AGENZIA ITALIANA DEL FARMACO

Controllo delle impurezze in DS e DP

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21/03/2025

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

Impurities: ICH Guidelines

Specifiche linee guida trattano il tema delle impurezze di sintesi e di degradazione, stabilendo i limiti di queste sulla base della dose massima 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

----------Altre linee guida correllate----------

- ICH Q6A -> Specifications
- ICH Q2(R2) Guideline on validation of analytical procedures
- ICH Q1(R2) -> Stability testing of new drug substances and products

Inoltre -> monografie Eur. Ph., metodiche analitiche Eur. Ph.

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:

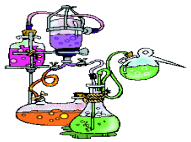
"Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product."

Classification of Impurities

- Organic impurities
  - Non mutagene -> ref. ICH Q3A (DS), ICHQ3B (DP)
  - Mutagene -> ref. 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. ICH Q3A, ICH Q3B, ICH Q3D

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.

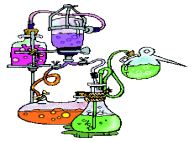
- Residual solvents -> ref. ICHQ 3C and related annexes

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

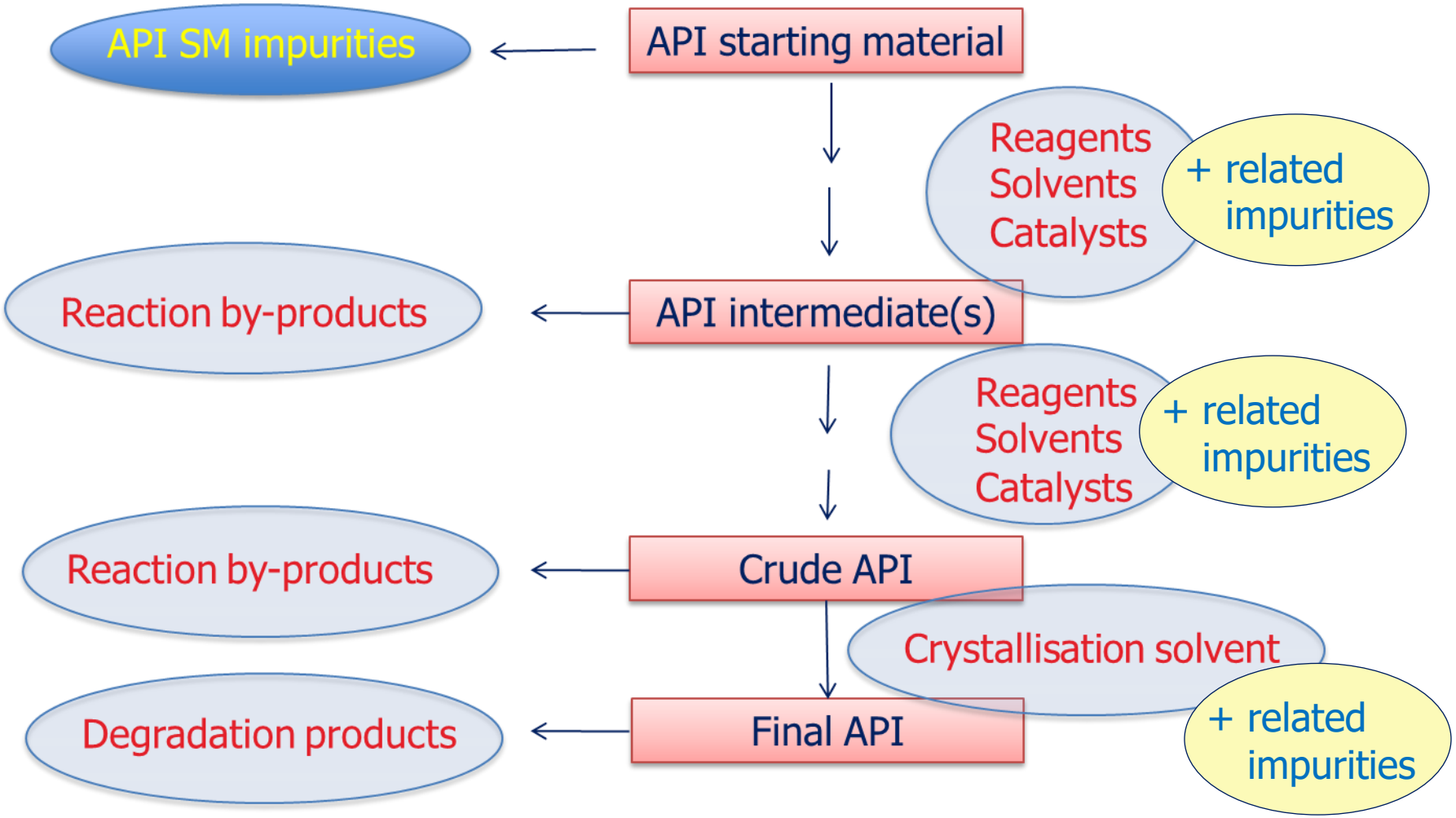
Degradation impurities + process impurities



- Residual Solvents

- Inorganic Impurities

Potential impurities in API Synthesis



Potential impurities in Drug Substance

- Eventuali residui di starting materials (SM) non rimossi dal processo
- Eventuali residui di solventi e reagenti non rimossi dal processo
- Impurezze presenti negli starting materials (SM), reagenti e solventi
- Prodotti collaterali di processo
- Prodotti di degradazione
- Prodotti derivanti dall'interazione con materiali di confezionamento
- Prodotti di 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

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

Aspetti GMP

Potential impurities in Drug Substance

Altri aspetti GMP che possono impattare il profilo di impurezze

- Produzioni a campagna (senza effettuare bonifiche intracampagna delle apparecchiature tra un lotto e il successivo)

- Reintroduzione di materiali recuperati (es. solventi o DS/intermedi recuperati da acque madri di processo) il cui processo di recupero e/o la relativa gestione non risulta adeguata

- Utilizzo (e riutilizzo) di materiali ausiliari di produzione che vanno a contatto con il prodotto che possono alterare il profilo di impurezze della DS (es. resine utilizzate nella separazione cromatografiche, materiali plastici teli centrifughe/presso filtri, teli in PE utilizzati negli essiccatori statici, etc.)

ICH Q3A 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

Soglia minima di reporting delle impurezze non-note

Limite impurezze non-note, superato il quale devo caratterizzare strutturalmente l'impurezza -> «impurezza nota»

Limite impurezze note, superato il quale devo qualificare tossicologcamente l'impurezza

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 (R2)

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

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.

CPMP/QWP/122/02, rev 1 corr "Stability testing of existing active substances and related finished products"

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures.

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

Impurities evaluation

3.2.S.2.2 "Description of Manuf. Process and Process Controls" (ASMF RP)

Individuare dalla flowchart di sintesi SM, intermedi/solventi/reagenti/catalizzatori e 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")

↓

Per solventi/reagenti/catalizzatori/SM/intermedi non controllati a livello di opportuno intermedio/API verificare se l'omissione della specifica è stata adeguatamente discussa/giustificata (es. Carry over/spiking/purging studies)

Dossier - Module 3.2.S

Impurities evaluation

3.2.S.2.3 "Control of Materials" (ASMF RP)

Visionare le specifiche di SM (Vs SM flowchart) solventi/catalizzatori per individuare potenziali impurezze in SM/solventi/reagenti/catalizzatori

Alcuni contaminanti sono noti (es. Solventi di classe 1 come benzene e tetracloruro di carbonio potenzialmente presenti in diversi solventi – vedi dopo)

↓

Verificare se tali impurezze vengono adeguatamente controllati a livello di SM intermedi (3.2.S.2.4) o a livello della DS (3.2.S.4.1 "Specification")

↓

Per impurezze potenzialmente presenti in SM/solventi/reagenti/catalizzatori non controllati in intermedi/API verificare se l'omissione della specifica è stata adeguatamente discussa/giustificata (es. Carry over/spiking/purging studies)

Dossier - Module 3.2.S

Impurities evaluation

3.2.S.3.2 "Impurities"

Verificare la completezza delle impurezze riportate rispetto a:

- verifiche sezioni precedenti (3.2.S.2.2, 3.2.S.2.3, 3.2.S.2.4 - RP);
- monografie E.P. (o USP) se disponibili;
- impurezze specifiche riportate in letteratura per l'API in questione o in ICH M7 o Annex Q&A su nitrosamine;
- verifiche incrociate con software specifici;
- verifiche incrociate con la sezione 3.2.S.7.1 (stress test studies) per la determinazione delle impurezze di degrdazione

Dossier - Module 3.2.S.

Impurities evaluation

3.2.S.4. "Control of the Active Substance" (ASMF AP)

Valutare se tutte le possibili impurezze sono controllate in accordo all'ICH Q3A/Q3C/M7 (e se le eventuali omissioni sono giustificate – vedere confronti con sezioni precedenti)

Verificare adeguatezza limiti selezionati Vs all'ICH Q3A/Q3C/M7 (considerando, ove necessario, la dose massima giornaliera prevista per l'API) da confrontare con batch analysis (3.2.S.4.4) e dati di stabilità (3.2.S.7.3) e relative giustificazioni (3.2.S.4.5)

Verificare metodi analitici utilizzati (3.2.S.4.2) relative convalide (3.2.S.4.3)

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 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 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 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 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.

degradation impurities

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%

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

Dossier - Module 3.2.P

Impurities evaluation

3.2.P.2.2 "Pharmaceutical development" → Valutare possibili impurezze derivanti dal confezionamento primario (per soluzioni)

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 e 3.2.P.7.3

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

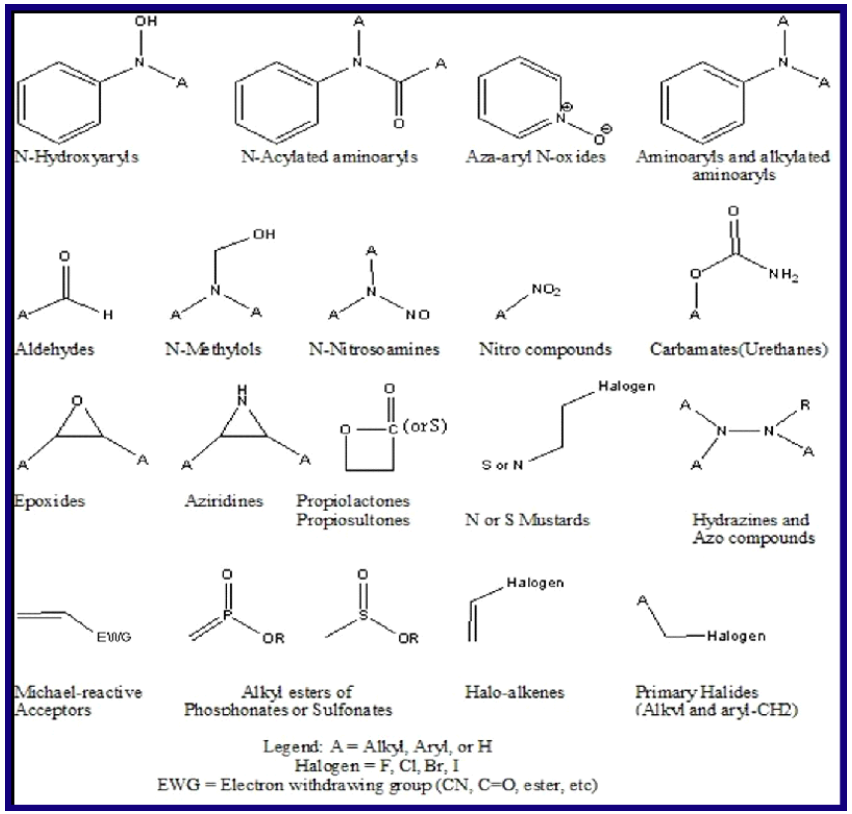
Controllo delle Impurezze nel prodotto finito

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 3.2.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
- 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

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.



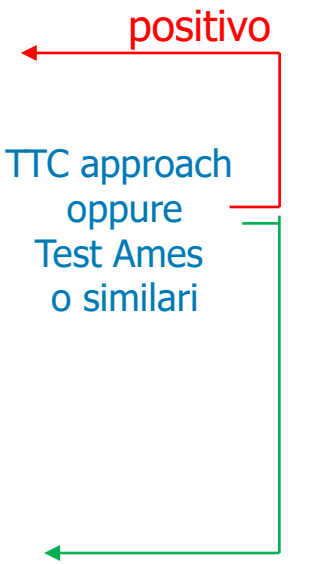
Structural alerts

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)



ICH Q3A/Q3B

Mutagenic Impurities

Acceptable intake

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.

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

Acceptable intake

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

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)

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

Control strategies by ICH M7 – Option4

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

Control strategies by ICH M7 – Option4

Calcolo teorico del purging factor

(Ref. 11*) Teasdale A, Elder D, Chang S-J, Wang S, Thompson R, Benz N, Sanchez Flores I. Risk assessment of genotoxic impurities in new chemical entities: strategies to demonstrate control. Org Process Res Dev 2013;17:221-230.

Table 2. Purge factors

physicochemical parameters	purge factor[a]
reactivity	highly reactive = 100
	moderately reactive = 10
	low reactivity/unreactive = 1
solubility[b]	freely soluble = 10
	moderately soluble = 3
	sparingly soluble = 1
volatility[c]	boiling point >20 °C below that of the reaction/process solvent = 10
	boiling point within ±10 °C of that of the reaction/process solvent. = 3
	boiling point >20 °C above that of the reaction/process solvent = 1
ionisability	ionisation potential of GTI significantly different from that of the desired product[d]
physical processes: chromatography	chromatography: 10−100 based on extent of separation
physical processes: e.g. other scavenger resins	evaluated on an individual basis.

[a]Purge factor = concentration before purging/concentration after purging. [b]This relates to solubility within the context of a recrystallisation process whereby the impurity in question, if highly soluble, will remain within the mother liquors and hence be purged from the desired product. [c]This refers to the deliberate removal of a solvent through solvent distillation or solvent exchange. [d]This relates to a deliberate attempt to partition the desired product/GI between an aqueous and organic layer, typically achieved through the manipulation of pH to change the ionised/un-ionised state of one of the components.

Mutagenic impurities

Control strategies by ICH M7 – Option4

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").

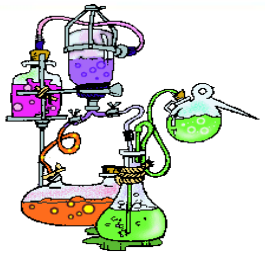
↓ Calcolo del purge factor sperimentale!

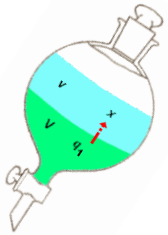
a) Spiking di impurezza nello sintesi dove è atteso che sia presente/si formi
b) Misura dell'impurezza nell'API finale (o intermedio successivo)

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

Residual solvents

ICH Q3C:





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 classification

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

Annex 1 - 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

- 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 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.

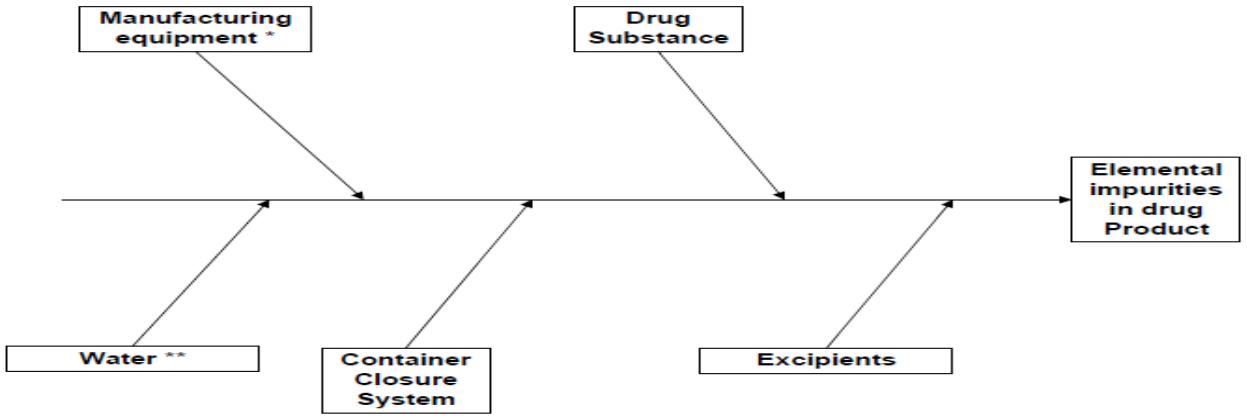
Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl 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 Assessmen



Elemental impurities 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:

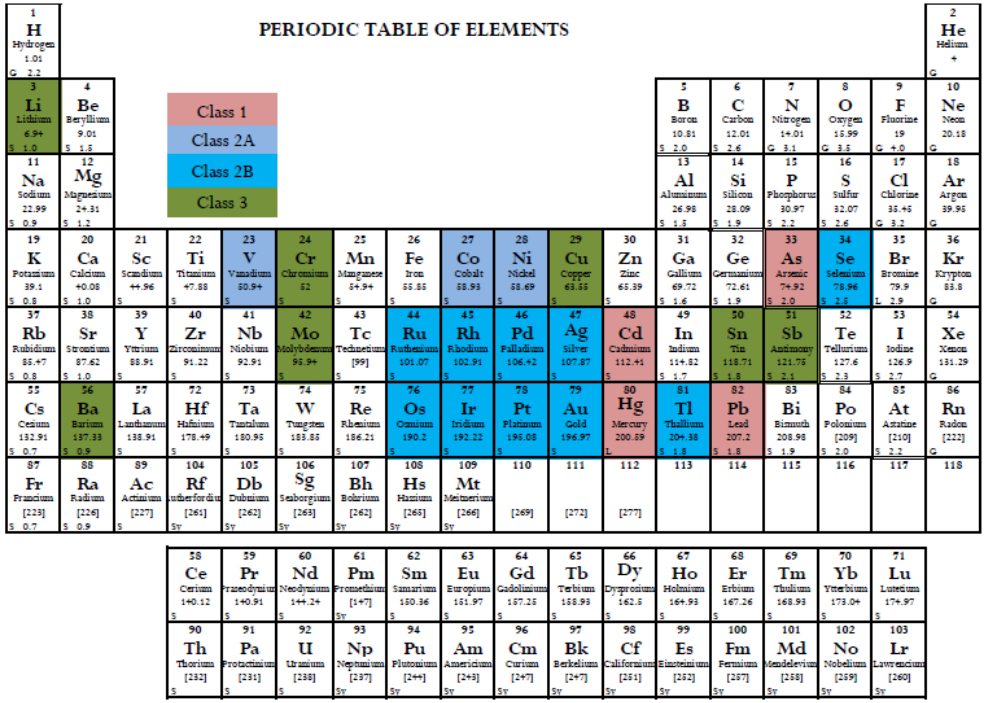
- Relatively high probability of occurrence in the drug product
- Require assessment across all potential sources and routes

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 3 classi in base alla loro tossicità (PDE) ed alla probabilità che siano presenti nel prodotto medicinale.

Elemental impurities 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

RA control of elemental impurities

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

1. Identificare le fonti delle impurezze elementali;

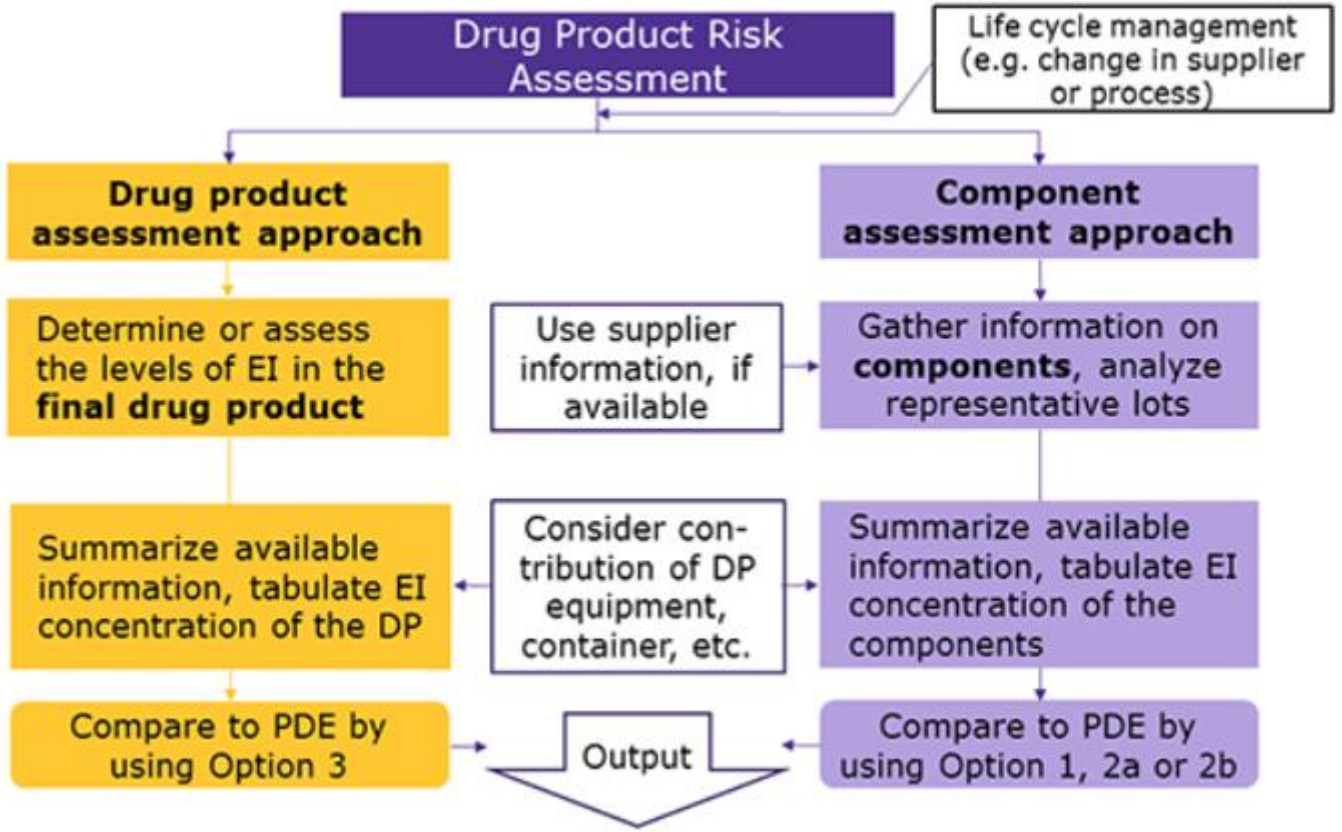
2. Valutare la presenza di ogni specifica impurezza elementale nel prodotto finito determinandone i livelli osservati e confrontandoli con il PDE stabilito;

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.

RA and control of elemental impurities

La Linea Guida descrive quattro opzioni accettabili per stabilire le concentrazioni delle impurezze elementali nel prodotto finito o nei singoli componenti, allo scopo di assicurare che il prodotto finito non ecceda il PDE.



RA and control of elemental impurities

The ICH Q3D offers four options for assessing the risk of elemental impurities:

•**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 of all elements falls below this threshold, no further action is needed.

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

•**Option 2b**: This option considers the concentration of elemental impurities in each individual product component.

•**Option 3**: Direct measurement of elemental impurity concentration in the final product.

RA and control of elemental impurities

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, non saranno richiesti ulteriori controlli.

Soglia di controllo

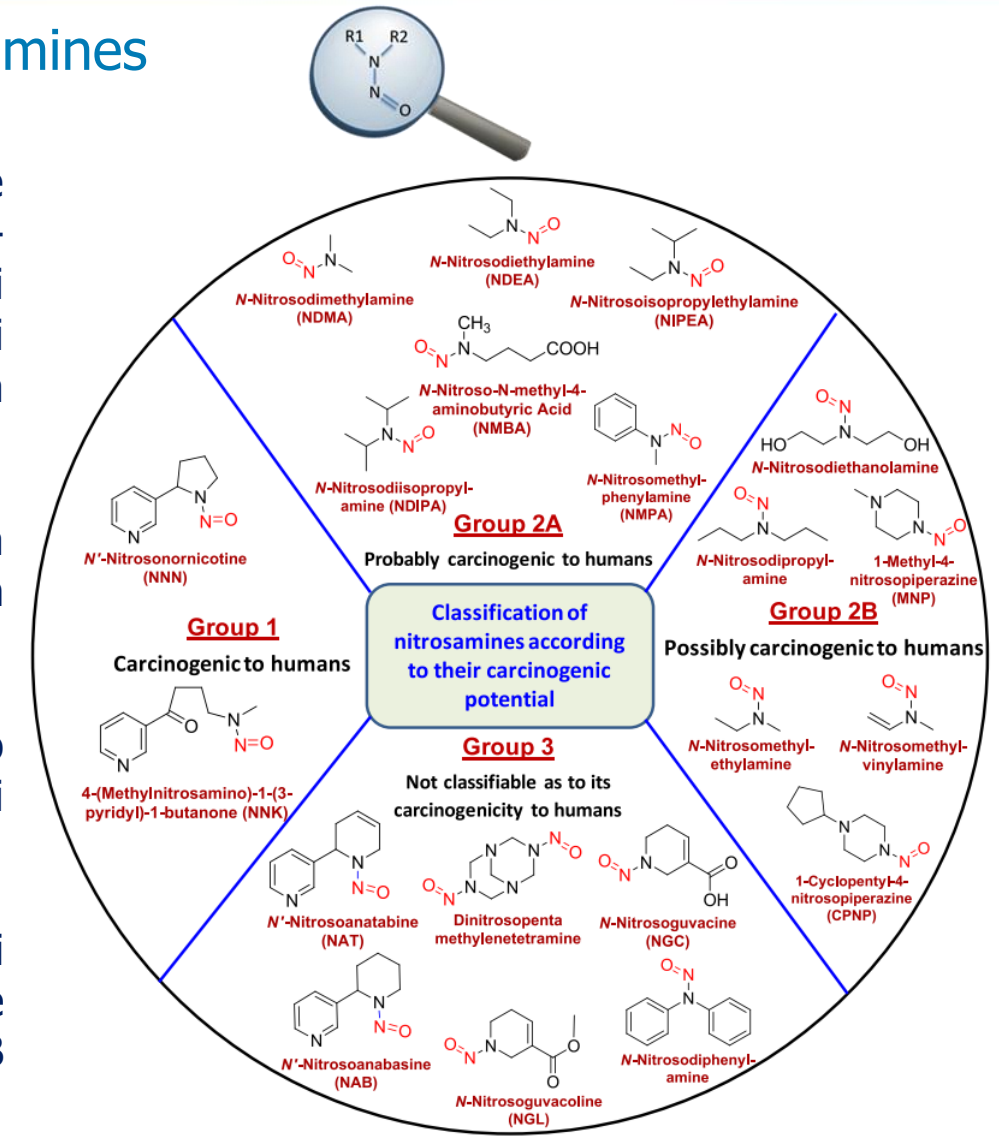
Qualora dal RA non si possa dimostrare che il livello della singola impurezza è inferiore alla soglia di controllo, allora dovranno essere stabiliti ulteriori controlli/azioni per assicurare che il livello dell'impurezza elementale non superi il PDE nel prodotto finito.

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 deve essere riportato nel paragrafo relativo alla Giustificazione delle Specifiche del prodotto finito -> Sez. 3.2.P.5.6

Nitrosamines

- Le N-Nitrosamine sono molecole contenenti il gruppo funzionale N-Nitroso. 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 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»

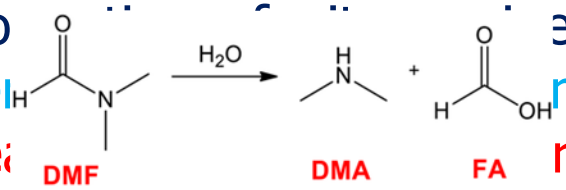


J. Med. Chem. 2021, 64, 2923−2936

Nitrosamines formation

Potential sources of sec./tert. ammines:

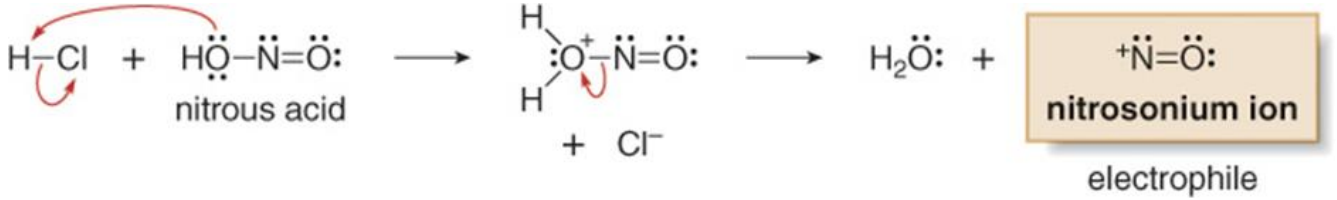
e.g. Ammides (eg. DMF, DMA)



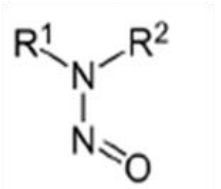
Fo es is possible in the presence of secondary, tel mmonium salts and nitrite salts under acidic rea rally pH≤3).

Other potential nitrosant agents:

Nitrogen Oxides (eg. N_2O_3, N_2O_4)
Alkyl Nitrites
Hydrazines in oxidating conditions
Nitrosonium salts
Nitroso halides



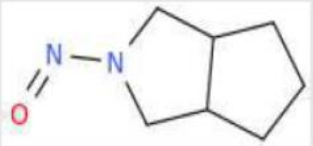
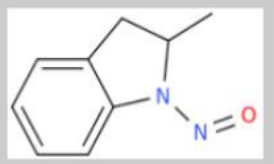
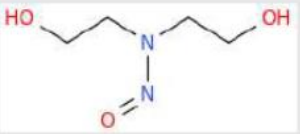
Diazonium salts ← + primary amines



← + sec./tert. amines

Nitrosamines

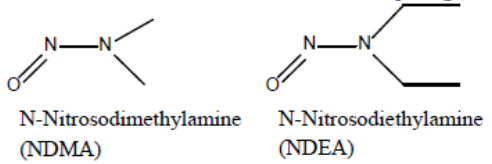
Nitrosamines in medicines…before the Valsartan "case"

API	Impurezza	Limiti	Struttura
Clopamide	cis-2,6-dimethyl-1-nitrosopiperidine	Absent (from risk assessment)	
Gliclazide	2-nitroso-octahydrocyclopenta [c] pyrrole (impurity B)	2 ppm	
Indapamide	(2RS)-2-methyl-1-nitroso-2,3-dihydro-1H-indole (impurity A)	5 ppm	
Trolamine (Triethanol amine)	N-nitrosodiethanolamine (impurity C)	24 ppb	

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.).



N-Nitrosodimethylamine (NDMA)

N-Nitrosodiethylamine (NDEA)

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

These recommendations follow EMA's review of NDMA and N-NDEA, which are classified as probable human carcinogens (substances that could cause cancer)

Companies had a transition period to make any necessary changes, during which strict temporary limits on levels of these impurities would have been applied.

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

CHMP's Article 5(3) referral on nitrosamine impurities

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2019
EMA/189634/2019
OBSOLETE PLESE REFER TO CHMP ASSESSMENT REPORT OF ARTICLE 5 (3) REFERRAL ON NITROSAMINES IMPURITIES IN HUMAN MEDICINAL PRODUCTS AND RELATED GUIDANCE

Information on nitrosamines for marketing authorisation holders

Request to evaluate the risk of the presence of nitrosamine impurities in human medicinal products containing chemically synthesised active pharmaceutical ingredients

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

27th March 2020
EMA/CHMP/428592/2019 Rev. 3
OBSOLETE PLESE REFER TO CHMP ASSESSMENT REPORT OF ARTICLE 5 (3) REFERRAL ON NITROSAMINES IMPURITIES IN HUMAN MEDICINAL PRODUCTS AND RELATED GUIDANCE

Questions and answers on "Information on nitrosamines for marketing authorisation holders"

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

19 July 2024
EMA/409815/2020 Rev.21

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

Q&A for MAHs/Applicants: Q2

Q2. What is the 'call for review'?

The call for review consists of 3 steps:

- 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 through submission of variation.

Q&A for MAHs/Applicants: Q3

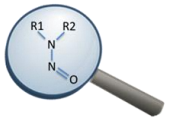
For the 'call for review' for chemically synthesised and biological medicinal products, when and how should MAHs report steps 1 and 2 to competent authorities?

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.

Q&A for MAHs/Applicants: Q4

What are the currently identified root causes for presence of nitrosamines?

Classification of the root causes

Risk factors

- Manufacture of the active substance (AS)
  - AS Manufacturing process/syntesis
  - Solvents, catalyst, reagents
  - Carry-over from raw materials
- Finished product
  - Storage
  - FP manufacturing process
  - Excipients
  - Packaging materials - Inks
- GMP aspects
  - Poor-controlled processes
  - Cross-contamination
  - Recovered/recycled solvents/materials

Q&A for MAHs/Applicants: Q8

Q8 How should confirmatory tests be conducted by MAHs and manufacturers?

For the purpose of confirmatory testing as part of step 2 of the call for review to MAHs, testing should generally be carried out on the FP.

FP testing →

However, some root causes may only be linked to the API manufacturing process (see Q&A 4). In these cases, testing of the API or intermediates upstream of the active substance could be used as a surrogate for testing the finished product, provided that the risk assessment performed on the FP concluded no additional risk factors for formation of nitrosamine impurities in the finished product (see Q&A 4, risk factors related to the finished product).

API/ intermediates testing →

In any case, if the control point of nitrosamines is not in the finished product, the responsibility for quality lies with the MAH.

Q&A for MAHs/Applicants: Q8

How should confirmatory tests be conducted by MAHs and manufacturers?

The number of batches to be tested should be commensurate with the risk. MAHs and manufacturers should test a representative number of batches of FP and the relevant SM, intermediates, API or raw materials as applicable.

- If the source of risk has been identified and is well understood (e.g. by spike and purge studies) such that impurity levels are expected to be consistent from batch to batch, testing should be conducted on 10% of annual batches, or 3 per year, whichever is highest. This includes testing not only of newly produced batches but also retained samples of batches still within expiry date.

- If fewer than 3 batches are manufactured annually, then all batches should be tested.

If multiple manufacturers, manufacturing processes and/or sources of at-risk raw materials are used, then testing of additional batches would be necessary to cover these risk factors.

If a product is available in multiple strengths of the same dosage form with the same risk factors applicable to each, then testing could be rationalised by testing only the worst-case scenario strength.

The worst-case approach should be justified by the MAH on a case by case basis.

Q&A for MAHs/Applicants: Q9

What are the requirements of the analytical method(s)?

The analytical methods need to be sufficiently sensitive in order to adequately detect and quantify trace levels of nitrosamine impurities.

nitrosamines quantity ($10^{-6} \div 10^{-9}$)

- The limit of quantification (LoQ) provides the minimum level at which an analyte can be quantified with acceptable accuracy and precision and should thus be used for impurity testing and decision-making;

If quantitative testing is performed:

1. as a routine control -> LoQ ≤ of the acceptable limit (AL)*;
2. to justify skip testing -> LoQ ≤ 30% of the AL;
3. to justify omission of specification -> LoQ ≤ 10% of the AL.

*The AL should be based on the relevant acceptable intake (AI) for the respective nitrosamine impurity

Q&A for MAHs/Applicants: Q10

Which limits apply for nitrosamines in medicinal products? (1/2)

Establishment of the AIs

Two scenarios are foreseen for detection of new nitrosamines:

A. If N-nitrosamines are identified with sufficient substance specific animal carcinogenicity data, the TD50 should be calculated and used to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R2) guideline.

B. If N-nitrosamines are identified without sufficient substance specific data to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R2) guideline,

   1. The Carcinogenic Potency Categorization Approach (CPCA) for N-nitrosamines (Appendix 2) should be used to establish the AI, unless other robust data are available that would override this AI.

   2. A negative result in an GLP-compliant enhanced Ames test (EAT, Appendix 3) allows control of the N-nitrosamine at 1.5 µg/day. For substances testing positive, the AI should be established using options 1 or 3. For reporting requirements see Q&A 3 above.

   3. If a surrogate nitrosamine is available with sufficiently robust carcinogenicity data, the TD50 from the surrogate substance can serve as a point of departure for derivation of AI by SAR and read across.

   4. A negative result in a relevant well-conducted in vivo mutagenicity study can allow control of the N-nitrosamine as a non-mutagenic impurity (NMI), i.e. according to ICH Q3A(R2) and ICH Q3B(R2) limits, irrespective of the limit calculated through option 1, 2 or 3. For substances testing positive, the AI should be established using options 1 or 3. For reporting requirements see Q&A 3 above.

Q&A for MAHs/Applicants: Q10

Which limits apply for nitrosamines in medicinal products? (2/2)

Appendix 1 lists the nitrosamines for which acceptable intakes have been established by the Non-clinical Working Party. If the nitrosamine is not included in Appendix 1, MAH/MA applicants can also refer to a CPCA category from another source e.g. CPCA categories published by other regulatory authorities, but this will need confirmation to allow control of the substance at the level corresponding to that category.

Come calcolare il limite di accettazione in ppm

Calculation of the limit when a single known nitrosamine is identified

The conversion to a specification limit in ppm for a particular medicinal product is calculated by dividing the respective AI in Appendix 1 (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC.

Q&A for MAHs/Applicants: Q12

Which are the measures to mitigate the risk of presence of nitrosamines ?

The presence of N-nitrosamines in the FP shall be mitigated and shall be at or below the limit.

MAHs shall design or adapt the manufacturing process of their FPs to prevent formation of and contamination with nitrosamines.

Some examples:

- Changes in manufacturing process,
- Changes in SM/raw material/excipients quality,
- Changes in suppliers of raw materials/starting materials/excipients;
- Segregating some production steps in dedicated equipment (in order to avoid cross contamination),
- Avoiding the use of recycled/recovered materials;
- Changes in packaging systems/materials;
- Changes in formulation;
- Changes in storage conditions of DS/DP.

Q&A for MAHs/Applicants: Q14

What is the approach for new and ongoing marketing authorisation applications (MAA)?

At the submission stage:

Step 1

The risk evaluation should be submitted as an attachment to Module 1 with a corresponding reference in Module 3.2 of the MA dossier.
To supplement the detailed risk evaluation, the template located on the CMDh nitrosamine website could also be submitted: https://www.hma.eu/human-medicines/cmdh/advice-from-cmdh/nitrosamine-impurities.html.

The template is optional for CAPs. For NAPs, and DCPs, the template is mandatory and the CMDh practical guidance located in the same section of the same website should be followed.

Step 2

If a risk of presence of nitrosamines in the medicinal product is identified, applicants are required to provide the risk assessment outlining the impact on the benefit-risk balance of the product and a risk mitigation strategy. Applicants should also submit confirmatory testing plans or confirmatory testing data as mentioned in step 2 (see Q&A 2).

Q&A for MAHs/Applicants: Q14

What is the approach for new and ongoing marketing authorisation applications (MAA)?

May 2022
CMDh/439/2022

Risk evaluation CMDH template

Currently identified risk factors for presence of nitrosamines (Q4 of EMA/409815/2020)		Evaluated? (Yes / No)						Reference to annexed background documents
		DS manuf. 1	DS manuf. 2	DS manuf. …	DP manuf. 1	DP manuf. 2	DP manuf. …	
	Risk factors related to the manufacture of the active substance:							
1	Use of nitrite salts and esters (e.g. $NaNO_2$, alkyl nitrites), or other nitrosating agents (e.g. nitroso halides, nitrosonium salts, nitrogen oxides, nitro alkanes, halogenated nitro alkanes, Fremy's salt, nitroso sulfonamides), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process. Sources for secondary or tertiary amines can also be starting materials, intermediates, reagents, solvents (e.g. DMF, DMAc and NMP) and catalysts, which contain amine functionality, amine impurities (e.g. quaternary ammonium salts) or which are susceptible to degradation to reveal amines.				NA	NA	NA	
2	Nitrite formation by oxidation of hydroxylamine or nitrite release from nitro-aromatic precursors (e.g. by fluoro de-nitration), in the presence of secondary or tertiary amines within the same or different steps of the manufacturing process (see 1).				NA	NA	NA	
3	Use of disinfected water (chlorination, chloro-amination, ozonisation) in the presence secondary or tertiary amines within the same or different steps of the manufacturing process (see 1).				NA	NA	NA	
4	Oxidation of hydrazines, hydrazides and hydrazones by hypochlorite, air, oxygen, ozone and peroxides in the manufacturing				NA	NA	NA	

Q&A for MAHs/Applicants: Q14

What is the approach for new and ongoing marketing authorisation applications (MAA)?

For new and on-going marketing authorisation applications, the number of batches to be tested as part of any confirmatory testing should be commensurate with the risk in line with ICH M7(R1) guideline.

The source of risk has to be well understood (e.g. by spike and purge studies) such that impurity levels are expected to be consistent from batch to batch. Test results from a minimum of 6 pilot scale batches or 3 production scale batches may be sufficient. Depending on the risk factors for nitrosamine presence, e.g. with risk factors being closer to the FP, more batches may need to be tested.

If multiple manufacturers, manufacturing processes and/or sources of at-risk raw materials are used, then testing of additional batches would be necessary to cover these risk factors.

Q&A for MAHs/Applicants: Q15

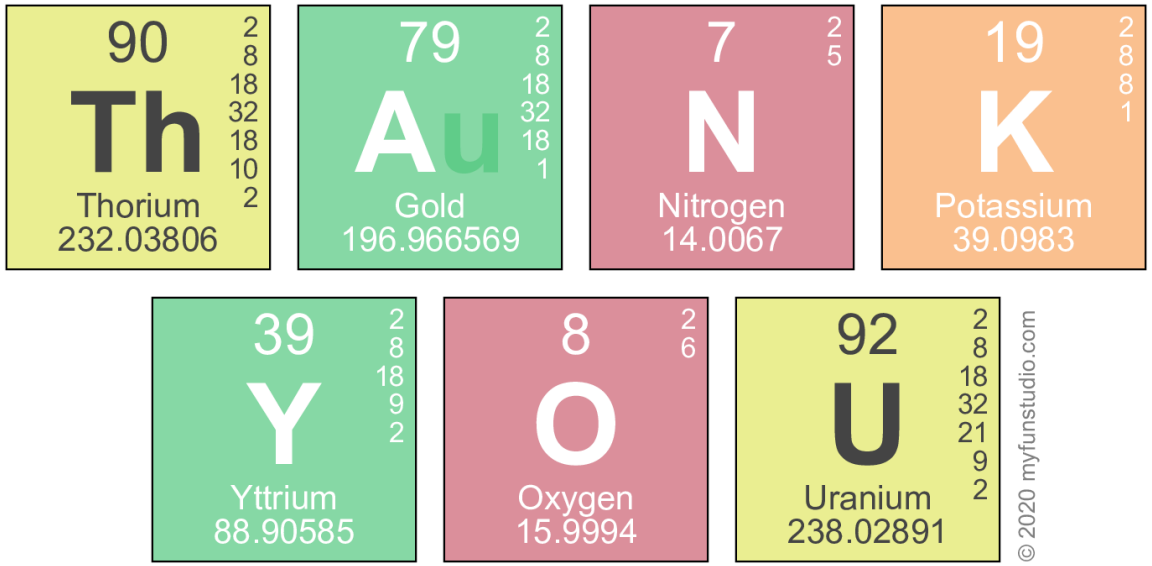
When should a test for nitrosamines be included in the MA dossier?

Testing of raw materials (e.g. excipients) should also be considered if these are potential sources of nitrosamine impurities.

Exceptions from routine testing may be possible, if the root cause of contamination is demonstrated to be well-understood:

- Only if the amount of nitrosamine present is consistently below 10% of the acceptable limit based on AI in the API or in the finished product, then a test for the nitrosamine could be omitted from the specification. → *No testing*

- Only if levels of a single nitrosamine are consistently below 30% of the acceptable limit based on AI in the API or the finished product, skip-testing according to the ICH Q6A definition could be acceptable. → *Skip testing*



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