ICH M7 – An Industry Perspective

November 15th 2018

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Genotoxicity
“A broad term that refers to any deleterious change in the genetic material regardless of the mechanism by which the change is induced” - ICH S2 & M7

This covers damage at both DNA level and chromosomal level. Chromosomal damage is generally associated with a threshold (with exceptions of clastogens!).

Chromosomal aberrations include
- Structural chromosomal damage (clastogenicity)
- Numerical chromosomal damage (aneuploidy)

Mutagenicity
This involves the direct interaction of a chemical agent with specific genes (DNA) resulting in mutation of the gene (permanent change) which may result in carcinogenesis

Cancer
Uncontrolled growth of abnormal cells in the body.
“broad group of various diseases involving unregulated cell growth”
Threshold & non-threshold genotoxicants

Fig. 1. Overview of mechanisms by which direct and indirect acting genotoxicants and other molecules can play a role in carcinogenesis (Adapted from Kirsch-Volders et al., 2000).

Indirect mechanisms of genotoxicity; M Kirsch-Volders et al. Tox. Letters 140/141 (2003) 63/74
Regulatory position for mutagenic impurities in pharmaceuticals

- 2006 - GTI Task Force White Paper (PhRMA); Muller et. al., 2006
- 2008 - FDA draft Guidance 2008
- 2008 - EMEA Q&A 2008
- June – 2014 - ICH M7; Assessment And Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (Step 4)
- May – 2017 - ICH M7 R1 Step 4: Addendum to ICH M7: Application of the principles of the ICH M7 Guideline to calculation of Compound-Specific Acceptable Intakes
- Nov – 2018 - ICH M7 R2: Development of a list of compounds in the 2nd Addendum (final list) & alternate calculations for compound specific limits
SCOPE OF ICH M7 GUIDELINE – INTENDED FOR

• New DS and DP for clinical development and marketing applications

• Current marketed products:
  
  – Changes to the drug substance synthesis result in new impurities or increased acceptance criteria for existing impurities;
  
  – Changes in the formulation, composition or manufacturing process result in new degradation products or increased acceptance criteria for existing degradation products;
  
  – Changes in indication or dosing regimen are made which significantly affect the acceptable cancer risk level.

• Impurities in excipients that are used for the first time in a drug product and are chemically synthesized.
SCOPE OF ICH M7 GUIDELINE – NOT INTENDED FOR

• Drug substances and drug products:
  – Biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, and crude products of animal or plant origin

• Drug substances and drug products intended for advanced cancer indications (as defined in the scope of ICH S9)
  – What are serious and life threatening malignancies?
  – Caveat: You may be challenged by regulators here
  – ICH M7 to be considered when an anticancer pharmaceutical is further investigated in cancer patient populations with long expected survival (Q&A to ICH S9)

• Drug substance is itself genotoxic at therapeutic concentrations
  – Encloses exemption of impurities with structural similarities with the API (related substances) as well as all other potential impurities that are unrelated

• Excipients used in existing marketed products, flavoring agents, colorants, and perfumes.
Why is ICH M7 a Multidisciplinary guideline?

- Mutagenic impurity assessment & control requires highly cross-functional approach
- The way this issue is handled varies from organisation to organisation
- However, role of each function is equally important
How to conduct a mutagenic impurity assessment
How to conduct a mutagenic impurity assessment

- Identification of process impurities (M7 Section 5.1 Synthetic impurities)
  - Evaluate synthetic route to evaluate potential process impurities
  - Starting materials, intermediates, reagents, solvents, impurities and potential by-products in the ROS from SMs to drug substance
  - Where should I start my assessment?
  - Identified impurities present in starting materials and intermediates
  - For starting materials that are introduced late in the synthesis, the final steps of the SM synthesis should be evaluated for pMIs

**BE SMART IN SUBMITTING/PRESENTING DATA TO REGULATORS!**
Cut down discussion on hypothetical impurities (by-products) not observed in your drug substance to avoid unwarranted queries.
How to conduct a mutagenic impurity assessment

- Identification of degradation impurities (Sec 8.34)
  - Packaging and storage of DS
  - Manufacture of DP
  - Excipient compatibility
  - Packaging and storage of DP
- Link the degradation studies to pMI assessment process
- There is often a strong relationship between degradation products and metabolites
- ICH M7 does not provide specific guidance on mutagenic metabolites

BE SMART IN SUBMITTING/PRESENTING DATA TO REGULATORS!
Degradation pathways of potential concern

Peroxide Oxidation

Autoxidation

Oxidation

Oxidation related
Use of LBSAs as part of an expert review process, without considering mitigating factors, could result in many more false positives and potentially the need to carry out additional and unnecessary Ames tests.
LBSA & Misattributed alerts for mutagenicity

- Alkyl and aryl sulfonic acids or sulfonate anions; *only alkyl/aryl esters are alerting*
- Aromatic aldehydes; *only alkyl aldehydes are alerting (formaldehyde & some di-aldehydes)*
- Amines in general; *only aromatic amines are alerting*
  - Derek Nexus (Lhasa Limited) provides an in-depth insight on aromatic amines
- Aromatic halides and tertiary alkyl halides – *only primary and secondary alkyl halides are alerting; chain length and modifications impact the mutagenic potential of alkyl halides*
- Mesityl oxide and diacetone alcohol
- Carbamates; *only vinyl carbamate/ethyl carbamate*
- Michael Acceptors (soft electrophiles)
- N-Oxides in general; *Only 'certain' aromatic N-oxides (e.g. must have > 1 aromatic ring)??*
  - 35 mutagenic N-oxides identified
  - All were *confounded* i.e. contained multiple alerts as well as being N-oxides
  - Results are generally consistent with the matching alerts for example TA98 & TA100 (+/-S9) for primary aromatic amines and aromatic nitros
  - more on this in the coming slides......
- **Snodin’s letter to the editor OPRD (example for discussion)**..
A pharma-wide approach to address the genotoxicity prediction of primary aromatic amines


ARTICLE INFO

Keywords
Primary aromatic amines
Mutagenicity
Ames test
Expert review

ABSTRACT

Primary aromatic amines (pAAs) are attractive building blocks in medicinal chemistry programmes yet their potential for mutagenic activity causes real concern owing to the risk of genotoxicity-related drug attrition. In addition, despite the existence of a substantial body of experimental data, the prediction of aromaticamine mutagenicity still poses a significant challenge for in silico tools. Major contributors to this dilemma are the stability and physicochemical properties of a subset of aromatic amines that affords them capricious mutagenic properties in the Ames test. Such inconsistent mutagenic potential is also compounded by the inherent variability with the assay itself and underscores the need for a rigorous approach in executing the experimental protocol. In order to understand the utility of the in silico approach towards the prediction of pAAs mutagenicity and to widen the availability of mutagenicity data, a group of pharmaceutical companies has formed a consortium with the aim of exchanging their in-house data and making them publicly available for the first time. Summary data compiled during the first phase of this effort is disclosed here and its utility in conjunction with in silico prediction is discussed. Conclusions from this analysis highlight the critical role of expert judgement in
Myatt et al. concluded based on SARs that the general class of aromatic N-Oxide is not an alert for predicting DNA-reactive mutagenicity (except quindioxins).
**Mutagenic Impurity Risk Assessment Process**

**Step 1**
Identification of Potential Impurities in Drug Substance and Drug Product –
Review the synthetic process – including starting materials / reagents / intermediates / known impurities + drug substance and product degradants

**Step 2**
Conduct SAR evaluation (Derek, Nexus / Sarah Nexus)

**Step 3**
Structural Alert?

- **Yes**
  - **Assessment of Risk of Potential Carryover of Impurities** – Evaluate risk of carryover at levels of concern into DS/DP – Does the impurity pose any significant risk of carryover?

- **No**
  - Safety Assessment

**Step 4**
Assessment of Risk of Potential Carryover of Impurities – Evaluate risk of carryover at levels of concern into DS/DP – Does the impurity pose any significant risk of carryover?

**Step 5**
Quantification
Analyze level of impurity

**Step 6**
Finalize Risk assessment
Is the impurity genotoxic? Is the level >TTC?

- **Genotoxic**
  - Genotoxic / level < TTC
    - Suitable for clinical use
  - Genotoxic / level > TTC
    - Define strategy to achieve acceptable limits
      - **Options:**
        1. Modification of synthetic process.
        2. Additional genotoxicity testing (typically in vivo)
      - Nongenotoxic
        - Treat as a general impurity

- **No**
  - No further action

**Step 7**
Safety Testing
Perform appropriate genotoxicity test
Typically Ames test

**Chemistry**
In-Silico Computational Tools

<table>
<thead>
<tr>
<th>Knowledge base/Rule base</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derek Nexus</td>
<td>MULTICASE</td>
</tr>
<tr>
<td>Leadscope</td>
<td>Sarah Nexus</td>
</tr>
<tr>
<td>TOXTREE</td>
<td>LAZAR</td>
</tr>
<tr>
<td>CASE Ultra</td>
<td>MOLCODE</td>
</tr>
<tr>
<td>ACD Labs</td>
<td>TOPKAT</td>
</tr>
<tr>
<td>OASIS TIMES</td>
<td>CAESAR</td>
</tr>
</tbody>
</table>

- To comply with ICH M7 requirements, the in-silico assessment should be performed using both i.e. rule based and statistical softwares

- The in-silico assessment should be concluded with an expert opinion
Note 3 Tests to Investigate the *in vivo* Relevance of *in vitro* Mutagens (Positive Bacterial Mutagenicity)

<table>
<thead>
<tr>
<th><em>In vivo</em> test</th>
<th>Factors to justify choice of test as fit-for-purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transgenic mutation assays</td>
<td>• For any bacterial mutagenicity positive. Justify selection of assay tissue/organ</td>
</tr>
<tr>
<td><em>Pig-a</em> assay (blood)</td>
<td>• For directly acting mutagens (bacterial mutagenicity positive without S9)*</td>
</tr>
<tr>
<td>Micronucleus test (blood or bone marrow)</td>
<td>• For directly acting mutagens (bacterial mutagenicity positive without S9) and compounds known to be clastogenic*</td>
</tr>
<tr>
<td>Rat liver Unscheduled DNA Synthesis (UDS) test</td>
<td>• In particular for bacterial mutagenicity positive with S9 only</td>
</tr>
<tr>
<td></td>
<td>• Responsible liver metabolite known</td>
</tr>
<tr>
<td></td>
<td>o to be generated in test species used</td>
</tr>
<tr>
<td></td>
<td>o to induce bulky adducts</td>
</tr>
<tr>
<td>Comet assay</td>
<td>• Justification needed (chemical class specific mode of action to form alkaline labile sites or single-strand breaks as preceding DNA damage that can potentially lead to mutations</td>
</tr>
<tr>
<td></td>
<td>• Justify selection of assay tissue/organ</td>
</tr>
<tr>
<td>Others</td>
<td>• With convincing justification</td>
</tr>
</tbody>
</table>

*For indirect acting mutagens (requiring metabolic activation), adequate exposure to metabolite(s) should be demonstrated.*
## Hazard Assessment Classification of GTIs

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Proposed Action for control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Known mutagenic carcinogens</td>
<td>Control at or below compound-specific acceptable limit</td>
</tr>
<tr>
<td>2</td>
<td>Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive, no rodent carcinogenicity data)</td>
<td>Control at or below acceptable limits (generic or adjusted TTC)</td>
</tr>
<tr>
<td>3</td>
<td>Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data</td>
<td>Control at or below acceptable limits (generic or adjusted TTC) or do bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2</td>
</tr>
<tr>
<td>4</td>
<td>Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic</td>
<td>Treat as non-mutagenic impurity</td>
</tr>
<tr>
<td>5</td>
<td>No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity</td>
<td>Treat as non-mutagenic impurity</td>
</tr>
</tbody>
</table>
The Threshold of Toxicological Concern (TTC)

Developed as a ‘threshold of regulation’ for food materials

Linear extrapolation from the carcinogenic potencies of 700+ carcinogens (lifetime studies)

*(TTC limits in food 0.15 µg/day - Kroes et. al.)*

**Pharmaceuticals provide benefit to patients**

Default limit for GTIs: 1.5 µg/day in pharmaceuticals (TTC)

A 1.5 µg intake of GTI per day = cancer risk < 1 per 100,000

**Virtually safe dose for a compound of unknown carcinogenic potency**

“exceeding the TTC is not necessarily associated with an increased cancer risk”

**TTC limit applicable to:**

– DNA-reactive impurity
– no evidence for a threshold
– no carcinogenicity data
– chronic treatment in non-life-threatening indications
Exceptions to the 1.5 μg/day (TTC) limit

- Compounds with evidence for a threshold
- Compounds with carcinogenicity data
- Treatment duration
- Severe indications (life-threatening / life expectancy)
- Susceptible population (pediatric medicines)?
- Multiple GTIs
- Additional genotoxicity (in vivo) data
- Impurities - significant metabolites of parent drug
- Genotoxicity similar to active drug
- Existing products, unless “there is a cause for concern”
ICH M7 Note 5: Compound specific limits

A compound-specific calculation of acceptable intakes for mutagenic impurities may be applied for mutagenic impurities (without carcinogenicity data) which are structurally similar to a chemically-defined class of known carcinogen. For example, factors that are associated with the carcinogenic potency of monofunctional alkyl chlorides have been identified (Ref. 15) and can be used to modify the safe acceptable intake of monofunctional alkyl chlorides, a group of alkyl chlorides commonly used in drug synthesis. Compared to multifunctional alkyl chlorides the monofunctional compounds are much less potent carcinogens with TD50 values ranging from 36 to 1810 mg/kg/day (n=15; epichlorohydrin with two distinctly different functional groups is excluded). A TD50 value of 36 mg/kg/day can thus be used as a still very conservative class-specific potency reference point for calculation of acceptable intakes for monofunctional alkyl chlorides. This potency level is at least ten-fold lower than the TD50 of 1.25 mg/kg/day corresponding to the default lifetime TTC (1.5 μg/day) and therefore justifies lifetime and less-than-lifetime daily intakes for monofunctional alkyl chlorides ten times the default ones.

Did I understand ICH M7 Note 5 correctly? Really?

ICH M7 assessment with Derek and Sarah Nexus returns compound specific acceptable intakes for Class 1 impurities
Some additional compound specific limits

<table>
<thead>
<tr>
<th>Compound</th>
<th>In vitro Mutagen*</th>
<th>Rodent Carcinogen</th>
<th>Limit (AI or PDE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde (CAS# 75-07-5)</td>
<td>Yes (mammalian)</td>
<td>Yes</td>
<td>PDE = 2 mg/day</td>
</tr>
<tr>
<td>Acetamide (CAS# 60-35-5)</td>
<td>No</td>
<td>Yes</td>
<td>PDE = 8.8 mg/day</td>
</tr>
<tr>
<td>Acrolein (CAS# 107-02-8)</td>
<td>Yes</td>
<td>No</td>
<td>PDE = 25 µg/day</td>
</tr>
<tr>
<td>p-Aminophenol (CAS# 123-30-8)</td>
<td>Yes</td>
<td>No</td>
<td>PDE = 2 mg/day</td>
</tr>
<tr>
<td>t-Butyl alcohol (CAS# 75-65-0)</td>
<td>No</td>
<td>Yes</td>
<td>PDE = 16 mg/day</td>
</tr>
<tr>
<td>t-Butyl chloride (CAS# 507-20-0)</td>
<td>No</td>
<td>Inadequate</td>
<td>No PDE assigned. Maintain below ICH Q3A qualification thresholds.</td>
</tr>
<tr>
<td>Epichlorohydrin (CAS# 106-89-8)</td>
<td>Yes</td>
<td>Yes</td>
<td>AI = 3 µg/day</td>
</tr>
<tr>
<td>1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDAC, CAS Number: 25952-53-8)</td>
<td>Yes</td>
<td>Not Tested</td>
<td>No PDE assigned. Maintain below ICH Q3A qualification thresholds</td>
</tr>
<tr>
<td>Formaldehyde (CAS# 50-00-0)</td>
<td>Yes</td>
<td>Oral: No</td>
<td>PDE = 10 mg/day</td>
</tr>
<tr>
<td>1-Hydroxy-7-azabenotriazole (HOAt, CAS # 39968-33-7) and O-(7-azabenotriazol-1-yl)-N,N,N',N'-tetramethylrhodium hexafluorophosphate (HATU, CAS# 148893-10-1)</td>
<td>No</td>
<td>Not tested</td>
<td>No PDE assigned. Maintain below ICH Q3A qualification thresholds</td>
</tr>
<tr>
<td>Hydroxyamine (CAS# 7803-49-3)</td>
<td>No</td>
<td>Yes</td>
<td>PDE = 23 µg/day</td>
</tr>
<tr>
<td>Mesityl oxide (CAS# 141-79-7)</td>
<td>No</td>
<td>Not tested</td>
<td>PDE = 2 mg/day</td>
</tr>
<tr>
<td>Methyl bromide (CAS# 74-83-9)</td>
<td>Yes</td>
<td>No</td>
<td>PDE = 467 µg/day</td>
</tr>
<tr>
<td>Methyl iodide</td>
<td>No</td>
<td>Yes</td>
<td>PDE = 375 µg/day</td>
</tr>
<tr>
<td>p-Nitrophenol (CAS# 100-02-7)</td>
<td>No</td>
<td>Yes</td>
<td>PDE = 5 mg/day</td>
</tr>
<tr>
<td>Styrene (CAS# 100-42-5)</td>
<td>Yes</td>
<td>Yes</td>
<td>AI = 154 µg/day</td>
</tr>
<tr>
<td>Triphenylphosphine (CAS# 603-35-0)</td>
<td>No</td>
<td>Not tested</td>
<td>PDE = 250 µg/day</td>
</tr>
<tr>
<td>Triphenylphosphine oxide (CAS# 791-28-6)</td>
<td>No</td>
<td>Not Tested</td>
<td>PDE = 200 µg/day</td>
</tr>
<tr>
<td>Vinyl acetate (CAS# 108-05-4)</td>
<td>Yes (mammalian)</td>
<td>Yes</td>
<td>PDE = 2 mg/day</td>
</tr>
</tbody>
</table>

- M7 R1 contains compound specific AI for 14 Class 1 impurities
- Carcinogenic Potency Database (CPDB), Toxnet contains results of 6540 chronic, long-term animal cancer tests on 1547 chemicals
Deriving Compound Specific MI limits from Risk Specific Dose

Linear extrapolation from Risk Level 1 in 2 (TD\textsubscript{50}) to 1 in 100,000 (ICH M7 Note 4)

Alternate approaches to derive compound specific limits:
BMDL10 [Benchmark Dose Lower Confidence Limit 10%] ÷ 10

Published recommended values from WHO, JECFA, EFSA etc.
Less than life-time exposure to mutagenic impurities

To address Less-Than-Lifetime (LTL) exposures to mutagenic impurities in pharmaceuticals, an approach is applied in which the acceptable cumulative lifetime dose (1.5 μg/day x 25,550 days = 38.3 mg) is uniformly distributed over the total number of exposure days during LTL exposure.

In the case of intermittent (non-daily) dosing, the acceptable intake will be capped by the total cumulative dose or the maximum acceptable intake (i.e., 120 μg/day), whichever is lower.

**Acceptable intake for individual Class 2 and Class 3 impurities**

<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>120</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Acceptable intake for multiple Class 2 and Class 3 impurities**

<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>120</td>
<td>60</td>
<td>10(30*)</td>
<td>5</td>
</tr>
</tbody>
</table>
Establishing Less Than Lifetime exposure Limits (ICH M7 Note 6)

Less-than-lifetime AI = \(1.5 \, \mu g \times (365 \, \text{days} \times 70 \, \text{years lifetime} = 25,550)\)

Total number of treatment days

38325\(\mu g\) single dose!
ICH M7 Note 7: Acceptable intakes for LTL exposures

Note 7 is often challenged by regulators since drug label does not specify duration of treatment.

ARVs not considered under LTL exposure anymore.

MI limits in non-genotoxic anti-cancer drugs like Imatinib.

Table 4: These are only examples!

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Acceptable Intake (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration of ≤ 1 month: e.g., drugs used in emergency procedures</td>
<td>120</td>
</tr>
<tr>
<td>(antidotes, anesthesia, acute ischemic stroke), actinic keratosis,</td>
<td></td>
</tr>
<tr>
<td>treatment of lice</td>
<td></td>
</tr>
<tr>
<td>Treatment duration of &gt; 1-12 months: e.g., anti-infective therapy</td>
<td>20</td>
</tr>
<tr>
<td>with maximum up to 12 months treatment (HCV), parenteral nutrients,</td>
<td></td>
</tr>
<tr>
<td>prophylactic flu drugs (~ 5 months), peptic ulcer, Assisted</td>
<td></td>
</tr>
<tr>
<td>Reproductive Technology (ART), pre-term labor, preeclampsia, pre-</td>
<td></td>
</tr>
<tr>
<td>surgical (hysterectomy) treatment, fracture healing (these are acute use</td>
<td></td>
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<tr>
<td>but with long half-lives)</td>
<td></td>
</tr>
<tr>
<td>Treatment duration of &gt; 1-10 years: e.g., stage of disease with short</td>
<td>10</td>
</tr>
<tr>
<td>life expectancy (severe Alzheimer’s), non-genotoxic anticancer treatment</td>
<td></td>
</tr>
<tr>
<td>being used in a patient population with longer term survival (breast</td>
<td></td>
</tr>
<tr>
<td>cancer, chronic myelogenous leukemia), drugs specifically labeled for</td>
<td></td>
</tr>
<tr>
<td>less than 10 years of use, drugs administered intermittently to treat</td>
<td></td>
</tr>
<tr>
<td>acute recurring symptoms (chronic Herpes, gout attacks, substance</td>
<td></td>
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<tr>
<td>dependence such as smoking cessation), macular degeneration, HIV</td>
<td></td>
</tr>
<tr>
<td>Treatment duration of &gt; 10 years to lifetime: e.g., chronic use</td>
<td>1.5</td>
</tr>
<tr>
<td>indications with high likelihood for lifetime use across broader age</td>
<td></td>
</tr>
<tr>
<td>range (hypertension, dyslipidemia, asthma, Alzheimer’s (except severe</td>
<td></td>
</tr>
<tr>
<td>Alzheimer disease), hormone therapy (e.g., growth hormone, thyroid</td>
<td></td>
</tr>
<tr>
<td>hormone, parathyroid hormone), lipodystrophy, schizophrenia, depression,</td>
<td></td>
</tr>
<tr>
<td>psoriasis, atopic dermatitis, Chronic Obstructive Pulmonary Disease</td>
<td></td>
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<tr>
<td>(COPD), cystic fibrosis, seasonal and perennial allergic rhinitis</td>
<td></td>
</tr>
</tbody>
</table>
Control strategies (Section 8 of ICH M7)

Option 4
So reactive – no testing required
Understanding of process parameters and impact on residual impurity levels (including fate and purge knowledge)
Involves calculation of purge factors

Option 3
Test for the impurity in raw material/starting material, intermediate or in-process with a higher limit + demonstrated understanding of fate and purge (process capacity)
Involves calculation of purge factors

Option 2
Test for the impurity in the specification for a raw material, starting material or intermediate, or in-process control at permitted level

Option 1
Test the impurity in the drug substance at permitted level (skip testing may be acceptable).

Mirabilis can be very useful for determining purge factors
Calculation of purge factors – Andrew Teasdale

A Tool for the Semiquantitative Assessment of Potentially Genotoxic Impurity (PGI) Carryover into API Using Physicochemical Parameters and Process Conditions

OPRD 2010, 14, 945-945

Should be supported with experimental data on physicochemical properties, literature references or purge studies

Mirabilis can be very useful!

<table>
<thead>
<tr>
<th>Table 1. Physicochemical parameters and associated standard purge factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>physicochemical parameters</td>
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<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>reactivity</td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td>solubility(^a)</td>
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<td></td>
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<tr>
<td>volatility</td>
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<td></td>
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<tr>
<td>ionisability</td>
</tr>
<tr>
<td>physical processes -</td>
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<tr>
<td>chromatography</td>
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</tbody>
</table>

\(^a\) This relates to solubility within the context of a recrystallisation process whereby the impurity in question, if highly soluble, will remain within mother liquors and hence be purged from the desired product.

\(^b\) This relates to a deliberate attempt to partition the desired product/GI between an aqueous and organic layer, typically achieved through the manipulation of pH to change the ionised/unionized state of one of the components.
Purge ratio = \[ \frac{\text{Predicted Purge Factor for PMI}}{\text{Required Purge Factor PMI \@ TTC or PDE for PMI}} \]

<table>
<thead>
<tr>
<th>If ( PR \geq 1000 )</th>
<th>If ( 1000 &gt; PR \geq 100 )</th>
<th>If ( PR &lt; 100 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Collection Recommendations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of additional experimental data not necessary to support scientific rationale for non-commercial or commercial API routes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of additional non-trace experimental data (solubility, reactivity, and volatility) recommended to support scientific rationale for both non-commercial and commercial API routes.</td>
<td></td>
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<tr>
<td>Collection of additional trace PMI analysis not necessary to support scientific rationale for non-commercial or commercial API routes</td>
<td></td>
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<tr>
<td>For non-commercial API routes, experimentally measure PMI purging, including trace PMI analyses as appropriate, to support scientific rationale. Note: Additional data are expected to support an Option 4 control strategy when PMI Purge Ratio (&lt;100x). For commercial API routes, detailed experimental fate &amp; purge studies are expected to support a commercial Option 4 control strategy for all PMIs.</td>
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</tbody>
</table>

Risk Assessment of Genotoxic Impurities in new Chemical Entities: Strategies to Demonstrate Control”

Understanding formation and fate of MIs

- Assessment of the mechanisms that favours formation of MIs (Risk assessment)
- Introduction of appropriate process control strategies to limit formation
- Fate of MIs in downstream manufacturing process
  - Spike purge studies or Mirabilis
- All MIs are typically chemically reactive and will not survive > 4 steps of downstream synthesis
- Scientific justifications based on properties
  - Chloromethane (Boiling point: -24.2°C)
  - Chloroethane (Boiling point: -12.3°C)
- Sulfonate esters
  - Sulfonate esters can theoretically result from interaction of sulfonic acids with alcohols
  - Sulfonate ester formation is dramatically reduced at lower temperatures and
  - In the presence of small amounts of water
  - In the presence of a slight excess of base, ester formation does not take place

Understanding formation and fate of Mls: DMS

DMS turned out to be an analytical artefact and not a potential by-product!!
DMS was probably formed from residual methanol or DMSO during derivatization

Authors conclude, to date, DMS has not been detected in any drug substance batches (<0.1 ppm, LOD).
THANKS for your attention!!!

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