Question 1

What is a PAES imposed in accordance with the Commission Delegated Regulation?

PAES imposed in accordance with the Commission Delegated Regulation (EU) No 357/2014 is meant an efficacy study which is requested by a Competent Authority pursuant to at least one of the situations set out in this said regulation. The resultant data from such a PAES conducted within an authorised therapeutic indication are required to be submitted as they are considered important for complementing available efficacy data in the light of a well-reasoned scientific uncertainties on aspects of the evidence of benefits that is to be, or can only be, addressed post-authorisation. The results of the PAES have the potential to impact on the benefit-risk of the medicinal product or product.

Such efficacy study conducted post-authorisation can be imposed either:

- at the time of granting the initial marketing authorisation (MA) where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed; or

- after granting of a MA where the understanding of the disease or the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly or;

It is also possible to impose the conduct of post-authorisation efficacy studies in the specific situations of a conditional MA, a MA granted in exceptional circumstances, a MA granted to an advanced therapy medicinal product, the paediatric use of a medical product a referral procedure initiated under Article 31 or article 107i of Directive 2001/83/EC or Article 20 of Regulation (EC) No 726/2004, however these fall outside the scope of the Delegated Regulation.

References:

- Regulation (EC) No 726/2004
- Directive 2001/83/EC
- Commission Delegated Regulation (EU) No 357/2014
- Link Scientific guidance on post authorisation efficacy studies (after finalisation)
**Question 2**
*How and where the PAES imposed in accordance with the Commission Delegated Regulation will be reflected in the marketing authorisation?*

For MRP/DCP authorised medical products, a PAES imposed as a condition to the MA is reflected in the AR Overview under section “Conditions for marketing authorisation” and the End of Procedure Letter.

The study objective and the deadline for the submission of the final study results are specified in the AR Overview. In the beginning of the description of the study, such efficacy study imposed in accordance with the Delegated regulation is explicitly named ‘Post-Authorisation Efficacy Study (PAES)’.

The imposition of such PAES shall meet one of the criteria set out in the Delegated regulation. Such justification will be provided in the AR Overview.

If the RMS requests to review the protocol for endorsement, this will also be reflected in the AR Overview in the wording of the condition (e.g. “according to an agreed protocol”). Any post-approval amendments to the conditions in AR Overview (objective and/or due date) should be duly justified and submitted as a variation, type IB C.I.11.z (for change in the due date or type II C.I.11.b)

As for any imposed post-authorisation efficacy studies, those imposed in accordance with the Delegated regulation should also be reflected in the risk management plan (“RMP”), part IV ‘Plans for post-authorisation efficacy studies’ and if applicable under part III in case of important safety concerns addressed by this study as well.

An imposed post-authorisation study may have both efficacy and safety objectives. In such case this study will be classified either as a PAES or a PASS taking into account the uncertainty(ies) leading to the imposition of the study and the primary endpoint of the study. This is needed in particular when the study is a non-interventional study as this will define the requirements to be followed for the submission of the protocol and the final study results.

**References:**
- Commission Delegated Regulation (EU) No 357/2014
- GVP module on RMP

**Question 3**
*Following which procedure will my imposed PAES protocol be assessed?*

If the review of the imposed PAES protocol has been reflected in the AR Overview and EoP Letter, the MAH will have to submit a draft protocol to the RMS via an appropriate variation. Otherwise, the review of the protocol is not deemed necessary.

The MAH is generally advised to consider seeking scientific advice on the study design irrespective of whether the submission of the protocol has been requested, in order to discuss the design of the study and ensure that it meets the intended objectives.

In case the PAES is a clinical trial, it also falls under the scope of Directive 2001/20/EC (to be superseded by the Clinical Trial Regulation EU No 536/2014) and is subject to the national clinical trial authorisations.

**References:**
- Scientific advice procedure
- Directive 2001/20/EC (thereafter, new Clinical Trial Regulation EU No 536/2014)
**Question 4**

*When should I submit my imposed PAES protocol?*

If the submission of the protocol has been requested as stated in the AR Overview and EoP Letter, the MAH should submit the protocol in accordance with the timeframe specified in the RMP, part IV as timelines for protocol submission are not specified in the AR Overview and EoP Letter.

At time of imposition, the MAH is asked to propose appropriate dates for the submission of the protocol and the post-authorisation data that are proportionate to the uncertainty to be addressed. The proposed dates for submission are subject to agreement with the RMS. If the MAH would be unable to provide the protocol by the specified deadline, the MAH must inform the RMS and the CMDh if applicable in writing as early as possible in advance of the submission due time. The delay must be duly justified and a new submission date should be proposed. Such request should be sent to the RMS.

If the submission date of the final study results mentioned in the AR Overview is impacted, this requires the submission of a type IB variation C.I.11.z.

**Question 5**

*In which timeframe will my imposed PAES protocol be evaluated (time table)?*

The evaluation of the PAES protocol will be led by the responsible RMS with PRAC consultation where foreseen.

**Question 6**

*What are the possible outcomes of the evaluation of an imposed PAES protocol?*

The responsible RMS, taking into account PRAC advice where provided, will conclude the assessment of the protocol according to the following options:

- endorsement of the protocol;
- objection to the protocol;

In case of endorsement, the assessment report may still include recommendations for amendments to the protocol. These recommendations are for consideration by the MAH and do not require resubmission of the protocol.

In case of objection, resubmission of an amended protocol for reassessment will be required as this will detailed in the assessment report.

**Question 7:**

*Do I have to submit interim results?*

There is no obligation to submit interim results, unless it has been requested by the RMS. However, when requested, interim results can be submitted, unless there is an impact on the product information. In such case a variation should be submitted.
**Question 8:**

Do I have to submit the final results of my imposed PAES?

Upon completion of the study, a final study report shall be submitted by the deadline specified in AR Overview and EoP Letter via the appropriate variation procedure irrespective of changes to the product information.

The MAH should consider whether the final results have an impact on the marketing authorisation/product information. If the MAH concludes that this is the case, the MAH should submit the results together with the proposed changes to the product information.

The classification of the variation will depend on whether there are proposed changes to the product information. Please refer to the relevant classification Information: [http://ec.europa.eu/health/files/eudralex/vol-2/2013_05_16_c2804_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/2013_05_16_c2804_en.pdf)

With the application submitted, the MAH should indicate in the table of the cover letter of the application which post-authorisation measure is being addressed, including the full description of the relevant measure.

The responsible RMS will lead on the assessment of the study results and will conclude on either the maintenance or the variation of the terms of the marketing authorisation, taking into account PRAC advice where provided.

In addition, it is reminded that the MAH should provide in the PSUR, as usual, a summary of the clinically important efficacy and safety findings obtained from the study during the reporting interval.

**Question 9:**

Do I have to pay fees for the protocol and final study results submission?

Fees are generally handled on a national basis. For further information please contact the relevant NCA.

**Question 10:**

Will there be any publication on the outcome of my PAES protocol and final study results assessment?

Outcome of protocol assessment are not published. However, in case of a clinical trial the protocol and summary will be available in the clinical trials database.

Outcome of final study results will be published in the PAR. Relevant results of the study will be included in the SmPC. However if the final study results lead to an extension of indication, this will be published via PAR.

To support transparency on PAES that are outside the scope of Directive 2001/20/EC and which are conducted pursuant to a condition of the MA or voluntarily, study information (including for studies conducted outside the EU) should be made available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency.

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**Question 11:**
Who should I contact if I have a question when preparing my application?

If you cannot find the answer to your question in this Q&A when preparing your application, please contact the responsible RMS.