

1.10

ICH Q3BR Guideline

Impurities in New Drug Products

ICH Step 4

Comments for its application

Impurities in New Drug Products ICH Q3AR

1. Introduction

1.1 Objective of the Guideline

Guidance for registration or marketing application on the content and qualification of impurities in new drug products, chemically synthesised not registered in a region or member state

1.2 Background

Annex to Q3A which should be consulted for basic principles

1.3 Scope of the Guideline

Addresses only

- degradation products of active ingredient or
- reaction products with excipients and/or
- immediate container/closure system.

Guideline does not address clinical trial batches.

Excluded are:

- extraneous contaminants,
- polymorphic forms,
- solid state property of drug substance
- enantiomeric impurities.

Impurities present in new drug substances need not to be monitored or specified in drug products unless they are also degradation products

2. Rationale for the Reporting and Control Degradation Products

The degradation products observed during .stability studies should be summarised.

Summary based on:

- Potential degradation pathway,
- Impurities arising from interaction with excipients and/or
- The immediate container /closure system

Laboratory studies to detect degradation products

Summary should include test results of batches:

- manufactured during development process
- representative of proposed commercial process.

A rational should be provided for exclusion, of those impurities which are not degradation products.

Comparison of impurity profiles of

- representative batches of proposed commercial process
- with those used in development .

Degradation products observed in stability studies at recommended storage conditions should be identified when present at levels > identification threshold

If identification is not feasible, laboratory studies should be reported

Degradation products of \leq the threshold would not need to be identified

Conventional rounding rules, results presented with same number of decimals as given in the limit

Thresholds for identification of degradation products in new drug products

Maximum Daily Dose	Threshold
< 1 mg	1% or 5 μ g TDI ¹ , whichever is lower
1 mg - 10 mg	0.5% or 20 μ g TDI ¹ , whichever is lower
> 10 mg - 2 g	0.2% or 2 mg TDI ¹ , whichever is lower
> 2 g	0.1%

3. Analytical Procedures

- Analytical procedures must be validated and
- Suitable for the detection and quantitation of degradation products.
- Impurities unique to the new drug substance should not interfere or be separated from specified and unspecified degradation products.

☐ **Degradation product levels can be measured by a variety of techniques:**

- Comparison of an analytical response for a degradation product to that of an appropriate reference standard.
- Comparison to the response of the new drug substance itself

Reference standards used should be evaluated and characterised according to the intended use.

If response factors are not close a correction factor is applied.

Acceptance criteria and analytical procedures used to estimate identified or unidentified degradation products are often based on assumption.

These assumption have to be discussed

Differences in analytical procedures used during development and those proposed for the commercial product should be discussed.

4. Reporting Degradation Content of Batches

Analytical results in tabular format for all relevant batches used for

- clinical,
- safety,
- stability
- representative for proposed commercial process.

Reporting level should be set below the identification threshold.

Thresholds for reporting degradation products

Maximum Daily Dose	Threshold
≤ 1 g	0.1%
> 1g	0.05%

If impurities in addition to degradation products are seen, origin should be discussed

4. Reporting Degradation Content of Batches

Chromatograms from representative batches including long term and accelerated stability conditions. Chromatogram should show location of observed degradation products and be available on request

For each batch described in application, the documentation should include:

- Batch identity, strength and size
- Date of manufacture
- Site of manufacture
- Manufacturing process, where applicable
- Immediate container/closure system
- Degradation product content, individual and total
- Use of batch
- Reference to analytical procedure(s) used
- Batch number of the drug substance
- Storage conditions for stability studies

5. Listing of Degradation Products in Specifications

- Specifications should include limits for degradation products expected to occur:**
 - during manufacture
 - under recommended storage conditions,
- Stability profile based on:**
 - Stability studies
 - degradation pathway

- product development studies
- laboratory studies.
- Selection based on degradation products found in batches manufactured by proposed commercial process

Rationale should be given for inclusion or exclusion of impurities in specification based on impurity profiles observed in

- safety studies
- clinical studies
- proposed commercial process

☐ Fixing Acceptance Criteria:

- Acceptance criterion of drug substance if relevant
- Increase during stability studies
- Proposed shelf life and recommended storage conditions
- Qualified level

<h2>5. Listing of Degradation Products in Specifications</h2>

☐ Acceptance Criteria should include, where applicable limits for

- each specified identified degradation product
- each specified unidentified degradation product
- any unspecified degradation product with an acceptance criterion of not more than (\leq) the identification threshold
- total degradation products.

All impurities > reporting threshold should be summed and reported as Total impurities.

<h2>6. Qualification of Degradation Products</h2>

Established data of biological safety of individual degradation product or degradation profile at level specified.

Rationale for selecting degradation product limits based on safety considerations

Qualified are degradation products

- In safety studies,
- In clinical studies
- Metabolites, animal and human

Thresholds for the qualification of degradation products in new drug products

Maximum Daily Dose	Threshold
< 10 mg	1% or 50 µg TDI ¹ , whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI ¹ , whichever is lower
> 100 mg - 2 g	0.2% or 2 mg TDI ¹ , whichever is lower
> 2 g	0.1%

Higher or lower thresholds may be appropriate based on scientific rationale:

- Amount of degradation product administered in safety and/or clinical studies and found to be safe,
- the percentage change in the degradation product
- other safety factors.

Qualification threshold exceeded

- Data from the scientific literature
- No data available, additional safety testing considering
 - patient population
 - daily dose
 - route and duration of product administration
- Studies on product or substance containing the degradation product to be controlled.

6. Qualification of Degradation Products

If in the course of development new degradation products may exceed identification or qualification threshold.

They should be identified and/or qualified.

Comparison of results of safety testing of the

- product or substance containing representative level of degradation product
- With previously qualified material.

Studies using isolated degradation products are acceptable but may not always have clinical significance

Attachment I

Thresholds for reporting of degradation products in new drug products

Maximum Daily Dose	Threshold
≤ 1 g	0.1%
> 1 g	0.05%

Thresholds for identification of degradation products in new drug products

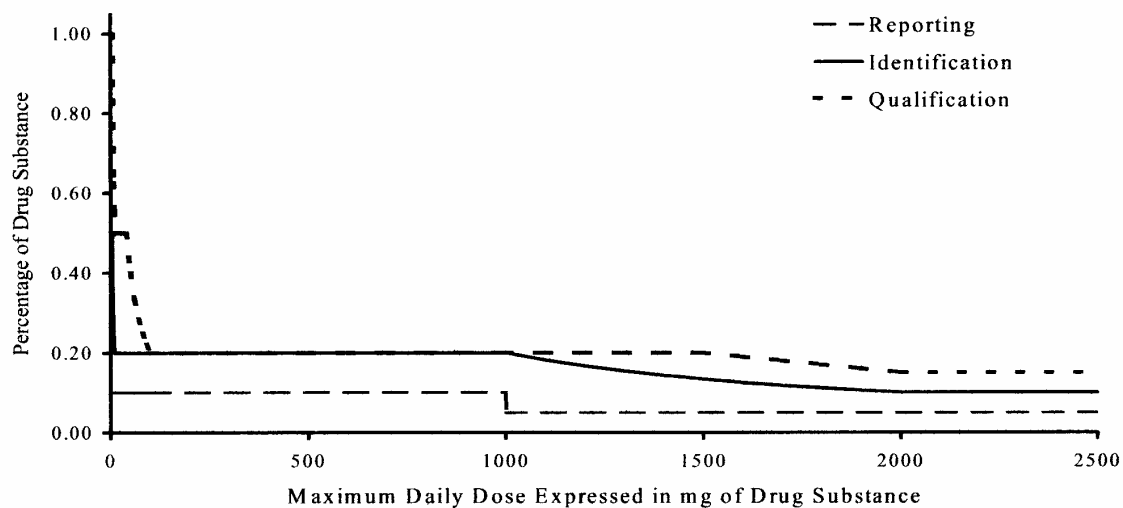
Maximum Daily Dose	Threshold
< 1 mg	1% or 5 µg TDI ¹ , whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI ¹ , whichever is lower
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> 2 g	0.1%

Thresholds for the qualification of degradation products in new drug products

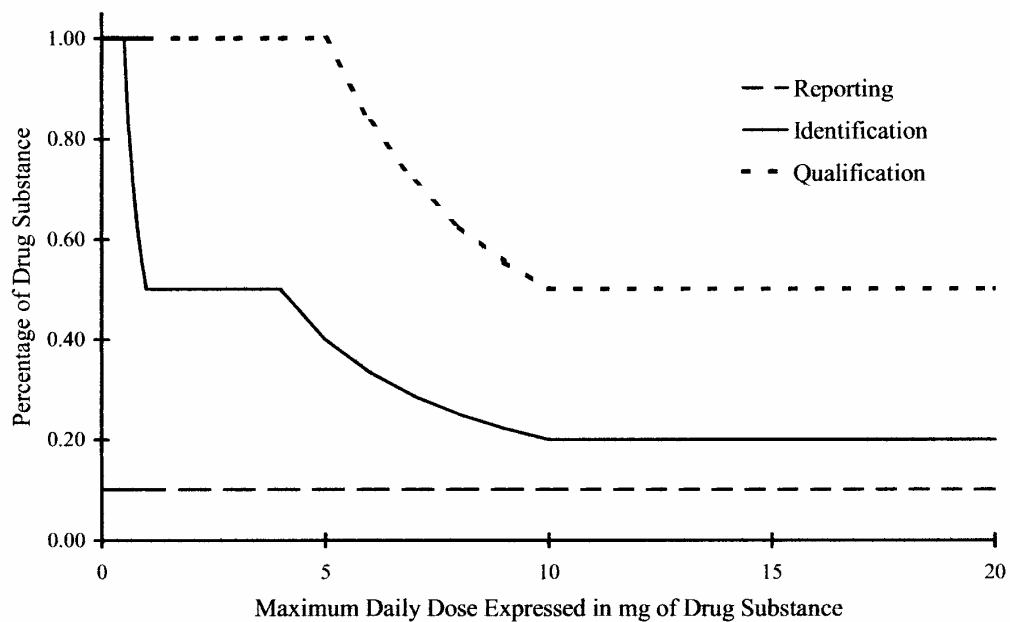
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TDI¹ Total Daily Intake

Illustration of Thresholds for Reporting, Identification, and Qualification of Degradation Products in New Drug Products as a Function of Maximum Daily Dose¹



Expanded Scale:



Attachment 2: Illustration of Reporting Degradation Product Results for Identification and Qualification in an Application

50 mg Maximum Daily Dose

'Raw' Result (%)	Reported Result (%) (Reporting Threshold = 0.1%)	Total Daily Intake (TDI) of the Degradation Product (rounded result in µg)	Identification Threshold 0.2%	Action Qualification Threshold 200 µg TDI (equivalent to 0.4%)
0.04	Not reported	20	None	None
0.2143	0.2	100	None	None
0.349	0.31	150	Yes	None (1)
0.550	0.61	300	Yes	Yes (1)

1.9 gram Maximum Daily Dose

'Raw' Result (%)	Reported Result (%) (Reporting Threshold = 0.05%)	Total Daily Intake (TDI) of the Degradation Product (rounded result in mg)	Identification Threshold 2 mg TDI (equivalent to 0.11%)	Action Qualification Threshold 3 mg TDI (equivalent to 0.16%)
0.049	Not reported	1	None	None
0.079	0.08	2	None	None
0.183	0.181	3	Yes	None (1,2)
0.192	0.191	4	Yes	Yes (1)

Notes on Attachment 2

- 1 After identification, if the response factor is determined to differ significantly from the original assumptions, it can be appropriate to re-measure the actual amount of the degradation product present and re-evaluate against the qualification threshold (see Attachment 1).
2. Although the reported result of 0.18% exceeds the calculated threshold value of 0.16%, in this case the action is acceptable since the TDI (when rounded) does not exceed 3mg.