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## **WORKSHOP 1: Process Description and Definition of Starting Materials**

**Dr Cornelia Nopitsch Mai, Federal Ministry of Health, Germany**

National assessor taking part in Certification

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The presentation starts with an overview of the Guidelines which refer to starting materials. The focus is on the requirements for starting materials outlined in the Draft ICH Q11 which are still under discussion. Additionally, the reasons for the development of the Draft ICH Q11 are highlighted.

The discussion on starting materials originates from the general trend observed by pharmaceutical assessors towards shorter synthetic routes. The consequences when re-definition of starting material is requested are outlined together with the basic requirements.

A possible approach for selection of the starting material is detailed.

At the end of the presentation eight case studies are presented dealing with acceptability or need for re-definition of proposed starting materials.

**Mrs Hilde Vaneste, Cefic/APIIC**

Industry representative

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Current guidance on definition of starting materials (SM) is no longer adequate and needs updating in line with the science based approach of ICH Q8-9-10. ICH Q11 is a first step, but will be a high level document and will need practical guidance not only for regulators, but also for industry.

ICH Q11 (currently in pre-step 4 stage) introduced the principles of a science based definition of SM: process knowledge resulting in an understanding of formation, fate and purge of impurities and resulting in an adequate control strategy, should allow regulatory authorities to assess the adequacy of the proposed controls (either in the form of a specification or process parameter control).

The impact and importance of multiple API process steps should be balanced against the other materials also entering the medicinal product process or the API process at a late stage.

In dedicated API industry, where intermediates and API are sold to other intermediate and API producer's information on starting material synthesis is often proprietary information. Therefore, providing this information to a customer/competitor causes an issue that needs a solution (e.g. through allowing those manufacturers to provide information directly to the health authority?)

**Mr Lionel Viorner, Afssaps, France**  
National Inspector

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The definition of starting materials for registration of an Active Substance (AS) is decided by assessors during the evaluation process. This decision has an impact on the actors involved in the supply chain since only those acting after the introduction of the starting materials have to comply with GMP and GDP. Recent experience shows an increasing number of files describing shorter routes of production of AS and the outsourcing of complex starting materials. This presentation will provide some elements of information related to incoming materials management and expectations from a GMP inspector's perspective.

## **WORKSHOP 2: The EDQM inspection programme and international collaboration in the area of inspections of API manufacturers**

**Dr Janice Soreth, Deputy Director, FDA Europe Office, Liaison to EMA**  
U.S. Food and Drug Administration

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No abstract is available.

**Mr Bill Turner, Office Head of the Office of Manufacturing Quality**  
Therapeutic Goods Administration – TGA – Australian Inspectorate

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No abstract is available.

**Mr Olivier Gross, Scientific Administrator**  
European Medicines Agency - EMA

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The European Medicines Agency (EMA), the European Directorate for the Quality of Medicines and Healthcare (EDQM), the EU Member States and their international partners in the United States and Australia are currently cooperating within the International Active Pharmaceutical Ingredient (API) Inspection Programme. The initiative focuses on increasing international regulatory collaboration among the regulatory agencies so that drug quality and safety can be enhanced globally.

The International API Inspections Programme demonstrates the success of information sharing and collaboration on API inspections among the participating authorities and involved the exchange of considerable amounts of information and the establishment of a Master list identifying the sites of common interest, the sharing of inspection reports as well as inspections carried out jointly by the participants.

This international cooperation led as expected to increased levels of understanding between the agencies, and a greater number of inspections of value to more than one authority.

## **WORKSHOP 3: Quality of antibiotics and fermentation products**

**Prof. Jos Hoogmartens, Chair of the EDQM Group of Experts on Antibiotics**

Quality of fermentation products

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This presentation is an introduction to the workshop “Quality of antibiotics and fermentation products”. The subject of this workshop mainly concerns the setting of specifications for impurity limits in monographs for antibiotics and this in the light of ICH prescriptions for chemical drug substances. Differences between antibiotics and common drug substances are highlighted. Further, it is briefly discussed how the setting of limits for impurities in antibiotics was performed in the past and this is illustrated with some examples. A major change in the policy of limit setting for impurities was observed with the introduction of chapter 5.10 reporting a new interpretation of the expression “any other impurity”. Although this policy is not immediately applicable to antibiotics, efforts are made to comply with the new interpretation wherever possible.

**Dr Tone Agasoster, Norwegian Medicines Agency**

New EU Guideline on antibiotics

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In 2006 the EDQM organised a symposium titled Setting Specifications for Antibiotics and Synthetic Peptides in order to discuss an approach for setting specifications for these substances, since peptides, fermentation products and semi-synthetic substances were exempted from the scope of ICH Q3A and consequently also from the general monograph Substances for Pharmaceutical Use (2034). For the peptides much progress was made at the symposium, and soon afterwards thresholds for reporting, identification and qualification for related impurities in peptides were included in the general monograph. For the antibiotics manufactured by fermentation or semi-synthesis the situation was more complex, and in 2007 the QWP decided to start work on a guideline titled Setting Specifications for Related Impurities in Antibiotics.

The guideline recently adopted by the QWP gives thresholds for reporting, identification and qualification for substances manufactured by fermentation or semi-synthesis. For single component substances prepared by semi-synthesis the thresholds are the same as for synthetic substances. On the other hand, for substances prepared by fermentation higher thresholds are set. For the substances consisting of more than one active component it is possible to have a wide qualification threshold (0.50%) for impurities which may be defined as “structurally closely related”. It is also described how in some situations the thresholds should be applied with some flexibility.

The guideline will facilitate consistency in assessment, and is intended to serve as a stimulus to initiate revision of relevant Ph. Eur. monographs.

Comments to the Guideline on setting specifications for related impurities in antibiotics

As drug substances manufactured by fermentation and semi-synthesis are excluded from the scope of ICH Q3A (R) on "Impurities in new drug substances", most of the antibiotic substances are not covered by ICH impurity guidelines. In order to make a harmonised assessment of impurities in antibiotic substances/products possible, a guideline has been drafted and issued for consultation by EMA in 2010: "Guideline on setting specifications for related impurities in antibiotics".

Comments to this draft could be submitted until 31 January 2011.  
In the meantime a new version has been agreed by the QWP in February 2012. The scope is still pending.

The latest version of the guideline has proposed separate thresholds for impurities in antibiotics manufactured by

- 1) semi-synthesis
- 2) fermentation, single compound
- 3) fermentation, family of compounds
- 4) peptides

However, many of the antibiotics which are already for several years on the EU market without safety problems will not be able to meet the strict thresholds proposed by this guideline. In order to avoid that extensive efforts need to be done to get into compliance or that in the worst case some of these substances should be taken from the market if the guideline becomes final, it is advisable to bring the requirements in line with the quality of the antibiotic substances currently approved for the EU market. This presentation tries to indicate the main issues with the proposed requirements of the latest version of this guideline and gives directions for possible solutions.