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Multinational assessment team concept

The next phase – Broadening the concept to the post-authorisation phase

1. Background

At a meeting of the Baltic Sea Consortium, held in November 2012, the idea of setting-up multinational assessment teams (MNATs) was launched. The aim of the MNAT concept is to allow a broader involvement of national competent authorities (NCAs) in the work of the EMA scientific committees, as well as optimising the use of national resources, whilst maintaining the high quality scientific work of the committees.

In practice, the MNAT concept provides the option for an assessment team to be formed from different NCAs and allows payment by EMA to the individual NCAs of the assessment team according to the share of the remuneration agreed by the involved NCAs as set out in the remuneration share letter. It is important that the fees are paid directly by EMA to each NCA involved as this avoids administrative costs that would otherwise occur if the NCAs would have to split the fee themselves following payment by EMA to the (Co)-Rapporteur/Coordinator.

At this stage the MNAT concept is available to all Member States, and it applies to:

- Rapporteurs and Co-Rapporteurs for initial marketing authorisation applications for human and veterinary medicines.
- Rapporteurs for MRL applications.
- Coordinators for scientific advice procedures for both human and veterinary medicines.

Feedback received from the NCAs currently involved in the MNAT concept is that the process works very well. Also, an increase in uptake has been noticed over the past months. The status of the MNAT uptake up to the end of Q2 2016 is provided in annex 1.

2. Request for a broadening of the MNAT concept

Building on this positive experience a request has been made by some NCAs in Q4 2015 to extend the MNAT concept to post-authorisation procedures for human medicines which have already been authorised using this concept for the Co-Rapporteur's team. Meetings were held with CHMP members of these Member States in the margin of the October and November 2015 CHMP meetings to better

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understand their request and their expectations. It was clarified that their interest relates to extension of indication and line extension applications, but not to renewal procedures.

3. Analysis of the request

An analysis of the current request, limited to extension of indication and line extension applications, shows that a number of issues need to be considered, such as:

- Taking the following real-life scenario[1] for a medicinal product X with the following NCA representation in the pre-authorisation phase:
  - Co-Rapporteur: Member State A
  - Q assessment: Member State B
  - Non-C assessment: Member State B
  - C assessment: Member State D (for PK/PD) and A (for clinical efficacy and safety)

  Shall, as a matter of principle, the distribution for a post-authorisation procedure be identical to the distribution in the pre-authorisation phase? Not necessarily, since due consideration will have to be given to a number of aspects such as:
  - The type of data that will be submitted as part of the post-authorisation procedure. If for instance in the case of the previous example the extension of indication application would include clinical efficacy and safety data as well as PK/PD data the fee would have to be split between Member States D and A. If on top also non-C data would be submitted Member State B would again need its part of the fee as well. Therefore, it is paramount to know in advance, before the submission of the application, what type of data will be submitted to subsequently determine the share of remuneration.
  - The availability of the necessary resources and the availability of the needed scientific expertise (sometimes also linked to the organisational arrangements put in place at NCA level). For instance a Member State may have the necessary resources and expertise in the pre-authorisation phase, but this may no longer be or become available in the post-authorisation phase.
- If a Member State has applied the MNAT concept pre-authorisation for Co-Rapporteurships, three scenarios may occur in the post-authorisation phase:
  - The Member State is currently not interested at all to apply the MNAT concept in the post-authorisation phase.
  - The Member State would like to apply this approach on a case-by-case basis post-authorisation.
  - The Member State would like to apply this concept for all extension of indication and line extension applications.
- Although the request currently relates to extension of indication and line extension applications, it can at this stage not be excluded that later on the request will be broadened to other post-authorisation procedures. Likewise, a scenario could be envisaged where no MNAT concept was applied in the pre-authorisation phase but demands are made at a given moment for it to be introduced at some time point in the post-authorisation phase.

[1] It should be recognised that this is an example of a complex MNAT. The majority of MNATs consist of fewer NCAs.

Taking into account all the aforementioned considerations there is a need to establish a number of ground rules to allow for a successful implementation of the MNAT concept post-authorisation in the most efficient way.

4. Proposed way forward

4.1. General considerations

At its launch in November 2012 the MNAT concept envisaged to allow a broader involvement of NCAs in the work of the EMA scientific committees and to optimise the use of national resources, whilst also maintaining the high quality scientific work of the committees. In addition, it should be noted that the implementation first focussed on Co-Rapporteurships in the pre-authorisation phase, later on followed by Rapporteurships in the pre-authorisation phase.

However, as a result of the success of the MNAT concept in these situations the focus now has shifted towards the post-authorisation phase. Whilst fully embracing the MNAT concept and its initial aim, there is, however, a need to provide some clarifications from a more general nature, but also to draw up ground rules in order to ensure a continued successful implementation and sustainable operation of the MNAT concept for both human and veterinary medicinal products.

Especially the post-authorisation phase, covering the lifespan of a medicinal product, has some specific challenges. In addition to its length compared to the pre-authorisation phase, it is also characterised by its complexity with a wide variety of different processes and procedures which may also run in parallel. Even if the current request for a broadening of the MNAT concept to the post–authorisation phase only relates to extension of indication and line extension applications, it cannot be ruled out that other procedures also may come within the scope at a later phase. Therefore, the approach to be developed for this next phase should cater for all possible post-authorisation scenarios. One important factor to be taken into account in this respect is that there exists – at least from a theoretical viewpoint – the possibility for a multitude of different compositions of the MNAT concept in the post-authorisation phase.

4.2. Ground rules for a sustainable solution for the post-authorisation phase

In order to achieve a sustainable solution for the post-authorisation phase, the most optimal balance needs to be found between:

- Allowing for utmost flexibility.
- Maintaining a medicinal product's knowledge.
- Making proportionate investments vis-à-vis the anticipated benefits (e.g. in terms of the number of interested NCAs/the number of affected post-authorisation procedures).

The following ground rules are, therefore, proposed:

Ground rule 1: Allowing for utmost flexibility in choosing for a MNAT approach whilst respecting some boundaries

Various scenarios can exist in the pre- and the post-authorisation phases:

- Rapporteurships:
  - MNAT pre-authorisation -> No MNAT post-authorisation
  - MNAT pre-authorisation -> MNAT post-authorisation
  - No MNAT pre-authorisation -> MNAT post-authorisation
- Likewise, for Co-Rapporteurships:
  - MNAT pre-authorisation -> No MNAT post-authorisation
  - MNAT pre-authorisation -> MNAT post-authorisation
  - No MNAT pre-authorisation -> MNAT post-authorisation
- In addition, for the same medicinal product both the Rapporteur and the Co-Rapporteur can apply the MNAT concept.

In those situations where no MNAT concept existed pre-authorisation and where now a request is made to introduce this concept post-authorisation such request can be accommodated. However, taking into account the need for the MNAT post-authorisation to build on the knowledge obtained in the pre-authorisation phase, it is important for the (Co)-Rapporteur to remain the same.

Any existing remuneration for the lead (Co)-Rapporteur, stemming from the pre-authorisation phase, should always be fixed in the post-authorisation phase to 10% of the total fee for the post-authorisation procedure. The remaining 90% of the fee will be distributed based on the type of data submitted as part of the procedure.

Ground rule 2: Ensuring knowledge transfer

Maintaining the high quality scientific work of the committees is paramount as already stated before. In addition, the accountability as regards the outcome of the scientific review process needs to be safeguarded irrespective of the modalities chosen for the MNAT concept. Building up the knowledge of a medicinal product, ensuring transfer of such knowledge from the pre-authorisation to the post-authorisation phase and subsequently maintaining such knowledge during a medicinal product's lifespan are pivotal elements to meet these objectives. Consequently, the aim is to have the same composition of the assessment team, i.e. the involvement of the same NCAs post-authorisation vis-à-

vis pre-authorisation. Exceptions can only be allowed in very specific and justified circumstances, in particular when expertise is no longer available. In such situations the (Co)-Rapporteur has to ensure the necessary knowledge transfer to the NCA for performing the requested service, although ultimately the (Co)-Rapporteur remains accountable for the overall quality of the scientific review irrespective of any change in the composition of the assessment team.

Ground rule 3: Striving for an efficient and transparent process

Taking into account the complexity of the post-authorisation phase, which in turn may result in the MNAT concept not being systematically applied post-authorisation, there is a need to have an as efficient process as possible, coupled with full transparency on the choices made.

Since the fees in the pre-authorisation phase are paid directly by EMA to the NCAs as per the agreed remuneration share letter, this concept should also be applied post-authorisation, the main reasons being:

- Continued compliance with the existing legal framework applicable to EMA.
- Continue to avoid administrative costs for the NCAs.
- Continue to gather all necessary information at a central point, i.e. at EMA level.

This will, however, require that the NCAs have a clear picture in the complex post-authorisation phase if and how fees should be shared and that EMA is informed sufficiently in advance of the start of the procedure. It is also very important, in order to come to a more robust planning process, that both the (Co)-Rapporteurs and EMA have advance information on the planned submissions by a pharmaceutical company.

4.3. Proposed MNAT scenario post-authorisation

The following steps are proposed:

Step 1

Two situations need to be considered:

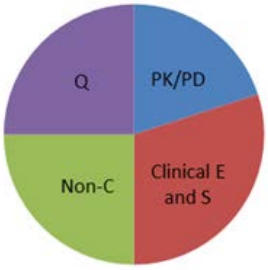
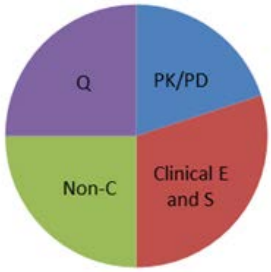
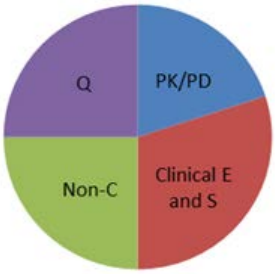
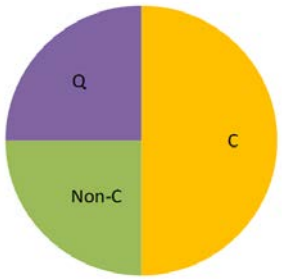
- No MNAT pre-authorisation.
- MNAT pre-authorisation.

In case there was a MNAT pre-authorisation, the Rapporteur/Co-Rapporteur, following the European Commission Decision and prior to any submission of a post-authorisation procedure, informs EMA if the MNAT concept will be applied post-authorisation or not. In the case there was no MNAT pre-authorisation, the Rapporteur/Co-Rapporteur, following the European Commission Decision and prior to any submission of a post-authorisation procedure, informs EMA only if the MNAT concept will be applied post-authorisation.

If a request to introduce the MNAT concept post-authorisation is not made at the time of the European Commission Decision, it can always be made at a later stage during the life span of the medicinal product, by the Rapporteur/Co-Rapporteur through written notification to EMA. Furthermore, once the MNAT concept is started post-authorisation it can be stopped by the Rapporteur/Co-Rapporteur at any time through written notification to EMA.

Step 2

Subsequently, in case the MNAT concept is applied, the (Co)-Rapporteur informs EMA[2] if the existing share distribution from the pre-authorisation phase is maintained post-authorisation, or if a different share distribution should be applied (see examples in below illustration). However, no further subdivisions are permitted in the post-authorisation phase than those presented in the examples below, e.g. Q cannot be shared between two different NCAs, to avoid too much granularity and difficulties in implementation.

	Pre-authorisation		Post-authorisation
Example 1		->	
Example 2		->	

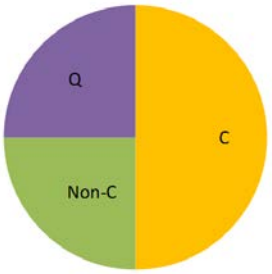
[2] It should be noted that both steps can also be combined if the (Co)-Rapporteur wishes to do so.

Step 3

As a next step the share distribution will be applied proportionally to each procedure type depending on the data submitted. EMA upon receipt of the post-authorisation procedure file will, during the validation stage, and on the basis of the data type submitted, indicate the areas of the dossier affected by the procedure towards an automatic application of the share distribution as notified to EMA during step 2, and EMA will afterwards initiate payment to the NCAs accordingly. As such the improvements to the validation process that have been achieved in particular in relation to the determination of the fees and payments should not be jeopardised. However, it is important to emphasise that the share distribution cannot change within a procedure type from procedure to procedure; the share distribution for clinical Type II procedures should be the same for any clinical Type II procedure (see examples in below illustration).

Example 1

MNAT share distribution chosen post-authorisation



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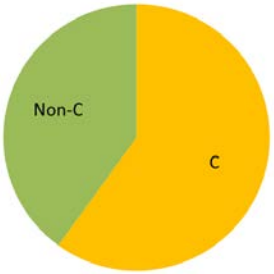
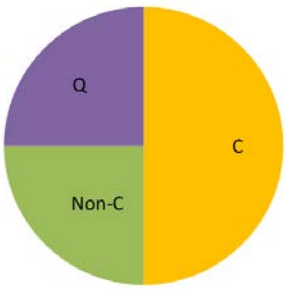
Extension of indication procedure (non–C and C data)



Example 2

MNAT share distribution chosen post-authorisation



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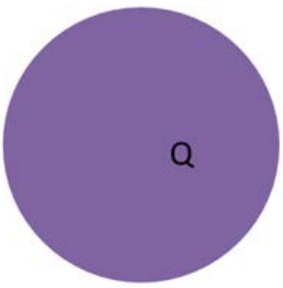
Quality Type II procedure



4.4. Implementation of the proposed MNAT scenario post-authorisation

It is proposed that implementation is undertaken in a phased approach as follows:

- 1st phase: existing MNAT pre-authorisation (Co)-Rapporteurships -> MNAT post-authorisation (Co)-Rapporteurships for extension of indication (and, additionally for veterinary medicines, addition of non-food target species) and line extension applications.
- 2nd phase: taking into account any lessons learned from the 1st phase, broadening as follows: no existing MNAT pre-authorisation Rapporteur and/or Co-Rapporteurships -> MNAT post authorisation Rapporteur and/or Co-Rapporteurships for extension of indication and line extension applications.
- 3rd phase: once also the 2nd phase is fully implemented, and if there is demand from the NCAs to further extend to other procedures: idem as above, but for other Type II procedures with the exception of PRAC led safety Type II procedures and worksharing procedures.
- 4th phase: if there is further demand, all the procedures excluded in the 3rd phase, as well as other post-authorisation procedures involving PRAC.

Following agreement by the Management Board and HMA, EMA proposes to start with phase 1 in 2017.

Annex 1

Number of MNATs per procedure type in the pre-authorisation phase, covering the period 2014-Q2 2016

Number of MNAT teams per procedure type	2014	2015	Q2 2016	Total
Initial application -Rap (H)		2	4	6
Initial application - Co-Rap (H)	8	10	3	21
Scientific Advice (H)		8	16	24
Initial application -Rap (V)			2	2
Initial application - Co-Rap (V)		2	3	5
MRL (V)		1	0	1
Scientific Advice (V)		0	0	0