AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Drug substance. Module 3.2.S. Impurities in drug substances and drug products

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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	☐	X	☐	☐ optional

*Laura Galatti, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. I am not receiving any compensation

3.2.S
Principi attivi

I principi attivi possono essere classificati in:

Nuovi principi attivi, usati per la prima volta in un prodotto medicinale per uso umano o veterinario

Principi attivi esistenti, non descritti in Farmacopea Europea o in una delle Farmacopee degli stati membri UE

Principi attivi esistenti, descritti in Farmacopea Europea o in una delle Farmacopee degli stati membri UE

Principi attivi: come sono presentate le informazioni? (1)

In base al tipo di principio attivo è possibile presentare i dati seguendo una delle tre possibili opzioni:

- CEP (Certificate of Suitability European Pharmacopoeia): solo in caso di p.a. riportati in Ph.Eur.

- ASMF – Active Substance Master File: in riferimento sia a nuovi principi attivi, sia a principi attivi esistenti non inclusi in Farmacopea Europea (o in una Farmacopea di uno stato membro), sia a principi attivi inclusi in Farmacopea Europea (o in una Farmacopea di uno stato membro).

- Dati completi presenti sul modulo 3

Principi attivi: come sono presentate le informazioni? (2) ASMF

I dati sul p.a. possono essere presentati in un ASMF. Le informazioni sono suddivise in due parti:

"Closed part": informazioni confidenziali
Descrizione dettagliata del processo di produzione
QC durante il processo di produzione
Convalida del processo

Applicant's (open) part:
Tutte le informazioni necessarie perchè l'Applicant possa assumersi le proprie responsabilità sul p.a. (es. schema della sintesi, specifiche, dati sui lotti, stabilità ...)

Principi attivi: come sono presentate le informazioni? (3)
CEP (Certificate of Suitability European Pharmacopoeia)

Rilasciato dall'EDQM (European Directorate for the Quality of Medicines)

Nel caso di p.a. descritti in Ph. Eur. l'Applicant può utilizzare il CEP per sostituire alcune delle informazioni necessarie sul modulo 3

La presentazione del CEP è opzionale e non obbligatoria per i p.a. di Ph. Eur., tuttavia rappresenta l'opzione da preferire a dimostrazione che un p.a. utilizzato nella produzione di un prodotto medicinale è conforme ai requisiti di Ph. Eur.

Il CEP sostituisce i dati delle corrispondenti sezioni del modulo 3 e pertanto non è necessario richiedere ulteriori informazioni eccetto quelle relative a quelle caratteristiche fisico-chimiche del p.a. non coperte dal CEP o eventualmente i dati di stabilità.

OVERVIEW ASMF CONTENTS

Table 1	CTD format	Applicant's Part	Restricted Part
3.2.S.1	General information	x	
3.2.S.1.1	Nomenclature	x	
3.2.S.1.2	Structure	x	
3.2.S.1.3	General properties	x	
3.2.S.2	Manufacture	x	X
3.2.S.2.1	Manufacturer(s)[2]	x	
3.2.S.2.2	Description of Manufacturing Process and Process controls	a)	b)
3.2.S.2.3	Control of Materials		X
3.2.S.2.4	Control of critical steps and intermediates	c)	d)
3.2.S.2.5	Process validation and/or Evaluation		X
3.2.S.2.6	Manufacturing Process Development		X
3.2.S.3	Characterisation	x	
3.2.S.3.1	Elucidation of Structure and other Characteristics	x	
3.2.S.3.2	Impurities	x	e)
3.2.S.4	Control of Drug Substance	x	
3.2.S.4.1	Specification	x	
3.2.S.4.2	Analytical procedures	x	
3.2.S.4.3	Validation of analytical procedures	x	
3.2.S.4.4	Batch analysis	x	
3.2.S.4.5	Justification of specification	x	f)
3.2.S.5	Reference standards or materials	x	
3.2.S.6	Container Closure System	x	
3.2.S.7	Stability	x	
3.2.S.7.1	Stability summary and conclusion	x	
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	x	
3.2.S.7.3	Stability data	x	

3.2.S. Drug Substance

3.2.S.1 General Information
3.2.S.2 Manufacture
3.2.S.3 Characterisation
3.2.S.4 Control of Drug Substance
3.2.S.5 Reference Standards or Materials
3.2.S.6 Container Closure System
3.2.S.7 Stability

3.2.S.1 General Information

In tale sezione vengono riportate informazioni generali quali :

Nomenclatura
Struttura
Proprietà generali del principio attivo (es. pKa, solubilità, polimorfismo, etc...)

3.2.S.2 Manufacture

Devono essere riportati:
-Nome, sede e responsabilità del(i) produttore(i)
- Descrizione del processo produttivo e relativi controlli in-process, i controlli dei materiali utilizzati, degli step critici e degli intermedi
La convalida del processo produttivo (quest'ultima obbligatoria solo nel caso di produzione in asepsi e per la sterilizzazione).
Il processo produttivo e relativi controlli in-process devono essere descritti in maniera adeguata.
E' necessario che siano elencati tutti i materiali utilizzati nel processo produttivo, fornendo informazioni che dimostrino la loro qualità.
Porre particolare attenzione a: starting material (vedere slides successive) solventi e catalizzatori impiegati nella sintesi.

3.2.S.3 Characterisation

3.2.S.3.1 Elucidation of Structure and other Characteristics

Informazioni riguardo la struttura e altre caratteristiche del principio attivo
La struttura chimica del principio attivo è confermata generalmente attraverso comuni analisi spettrometriche (IR, NMR, Massa)
Informazioni relative al potenziale isomerismo, identificazione della stereochimica e caratteristiche fisico-chimiche, quali il polimorfismo

3.2.S.3 Characterisation

3.2.S 3.2 Impurities
Caratterizzazione

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 (vedere slides successive su controllo impurezze).

3.2.S.4 Control of Drug Substance

Devono essere descritte le specifiche del principio attivo, insieme con le procedure analitiche impiegate, le convalide di dette procedure e i risultati ottenuti sui lotti testati

Le specifiche devono essere adeguate a controllare la qualità del p.a.

Ogni specifica proposta deve essere opportunamente giustificata (GL ICH Q6A)

Le procedure analitiche utilizzate per il rilascio del principio attivo vanno descritte dettagliatamente e convalidate.

3.2.S.5 Reference Standards or Materials

Informazioni riguardanti gli standard di riferimento impiegati per l'analisi del principio attivo

Gli standard di riferimento sono utilizzati per effettuare identificazione, titolo e purezza di un principio attivo; devono essere testati per dimostrarne l'idoneità allo specifico utilizzo

Se non ottenuti da fonte ufficiale (Ph.Eur., USP), come nel caso degli "in-house" Reference Std, occorre fornire i dati per la loro caratterizzazione

3.2.S.6 Container Closure System

Deve essere descritto il sistema di confezionamento e chiusura, inclusi dettagli sui materiali che compongono il confezionamento primario e le loro specifiche. Le specifiche devono includere: descrizione, identificazione, dimensioni

Devono essere forniti dettagli sul confezionamento secondario, così come una giustificazione sulla scelta del tipo di confezionamento in base alla protezione che questo fornisce al principio attivo (luce, umidità) e alla sua compatibilità con lo stesso

3.2.S.7 Stability

- Riassunto degli studi di stabilità effettuati sul principio attivo e le conclusioni relative alle condizioni di conservazione e al “re-test period “
- Protocolli post -approval ed eventuali commitment
- Dati di stabilità inseriti in forma appropriata

Criticità degli ASMF

Il controllo delle impurezze di processo e di degradazione, incl. impurezze mutagene, dei solventi residui e delle Elemental Impurities nel principio attivo e nel prodotto finito rappresenta una fra le maggiori criticità del dossier insieme al problema della ridefinizione degli starting materials. Rappresentano obiezioni maggiori che impediscono la conclusione positiva delle domande di AIC.

Selection of Starting Materials (rif. ICHQ11) (1)

In general, changes in material attributes or operating conditions that occur near the beginning of the manufacturing process have lower potential to impact the quality of the drug substance;

The relationship between risk and number of steps from the end of the manufacturing process is the result of two factors, one concerning the physical properties of the drug substance and the other concerning the formation, fate, and purge of impurities.

Impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations (e.g., washing, crystallisation of isolated intermediates) than impurities generated late in the manufacturing process, and are therefore less likely to be carried into the drug substance.

Selection of Starting Materials (rif. ICHQ11) (2)

Regulatory authorities assess whether the controls on the drug substance and drug substance manufacturing process can be considered adequate, including whether there are appropriate controls for impurities. To conduct this assessment, enough of the drug substance manufacturing process should be described in the application for regulatory authorities to understand how impurities are formed in the process, how changes in the process could affect the formation, fate, and purge of impurities, and why the proposed control strategy is suitable for the drug substance manufacturing process.

Selection of Starting Materials (rif. ICHQ11) (3)

Each branch of a convergent drug substance manufacturing process begins with one or more starting materials. The Good Manufacturing Practice (GMP) provisions apply to each branch beginning with the first use of a starting material. Performing manufacturing steps under GMP together with an appropriate control strategy provides assurance of quality of the drug substance;

A starting material is incorporated as a significant structural fragment into the structure of the drug substance. “Significant structural fragment” in this context is intended to distinguish starting materials from reagents, solvents, or other raw materials.

Nota: Dopo la ridefinizione, la produzione del nuovo intermedio (ex starting material) deve essere coperta dalla dichiarazione QP.

Selection of Starting Materials (rif. ICHQ11) (4)

Selection of source and starting materials for biotechnological/ biological drug substances

Cell banks are the starting point for manufacture of biotechnological drug substances and some biological drug substances.

In some regions, these are referred to as source materials; in others, starting materials.

Prendere in considerazione anche ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological / biological entities) – questions and answers

Classification of Impurities

- Impurities can be classified into the following categories:
- Organic impurities; ref. ICHQ3A (active substance) and ICHQ3B (drug product)
- Inorganic impurities; ref. ICHQ3D (Elemental Impurities)
- Residual solvents; ref. ICHQ3C

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

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

- Residual Solvents

- Inorganic Impurities

ICHQ3A Thresholds

Attachment 1: Thresholds

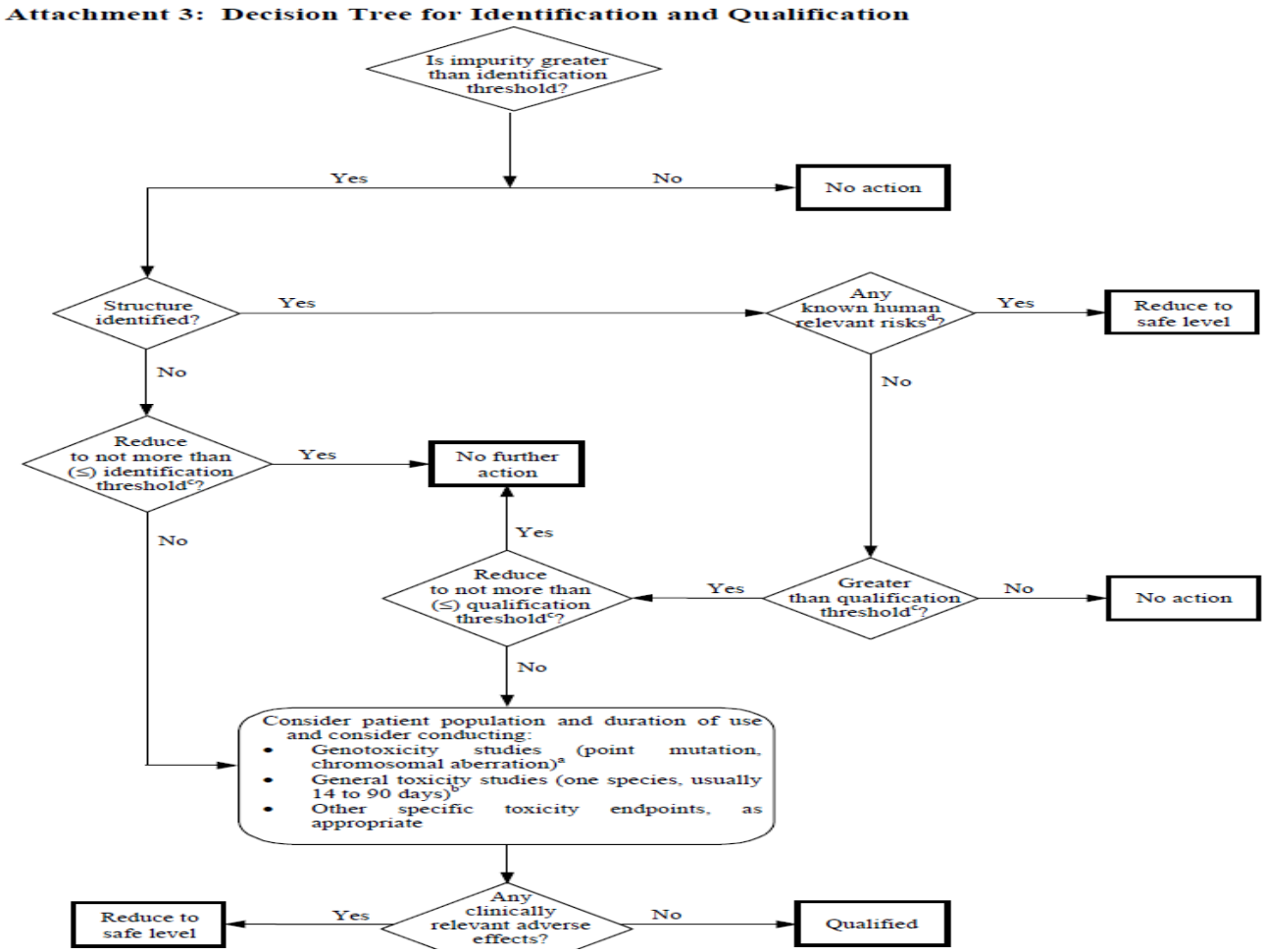
Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

[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

The impurities reported in the EU PH Monographs are always qualified.

Impurities in the Drug substances



Controllo delle Impurezze nel principio attivo

Allo scopo di controllare adeguatamente le impurezze nel principio attivo è fondamentale la valutazione del carry over di tutte le possibili impurezze da starting materials ed intermedi nel principio attivo.
L'analisi del carry over delle impurezze rappresenta una delle maggiori criticità degli ASMF.

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.

ICHQ3B thresholds

Reporting Thresholds

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

Identification Thresholds

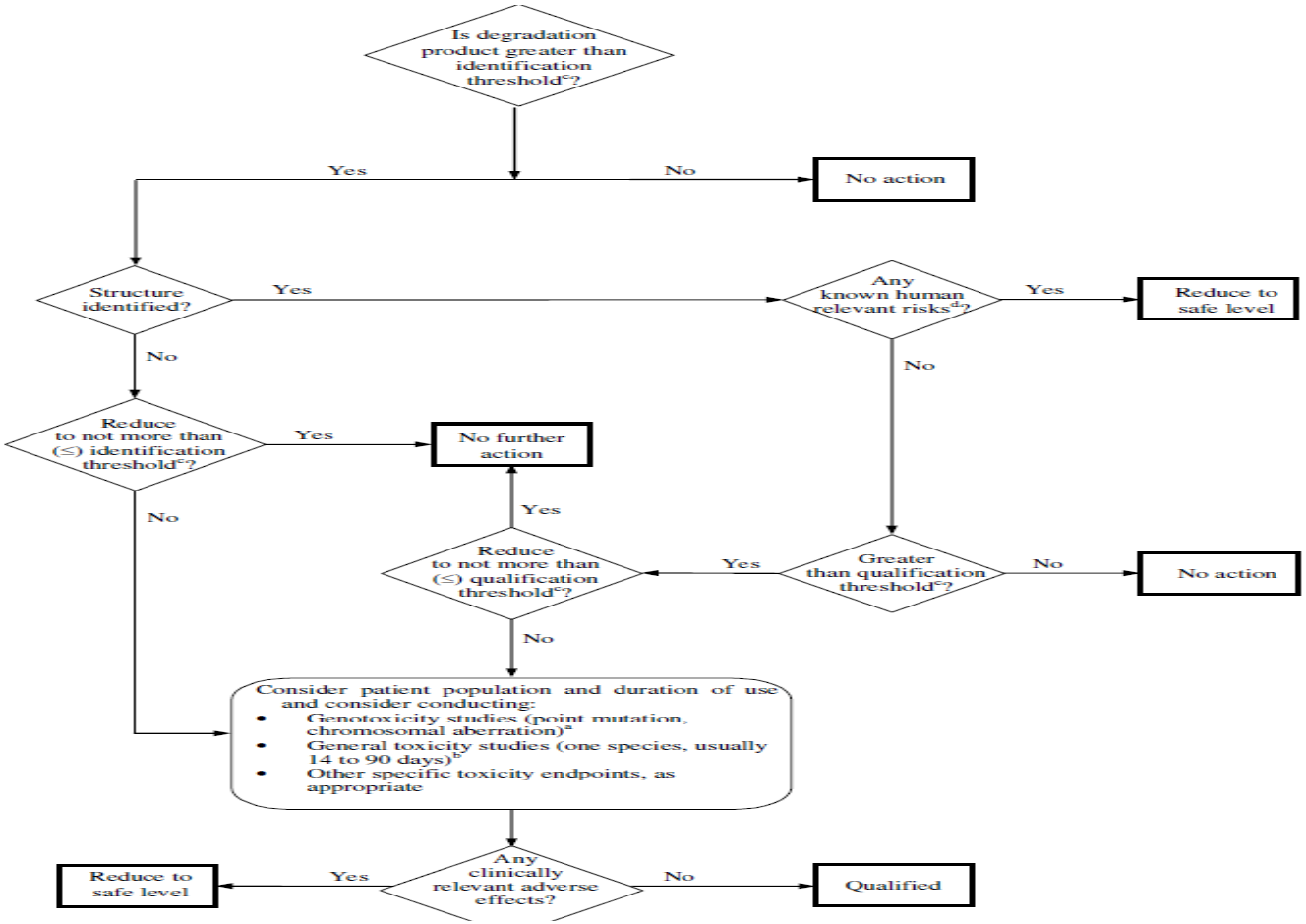
Maximum Daily Dose[1]	Threshold[2, 3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

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)



Impurezze nel prodotto finito (ICHQ3B)

Se viene superata la soglia di qualificazione talvolta la riduzione dei livelli del prodotto di degradazione (es. uso di un contenitore protettivo o modifica delle condizioni di conservazione) sotto la soglia stessa può essere la soluzione più semplice.

I prodotti di degradazione che sono anche metaboliti si considerano generalmente qualificati.

Nel caso degli antibiotici si applica la Guidance on setting specifications for related impurities in Antibiotics.

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

Acceptable intakes (1):

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 (2):

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 (3):

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

Reference: GUIDELINE FOR RESIDUAL SOLVENTS (ICHQ3C)

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.
Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements.

Residual solvents

Residual solvents assessed in this guideline were evaluated for their possible risk to human health and placed into one of three classes as follows:

- 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

Table 1. Class 1 solvents in pharmaceutical products (solvents that should be avoided).

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Acetone, Toluene, Methanol, Ethanol, Isopropanol, Xilene, Hexane and Petroleum Ether could be contaminated by Benzene.

Dichloromethane could be contaminated by Carbon tetrachloride.

Residual solvents

Annex I: specifications for class 1 and class 2 residual solvents in active substances:

A. Class 1 solvents used as starting materials

Certain class 1 solvents can be used as starting materials. Indeed, the use of benzene as a starting material is unavoidable when benzene is a structural part of the active substance.

Benzene, as a starting material, is commonly used in the very early steps of syntheses, well before the key starting material obtained.

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.

Residual solvents

B. Class 1 solvents present as an impurity (1)

Where a class 1 solvent might be present in another solvent, 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;

Residual solvents

B. Class 1 solvents present as an impurity (2)

Where a class 1 solvent might be present in another solvent, a routine test for this class 1 solvent, on a suitable intermediate or on the final active substance, is not required when:

- 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

Specifications for class 2 solvents

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 active substance depending on the step(s) of the syntheses in which they are used.

The limit set for class 2 solvents in the final active substance should comply with the requirements of the relevant aforementioned ICH/VICH guideline on impurities: residual solvents.

A. 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.

Residual solvents

B. Class 2 solvents used prior to the last step of the synthesis

Class 2 solvents used prior to the last step in the synthesis have not to be included in the drug substance specification if it has been demonstrated, on a suitable intermediate or on the final active substance, that the content of class 2 solvents is not more than 10 % of the acceptable concentration limit.

To support the absence of a routine test for class 2 solvents in the final active substance or in the suitable intermediate, results of the content of class 2 solvents should be presented from 6 consecutive pilot scale batches or 3 consecutive industrial scale batches of the suitable intermediate or the final active substance.

GUIDELINE FOR ELEMENTAL IMPURITIES (ICHQ3D)

EU Ph. Monographs:

5.20. Elemental impurities

2.4.20. Determination of 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

Safety assessment of potential elemental impurities

Levels of elemental impurities higher than an established PDE (see Table A.2.1) may be acceptable in certain cases. These cases could include, but are not limited to, the following situations:

- Intermittent dosing;
- Short term dosing (i.e., 30 days or less);
- Specific indications (e.g., life-threatening, unmet medical needs, rare diseases).

Element classification

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. The likelihood of occurrence is derived from several factors including:

probability of use in pharmaceutical processes,

probability of being a co-isolated impurity with other elemental impurities in materials used in pharmaceutical processes,

and the observed natural abundance and environmental distribution of the element.

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

In developing controls for elemental impurities in drug products, the principles of quality risk management, described in ICH Q9, should be considered. In the case of elemental impurities, the product risk assessment would therefore be focused on assessing the levels of elemental impurities in a drug product in relation to the PDEs presented in this guidance. Information for this risk assessment includes but is not limited to: data generated by the applicant, information supplied by drug substance and/or excipient manufacturers and/or data available in published literature.

A summary of the Risk Assessment and any measures taken to ascertain compliance should be added in the new application file and, in case of variation, among the variation documents.

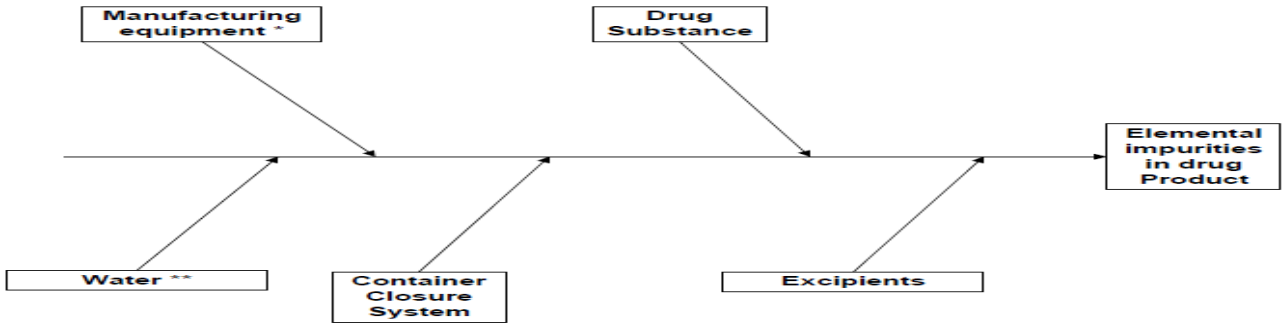
Risk assessment and control of elemental impurities

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

- Identify known and potential sources of elemental impurities that may find their way into the drug product.
- 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.
- 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 water quality requirements.

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).

Special Considerations for Biotechnologically-Derived Products (1)

For biotechnology-derived products, the risks of elemental impurities being present at levels that raise safety concerns at the drug substance stage are considered low.

a) elements are not typically used as catalysts or reagents in the manufacturing of biotech products;

b) b) elements are added at trace levels in media feeds during cell culture processes, without accumulation and with significant dilution/removal during further processing;

c) typical purification schemes used in biotech manufacturing such as extraction, chromatography steps and dialysis or Ultrafiltration-Diafiltration (UF/DF) have the capacity to clear elements introduced in cell culture/fermentation steps or from contact with manufacturing equipment to negligible levels.

Special Considerations for Biotechnologically-Derived Products (2)

As such, specific controls on elemental impurities up to the biotech drug substance are generally not needed. In cases where the biotechnology-derived drug substance contains synthetic structures (such as antibody-drug conjugates), appropriate controls on the small molecule component for elemental impurities should be evaluated.

However, potential elemental impurity sources included in drug product manufacturing (e.g., excipients) and other environmental sources should be considered for biotechnologically-derived drug products. The contribution of these sources to the finished product should be assessed because they are typically introduced in the drug product manufacture at a step in the process where subsequent elemental impurity removal is not generally performed.

Control of elemental impurities (1)

Control of elemental impurities is one part of the overall control strategy for a drug product that assures that elemental impurities do not exceed the PDEs. When the level of an elemental impurity may exceed the control threshold, additional measures should be implemented to assure that the level does not exceed the PDE. Approaches that an applicant can pursue include but are not limited to:

- Modification of the steps in the manufacturing process that result in the reduction of elemental impurities below the control threshold through specific or non-specific purification steps;
- Implementation of in-process or upstream controls, designed to limit the concentration of the elemental impurity below the control threshold in the drug product;

Control of elemental impurities (2)

Control of elemental impurities is one part of the overall control strategy for a drug product that assures that elemental impurities do not exceed the PDEs. When the level of an elemental impurity may exceed the control threshold, additional measures should be implemented to assure that the level does not exceed the PDE. Approaches that an applicant can pursue include but are not limited to:

Establishment of specification limits for excipients or materials (e.g., synthetic intermediates);

Establishment of specification limits for the drug substance;

Establishment of specification limits for the drug product;

Selection of appropriate container closure systems.

Control of elemental impurities (3)

In case a variation is needed to assure that the level does not exceed the PDE, it should be:
Categorised according the Variation Guidelines (Official Journal 2013/C 223/01)

Accompanied with the documentation required in the Variation Guideline.

In addition it should contain a summary of the Risk Assessment and the conclusions drawn.

Converting between PDEs and concentration limits

The PDEs, reported in micrograms per day (µg/day) provided in this document give the maximum permitted quantity of each element that may be contained in the maximum daily intake of a drug product. Because the PDE reflects only total exposure from the drug product, it is useful to convert the PDE, into concentrations as a tool in evaluating elemental impurities in drug products or their components.

The options listed in the Guidance describe some acceptable approaches to establishing concentrations of elemental impurities in drug products or components that would assure that the drug product does not exceed the PDEs.

Converting between PDEs and concentration limits

Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily intakes of not more than 10 grams:

$$Concentration(\mu g / g) = \frac{PDE(\mu g / day)}{daily\ \ amount\ of\ drug\ \ product(g / day)}$$

Option 2a: Common permitted concentration limits across drug product components for a drug product with a specified daily intake.

Converting between PDEs and concentration limits

Option 2b: Permitted concentration limits of elements in individual components of a product with a specified daily intake:

$$PDE(\mu g/day) \geq \sum_{k=1}^{N} C_k \cdot M_k$$

k = an index for each of N components in the drug product
C_k = permitted concentration of the elemental impurity in component k (µg/g)
M_k = mass of component k in the maximum daily intake of the drug product (g)

Option 3: Finished Product Analysis .The concentration of each element may be measured in the final drug product. Equation 1 may be used with the maximum total daily dose of the drug product to calculate a maximum permitted concentration of the elemental impurity.

Implementation strategy of ICHQ3D guidance (1)

The aim is addressing specific considerations to enable the practical

implementation of ICH Q3D Guideline for Elemental Impurities in the European Union.

Different Approach to risk assessment

Drug Product Approach and Component Approach (recommended)

Particulars for Intentionally added elements

Catalyst introduced in the last step of the synthesis (the catalyst should be purged to levels consistently below the control threshold (<30% of the PDE) otherwise a specification together with skip testing may be acceptable (by option 1).

Implementation strategy of ICHQ3D guidance (2)

ASMF/CEP: dossier expectations and assessment strategy (1):

The requirements and the standards of assessment are the same between an ASMF and a CEP dossier.
The route of synthesis of the drug substance must be described including information on all intentionally added catalysts and reagents. A summary of the drug substance risk assessment/risk management on the potential for intentionally added elemental impurities in the drug substance is to be included in the ASMF/CEP and made available to the drug product manufacturer allowing his overall risk management as well as the competent authority.

Implementation strategy of ICHQ3D guidance (3)

ASMF/CEP: dossier expectations and assessment strategy (2):

It is also recommended that the ASMF/CEP dossier contains a summary of a risk assessment/ management that also covers all other potential elemental impurities from other sources than the intentionally added elements to inform the drug product manufacturers overall risk assessment including any mitigation steps necessary.

Implementation strategy of ICHQ3D guidance (4)

When granting a CEP the EDQM should consider the need for transparency for substances within the scope of ICH Q3D with regard to:

The use of any elements intentionally added such as, e.g. metal catalysts (mandatory – assessed by the CEP assessor).

Any specifications in place in the drug substance or process intermediate to limit the levels of elemental impurities as applied by the drug substance manufacturer.

Summary or outcome of manufacturers risk assessment/management on intentionally/nonintentionally added elements, if it is provided by the CEP holder (appended to the CEP).

Criticità osservate nei Summary di RA presentati (1)

Errore nel calcolo della massima dose giornaliera somministrata e conseguente inaccettabilità dell'intero RA. Ci sono casi in cui l'azienda non fa volutamente il calcolo rispetto all'intero prodotto finito ma solo rispetto al principio attivo pur usando l'opzione 3 (non accettabile!)

Opzione di calcolo utilizzata per la conversione del PDE in concentrazioni limite non esplicitata (talvolta l'assessor deve dedurre l'opzione sulla base dei risultati ottenuti).

Criticità osservate nei Summary di RA presentati (2)

- Descrizione del calcolo della concentrazione dei limiti in base alla massima dose giornaliera senza la presenza dei risultati sui lotti a dimostrazione del rispetto del limite inferiore al 30% del PDE (es. l'Applicant calcola la concentrazione limite con l'opzione 2A per singoli componenti ma poi non fornisce i risultati dei lotti).

  Questa rappresenta una grossa criticità del dossier.

Criticità osservate nei Summary di RA presentati (3)

Approccio basato sull'analisi dei singoli componenti: dati carenti (es. mancano i risultati sui lotti di principio attivo o di eccipiente; l'Applicant si limita a dichiarare che la contaminazione è trascurabile, senza fornire i dati a supporto e le referenze). Talvolta si usa come riferimento la specifica del controllo dei metalli pesanti nel principio attivo (tale controllo oramai non è accettato ed è stato eliminato dalle monografie della Farmacopea Europea).

Criticità osservate nei Summary di RA presentati (4)

Difficoltà a calcolare il PDE di medicinali con via di somministrazione differente da quella orale, parenterale o inalatoria (vie riportate nella GU).
Mancanza di adeguata giustificazione della scelta di una specifica via di somministrazione di riferimento.
Mancanza dei dati a giustificazione del calcolo effettuato.

Es. l'azienda sceglie una via di somministrazione non giustificata e meno cautelativa, spesso senza una adeguata discussione farmacocinetica.

Criticità osservate nei Summary di RA presentati (5a)

- Difficoltà a calcolare il contributo fornito dal contenitore primario al livello delle Elemental Impurities. La linea guida ICHQ3D riporta quanto segue: “elemental impurities from container closure systems and manufacturing equipment should be taken into account before calculating the maximum permitted concentration in the remaining components (excipients and drug substance). If it is determined during the risk assessment that the container closure systems and manufacturing equipment do not contribute to the elemental impurity level in the drug product, they do not need to be considered...”.

Criticità osservate nei Summary di RA presentati (5b)

La linea guida ICHQ3D riporta anche quanto segue: “.....Where contributions from container closure systems and manufacturing equipment exist, these contributions may be accounted for by subtracting the estimated daily intake from these sources from the PDE before calculation of the allowed concentration in the excipients and drug substance”.

L’azienda dimostra di avere spesso difficoltà ad attuare quanto richiesto dalla GU.

Criticità osservate nei Summary di RA presentati (6)

Assenza dei risultati sui lotti di “mined excipients”: l’Applicant si limita a dichiarare l’assenza di Elemental Impurities intenzionalmente aggiunte. Ciò è insufficiente dato il tipo di eccipienti. Devono essere forniti i risultati completi e spesso 3 lotti industriali o 6 lotti pilota non sono sufficienti.

Es. dichiarazione del fornitore di eccipiente Talco nella quale viene riportato che il rischio è trascurabile poichè non ci sono EI intenzionalmente aggiunte (dichiarazione non accettabile).

Criticità osservate nei Summary di RA presentati (7)

Nell'approccio per componenti talvolta vengono "estrapolati" dati da componenti differenti rispetti a quelli realmemnte esistenti nella formulazione; ciò non è accettabile. Devono essre sempre forniti i risultati sui lotti dei singoli componenti effettivamente presenti nella formulazione.

Es. Talvolta vengono forniti dati su eccipienti "simili" a quelli realmente presenti nel medicinale.

L'approccio "worst-case" fornendo dati su altri componenti (anche altri principi attivi) non è accettabile.

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Thank you!

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