EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SÚKL

Highlights from recent scientific advice and protocol assistance on quality issues

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Introduction

- Brief information about scientific advice procedure
- Overview of scientific advice – quality issues
- Illustrative questions and answers given in recent years
- Conclusion

Brief information about scientific advice procedure (1)

Scientific advice for medicinal products for human use and protocol assistance for orphan medicinal products is provided by Scientific Advice Working Party (SAWP)

The SAWP is a Multidisciplinary Expert Group and includes the Chairperson and 28 Members, among which 1 Vice-Chairperson, one member from the Committee for Advanced Therapies (CAT), at least two and not more than three Members from the Committee for Orphan Medicinal Products (COMP) and 1 one member from the Paediatric Committee (PDCO).

Brief information about scientific advice procedure (2)

The aims of SAWP:

- Facilitate access by optimising research and development
- Reduce uncertainties of regulatory outcome
- Accelerate time to approval

The applicants are encouraged to engage in a on-going dialog as early as possible

Brief information about scientific advice procedure (3)

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 development of a medicine, whether the medicine is eligible for the centralised authorisation procedure or not.

Protocol assistance is the special form of scientific advice available for companies developing designated orphan medicines for rare diseases.

The Agency gives scientific advice by **answering questions** posed by companies. The advice is given in the light of the current scientific knowledge, based on the documentation provided by the company.

Brief information about scientific advice procedure (4)

Example of the timelines for scientific advice procedure

Start of procedure SAWP meeting	Presubmission meeting					SAWP 1 (start of procedure)	SAWP 2 (reports discussed)	Finalisation day 40 (adoption at CHMP)	SAWP 3 if needed (Meeting with company)	Finalisation day 70 (adoption at CHMP)
	YES			NO						
	Deadline for submission of:									
	Letter of Intent [1] by	*Dates of presubmission meeting*	Revised draft request by	Letter of Intent [2] by	Final draft request by					
31 Mar – 02 Apr 14	22 Jan 14	*17 Feb 14 – 14 Mar 14*	24 Mar 14	19 Feb 14	17 Mar 14	31 Mar – 02 Apr 14	05 – 07 May 14	19 – 22 May 14	02 – 04 Jun 14	23 – 26 Jun 14
05 – 07 May 14	19 Feb 14	*17 Mar 14 – 16 Apr 14*	28 Apr 14	19 Mar 14	22 Apr 14	05 – 07 May 14	02 – 04 Jun 14	23 – 26 Jun 14	07 – 09 Jul 14	21 – 24 Jul 14
02 – 04 Jun 14	19 Mar 14	*17 Apr 14 - 16 May 14*	26 May 14	23 Apr 14	19 May 14	02 – 04 Jun 14	07 – 09 Jul 14	21 – 24 Jul 14	01 – 03 Sep 14	22 – 25 Sep 14

Overview of scientific advice – quality issues (1)

The quality issues are concerning whole spectrum of areas.

For drug substance

Synthesis of drug substance, starting materials designation

Specification – proposal of limits for impurities

Overview of scientific advice – quality issues (2)

For drug product

Composition and formulation questions in line with development of products, acceptability of proposed formulation for paediatric population

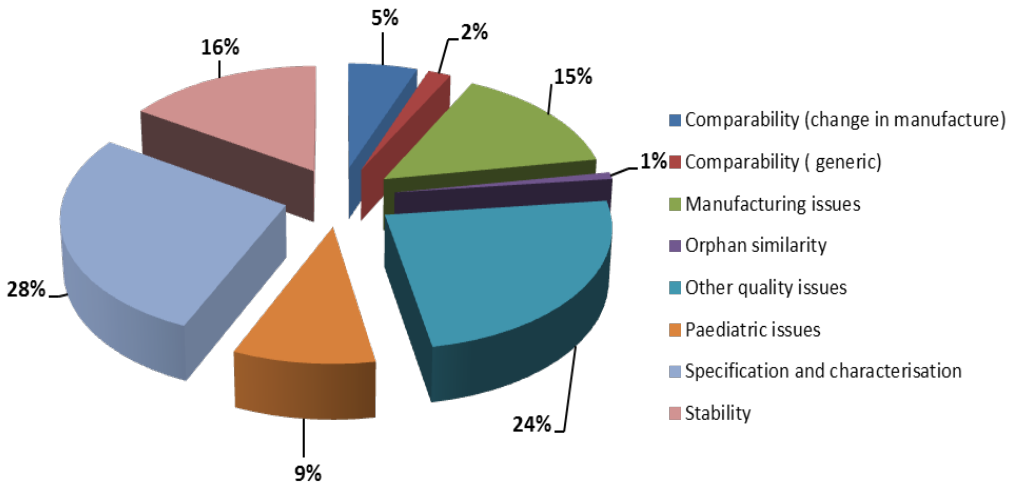
Manufacture – transfer of manufacture, comparability issues, use of advanced techniques during manufacture

Specification – setting of specification, proposal of limits for impurities

Stability issues

Overview of scientific advice – quality issues (3)

2012-2013



Illustrative questions and answers

starting materials (1)

Does the EMA agree that substance A and B can be defined as the drug substance starting materials to support MAA submission and product registration?

There are a sufficient number of chemical steps between the introduction of the designated DS starting materials and isolation of the final DS to allow for the control of any impurities introduced by the starting materials.

The synthetic processes for manufacture of DS starting materials A and B are shown.

Illustrative questions and answers

starting materials (1)

CHMP answer

The starting materials as currently proposed are not acceptable.

- Assessment of criticality of all steps (including those upstream from starting materials) is missing.
- Impurities present in the API originate in steps upstream from the starting materials.
- Starting materials are made by custom synthesis using a series of genotoxic reagents and via genotoxic intermediates. Changes to the synthetic route upstream from the starting materials could therefore significantly affect the impurity profile, and thus safety profile, of the API and would not be subject to regulatory assessment.

Illustrative questions and answers

starting materials (2)

Does the CHMP agree that the manufacture can be a single stage process from a common starting material for pharmaceutical manufacture due to the simple nature of the chemical (i.e. less than three steps for future clinical trials and marketing authorisation)?

The current GMP manufacture of the active substance is a single stage process from the starting material, EP grade common substance, commercially available, several purification steps and controls

Illustrative questions and answers

starting materials (2)

CHMP answer

Considering that starting material is of Ph. Eur. quality, it is normally considered acceptable to use this complex compound as starting material.

Illustrative questions and answers

starting materials (3)

Does the CHMP concur with the proposed designation of starting materials?

S2 S3

S1 => (B) => C => D => (E) => F => API

Illustrative questions and answers

starting materials (3)

CHMP answer

The manufacturing process proceeds via seven chemical conversions, plus a salt formation.

The Applicant proposes S1, S2 and S3 as starting materials. All of them are commercially available and their syntheses have been disclosed. Based on the briefing documentation provided, the starting materials are considered acceptable.

In addition, specifications should be provided for all the solvents, reagents and auxiliary materials used (fresh and recovered).

The possible formation as well as carryover of the impurities from the starting materials, intermediates and reagents should be discussed and supported by batch analysis data. Moreover the fate of each impurity should be discussed.

Illustrative questions and answers

formulation

Does the CHMP agree that the current drug product formulation is acceptable for use in the paediatric population?

Injection for intravenous administration

containing sorbitol and some unknown excipients

CHMP answer:

Justification why other possible dosage form has not been provided

The use of sorbitol in paediatric population should be discussed and justified.

Commonly used excipients are recommended to be used in formulation.

Illustrative questions and answers

specification

Does the CHMP agree with the proposed level of impurities?

The API contains two unidentified impurities representing a total of up to 2.3 %.

The chemical structure of the active substance does not belong to any class of known high potency genotoxic carcinogens.

The efforts to identify these impurities were unsuccessful.

Illustrative questions and answers

specification

CHMP answer

Based on the data provided, it cannot be evaluated whether the proposed total impurities levels are acceptable. Additional data should be provided in the clinical trial application. Historical batch analysis results should be provided and the analytical methods should be described. Results should be reported for each specified and unspecified impurity (identified by relative retention time).

Regarding unidentified impurities, it should be stated if they are synthesis-related or degradation products and the efforts undertaken to identify them should be described.

Most importantly, the proposed levels of impurities should be supported by results on pre-clinical batches.

Illustrative questions and answers

control strategy

Potential sources of genotoxic impurities will be controlled during in process validation, change control, and in the drug substance specification. These impurities will not be controlled in the finished product specification. Does the Agency agree with this approach?

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Illustrative questions and answers

control strategy

CHMP answer

Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product unless they are also degradation products (refer to the ICH Guideline Impurities in New Drug Products). Potential genotoxic impurities/ process impurities from the new drug substance synthesis should be controlled during drug substance testing.

In view of the GL on genotoxic impurities the applicant should therefore justify the use of these 2 genotoxic substances in the synthesis of the active substances

Illustrative questions and answers

Does the Agency agree that the outlined drug manufacturing process and the applied control are adequate to support approval for a marketing authorization?

CHMP answer

The Applicant should be aware that no pre-assessment is made at this stage and the full documentation has not been assessed. However, some parameters of the manufacturing process are commented on below.

Illustrative questions and answers

method description

Does the CHMP agree that the study conditions, used to carry out the comparative in vitro dissolution tests between the reference product and test product, are correct?

Information about apparatus, volume of dissolution medium, agitation, temperature, sampling schedule has been provided.

Illustrative questions and answers

method description

CHMP answer

The applicant has briefly described the study conditions used to perform the comparative in vitro dissolution tests between the reference product and test product seem adequate.

At the time of MAA submission, the applicant is requested to provide more detailed information on the apparatus used for the dissolution test in order to fully demonstrate compliance with Ph.Eur monograph 2.9.3. Any deviation from the Ph.Eur. should be properly justified

Illustrative questions and answers

stability

Does the Agency agree with the planned stability strategy?

3 strength manufactured using the same formulation and proportional composition, intends to apply stability bracketing

Pilot scale

Batch xy	Batch xx	Batch yy
5 mg	5 mg	5 mg
	10 mg	
20 mg	20 mg	20 mg

Illustrative questions and answers

stability

CHMP answer

The planned stability strategy is considered acceptable.

Conclusion

Wide range of questions concerning quality issues can be submitted to the SAWP.

Information provided by applicant should be clear and comprehensive.

Questions should be formulated carefully and should not be general

Outcome of SA should be taken into account when submitting application for MA.

Thank you for your attention!