Training Program

CEP Procedure

ASMF Procedure

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Certification Procedure

- Show for a pharmaceutical substance:
- Suitability of the Ph Eur Monograph to control the quality of a substance
- Compliance with European regulatory requirements
- Created in 1994, scope enlarged
- Managed by EDQM (European Directorate for the Quality of Medicines)
- CEP = Certification of suitability of the monographs of the European Pharmacopoeia

Scope of the procedure

- Substances covered by a specific Ph Eur monograph:

  Active, excipients, herbal drugs/herbal preparations
- TSE risk products (starting materials, intermediates, reagents,…)
- Not applicable for biotechnological products, products from human tissues, semi-finished or finished products, substances not included in Ph Eur

Confidentiality respected

- CEP dossiers submitted directly by manufacturers
  - No applicant part
- Independently of any marketing application
- Archived in a specific restricted area (EDQM)
- Assessment on the premises of EDQM

At receipt (1)

- Dossier checked for completeness
- Applications blocked if deficient:
  - Missing pieces (form, declarations, dossier, QOS…)
  - Content of the dossier:
    - Refer to the current Ph. Eur monograph
    - Use of Class I solvents without justification and control
    - Suitable information on impurities, solvents,…
    - Validation data missing

At receipt (2)

- Content of the dossier (cont):
  - Quantitative method to replace a non-specific TLC test of the monograph
  - Sterile substances: validation of the sterilisation process

A number (up to 27%) blocked at this step in 2008 = not suitable to start the evaluation

Application blocked --> the clock does not start until suitable information is given.

! An incomplete application delays the CEP

Read PA/PH/Exp CEP/T (08) 37 Note for applicants:
« Procedure for validation of new applications »

After evaluation (the clock has started) (1)

- Most applications require requests for additional information (5% only of applications accepted at the time of first evaluation)
- Evaluation of additional information takes 4 months

! A deficient application delays the CEP

After evaluation (the clock has started) (2)

- ! Since 1st September 2008, the evaluation of new dossiers is handled in two phases:
  - the evaluation of the original dossier
  - if necessary, a single request for additional information.
  - Final decision whether a CEP can be granted is taken
  - For this: improve quality of dossiers (applicants), implement risk-based assessment (assessors)

Application form (1)

- Name and addresses of the parties involved
- Agreement letters
  - Representative agent or when holder ≠ manufacturer
- Declaration of Manufacture according to the dossier and GMP (ICH Q7/EU GMP if sterile)
- Declaration of Willingness to be inspected
  - Manufacturer, and holder if different
- Use of animal (TSE risk or other origin) / human material
- Commitment to provide samples upon request

Application form (2)

- Summarise the commercial history - make clear if, and in what product THIS source of API is on the EUROPEAN market. Information on ASMF submitted for the same substance
- Give as much information as possible (companies, products names, countries, registration dates, marketing dates).

--> Impact on Qualification (limits) of impurities

The certficate states (1)

- CEP number
  - RO-CEP 2007-001-Rev 00
- Name of the substance
- Holder, manufacturing sites
- Monograph referred to (specific, general on TSE)
- Validity date

The certficate states (2)

- As necessary:
- Additional impurities/solvents/catalysts with limits and methods
- Retest period, with storage conditions + container
- Use of substances of animal/human origin
- Production Section of monographs
- Omission of tests of the monograph when not relevant (TLC when replaced, specific solvent,…)

The certficate states (3)

- For a TSE certificate:
- Country(ies) of origin of animals
- Animal and nature of tissue(s) used
- Manufacturing process applied
  (when relevant, eg gelatins)

Retest period

- Option
- Specify the proposed retest period:
  - Justified by stability data
  - Studies according to ICH conditions
- Recommended storage conditions
- Specify the packaging material

Substances for Pharmaceutical Use*

* identical with ICH Q3A

- The implementation of the ICH-limits for impurities into the Monograph Substances for Pharmaceutical use leads to a lot of problems regarding the dealing with old monographs
- The use of a TLC method for the determination of impurities is not acceptable, because this method is not a quantitative method

„Old“ monograph via „new“ monograph

- Structure of an „old“ monograph
- ...
- Test for related substances:
- TLC – each impurity is limited to NMT 0.5%
- No list of possible impurities

- Structure of a „new“ monograph
- ...
- Test for related substances:
- Consideration of the monograph „Substances for pharmaceutical use“
- Quantitative method
- Impurities A, C NMT 0.5%
- Any other impurity NMT 0.2%
- Disregard limit: 0.05%
- List of possible impurities (Transparency Box): A to F

Dealing with old monographs from the BfArM's point of view (1)

- If a CEP is used which refers to an "old" monograph, a revision of the CEP is required regarding the development of a quantitative method
- The CEP will be blocked; the applicant is asked to initiate the revision procedure of the CEP by the EDQM

Dealing with old monographs from the BfArM's point of view (2)

- The development of a quantitative method is also required during an ASMF procedure, if the active substance refers to an old monograph
- The Manufacturer of the drug substance is asked to develop a quantitative method

Dealing with old monographs from the BfArM's and EDQM's point of view

- The use of a TLC method is also not applicable, even if the manufacturer of the active substance demonstrates that no impurities are detectable in his active substance. This is based on analysis data of some batches.
- The manufacturer of an active substance should demonstrate that he is always able to control the synthesis of the active substance regarding impurities.

Conclusion
(Use of TLC method)

- A quantitative method should be developed even if it could be demonstrated that the reporting threshold of the TLC method is kept with a limit of 0.05% (0.03% respectively)
- Case-by-case decisions are necessary taking into consideration that only limit tests are applicable for single impurities in some cases

How to deal with impurities from EDQM's point of view

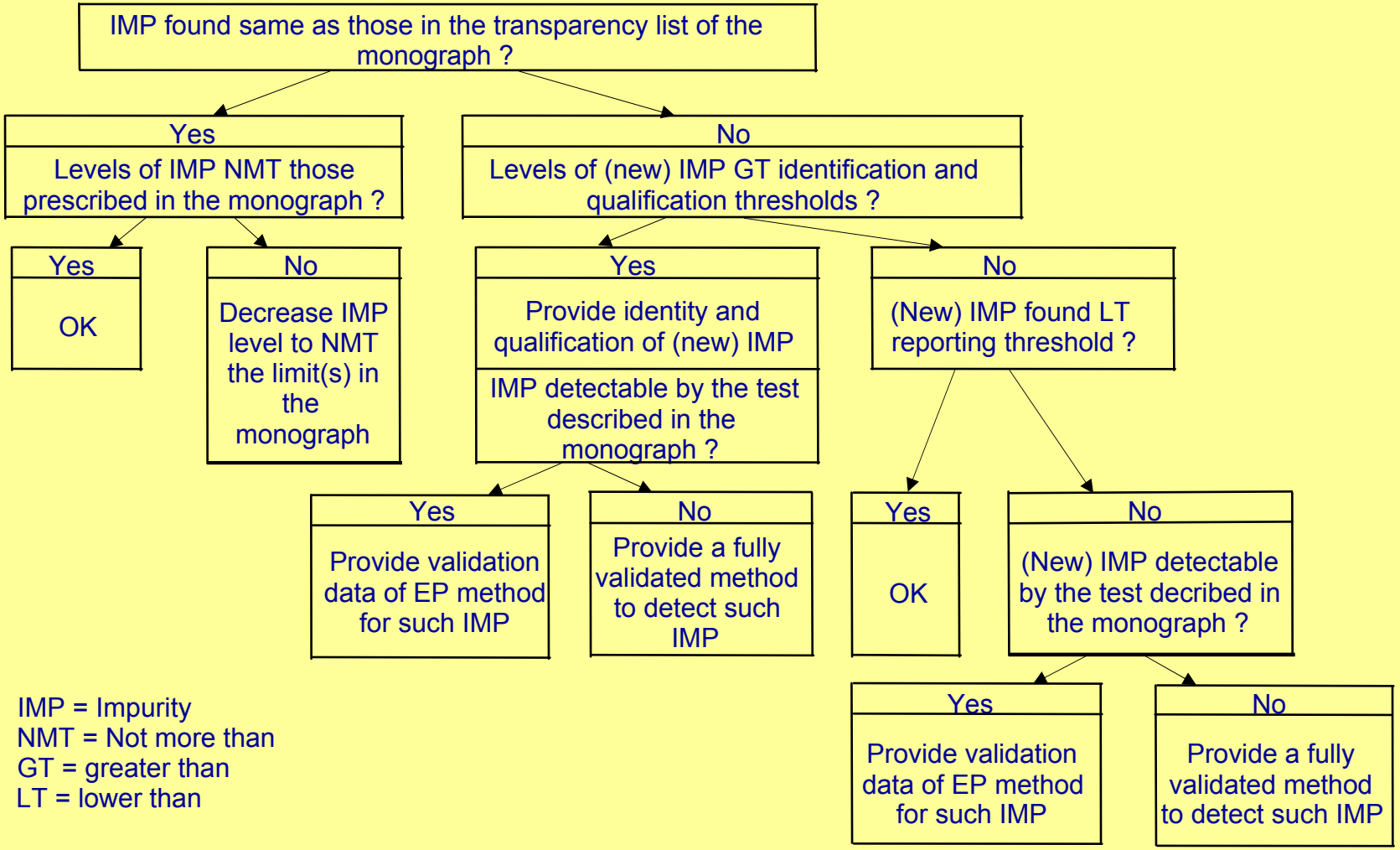
- Impurities
  - update with impurities mentioned in the transparency list
  - impurities above 0.1 % should be identified
  - if different from those mentioned in the monograph their possible toxicity is addressed
  - should be mentioned on the Certificate with a justified limit
  - the analytical method will be annexed, if different from the method of the Pharmacopoeial monograph

How the EDQM deals with impurities

- Impurities which are found beneath 0.10 % (0.05 %) are mentioned on the Certificate as “any other impurity with a limit of NMT 0.10 % (0.05 % respectively)

Decision tree for the assessment of related substances in a dossier

Existing drug substance described in Ph Eur or EU MS



IMP = Impurity
NMT = Not more than
GT = greater than
LT = lower than

History of the product (EDQM)

- How long the substance has been on the European market, using the route of synthesis described
- Information on ASMF submitted for the same substance
- Give as much information as possible
  (companies, products names, countries, registration dates, marketing dates)

► Impact on Qualification (limits) of impurities

Question 1

- **Content of the MA Dossier when the CEP procedure is used –**
- What additional information should be provided in the dossier ? We have studied the Guideline CHMP/QWP/297/97 (Guideline on summary of requirements for active substances in the quality part of the dossier), but even when the retest period is mentioned on the CEP, we are asked very often to supply the stability study (and other requirements).

Answer to question 1

- The requirments of the content of the dossier are outlined in the public policy paper „Content of the dossier for chemical purity and microbiological quality“ (PA/PH/CEP (04) 1 4R as well as in the policy paper:
- „Content of the dossier for herbal drugs and herbal drug preparations quality evaluation“
- Both papers are published on the EDQM web site
- If a re-test period should be mentioned on the CEP, stability data should be provided according to the Stability Guideline for existing active substances and drug products

Question 2

- **Revision of CEP**
- when a new version of CEP is submitted to the Regulatory Authorities, is the MA applicant obliged to provide detailed information regarding the change ? (i.e. the reason for the revision of CEP), even when it is declared from the API manufacturer that the specification and manufacturing process are unchanged (for example to supply the flow chart)

Answer to question 2

- If specification and manufacturing process remain the same, it is not necessary to provide full information to the MA applicant. However, in most cases it is very helpful for the MA applicant to get more infromation. For example, if an additional solvent is used during the manufacture of the active substances. Some changes may have an impact on the drug product, even if specifications and synthesis are unchanged.

Question 3

The product should be of Pharmacopoeia quality –

- Does it mean that we are not allowed to set stricter limit for any impurity ? (for example ethanol is limited in Oxycodone hydrochloride to 1.0 % by the separate test, our in house limit is 0.1 % (within the test for residual solvents), which conforms to the limit stated for Class 3 solvents in the ICH Guideline – is it acceptable ?).

Answer to question 3

Stricter limits are possible in all cases.

Question 4

Additional tests reported on the CEP -

- should all these additional tests be performed in routine analysis/batch release for every batch? (for example additional test for specified residual solvent or metal – is it acceptable to prove on certain set of batches that this potential impurity is not present, and CoAs for the following batches could be issued without results from these tests ?

Answer to question 4

The additional tests performed and the limits set for residual solvents, impurities, catalysts belong to the specification. Therefore these additional tests should be performed routinely.

Question 5

Particle size and bulk density reported on the CEP - when we have other requirement for the particle size and bulk density (another grade of API) and corresponding Certificates of Analysis are issued for our company by the manufacturer of API (consequently CoAs do not correspond to the CEP) – should we incorporate the whole DMF into the registration file instead of CEP ?

Answer to question 5

The manufacturer of the drug product can use an own specification together with other limits set.

However, according to the Guideline for ASMF procedure, the applicant does not need to accept redundant specifications.

The incorporation of the whole DMF into the registration file is not necessary.

ASMF-Procedure (1)

- ASMF-Procedure is applicable for
  - API not described in Ph Eur or in any European Pharmacopoeia
  - APT covered by a monograph
  - Exclusively connected with licencing affair of a drug product

ASMF Procedure (2)

- Applicant‘s Part and Restricted Part
- All information should be provided in CTD form (S1 to S7)
- The Applicant should get all information regarding synthesis and control methods for the drug product
- Additional details (information considered not necessary for the Applicant) are outlined in the Restricted Part
- Quality Overall Summary for Applicant‘s Part und Restricted Part

How to assess Fermentation Products (1)

- Toxicological considerations: From the point of view of our toxicological experts, there is no reason to set limits for impurities of fermentation products less strict than for impurities coming from chemical synthesis

How to assess Fermentation Products (2)

- Impurities found during clinical and pre-clinical studies are considered qualified
- Qualified by use acceptable

- Product history, provided there is no change of the fermentation procedure
- Comparison of impurity profile with a product which is still on the market

How to assess Fermentation Products (3)

Toxicological experts will take under consideration:

- Maximal daily dose
- Long-term application
- Short-term application
- Possible genotoxic impurities which may arise from fermentation
- Risk/benefit considerations

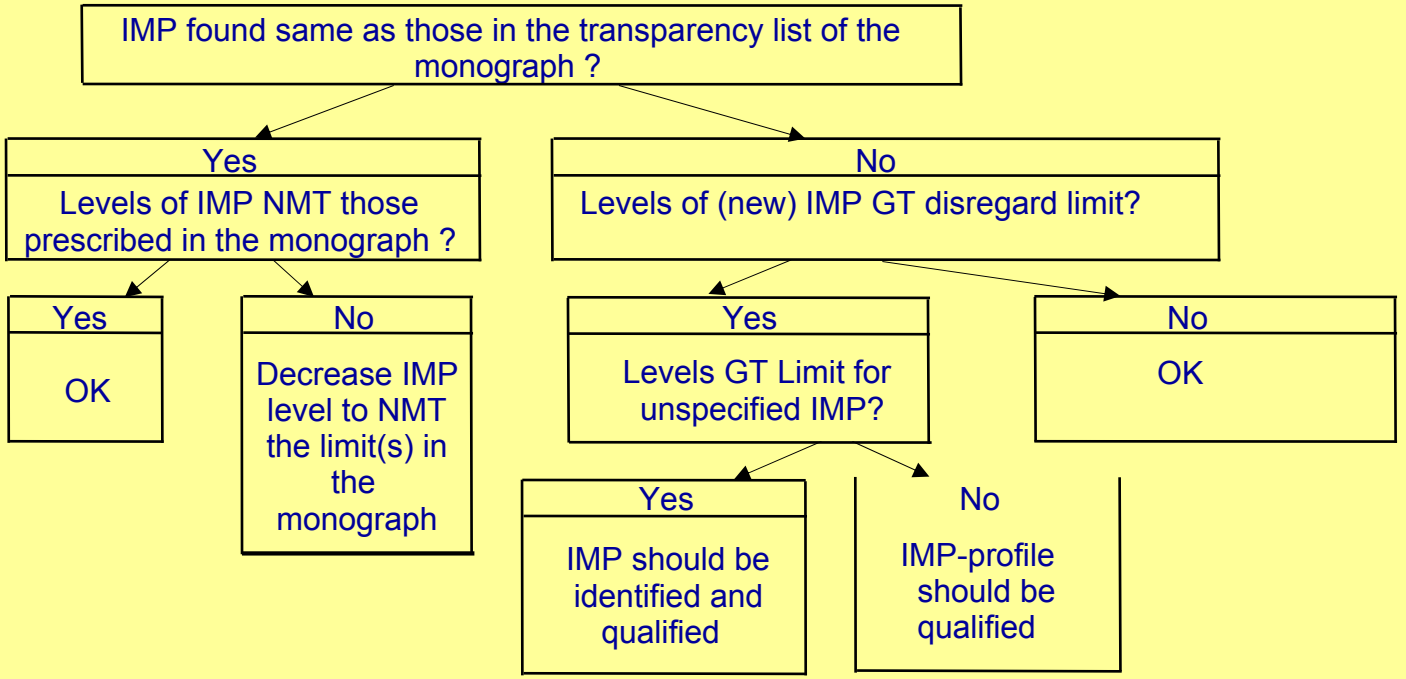
5.10 Control of Impurities in Substances for Pharmaceutical Use (2)

- The general acceptance criterion applies to:

- all unspecified impurities

- Specified impurities, except those that have their own specific acceptance criterion in the monograph

Decision tree for the assessment of related substances in fermentation products described in Ph Eur or EU MS



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Problem statement (1)

- The use of European regulatory procedures with the current ASMF procedure is increasingly resulting in logistic and administrative issues and duplication of scientific work.

Problem statement (2)

- It results in inconsistencies in assessment of the ASMFs within and among member states and may result in lack of regulatory and/or GMP compliance to the European legislation.

Problem statement (3)

- Reference number system is unclear
- Every agency has an own reference number system
- Assessors do not know what is the actual updated version

Proposals (1)

- Sharing of assessment reports and responses for ASMFs is considered a useful step forward.
- During a DC Procedure, where a new ASMF has been assessed by the RMS, the RMS assessor will be indicated as rapporteur for the corresponding Drug Master File.

Proposals (2)

- The “ASMF-Rapporteur” will be also responsible for the up dates of the ASMF, all variations etc.
- Introduction of of an ASMF database:

1. All assessment reports regarding this ASMF will be included in a data base where the European agencies will be licensed to have direct access to the data base.
2. Each agency is responsible to include all the information regarding the relevant ASMF in the data base.

Proposal for improvement of assessment report

- Restricted Part
  - Short summary of the manufacturing process
  - List of all reagents and solvents used after every step

Proposal for improvement of the assessment report (1)

Name	Company Specification	Ph Eur Specification	Typical levels (from batch data)	Typical levels (from stability data)
Impurity A	0.2 %	0.5 %	0.03-0.05	0.03 -0-06 %
Impurity B	0.5 %	0.5 %	0.1 %-0.15 %	0.1 %-0.3 %
Impurity X	0.15 %	Not given	0.04 -0.08 %	0.06-0.09 %

Proposal for improvement of the assessment report (2)

Name of solvent	ICH class	ICH limit	Typical levels (from batch data)	Use during synthesis step x
Acetone	Class 3	0.5 %	3000 ppm	Used during step 3
Ethanol	Class 3	0.5 %	400 -600 ppm	Used during the last step
Hexane	Class 2	290 ppm	10 ppm	Used during step 2

Proposal for improvement of the assessment report

3.2.S.4.3 Method validation

- The validation report should be summarized. It is very helpful to mention LOD and LOQ numerically.