IMPURITY PROFILING
IDENTIFICATION AND CHARACTERIZATION

INSTITUT FRESENIUS

CHALLENGE

OCCURRENCE OF IMPURITY – WHAT TO DO?

Impurities can arise at numerous points in the process. If the impurity occurs in the production of the active substance the product is tied with considerable financial resources and high time pressure. Structure clarification of the impurity is essential to identify and rectify the triggering fault and/or carry out a toxicological evaluation. It is the only basis to identify whether the product batch can be used, is transferable in a usable state or, in a worst-case scenario, has to be destroyed. Rushed actions at this point lead to an effect on the budget but not to a solution and cost valuable time.

WHAT IS ESSENTIAL FOR SUCCESS?

Information gathering
- How many batches are affected?
- Figure of the economic damage
- Third party information (e.g., suppliers)
- Known side effects of the synthesis
- Storage stability
- Complexity of synthesis process
- Information from QC method

Fault analysis & risk assessment
- New reactants/change of supplier?
- Other solvents (change in quality)?
- Changed reaction conditions (T, t, p)?
- Changed reaction components?
- Changed production process materials?
- QC analytical method valid?

Information transfer to analytical lab

PRINCIPAL TESTS

OUR PROCESS FROM UNKNOWN TO STRUCTURE PROPOSAL

- Method transfer: verification of result
- Method adaption: product analysis method is often not suitable for structure-determination equipment (e.g., salts, solvents, ion pair reagents)
- Data gathering
- Data evaluation & verification
- Structure proposal by analyst with expertise and sufficient information to survey the issue in all its facets

METHOD SUPPORT

For volatile & semi-volatile organic compounds
- HS-GC-MS (EI)
  headspace analysis with MS-library comparison (NIST & SGS)
- GC-TEA
  NO & NO_2-sensitive detector for nitrosamine quantification
- GC-FID/MS (EI)
  semi-volatile analysis with MS-library comparison (NIST & SGS)
- GC-FID/QToF (CI)
  high-resolution MS for accurate mass determination

For non-volatile organic compounds
- HPLC-DAD (fraction collector)
  purification and isolation of analytes
- HPLC-DAD/QToF (ESI, APCI)
  high-resolution MS for accurate mass determination
- HPLC-MS/MS
  triple-quadrupole MS for identification and quantification of trace level analytes

For structure elucidation
- High-resolution mass spectroscopy
  highly selective detector with 0.001 atomic mass unit resolution
- NMR spectroscopy
  chemical molecular structure determination

SERVICES FOR ELEMENTAL IMPURITIES

The USP and EMA directives specified the allowed content of a metal for their controlled market. Every pharmaceutical manufacturer has to comply with these guidelines. But not every metal is under observation. Be careful to invest only in necessary measurements.

GMP analysis for batch release
- ICP-MS
  robust multi-element analysis at trace level
- AAS
  selective quantification of 70 elements in liquid and solid samples

Non-GMP analysis for R&D investigation
- SGS screening method:
  fast
  cheap
  informative

RESULTING CONSIDERATIONS

- Is the source of impurity determined?
  - raw material?
  - process conditions?
- Is a toxicological assessment necessary?
- Do processes need to be adjusted (CAPA, updating of SOPs)?

ADDITIONAL SERVICES

- Extractables & Leachables chemical characterization
- Particle identification and particle distribution
- Cleanness of surfaces
- Material failures and damage analysis by analytical method

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IMPURITY PROFILING
ELEMENTAL IMPURITIES ACCORDING TO ICH Q3D AND USP <232>

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ELEMENT	USP <232> ELEMENTAL IMPURITIES – LIMITS			ICH GUIDELINE Q3D ON ELEMENTAL IMPURITIES EMA/CHMP/ICH/353369/2013				ELEMENT UNDER INVESTIGATION DURING SGS SCREENING
	ORAL DAILY DOSE PDE (µg/DAY)	PARENTERAL DAILY DOSE PDE (µg/DAY)	INHALATIONAL DAILY DOSE PDE (µg/DAY)	EMA CLASSIFICATION	NOT INTENTIONALLY ADDED			
					ORAL	PARENTERAL	INHALATION	
Cadmium (Cd)	5	2	2	1	Yes	Yes	Yes	✓
Lead (Pb)	5	5	5	1	Yes	Yes	Yes	✓
Arsenic (As)	15	15	2	1	Yes	Yes	Yes	✓
Mercury (Hg)	30	3	1	1	Yes	Yes	Yes	✓
Iridium (Ir)	100	10	1	2B	No	No	No	✓
Osmium (Os)	100	10	1	2B	No	No	No	✓
Palladium (Pd)	100	10	1	2B	No	No	No	✓
Platinum (Pt)	100	10	1	2B	No	No	No	✓
Rhodium (Rh)	100	10	1	2B	No	No	No	✓
Ruthenium (Ru)	100	10	1	2B	No	No	No	✓
Chromium (Cr)	11,000	1,100	3	3	No	No	Yes	✓
Molybdenum (Mo)	3,000	1,500	10	3	No	No	Yes	✓
Nickel (Ni)	200	20	5	2A	Yes	Yes	Yes	✓
Vanadium (V)	100	10	1	2A	Yes	Yes	Yes	✓
Copper (Cu)	3,000	300	30	3	No	Yes	Yes	✓
Cobalt (Co)	–	–	–	2A	Yes	Yes	Yes	✓
Thallium (Tl)	–	–	–	2B	No	No	No	✓
Gold (Au)	–	–	–	2B	No	No	No	(✓in addition)
Selenium (Se)	–	–	–	2B	No	No	No	✓
Silver (Ag)	–	–	–	2B	No	No	No	✓
Lithium (Li)	–	–	–	3	No	Yes	Yes	✓
Antimony (Sb)	–	–	–	3	No	Yes	Yes	✓
Barium (Ba)	–	–	–	3	No	No	Yes	✓
Tin (Sn)	–	–	–	3	No	No	Yes	✓
Manganese (Mn)	–	–	–	–	–	–	–	✓
Iron (Fe)	–	–	–	–	–	–	–	✓
Zinc (Zn)	–	–	–	–	–	–	–	✓

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