EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# *Recent experience in scientific advice and marketing authorisations*

BfArM

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# Introduction

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# Brief introduction to scientific advice procedure

Scientific Advice Working Party (SAWP) provides scientific advice for medicinal products for human use and protocol assistance for orphan medicinal products.

**Scientific advice** is when the Agency gives advice to a company on the appropriate tests and studies in the development of a medicine.

Companies can request scientific advice from the European Medicines Agency at any stage of the development of a medicine, whether the medicine is eligible for the centralised authorisation procedure or not.

# Brief introduction about scientific advice procedure

The Biologics Working Party (BWP) is systematically consulted on all quality questions on biotechnology and biological medicinal products, including quality issues for blood products. Each SA/PA request is discussed during the BWP meetings. The BWP report is then incorporated in the final advice letter.

The applicant is encouraged to engage in a on-going dialog as early as possible, to

- facilitate and optimise research an development
- reduce uncertainties of the regulatory outcome
- accelerate time to approval

# Ask the right question

Scientific advice is given by answering the questions posed by the Company. The advice is based on the documentation provided by the Company in the light of the current scientific knowledge.

The quality of the questions impacts on the outcome of the advice a company gets.

Scientific Advice is not on how to develop a product. Companies have the responsibility for the development of their products.

Scientific advice is prospective in nature. It focuses on development strategies rather than pre-evaluation of data to support a marketing authorisation application.

Assessment of materials for clinical trial applications is under the responsibility of the National Competent Authorities and not within the remit of the Scientific advice procedure.

# Brief introduction about scientific advice procedure

Scientific advice helps the company to develop the product and the process in such a way that no major objections are likely to be raised during evaluation of the marketing-authorisation application.

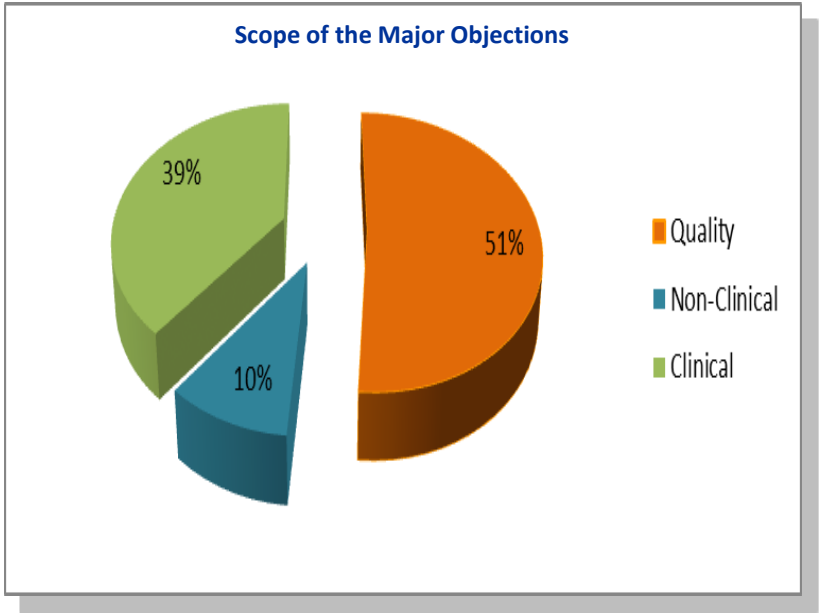
Major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of the marketing authorisation.

Following the Agency's advice increases the probability of a positive outcome.

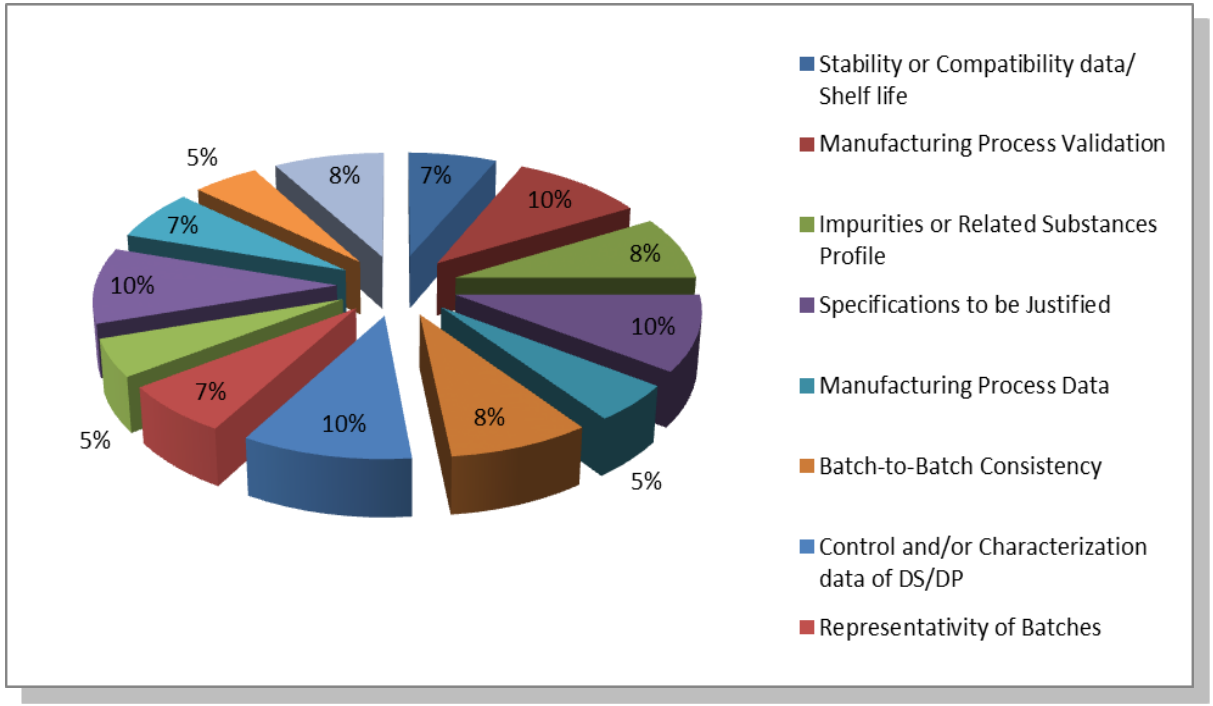
# Major Objections for MAAs

The Quality dossier Module 3 of the CTD continues to be a problematic area. From 2011- 13 approx. 46% of the major objections raised were on the quality documentation (submitted by SMEs).

51 % of the Major Objections on MAA for biologics were on Quality.



# Major Objections in Quality Aspects for MAAs of Medicines containing Biological Entities with Negative Opinion (*2011-2013)*



# Areas of Major Objections for SMEs Applications of Biological Entities

- Manufacturing Process Validation Incomplete;
- Lack on the Control and/or Characterization data of Drug Substance/Drug Product;
- Setting of Specifications to be Justified;
- Issues on the Manufacturing Process Development/Control Strategy;
- Issues on the Pharmaceutical Development;
- Lack of Evidence of Consistency between Batch-to-Batch;
- Issues on the GMP Compliance/ GMP Certification.

# Illustrative questions and answers

# Q 1: Does the Agency endorse the current test strategy for the MCB and working cell bank (WCB) and the proposed test strategy for the end-of production cell (EOPC) in principle to provide adequate data for assessment at MAA?

The proposed strategy to qualify the MCB and WCB is generally in line with the applicable guidelines (ICH Q5B and Q5D). The proposed testing of end-of-production cells seems appropriate.

It is not fully understood why a distinction is made between release tests and characterisation tests for the cell bank system. They should both be part of the specifications of the MCB and the WCB.

# Cont'd Q 1

The company should also take into account the remark regarding purity of cell substrates in ICH Q5D, if applicable. It should be investigated whether purity can be compromised through contamination by cell lines of the same or different origin. Whenever another cell line was present in the cell banking room at the same time as open cell banking procedures were being performed, the cell banks should be tested for the presence of cells from (or products derived from) the second cell line.

# MO on Specifications

An exhaustive description of the rationale used to define specifications for the drug substance and drug product is not provided in the dossier, only a very general statement which is not considered in agreement with the ICH Q6B guideline recommendations. This approach is not considered acceptable. A complete re-assessment of the suitability of acceptance criteria for DS and DP to ensure desired quality and product consistency in line with data from pre-clinical/clinical and stability batches, need to be performed. In doing so, the Applicant should take the following points into consideration……

# Q2: Are that the tests proposed for release and stability testing of Protein X drug substance and drug product are adequate as part of marketing authorization application?

The information on the proposed specifications is too limited.

- Tests as outlined in the Ph. Eur. Monograph are not considered providing sufficient information for a comprehensive quality control. They are minimal requirements.
- Selection of methods for the drug substance and drug product specifications should be based on the characterisation data.
- The acceptance limits for the individual parameters should be justified by batch release and stability data respectively.
- Purity and impurities should be addressed by suitable methods
- Stability indicating methods should be identified.

# Cont'd Q2

- Limits for oxidised forms should be established and these should be measured as well in the drug product at release and throughout stability studies.
- A process-specific test for HCP should be developed employing process-specific antibodies.
- Clarity and colour of solution should be included into the drug product specification
- The extractable volume should be included into the stability protocol, at least at the last time point.
- The list of methods used for stability analysis may benefit from adding following methods: Isoform distribution pattern, reduced SDS-PAGE, sialic acid content determination and osmolality analysis.

# MO on Process Validation

Appropriate validation data covering the entire drug substance manufacturing process has not been presented. Consequently reproducibility and robustness of the proposed drug substance manufacturing process has not been demonstrated. The applicant should provide comprehensive validation data to demonstrate that the proposed manufacturing process is reproducible, robust and capable of consistently producing product meeting all pre-defined in-process parameters and a pre-defined specification. Only limited IPCs are in place for this very complex active substance manufacturing process and thus, the drug substance manufacturing process is considered not sufficiently controlled. For the entire manufacturing process additional process controls together with the respective acceptance criteria should be included and reflected in the process validation.

# Q3: Does the agency agree that the proposed process validation of the commercial process for Protein X is appropriate?

The described approach is generally appropriate. However, a few more aspects should be taken into account for the fine tuning of the approach…,

The suitability of proposed down-scaled models needs to be fully demonstrated in the marketing authorisation application.

All pooling steps which are foreseen in the manufacturing processes of drug substance, formulated bulk drug substance and drug product need a justification supported by data.

# MO on Process Development and Comparability

In Module 3.2.S.2.6 "Development of the Manufacturing Process " the applicant has not substantiated the comparability of the drug substance materials originating from the different manufacturing processes preceding the final commercial manufacturing process. This limits the evaluation of data for the proposed application.

The applicant should evaluate the process changes taking into consideration ICH Q5E requirements and justify the comparability of materials used for pre-clinical and clinical studies with the commercial material. Representativeness of materials used for characterisation, justification of specification and stability for the commercial material need to be verified as well.

## Q4: Does the CHMP agree that the proposed analytical comparability plan is sufficient to evaluate the comparability of Process 3 to Process 2? Does the CHMP concur that if the prospective comparability criteria are met, Process 3 material can be included in the MAA submission for licensure without the need for any additional preclinical or clinical studies?

*Change of contract manufacturer and modifications were made to cell banks, fermentation and purification to address equipment adaptations, reduce use of animal derived raw materials, enhance manufacturing consistency, efficiency, and adjust process scale to fit into existing manufacturing equipment.*

# Q4

The overall approach consisting of process development using quality risk management approach, as well as a comparability exercise and a traditional validation of the new manufacturing site is endorsed.

However, the following points should be taken into account:
The applicant uses certain non-ICH nomenclature and it is requested that the different terminology used for the controls of input /output (Critical process parameter/ Key Parameter/ In Process Controls, Critical quality attribute/Key Quality Attributes) and how they interact in the control strategy is further clarified at the time of the MAA.

# Cont'd Q4

The strategy for comparing the old and new manufacturer is found acceptable. The protein is considered well characterised and the structure allows many sensitive and selective methods (including NMR) to be used. The range of methods proposed to show comparability at the protein level is to the greatest extent considered acceptable.

To serve as a valid comparator, the age of the process 3 material should be of a comparable age as the batches included in the clinical batches unless the difference can be shown to have no impact on the quality of the material.

# Cont'd Q4

As regards each different change, the following remarks would have to be taken into consideration:

- Regarding the evaluation of the performance of steps where changes were introduced, the choice of the tests/parameters that would be followed should be fully justified
- ……
  …….

Provided that the results of the comparability exercise after having taken into account the above recommendations, demonstrate that Process 3 and is comparable to Process 2 it is agreed that Process 3could be included in the MAA submission, without the need for any additional pre-clinical and clinical studies.

# MO on stability

Adequate stability data for the DP manufactured with the commercial process should be submitted. The choice of stability-indicating parameters is not clearly substantiated with data. Stability-indicating methods should be included in the stability studies using validated assays. A clear protocol for the ongoing study should be provided: Section xx only contains some considerations for future stability studies. The exact container-closure system (type and size) used in the studies described in the dossier should be stated; it should be the commercial container-closure system.

# Q5: Does the Agency agree that the proposed plan for stability testing of the drug substance and drug products will provide adequate and sufficient evidence of stability in support of a marketing authorisation application?

The final decision on the drug substance shelf life will be made based on the actual data provided in support of the marketing application

The proposed drug substance stability and drug product stability protocol is in general considered adequate to support the long term storage at -20°C and 5±3 °C resp.

……additional analytical methods and respective acceptance criteria may be required and should be considered for the stability-indicating profile.

# Cont'd Q5

Particular emphasis should be placed on appropriate analytical methods for testing the purity and impurity profiles. The test methods should provide assurance that changes in, e.g., purity and impurity profile will be detected.

In-use stability testing should reflect the specific physico-chemical characteristics of the formulation.

A test for preservative/antimicrobial agent should be included in the stability studies at appropriate time points.

Moreover, in-use stability should also be studied with a batch at the end of its shelf-life and should also address dosing properties (dose accuracy as per ISO 11608-3) of cartridges using recommended pen-injectors.

# Cont'd Q5

The proposal to demonstrate compatibility of the drug product formulation (stored in vials) with the rubber stopper is not considered sufficient to determine the suitability of the rubber stopper material during the proposed shelf life.

Compatibility studies should be provided for the cartridges and the respective stopper material as well.

The recommended storage period of four weeks only at 5±3°C should be significantly extended until the proposed shelf-life of the drug product. This does not replace extractable/leachable studies with the primary packaging material.

# Q6: Does the Agency agree that the proposed drug product process validation strategy is acceptable to support a MAA including a fill range of 1000 – 25000 vials min. load – max. load?

Technical runs using verum/placebo to demonstrate robustness of the lyophilisation process at max load (thawing of drug substance, mixing, filling and lyophilisation)

Media Fills to demonstrate aseptic processing

Holding Time Study to demonstrate product integrity and stability throughout the DP process

3 consistency runs in: 1 GMP batches at min. load, 1 GMP batch at medium and 1 GMP batch at max. load

# Q6

Overall, the proposed drug product process validation strategy is considered acceptable. The main focus in the validation plan is laid on the lyophilisation step. It is acknowledged that this step is the most critical step in the drug product manufacturing process.

However, it is questioned whether one batch of max. load would be sufficient to validate the process at the upper batch size.

To perform product hold time studies is considered an essential part of the overall drug product process validation to demonstrate stability of product intermediates during the drug product manufacturing process.

# Conclusion

A wide range of questions concerning quality issues can be submitted.

Questions should be focussed and carefully formulated.

Information provided in the briefing book should be clear and comprehensive.

Outcome of the SA should be taken into account when submitting a MAA

# Thank you for your attention

## Further information

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