AGENZIA ITALIANA DEL FARMACO

Impurities in Drug Substance and Drug Product

Regulatory aspects

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Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	X	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	X	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	X	☐	☐	☐ facoltativo
2. Consulenza per una società	X	☐	☐	☐ facoltativo
3. Consulente strategico per una società	X	☐	☐	☐ facoltativo
4. Interessi finanziari	x	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	X	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	X	☐	☐	☐ facoltativo
7. Sperimentatore	X	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	X	☐	☐	☐ facoltativo
9. Interessi Familiari	x	☐	☐	☐ facoltativo

* Luca Ginnari Satriani, secondo il Regolamento per la disciplina dei conflitti di interesse all'interno dell'Agenzia Italiana del Farmaco approvato dal CdA AIFA con Delibera n. 37 del 13 ottobre 2020.

N.B. Per questo intervento non ricevo alcun compenso

Impurities: ICH Guide Lines

Specifiche linee guida trattano il tema delle impurezze di sintesi e di degradazione, stabilendo i limiti di queste sulla base della dose giornaliera del farmaco, e i casi in cui è necessario identificare e qualificare le impurezze da un punto di vista tossicologico mediante specifici studi.

- ICH Q3A (R2) Impurities in new Drug Substances
- ICH Q3B (R2) Impurities in New Drug Products
- ICH guideline Q3C (R8) on impurities: guideline for residual solvents and related Annexes
- ICH guideline Q3D (R1) on elemental impurities
- ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

ICH GL: The European Medicines Agency publishes scientific guidelines on human medicines that are harmonised by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Impurities

Impurity (Glossary - ICH Q6A):

IN THE DRUG SUBSTANCE: 

"Any component of the new drug substance which is not the chemical entity defined as the new drug substance."

IN THE DRUG PRODUCT: 

"Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product."

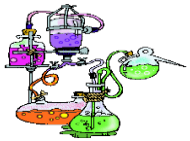
Classification of Impurities

- Organic impurities-> ref. ICHQ3A (DS), ICHQ3B (DP), ICH M7

  Organic impurities can arise during the manufacturing process and/or storage of the new drug substance/drug product.

  → Process impurities

  → Degradation products

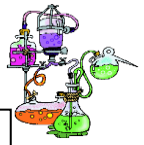


- Inorganic impurities -> ref. ICHQ3A, ICHQ3B, ICHQ3D

  Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

  - Reagents, ligands and catalysts
  - Heavy metals or other residual metals
  - Inorganic salts.

  → Process impurities



- Residual solvents -> ref. ICHQ3C and related annexes

Impurities in the Drug Substance (ICHQ3A)

- The new drug substance specification should include, where applicable, the following list of impurities:
- Organic Impurities
  - Each specified identified impurity
  - Each specified unidentified impurity
  - Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold

- Total impurities

Degradation impurities + process impurities

- Residual Solvents

- Inorganic Impurities

ICHQ3A Thresholds

Attachment 1: Thresholds

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

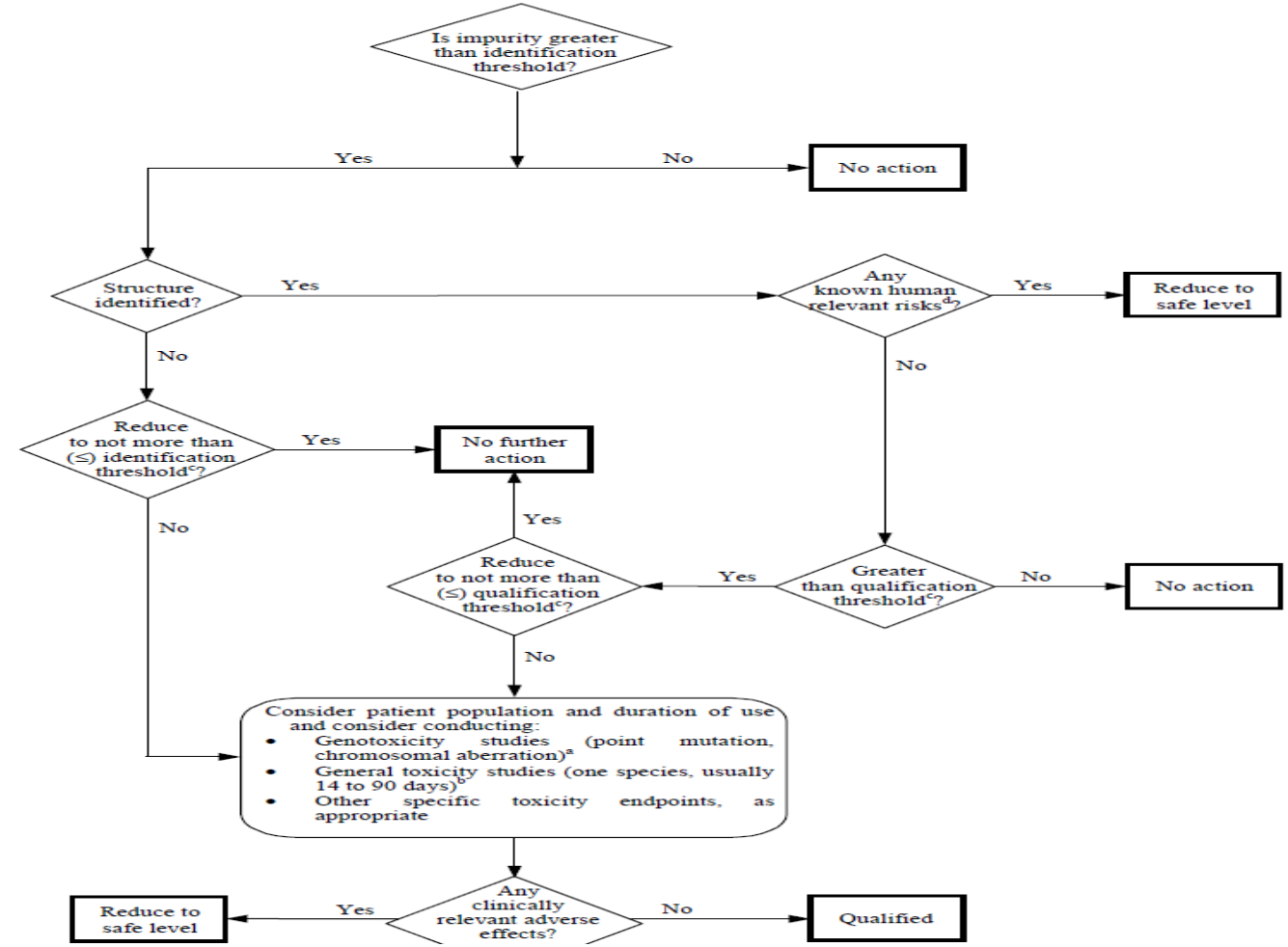
[1] The amount of drug substance administered per day

[2] Higher reporting thresholds should be scientifically justified

[3] Lower thresholds can be appropriate if the impurity is unusually toxic

Impurities in the Drug substances

Attachment 3: Decision Tree for Identification and Qualification



Detection of impurities by suitable validated analytical method

Impurities methods described in EP monographs?

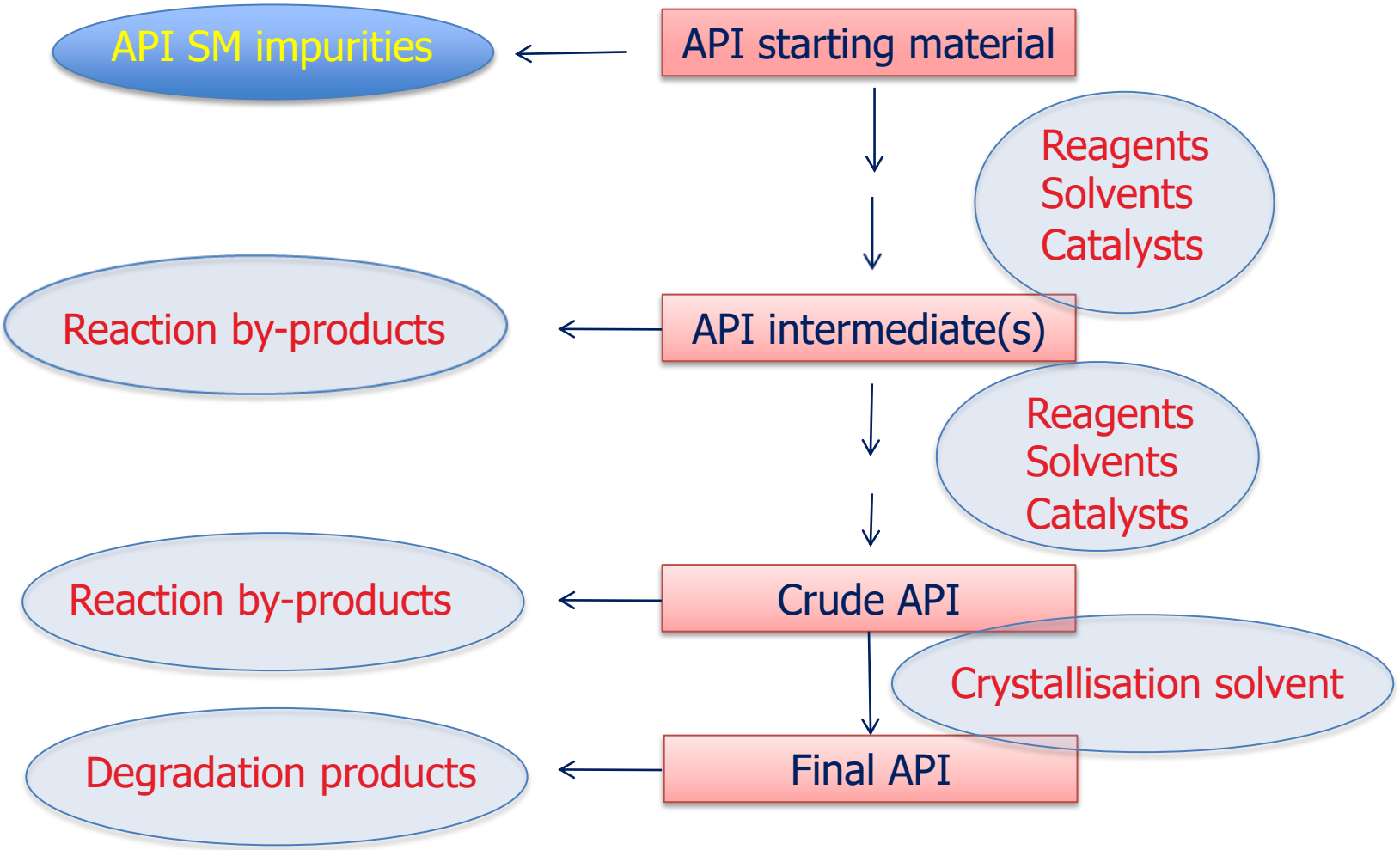
yes → No complete validation is required

No ↓

Complete validation is required according to the ICH Q2 (R1)

→ Verification of selectivity, linearity, accuracy, precision, LOD, LOQ, etc…

Potential impurities in API Synthesis



Dossier - Module 3.2.S

EMA/454576/2016 "Guideline on the chemistry of active substances": Impurities 3.2.S.3.2 section

- Information on impurities and their carry-over should be provided. This includes related substances, residual solvents, elemental impurities, reagents and those derived from reagents.

  → Starting materials (SM)

- The related substances considered as potential impurities arising from the synthesis and degradation products should be discussed and described briefly including an indication of their origin.
- The mutagenic potential of impurities should be addressed.
- Possible routes of degradation should also be discussed - please see section 3.2.S.7.1.

  → Stress test studies

- Copies of relevant chromatograms should be provided

Dossier - Module 3.2.S

3.2.S sections for the impurity evaluation

3.2.S.2.2 "Description of Manufacturing Process and Process Controls" (ASMF RP) → to compare the process flowchart Vs 3.2.S.4.1 "Specification" and Vs 3.2.S.3.2 "impurities"

3.2.S.2.3 "Control of Materials" (ASMF AP/RP) → to evaluate the SM/solvents/catalyst "specification", the potential carryover in the API Vs 3.2.S.4.1 "Specification"

SM flowchart synthesis

3.2.S.4. "Control of the Active Substance" (ASMF AP) → to evaluate impurities specs, related limits, analytical methods and related validation data, CoA, Justification of the limits Vs ICH Q3A

3.2.S.7 "Stability" (ASMF AP) →

1. to evaluate the stress tests Vs the 3.2.S.3.2 section
2. to compare the stability data Vs 3.2.S.4.1 Shelf life impurities limits

Controllo delle Impurezze nel principio attivo

Obiezioni frequenti nella valutazione dei dossier

- Spesso la valutazione del carry over di tutte le possibili impurezze da starting materials ed intermedi nel principio attivo non risulta adeguata.
- La sezione 3.2.S.3.2 "impurities" non dettaglia adeguatamente le possibili impurezze di processo e quelle di degradazione, anche alla luce degli studi di stress test.
- non vengono presentati gli studi di stress test a supporto del metodo analitico, e delle impurezze di degradazione individuate
- Gli studi di stress test presentati non riportano il bilancio di massa tra l'assay e tutte le singole sostanze correlate al fine di dimostrare che il metodo analitico sia "stability indicating" e di supportare, così, le informazioni riportate nella sezione 3.2.S.3.2

Controllo delle Impurezze nel principio attivo

Obiezioni frequenti nella valutazione dei dossier

- Non vengono discusse adeguatamente le potenziali impurezze genotossiche, il loro mancato controllo e/o i relativi limiti di accettazione, secondo quanto previsto dalla linea guida ICH M7
- I limiti di specifica non sono conformi all'ICH Q3A, e/o non sempre vengono qualificate tossicologicamente le impurezze nei casi previsti dalla GL
- I relativi metodi analitici non risultano essere sempre convalidati secondo i requisiti dell'ICH Q2(R1)

Impurities in the Drug Products (ICHQ3B)

Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product unless they are also degradation products.

The new drug product specification should include, where applicable, the following list of degradation products:

- Each specified identified degradation product
- Each specified unidentified degradation product
- Any unspecified degradation product with an acceptance criterion of not more than (≤) the identification threshold
- Total degradation products.

Only degradation impurities!

Degradation impurities and stress testing

ICH Q1(R2): "Stress testing of the drug substance can help identify the likely degradation products..

It should include:

- the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing,
- humidity (e.g., 75% RH or greater)
- where appropriate, oxidation, and photolysis on the drug substance.
- The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.
- photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

ICHQ3B thresholds

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

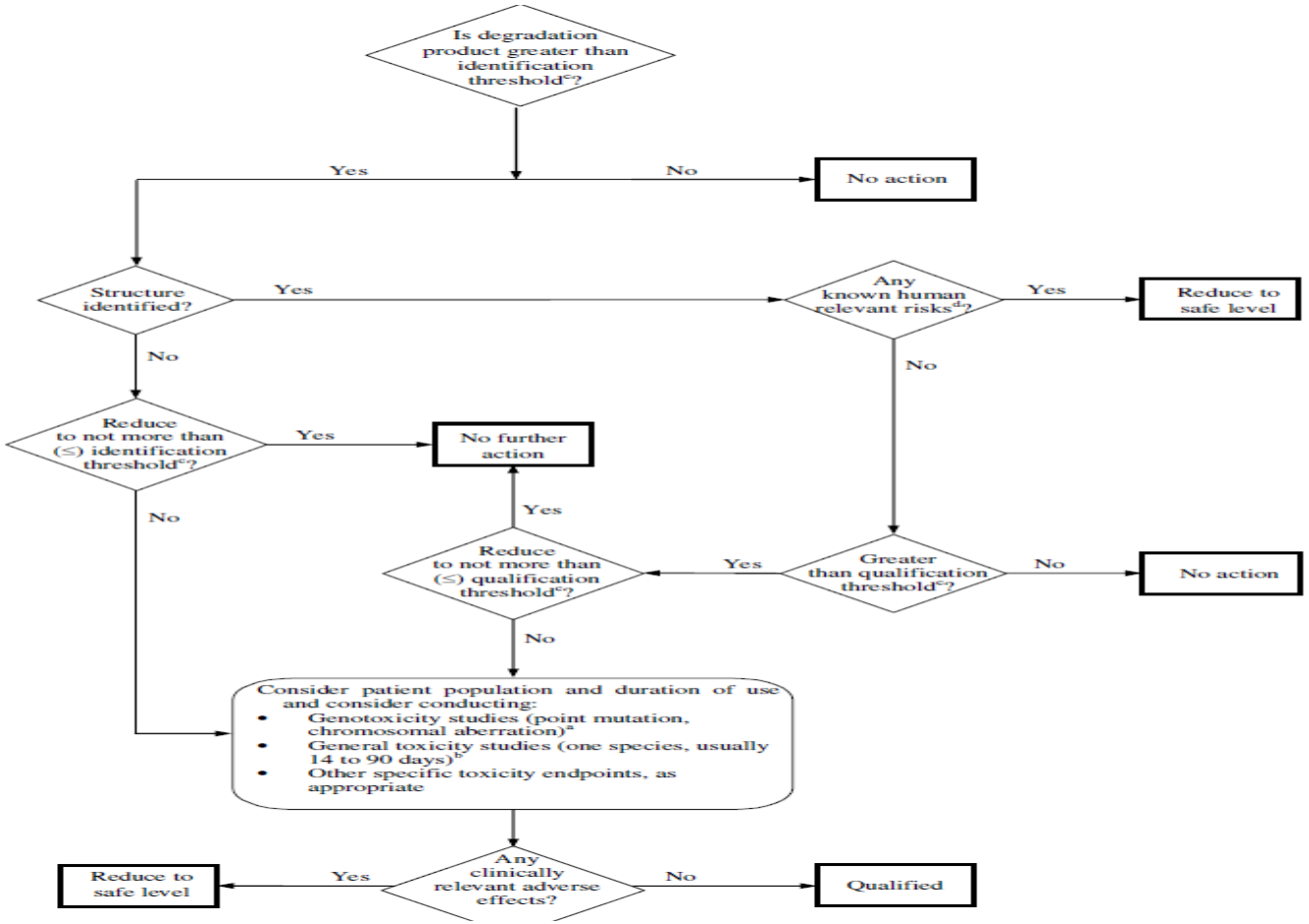
Maximum Daily Dose[1]	Threshold[2, 3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Degradation products that are also significant metabolites present in animal and/or human studies are generally considered qualified.

Impurities in the Drug Products (ICHQ3B)



Dossier - Module 3.2.P

Related sections for the impurity evaluation

3.2.P.5 Control of Drug Product

3.2.P.5.1 "Specification" → 1. to compare with the 3.2.S.3.2 section in order to evaluate if all degradation products have been considerated.
2. to evaluate specs limits Vs ICH Q3B

3.2.P.5.2 "Analytical Procedures"

3.2.P.5.3 "Validation of Analytical Procedures"

3.2.P.5.4. "Batch analysis"

3.2.P.5.5 "Characterisation" of impurities" → to compare with the "3.2.S.3.2 Impurities"

3.2.P.5.6 "Justification of Specification" → to evaluate Vs the ICH Q3B

Controllo delle Impurezze nel prodotto finito

Obiezioni frequenti nella valutazione dei dossier

- Per le specifiche relative al controllo delle impurezze non vengono sempre considerate tutte le impurezze di degradazione della sostanza attiva (spesso per carenza di informazioni del modulo 3 e/o per la mancata esecuzione/inclusione degli stress tests studies)
- I limiti di specifica non sono conformi all'ICH Q3B, e/o non sempre vengono qualificate tossicologicamente le impurezze nei casi previsti dalla GL
- I relativi metodi analitici non risultano essere adeguatamente convalidati secondo i requisiti dell'ICH Q2(R1) oppure non risultano essere stability indicating
- Il risk assessment relativo al rischio di contaminazione da elemental impurities e/o il relativo controllo come da ICH Q3D non risulta sempre adeguato
- Il risk assesment relativo al rischio di contaminazione da nitrosammine non risulta sempre adeguato

Mutagenic Impurities

Assessment and Control of DNA reactive (Mutagenic) impurities in Pharmaceuticals to limit potential Carcinigenic risk (M7)

The focus of this guideline is on DNA reactive substances that have a potential to directly cause DNA damage when present at low levels leading to mutations and therefore, potentially causing cancer.

A Threshold of Toxicological Concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects. For application of a TTC in the assessment of acceptable limits of mutagenic impurities in drug substances and drug products, a value of 1.5 µg/day corresponding to a theoretical 10^{-5} excess lifetime risk of cancer, can be justified.

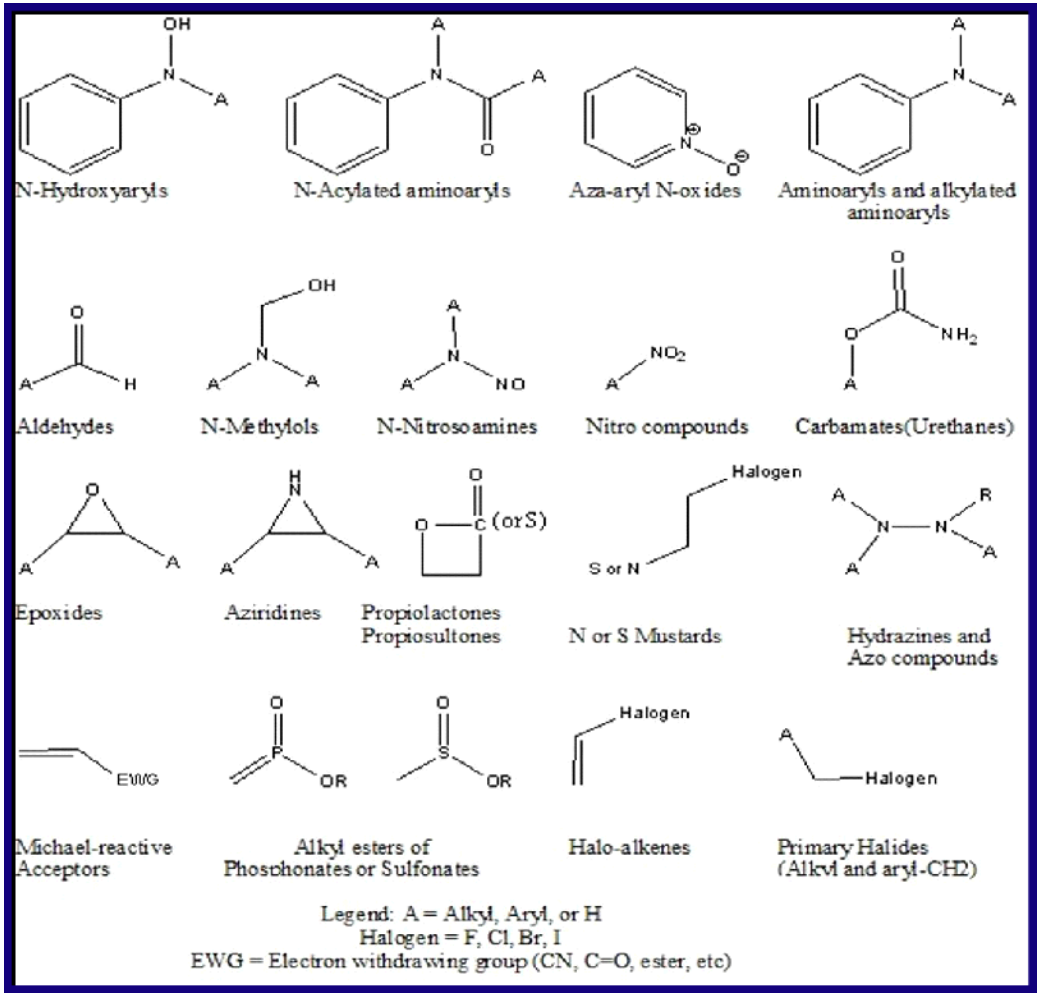
Mutagenic Impurities classification

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions

Class	Definition	Proposed action for control (details in Section 7 and 8)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	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	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

*Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations (e.g., positive findings in *in vivo* gene mutation studies)

Mutagenic Impurities: structural alerts



Mutagenic Impurities

Acceptable intakes (1):

Acceptable intakes based on compound-specific risk assessments; Mutagenic impurities with positive carcinogenicity data

Compound-specific risk assessments to derive acceptable intakes should be applied instead of the TTC based acceptable intakes where sufficient carcinogenicity data exist. For a known mutagenic carcinogen, a compound-specific acceptable intake can be calculated based on carcinogenic potency and linear extrapolation as a default approach. Alternatively, other established risk assessment practices such as those used by international regulatory bodies may be applied either to calculate acceptable intakes or to use already existing values published by regulatory authorities. Compound-specific calculations for acceptable intakes can be applied case-by-case for impurities which are chemically similar to a known carcinogen compound class (class-specific acceptable intakes) provided that a rationale for chemical similarity and supporting data can be demonstrated.

Mutagenic Impurities

Acceptable intakes (2):

TTC-basec Acceptable Intakes (Classi 2 e 3): A TTC-based acceptable intake of a mutagenic impurity of 1.5 µg per person per day is considered to be associated with a negligible risk and can in general be used for most pharmaceuticals as a default to derive an acceptable limit for control. This approach would usually be used for mutagenic impurities present in pharmaceuticals for long-term treatment (> 10 years) and where no carcinogenicity data are available.

Mutagenic Impurities

Acceptable intakes (3):

Acceptable Intakes in Relation to LTL (Less-Than-Lifetime) Exposure: The TTC-based acceptable intake of 1.5 µg/day is considered to be protective for a lifetime of daily exposure. To address 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. This would allow higher daily intake of mutagenic impurities than would be the case for lifetime exposure and still maintain comparable risk levels for daily and non-daily treatment regimens.

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

Mutagenic Impurities

Acceptable intakes (4):

Acceptable Intakes for Multiple Mutagenic Impurities

The TTC-based acceptable intakes should be applied to each individual impurity. When there are two Class 2 or Class 3 impurities, individual limits apply. When there are three or more Class 2 or Class 3 impurities specified on the drug substance specification, total mutagenic impurities should be limited as described in Table 3 for clinical development and marketed products. For combination products each active ingredient should be regulated separately.

Table 3: Acceptable Total Daily Intakes for Multiple Impurities

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Total Daily intake [µg/day]	120	60	30	5

Mutagenic Impurities

Eccezioni caso-specifiche per un accettabile quantitativo della sostanza possono essere giustificate ad esempio in caso di patologie gravi o aspettativa di vita ridotta.

Composti appartenenti ad alcune classi strutturali di mutageni possono mostrare potenza cancerogena estremamente alta (cioè aflatossine-simili, strutture N-nitroso ed alchil-azossi).In tali casi sono a rischio perfino quantitativi inferiori alla TTC.

Mutagenic Impurities

Control of Process Related Impurities (1)

Option 1

Include a test for the impurity in the drug substance specification with an acceptance criterion at or below the acceptable limit using an appropriate analytical procedure.

For an Option 1 control approach, it is possible to apply periodic verification testing. Periodic verification testing is justified when it can be shown that levels of the mutagenic impurity in the drug substance are less than 30% of the acceptable limit for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, a routine test in the drug substance specification is recommended.

Mutagenic Impurities

Control of Process Related Impurities (2)

Option 2

Include a test for the impurity in the specification for a raw material, starting material or intermediate, or as an in-process control, with an acceptance criterion at or below the acceptable limit using an appropriate analytical procedure.

Mutagenic Impurities

Control of Process Related Impurities (3)

Option 3

Include a test for the impurity in the specification for a raw material, starting material or intermediate, or as an in-process control, with an acceptance criterion above the acceptable limit of the impurity in the drug substance, using an appropriate analytical procedure coupled with demonstrated understanding of fate and purge and associated process controls that assure the level in the drug substance is below the acceptable limit without the need for any additional testing later in the process. This option can be justified when the level of the impurity in the drug substance will be less than 30% of the acceptable limit by review of data from laboratory scale experiments (spiking experiments are encouraged) and where necessary supported by data from pilot scale or commercial scale batches.

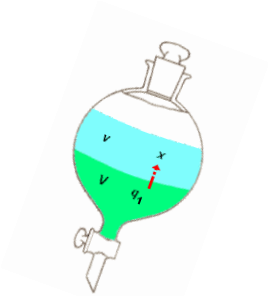
Mutagenic Impurities

Control of Process Related Impurities (4)

Option 4

Understand process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity. (i.e., the impurity does not need to be listed on any specification).

Residual solvents



ICH Q3C:

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products.

The solvents are not completely removed by practical manufacturing techniques (e.g. drying, distillation, lyophylization) .

Residual solvents

Residual solvents

ICH Q3C:

- Class 1 solvents: Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

- Class 2 solvents: Solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

- Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

Residual solvents

$$\text{Concentration (ppm)} = \frac{1000 \text{ x PDE}}{\text{dose}} \qquad (1)$$

Here, PDE is given in terms of mg/day and dose is given in g/day.

$$\text{PDE} = \frac{\text{NOEL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5}} \qquad (1)$$

PDE= Permitted Daily Exposue

NOEL= No-observed-effect level

Residual solvents: ICH Q3C classification

Class 1 solvents

Solvent	*Concentration limit (ppm)*
Benzene	2
Carbon tetrachloride	4
1,2-Dichloroethane	5
1,1-Dichloroethene	8
1,1,1-Trichloroethane	1500

ICH Q3C: Solvents in Class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect.

Annex 2 to ICH Q3C: The use of a class 1 solvent in the manufacture of the finished product is not considered acceptable.

Residual solvents: ICH Q3C classification

Class 1 solvents

Annex 1 to ICH Q3C:

- Class 1 solvents used as starting materials

When class 1 solvents are used as starting materials they should be routinely controlled, either in a suitable intermediate or in the final active substance.

- Class 1 solvents present as an impurity

Class 1 solvents in an active substance can be a by-product from a chemical reaction or may arise from another solvents.

Benzene may be present in some solvents: acetone, toluene, ethanol, methanol, isopropanol, xylene, hexane and petroleum ether

Carbon tetrachloride may be present in Dichloromethane

Residual solvents: ICH Q3C classification

Annex 1 to ICH Q3C: Where a class 1 solvent might be present in another solvent (e.g. toluene or acetone containing benzene), a routine test for this class 1 solvent, on a suitable intermediate or on the final active substance, is not required when:

- The limit applied to the originator solvent is such that the class 1 solvent will be present in the active substance at levels below the limits set out in the guideline, taking into account the maximum likely level of contamination of the class 1 solvent. The volatility of both solvents in the drying processes must be taken into account when applying this argument;
- It is demonstrated with a validated method that the class 1 solvent is not more than 30 % of the specified limit, in a suitable intermediate or in the final active substance. Supporting data should be presented on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches;
- The specification for the originator solvent used includes a routinely performed test and limit for the class 1 solvent.

Residual solvents: ICH Q3C classification

Class 2 Solvents

Table 2. Class 2 solvents in pharmaceutical products.

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene[1]	0.7	70
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1180
Methylisobutylketone[2]	45	4500
N-Methylpyrrolidone[3]	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200

When class 2 solvents are used as starting materials or solvents, they should be normally routinely controlled either in a suitable intermediate or in the final AS depending on the step(s) of the synthesis in which they are usedive

Residual solvents: ICH Q3C classification

Class 2 Solvents

Annexes to ICH Q3C:

- Class 2 solvents used in the last step of the synthesis

In all cases where a class 2 solvent is used in the last step of a synthesis it should be routinely controlled in the final active substance.

- Class 2 solvents used prior to the last step of the synthesis

Class 2 solvents have not to be included in the drug substance specification if it has been demonstrated, on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches of the suitable intermediate or the final active substance, that the content of class 2 solvents is not more than 10 % of the acceptable concentration limit (e.g., acetonitrile 41 ppm).

Residual solvents: ICH Q3C classification

Class 3 Solvents

Table 3. Class 3 solvents which should be limited by GMP or other quality-based requirements.

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	Triethylamine[5]

It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5%) would be acceptable without justification.

If only Class 3 solvents are present, a non-specific method such as loss on drying may be used (LOD ≤ 0.5%)

Guideline for elemental impurities (ICHQ3D)

- Focused on contamination in the whole drug product
- PDE for 24 elements (PDE for oral, parenteral and inhalation routes of administration)
- The elements included in this guideline have been placed into three classes based on their toxicity (PDE) and likelihood of occurrence in the drug product.
- Risk Assessment

Element classification

Class 1:

The elements, As, Cd, Hg, and Pb, are human toxicants that have limited or no use in the manufacture of pharmaceuticals. Their presence in drug products typically comes from commonly used materials (e.g., mined excipients*). Because of their unique nature, these four elements require evaluation during the risk assessment, across all potential sources of elemental impurities and routes of administration.

* Mined Excipients: e.g. Sodium chloride, Titanium dioxide, Calcium carbonate, Talc.

Element classification

Class 2:

Elements in this class are generally considered as route-dependent human toxicants. Class 2 elements are further divided in sub-classes 2A and 2B based on their relative likelihood of occurrence in the drug product.

Class 2A:

Class 2A elements have relatively high probability of occurrence in the drug product and thus require risk assessment across all potential sources of elemental impurities and routes of administration. The class 2A elements are: Co, Ni and V.

Element classification

Class 2B:

Class 2B elements have a reduced probability of occurrence in the drug product related to their low abundance and low potential to be co-isolated with other materials. As a result, they may be excluded from the risk assessment unless they are intentionally added during the manufacture of drug substances, excipients or other components of the drug product. The elemental impurities in class 2B include: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl.

Element classification

Class 3:

The elements in this class have relatively low toxicities by the oral route of administration (high PDEs, generally > 500 µg/day) but may require consideration in the risk assessment for inhalation and parenteral routes. For oral routes of administration, unless these elements are intentionally added, they do not need to be considered during the risk assessment. The elements in this class include: Ba, Cr, Cu, Li, Mo, Sb, and Sn.

Element classification

Elements to be Considered in the Risk Assessment:

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

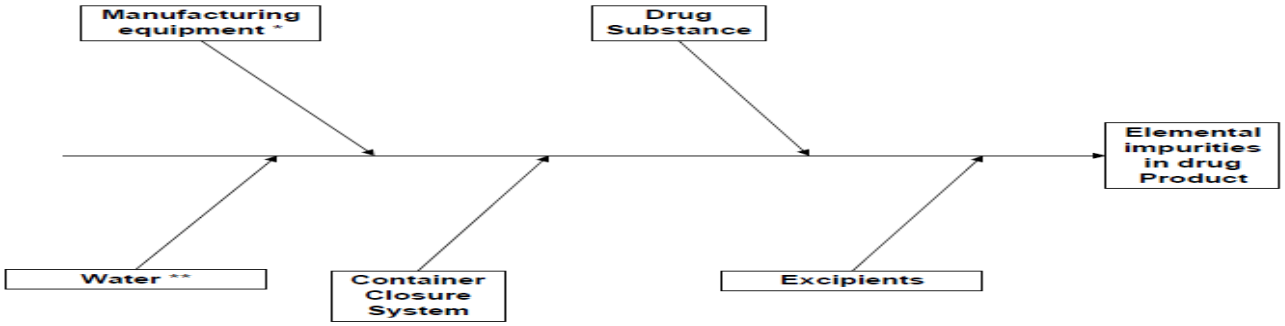
Risk assessment and control of elemental impurities

For the purposes of the guideline, the risk assessment process can be described in three steps:

1. Identify known and potential sources of elemental impurities that may find their way into the drug product.
2. Evaluate the presence of a particular elemental impurity in the drug product by determining the observed or predicted level of the impurity and comparing with the established PDE.
3. Summarize and document the risk assessment. Identify if controls built into the process are sufficient or identify additional controls to be considered to limit elemental impurities in the drug product.

Risk assessment and control of elemental impurities

Potential sources of elemental impurities



* The risk of inclusion of elemental impurities can be reduced through process understanding, equipment selection, equipment qualification and Good Manufacturing Practice (GMP) processes.

**The risk of inclusion of elemental impurities from water can be reduced by complying with compendial (e.g., European Pharmacopoeia, Japanese Pharmacopoeia, US Pharmacopeial Convention) water quality requirements, if purified water or water for injection is used in the manufacturing process(es).

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Risk assessment and control of elemental impurities

As the potential elemental impurity identification process is concluded, there are two possible outcomes:

1. The risk assessment process does not identify any potential elemental impurities. The conclusion of the risk assessment and supporting information and data should be documented.
2. The risk assessment process identifies one or more potential elemental impurities. For any elemental impurities identified in the process, the risk assessment should consider if there are multiple sources of the identified elemental impurity or impurities and document the conclusion of the assessment and supporting information.

Risk assessment and control of elemental impurities

The summary should consider the significance of the observed or predicted level of the elemental impurity relative to the PDE of the elemental impurity.

As a measure of the significance of the observed elemental impurity level, a control threshold is defined as a level that is 30% of the established PDE in the drug product. The control threshold may be used to determine if additional controls may be required (e.g. by submission of the requested variations).

Risk assessment and control of elemental impurities

At the time of submission, in the absence of other justification, the level and variability of an elemental impurity can be established by providing the data from three (3) representative production scale lots or six (6) representative pilot scale lots of the component or components or drug product.

For some components that have inherent variability (e.g., mined excipients), additional data may be needed to apply the control threshold.

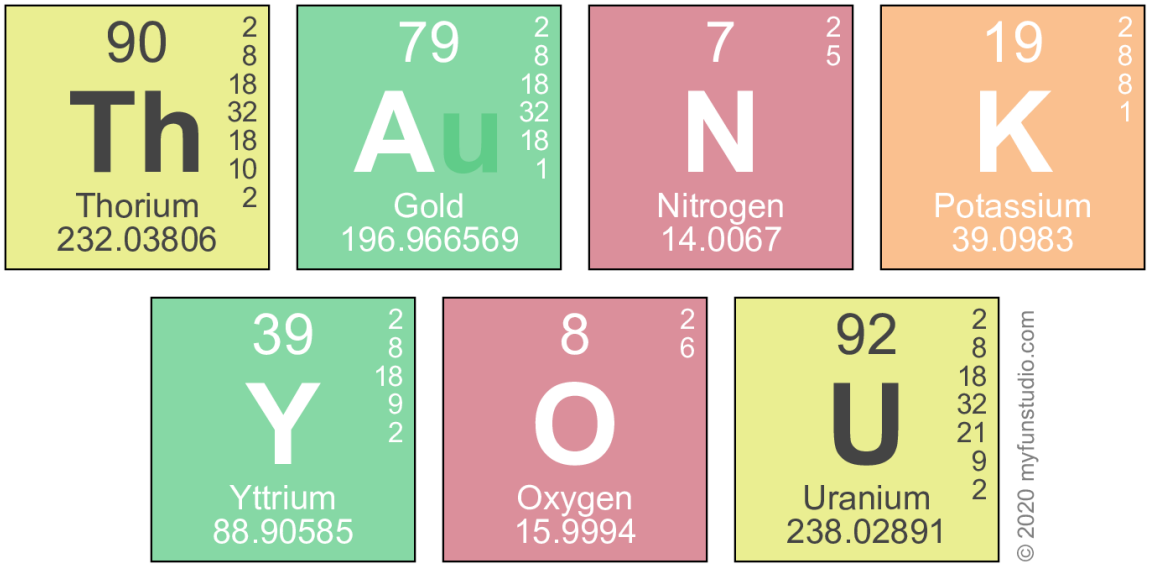
A Risk assessment should be exhaustive, including the whole data. Just analytical results are not enough.

Risk assessment and control of elemental impurities

If the total elemental impurity level from all sources in the drug product is expected to be consistently less than 30% of the PDE, then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities.

If the risk assessment fails to demonstrate that an elemental impurity level is consistently less than the control threshold, controls should be established to ensure that the elemental impurity level does not exceed the PDE in the drug product.

The Summary of the Risk Assessment should be included in the section on the Justification of Specifications (3.2.P.5).



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