IMPURITIES

Antony Fake
API Focal Point, PQTm
Introduction

This presentation is made with reference to the preparation of an API.

This is because the API is the source of the majority of impurities.

When considering FPPs, the focus is largely on degradants, although excipient-API and leaching from containers must not be overlooked.
What kinds of impurities are there?

Impurities we add during preparation:
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Impurities we add during preparation:
Solvents, metal catalysts, starting materials, reagents
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- Starting materials impurities; impurities within solvents, pesticides...
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**Unwanted impurities that are made during preparation:**
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Impurities we unintentionally add during preparation:
- Starting materials impurities; impurities within solvents, pesticides...

Unwanted impurities that are made during preparation:
- Reaction intermediates, related-substances
What kinds of impurities are there?

Impurities we add during preparation:
Solvents, metal catalysts, starting materials, reagents

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Starting materials impurities; impurities within solvents, pesticides...

Unwanted impurities that are made during preparation:
Reaction intermediates, related-substances

Impurities that are contributed after API preparation:
What kinds of impurities are there?

Impurities we add during preparation:
Solvents, metal catalysts, starting materials, reagents

Impurities we unintentionally add during preparation:
Starting materials impurities; impurities within solvents, pesticides...

Unwanted impurities that are made during preparation:
Reaction intermediates, related-substances

Impurities that are contributed after API preparation:
Degradation products
Leaching from containers
Excipient
Where do we find information on impurities?

**Impurities we add during preparation:**

- Solvents, metal catalysts – 3.2.S.2.2

**Impurities we unintentionally add during preparation:**

- SM impurities; impurities within solvents, pesticides - 3.2.S.2.3

**Unwanted impurities that are made during preparation:**

- Reaction intermediates (3.2.S.2.4), related-substances (3.2.S.3.2)

**Impurities that are contributed after API preparation:**

- Degradation products (3.2.S.7)

And of course 3.2.S.3.2 – Discussion of impurities
Types of Impurities

Organic impurities:
- Related substances and,
- Degradation products

Solvents
Metals
Genotoxins
All potential impurities

Observed impurities

Impurities needing to be controlled in specifications

Individually specified impurities

At what limit?
All potential impurities

Observed impurities
API Monographs

You cannot rely upon an API monograph entirely for potential organic impurities. Many impurities are specific to the manner of API preparation and may not have been considered when the monograph was published. Of course monographs are a great start.
Degradants

Forced degradation studies will provide information on major degradants.

Forced degradation studies will provide information on the acceptability of the analytical technique

Monographs tend to be better at listing degradants.
Reaction intermediates

In any chemical reaction you can expect there to remain some of the original unreacted material.

Reaction intermediates are therefore logical potential impurities. Almost without exception remnants of the reaction starting materials will be present in the API.
Related Substances

Reaction by-products more difficult to predict.

Test method sensitivity is extremely important. What can it detect?

Mass balance should be kept in mind.

If there are multiple pharmacopoeial monographs, then at the very least consider all of these impurities. At least for investigation purposes.
All potential impurities

Observed impurities

Impurities needing to be controlled in specifications
International Guidance

The thought process from moving from all potential impurities to what impurities need to be controlled in specifications is a theme common to all the main impurities guidance:

- ICH Q3A – Impurities in New Drug Substances
- ICH Q3C – Residual Solvents
- ICH Q3D – Elemental impurities
- ICH M7 – Genotoxins
Non-routine testing and skip testing

In most of the guidance as you work through the various decision trees you will have a set of impurities that:

- have real risk of occurrence, but
- are below the threshold for inclusion as a routine test in the specifications.
Non-routine testing and skip testing

i.e. a Class II solvent used prior to the last step, but which has been demonstrated to be present at below 10% of its ICH limit.

In such situations most guidance state “does not need to be routinely controlled”.

What does “does not need to be routinely controlled” mean?
Non-routine testing and skip testing

Some regulators interpret this to mean:
• does not need to be in the specification.

PQT medicines interprets this to mean:
• To be included as a skip test.

We do this for a practical reason.
Non-routine testing, skip testing

If the test is stated in the specifications then this brings this to the attention of an assessor evaluating a post-approval variation.

If it is not present in the specifications, there is a chance that the assessor will forget to consider if the solvent now needs to be routinely controlled, as a result of the post-approval change being proposed.
WHO PREQUALIFICATION TEAM – MEDICINES

All potential impurities

Observed impurities

Impurities needing to be controlled in specifications

Individually specified impurities

At what limit?
Q3A – Control of organic impurities in the API

The next slides assumes an investigation has already been performed into potential organic impurities.

It assumes the manufacturer has demonstrated or presented logical arguments justifying the target impurities. *i.e. just does not simply refer to impurities listed in a monograph.*

It assumes the manufacturer has used appropriately sensitive analytical techniques during investigations.

It assumes the routine analytical method is appropriate to control routinely occurring impurities.
Thresholds

QF Threshold
ID Threshold
Reporting Threshold
Threshold verses limit

A threshold is not a barrier.

The observed amounts of impurities may pass through (exceed) the threshold.

However, as the impurity level passes successive thresholds the requirements on the manufacturer increases.
Threshold verses limit

A limit is an acceptable level of impurity agreed between the manufacturer and regulator.

The impurity may not exceed this level.
Reporting threshold

For APIs taken less than 2g per day
0.05%

For APIs taken greater than 2g per day
0.03%
Exceeding the Reporting threshold

QF Threshold

ID Threshold

Reporting Threshold
Reporting threshold

Every time a peak is observed above the reporting threshold it needs to be recorded in the laboratory results. It avoids the applicant from having to report every little peak that is observed in the chromatogram.

A peak above the reporting threshold does not (necessarily) need to be specified in the API specifications.

However, any peak above the reporting threshold must be counted towards the Total impurity content reported in the Certificate of Analysis.

Therefore, these impurities are being controlled under the limit for any unknown impurity.
Exceeding the ID threshold

QF Threshold

ID Threshold

Reporting Threshold
Identification threshold

For APIs taken less than 2g per day
  The lesser of 0.10% or 1.0 mg TDI

For APIs taken greater than 2g per day
  0.05%
Exceeding the ID threshold

If a peak is observed **routinely** above the ID threshold then the impurity must be:

- Specified individually in the API specifications (by name or RRT).
- Identified (or efforts made to do so)
“Routinely Observed”

Normally, the decision to include an impurity in the specifications is based upon the likelihood it will occur routinely.

- For instance, when observed above the ID threshold in long-term stability data, or commonly occurs in batches when tested at release.

An impurity only occurring in accelerated stability trials, forced degradation trials, or during development may not need to be included.
Exceeding the QF thresholds
Qualification threshold

For APIs taken less than 2g per day
   The lesser of 0.15% or 1.0 mg TDI

For APIs taken greater than 2g per day
   0.05%

An impurity limit above the Qualification threshold must be known to be safe.
Justifying a limit exceeding the QF Threshold

Refer to a limit in a recognised monograph - **WARNING** – it must be a specified Impurity.

...Impurity A, no more than 0.25% - OK
...Any impurity no more than 0.5% - Not OK

Present literature evidence in support of the limit.

Present the results of toxicological studies supporting the safety of the limit.

Provide comparative impurity content data from innovator or PQ’d products

Set the limit to 0.15% (or 1 mg TDI) and modify the process to meet this limit.
Example time

The lesser of 0.15% or 1.0 mg TDI

Watch out!
Must be above...
2 significant figures
Example 1

A peak is observed at 0.086%.
At 1150 mg total daily dose
Is this above the Qualification threshold?

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<thead>
<tr>
<th>Raw value</th>
<th>Threshold</th>
<th>Above QF threshold?</th>
</tr>
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A peak is observed at 0.153%.
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Relative response factors

Which impurity is present in the greater amount?
Relative response factors

Which impurity is present in the greater amount?

It is impossible to tell without further information.
Relative response factors

The size of a peak in a chromatogram is determined by the amount of impurity present, but also how well it responds to the detector.

In HPLC-UV techniques the response is due to the inherent UV absorbance of the impurity at the detected wavelength.

Some impurities will not be detected at all!

RRF = Response of Imp/Response of API, but always check the formula just in case the ratio is described differently.
Response factors

At the time of initial development and investigation it is assumed the response factor = 1.

For reporting thresholds it is assumed the response factor = 1.

When impurities are identified their response factor must be considered.

The RRF for all identified impurities should be established.
Relative response factors

When an RRF of between 0.8 to 1.2 is it not mandatory to apply the correction.

The use of a RRF could shift an observed impurity from one threshold to another.

This is often of benefit to the applicant. If the response of an impurity is greater than the equivalent amount of API (RRF>1) it could mean a peak no longer exceeds the Qualification threshold.
Relative Response Factor (RRF)

Response factor:
Is the response (e.g. peak area) of drug substance or related substances per unit weight.

\[ RF = \frac{\text{peak area}}{\text{concentration (mg/ml)}} \]

Relative response factor (RRF):
Is the ratio of the Impurity RF verses the API RF

\[ RRF = \frac{RF_{\text{impurity}}}{RF_{\text{API}}} \]
Relative Response Factor (RRF)

If the amount of impurity is being calculated by reference to an Impurities Reference Standard then RRF is not a concern, since the determination is being made with direct comparison to a known amount (i.e. the reference standard).

However, if the impurity content is being determined by comparing the impurity peak to the API peak then the RRF of the impurity needs to be considered.
Relative Response Factor (RRF)

The simplest way of determining an RRF of an impurity is to compare the peak areas from injections of the same amount of impurity and API.

\[
RRF = \frac{\text{Impurity peak area}}{\text{API peak area}}
\]

(only if both have the same concentration)
Relative Response Factor (RRF)

In practice, since it is difficult to isolate suitable quantities of an impurity, the more common way of determining RRF of an impurity is to compare the slopes of the impurity and API over a range of concentrations.

$$RRF = \frac{\text{slope } \text{impurity}}{\text{slope } \text{API}}$$
Relative Response Factor (RRF)

Rifampicicine:
y = 31.312 x + 4.963

Rifampicicine Quinone:
y = 26.198 x + 1.154

RRF = 26.198 / 31.312
= 0.84
Questions

Antony Fake
Fakea@who.int