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Expected approach in Developing Control Strategies for Impurities in Drug Substances

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Note

The opinions expressed in this presentation are based on the speaker's experience as Pharmaceutical Assessor and do not necessarily reflect the views or policies of the MHRA.

Aims

- Focus on impurities of Chemical Drug Substances
- Types of impurities to be controlled
- Assessor’s expectations in MAAs – the ideal 3.2.S.3.2 section
- Deficiencies frequently encountered during assessment
- Control Strategy – considerations and examples

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Types of Impurities to be Controlled

Organic

- Starting materials, by-products, intermediates, degradation products, reagents, ligands, catalysts

Inorganic

- Reagents, ligands, catalysts, residual metals, inorganic salts, other materials (filter aids, charcoal)

Solvents

- Residues still present after a chemical reaction, re-crystallisation, washing, contaminants

Starting Materials

GMP synthesis should begin from starting materials that do not have a structure close to that of the Drug Substance, but which represents a significant structural fragment

The MAAs should contain information of early steps (i.e. the non-GMP synthesis) so that potential impurities in starting materials can be considered when assessing the proposed control strategy

Acceptance Specification - identity, assay & impurities – proposed limits should be justified

Fate of the SM potential impurities to be clearly discussed in the proposed control strategy

Starting Materials – Frequent Scenario

Often the structure of the proposed starting materials is too close to the structure of the Drug Substance

No justification provided. Only reference to ICH Q11 guidance

The proposed starting materials contain several chiral centres

Starting materials custom synthesised (i.e. one supplier only) claimed as chemicals commercially/widely available

Starting Materials – Frequent Scenario (cont'd)

One-step synthesis from proposed starting material to the Drug Substance (e.g. de-protection step or hydrolysis)

The redefinition of the starting material is therefore requested to be set to earlier steps in the process

The aim is to achieve more robust GMP during Drug Substance synthesis

Interpretation of ICH Q11 on Starting Materials

The term “significant fragment” in ICH Q11 guidance is intended to differentiate a starting material from a reagent/solvent

It’s not intended to obtain very close proximity of a starting material to the API at the expense of GMP

Safety and toxicity considerations are often provided to NCAs in the attempt to justify a shorter GMP synthesis of the API

Safety and toxicity aspects, although acknowledged, should not be used as a mean to circumvent GMP expectations

By-products

Impurities that can arise from side-reactions that are often predictable but sometimes also unexpected

During the Drug Substance synthesis, a molecule can side-react with itself and/or with others in close proximity

Crucial can be reaction conditions (e.g. equivalents of base/acid, as well as concentration, order of addition of reagents, impurities in reagents, solvents, etc.)

Critical is to maintain the chemo-selectivity by using appropriate protecting groups to avoid formation of additional impurities

Intermediates

Key molecules formed during the synthesis.

If stable, they are isolated (and have their own specifications)

If unstable they are not isolated and are normally represented in the synthetic scheme within [ ]

Formerly designated starting materials (i.e. unacceptable from GMP perspective) are often redefined as intermediates

Catalysts

Organic (e.g. DMAP used in esterification reactions)

Inorganic (e.g. Pt, Pd, Rh, Ru, MnO_2, etc.)

Organo-metallic (e.g. $Pd(dppf)Cl_2$, Grubbs' catalyst, etc.)

Key aspects to look at: destiny, solubility, removal by filtration, toxicity aspects, etc.

Metal Catalyst Residues

- Guideline on the specification limits for residues of metal catalysts or metal reagents
  - EMEA/CPMP/SWP/QWP/4446/2000
  - Effective 1st September 2008
  - 5 years transition period - existing marketed products
- Control of metal catalysts and reagents used in synthesis of Drug Substances and excipients
- Option 1 limits based on maximum daily dose of 10g
- Option 2 based on known maximum daily dose

Metal Catalyst Residues

- Class 1: Metals of significant safety concern
  - Class 1A: Pt, Pd — 10ppm (oral); 1ppm (parenteral)
  - Class 1B: Ir, Ph, Ru, Os — 10ppm* (oral); 1ppm* (parenteral)
  - Class 1C: Mo, Ni, Cr, V — 25ppm (oral); 2.5ppm (parenteral)

  * total limit for subclass
- Class 2: Metals with low safety concern
  - Cu, Mn — 250ppm (oral); 25ppm (parenteral)
- Class 3: Metals with minimal safety concern
  - Fe, Zn — 1300ppm (oral); 130ppm (parenteral)
- Separate limits for inhalation for Class 1

Option 2 approach

- Accepted concentration (ppm) = $\frac{\text{PDE [}\mu\text{g/day]}}{\text{MDD [g/day]}}$

PDE: permitted daily exposure

MDD: maximum daily dose

ICH guideline Q3D on elemental impurities

Adopted by CHMP – December 2014

Effective for new MA applications: June 2016

Effective for authorised medicinal products: December 2017

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Genotoxicity aspects

What is a genotoxic impurity?

Positive finding in established *in vitro* or *in vivo* genotoxicity tests

Focus on DNA reactive substances with potential for direct DNA damage

Isolated *in vitro* finding may be assessed for *in vivo* relevance (follow-up testing)

In absence of information, *in vitro* genotoxicants are assumed to be *in vivo* mutagens and carcinogens

Threshold of Toxicological Concern (TTC)

Approach recognising that the presence of very low levels of genotoxic impurities is not associated with unacceptable risk

TTC estimated to be 1.5 μg/person/day

NB aflatoxin-like, N-nitroso, azoxy-compounds are excluded and specific toxicity data required

Deviation from TTC may be appropriate

- Lack of *in vivo* relevance
- Higher limit – short term or life-threatening cases

Limits for genotoxic impurities

- Concentration limit (ppm) = $\frac{\text{TTC [}\mu\text{g/day]}}{\text{dose [g/day]}}$

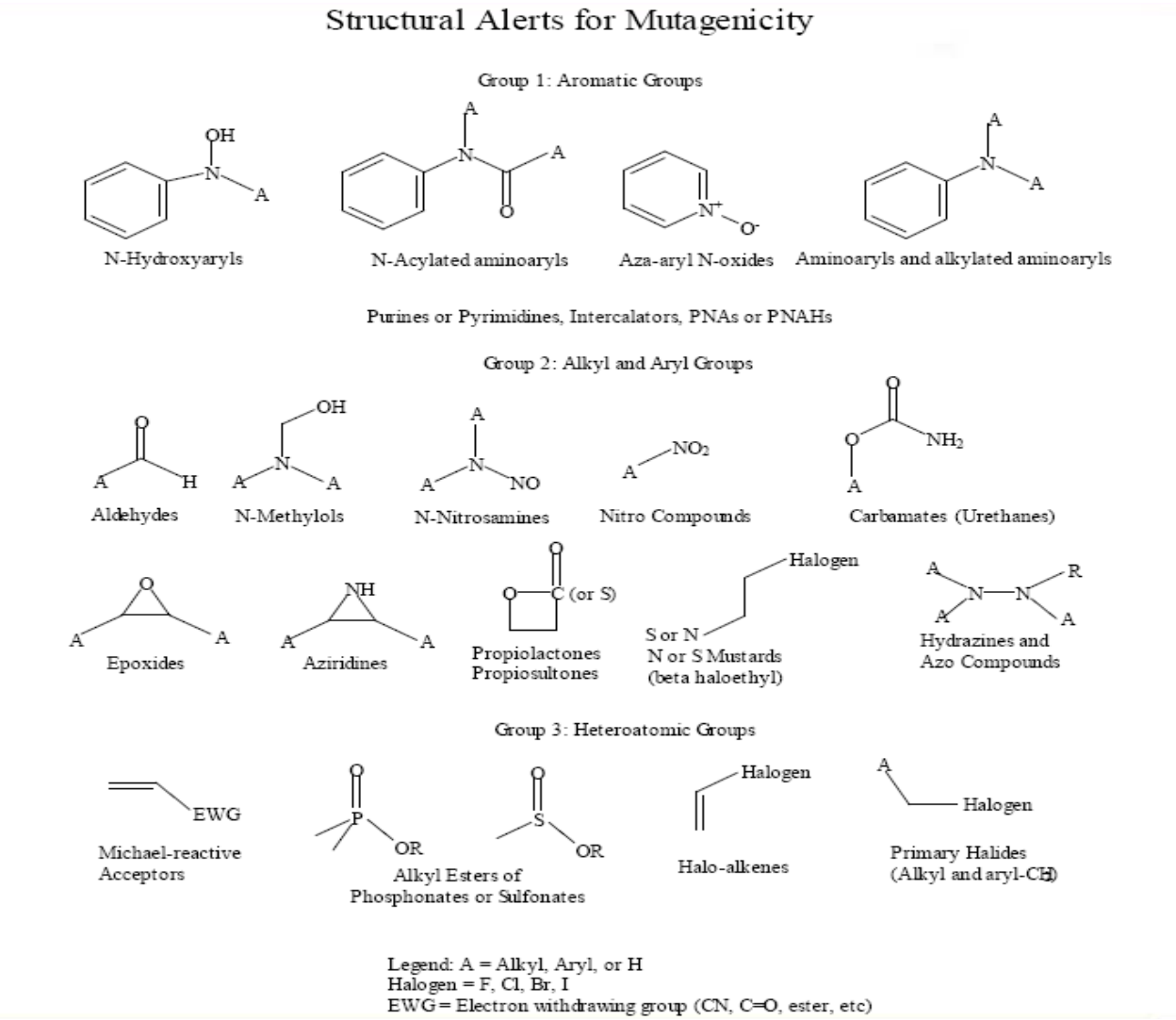
  daily dose 100mg – concentration limit: 15 ppm

  daily dose 500mg – concentration limit: 3 ppm

- TTC concept not to be used for carcinogens where adequate toxicity data are available

- Flow chart in NfG

FDA Structural Alerts



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What does an Assessor expect in MAAs?

Requirements for Regulatory Submission

Organic Impurities:

- Table with actual and potential impurities (from synthesis and degradation) clearly depicted
- Results for development batches, proposed commercial process, stress testing
- Studies to characterise actual impurities (also above identification threshold, at release and on storage)
- Summarise studies if unable to identify impurity
- Methods for potent impurities below ID threshold

Requirements for Regulatory Submission (cont'd)

Inorganic Impurities:

- Pharmacopoeial or other methods
- Residual catalysts
- Justification for inclusion/absence of impurities

Solvents

- ICH Q3C(R5) / Ph Eur General Chapter 5.4

Thresholds – Active Substances

Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 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%

Reporting Impurity Content of Batches

- Results for all clinical, safety and stability batches, and batches representative of commercial process
- Numerical results rather than “complies”
- Any impurity limit > reporting threshold
- Total impurities (all impurities > reporting threshold)

Reporting Impurity Content of Batches (cont'd)

- Details of analytical methods / chromatograms
- Below 1.0%: report to 2 decimal places (NB this does not require the specification limit to be set to 2 decimal places)
- At or above 1.0%: report to 1 decimal place
- Rounding using conventional rules

The ideal 3.2.S.3.2 section of e-CTD

Compound ID	Chemical Name	Chemical structure	Source	Destiny
			Drug substance	-
			Process impurity formed in step 2	Purged in step 5 following reaction work-up
			Degradation impurity	Controlled in 3.2.S.4.1
			Process impurity formed from impurity in reagent X	Purged in step 7 following distillation
			Genotoxic impurity confirmed by Ames test	Controlled in 3.2.S.4.1

Note:

Impurity Y562 is a potential impurity partially purged in steps 3 and 4 of the synthesis. It is not observed above 0.10% w/w and hence is not listed in 3.2.S.4.1

The ideal 3.2.S.3.2 section of e-CTD (cont'd)

Discussion on other potential impurities which may arise during synthesis (e.g. residual solvents, water, metal-containing impurities, reagents and inorganic residues)

Info on whether the commercial process removes them through quenches and aqueous washes or during the crystallisation of intermediate grade of Drug Substance

Impurities routinely observed in the Drug Substance should be defined as CQAs (particularly if QbD approach is used)

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Deficiencies frequently encountered

Deficiencies

3.2.S section of e-CTD lacking detailed discussion on impurities, their structures, their source (i.e. degradation or process) and their carry-over

No discussion on destiny of unwanted enantiomers and on potential genotoxicity despite functional groups depicted in FDA alerts

Omission of the solvents used in the final synthetic step from specification with no justification

No evaluation of potential degradation pathways (e.g. sulfide oxidation to sulfoxide and sulfone, cis/trans isomers, N-oxides, epoxides)

Deficiencies (cont'd)

Acceptance criteria too wide and not in line with ICH

Incomplete specifications for the designated starting materials, reagents, solvents and intermediates

No comparison of the Quality of the Drug Substance obtained with starting materials provided by different suppliers

Absence of discussion for Class 1 solvent as contaminant of another solvent

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Developing a Control Strategy

Control strategy - Definition

“A control strategy is a planned set of controls, derived from current product and process understanding that assures process performance and product quality (ICH Q10).”

“Every Drug Substance manufacturing process, whether developed through a traditional or an enhanced approach (or combination), has an associated control strategy (ICH Q11).”

Control strategy - Approaches

Traditional approach: emphasis on assessment of CQAs at the stage of the Drug Substance (i.e. end-product testing). It provides limited flexibility in the operating ranges to address variability (e.g. in raw materials).

Enhanced approach: sources of variability can be systematically identified. The control strategy might be developed through several iterations as the level of process understanding increases during the product lifecycle.

Combination of both approaches.

Control strategy – Key message

Raw materials used near the end of the synthesis have a greater potential to introduce impurities into the Drug Substance than raw materials used upstream.

Therefore, manufacturers should evaluate whether the quality of such materials should be more tightly controlled than similar materials used upstream.

Control strategy – An example from ICH Q11

Type of Control → / Drug Substance CQA (3.2.S.2.6) / Limit in Drug Substance↓	In process Controls (including In-process testing and process parameters)	Controls on material attributes (raw materials/starting materials /intermediates)	Impact of Manufacturing Process Design	Is CQA tested on drug substance/ included in Drug Substance specification (3.2.S.4.1)
Organic Purity Impurity X NMT 0.15%	Design space of the reflux unit operation composed of a combination of %water in Intermediate E and the reflux time in step 5 that delivers Intermediate F with Hydrolysis Impurity ≤0.30% (3.2.S.2.2)			Yes/Yes
Impurity Y NMT 0.20%	Process parameters step 4 (3.2.S.2.2) $p(H_2)$ ≥2 barg T <50°C In-process test step 4 (3.2.S.2.4) Impurity Y ≤0.50%			Yes/Yes
Any individual unspecified impurity NMT 0.10%		Specs for starting material D (3.2.S.2.3)		Yes/Yes
Total impurities NMT 0.50% Enantiomeric purity S-enantiomer NMT 0.50%		Spec for starting material D (3.2.S.2.3) S-enantiomer ≤0.50%	Stereocentre is shown not to racemize; (3.2.S.2.6)	Yes/Yes No/No
Residual Solvent				
Ethanol NMT 5000 ppm	In-process test during drying after final purification step (3.2.S.2.4) LOD ≤0.40 %		In-process results correlated to test results on drug substance.	No/Yes

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