Presentazione: Carry-over of impurities from materials for API Synthesis

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3. Strategic advisory role for a company	X	☐	☐	☐ optional
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Carry-over of impurities from materials for API Synthesis

The evaluation of potential carry-over of impurities is important for:

- Define the impurity profiling of API

- Define suitable specification for API

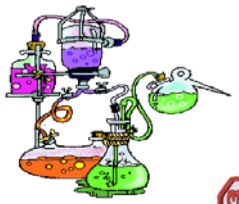
- Improve the knowledge of the manufacturing process

- Set up process parameters/in process control (IPC)

Possible source of contamination

Residues of Raw Materials, SM, intermediates etc..

Residues of by-products

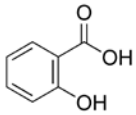


Residues of degradation products

Materials used during manufacturing

Residues of detergents/sanitizers

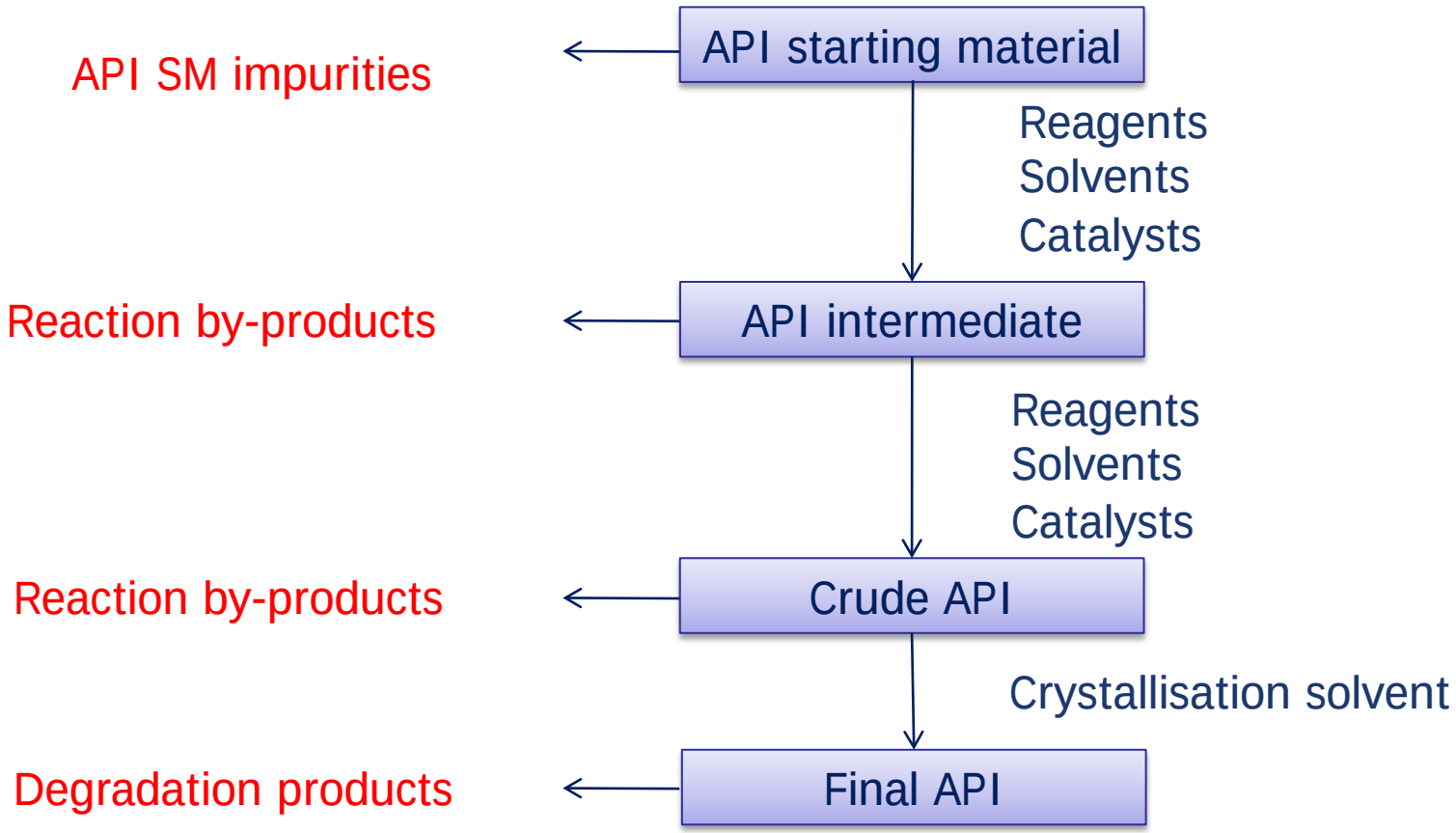
Residues of other API productions



Microbial contaminants, endotoxins

Quality Aspects ⇄ GMP Aspects

Potential impurities in API Synhesis



Potential impurities in API Synhesis

- Residue of the SM
- Residue of the intermediate
- Impurities in the SM
- Reagents
- Solvents
- Catalysts
- Reaction by-products
- Degradation products

API Starting Material definition

ICH Q7:

An "Active Substance Starting Material" is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance.

From this point on, appropriate GMP as defined in these guidelines should be applied to these intermediate and/or active substance manufacturing steps.

API Starting Material

Table 1: Application of this Guide to API Manufacturing

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology : fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

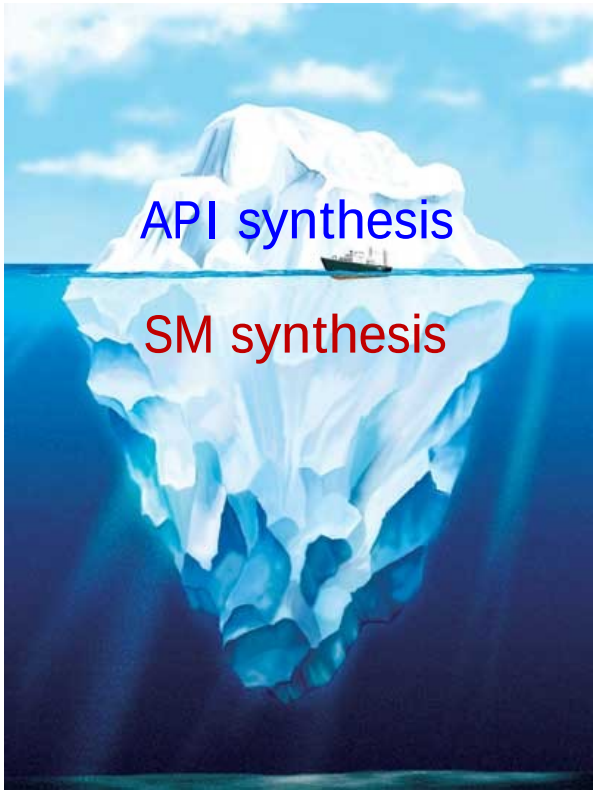
Selection of API Starting Material

Choice of API-SM in the synthetic pathway

-ICH Q11:

Manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in section 3.2.S.2.2 of the application;

Carry over of impurities/solvents from the Starting Materials



Reflection Paper EMA/448443/2014 - 16/09/2014

- The specification for a starting material should address impurities and is expected to consider suitable limits for known, unknown impurities and total impurities and where appropriate, limits for solvents, reagents and catalysts used during synthesis of a starting material.
- Moreover, the potential carry-over of impurities/solvents in the API should be discussed.

Information on the manufacturers and suppliers of starting materials should be provided, including name and address, and a scheme of the synthetic route used to manufacture them, showing all reagents, catalysts and solvents used. Without this information, the suitability of specifications cannot be adequately assessed.

Residues of raw materials

- Solvents: demonstrate the absence of particular solvents in the API used in particular production steps (e.g. in the last step) or set a limit in API specifications (or in suitable intermediate). This evaluation should be consider Class 1 solvents (eg. Benzene) as contaminants of other solvents. *ICH Q3C and related Annexes*

- Residues of catalysts: Demonstrate absence of residues of catalysts or set a limit in API specifications (or suitable intermediate).

  EMEA draft guideline on catalysts (CPMP/SWP/4446/00)

- Residues of Reagents: demonstrate the absence of particular reagents in the final substance or set a limit in API specifications (or in suitable intermediate). *ICH Q3A*

Carry over of inorganic/organic impurities

ICH Q3A:

- Inorganic Impurities

Inorganic impurities are normally detected and quantified using pharmacopoeial or other appropriate procedures. Carry-over of catalysts to the new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new drug substance specification should be discussed. Acceptance criteria should be based on pharmacopoeial standards or known safety data.

- Organic Impurities

The applicant should summarise the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance.

Acceptance criteria for organic impurities

ICH Q3A:

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

Organic Impurities

- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold
- Total impurities

Detection of impurities by suitable validated analytical method

Impurities methods described in EP monographs?

yes → No complete validation is required

↓ No

Complete validation is required according to the ICH Q2 (R1)

→ Verification of specificity, linearity, accuracy, precision, robustness, etc...

Carry-over of impurities in dedicated Equipment

Cleaning Validation of equimpments to defines:

1. Maximum campaign lenght;
2. Cleaning procedure;
3. Clean Holding time (CHT): the time between the completion of cleaning and the beginning of the next manufacturing operation;
4. Dirty Hold time (DHT): the time between the end of manufacturing and the beginning of cleaning procedure.

EU GMP Part II:

Equipments maintenance and cleaning: 5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

Cleaning Validation of dedicated equipment

Potential contamination in shared equipments/facilites

EU GMP Annex 15:

Cleaning validation: 10.6 Limits for the carryover of product residues should be based on a toxicological evaluation. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.

EMA/CHMP/CVMP/SWP/169430/2012 "*Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*"

Potential contamination from materials

Many materials used during production could represent a source of contamination if not removed or if mainteinence and/or assembling of the equipment are not performed correctly

•charcoal, 

•paper particles from filters,

•monomers released by polymeric resins

•lubricants from motors and bearings,

•fiber from personnel garments ,

•small slivers of stainless steel,

•etc.....

Potential contamination from materials

EU GMP Part II:

Sanitation and Maintenanance: 4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

Process equipment: 5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

Contamination control: 8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

Potential contamination from utilities

EU GMP Part II (*4.2*):

Utilities: 4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

HVAC system

Water production/distribution

Nitrogen storage/distribution

Qualified and monitored

Stressful production steps

The potential impact of stressful production steps on the impurity profile of API should be evaluated

- Milling/Micronization steps

- Gamma Radiation Sterilization

Conclusion

The evaluation of impurities' carry-over and its monitoring is a complex exercise which involves many quality and GMP aspects....

R&D

QA

Maintenance

QC

Production

Regulatory

Engineering

Contatti

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