Toxicology Support to Product Development:

Qualification of Impurities and Excipients

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Head of Toxicology
Teva Pharmacology
• Investigate the toxicological profile of the drug

• Advise Clinicians on potential safety liabilities

• Assess the safety of the non active ingredients and impurities
Impurities - Principles

- No benefit for patients
- Some impurities are toxic
- Some levels are unavoidable
- Impurities should be contained below the level of concern
- Accepted general limits: Thresholds
- Impurities above threshold levels should be toxicologically qualified

"Pop, is that where they make all of those new medicines with the bad side effects?"
What is Toxicological Qualification?

– Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level specified.

– The applicant should provide a rationale for establishing impurity acceptance criteria

– From ICH Q3
impurities

- Organics –
  - Drug Substance: Starting materials, Reagents, intermediates, byproducts, Degradations products.
  - Drug product impurities: Adducts of excipients, contaminations of inactive ingredients, Degradation products

- Elemental impurities –
  - Heavy metal (catalysts) and other elemental substances
Other Sources for Impurities

- Residual solvents:
- Extractables & Leachables (E/L):
  - Migrants from medical devices, manufacturing equipment and from primary & secondary packaging
  - Extractables: The full potential: What might extract
  - Leachables: The actual amount under use conditions and storage.
Impurities are qualified;

- If they were appropriately tested as part of the toxicology or clinical trials.
  - Sometimes, new impurities emerge at scale up or change in process or as in generics.
  - Degradation products are usually not subject to testing during development.

- If not appropriately tested: **Qualify**
Qualification: How?

- Preclinical or clinical studies.
- Data from scientific literature
  - Reliable data
- Existence as a metabolite
Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.

(Paracelsus)
- Impurities are of no benefit to patients.
- Therefore their presence is unforgiven unless very low.
- How low is low?
ICH Guidelines

- ICH International conference of Harmonization (US FDA, EU and Japan)
- Harmonization of requirements of Quality (manufacturing and control principles), clinical and preclinical drug development
  - ICH-Q (Quality)
  - ICH-S (Safety: Preclinical Safety)
  - ICH-E (Efficacy: Clinical)
  - ICH-M (Multi-disciplinary)
### Thresholds for Drug Substance ICHQ3A

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Reporting Threshold</th>
<th>Identification Threshold</th>
<th>Qualification Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2g/day</td>
<td>0.05%</td>
<td>0.1% or 1 mg/day</td>
<td>0.15% or 1 mg/day</td>
</tr>
<tr>
<td>&gt; 2g/day</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>
### Thresholds for Drug Product ICHQ3B

<table>
<thead>
<tr>
<th>Maximum Daily dose</th>
<th>Reporting Threshold</th>
<th>Identification Threshold</th>
<th>Qualification Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mg</td>
<td>0.1%</td>
<td>1.0% or 5 mcg/day</td>
<td>1.0% or 50 mcg/day</td>
</tr>
<tr>
<td>1-10 mg</td>
<td>0.1%</td>
<td>0.5% or 20 mcg/day</td>
<td>0.5% or 200 mcg/day</td>
</tr>
<tr>
<td>10 mg - 2g</td>
<td>0.1%</td>
<td>0.2% or 2 mg/day</td>
<td>0.2% or 3 mg/day</td>
</tr>
<tr>
<td>&gt; 2g</td>
<td>0.05%</td>
<td>0.1%</td>
<td>0.15%</td>
</tr>
</tbody>
</table>
What if you are above the Threshold?

- Toxicological Qualification is required!!
  - Perform genotoxicity tests (Ames test and chromosomal aberration) and general toxicity studies in one species for an appropriate duration (up to 3 months for chronic treatment)

[ICH Q3A & Q3B]
Impurities that interact with the genetic material of the cells or with cell replication have the potential to cause cancer or hereditary diseases. In principle, genotoxic impurities should not be present in medicinal products.
How do you know you have genotoxic impurities?

- ICH M7 requests you will evaluate all potential impurities
  - Starting materials, Reagents, intermediates, byproducts, Degradations products.
  - Potential for genotoxic impurities should be investigated regardless of their detection in analysis
  - The potential can be assessed theoretically based on structural elements.
Predictions

- Identifying potentially reactive structures
  - Initial analysis based on structurally alerting functional groups from Müller (2006)

Fig. 1. Some examples of structurally alerting functional groups that are known to be involved in reactions with DNA (this list is not exhaustive).
Prediction software

- ICH M7 requests you predict Genotoxic potential by two SAR prediction computerized applications
  - A statistically based program
  - A rule based program
  - Reaching consensus
  - Expert resolution of non consensus.
“6. HAZARD ASSESSMENT ELEMENTS

...........

If warranted, the outcome of any computer system-based analysis can be reviewed with the use of expert knowledge in order to provide additional supportive evidence on relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.”
## Using *in silico* tools

<table>
<thead>
<tr>
<th>Compound</th>
<th>Derek alert</th>
<th>Sarah alert</th>
<th>Consensus</th>
<th>Remarks</th>
<th>Control recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Adipic acid" /></td>
<td>Inactive</td>
<td>Negative (100% confidence)</td>
<td>Negative</td>
<td>Negative Ames test (Toxnet)</td>
<td>ICH Q3A qualification threshold</td>
</tr>
<tr>
<td><img src="image" alt="Compound" /></td>
<td>Plausible (potential alkylating agent)</td>
<td>Positive (alkyl halide)</td>
<td>Positive</td>
<td>Monofunctional alkyl halide (note 5 in M7)</td>
<td>TTCx10 15 µg/day or run Ames test</td>
</tr>
</tbody>
</table>
Using *in silico* tools

<table>
<thead>
<tr>
<th>Compound</th>
<th>Derek alert for mutagenicity</th>
<th>Sarah alert</th>
<th>Consensus Prediction</th>
<th>Remarks</th>
<th>Control recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Compound Image]</td>
<td>Inactive</td>
<td>Positive</td>
<td>Negative</td>
<td>1. The examples in the training set contain alerting moieties that are not present here.</td>
<td>ICH Q3A qualification threshold</td>
</tr>
<tr>
<td>![Compound Image]</td>
<td>Plausible (α,β - unsaturated aldehyde)</td>
<td>Positive</td>
<td>Positive</td>
<td>-</td>
<td>TTC or run Ames test</td>
</tr>
</tbody>
</table>

Predictions

- Positive predictions can be overruled by a negative Ames test.
- If negative, control the limits according to ICHQ3
- If positive, control as a Genotoxic impurity
In principle, genotoxic impurities should not be present in medicinal products.

Practically, you cannot reduce impurities to zero levels.

Safe does not mean zero risk (US Supreme court).

How to determine what is insignificant or acceptable risk?
For the general population, a 1:1,000,000 lifetime risk for cancer (over the natural incidence) is considered negligible.

For medicinal products, authorities accept a risk of 1:100,000.

Higher risk are acceptable where there is a higher benefit to risk ratio.
– FDA experts have calculated statistically the 1:100000 risk of hundreds of carcinogens using linear extrapolations from experimental data. Concept is now globally accepted!

– For most known carcinogens, a cancer risk for an exposure of 1.5 mcg/day for lifetime was found to be lower than 1:100000, except for a few exceptions (azo, nitroso and aflatoxin compounds).

– 1.5 mcg/day is therefore the universal Threshold of Toxicological Concern (TTC)
Other types of TTC

- Less than Lifetime (staged TTC).
- Compound specific TTC
- Class specific TTC
- Threshold dependent TTC.
  - TTC classical calculations assume linearity of risk.
  - If mechanism is known and can be assumed to be threshold dependent, a non linear computation of TTC can be made.
Qualification of Impurities and QBD

- Early flagging of impurities issues
- Identify problematic impurities
- Get a Toxicological Assessment
- Qualify as early as possible
  - If not successful,
    - Change process
    - Change supplier of materials

- Do not wait to the last minute.
Qualification of Excipients

- Inactive ingredients of the Product
- New excipients should be tested and are regulated like a new active material
- Full toxicological qualification for new excipient Overall >5 years + >$6M
  - Chronical tox in two species
  - Safety pharmacology
  - Reproduction & developmental tox
  - Genotoxicity
  - Carcinogenicity
  - ADME/PK

- If not listed at the same route and Potency, a full toxicological assessment should be given on all aspects of toxicity.
Qualification of Excipients

- There are lists of approved excipients in various countries
- In the US there is the IID list
- For every listed excipient, the list shows the maximal potency by route
- Potency is the maximal allowed exposure per patient assuming the maximal recommended daily dose.
- Use is allowed only by the listed route and lower potency.
- Presence in food, use in cosmetics, or in pharmaceuticals not approved in the US does not qualify.
- If not listed at the same route and potency, a full toxicological assessment should be given on all aspects of toxicity.
  - Either find the information in reliable scientific literature, or
  - Perform qualification studies
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