Workshop Session IMPURITIES
DNA-reactive impurities: An update from ICH M7

Peter Kasper
Federal Institute for Drugs and Medical Devices
Bonn, Germany

History of Guideline Development

• EU EMA GL on the Limits of Genotoxic Impurities (2007)
• Q&A on EU EMA Guideline (2008 -2010)
• ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
  • 2010 - 2014: seven EWG F2F Meetings
  • 23 June 2014: Step 4
ICH M7 content

1. Introduction
2. Scope
3. General Principles
4. Considerations for marketed products
5. Drug substance & drug product impurity assessment
6. Hazard assessment elements
7. Risk characterisation
8. Control
9. Documentation
   • Notes, Glossary, References, Note on Implementation

Assessment and control of mutagenic impurities

DS & DP impurity assessment:
What impurities need to be assessed?

Hazard assessment:
How to assess whether impurities are mutagenic?

Risk characterisation:
What are acceptable intakes for mutagenic impurities?

Control:
What are appropriate options for impurity control?
What impurities need to be assessed?

- Synthetic Impurities
  - Actual impurities that have been identified in DS
  - Potential impurities likely to be present in the final DS including starting materials (SM), reagents, intermediates
  - Assess risk of carryover into the DS of identified impurities in SMs and intermediates
  - For SMs introduced late in the synthesis of the DS the final steps of the SM synthesis should be evaluated

- Actual & potential degradation products

- All above products where the structures are known should be evaluated for mutagenic potential

Hazard Assessment

How to evaluate whether impurity is mutagenic?

- For all actual and potential impurities where the structures are known:
  - Conduct database & literature searches for genotoxicity and carcinogenicity data

  or (if data unavailable)

- perform a computational toxicology assessment using (Q)SAR methodologies that predict DNA reactivity/mutagenic potential (i.e., outcome of «Ames test»)
**In silico** assessment of impurities for prediction of mutagenic potential

- Two complementary QSAR systems
  - expert rule-based
  - statistical based

- Expert knowledge to review outcomes if warranted

- Bacterial mutation (Ames) test

Absence of structural alerts is sufficient to conclude that impurity is of no concern, and no further testing is required.

---

**Hazard Assessment (cont.)**

- To follow up on a structural alert a bacterial mutation assay can be performed
  - Testing material: neat impurity should be used

- A negative bacterial mutation assay would overrule any structure-based concern. These impurities should be considered non-mutagenic.

- Classification of all impurities (Class 1 to 5)
### Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Proposed action for control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Known mutagenic carcinogens</td>
<td>≤ compound-specific limit</td>
</tr>
<tr>
<td>Class 2</td>
<td>Known mutagens with unknown carcinogenic potential</td>
<td>≤ appropriate TTC</td>
</tr>
<tr>
<td>Class 3</td>
<td>Alerting structure, unrelated to structure of DS, no mutagenicity data</td>
<td>≤ appropriate TTC or conduct Ames test (non-mutagenic = Class 5; mutagenic = Class 2)</td>
</tr>
<tr>
<td>Class 4</td>
<td>Alerting structure, same alert in DS which have been tested and are non-mutagenic</td>
<td>Non-mutagenic impurity (ICH Q3A/B)</td>
</tr>
<tr>
<td>Class 5</td>
<td>No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity</td>
<td>Non-mutagenic impurity (ICH Q3A/B)</td>
</tr>
</tbody>
</table>

### Risk Characterization

**Acceptable Intakes for Class 2 & 3 Impurities**

- **Threshold of Toxicological Concern (TTC) concept applies**
  - TTC defines an acceptable intake for any mutagenic chemical that poses a negligible cancer risk
  - **1.5 µg/day/person for lifetime** corresponding to a theoretical $1 \times 10^{-5}$ cancer lifetime risk

- **Less than Lifetime (LTL) principle applies**
  - Shorter treatment durations have higher acceptable levels
Risk Characterization
Acceptable Intakes (AIs) for Class 2 & 3 Impurities

Table 2: Acceptable Intakes for an Individual Impurity

<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>≤ 1 month</th>
<th>&gt;1 - 12 months</th>
<th>&gt;1 - 10 years</th>
<th>&gt;10 years to lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily intake [µg/day]</td>
<td>120</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 3: Acceptable Intakes for Multiples Impurities*

| Daily intake [µg/day] | 120 | 60  | 30  | 5   |

* For 3 or more Class 2 and 3 impurities specified on the drug substance specification

Risk Characterization (cont.)
Class 1 Impurities – compound specific AI

- Select TD$_{50}$ from most sensitive species / sex / organ site (e.g. from Gold Carcinogenic Potency Database)
- Do linear extrapolation to $10^{-5}$ risk level (TD$_{50}$/50000)

Example Ethylene oxide

- TD$_{50}$ : 21.3 mg/kg/day
  - 2.1 300 µg/kg/day : 50 000 = 0.42 µg/kg/day
  - 0.42 µg/kg/day x 50 kg = 21 µg/day
  - 21 µg EO/day = $10^{-5}$ cancer risk level
- daily dose of e.g. 100 mg DS = EO impurity limit of 210 ppm acceptable
- CPMP NfG on the Limitations of EO (2001) = maximum 1 ppm!
Risk Characterization (cont.)
Class-specific AI (ICH M7, Note 5)

• **Example:** mono-functional alkyl chlorides (commonly used in drug synthesis)
  • Less potent carcinogens than poly-functional alkyl chlorides
  • TD₅₀ values ranging from 36 to 1810 mg/kg/day (n = 15)
  • 10-fold higher limit than the default ones acceptable

<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>&lt;1 month</th>
<th>&gt;1 - 12 months</th>
<th>&gt;1 - 10 years</th>
<th>&gt;10 years to lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily intake [µg/day]</td>
<td>1200</td>
<td>200</td>
<td>100</td>
<td>15</td>
</tr>
</tbody>
</table>

Control Options

• **Option 1:** Monitor the impurity in the drug substance
  • Acceptance criterion below acceptable limit
  • Appropriately sensitive analytical procedure needed
  • Can be useful when impurity is introduced in the final synthetic step
  • Periodic Verification Testing is possible in some situations
Control Options (cont.)

- Option 2: Monitor the impurity in starting material, intermediate or in-process control
  - Acceptance criterion below acceptable limit
  - Will assure that impurity in the drug substance is below the TTC

- Option 3: Monitor the impurity in starting material, intermediate or in-process control
  - Acceptance criterion above acceptable limit
  - with demonstrated understanding of fate and purge and associated process controls
  - Data showing process consistently reduces impurity in the drug substance to below the TTC

Control Options (cont.)

- Option 4: Process parameters that impact residual impurity level are understood with sufficient confidence that levels in DS will be below acceptable limit
  - Useful for impurities that are inherently unstable (e.g., thionyl chloride) or
  - impurities that are introduced early in synthesis and are effectively purged (supported with data)
  - Impurity does not need to be listed on any spec
Genotoxicity studies for qualification of impurities according to ICH Q3A/B: Is it still needed?

- ICH M7 Note 1:
  "In cases where the amount of the impurity exceeds 1 mg daily dose for chronic administration, evaluation of genotoxic potential as recommended in ICH Q3A/B could be considered."

- "A study to detect point mutation": M7 approach sufficient

- "A study to detect chromosome aberrations":
  - "could be considered" above 1 mg impurity/day
  - testing of drug substance containing a representative amount of impurity acceptable

Implementation of M7 Guideline

- "... application not expected prior to 18 months after publication." (M7 Step 4 published June 2014)

- Exceptions to 18 month timeline:
  - Ames tests should be conducted according to M7 upon publication. No need to repeat tests conducted prior to publication.
  - Ph 2b/3 clinical trials started prior to publication can be completed up to and including marketing application submission and approval
    - No need to comply with need for two (Q)SAR assessments, scope of product impurity assessment and documentation recommendations
  - For development of a commercial manufacturing process (that do not include Phase 2b/3 clinical trials), application of the above aspects would not be expected until 36 months after M7 publication.
ICH M7: Next steps

- **Addendum in preparation**
  - Monographs with proposed acceptable limits of known mutagenic impurities (with carcinogenicity data) commonly found or used in drug synthesis.
  - Document with first set of compounds released for public comments (step 2) in Dec 2014.
  - Additions to the addendum can be made in a fashion similar to that used for ICHQ3C “maintenance”.

- **ICH M7 Q&A document to address implementation issues?**

---

**Have a nice DNA!**
Thank you for your attention!
Impurities in Antibiotics

EDQM: 50 years of leadership in the quality of medicines – paving the way for the future
October 2014
Tone Agaasøster, Norwegian Medicines Agency

Structure

• Antibiotics made by fermentation or semi-synthesis – challenges
• Current regulatory requirements
• Role of the EP
• Current challenges in development and revision of monographs
• Future antibiotics monographs
Fermentation processes – less predictable

• Involve biological systems that are less predictable, less controllable and more complex than straightforward chemical reactions
• Impurity profile of a fermentation product may be more complex and less predictable than that of a synthetic product

Fermentation processes – related impurities

• By-products
• Intermediates
• Degradation products

Semi-synthetic substances:
Fermented starting material with related impurities, synthesis by-products, synthesis intermediates and degradation products
In general a lower level of impurities
Active substance vs impurity

• Some active substances consist of a mixture of closely related compounds that show the relevant biological activity
• Definition as active substance should be based on pre-clinical and clinical studies
• In EP monograph the active substance components are defined
• If not included in AS definition: Impurity!

Regulatory requirements

EMA guideline:
GL on setting specifications for related impurities in antibiotics
EMA/CHMP/CVMP/QWP/199250/2009 corr
From June 2013

(Out of the scope of other relevant GLs)
Based on manufacture: 3 classes

• Semi-synthesis (Q3A)

• Fermentation, single compound

• Fermentation, family
  Higher thresholds for fermentation products

If the structure is a peptide: as for synthetic peptides

---

### Thresholds

<table>
<thead>
<tr>
<th>Active substances</th>
<th>Semi-synthetic * (ICH)</th>
<th>Fermentation, single</th>
<th>Fermentation, family</th>
<th>Peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting</td>
<td>0.05%/0.03%</td>
<td>0.10%</td>
<td>0.10%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Identification</td>
<td>0.10%/0.05% (ICH)</td>
<td>0.15%</td>
<td>0.15%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Qualification</td>
<td>0.15%/0.05% (ICH)</td>
<td>0.15%</td>
<td>0.50%**/0.2%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

*) If the substance consists of a family of compounds, then thresholds for fermentation, family may be necessary

**) Structurally closely related impurity according to definition
Role of the European Pharmacopoeia

• Important to have good monographs for antibiotics – complicated substances/impurity profiles

• Important that monographs reflect regulatory policy

• Development in analytical methods for determination of impurities and in regulatory requirements since originator product was approved

• Revision of monographs can be a difficult task also taking into account products already on the EU market

Analytical challenges

• Some active substances will have an inherently high level of impurities and a very complex impurity profile, e.g. colistimethate sodium

• Other substances (e.g. erythromycins) are more pure from some manufacturers than from others

• In some cases there are problems regarding detectability

• In these cases it is difficult to solve all problems through the analytical method
Challenges in development and revision of monographs

• Revision of existing monographs is often the most difficult task

• Improvement in analytical method
  – Better separation
  – Detection

• Identification of impurities

Identification of impurities

• Monographs include limits for specified, identified impurities (at levels that have been qualified) and unspecified impurities. Specified unidentified impurities may also be possible.

• In order to reclassify an impurity from unspecified to specified, identification is normally necessary

• Difficult in cases where impurity profiles (for some manufacturers) are complex
Identification of impurities (cont.)

- Difficult for the EDQM to perform identification
- Easier for manufacturers, who should submit this information to the EDQM
- Inclusion of specified impurity will necessitate availability of CRS
- Need for samples and reference standards for analytical development and CRS establishment

Example – Netilmicin sulfate

- Pharmeuropa 26.4
- Aminoglycoside prepared by semi-synthesis

- The limit set for ‘any other impurity’ has been lowered from the previously proposed limit of 1.0 to 0.3 %, and additional unknown impurities have been included in the transparency list and are identified by their relative retentions
- Additional batch data/structural information on the impurities from manufacturers/authorities welcomed to further decrease limit in the future
Example - amoxicillin sodium

Future antibiotics monographs

• New monographs: largely in line with GL
• Existing monographs:
  – Many will get in line with GL thresholds
  – Some will be close to GL
  – Some exceptions that are more difficult (as foreseen in GL)
Legally binding in the EU are the following regulations:

- **GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS OR METAL REAGENTS** (EMEA/CHMP/SWP/4446/2000)
  Binding only for new drug applications. Implementation for existing drugs (announced for September 1st 2013) was deferred in expectation of the upcoming ICH guideline.

- **EUROPEAN PHARMACOPOEIA**
  - Limits for heavy metals (HM) (method 2.4.8.) or limits for specific elements known as potential impurities with specific methods are specified in most monographs.
  - General text 5.20. Metal catalyst or metal reagent residues reproduces the EMEA guideline verbatim.
  - General method 2.4.20. gives recommendations for the analysis of metal impurities. It lists suitable methods and sets validation and system suitability targets.
  - Cross-reference to both texts in a monograph or general monograph (e.g. 2034) was deferred in expectation of the upcoming ICH guideline.
Current Status

Common philosophy:

- Limits are set for substances for pharmaceutical use (SPU).
- If only SPUs complying to the limits are used in production of finished drug products, there is no need to test or to set limits for finished drug products.
- Limits are set taking into account the toxicity of the potential metal impurity and the technical feasibility of the limits.
- There is no or only a weak linkage between dosage of the drug product and limits for metal impurities.
- Testing for specific metal impurities is based on the likelihood of their presence (usage in the manufacturing process).
- Unspecific testing for HM (method 2.4.8.) and in some monographs for As (method 2.4.2.) is applied as general safety tests. (Rational for inclusion or omission of testing for As in monographs is obscure.)

Current Status

ICH Guideline for Elemental Impurities Q3D will come into force for new drug applications:

- It is likely that the EMA will withdraw its guideline on residues of metals.
- The European Pharmacopoeia announced in a press release from July 18th 2014 that it will replace in its chapter 5.20. the reproduction of the EMA guideline by the ICH guideline as soon as the latter has reached stage 5.
- In addition, it is planned to delete the cross-references to the test for heavy metals (2.4.8.) from all individual monographs (except for monographs on products for veterinary use only).
- The choice of an appropriate analytical strategy to control the presence (or absence) of elemental impurities in line with the ICH Q3D guideline will be left to the user.
- General method 2.4.20. will be revised to provide the user with additional guidance for the choice of method and appropriate validation.
ICH Q3D Guideline
What is new in the ICH Q3D guideline?

- The guideline focuses on setting limits for elemental impurities (EI) in finished drug products.
- Limits are based solely on toxicological considerations.
- Limits are given in the form of permitted daily exposures (PDE). It is up to the user to convert these limits into concentration limits by taking into account the dosage of the product.
- The guideline does not focus on the production process as source of EI but explicitly covers all potential sources of EI (besides synthesis e.g. the production equipment, the container/closure systems and even the environment).
- The testing strategy is based on risk assessment (RA). For certain EI and certain routes of administration the risk assessment explicitly includes potential sources of EI which are under the current philosophy excluded by application of GMP rules.

ICH Q3D Guideline
Classification of Elemental Impurities

- The elements included in the guideline are classified based on their toxicity and likelihood of occurrence in the drug product. Natural abundance is explicitly listed as a criterion. However natural abundance should not be a factor in a production process under GMP rules. It might however be a factor for SPU derived from natural sources (e.g. mined raw materials or raw materials of biological origin).
- Class 1: As, Cd, Hg and Pb
  Known human toxicants with no or limited use in pharmaceuticals should be considered in RA in any case.
ICH Q3D Guideline
Classification of Elemental Impurities

- Class 2: Route-dependent human toxicants
  - Class 2A: Co, Ni and V
    Elements with high probability of occurrence in the drug product must be considered in the RA for all routes of administration.
    - Question 1: Why must these elements be considered in RA for all routes of administration since they are route dependant toxicants?
  - Class 2B: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl
    Elements with low probability of occurrence in the drug product must be considered in the RA for all routes of administration only if they are added intentionally during the production process of components of the drug product.

- Class 3: Ba, Cr, Cu, Li, Mo, Sb and Sn
  Elements with relatively low oral toxicity which may require consideration in the RA for other routes of administration than oral.
  - Question 1: According to appendix 3 of the guideline there are no relevant data on inhalation exposure to Ba compounds. Still Ba needs to be considered in RA for drug products applied by the inhalation. The PDE is based on a TWA reported by the US DoL. What is the basis for this TWA, when there are no relevant data?
  - Question 2: According to appendix 3 of the guideline there are no relevant data on other routes than the oral route of administration for the exposure to Cu or Sn compounds. Still Cu needs to be considered for the parenteral and inhalation route and Sn for the inhalation route based on PDE derived from the oral PDE by the application of more or less arbitrarily set modifying factors

- Other elements: Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn
  These elements usually require no consideration in RA due to their low toxicity unless there are other needs or special circumstances which require their limitation.
ICH Q3D Guideline
Risk Assessment (RA)

- Step 1: Identification of potential sources of EI
  - Residual impurities resulting from elements added intentionally in the formation of components of the drug product (e.g. catalysts or reagents).
  - EI that are not intentionally added but still potentially present in components of the drug product or substances used in the manufacture of drug products (e.g. water)
    EI as natural contaminants in components of the drug products produced from natural sources or from mining fall in this category as well.
  - EI potentially introduced into components of the drug product or into the drug product from manufacturing equipment.
    This source should be controlled by adequate GMP (e.g. equipment qualification).
  - EI potentially leached into the drug product from container/closure systems.
    This source as well should be covered by adequate GMP and product development.
  - Table 5.1 provides guidance which elements to include into the RA process

ICCH Q3D Guideline
Risk Assessment

- Step 2: Evaluation of the presence of particular EI
  If during step 1 of the RA particular elements are identified as potential impurities, their levels in the drug product need to be evaluated.
  - Establish the source(s) of the particular element(s).
  - Establish the potential concentration level(s) of the particular element(s).
    - Use all kind of information available (literature, data from similar processes, supplier information).
    - Testing of the components of the drug product and/or of the drug product.
  - Consider possible efficient ways of depletion of the particular EI(s).
ICH Q3D Guideline
Risk Assessment

- Step 3: Summary of the risk assessment process
  - Combining all information gathered in steps 1 and 2, the relationship between the observed and predicted level of a particular EI and the established PDE leads to the final conclusion of the RA.
  - A control threshold is defined at a level of 30% of the established PDE.
  - EI expected to be potentially present, but are validated to be consistently at a level below the control threshold need no additional controls.
  - In the evaluation whether the control threshold is consistently met, further factors such as
    - Variability of the analytical method
    - Variability of the EI level in the specific source/drug product
    need to be considered.
  - If the risk assessment fails to show that a particular EI consistently meets the control threshold, controls must be established to ensure that the EI does not exceed the PDE in the drug product.

Consequences for the Monographs in the European Pharmacopoeia

Setting
- The ICH Q3D guideline focuses on setting limits for EI in finished drug products.
- Limits for EI in active pharmaceutical ingredients (API) can be deduced from the PDE considering the maximum daily dose of the API.
- It is not possible to deduce fixed limits for EI in excipients!
- If an EI is not expected to be consistently below the control threshold its level needs to be controlled.
Consequences for the Monographs in the European Pharmacopoeia

Possible actions for active pharmaceutical ingredients

- Group of experts to study all monographs with limits for particular EI.
  - Check whether actual limits comply with concentration limits derived from established PDE.
    - If the actual limit complies, add a statement to the monograph, that the substance may be used safely up to a daily uptake of the drug product of 10 g, Otherwise lower limits for EI might be necessary to comply with the provisions of the ICH Q3D guideline.
    - If it does not comply or if the expected common daily usage is more than 10 g, lower the limit for the particular EI to the technical feasible level and add a note to the monograph that the limit for EI is determined by technical feasibility. The usage in drug products and the compliance with ICH Q3D guideline is under the responsibility of the user.

- Long term action: Perform RA for all monographs for EI so far not limited in the monograph. If the presence of a particular EI above the control threshold can not be consistently excluded, introduce new test and limit into the monograph.

Possible actions for excipients

- Group of experts to study all monographs with limits for particular EI.
  - Check whether actual limits comply with concentration limits derived from established PDE by applying option 1.
    - If the actual limit complies, add a statement to the monograph, that the substance may be used safely up to a daily uptake of the drug product of 10 g, Otherwise lower limits for EI might be necessary to comply with the provisions of the ICH Q3D guideline.
    - If it does not comply or if the expected common daily usage is more than 10 g, lower the limit for the particular EI to the technical feasible level and add a note to the monograph that the limit for EI is determined by technical feasibility. The usage in drug products and the compliance with ICH Q3D guideline is under the responsibility of the user.

- Long term action: Perform RA for all monographs for EI so far not limited in the monograph. If the presence of a particular EI above the control threshold can not be consistently excluded, introduce new test and limit into the monograph as outlined above, otherwise introduce a statement, that the substance may be used safely up to a daily uptake of the drug product of 10 g.