BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

Overview of Applications for Marketing Authorisation

Recent experience in Quality Assessment

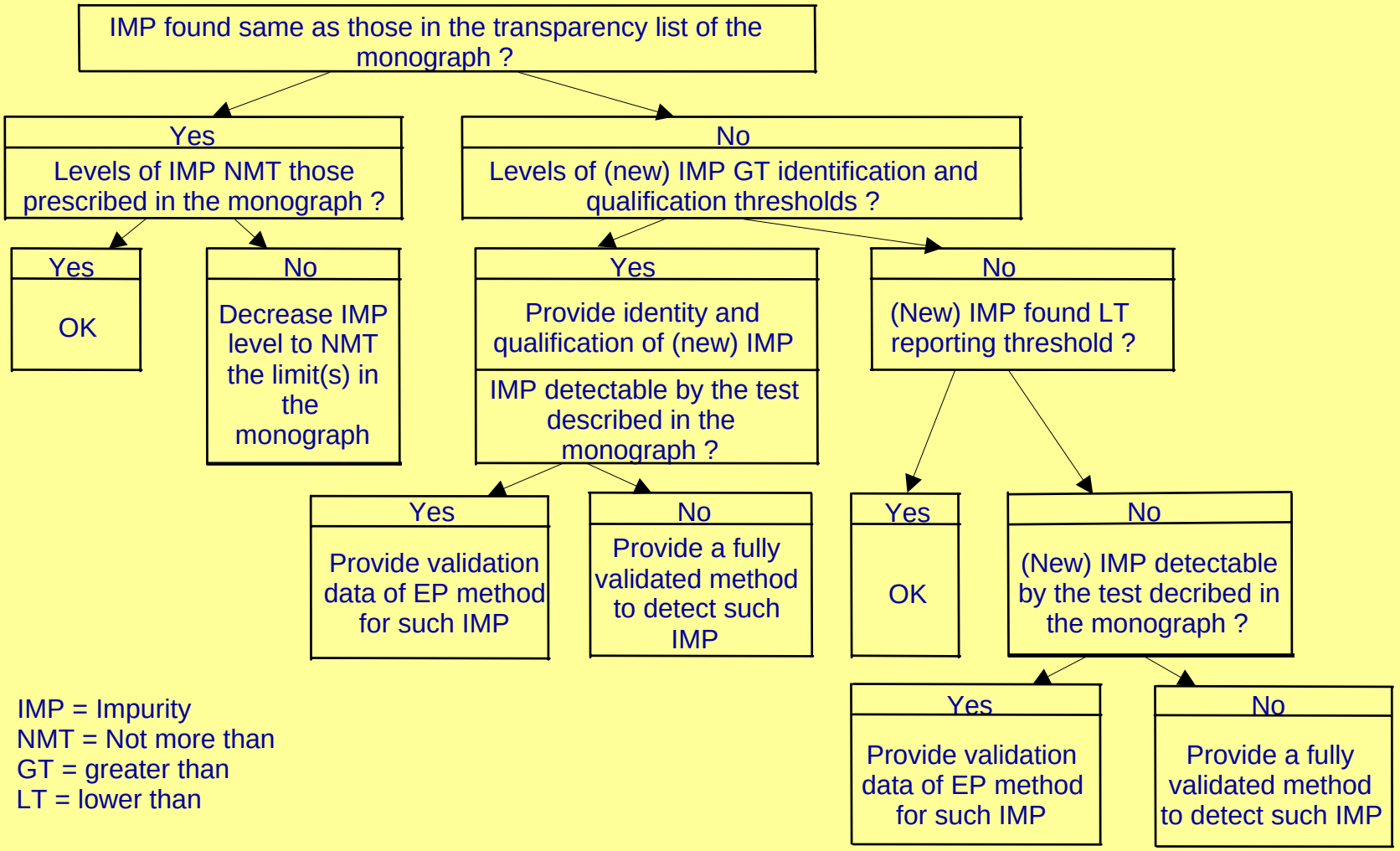
Table of Contents

Specification

- Specification
  - Each specified, identified IMP (> 0.10 %)
  - Each specified, unidentified IMP
  - Each unspecified, unidentified IMP
    [> 0.03 or 0.05 % (reporting threshold) and
    ≤ 0.05 or 0.10 % (identification threshold]
  - Sum of IMP
  - Threshold for qualification is 0.15 or 0.05 %

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

Existing Active Substances described in the Ph Eur or a Pharmacopoeia of an EU MS

- Qualification
  - Impurities (IMP) listed in an impurity section are qualified
  - Information as to the length of time that the active substance from the particular named source has been on sale in the European Union and elsewhere (product history, comparison to the impurity profile of products which are still marked.)
- New IMP
  - If it is not possible to draw conclusion from in the European Union or elsewhere licensed products, same requirements are applied claimed in the Guideline on Impurities in New Drug Substances (reporting level, identification level, qualification level).

Qualification of IMP found in a New Active Substance

- Qualified are:
  - The level of IMP that has been adequately tested in safety and/or clinical studies
  - Metabolites

Substances for Pharmaceutical Use

- 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

- The development of a quantitative method is required for a substance which is described with an “old” monograph during variation procedure as well as during licensing affair of a drug product.
- CEP will be blocked, applicant is asked to initiate revision of CEP.

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

Definition „Semi-synthetic Products“

- Semi-synthetic products are obtained from a fermented starting material by a process involving at least cleavage and formation of covalent bonds followed by extraction/purification steps

Semi-synthetic Products

- The starting material should be characterised (specifying a minimum purity with appropriate limits for impurities)
- The possibility of carrying impurities from fermentation process to the final substance should be discussed
- The impurity profile of intermediates should be controlled

Impurities regarding Semi-synthetic Products

- Setting specifications for semi-synthetic substances
  - The principle of the Guideline “Impurities in New Drug Substances” should be applied if the semi-synthetic substance is similar regarding purity and description of a chemical substance

Residual Solvents – Class 1

Benzene as unavoidable contaminant of a solvent (e.g. toluene)

- The routinely proof of benzene is not required if it is demonstrated that benzene is found not more than 30 % of the specified limit in an intermediate or the active substance* respectively

* 6 pilot batches or 3 production batches

Residual Solvents – Class 2

The routinely proof of a class 2 solvent is not required if it could be demonstrated that the content of the class 2 solvent is found to not more than 10% of the acceptable concentration in the intermediate or finished product* respectively

* 6 pilot batches or 3 production batches

Residual Solvents – Class 3 (1)

- Up to 0.5%
  - Amounts up to 0.5% (Option 1) are acceptable determined by Loss on Drying (LoD) without justification
  - A specific and validated method should be used if LoD is not suitable to determine the amount of a residual class 3 solvent

NFG on Specification Limits for Residues of Metal Catalysts Draft

- Guideline is applicable for active substances and excipients
- Guideline is not applicable for new active substances which are used in clinical trials
- Guideline is applicable for all formulations, but there are different limits for parenteral and oral formulations

Limits of residual catalysts by short-term use

- A higher limit for residual catalysts is acceptable:
  - if the medical product is used for a short period (max.30 days) or
  - regarding a single dose application or
  - regarding a very short-term use of the medical product
- But the limits should be justified regarding safety

How the EDQM deals with residual catalysts

- Catalysts are not mentioned on the CEP, if it is demonstrated that the catalyst is not detectable in the final substance (beneath Limit of Detection)

- Exception: The catalyst is to be considered as a very toxic agent

How the BfArM deals with residual catalysts

- NfG Guideline on Specification Limits for Residues of Metal Catalysts (Draft!)
- Case-by-case decisions
- With the help of toxicological experts
- Conclusions from Food Industry

Genotoxic Impurities (1)

- Impurities, which are considered to be genotoxic are acceptable with an daily exposure of 1.5µg per day
- It is very difficult to develop a method which is able to determine alcylating substances such as mesylates

Genotoxic Impurities (2)

- If the substance is not found to be on the European market, the company will be asked to provide a specific discussion as part of the overall discussion on impurities with regard to impurities with potential genotoxicity.
- If a genotoxic impurity is liable to be present in the substance then conformity to the requirements of the NFG Guideline on the Limits of Genotoxic Impurities should be demonstrated in the CEP application file.

Specification of Impurities in Drug Products

- Each specified, identified degradation product (> 0.2 %, 0.5 %, 1% respectively)
- Each specified , not identified degradation product
- Each unspecified degradation product [> 0.05, 0.1 % respectively (reporting threshold) und < 0.2, 0.5, 1 % respectively(identification threshold)]
- Sum of degradation products
- Qualification limit depends on the daily dose

Impurities in Drug Products

- The following impurities should be taken into consideration:
  - Degradation products of the active substance
  - Reaction products of the active substance with other components or with the container closure system
- The following impurities should not be taken into consideration:
  - Impurities, which arise from the active substance, such as products which come from the synthesis of the active substance

Degradation Products (1)

- 4-aminophenol may exist from paracetamol (100 ppm max in solution for injection)
- Some cephalosporine are able to give lactone
- Dihydropyridine (nifedipine) may produce the corresponding pyridine derivates

Degradation Products (2)

Suitability of packaging material with the finished product should be given:

- With plastic materials: Zn, Ca, bisphenol A, and other additives of PVC must be searched in solutions for injection
- With glass: aluminium content in large volume injections (> 100 ml) must not exceed 25 µg per liter, for parenteral nutrition therapy, according to USP 30 requirements

Setting specifications

- It is usual to set specifications in broader limits at the beginning of the life circle of a finished product (justification of limits are necessary)
- More experience means to tighten specifications according to batch results (Variation procedure)

Deficiencies
Drug Substance (1)

- **3.2.S.2.3:** lack of information on the declared starting materials. Lack of information on route of synthesis, impurity profile (related substances, reagents, solvents, catalysts), no discussion about possible carry-over of its impurities to the final substance
- **3.2.S.3.2:** Insufficient demonstartion of the absence of particular reagents in the final substance (e.g. Catalysts, alkylating agents,...)

Deficiencies
Drug Substance (2)

- 3.2.S.3.2: Residual solvents: Incomplete demonstration that all solvents used during synthesis are removed/limited in the final substance
- 3.2.S.4. Limits for impurities not in compliance with the specific Ph Eur monograph (misunderstanding of the transparency list of the specific monogtraph)
- 3.2.S.2.3: Specifications for all reagents, solvents not described/not sufficient

Deficiencies
Drug Product (1)

- Test methods are not validated (determination of assay/impurities, dissolution testing)
- No data belonging to individual validation characteristics are presented
- No validation data are presented because a monograph has been taken into account

Deficiencies
Drug Product (2)

- No information is given regarding qualification of degradation products for drug products containing a known active substance (reference should be made to the limits outlined in the Guideline for Impurities in New Drug Products)

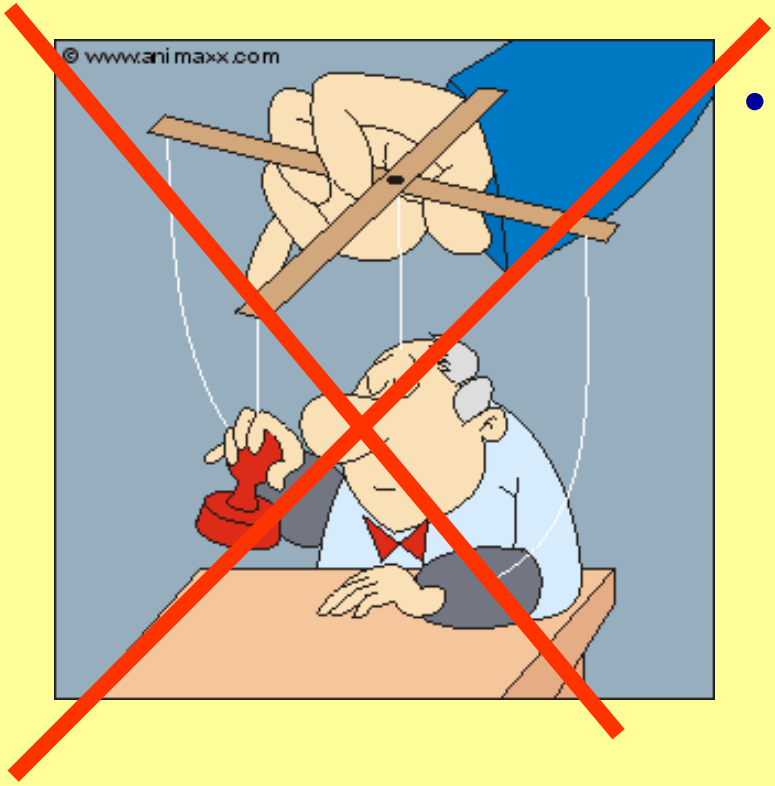
Deficiencies Drug Product (3)

- No limits have been set in the release specification and shelf life specification for each unspecified impurity and total of impurities
- Mass balance is not given during stability studies and therefore lack of justification for limits (re-validation of the method is necessary)
- Data for in-use stability are not given

Deficiencies
Drug Product (4)

- Data for demonstration of compatibility regarding mixtures for solution of infusion with other solutions for infusion are missing
- Stability studies do not refer to the drug product stored in the container closure system intended for market

Conclusion



- Case-by-case-decisions

  - Particular deviations from requirements of Guidelines are possible but should be justified