co-ordinators:

Level I (point 1.3 of Annex I)	5 300 EUR
Level II (point 1.2 of Annex I)	6 500 EUR
Level III (point 1.1 of Annex I)	10 400 EUR

Remuneration amounts proposed by the Commission for each of the co-ordinators, corrected for the Eurostat inflation rate (i.e., amounts increased by 13%):

Level I (point 1.3 of Annex I)	5 989 EUR
Level II (point 1.2 of Annex I)	7 345 EUR
Level III (point 1.1 of Annex I)	11 752 EUR

Explanation:
During the Council Working Party of 27 March, the Commission explained that the inflation rates used by Eurostat for the years 2021 and 2022 are 5.3% and 10.4% respectively. The rate used for the calculation of the fee and remuneration amounts as proposed by the Commission is 1.2%. The Commission explained that if the 1.2% is to be replaced by 5.3% and 10.4% for the years 2021 and 2022 respectively, the fee and remuneration amounts will increase by 13% as compared to their initial proposal. This would result in the above remuneration amounts.
The same calculation has been made for the other activities listed in this document.

Remuneration amounts proposed by NL for each of the co-ordinators:

Level I (point 1.3 of Annex I)	9 720 EUR
Level II (point 1.2 of Annex I)	13 440 EUR
Level III (point 1.1 of Annex I)	20 160 EUR

Substation of the adjusted amounts
Scientific Advice (SA) supports innovation in the EU and enables medicinal products to successfully negotiate the regulatory process. Statistics show a higher success rate for marketing authorisation applications where scientific advice has been sought, and thus scientific advice supports the timely availability of medicines to European patients[19],[20]. Furthermore, SA benefits industry and may save unnecessary expenditure, by steering the company towards focusing on key regulatory requirements. It is therefore of absolute essence that both EMA and NCAs are able to cover their costs. The remuneration amounts proposed by the Commission will not enable NCAs to cover their costs. Less NCAs may therefore be willing or capable to take on board the role of SA coordinator. This, whilst the SAWP requires that each member is responsible for at least four SAs each month, and there are currently already difficulties in allocating coordinators for this activity. Also, the quality of the work may no longer be guaranteed if costs incurred cannot be covered, which may affect the quality of applications for a marketing authorisation. In the long term, this could be detrimental for the availability of medicines and innovation in the EU. EFPIA, in their response to the published proposed fee regulation, expressed concerns that the remuneration for NCAs is too low to ensure the continuity of the service required.

[19] Regnstrom et al: Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur.J.Clin.Pharmacol. 66, 39-48; 2010.
[20] Nadia Amaouche, Hélène Casaert Salomé, Olivier Collignon, Mariana Roldao Santos, Constantinos Ziogas, Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes, Drug Discovery Today, Volume 23, Issue 10, 2018, Pages 1801-1805, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2018.06.018.

The proposed adjustment of the remuneration amounts reflects actual costs of the work performed by NCAs. The increase in NCAs' costs as compared to the data collected in 2016 – 2017 is mainly due to inflation (which is reflected in the general adjustment of 20%) as well as increased complexity of the SA. This results in a higher average of hours spent per procedure and the need to involve more senior (i.e., more expensive) staff and specific experts (i.e. statisticians). The increase in complexity can be attributed to:

- Novel classes of development candidates like ATMP's and mRNA vaccines; consequently, new targets became "drugable" and new technologies like continuous manufacturing became available. In addition, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- SA for biosimilar development are getting more complex, since there are in-depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, NCAs needed to increase the number of qualified assessors (especially statisticians). And the numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.

24.Type II variations

Current remuneration amount:

Procedure	Rapp renumeration	Co-Rapp renumeration
Type II variation indication + other	23 500 EUR	23 500 EUR
Type II variation quality (not containing non-clinical or clinical data)	17 650 EUR	17 650 EUR
Type II variations - 3rd & subsequent type II	5 925 EUR	5 925 EUR

Currently, if there is no co-rapporteur involved, the rapporteur also gets the renumeration of the co-rapporteur.

Remuneration proposed by the Commission:

Procedure	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	29 400 EUR	29 400 EUR
Type II variation other	6 800 EUR	0 EUR

For Type II grouped variations:
For each Type II variation that is grouped in a single application the corresponding remuneration shall be paid as set out above. See 5.3 of Annex I of the Commission proposal for a Regulation on fees (Link to EC website). Example: for a grouped Type II variation consisting of 3 Type II variations (no indication) the renumeration will be 3 x €6.800.

For Worksharing (WS) variations:
No additional renumeration for rapporteur / co-rapporteur. See 5.4 of Annex I of the Commission proposal.

Remuneration proposed by the Commission corrected for Eurostat inflation rate (i.e., amounts increased by 13%):

Procedure	Rapp renumeration	Co-Rapp renumeration
Type II variation indication	33 222 EUR	33 222 EUR
Type II variation other	7 684 EUR	0 EUR

Remuneration proposed by NL:

Procedure	Role	Proposal adjusted
Single type II variation indication:	Rapp	**64 400 EUR**
	Co-Rapp	**64 400 EUR**
Single Type II variation other:	Rapp	**10 100 EUR**

Main changes of the Commission proposal as compared to the current fee legislation:

- The higher remuneration is no longer applicable for Type II variations supported by clinical and non-clinical data, but only for Type II variations - addition of a new therapeutic indication or modification of an approved indication.
- For Type II variations supported by clinical and non-clinical data and Type II quality variations only involvement of the rapporteur by default.
- Increase (25%) of renumeration for Type II - addition of therapeutic indication or modification.
- Decrease of renumeration for Type II other.
- The rapporteur no longer receives the renumeration of the co-rapporteur, when there is no co-rapporteur involved.

Remarks on the new Commission proposal:

- The proposal to have a higher renumeration for Type II addition of therapeutic indication or modification than for all other kind of Type II variations is considered acceptable. All other kind of Type II variations should be considered the same in regards costs incurred, as average NCA time spent on Type II safety, Type II quality and Type II other is largely comparable and considerably less than for Type II addition of therapeutic indication or modification.
- Introducing an in-between level for “complex” Type II variations (including complex quality variations) is not desirable, as this would require a definition of “complex”. It is doubtful whether a sufficiently distinct definition can be drawn up. For example, a Type II posology change cannot be considered complex by default. In addition, more levels will make the fee regulation complicated, and the goal of this revision is the opposite.
- However, both the higher and especially the lower renumeration are considered not sufficient to cover the NCAs’ expenses.

- The proposed lower renumeration does not adequately reflect the complexity of some Type II variations (e.g. change in posology or reformulation supported by a bioequivalence study).
- It is considered acceptable to have no differentiation in renumeration between rapporteur and co-rapporteur for Type II addition of therapeutic indication or modification.
- It is considered acceptable to have no renumeration for the co-rapporteur for Type II other. However, if EMA asks involvement of the co-rapporteur, the renumeration should be the same as the renumeration for the rapporteur (i.e., the remuneration for the rapporteur should not be divided by 2).
- The additional renumeration for grouped Type II variations seems plausible. In the current Fee Regulation the rapporteur receives for the 1st and for the 2nd Type II variation the normal renumeration amount and a reduced renumeration amount for the 3rd and subsequent Type II variations. As each Type II variation in a grouped variation requires an assessment, it is considered plausible to have the same renumeration amount for each individual Type II in a grouped variation.
- WS type variations do no require additonal assessment time by NCAs. Therefore, no additional renumeration for a WS type compared to a single Type II variation is considered acceptable. However, in case the WS variation consists of a grouped variation with more than one Type II variation, each Type II variation should be renumerated as mentioned in section 5.3 of Annex I of the proposed regulation. The relevant clarification should be added to point 5.4 of Annex I.
- If the PRAC rapporteur instead of CHMP rapporteur performs the assessment, then the PRAC rapporteur should receive the renumeration.
- Equal renumeration for both the rapporteur and co-rapporteur for Type II addition of therapeutic indication or modification is based on the assumption that both perform a full assessment. However, this does not take into account the possibility of the "co-rapporteur critique" approach. It is proposed that the new fee proposal takes into account the possibility of the "co-rapporteur critique" approach, including a matching renumeration proposal.

Proposal for new remuneration amounts and data collection:
To keep the renumeration for Type II variations simple and cost effective for both EMA and NCAs, it is proposed to maintain the principles of the Commission proposal. However, the renumeration for Type II variation indication and for Type II variation other (point 5.1 and 5.1 of Annex I) should both be increased in order to cover NCA's expenses. Based on the average hours spent and the average hourly rate, the renumeration should be increased as stated above.

Supporting data for the targeted approach:
New data were collected from a number of NCAs. Based on these data, the average hours and average hourly rate were calculated. Numbers are shown in the table below.

		Average		**Proposal – adjusted remuneration amount**
		hours	**Rate (this includes the general adjustment of 20%)**	
Add.	**Rapp**	347	185.60 EUR	**64 400 EUR**

indication	**Co-Rapp**	347	185.60 EUR	**64 400 EUR**
Quality and Safety	**Rapp**	58	174,15	**10 100 EUR**

25.Pharmacovigilance referrals (point 6.7 of Annex I)

	Role	**Current remuneration amount**	**Commission proposal**	**Commission proposal, corrected for Eurostat inflation rate (i.e., +13%)**	**Proposal NL**
Point 6.7.1 of Annex I	Rapporteur	67 145 EUR	17 500 EUR	19 775 EUR	85 000 EUR
	Co-Rapporteur	67 145 EUR	17 500 EUR	19 775 EUR	85 000 EUR

In the Commission proposal the remuneration amount for the rapporteurs is strongly decreased by more than 3-fold, from €67,145 to €17,500. This decrease is of public health concern, because there is a genuine risk that EMA will not find rapporteurs among Member States due to the work being significantly undercompensated. The Netherlands proposes to increase the remuneration of the rapporteurs to €85,000, based on the increased average time spent and a correction of the hourly rate.

In detail:
The NCA mean time for pharmacovigilance referrals in the MBDG group report from 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on the ratio [hours spent by scientific staff : hours spent by administrative staff]. According to page 27 of the MBDG report, time spent by NCAs for referrals is mainly of a scientific nature.

For the targeted approach, time data was collected from 13 NCAs on 48 procedures (half rapporteur, half co-rapporteur). The updated mean time was 30% higher than the time in the MBDG report, more specifically: MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs.
Further, in the Commission proposal an hourly rate of €38.50 is used. This hourly rate falls considerably short for the NCAs to carry out the necessary tasks. A more accurate rate is €144 per hour (this includes the general adjustment). This means: 590 hours X €144 = €85 000 for each of the rapporteurs.

Further, we propose only a single remuneration amount for pharmacovigilance referrals, contrary to the Commission proposal, as in our view this would cover NCAs' costs regardless of the number of active substances or combination of active substances and the number of MAHs.

26.Periodic Safety Update Report (PSUR)

Current remuneration amount:

PSURs	14 750 EUR

Remuneration amount proposed by the Commission:

PSURs	12 900 EUR

Remuneration amount proposed by the Commission, if corrected for the Eurostat inflation rate (i.e., + 13%):

PSURs	14 577 EUR

Proposal NL for adjusted remuneration amount:

PSURs	**16 560 EUR**

Background and Justification:
The PSUSA procedure may require a multidisciplinary evaluation. The development of innovative products with new technology implies that assessment capacity needs to be developed and updated. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available with different areas of expertise depending on the nature of a certain risk.

Various activities are required and need to be compensated for, for example:

- PSUR procedures need to be presented frequently at the respective regulatory committee; PRAC → CMDh or PRAC → CHMP.
- EMA funded studies regarding the impact of pharmacovigilance measures requiring rapporteur assessment and preparation of the presentation at PRAC.
- Costs for resources to assess ADR and to perform bibliographic research to determine causality assessment (average time spent per ADR assessment and treatment: 2h).

27.Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship

The role of PRAC rapporteur is not always financially compensated where duly justified. This leads to this role being unattractive and unaffordable to NCAs, whereas strong PRAC rapporteurships are **essential in regards guaranteeing patient safety**. Based on costs incurred, the Netherlands proposes new remuneration amounts for the PRAC rapporteur. These amounts are based on the Commission proposal if corrected for the actual inflation rate (use of Eurostat data: 5.3% for 2021 and 10.4% for 2022, instead of 1.2%). In other words, the amounts proposed by the Commission have been increased by 13%; these amounts are the basis for the remuneration amounts proposed by NL. For clarity, also numbers have been included prior to correction for inflation (second column to the right).
In this situation, no general adjustment of 20% has been applied, as the Netherlands does not oppose to the total remuneration amounts proposed by the Commission, that is, as long as they are corrected for the actual inflation rate. In addition, the amounts proposed below require further adjustment prior to adoption of the regulation, because they don't include the actual inflation rate for 2023.

Type of fee	Role	Commission proposal	Commission proposal corrected for Eurostat inflation rate (i.e., plus 13%)	Proposal NL based on initial Commission proposal	Proposal NL based Commission proposal corrected for the Eurostat inflation rates (i.e., plus 13%)
Annual fee under point 1.1 of Annex III	CHMP rap	6 400 EUR	7 232 EUR	5 760 EUR	6 509 EUR
	CHMP co-rap	5 600 EUR	6 328 EUR	5 040 EUR	5 695 EUR
	PRAC rap	0	0	1 200 EUR	1 356 EUR
Annual fee under point 1.2 of Annex III:	CHMP rap	12 900 EUR	14 577 EUR	11 610 EUR	13 119 EUR
	CHMP co-rap	11 400 EUR	12 882 EUR	10 260 EUR	11 594 EUR
	PRAC rap	0	0	2 430 EUR	2 746 EUR
Annual fee under point 1.3 of Annex III:	CHMP rap	25 700 EUR	29 041 EUR	23 130 EUR	26 137 EUR
	CHMP co-rap	22 700 EUR	25 651 EUR	20 430 EUR	23 086 EUR
	PRAC rap	0	0	4 840 EUR	5 469 EUR
Procedural fee under point 3.1 of Annex I	CHMP rap	217 300 EUR	245 549 EUR	206 435 EUR	233 272 EUR
	CHMP co-rap	189 300 EUR	213 909 EUR	179 835 EUR	203 214 EUR
	PRAC rap	0	0	20 330 EUR	22 973 EUR
Procedural fee under point 3.2 of Annex I:	CHMP rap	153 000 EUR	172 890 EUR	145 350 EUR	164 246 EUR
	CHMP co-rap	143 300 EUR	161 929 EUR	136 135 EUR	153 833 EUR
	PRAC rap	0	0	14 815 EUR	16 741 EUR
Procedural fee under point 3.3 of Annex I:	CHMP rap	141 500 EUR	159 895 EUR	134 425 EUR	151 900 EUR
	CHMP co-rap	83 000 EUR	93 790 EUR	78 850 EUR	89 101 EUR
	PRAC rap	0	0	11 225 EUR	12 684 EUR
Procedural fee under point 3.4 of Annex I:	CHMP rap	236 500 EUR	267 245 EUR	224 675 EUR	253 883 EUR
	CHMP co-rap	151 700 EUR	171 421 EUR	144 115 EUR	162 850 EUR
	PRAC rap	0	0	19 410 EUR	21 933 EUR

Procedural fee under point 3.5 of Annex I:	CHMP rap	160 600 EUR	181 478 EUR	152 570 EUR	172 404 EUR
	CHMP co-rap	149 400 EUR	168 822 EUR	141 930 EUR	160 381 EUR
	PRAC rap	0	0	15 500 EUR	17 515 EUR
Procedural fee under point 3.7 of Annex I:	CHMP rap	89 100 EUR	100 683 EUR	84 654 EUR	95 649 EUR
	CHMP co-rap	89 100 EUR	100 683 EUR	84 654 EUR	95 649 EUR
	PRAC rap	0	0	8910 EUR	10 068 EUR

General comment:

NCAs receive a share of the CAP annual fee (point 1 of Annex III) for products for which they are CHMP rapporteur or CHMP co-rapporteur. This means that the PRAC rapporteur, which is a different NCA for new products[21], does not receive financial compensation for additional activities they play an important or even leading role in, for instance signal detection. Similarly, the PRAC rapporteur plays a significant role in the assessment of initial marketing authorisation applications in their assessment of the risk management plan (RMP) and pharmacovigilance plan, as well as in the assessment of the RMP for certain Type II variations, but also there does not receive remuneration. This makes the PRAC rapporteur role unattractive, which is problematic as it is an important role in regards guaranteeing patient safety. The fact that the proposed remuneration amounts for several pharmacovigilance activities (pharmacovigilance referrals, PSUR, Type II safety) are insufficient to cover costs incurred adds to this. The Netherlands has therefore made a proposal for redistribution of certain CHMP (co-)rapporteurs' remuneration amounts to also compensate the PRAC rapporteur role. This proposal does not lead to amendment of the fee to be paid by industry or to amendment of the fee share for EMA, it only leads to amended remuneration amounts for the CHMP (co-)rapporteur and new remuneration amounts for the PRAC rapporteur (i.e., the amounts for the CHMP rapporteurs are partially re-distributed to the PRAC rapporteur).

The proposal only relates to the PRAC rapporteur, because the PRAC co-rapporteur generally has a limited role. In addition, the redistribution of the share for NCAs, instead of a top-up (which would make total fees and total remuneration amounts higher), is considered sufficient to generally cover NCAs' costs. Reason is that for legacy products, the NCA that is CHMP rapporteur is also the PRAC rapporteur, meaning that the relevant NCA already receives a share of the CAP annual fee and procedural fee for marketing authorisation applications. For new products (i.e., products for which the marketing authorisation was applied for after the application of the new pharmacovigilance legislation), however, the NCA that acts as PRAC rapporteur is not the same as the NCAs that act as CHMP rapporteurs.

Annual fee:

The proposed share in the annual fee for the PRAC rapporteur is based on PRAC rapporteur activities such as signal assessments as well as assessment of the RMP for variations. To

[21] "New product" refers to products for which an application for marketing authorisation was made after the date of application of the pharmacovigilance legislation. For legacy products, it was decided that the CHMP rapporteur would also act as PRAC rapporteur.

cover these costs, the PRAC rapporteur is to receive 10% of the proposed remuneration amount of the CHMP rapporteur **PLUS** 10% of the proposed remuneration amount of the CHMP co-rapporteur. This means that both CHMP rapporteurs receive 90% of the remuneration amounts initially proposed for these roles. These percentages are based on medium hours and hourly rates per relevant activity.

Applications for marketing authorisation:
The proposed share in the procedural fees for the PRAC rapporteur is based on costs incurred by the PRAC rapporteur for assessment of the RMP and the pharmacovigilance plan. To cover these costs, the PRAC rapporteur is to receive 5% of the proposed remuneration amount of the CHMP rapporteur **PLUS** 5% of the proposed remuneration amount of the CHMP co-rapporteur. This means that both CHMP rapporteurs receive 95% of the remuneration amounts initially proposed for these roles. These percentages are based on medium hours and hourly rates per relevant activity.

For generic applications, no actual numbers have been included, since a new remuneration amount will be put forward by other Member States based on their data. We propose, however, to apply the same 5% rule as described here.

28.Inspections

Proposal NL for adjusted remuneration amounts
Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fee and remuneration amounts proposed by the Commission in euros **(figures in blue are the amounts if corrected for the Eurostat inflation rate, i.e. increase of 13%)**			**Fee and remuneration amounts proposal- adjusted in euros**		
Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	**Leading**	**Supporting**
GMP	37 800 (42 714)	15 600 (17 628)	9 400 (10 622)	70,800 (↑87%)	**34 000**	**24 000**
GCP	44 200 (49 946)	19 600 (22 148)	10 400 (11 752)	65,200 (↑48%)	**32 000**	**19 000**
PMF	36 100 (40 793)	13 400 (15 142)	8 200 (9 266)	54,500 (↑51%)	**20 000**	**20 000**

Background
Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive and challenging, as inspectors are offsite for the duration of the inspection and as inspections may involve significant travelling to and within unfamiliar countries.

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase of fee and remuneration amounts, the remuneration amounts proposed by the Commission remain inadequate to cover the costs and do not reflect the workload of the NCAs. The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).

Therefore, new remuneration amounts are proposed, based on a cost-based approach, in order to ensure that the actual costs incurred by NCAs during inspections outside of the EU are covered. Costs included in this approach are:

(u) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive. The actual inspection is performed by an inspection team traveling to one or several sites and includes a range of activities from planning, travel to various stages of elaboration of the report. In case of a negative outcome, the process becomes more complex and the inspectors' work increases significantly.

Inspections of particular complexity (in terms of products or dosage forms and/or large sites) regularly require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time has not been considered in the current proposal.

(v) Indirect costs

Building a qualified inspection workforce is costly in terms of time and resources. As per EU requirements inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme on scientific or regulatory developments is in place.

Some particular products such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training.

An increase in inspection fees is needed due to increased hours from the data gathering exercise. In addition, costs estimation in the Commission proposal does not account for:

6. Need to create/support (larger) inspection teams, frequently with more than one inspector per NCA.
7. Senior inspection costs versus average scientific salaried.
8. Need to spend more time on site/extend inspection duration.
9. Inspector mentoring, training and qualification.
10. Increased inflation rate.

Detailed explanations and data on actual costs and ratio of cost recovery based on past inspections and compared to the Commission proposal are included in annexes II and III.

Annex II – detailed explanation of costs and proposed remuneration amounts

Costs of providing the service to be included in the remuneration to NCAs:

(a) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection. They are also challenging as they may involve significant travelling to and within unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, review of the documentation provided by the inspectee, actual on-site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.

Moreover, inspections abroad normally require an inspection team, which may involve more than one inspector from the NCAs. Normally, one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).

Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the fee is awarded per inspected product.

(b) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialised training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.

Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).

A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network
There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload and costs is necessary to ensure the sustainability of inspection resources in the network.
Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs' cost recovery
It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCAs. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCAs may have been underestimated in the costing exercise. Indeed, when calculating the actual costs for NCAs, the recovery rate in reference to the proposed remuneration amounts is significantly lower than 1.0 (where 1.0 = full recovery of direct and indirect costs).

The table below shows the cost-recovery for NCAs based on the remuneration amounts proposed by the Commission:

	Fees and remuneration amounts as proposed by the Commission 13/12/22 (in EUR)			**Actual costs in EUR and cost recovery in %**			
Inspection type	**EMA fee**	**Leading**	**Supporting**	**Average actual costs (lead)**	**Cost recovery (lead)**	**Average actual costs (support)**	**Cost recovery (support)**
GMP	37 800	15 600	9 400	33 847	0.46	23 275	0.40
GCP	44 200	19 600	10 400	31 724	0.62	16 748	0.63
PMF	36 100	13 400	8 200	19 244	0.70	19 244	0.43

Conclusion and proposal for modification of remuneration amounts
The points made above illustrate the need for an increase in remuneration amounts for inspections. This is further illustrated by the hard data provided in annex II. The information provided shows:

19. Evidence of increased hours per inspection from the data gathering exercise.

20. Evidence that the remuneration amounts do not cover NCAs' costs; costs estimation does not account for:

KK) Inspector mentoring, training and qualification.

LL) Need to create/support inspection teams, frequently with more than one inspector per NCAs.

MM) Need to spend more time on site/extend inspection duration.

NN) Increased inflation rate.

OO) Senior inspection costs versus average scientific salaried.

Based on the above, adjusted fee and remuneration amounts are as follows (see also the first table in this section):

Inspection type	Revised EMA fee (total)	Leading	Supporting
GMP	70,800 EUR (↑87%)	34 000 EUR	24 000 EUR
GCP	65,200 (↑48%)	32 000 EUR	19 000 EUR
PMF	54,500 (↑51%)	20 000 EUR	20 000 EUR

Annex III – hard data and detailed calculations for inspections

Table 1-3: Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification.
Cost/fees are calculated on the basis of 1 product per location/inspected site.
Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided,
and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Table 1

Country 1

		Fee and remuneration amounts as proposed by the Commission 13/12/22 (EUR)										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Table 2

Country 2		Fees and remuneration amounts as proposed by the Commission 13/12/22 (EUR)						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs	Cost recovery ratio	Actual costs +10%	Cost recovery ratio (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65
GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Table 3

Country 3		Fees and remuneration amounts as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading	Actual costs Supporting	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%)	Actual costs Supporting (incl. 10%)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.70	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.60	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.40	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.80	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.70	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.30	21,354.30	0.63	0.38

Table 4: Hours and remuneration proposed by Commission per type procedure, EMA and NCAs
Percentage of time/resources is not proportional to the remuneration.
GMP Inspections outside of Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	37 800	12 800 (34%)(*)	15 600 (41%)	9 400 (25%)
Time AD (Scientific, h)	167,21	15,59 (9,3%)	75,81 (45,3%)	75,81 (45,3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	44 200	14 200 (32%)	19 600 (44%)	10 400 (23%)
Time AD (Scientific, h)	767	56,21 (7,3%)	462,14 (60%)	248,65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total (EUR)	EMA	Lead inspector	Supporting inspector
Fee/remuneration	36 100	14 500 (40%)	13 400 (37%)	8 200 (22%)
Time AD (Scientific, h)	163,2	20 (12%)	71,60 (43,8%)	71,60 (43,8%)

(*) Hours calculated as per EMA declaration.

PORTUGAL

PT proposal on the targeted approach for revision of the EMA Fees

- *A general adjustment for the NCA remuneration, taking into consideration the developments in recent years (for example inflation etc.). This could preferably be expressed as a percentage on the current fee proposal.*

Considering that the Data gathering exercise on which the proposal for the new Fee Regulation is based on data from 2016 and that the evolution of the medicines evaluation framework is constantly evolving and becoming more complex and demanding, a general adjustment for all procedures of 20% is proposed.
This considers, complexity and sustainability factors such as:

- the constraints with the limited human resources and difficulties in retaining them by the National Agencies,
- the involvement of senior assessors considering the necessary expertise,
- the need for continuous training of assessors,
- the increased workload to national activities resulting from EU priorities (e.g. referrals and periodic safety reports),
- the need to maintain national IT databases.

The evolution of the inflation rate for 2023 and 2024 should also be considered.

- Concrete proposals for adjusted remuneration to NCAs for the agreed procedures; Scientific Advice, Generics, Type II variations, Referrals, Periodic Safety Update Reports (PSURs), Inspections, Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship.

Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	1

Generics	Annex I, point 3.6 & 3.8	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 99 122 for rapporteur. b) A fee of 141 200 EUR shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	2
Type II variations	Annex I, point 5	Single type II variation – indication extension: Rapp/Co-Rapp: 64 400 EUR Single type II variation – other: 10 100 EUR	3
Referrals	Annex I, point 6	27 326 EUR	4
Periodic Safety Update Reports (PSURs)	Annex I, point 14	16 560 EUR	5
Inspections	Annex IV, point 1	GMP: Leading: 34 000 EUR, Supporting: 24 000 EUR GCP: Leading: 32 000 EUR, Supporting: 19 000 EUR PMF: Leading: 20 000 EUR, Supporting: 20 000 EUR	6
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration	No data provided.	

- *A clear and detailed justification for the proposed NCA remuneration adjustments. This could preferably be done by supporting data, such as time- and cost data (where feasible), and other information deemed relevant for the procedures.*

The proposed adjustments are based on medium hourly rates/procedure based on internal data that conclude that the initial proposed remuneration did not adequately address the work performed at national level.
The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

1 - Scientific Advice

The proposed renumerations will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice.
The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.

The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.
Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.

Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.
Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Sc Adv (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries). Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level. In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains. The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the renumeration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity

to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

2- Generics

The EC proposal considered the data gathering exercise which does not reflect the contribution of the NCA regarding the assessment of the quality, safety and efficacy of generic medicinal products including expertise on the fields of pharmacokinetics.
The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed (50% split). The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering1 is of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee. Therefore, a total increase % fee increase adjustment of 40.4% is warranted.

3- Type II variations

The variations are becoming more complex requiring very often the involvement of a larger team of assessors. As new procedures are approved, the post MA procedures increase and are more demanding as new MA approvals often included accelerated assessment or conditional approval and therefore there is a higher pressure for post MA procedures. The complexity of some of the variations has increased to a point that the current timetable is challenging to comply due to the length of the documentation to be assessed. Therefore, NCA have to ensure that capacity follows this trend.
The renumeration for Type II variation indication and for Type II variation other (5.1 and 5.1 of Annex I to the Regulation of the EC on fees) should both be increased in order to cover NCA expenses
Based on the average hours spend and the average hourly rate, the renumeration should be increased as stated above. The sustainability factor of 1.2 (+20 %) is considered.

4- Referrals

PT experience regarding pharmacovigilance referrals, shows that the amount of time allocated to these procedures, is much higher that the data collected during the Data gathering exercise.
As the scope of these procedures involves, quite often, several medicinal products which translates in a significant volume of work and complex review of the state of the art of the knowledge of medicinal products, we believe that any reduction in this area will not allow an adequate participation of the MS.
In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros. This decrease is of public health concern.

5- Periodic Safety Update Reports (PSURs)

The PSUSA procedure might require a multidisciplinary evaluation. The development of innovative products, with new technology, imply that the assessment capacity needs to update and develop. When assessing any PSUR data, the main assessor must have expertise within the product's indication, but a multidisciplinary team must also be available, with different areas of expertise. Depending on the nature of a certain risk, frequently there is the need to have input from clinical experts with different areas of expertise. Frequently the PhV procedures need to be presented at the respective regulatory committee; PRAC->CMDh or PRAC->CHMP. EMA funded studies regarding the impact of Phv measures, with the need of the Rapporteur assessment and preparation of the presentation at PRAC. The work in Pharmacovigilance relies on the maintenance and updates of the national IT " database as well as maintenance and updates of other supportive national database (e.g. PT IT datases: Product's Information database, SATS, GRCM, SGA, Cloud, GiMed). It must also be considered and assured the costs with resources to assess ADR and to perform bibliographic research to determine causality assessment.

6- Inspections

It is key that their operating costs are covered, including the costs for inspections outside of the EU.
As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors.
The inspectors require a continuous training programme, on scientific or regulatory developments. For some particular products, such as blood products, biologicals or immunological products, or ATMPs is required to comply with the necessary expertise and training. Inspections are becoming more complex (e.g. with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion)).
Inspections require an inspection team, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).
Inspection work consists of inspection planning, travel and accommodation preparation, review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee, and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.
To ensure that the fees cover the costs of these inspections, it is imperative that the fee is awarded per inspected product.

Final remarks:
The data and justifications provided resulted from a collaboration and constructive contribution between all the authorities of the network, which we hope can contribute to the future regulation ensuring and promoting a fair and balanced approach for the sustainability and resilience of the European system. It is crucial that the fees remunerat the various dimensions of the highly specialized scientific technical evaluation work provided by the national authorities, ensuring a sound financial basis for the activities of the Agency and for the National Authorities.

ROMANIA

Procedure	Article	General adjustment for all procedures (%)	Total remuneration to NCAs (incl. general adjustment)	Justification
Scientific Advice	Annex I, point 1	42,58% 39,49% 31,52%	1.1: EUR 23 504 1.2: EUR 17 652 1.3: EUR 11725	We do not agree with reduction of remuneration for NCA because the work involved in procedures is the same and also the costs for NCA are higher. The evaluation of the scientific expertise/advice of the NCA are undervalued.
Generics	Annex I, point 3.6 & 3.8	21,53% 25,36%	3.6: EUR 70 600 3.8: EUR 13 800	We do not agree with reduction of remuneration for NCA because the work involved in procedures is the same and also the costs for NCA are higher. The degree of complexity of assessments has increased due to scientific progress.
Type II variations	Annex I, point 5	259,57%	5.2: EUR 17 680 5.3: idem 5.1 & 5.2 5.4: idem 5.1 & 5.2	We do not agree with reduction of remuneration for NCA because the work

				involved in procedures is the same and also the costs for NCA are higher.
Referrals	Annex I, point 6	23,35% 24,83% 23,33% 23,33%	6.7.1: EUR 60 235 rapp and EUR 60 235 co-rapp 6.7.2: EUR 86 067 rapp and EUR 86 067 co-rapp 6.7.3: EUR 105 286 rapp and EUR 105 286 co-rapp 6.7.4: EUR 142 829 rapp and EUR 142.829 co-rapp	We do not agree with reduction of remuneration for NCA because the work involved in procedures is the same and also the costs for NCA are higher.
Periodic Safety Update Reports (PSURs)	Annex I, point 14	19,40%	14.1: EUR 18 139	We do not agree with reduction of remuneration for NCA because the work involved in procedures is the same and also the costs for NCA are higher. NCA RO wants to highlight that the fee for PSUR assessment does not take into consideration the number of PSURs submitted by MAHs involved (some procedures involve more than one PSUR. The degree of

				complexity of assessments has increased due to scientific progress.
Inspections	Annex IV, point 1	26,4%	1.1.1.: EUR 10 870 & EUR 6 573 1.1.2.: EUR 19 718 & EUR 11 882 1.1.3.: EUR 18 581 & EUR 11 502 1.1.4.: EUR 24 774 & EUR 13 146 1.1.5.: EUR 16 938 & EUR 10 365 1.1.6.: EUR 16 938 & EUR 10 365 1.1.7.: EUR 16 685 & EUR 10 997 1.1.8: EUR 20 477 & EUR 12 766	It is suggested that the fees and renumerations levied is proportional and add the harmonization index
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration required		EUR 40 000 rapp EUR 40000 co-rapp	NCA RO proposes that the renumeration for rapp and co-rapp should be the same, because the work of rapp and co-rapp involved is similar. Also, it should be in line with section 6.7 of Annex 1. The degree of complexity of

				assessments has increased due to scientific progress.
Renewals	No fee was proposed		EUR 3 850 for Rapp and EUR 3850 for CoRapp	In the proposed EMA fee Regulation, no renewal fee was proposed. RO NCA does not agree and proposes to add a fee for renewals as the assessment is still performed by Rapp and CoRapp. The degree of complexity of assessments has increased due to scientific progress.

SLOVENIA

Procedure	Article	General adjustment for all procedures (%)	Total remuneration to NCAs (incl. general adjustment)	Justification
Scientific Advice	Annex I, point 1			
Generics	Annex I, point 3.6 & 3.8	3.6.(a): 40,4 % 3.6.(b): /	a) A fee of EUR 198 244 shall apply to an application. The remuneration to NCAs of EUR 97 244 for rapporteur. b) A fee of EUR 141 200 shall apply to an application. The remuneration to NCAs of EUR 40 200 for rapporteur.	a) Whereas, the European Commission has adjusted the EMA human medicines fees upwards by 14% (proposed fee in 2021 vs 2022 commission proposal) due to inflation rate, therefore a similar financial adjustment is acceptable if used by any member state proposal. The proposal has calculated a current average country coefficient based explicitly on the country coefficient of the rapporteur. This therefore does not reflect the reality where countries with high country weighted co-efficient carryout the scientific assessment. The average country coefficient for rapporteurships that have been finalised over 2019 and 2022 article 10.1 (generic) procedures is calculated to be 89%. Since, this calculation does not consider the setting up of Multinational teams, it is proposed to use the average country co-efficient of 109% as assigned to the Netherlands (seat of the EMA). Therefore, an adjustment in fees for generic medicines is warranted of 19.4 %. The EMA mean hours for a Generic is recorded at: 272.49 hours while the NCA mean average is 507.19 hours the % is therefore 35% vs 65%. The fees therefore have to be amended appropriately and the appropriate percentage distribution is proposed.

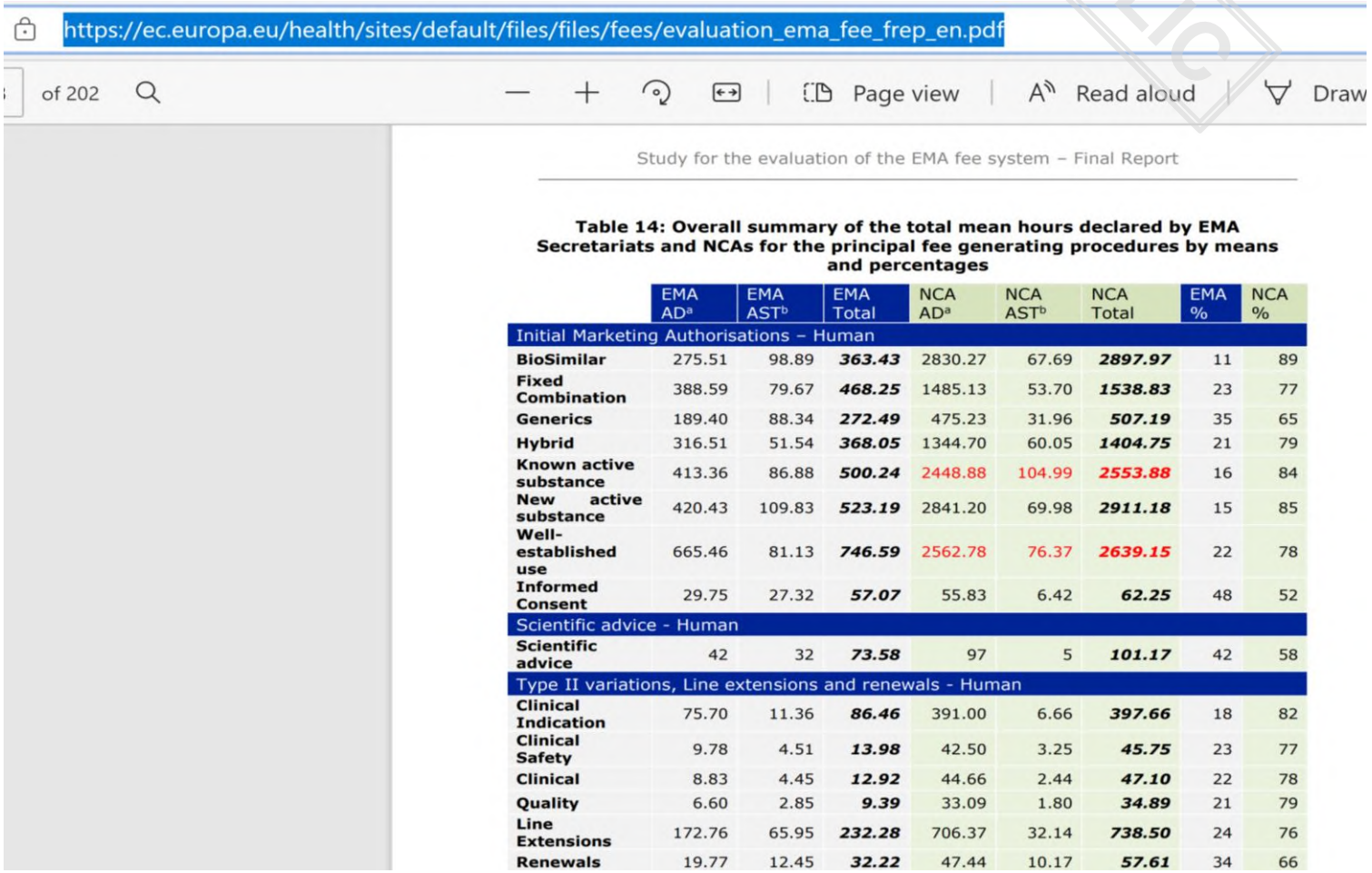
				The time used by the commission in its model is 401.37 hours. The time adopted by the EMA MB 2017 data gathering[1] of 507.19 hours. A discrepancy of 21% in time is to be adjusted to the proposed fee. Since one of the aims of the multinational team assessment, is to enable involvement of all EU member states to contribute to the scientific evaluation of medicinal products, a total increase % fee increase adjustment of 40.4% is warranted. The proposed new fee is also more appropriate when considering the fees charged by the FDA for the evaluation of a generic medicinal product (app. $240,000 for an abbreviated new drug application for access to a 380 million market). b) A separate fee for informed consent MAAs is warranted for legal clarity.
Type II variations	Annex I, point 5	5.1: 29 5.2: new fee 5.3. 43	5.1 A fee of EUR 139 800 shall apply to an application for a major variation of type II for an addition of a new therapeutic indication or modification of an approved indication. The remuneration shall be EUR 49 400 for the rapporteur and EUR 49 400 for the co-rapporteur.	The proposal envisages a higher fee only for new therapeutic indications or changes to an approved indication (under 5.1). A single fee is provided for all other type II changes (covered under 5.2), which does not adequately reflect to the possible complexity of some variations (e.g. change in posology). Similarly, a very low fee is provided for quality changes of type II, which may also include some very complex ones, e.g. assessment of BE studies (in relation to changed

			5.2 A fee of EUR 80 500 shall apply to an application for a major variation of type II, complex clinical/non-clinical/quality variation of type II, not covered by point 5.1. The remuneration shall be EUR 56 350 for the rapporteur. 5.3 A fee of EUR 23 000 shall apply to an application for a variation of type II, not covered by points 5.1 and 5.2. The remuneration shall be EUR 16 800 for the rapporteur.	formulation of MP). Even in this case, both the amount and the distribution of the fee for the services provided are not appropriate and are insufficient for the work done by the NCAs.[1] As per EMA Management Board data gathereing document the hours to evaluate variations is documented to be 76-82% (NCA) vs 18-24 % (EMA). The commission proposal as it stands undermines the sustainability of the EU medicines regulatory network and therefore in this respect three levels of variations are proposed.
Referrals	Annex I, point 6			
Periodic Safety Update Reports (PSURs)	Annex I, point 14			

Inspections	Annex IV, point 1			
Pharmacovigilance Risk Assessment Committee (PRAC) rapporteurship	New fee and remuneration required			

Notes:

1. **Reference:** [evaluation_ema_fee_frep_en.pdf (europa.eu) https://ec.europa.eu/health/sites/default/files/files/fees/evaluation_ema_fee_frep_en.pdf](https://ec.europa.eu/health/sites/default/files/files/fees/evaluation_ema_fee_frep_en.pdf).



https://ec.europa.eu/health/sites/default/files/files/fees/evaluation_ema_fee_frep_en.pdf

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Table 14: Overall summary of the total mean hours declared by EMA Secretariats and NCAs for the principal fee generating procedures by means and percentages

	EMA AD[a]	EMA AST[b]	EMA Total	NCA AD[a]	NCA AST[b]	NCA Total	EMA %	NCA %
Initial Marketing Authorisations – Human								
BioSimilar	275.51	98.89	***363.43***	2830.27	67.69	***2897.97***	11	89
Fixed Combination	388.59	79.67	***468.25***	1485.13	53.70	***1538.83***	23	77
Generics	189.40	88.34	***272.49***	475.23	31.96	***507.19***	35	65
Hybrid	316.51	51.54	***368.05***	1344.70	60.05	***1404.75***	21	79
Known active substance	413.36	86.88	***500.24***	2448.88	104.99	***2553.88***	16	84
New active substance	420.43	109.83	***523.19***	2841.20	69.98	***2911.18***	15	85
Well-established use	665.46	81.13	***746.59***	2562.78	76.37	***2639.15***	22	78
Informed Consent	29.75	27.32	***57.07***	55.83	6.42	***62.25***	48	52
Scientific advice - Human								
Scientific advice	42	32	***73.58***	97	5	***101.17***	42	58
Type II variations, Line extensions and renewals - Human								
Clinical Indication	75.70	11.36	***86.46***	391.00	6.66	***397.66***	18	82
Clinical Safety	9.78	4.51	***13.98***	42.50	3.25	***45.75***	23	77
Clinical	8.83	4.45	***12.92***	44.66	2.44	***47.10***	22	78
Quality	6.60	2.85	***9.39***	33.09	1.80	***34.89***	21	79
Line Extensions	172.76	65.95	***232.28***	706.37	32.14	***738.50***	24	76
Renewals	19.77	12.45	***32.22***	47.44	10.17	***57.61***	34	66

SPAIN

Hereby Spain provides, following the Presidency request, a proposal to adjust remunerations to National Competent Authorities (NCAs) for some of the articles, together with a rationale for the proposal. This does not preclude the capacity to include additional proposals for other articles, as per the Presidency's invitation, following the discussions at the working group.

Note that for the changes proposed pertaining GXP inspections (GMP, GCP and PMF) additional rationale has been provided as Annex 1.

- **GMP inspections: Good Manufacturing Practices inspections**
  GCP inspections: Good Clinical Practices inspections
  PMF: Plasma Master File inspections

General adjustment for all procedures			
		Adjustment (%)	**Justification**
General adjustment for the NCA remuneration		Inflation rate, not included in the proposal for increases detailed below.	
Targeted approach for the chosen procedures			
Procedure	**Article**	**Total remuneration to NCAs (incl. general adjustment) (EUR)**	**Justification**
Scientific Advice	Annex I, point 1.1, 1.2 & 1.3	Level I: 9 720 EUR Level II: 13 440 EUR Level III: 20 160 EUR	See Annex; based on medium hourly rates/procedure
Referrals	Annex I, point 6	27 326 EUR	See Annex; based on medium hourly rates/procedure
Inspections	Annex IV, point 1 (Inspections outside of EU only)	GMP lead 34,000 € (117%) GMP support 24,000 € (155%) GCP lead 32,000 € (63%) GCP support 19,000€ (82%) PMF distinct inspections 20,000€ (49%)	Evaluation of cost for inspections for each type of inspection, based on the average of actual costs from a set of inspections files of international inspections (EMA requests) incurred by several NCAs. Proposal for revision of remuneration is based on a full recovery of inspection costs, including indirect costs of building and maintenance of a qualified inspection workforce, including costs of qualification and training. Additional information is provided in the Annex.

Annex – Justification of Fee adjustments:

I. General adjustment for the NCA remuneration – for all procedures:

Actual cost of procedures based on hard data has been provided by a significant number of national competent authorities (NCA) in a very short time. NCA costs represent the situation in 2022; increase in complexity per procedure is calculated towards the data used for the data gathering in 2016. However, when the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council, will come into force probably in 2024, an adjustment for inflation for years 2023 and 2024 will be necessary.
The European Commission already indicated that it considered inflation rates of 1.2% until 2024 and 1.4% the following years. These rates would need an uplift.

There are different sources of estimated inflation rates (Eurostat, European Central Bank, etc.) and it needs to be decided which estimations would apply to all procedures of the targeted approach.

NCAs participating in the targeted approach agreed to apply a so called "Sustainability factor" that would include the uplifted inflation rate.

This factor was estimated at 20% increase of actual average costs and would help to cover the needs of the network at the time of implementation of the regulation including, beside inflation:

- Increase in complexity/innovative developments or methodologies.
- Increased involvement of senior assessor and external experts to cover the requested expertise.
- Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
- Current limitation of human resources in NCA and retention of expertise at smaller agencies relying on external experts
- Increase burden of work subsequent to European priority actions

II. Targeted approach for the chosen procedures:

II.1: Procedure Scientific Advice, Article: Annex I, point 1:

Current fee:

Level I	11 725 EUR
Level II	17 650 EUR
Level III	23 500 EUR

Fee proposal by EC:

Level I	5 300 EUR
Level II	6 500 EUR
Level III	10 400 EUR

Fee proposal – adjusted:

	Proposal – adjusted
Level I	**9 720 EUR**
Level II	**13 440 EUR**
Level III	**20 160 EUR**

1. Background

Scientific Advice (SA) supports innovation on the EU market and enables products to successfully negotiate the regulatory process. Statistics show a higher success rate for MAAs where scientific advice has been sought and thus scientific advice supports the timely availability of medicines to European patients.

2. Cost of providing the service

As outlined below, there is evidence that the cost of providing the service has increased. This is due to both the increase in inflation from the initial, the increased complexity of SA and

from the use of the average scientific salary. This salary rate does not reflect that NCA's are using their most expensive resources for scientific advice, particularly clinical advice.

3. Increased complexity of procedures

The complexity of topics covered by the advice has significantly increased over time:

- Novel classes of development candidates like ATMP's and mRNA vaccines came up, new targets consequently became drugable and new technologies like continuous manufacturing became available. Above that, qualification advices turned out to be the most challenging ones based on the number of hours needed per procedure and the need for the most experienced (and expensive) staff.
- Even scientific advices for Biosimilar development are getting more complex since there are in depth discussions ongoing intending to waive clinical efficacy testing, challenging comparability testing on quality grounds and reliability of PD parameters.
- To address these challenges, we needed to increase the number of qualified assessors (especially statisticians)
- The numbers of advises requiring clinical modelling and simulation and input from statisticians increased considerably.
- Additionally, the amount of information covered by briefing books and attached documents also significantly increased over time.

4. Sustainability of the network

The proposed fee structure for Scientific Advice (SA) is not in line with what the Head of the SA office at EMA states in future policy for the Scientific Advice Working Party (SAWP). The intentions are to keep the same "expertise" and to have the working party with full partition. Now there are only 67 members of the SAWP active out of 72 members. Requests for advice have increased in the past years and the requests for advices have got more complicated.

The status in January 2023 was that 15 SA out of 67 were not allocated in the first round and it is getting more difficult every year to get anyone to take e.g., paediatrics-only SA. Looking into the fee structure advanced in the European Commission's proposal this will most likely be near to impossible to accommodate. The proposed change in fee structure is based on a 7 year old time audit that was already criticised at that time. If agencies can not contribute to

the network by doing SA the service by EMA is put at risk which could lead to pharmaceutical companies waiting longer or seeking SA elsewhere.

Based on the fee reduction in the EC's proposal some agencies may not be able to sustain the SA within the agency and fear that high level experts could resign since they cannot use those experts in other assignments. Therefore those agencies will most likely not be able to contribute to the SAWP in the way they have done in the past and it will be more difficult for EMA to find rapporteurs and co-rapporteurs for SA.

If this fee proposal will be approved, undermining the SA platform, there is also a great risk that the quality of SA will decrease and the quality of submitted MA applications will be lower leading to rejection of MA applications in the assessment phase forcing applicants to repeat the clinical trials. That will be of much more cost for the companies and resulting in greater cost for the health industry and society for drugs coming later on market with added detriment for the patients.

5. Developing capacity

The NCAs need to have experts to "give" the SA. To do so, they need to continuously build up the expertise and hold on to experts with experience. If the NCAs do not have the capacity to do so it will be much harder to have the expertise for SA within the NCAs and they will no longer have the capacity to contribute to SA. This specifically applies for small agencies.

It may be presumed that it will also be more costly for the pharmaceuticals companies to get a SA since there will be much more difficult to develop and have available the expertise in the field needed for the SA.

6. Investing in the network is a real cost of the system

For NCAs who invest in scientific advice, it is a pathway to developing resources that can provide, not only, a technical appropriate service to the industry and EMA, but also to grow the overall capacity and expertise within the agency. Employing, mentoring and training these resources is labour intensive but is not reflected in the hours spent on centralised activities. Indeed, a new technical resource will generate little fee income in year one as they are often mirroring more experienced colleagues. Covid and the last number of years have shown how stretched the resources are in the network. Simply recruiting a new resource is not sufficient as even the most academic/ experienced new member of staff will still need to be trained in regulation and assessment. By only calculating the cost and related fee based on the hours spent on the process, the fee does not reflect the real cost of developing staff to

provide that service. With staff turnover this is an ongoing investment required by the NCAs to deliver the service. While it is not a *direct cost of the procedure* it is a *real cost of delivering the service*. The methodology allowed full cost recovery for the EMA so they can fund these costs but for the NCAs it was only partial recovery. The real cost of providing the scientific assessment for all European medicines is not limited to the hours spent on those procedures. It is also not limited to all the ancillary work such as attending and contributing to committees, national work on centralised products etc. It also includes developing a sustainable, efficient and a scientifically appropriate service to the EMA and the patients of Europe.

7. National competent authorities and value for money

The costing exercise on fees has shown that the current model, whereby the NCAs provide all the scientific and inspection resources, provides real value for money to the companies as the cost of the NCAs is significantly less than that of the EMA. However, while it is not suggested that the NCAs are remunerated at the same rate as the EMA, the discrepancy in costs is of itself, evidence that the costing exercise has failed in properly identifying the costs of the NCAs. In relation to SA, despite the fact that it is the NCAs that review, draft and deliver the scientific advice, the Rapp and Co-rapp share less than 30% of the fee. This is despite the fact that they provide approximately 60% of the time spent on SA. This suggests that the costs of providing the service have been understated.

High level Explanation of the Proposal

The fee as proposed by European Commission results in a significant decrease in NCA income that it is inadequate to cover the national costs. The consequences of a poor remuneration are several and needed to be considered as they mainly impact the ability of the European regulatory system to support European research and innovation with the ultimate goal to provide a timely access to patients to innovative medicines. This last goal is a key and common element in each of the last European Regulatory Network for Medicinal Products (ERNM) publications. In order to accomplish it, National competent authorities (NCAs) should rely on an appropriate remuneration ensuring them to provide a highly scientific advice and assessment.

Overall factors influencing the new proposal

1. Increase in complexity/innovative developments or methodologies.

2. Subsequently need to involve senior assessor and external experts to cover the requested expertise.
3. Training activities needed to develop and/or improve skills and knowledge of internal agency's employees in handling advices involving upcoming scientific developments.
4. Increase burden of work subsequent to European priority actions aiming at reinforcing scientific advice system also in coordination with clinical trials approval/design.
5. Sustainability of the network.
6. Current limitation of human resources in NCA.
7. Identical and overlapping role, responsibilities and activities for each of the two EMA Coordinators appointed for each Scientific Advice.
8. Increase number of experts by SA level.
9. Difference in average hours spent by SA level

High level Explanation of the Proposal

This fee as proposed results in a significant decrease in NCA income and will reduce the ability of the network to support public health and foster innovation in Europe through the regulation of medicines, namely through the provision of scientific advice

The new Fee Regulation needs to ensure that EU network reinforces and increases the level of response to the scientific procedures.

The EU network relies on the scientific assessment of the experts of the MS to provide response to the challenges of the innovation. As these challenges become more demanding it is fundamental that the system maintains its capacity, resilience and sustainability. The work of all parties involved in the procedures must be adequately distributed.

Member Sates experts are also frequently requested to participate in several working parties and groups, some with regulatory decisions. Decrease in income will have an impact on the reinforcement and qualification of human resources and in the retention and development of expertise.

There is also need to constantly update technology and data security nationally as well. There might be an increase in backlog and delay in the implementation of safety regulatory outcomes with clear impact in public health.

The reduction of the fee to the NCA is not adequate to maintain the level of response needed at EU level.

Remarks on the proposed fees for Scientific advice

Scientific advice is the tool to assist on the development of medicinal products in the EU. It requires well trained assessors that are familiar with the EU regulatory system and that have recognised expertise and knowledge of the field of action. The level of advice provided must be assured in order to provide an adequate scope to continue to foster and support innovation in the EU.

Scientific Advice has become more demanding and complex including several areas of expertise requiring the participation of a broader pool of assessors, thus increasing the cost of providing this service. There has also been an increase in requests for Scientific Advise (2019: 674, 2020: 787, 2021: 853). Additionally, accelerated TT are adopted for the several of procedures. Timetables are more demanding: procedures are started as they come. There has been an increase in the number of requests with shorter timetables and additional complexity (e.g. new complex CT, definition of the population to be included in CT, use of RWE and registries).

Additionally, for COVID-19 /mpox vaccines and treatments also interactions with ETF, CTCG are required which also implies further interactions and coordination at national level.

In a time where new procedures are arising, where NCAs need to cope with innovation and highly complex products, bringing to the table adequate scientific expertise, the fee revision must follow the same path and be aligned with the increased demand of the procedures and complexity of products. This also includes making significant investments in training of new experts, that need to have a comprehensive knowledge of scientific, technical and regulatory domains.

The SAWP requires that each member is responsible for, at least, 4 advices / month and there are currently difficulties in allocating Coordinators for this activity. The decrease in the remuneration to the NCA will undermine the participation of MS in the scientific assessment and the national capacity to take this EU work. This will ultimately impact all parties involved and result in a weakened network and response of EU to innovation. The proposed new fee must reflect the real cost of the work performed.

II.2: Referrals, Article: Annex I, point 6

Current fee:

PV Referrals	67 145 EUR

Fee proposal by EC:

PV Referrals	17 500 EUR

Fee proposal – adjusted:

PV Referrals	**27 326 EUR**

Background and Justification:

Targeted type of referrals : art. 20, art 31 and art. 107

In the EC proposal the fee for NCAs will strongly decrease more than 3-fold from 67 145 euros today to 17 500 euros.

This decrease is of public health concern because the risk that EMA will not find rapporteurs among Member States because the work is not sufficiently paid. How could these procedures be sufficiently attractive for NCAs to engage adequate assessment, based on robust expertise?

The network proposes to increase the remuneration of Member States based on the increased average time of the work involved up to 27 326 EUR.

Data calculations:

The NCA mean time for PhV referrals in the MBDG group report 2017 was 454.42 hours (MIN 190.75 hours, MAX 587.50 hours, MEDIAN 585.00 hours, based on only 3 procedures). No data is provided in the report on scientific/administrative ratio (according to page 27 it seems to be agreed that for referral, time spent by NCAs is mainly scientific).

Time data was collected from 13 NCAs onr 48 procedures (half rapp, half co-rapp). The updated mean time was 30% higher than the time in the MBDG report.

MEAN: 590 hs; MIN: 86 hs; MAX: 2127 hs

The target proposal for PhV referrals is based on uplifting the mean time by 30% and multiplying by a sustainability factor of 20% that includes adjustment by inflation (for 2023 and 2024).

II.3: Justification of revision of remuneration for GMP, GCP and PMF inspections outside EU

Background

Inspection is the lynch pin of the regulatory system. It is particularly important in third countries where the inspection is a key tool providing assurance in relation to the quality of the medicines, by the knowledge that they were manufactured under GMP or that the trials were carried out under GCP. Inspection of APIs in third companies, when required, is critical for assuring quality. Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries.

Updated Proposal

Based on a review of the direct costs of inspections and the overall cost of providing the service, outlined below, the following are the posed fees:

	Fees as proposed by the European Commission 13/12/22			**Revised fee proposal**		
Inspection	EMA fee (total)	Leading	Supporting	Revised EMA fee (total)	Leading	Supporting
GMP	37,800	15,600	9,400	70,800 (↑87%)	34,000 (↑117%)	24,000 (↑155%)
GCP	44,200	19,600	10,400	65,200 (↑48%)	32,000 (↑63%)	19,000 (↑82%)
PMF	36,100	13,400	8,200	54,500 (↑51%)	20,000 (↑49%)	20,000 (↑143%)

High level Explanation of the Proposal

It is important for NCAs to be financially viable, so they can conduct their work sustainably, both now and in the future. Therefore, it is key that their operating costs are covered, including the costs for inspections outside of the EU. This also vital with regards to the sustainability of the inspection network in the EU, as it is important for all Member States to be able to participate in the inspection programs. Despite the welcome increase to the fees, the inspection fee as proposed remain inadequate to cover the costs and does not reflect the workload assumed by the NCAs. This document details what is needed to ensure that the proposed fees cover the actual costs incurred by NCAs during inspections outside of the EU. Data on actual costs and ratio of cost recovery based on past inspections and compared to the regulation proposal are included in Appendix 1, for GMP, PMF and GCP Inspections.

The data indicates that the cost recovery ratio for GMP inspections ranges between 0.31 and 0.70 (for lead and support inspectors). On average, coverage ratio is lower for supporting inspectorates versus lead inspectorates (0.60 vs 0.47). For GCP inspections, the data is similar; cost recovery ratio ranges between 0.38 and 0.84. The same applies to PMF inspections, where the recovery ratio ranges from 0.70 (for distinct inspections) to 0.42 (for consecutive).

The proposed revised remuneration is included below, following a cost-based approach.

Costs of providing the service

(a) Direct Costs

Inspection activities include GMP inspections, for dosage forms and active pharmaceutical ingredients, inspections linked to plasma master files (PMF) and GCP inspections, for clinical trials.

Inspections are labour intensive as inspectors are offsite for the duration of the inspection and challenging as it may involve significant amounts of travel to and in unfamiliar countries. The actual inspection is performed by an inspection team traveling to one or several sites (outside of the EU for the purposes of this document). Inspection work consists of inspection planning, travel and accommodation preparation, , review of the documentation provided by the inspectee, actual on site inspection (one or more sites, may take between 4-8 working days), drafting of initial inspection report, review/assessment of responses from the inspectee,

and drafting of the final inspection report. If a negative outcome occurs, the process become more complex and the inspectors' work increases significantly.

Moreover, inspections abroad normally require an **inspection team**, which may involve more than one inspector from the NCAs. Normally one member of the team is lead/coordinating inspector, usually a senior specialized inspector with other senior inspectors forming part of the inspection team. Inspections of particular complexity, in terms of products or dosage forms and/or large sites, would normally require larger inspection teams and more inspection days. The need to incorporate more inspectors to the team and/or extend the inspection time have not been considered in the current proposal. If a fixed fee is to be included in the proposal, the amount should be raised to reflect these inspections (more time, large teams).

Current proposal does not seem to address the question of several products/dosage forms at the same site; it is unclear how the mentioned fees will be applied – one fee per inspection irrespective to the number of products or are they calculated per product/site. Inspections at particular sites often include multiple products. To ensure that the fees cover the costs of these inspections, it is imperative that the fee is awarded per inspected product.

(b) Indirect costs

Building a qualified inspection workforce is costly, in terms of time and resources. As per EU requirements, inspectors need to undergo a formal qualification programme that includes inductive and specialized training and mentoring with senior inspectors. It is also expected that a continuous training programme, on scientific or regulatory developments, is in place.

Some particular products, such as blood products, biologicals or immunological products, or ATMPs require particular expertise and training. Inspections are gaining in complexity, with the introduction of product lifecycle management concepts (ICH Q12) or the expansion of scope of inspections to include environmental matters (currently under discussion).

A second invisible cost for inspections is that inspectors are out of the country, often in different time zones. Due to this, their general role as senior members of staff stops for the duration of the inspection. Consequently, the support needed within inspectorates is higher than in other assessment functions. Again, this is an invisible but a real cost of inspections.

Sustainability of the network

There is a growing need for qualified inspection resources, which has been acknowledged by EMA. It is sometimes difficult for NCAs to allocate enough resources to inspections outside of the EU for CAPs. Adjusting the remuneration to the real workload will contribute to the sustainability of inspection resources in the network.

Therefore, it is in the interest of the EMA to contribute to the creation of a stable workforce of qualified inspectors in the NCAs, who can perform inspections both within EU and abroad, able to cope with a more demanding inspection environment and help to build mutual reliance with MRA partners.

NCAs and EMA workload on inspection procedures.

It is appreciated that, for all fee-earning activities, the EMA plays an important role and facilitates many of the meetings, which lead to assessment outcomes. However, in the case of inspections, these are completely offsite and are carried out entirely by the NCA's. EMA makes the inspection request, receives the inspection report and GMP certificate eventually (if the inspection is favourable). By contrast, NCAs appoint and support the experts (inspectors), provide for inspectors' continuous training and qualification, performs the inspection, manages and organizes travel and accommodation (although costs are covered by the company), produces the inspection report, and uploads the GMP certificate on EudraGMDP. Despite this difference, one third of the fee goes to the EMA. This discrepancy in costs indicates that the costs of the work of the NCA's have been understated in the costing exercise.

Conclusion and proposal for Modification of fees

Hard data in relation to the proposal (will illustrative and can be country specific)

See **appendix 1**
The points made above illustrate the need for an increase in inspection fees and is further illustrated in the hard data provided in appendix 1. The information provided shows:

1. Evidence of increased hours from the data gathering exercise.
2. Evidence that the fee does not cover the costs; costs estimation does not account for :
   A) Inspector mentoring, training and qualification. See appendix 1, estimated 10% increase.
   B) Need to create/support inspection teams, frequently with more than one inspector per NCAs.
   C) Need to spend more time on site/extend inspection duration.

D) Increased inflation versus those used in the Rand modelling.

Senior inspection costs versus average scientific salaried.

Proposal for modification of fees.

Inspection overall costs, in the three examples provided, are higher than the remuneration as per the proposal.

Average Cost recovery ratios are below 1 (being 1= full recovery of direct and indirect costs). Below is a table showing the average costs and the shortfall in the current fee. The NCA's have also proposed a fee that will cover the costs under table II for consideration.

TABLE 1

Average	Fees as proposed by the EC 13/12/22						
Inspection	EMA fee	Leading	Supporting	Average Actual costs (lead)	Cost recovery (lead)	Average Actual costs (support))	Cost recovery (support)
GMP	37,800	15,600	9,400	33,847	0.46	23,275	0.40
GCP	44,200	19,600	10,400	31,724	0.62	16,748	0.63
PMF	36,100	13,400	8,200	19,244	0.70	19,244	0.43

Appendix 1

Table- Cost estimation and ratio of cost recovery. 10% increase of costs reflect investment in inspector mentoring, training and qualification. Cost/fees are calculated on the basis of 1 product per location/inspected site.

Several examples from three different Member States are included. The actual costs for representative inspections (direct and indirect costs) are provided and the ratio of cost recovery with the remuneration as per the EC proposal are provided.

Member State 1		**Fees as proposed by the European Commission 13/12/22**										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading (€)	Actual costs Supporting (€)	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%) (€)	Actual costs Supporting (incl. 10%) (€)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	23,275	23,275	0.67	0.40	25,602	25,602	0.61	0.37
GCP	Outside Europe	44,200	19,600	10,400	23,256	18,900	0.84	0.55	25,581	20,790	0.77	0.50
PMF	Distinct inspections	36,100	13,400	8,200	19,075	19,075	0.70	0.43	20,982	20,982	0.64	0.39

Member State 2		Fees as proposed by the EC 13/12/22						
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs (€)	Cost recovery ratio	Actual costs +10% (€)	Cost recovery ratio (incl. 10%) (€)
GMP	Outside Europe	37,800	15,600	9,400	50,175	0.31	55,192.50	0.28
GMP	Outside Europe	37,800	15,600	9,400	36,525	0.43	40,177.50	0.39
GCP	Outside Europe	44,200	19,600	10,400	34,620	0.57	38,082.00	0.51
GCP	Outside Europe	44,200	19,600	10,400	27,210	0.72	29,931.00	0.65
GCP	Outside Europe	44,200	19,600	10,400	47,250	0.41	51,975.00	0.38

Member State 3		Fees as proposed by the EC 13/12/22										
Inspection	**Inspection type**	EMA fee	Leading	Supporting	Actual costs Leading (€)	Actual costs Supporting (€)	Cost recovery lead	Cost recovery support	Actual costs leading (incl. 10%) (€)	Actual costs Supporting (incl. 10%) (€)	Cost recovery lead (incl. 10%)	Cost recovery support (incl. 10%)
GMP	Outside Europe	37,800	15,600	9,400	22,227	-	0.70	-	24,449.7	-	0.64	-
GMP	Outside Europe	37,800	15,600	9,400	-	17,456	-	0.54	-	19,201.6	-	0.49
GMP	Outside Europe	37,800	15,600	9,400	37,034	-	0.42	-	40,737.4	-	0.38	
GCP	Outside Europe	44,200	19,600	10,400	26,288	-	0.75	-	28,916.8	-	0.68	-
GCP	Outside Europe	44,200	19,600	10,400	-	14,597	-	0.71	-	16,056.7	-	0.65
PMF	Distinct inspections	36,100	13,400	8,200	19,413	19,413	0.69	0.42	21,354.3	21,354.3	0.63	0.38

Appendix 2: Hours and remuneration per type procedure, EMA vs NCAs

Percentage of time/resources is not proportional to the remuneration.

GMP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total	EMA	Lead inspector	Supporting inspector
Fee/remuneration (€)	37,800	12,800 (34%)(*)	15,600 (41%)	9,400 (25%)
Time AD (Scientific, h)	167.21	15.59 (9.3%)	75.81 (45.3%)	75.81 (45.3%)

(*) Hours calculated as per EMA declaration.

GCP Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total	EMA	Lead inspector	Supporting inspector
Fee/remuneration (€)	44,200	14,200 (32%)(*)	19,600 (44%)	10,400 (23%)
Time AD (Scientific, h)	767	56.21 (7.3%)	462.14 (60%)	248.65 (32%)

(*) Hours calculated as per EMA declaration.

PMF Inspections outside Europe: time and remuneration distribution between EMA and NCAs.

	Total	EMA	Lead inspector	Supporting inspector
Fee/remuneration (€)	36,100	14,500 (40%)(*)	13,400 (37%)	8,200 (22%)
Time AD (Scientific, h)	163.2	20 (12%)	71.60 (43.8%)	71.60 (43.8%)

(*) Hours calculated as per EMA declaration.

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CONTRIBUTION

From:	General Secretariat of the Council
To:	Working Party on Pharmaceuticals and Medical Devices (Attachés) Working Party on Pharmaceuticals and Medical Devices (EMA fees)
Subject:	EMA fees proposal - targeted approach

Delegations will find attached comments from delegations on the targeted approach.