Regulatory expectations on impurities in drug substances - Pavia, October 2, 2015

REFERENCE GUIDELINES ON IMPURITIES IN DRUG SUBSTANCES: THE STATE-OF-THE-ART

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Impurities in drug substances

An Impurity is defined as any substance or element present in a drug substance (DS) that is not the chemical entity defined as the drug substance.

Impurities lower the quality of the DS in terms of purity and they can potentially affect the efficacy and/or safety of the final Drug Product.

Impurities can be toxic, affect stability or efficacy of final product.

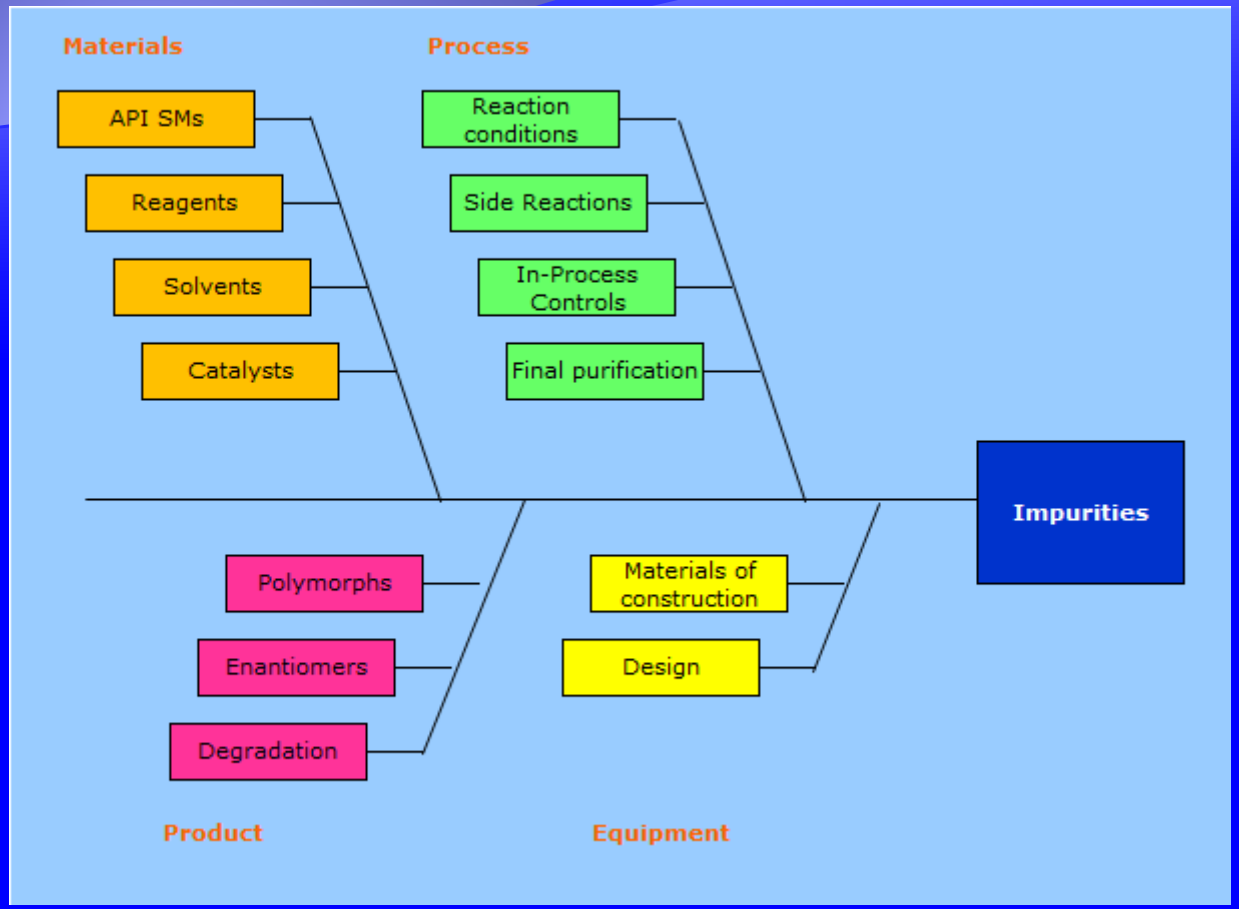
Even if completely inert, they do not add any therapeutic benefit, so they are always considered as unwanted components.

The origin of impurities

Impurities come from the manufacturing process.
No process (chemical synthesis, extraction, fermentation, biological/ biotechnological pathway) can assure the complete absence or removal of impurities.

The product itself can be a source of impurities, in case of degradation due to improper packaging or storage conditions.

The origin of impurities



The control strategy

The control strategy is based on:

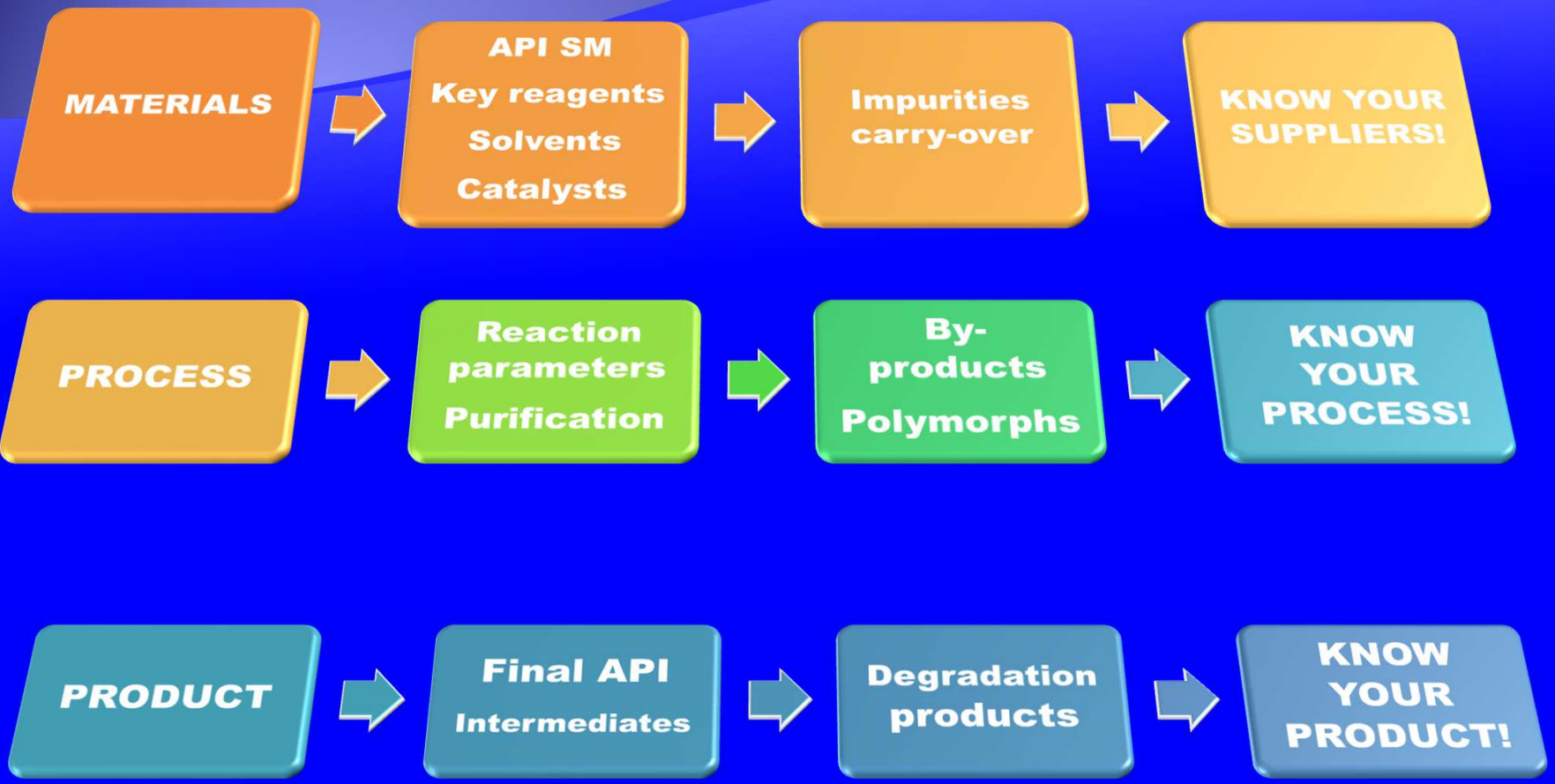
A thorough knowledge of the product characteristics (enantiomers, polymorphic forms, isomers, temperature/light/moisture sensitivity ...).

Knowledge of all manufacturing steps (raw materials properties, process parameters, final purification capabilities).

Availability of suitable analytical methods to ensure the appropriate control of all the impurities (including degradation products).

A good knowledge helps also in evaluating changes to the original process.

The control strategy



The impurity profile

A good knowledge of the process is necessary to determine the impurity profile of the product.

Impurity profile is the list of any single and/ or total identified and unidentified impurities present in a standard batch of DS, obtained by a specific manufacturing process and tested by a suitable analytical method.

It includes the identification of each impurity (e.g. chemical name or RRT) and the typical level (as area % or as other unit).

Being the impurity profile process-based, not always it corresponds to the compendial monograph one. Unexpected or different impurities can be found in the product if obtained by a route different from the historical one upon which the monograph was prepared.

Regulatory requirements

Regulatory authorities expect to find in the ASMF or Application Dossier all the information needed to assess if the DS/DP represents a risk for the health of the patient.

Data relevant to impurities are a critical point in this assessment.
The US-FDA issued on 2014 a guidance for industry titled «ANDAs submissions- Refuse-to-receive for lack of proper justification for impurity limits».

The International Conference On Harmonisation, ICH, founded on 1990, issued, starting from late 90's, different specific guidelines on Impurities, identified as ICH Q3 series, replacing the different, several documents previously available, to harmonise expectations on this topic.

The ICH Guidelines. At the beginning…

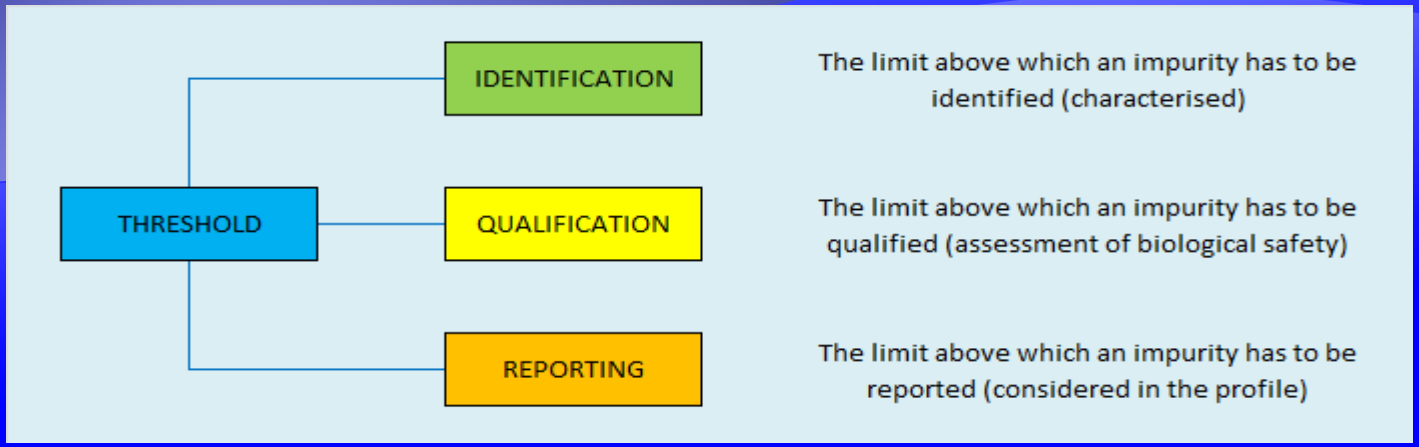
Being most APIs manufactured by chemical synthesis, the first guideline – ICH Q3A- specifically addressed to Impurities in DS is focused only on synthetically obtained APIs, classifying impurities in 3 classes

- Organic impurities
- Inorganic impurities
- Residual solvents

It gives recommendations on both chemical and safety aspect of impurities.
In particular, three thresholds are defined for impurities identification, reporting and qualification, based on the typical daily dosage of DS.

In case the proposed limits cannot be met, additional information and proper justification has to be provided.

The ICH Guidelines. At the beginning…



General notes on setting specs for organic impurities

- Any impurity routinely observed in standard batches or long-term stability trials should be controlled by the impurity specifications.
- Impurities observed below the ICH identification threshold need not be individually specified in the specifications. They can be controlled under the limit for any unspecified impurity.
- Impurities above the ICH identification threshold need to be identified and individually specified in the specifications.
- A test for any unspecified impurity and total impurities should be included.

General notes on setting limits for impurities

- The limit for any unspecified impurity should be at the ICH identification threshold.
- The limit for total impurity content should reflect batch data.
- Residual Solvents and Elemental impurities follows specific guidelines

General notes on qualification

- Based on Toxicological data or Structure-activity studies
- Based on literature
- Based on limit in pre-approved applications

The ICH Guidelines. At the beginning…

ATTACHMENT 1

Thresholds

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%

… And how they are changing.

The attention on impurities continues to evolve because of scientific and technological advancements make impurity measurements and control strategies more effective.
These changes, in combination with advancements in the field of toxicology, have contributed to the evolution of regulatory (and consequently compendial) standards for the control of impurities in drug substances and drug products.

During time, it was considered necessary to have specific guidelines on Residual Solvents, considering their number and their different characteristics; on Elemental impurities, due to their potential ubiquitous nature; on Genotoxic impurities for safety concerns they pose.

Moreover, after the issuance of ICH Q8, Q9 and Q10 that underlined the need of quality applied to all the DS/DP lifecycle, impurities have been considered as an important part of process development and, in general, of Quality Risk Management.

The main guidance documents

Source	Title & Content	Year of issuance
ICH	Q3A(R2) – Impurities in new Drug Substances	2006
The Guideline addresses the chemistry and safety aspects of impurities, including the listing of impurities in specifications and defines the thresholds for reporting, identification and qualification.		
ICH	Q3B(R2) – Impurities in new Drug Products	2006
The Guideline specifically deals with those impurities which might arise as degradation products of the drug substance or arising from interactions between drug substance and excipients or components of primary packaging materials.		
ICH	Q3C(R5) – Impurities. Guideline on Residual Solvents	2011
It recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms, and sets pharmaceutical limits for residual solvents (organic volatile impurities) in drug products. R6 available for comments.		
ICH	Q3D – Guideline on Elemental Impurities	2014
This guidance aims to provide a global policy for limiting metal impurities (included in ICH Q3A as inorganic ones) qualitatively and quantitatively in drug products and ingredients. Implementation on going.		

The main guidance documents

Source	Title & Content	Year of issuance
ICH	Q5A – Q5E – Quality of Biotechnological Products	1999 - 2004
This group of guidelines specifically addresses quality aspects, including impurities, relevant to DS and DP obtained by biological sources and biotechnology		
ICH	Q6B – Test procedures and acceptance criteria for Biological and Biotechnological Products	1999
It provides guidance on justifying and setting specifications for proteins and polypeptides which are derived from recombinant or non-recombinant cell cultures		
ICH	Q11 – Development and manufacturing of DS	2012
It addresses aspects of development and manufacture that pertain to drug substance, including the presence of steps designed to reduce impurities.		
ICH	M7 – Genotoxic impurities	2014
It offers guidance on analysis of SAR for genotoxicity. Also it is intended to resolve questions such as whether impurities with similar alerts that potentially have similar mechanism of action should not be combined in calculating a Threshold of Toxicological Concern (TTC) and whether the TTC may differ based on differences in the approved duration of use. Implementation on going. R1 distributed for comments.		

The main guidance documents

Source	Title & Content	Year of issuance
US-FDA	ANDAs . Refuse-to-receive for lack of proper justification for impurity limits (Draft)	2014
The guidance highlights deficiencies in relation to information about impurities that may cause FDA to refuse to receive an ANDA. A refuse-to-receive decision indicates that FDA determined that an ANDA is not sufficiently complete to permit a substantive review.		
EMA	CHMP/CVMP/QWP/199250 – Setting specifications for related impurities in antibiotics.	2013
It provides guidance in setting limits for impurities in antibiotics from fermentative or semi-synthetic route.		
EMA	CPMP/QWP/2820/00 Rev.2 – Guideline on specifications: test procedures and acceptance criteria for herbal substances (…)	2011
It provides guidance in setting limits for impurities in APIs from vegetal origin		
WHO	Technical Report Series No 953 – Annex 4 –Suitability of Drug Substances for pharmaceutical products	2009

And the compendial requirements

Basically, ICH concepts and proposed limits have been adopted by USP, EP and JP.

Moreover, ICH recommendations have been described in general chapters or monographs that are complemental to single product monographs.

For example: EP General Monograph Nr.2034 – Substances for pharmaceutical use; EP General Chapter 5.10 – Control of impurities in substances for pharmaceutical use; USP <1086> Impurities in Drug Substances and Drug Products; USP <476> Organic Impurities in DS and DP (new)…

Also in this case a continual improvement and revision program is ongoing.

No conclusion…

"Impurities" is an always ongoing topic, for both manufacturers and regulators.

A number of open points are still present, for example

- **Existing DSs. On which extent guidelines are applicable to old DSs?**
- **Guidance for other product type?.**
- **Toxicology and Genotoxicity. Is it possible to qualify impurities without the need to undertake additional studies? Are the currently proposed limits correct? What is the role of DS manufacturer?**

In the future new challenges will arise….


thank you!