Safety assessment of pharmaceutical impurities
A “reflection” paper

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All drugs contain more than the active entity!

- API
- Related substances
- Process residues
- Degradation products
- Excipients, Adjuvants
- Extractables,
- Leachables
- Others …
How safe is this drug product?

From Stephen Barat, Forest Laboratories
How safe is this drug product?

« Packaging » materials
Any surface the drug comes in contact with is a source for potential chemical contamination
vial, closures (screw caps, rubber stoppers), …
Can arise from various parts

Based on the results of a “migration” study, 11 substances were identified in this pre-filled syringe…

2,4-Bis(1,1-dimethylethyl)-phenol, 1,1’,1”-phosphate
2,4 Di t-butyl phenol
Eruamide1.5
3-(3’,5’-di-t-Butyl-1’-hydroxy-4’-oxacyclohexa-2’,5’-dienyl) propanoic acid
Benzo(a)pyrene
Octadecane
2-Bromo-4-(1,1-dimethyl-propyl)-phenol
Hexamethylcyclotrisiloxane
3 unidentified

… at non negligible concentrations … up to 1,5 μg/syringe
Typical source of impurities ("foreign substances")

- Starting materials
- Intermediates
- Catalysts
- Solvents
- Processing
  - Formulation
  - Dosing devices
  - Sterilisation
- ‘Impurities’
  - Excess reagents
  - Starting materials
  - By-products etc

Drug substance → Drug Product → Packaging

Excess materials
By-products
Leachables
Extractables
Degradation products
Storage?

From Colin Fish, GSK
Impurities ≠ Inert

Impurities in drug substances and/or drug products have the potential to cause adverse effects
- potentially toxic (especially mutagens and/or carcinogens)
- PGI = Potential Genotoxic Impurity

Impurities may impact the development time (and cost!) of a compound
- e.g. the time required to develop drugs can be significantly increased when it is necessary to carry out multiple methods to characterize and/or remove impurities to acceptable levels.

Perception of consumers may be strongly impacted when drugs have to be removed from the market due to “contamination” by a genotoxic substance
- Viracept® (HIV protease inhibitor) removed from the market in Europe due to contamination by a genotoxic impurity (ethyl methanesulfonate)
Pharmaceutical development considerations

- Try to avoid (known) genotoxic reagents (or their generation)

- Try to limit (if possible) at an intermediate stage rather than at the active Drug Substance

- Introduce a specific purification step (to remove the genotoxic impurity)

- Consider – if possible
  - “forced” degradation studies as integral part of the IMPD dossier
  - modification in specification of existing analytical methods (LOD and LOQ)
Future drugs must be recognized as safe and effective. Residual impurities resulting from manufacturing and formulation/degradation of active pharmaceuticals, and excipients may be present in the finished pharmaceutical products. As well, changes can be introduced in the fabrication procedure at late stage in the development and can affect the drug product performance characteristics, safety, and quality attributes. Drug product may contain toxic residual solvents or impurities. A subset of these may present a potential for genotoxicity which have the capacity to interact with human DNA to cause mutations and cancer, even at extremely lowest levels.

PGI = Potential Genotoxic Impurity

Key: are there any issues related to human safety?

What I know

What I don’t suspect
Regulatory considerations

- Reg. requirements for assessing safety of impurities covered by 3 quality guidelines from the International Conference on Harmonization:
  - Guideline for metal impurities ICH Q3D under preparation - will include elements and limits for heavy metal impurities.

  Threshold levels for impurities are listed at which they must be identified, reported, and qualified. In some circumstances, specific qualification studies may be required.


- EMEA, Safety Working Group, Questions and Answers on the Guideline on the Limits of Genotoxic Impurities (2012)

- ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (2014)
  - ‘official’ introduction to the TTC
Guidelines are “guides” to achieve goals

- Not specifically detailed documents,
- A number of important issues are not addressed - for example, acceptable levels of impurities in drugs during development
- do not provide clear recommendations how to handle these compounds.

Controversial aspect of the guidances

- Example: Q3A(R2) notes that qualification testing of impurities can be performed on the API containing the impurity - Isn't it is preferable to test the synthesized impurity alone?
- Q3B(R) excludes a spectrum of products including biopharmaceuticals, peptides, oligonucleotides, radiopharmaceuticals, fermentation products, …. Not clear why these products are excluded.
- Q3C recommends acceptable amounts of residual solvents in marketed drug products, not materials used in clinical trials.

Note: there are currently no regulatory guidelines in place for assessing the risk of leachables and extractables

- Extractables - migrate from a system and/or other packaging components in vehicle or solvent under exaggerated conditions (extreme Temp, time conditions)
- Leachables - migrate spontaneously from a system and/or other packaging components normal conditions of use and storage
Impurity management

- Impurity identification
  - Qualitative and quantitative description of the impurity profile
    - What? How much?
    - When? In which conditions?

- Analytical methods
  - Generally sensitive enough to detect impurities at level 0.01 to 0.05 %
  - GC, LC, mass spectrometry, nuclear magnetic resonance, others …

- Impurity toxicological assessment
  - What is the risk related to the impurity?
  - Are there toxicological concerns expected at the concentration analysed?
  - Scientific data/ structural alerts
    - Should be focused on mutagenic and/or carcinogenic effects
    - Use in silico tools such as DEREK, Multicase
Impurity qualification

Why?
- « acquire and evaluate available data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified » ICH guidelines

How?
- Data from clinical or preclinical (pharmacology) studies
- Data from scientific literature
- Presence of structural alerts.
- Toxicological studies
- Presence in other medicinal products

What process to adopt?
- The qualification should be under the responsibility of a certified toxicologist
- At least toxicology evaluation is expected
Toxicological (… and risk) assessment

- Should be pragmatic and based on a weight-of-evidence approach
  - For a pharmaceutical, the impurity could be qualified as part of the toxicology program, for both long term dosing, genotoxicity and carcinogenicity. Thus is the risk reduced??
  - For vaccines, e.g. - no genotoxicity or carcinogenicity tests are generally conducted. Thus the impurity in the vaccine is not qualified as is the pharmaceutical impurity (as part of the toxicology program)

- The golden rule first: the level of impurities in drugs must be reduced to acceptable safety limits → to be addressed by the sponsor
  - This the concept of controlling levels to “as low as reasonably practicable” (ALARP)
  - i.e. every effort should be made to prevent the formation of such impurities during drug substance synthesis and, if this is not possible, technical effort should be made post-synthesis to reduce impurities.

- A comprehensive assessments should be performed for each chemical
  - Comprehensive, integrated judgment of all relevant information supporting conclusions regarding a toxicological effect
Some practical considerations

- The following databases could be searched:
  - A general internet search (i.e. Google) in first instance, and Material Safety Data Sheet
  - TOXNET, PubMed, EMA (European Medicines Agency), WHO (World Health Organisation), US FDA (Food and Drug Administration), NTP (National Toxicology Program), drug@FDA, …
  - Others?

- No action may be required for an unidentified impurity, if the impurity is below the ICH identification threshold.

- The absence of a structural alert could be considered sufficient evidence to justify performing no additional qualification studies.

- If a structural alert is present, impurity should be regarded as a “Potential Genotoxic Impurity” and additional tests should be envisaged
  - Ames, and MLA in vitro
    - negative tests -> managed as a standard impurity
    - positive tests -> follow the procedure on mutagen/carcinogen, i.e. develop sensitive analytical methods, apply the ALARP principles and/or TTC
Toxicological assessment (2)

- If the formation of impurities could not be avoided (or not completely removed) a toxicology evaluation is needed to establish where there is a negligible risk to human health.

- Evaluation would be based on an estimation of total daily exposure (of each impurity) under the conditions of use of the drug product.
  - Assessments would be based upon analysis of the chemical structure (i.e. in silico DEREK database first) as well as available animal and human toxicology data to permit calculation of safety factors (Maximum Acceptable Dose, Permissible Daily Dose, Acceptable Daily Intake….) based on NOAEL obtained in the most relevant tox. study.
  - Ideally, these approaches would require the availability of adequate data from long-term carcinogenicity studies.
  - But in most cases only limited data are available ….

- Based on this evaluation, conclusions and/or next steps could be described.

- If no data can be found, or if no PDE, MAD can be calculated use of a Threshold of Toxicological Concern (TTC)?
Application of TTC?

The TTC is a pragmatic toxicological tool, initially developed by FDA for chemicals migrating from food packaging materials. It is a tool to help qualify the acceptance of an impurity in a product. 'Tool' which is used to establish a human exposure threshold for which there is no appreciable risk of an event (e.g. cancer) occurring over a lifetime intake. At a TTC of 1.5 μg intake per day, the risk of a carcinogenic response is considered negligible for genotoxic impurities in human medicines (cancer risk of 1/100,000 over a lifetime (considered to be 70 years)).

The TTC is accepted by the regulatory authorities. Applied in the food industry (FDA guideline). Acceptance of potential 'genotoxic' impurities in pharmaceutical medicines (ICH guideline; EMA). Too conservative? Could the principles be considered in a toxicological evaluation to determine acceptable threshold levels for process residues, extractable and leachables, contaminants?

In presence of several PGIs, TTC should be applicable individually if impurities are structurally unrelated and to the sum if they are structurally similar (e.g. group of mesylates).

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Food and Chemical Toxicology 37 (1999) 387–412

A Tiered Approach to Threshold of Regulation

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(Accepted 1 September 1998)
The staged TTC

Available online at www.sciencedirect.com

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A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity

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Genotoxic impurities: how to manage them

- Are considered unsafe at any levels, even if very low.

- Existing Q3 guidelines not clear on how to handle genotoxic impurities

- ICH Q3A(R) – no need to identify structure below 0.1% (1000 ppm) or 0.05% (500 ppm) if dose >2g/day
  - A limit for a genotoxin with an understood toxicity can be calculated based upon the known PDE.
  - A limit for a genotoxin without sufficient toxicity information must determine based upon a TTC (= Threshold of Toxological Concern)
    - 1.5 μg total daily dose for life considered “safe”
    - Levels above this limit need to justified toxicologically.

- Ames test on the isolated impurity as any chemical (OECD 471) up to 5000 μg/plate.
  - If not possible to isolate the impurities: exacerbation of the process to overload with the impurity allowing testing up to 250 μg/plate (not masked by the cytotoxicity limit of the API).
  - Spiking with the impurity is not accepted since it implies that it can be isolated.
Genotoxic impurities: case study

- Compound candidate selected at the early stage. No major toxicological concern anticipated.

- On this basis, initiation of the regulatory pre-clinical program with all the studies conducted in parallel in order to reduce the time course to enter Phase I:
  - Genotoxicity
  - Chronic studies
  - Fertility/Teratogenicity

- For the need of this program, 25 kg of compound was newly synthetized.

**Ames test results**

- without metabolic activation ; with metabolic activation

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**Lot Industriel**

- **Lot laboratoire de synthèse**
Genotoxic impurities: case study (con’d)

Decision was made to evaluate each intermediate which can be isolated as a stable form.

For the needs of the pre-clinical program, the synthesis of the compound was relocated in another plant.

A catalyst has been changed for an equivalent one in term of final result.

This catalyst brought residual Chrome VI which accumulates during the manufacturing process.

Consequences:
- Acceptability/relevance of the ongoing in vivo tox program (especially for fertility/teratogenicity)?
- Repeat the studies with a new batch?
- Timeline/delay/cost
- Entering to Phase I compromised?
Management of impurities may be challenging for any team and the approach must be risk-based.

Impurities may be observed during the complete life cycle development of the future drug.

Most of time the risk is associated with the active principle rather than the impurities.
- Analytical methods are sometimes under development
- Consequently less rigid criteria could be used in phase I while ICH criteria should be applied to phase III or marketed product

Thresholds are different for DS, DP and depend on the maximal daily intake of the drug. The determination of acceptable amounts in DS/DP products is based on the qualification and risk assessment.
Final thoughts (con’d)

- Regulatory/CMC and Safety professionals should be involved to evaluate the impact of the impurity on drug quality and safety.
  - What is it ?
  - Where is it coming from ?
  - Is it toxic ?

- Summarize the potential impurities and discuss their possible origin and impact on safety
  - Assessment from the applicant justifying the potential presence is a key element

- If not possible to avoid potential PGIs then go through relevant safety studies
  - The risk associated with impurities should be evaluated with a good relevance - Not overestimated but not under-evaluated
  - If toxicological concerns are identified specific toxicity studies may be required
    - Genotoxicity (full package ?)
    - 14-day to 1-month study in one species, 2-3 doses tested
    - Use a representative batch with the expected % of impurities to be qualified

- Consider new ICH M7

- In case of doubt, regulatory/scientific advice can always be requested (HA)
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Let’s start the conversation
BACK UP SLIDES
Impurity classification

- As proposed by Müller et al. 2006*

- Class 1 - Impurities known to be both mutagenic and carcinogenic
  - includes known animal carcinogens with reliable data for a genotoxic mechanism

- Class 2 - Impurities known to be genotoxic (mutagenic), but with unknown carcinogenic potential

- Class 3 - Alerting structure, unrelated to the structure of the API and of unknown mutagenic potential
  - includes impurities with functional moieties that can be linked to genotoxicity based on structure, but which have not been tested as isolated compounds

- Class 4 - Alerting structure, related to the API
  - includes impurities that contain an alerting functional moiety that is shared with the parent structure.

- Class 5 - No alerting structure or sufficient evidence for absence of genotoxicity

*Reg Tox & Pharm, 2006, 44, 198–211
Qualification strategy (proposed by PhRMA*)

Class 1: Genotoxic carcinogens
- Eliminate impurity?
  - Not possible
    - Risk assessment?
      - Not established
        - Limited data
          - (Staged) TTC (see Table 1)
  - Risk assessment?
    - Established
      - Threshold mechanism?
        - Not tested
          - Impurity genotoxic? 1
            - No
              - Control as an ordinary impurity
            - Yes/
              - API genotoxic? 2
                - No
                  - Control as an ordinary impurity
                - Yes/
                  - Class 3: Alert – unrelated to parent
                    - Yes/
                      - Class 4: Alert – related to parent
                        - Yes/
                          - Class 5: No alerts
                        - No
Some definitions

- **Drug Substance (= Active Pharmaceutical ingredient)**
  - Exerting the pharmacological action, used to formulate the drug product.

- **Drug Product (= finished product, the dose form)**
  - one or more DS
  - usually with excipients

- **Excipients**
  - included in the formulation to facilitate manufacture, enhance stability, control release of API from the product, assist in product identification, or enhance other product characteristics (flavors, ...).

- **Impurity**
  - any component of the medicinal product which is not the chemical entity, or an excipient of the product
    - the desired product,
    - a product-related substance,
    - or excipient, (including buffer components).
  - It may be either process- or product-related.
  - It may be the result of active principle degradation during holding/processing.
## Drug substance guideline ICH Q3A (R2)

<table>
<thead>
<tr>
<th>Maximum daily dose</th>
<th>Threshold beyond of which the impurity should be reporting</th>
<th>Threshold of identification</th>
<th>Threshold of qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 grams</td>
<td>0.05%</td>
<td>0.10% or 1mg/day (the lowest should be selected)</td>
<td>0.15% or 1mg/day (the lowest should be selected)</td>
</tr>
<tr>
<td>&gt; 2 grams</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>
### Drug product guideline ICH Q3B (R2)

<table>
<thead>
<tr>
<th>Maximum daily dose</th>
<th>Threshold of qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mg</td>
<td>1% or 50 µg/day (the lowest should be selected)</td>
</tr>
<tr>
<td>10 mg - 100 mg</td>
<td>0.5 % or 200 µg/day</td>
</tr>
<tr>
<td>100 mg - 2 grams</td>
<td>0.2% or 3 mg/day</td>
</tr>
<tr>
<td>&gt; 2 grams</td>
<td>0.15%</td>
</tr>
</tbody>
</table>