Controllo delle impurezze nella sostanza attiva e nel prodotto finito

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10/04/26

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	X	X facoltativo
10. Gravi ragioni di convenienza	X	☐	☐	☐ facoltativo

* Tommaso Eliseo, secondo il Regolamento per la prevenzione e gestione dei conflitti di interessi all'interno dell'Agenzia Italiana del Farmaco approvato con Delibera CdA n.9 del 12 febbraio 2025.

N.B. Il compenso ricevuto per questo intervento è regolato dalla contrattazione collettiva.

Impurities as a critical issue

- Impurities represent a **critical aspect** to be addressed for any medicinal product
- Extensive resources are dedicated to characterisation and assessment of the impurity profile of active substances and medicinal products
- Related to **Quality** and **Safety**
- Issues related to impurities can be a PSRPH (Potential Serious Risk to Public Health) leading to refusal of Marketing Authorisations or market recalls

Impurities: definitions (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."

Disclaimer: impurities addressed in this presentation

- Discussion limited to impurities associates with chemical entities (not biological/immunological active substances or ATMP)
- No discussion on stereoisomeric impurities
- No discussion on impurities associated with fermentation or semysinthesis products, peptides, oligonucleotides, radiopharmarceuticals, nanomedicines, herbal or homeopathic preparations
- Dedicated GLs for these product types

Impurities: Ph. Eur. and guidelines

- General Ph. Eur. monograph Substances for pharmaceutical use (2034)
- Individual Ph. Eur. monographs (substance-specific and pharmaceutical preparations-specific)

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

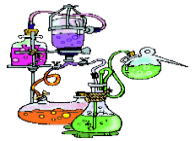
- ICH Q6A -> Specifications
- ICH Q2 (R2) Guideline on validation of analytical procedures
- ICH Q1 (R2) and CPMP/QWP/122/02, rev 1 corr -> Stability testing of drug substances and products

Source of Impurities

- **Organic impurities**
  - Non-mutagenic -> ICH Q3A (DS), ICHQ3B (DP)
  - Mutagenic -> ICH M7

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

- Process impurities



- Degradation products

General classification of Impurities

- **Inorganic impurities** > ICH Q3A, ICH Q3B, ICH Q3D

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

- Reagents, ligands, catalysts, auxiliary materials
- Heavy metals or other residual metals
- Inorganic salts

- **Residual solvents** -> ICH Q3C and related annexes

- **Nitrosamines** -> CHMP AR on Referral on nitrosamines and associated Q&A document

Impurities in the Drug Substance (ICH Q3A)

The drug substance specification should include 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

- **Residual Solvents**

- **Inorganic Impurities**

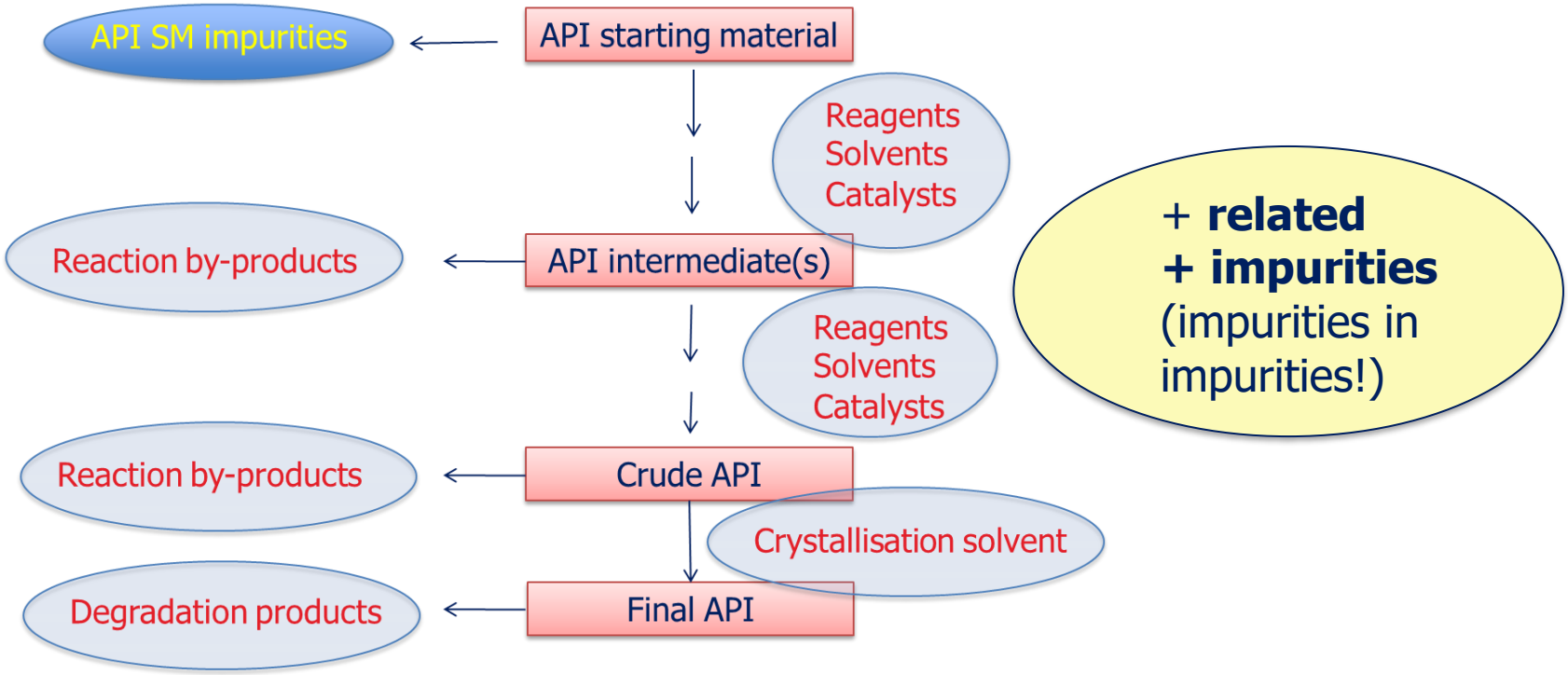
Impurities in the Drug Substance (ICH Q3A)

- **Specified Impurity:** An impurity that is **individually listed** and limited with a **specific acceptance criterion** in the new drug substance specification. A specified impurity can be either identified or unidentified.

- **Identified Impurity:** An impurity for which a **structural characterisation** has been achieved >>> **structure assigned** to a specific analytical signal/response

- **Unidentified Impurity:** An impurity for which a structural characterisation has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Potential impurities in API Synthesis



Cross-contamination

Es. Linee di produzione non adeguatamente isolate/separate da altre linee produttive

Es. procedure di cleaning non adeguate nel caso di impianti *multipurpose* o tra campagne successive

Es. Utilizzo di solventi recuperati in processi differenti da quelli che li hanno generati

- Utilizzo (e riutilizzo) di materiali ausiliari a contatto con il prodotto (es. resine utilizzate nella separazione cromatografiche, materiali plastici teli centrifughe/presso filtri, teli in PE utilizzati negli essiccatori statici, etc.)

Aspetti GMP

ICH Q3A Thresholds

- **Reporting Threshold:** A limit above (>) which an impurity should be **reported**. Reporting threshold is the same as reporting level in Q2B.
- **Identification Threshold:** A limit above (>) which an impurity should be **identified**.
- **Qualification Threshold:** A limit above (>) which an impurity should be **qualified** (provide evidence for safety)*

* Reflection paper on the qualification of non-mutagenic impurities (EMA/CHMP/543397/2024, public consultation phase ended)

ICH Q3A Thresholds (**DS**)

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

Analytical methods

Impurities methods described in EP monographs?

yes → Typically validation not required

No → Complete validation is required according to the ICH Q2 (R2) → Verification of specificity, linearity, accuracy, precision, LOD, LOQ, robustness, etc…

Stress testing studies

Generate on purpose **degradation products** under stress conditions (**forced degradation**):

- establishing **degradation pathways**
- developing and validating **suitable analytical procedures.**

It should typically include:

- the effect of **temperatures** (above that for formal accelerated testing)
- **humidity** (e.g., 75% RH or greater)
- susceptibility of the drug substance to hydrolysis across a wide **range of pH values**.
- **oxidation**
- **photostability** (described in ICH Q1B).

DS impurities evaluation (3.2.S)

- Information on **impurities and their carry-over** should be provided (3.2.S.3.2).
- This includes related substances, residual solvents, elemental impurities, reagents/catalysys/auxiliary materials and those derived from.
- Potential impurities (from the synthesis and degradation products) **should be discussed (control strategy)** and described briefly including an indication of their **origin/step** in which are formed and **fate/purification**. Copies of relevant chromatograms should be provided
- The **mutagenic potential** of impurities should be addressed.
- Possible routes of degradation should also be discussed (3.2.S.7.1).

DS impurities evaluation (3.2.S)

- Individuare dalla sintesi della DS gli Starting Materials (SM), intermedi, solventi/reagenti/catalizzatori
- Verificare se questi vengono adeguatamente controllati a livello degli intermedi (sezione 3.2.S.2.4) o a livello della DS (3.2.S.4.1 "Specification") in accordo all'ICH Q3A/M7/Q3C/Q3D
- Per solventi/reagenti/catalizzatori/SM/intermedi non controllati a livello di opportuno intermedio/DS verificare se l'omissione della specifica è stata adeguatamente discussa/giustificata (es. *Carry over/spiking/purging studies*)

DS impurities evaluation (3.2.S)

- Utilizzare metodi idonei e convalidati
- Stabilire limiti di accettazione appropriati sulla base della Ph.Eur., linee guida, della sicurezza e della *batch analysis*

Alcuni contaminanti sono noti in determinate sostanze (es.: solventi di classe 1 come benzene e tetracloruro di carbonio potenzialmente presenti in diversi solventi)

Alcune impurezze potrebbero venire dal processo di sintesi degli SM

Criticità impurezze sostanza attiva

- Spesso la valutazione del *carry over* di tutte le possibili impurezze da *starting materials* e/o da intermedi di acquisto 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 dei risultati degli studi di stabilità e di *stress test*.

- Non vengono presentati gli studi di stress test a supporto del metodo analitico e delle impurezze di degradazione individuate o non è discusso il bilancio di massa tra l'*assay* e tutte le singole sostanze correlate al fine di dimostrare che il metodo analitico sia "*stability indicating*".

Criticità impurezze sostanza attiva

- Non vengono discusse adeguatamente le potenziali impurezze mutagene rispetto ai possibili alert strutturali, le strategie di controllo e/o i relativi limiti di accettazione, secondo quanto previsto dalla linea guida ICH M7

- I limiti di specifica non sono conformi ai requisiti dell'ICH Q3A, e/o non sempre vengono qualificate tossicologicamente le impurezze quando questi limiti sono superiori al qualification threshold della GL

- I relativi metodi analitici non risultano essere sempre convalidati secondo i requisiti dell'ICH Q2(R1)

Impurities in the Drug Product (ICH Q3B)

Same principles and considerations as for DS:

- Different sources and types (organic, mutagenic, residual solvents, elemental impurities, nitrosamines, **leachables**)
- Evaluate process and materials (including packaging, utilities, risk of cross-contamination)
- Identify, evaluate (toxicological risk), control
- Appropriate acceptance limits
- Suitable and validated analytical methods

Impurities in the Drug Product (ICH Q3B)

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.

ICHQ 3B 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%

DP impurities evaluation (3.2.P)

3.2.P.2.2 "Pharmaceutical development" → Valutare possibili impurezze derivanti da filtri e da confezionamento primario per preparazioni non solide (*extractables/leachables*)

3.2.P.5.1 "Specification" →

1. Comparare con la sezione 3.2.S.3.2 per assicurarsi che almeno le impurezze di degradazione vengano testate e con la 3.2.P.5.5/3.2.P.5.6
2. Valutare limiti Vs ICH Q3B/M7 e confrontare con 3.2.P.5.4 (*batch analysis*) e 3.2.P.7.3 (*stability studies*)

DP impurities evaluation (3.2.P)

3.2.P.5.2 ”Analytical Procedures”, 3.2.P.5.3 ”Validation of Analytical Procedures

3.2.P.5.5 “Characterisation” of impurities” → Confrontare con la sezione "3.2.S.3.2 Impurities“; verificare siano presenti potenziali impurezze derivanti da eccipienti

3.2.P.5.6 "Justification of Specification" → Da valutare vs the ICH Q3B, ICH Q3D e Q&A Nitrosammine

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

Criticità impurezze prodotto finito

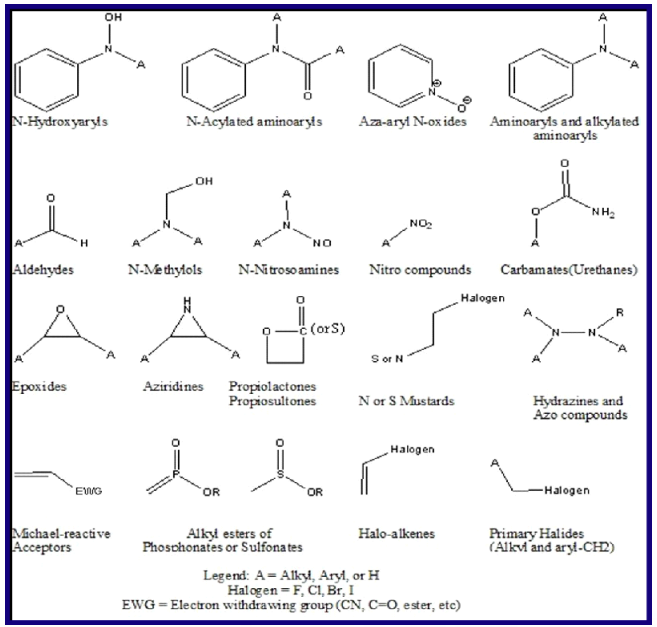
- Non vengono sempre considerate tutte le impurezze di degradazione della sostanza attiva (spesso per carenza di informazioni del modulo 3.2.S e/o per la mancata esecuzione/inclusione degli stress tests studies)
- I limiti di specifica non sono conformi all'ICH Q3B, e/o non sempre vengono qualificate 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*

Criticità impurezze prodotto finito

- Il *risk assessment* relativo al rischio di contaminazione da *elemental impurities* e/o il relativo controllo come da ICH Q3D non risulta sempre adeguato
- La *risk evaluation* relativa al rischio di contaminazione da nitrosammine non risulta sempre adeguata
- Alcune impurezze possono originare solo dall'interazione/reazione dei componenti del prodotto finito (DS, eccipienti, packaging)

Mutagenic Impurities

ICH M7: 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.



Structural alerts:
dedicated databases
and softwares

Mutagenic Impurities ICH M7 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)

Positivo >>> LIMITE SPECIFICO

(LIMITE GENERALE (TTC) o
Test mutagenicità (es. Ames)

Negativo >>> ICH Q3A/Q3B

Mutagenic Impurities

For a known mutagenic carcinogen (**Class 1**), a **compound-specific acceptable intake** can be calculated based on carcinogenic potency and linear extrapolation as a default approach.

TTC-basec Acceptable Intakes (**Classes 2, 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.

Threshold of Toxicological Concern (TTC) concept: an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects. A value of **1.5 µg/day** corresponding to a theoretical 10^{-5} excess lifetime risk of cancer can be justified.

Mutagenic Impurities

Acceptable Intakes in Relation to LTL (**Less-Than-Lifetime**) Exposure:
TTC-based acceptable intake of 1.5 µg/day considered to be protective for a lifetime of daily exposure.

For drugs administered/taken **for less than lifetime:**
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.
Higher daily intake allowed but still maintain comparable risk levels

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

Posology/duration of treatment
>>> identify allowed daily intake

Mutagenic impurities control strategies by ICH M7

Option 1

Controllo a livello dell'API con limite ≤AL (rutinario o periodico)*

Analisi su 3/6 lotti industriali/pilota di API -> risultati inferiori al 30% dell'AL

Option 2

Controllo a livello di SM/RM/intermedio, con limite ≤AL (rutinario)

Check if formation/contamination is not possible downstream

*AL = Acceptable limit based on Maxiumum Daily Dose (MDD) for the substance and its intended use

Mutagenic impurities control strategies by ICH M7

Option 3

Controllo a livello di SM/RM/intermedio, con limite≥AL (rutinario)

Contenuto impurezza ≤ 30% dell'AL nell'API (es. tramite spiking experiments)

Option 4

*Nessun controllo – impurezze molto reattive/facilmente eliminabili dal processo**

purging factor

AL= Acceptable limit
SM=Starting Material
RM=Raw Material

Mutagenic impurities: 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.

Elements of a scientific **risk assessment** can be used to justify an option 4 approach.

The risk assessment can be based on physicochemical properties and process factors that influence the fate and purge of an impurity including **chemical reactivity, solubility, volatility, ionizability and any physical process steps** designed to remove impurities.

The result of this risk assessment might be shown as an **estimated purge factor** for clearance of the impurity by the process (Ref. 11).

Mutagenic impurities: Option 4

For Option 4 approaches where justification based on scientific principles alone is not considered sufficient: **analytical data** to support the control approach is expected.

This could include as appropriate information on the structural changes to the impurity caused by downstream chemistry ("fate"), analytical data on pilot scale batches, and in some cases, laboratory scale studies with intentional addition of the impurity ("**spiking studies**").

Calcolo del purge factor sperimentale!

a) Spiking di impurezza nello sintesi dove è atteso che sia presente/si formi
b) Misura dell'impurezza nell'API finale (o intermedio successivo)

Purge factor= Quantità residua/quantità introdotta (spiking + quantità già presente)

Residual solvents: ICH Q3C classification

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.

- **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: ICH Q3C class 1

ICH Q3C: Solvents in Class 1 should **not be employed** in the manufacture!

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

→ Based on 10 g of product daily intake

Annex 1 - ICH Q3C (CPMP/ICH/283/95):

- Class 1 solvents used as a starting materials (**very exceptional!**)

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 solvent**.

Residual solvents: ICH Q3C control strategy

- Class 1 solvents present as an impurity -> Control strategies

Annex 1 to ICH Q3C: 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 class 2

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

Based on 10 g of product daily intake

Class 2 Solvents

Residual solvents: ICH Q3C class 2

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

Annexes to ICH Q3C (CPMP/ICH/283/95):

- 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 class 3

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]

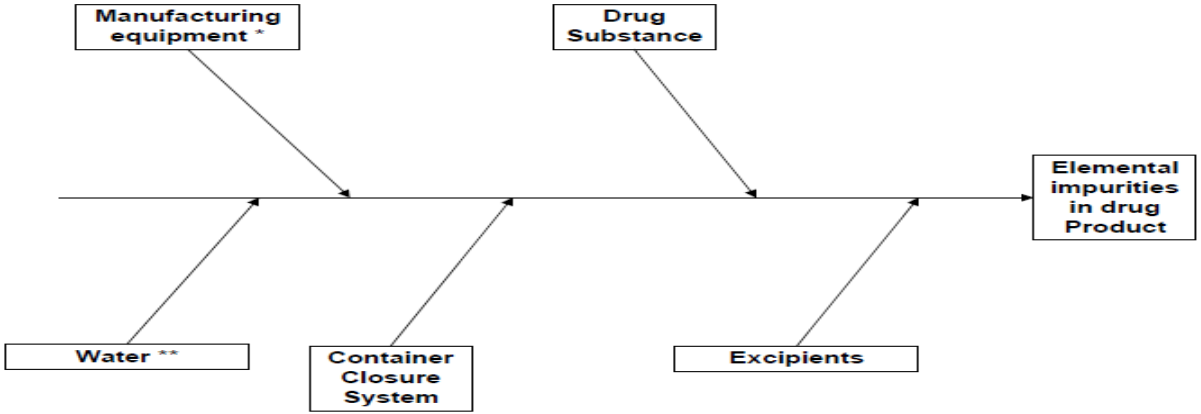
Residual solvents: ICH Q3C class 3

It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5% based on 10 g of product daily intake) 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%)

Elemental impurities (ICH Q3D)

- Focused on contamination in the whole drug product
- PDE for 24 elements (for oral, parenteral, inhalation routes of administration)
- Cutaneous and transcutaneous route has a dedicated Appendix (limited absorption; local toxicity; sensitization to certain elements: Ni and Co)
- **Risk Assessment**



Elemental impurities: ICH Q3D classification

Class 1 – Significant human toxicants
- Elements with significant human toxicity and limited or no use in pharmaceutical manufacturing.
- Due to their potential presence in many materials, should be considered in all product assessments.

Class 2 - Route dependent toxicants

Class 2a:
- Relatively high probability of occurrence in the drug product
- Require assessment across all potential sources and routes

Class 2b
- Reduced probability of occurrence
- Can be excluded from assessment unless they are intentionally added in components used in the manufacture of drug products

Class 3
- Low toxicities by the oral route
- May need to be included in the assessments for parenteral and inhalation routes

La Linea Guida ICH Q3D suddivide gli elementi in classi in base alla loro tossicità (PDE) ed alla probabilità che siano presenti nel prodotto medicinale.

Elemental impurities: ICH Q3D classification

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

Elements to be considered in the Risk Assessment:

Elemental impurities: ICH Q3D classification

Appendix 2: established PDEs for elemental impurities

Table A.2.1: permitted daily exposures for elemental impurities[1]

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	3
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	6
Tl	2B	8	8	8
Au	2B	300	300	3
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	15	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

PDE (µg/day): toxicological assessment in ICH Q3D appendixes

Elemental impurities: Risk Assessment

Il processo su cui basare il **risk assessment (RA)** è costituito dai seguenti step:

1. **Identificare** le fonti delle impurezze elementali;

2. **Valutare** la presenza di ogni specifica impurezza elementale nel prodotto finito determinandone i livelli osservati e confrontandoli con il PDE stabilito;

3. **Riassumere e documentare** il risk assessment. Identificare se i controlli in essere sono sufficienti o identificare ulteriori controlli finalizzati a limitare le impurezze elementali nel prodotto finito (es. attraverso la presentazione delle relative variazioni).
   - modifiche degli step del processo di produzione allo scopo di ridurre le impurezze sotto la soglia di controllo;
   - implementazione di controlli in process;
   - introduzione di limiti di specifica per eccipienti e materiali (es. intermedi di sintesi), principio attivo o prodotto finito;
   - scelta di contenitori adeguati (o equipment qualificato).

Elemental impurities: ICH Q3D Control Strategy

•**Option 1**: Applicable when the daily dose is below 10 grams. The assessment considers a control threshold of 30% of the established PDE. If the estimated concentration (micrograms per gram = ppm) of **each individual product component** falls below this **default concentration limit**, no further action is needed.

•**Option 2a**: Applied when the daily dose exceeds 10 grams. This option establishes a fixed maximum **concentration** (micrograms per gram = ppm) for **each individual product component** t based on the actual daily intake.

•**Option 2b**: This option considers the **total daily intake (**μg/day**)** of each elemental impuritty in **each individual product component** and comparison **against PDE** (μg/day).

•**Option 3**: Direct measurement of total conent of each elemental impurity **in the final product** and comparison against the respective PDE (μg/day) or conversion to concentration (micrograms per gram = ppm) .

Elemental impurities: ICH Q3D Control Strategy

Qualora sia previsto dal RA che il livello totale della singola impurezza elementale proveniente da tutte le fonti nel prodotto finito è inferiore al 30% del PDE in maniera riproducibile, non sono richiesti ulteriori controlli.

Qualora dal RA non si possa dimostrare che il livello della singola impurezza è inferiore alla soglia di controllo, allora dovranno essere stabiliti ulteriori controlli/azioni per assicurare che il livello dell'impurezza elementale non superi il PDE nel prodotto finito.

Il livello e la variabilità di un'elemental impurity possono essere stabiliti fornendo i dati su almeno 3 lotti industriali o 6 lotti pilota dei singoli componenti/del prodotto finito.

Il Summary del Risk Assessment è normalmente riportato nel paragrafo relativo alla caratterizzazione delle impurezze del prodotto finito -> Sez. 3.2.P.5.5

Nitrosamines

- Le **N-Nitrosamine** sono molecole contenenti il gruppo funzionale N-Nitroso (NO legato ad azoto). Si tratta di inquinanti ambientali ubiquitari presenti a livelli di concentrazione generalmente bassi (da ppm a ppb).

- Nel 1956 è stata osservata per la prima volta la carcinogenicità di NDMA (N-dimethylamine)in un gran numero di specie animali.

- Molte nitrosamine si ritiene che siano mutagene e cancerogene con forti differenze tra le diverse classi.

- Lo IARC ha classificato quelle per le quali si dispongono di dati su animali nelle classi 2A, «*probably carcinogenic*» e 2B «*possibly carcinogenic*»

Nitrosamines in sartan medicines

In June 2018, a manufacturer detected *N*-nitrosodimethylamine (NDMA) in valsartan active substance batches.

Nitrosamines contamination (NDMA e NDEA) was found in other Sartans (e.g. Losartan, Irbesartan, etc.).

On 31 January 2019, EMA recommended that companies making sartan medicines review their manufacturing processes so that they do not produce nitrosamine impurities.

Companies have been requested to demonstrate that their products have no quantifiable levels of these imp. before they can be used in the EU.

Nitrosamines in other medicines

On 10 September 2019, a referral according to Article 5(3) of Regulation (EC) No 726/2004 was triggered by the EMA Executive Director (ED) requesting the CHMP to conduct a scientific evaluation on the presence of nitrosamine impurities in human medicines containing chemically synthesised active pharmaceutical ingredients (APIs)

As a result of the first phase of the referral, a "call for review" to MAHs was launched on 19 September 2019 requesting MAHs for human medicines containing chemically synthesised APIs to review their medicines for the possible presence of N-nitrosamines, to test all products at risk and to introduce changes to the marketing authorisations (MAs) within 3 years.

The "Call for review" to MAHs

The call for review consists of **3 steps** (visit dedicated HMA page):

- **Step 1:** MAHs to **perform a risk evaluation** to identify if APIs and/or FPs could be at risk of presence of nitrosamine;

- **Step 2**: if a risk is identified, MAHs to proceed with **confirmatory testing** in order to confirm or refute the presence of nitrosamines. MAHs should report outcomes as soon as possible;

- **Step 3:** if the presence of nitrosamine(s) is confirmed, MAHs should implement effective **risk mitigating measures** and **update MA dossier** through submission of variation.

"Call for review" deadlines

Submission of step 1 outcome:

For product containing:

Chemically synthesised APIs -> latest by 31st March 2021.

Biological APIs -> latest by 01st July 2021.

Submission of step 2 outcome:

Chemically synthesised APIs -> latest by 26th September 2022.

Biological APIs -> latest by 01st July 2023.

Submission of any changes required to MA (Step 3):

Chemically synthesised APIs -> latest by 01st October 2023.

Biological APIs -> latest by 01st July 2023.

Nitrosamines guidance documents

Assessment report for Article 5(3) EMA's CHMP opinion on referral on nitrosamine impurities

- Detailed scientific discussion on quality and toxicological aspects
- Established limits for certain common N-nitrosamines

Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products

- Frequently updated
- Appendix 1 : Acceptable intakes established for N-nitrosamines (living list)
- Appendix 2 : Carcinogenic Potency Categorisation Approach for N-nitrosamines
- Appendix 3 : Enhanced Ames Test Conditions for N-nitrosamines

Nitrosamines guidance documents

- **Q&A n. 4: What are the currently identified risk factors for presence of nitrosamines?**
- **Q&A n. 7: How should the risk evaluation be performed?**
- Q&A n. 8: How should confirmatory tests be conducted by MAHs and manufacturers?
- Q&A n. 9: What are the requirements of the analytical method(s)?
- **Q&A n. 10: Which limits apply for nitrosamines in medicinal products?**
- Q&A n. 12: Which are the measures to mitigate the risk of presence of nitrosamines?
- Q&A n. 13: Which changes would be required for Marketing Authorisations?
- Q&A n. 14: What is the approach for new and ongoing marketing authorisation applications (MAA)?
- **Q&A n. 15: When should a test for nitrosamines be included in the MA dossier?**
- **Q&A n. 20/21/22: Steps taken when nitrosamines are identified above AI**
- Annex 1: Decision tree with control options for products containing multiple N-nitrosamines

Take home messages

- Impurities are a **very critical aspect** of medicinal products
- Issues related to impurities can be a PSRPR (Potential Serious Risk to Public Health) leading to refusal of Marketing Authorisations or market recalls
- Impurities come from different sources and are of different nature
- Require thorough process and product understanding
- **Lifecycle management** (change in suppliers, process, control strategy)

- **Identify, quantify, evaluate, control, document**

Special thanks to Luca Ginnari (AIFA)

Thank you ALL

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