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Regulatory Aspects of Impurity: A Concise Review

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ABSTRACT

Impurity is defined as any chemical component excluding API and excipients which affect the safety and efficacy of the molecule. It continues an essential topic across several disciplines including process development, chemical analysis, toxicology, and regulatory affairs. There are many types of impurity specified in regulatory guidelines such as genotoxic impurities, organic impurities, Inorganic impurities, residual solvents. In ICH Q3A and Q3B Guidelines, the detail information is given. But this information is very vast and complicated to understand. The identification and qualification of impurities in new drug substances and new drug product are very essential. Hence the attempt has been carried to write that information concisely. This article deals with a concise review of various type of impurities concerning their classification, source, limits as per guidelines.

1. INTRODUCTION

1.1 Genotoxic impurities (GIs)

It continues to be a "hot" topic across several disciplines including process development, chemical analysis, toxicology, and regulatory affairs. The synthesis of drug substances involves the use of reactive chemicals, reagents, solvents, catalysts, and other processing aids.[1]

Definition

According to ICH guidance on genotoxicity testing [ICH S2 (R1)], can be defined as: “a broad term that refers to any deleterious change in the genetic material regardless of the mechanism by which the change is induced. [2]

1.2 Scope of guidance:

This document is intended to guide new drug substances and new drug products during their clinical development and subsequent applications for marketing. It also applies to post-approval submissions of marketed products, and to new marketing applications for products with a drug substance that is present in a previously approved product in both cases, only where

1. Changes in the drug substance synthesis result in new impurities or increased acceptance criteria for existing impurities;

2. Changes in the formulation, composition or manufacturing process result in new degradation products or increased acceptance criteria for existing degradation products.

3. Changes in indication or dosing regimen are made which is significantly affect the acceptable cancer risk level.

Assessment of the mutagenic potential of impurities as described in this guidance is not intended for the following types of drug substances and drug products such as biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation, herbal, and crude products of animal or plant origin.

Assessment of the mutagenic potential of impurities as described in this guidance is not

intended for excipients used in existing marketed products, flavoring agents, colorants, and perfumes.

Application of this guidance to leachable associated with drug product packaging is not intended, but the safety risk assessment principles outlined in this guidance for limiting potential carcinogenic risk can be used if warranted. The safety risk assessment principles of this guidance can be used if warranted for impurities in excipients that are used for the first time in a drug product and are chemically synthesized.

2. General Principles

1. The focus of this guidance 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 cause cancer. This type of mutagenic carcinogen is usually detected in a bacterial reverse mutation (mutagenicity) assay.

2. The other types of genotoxicants that are non-mutagenic typically have threshold mechanisms and usually, do not pose a carcinogenic risk in humans at the level ordinarily present as impurities.

3. Therefore, to limit a possible human cancer risk associated with the exposure to potentially mutagenic impurities, the bacterial mutagenicity assay is used to assess the mutagenic potential and the need for controls.

4. Structure-based assessments are useful for predicting bacterial mutagenicity outcomes based upon the established knowledge.

5. There are a variety of approaches for conducting this evaluation, including a review of the available literature and/or computational toxicology assessment. [3]

3. A threshold of Toxicological Concern (TTC) Concept

- The 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.

- The methods upon which the TTC is based are generally considered to be very conservative since they involve a simple linear extrapolation from the dose giving a 50%

tumor incidence (TD50) to a 1 in 106 incidences, using TD50 data for the most sensitive species and most sensitive site of tumor induction.

- For the application of a TTC in the assessment of acceptable limits of mutagenic impurities in drug substances and drug products, a value of 1.5 micrograms (µg)/day corresponding to a theoretical 10-5 excess lifetime risk of cancer can be justified.

- Some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk.

- This group of high potency mutagenic carcinogens referred to as the cohort of concern, comprises aflatoxin-like, N-nitroso-, and alkyl-azoxy compounds. [3]

4. Drug Substance and Drug Product Impurity Assessment

4.1 The impurity assessment is a two-stage process[4]:

- Actual impurities that have been identified should be considered for their mutagenic potential.

- An assessment of potential impurities likely to be present in the final drug substance is carried out to determine whether further evaluation of their mutagenic potential is warranted.

4.1.2 Synthetic Impurities

Actual impurities include those observed in the drug substance above the ICH Q3A reporting thresholds. Identification of actual impurities is expected when the levels exceed the identification thresholds outlined by ICH Q3A. It is acknowledged that some impurities below the identification threshold may also have been identified.

Potential impurities in the drug substance can include starting materials, reagents, and intermediates in the route of synthesis from the starting material to the drug substance.

4.1.3: Degradation Products

Actual drug substance degradation products include those observed above the ICH Q3B reporting threshold during storage of the drug substance in the proposed long-term storage conditions and primary and secondary packaging, and also include those impurities that arise

during the manufacture of the drug product.

5. Impurities Classification

5.1 Structurally alerting functional groups[4]

5.1.1 Aromatic Group:

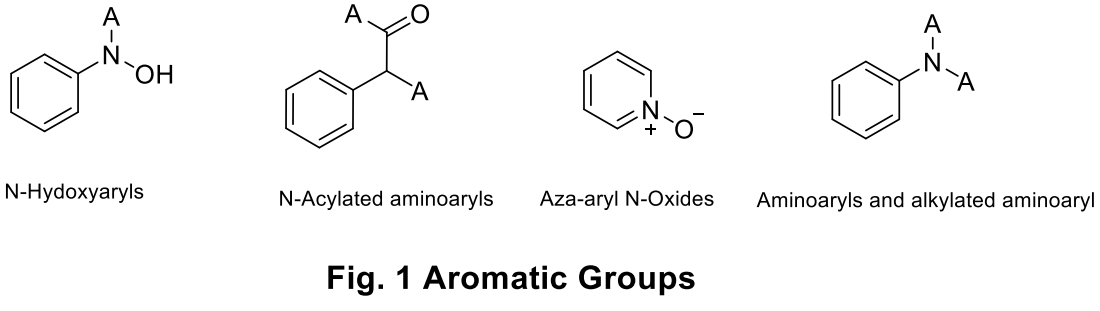

Fig. 1 Aromatic Groups

5.1.2 Heteroatomic groups4:

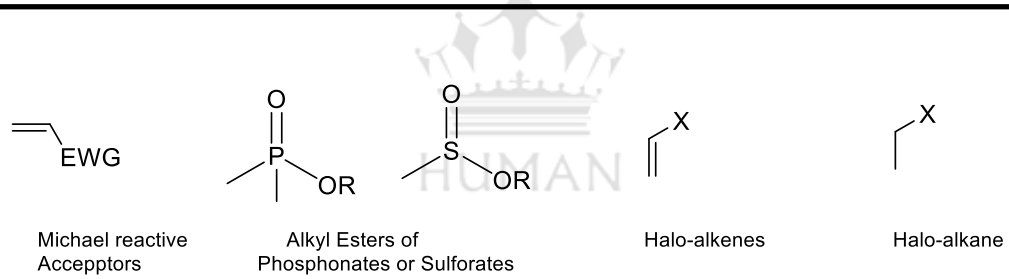

Fig. 2 Heteroaromatic groups

5.1.3 Alkyl and aryl groups[4]

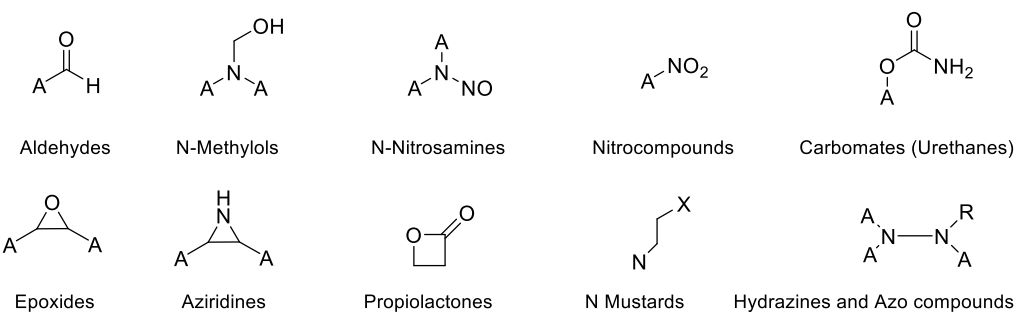

Fig.3 Alkyl and Aryl Groups

Interim Limit for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)

Table No. 1: Genotoxic impurities present in different classes of losartan

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)	Acceptable Intake NDMA (ppm)	Acceptable Intake NDEA (ng/day)	Acceptable Intake NDEA (ppm)
Valsartan	320	95	0.3	26.5	0.083
Losartan	100	96	0.96	26.5	0.27
Irbesartan	300	96	0.32	26.5	0.088
Azilsartan	80	96	1.2	26.5	0.33
Olmesartan	40	96	2.4	26.5	0.66
Eprosartan	800	96	0.12	26.5	0.033
Candesartan	32	96	3.0	26.5	0.83
Telmisartan	80	96	1.2	26.5	0.33

* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in 1:100,000 cancer.

**These values are based on a drug's maximum daily dose as reflected in the drug label.

6. Definition of Genotoxic Impurity (GI) And Scope Of Eu Regulatory Guidance[2]:

- In the EU guideline, genotoxic impurities are defined as: "DNA-reactive substances that have a potential for direct DNA damage". In the context of EU guidance, "genotoxic" is focused on a particular type of mutagenicity, essentially that detected by the Ames test.

- It can be argued that in vitro chromosomal aberration data have essentially no role in the characterization of potential genotoxic impurities (PGIs) since clastogenic events reflect effects at the chromosomal level rather than direct DNA damage and are generally considered to be thresholded.

- This distinction is emphasized by the Q&A supplement 2 to the EU guideline and by the draft FDA guidance 3 which indicate that no further testing is required (in terms of genotoxicity) if a structurally alerting compound is shown to be negative result in Ames test.

For example, if a compound is tested only in the Ames assay and is found to be negative, it will not be considered as a GI. The compound could well show clastogenic effects if

evaluated in vitro; however, the Q&A document does not call for such testing, and so it follows that in vitro clastogenic activity is not relevant under the terms of reference of the EU guideline.

- According to a remark made at a recent presentation by the rapporteur for the EU guideline, results from mammalian-cell in vitro tests, such as the mouse lymphoma assay, can also be discounted provided that a compound is clearly shown Ames-negative.

- Chromosomal effects are detected in vitro, often only at high cytotoxic concentrations, for many Ames-negative compounds including a high proportion (>25%) of pharmaceutical APIs.

For example, benzaldehyde and many other aldehydes give sporadic positive results in terms of in vitro chromosomal aberrations (see case study below) but are considered to be no genotoxic and suitable for use in foods. Moreover, positive *in vitro* chromosomal aberration assay results on Ames-negative compounds are extremely poorly correlated with carcinogenic potential, the false-positive rate (in terms of the correlation between in vitro genotoxicity data and in vivo rodent bioassay results) being estimated to be at least 75% studied by Kirkland et al.

- Identified chemicals that were noncarcinogenic after testing in both male and female rats and mice.

- The specificity of the Ames test was reasonable (73.9%); however, all mammalian-cell tests had very low specificity (i.e., below 45%), and this declined to extremely low levels in combinations of two and three test systems.

- When all three tests were performed, 75-95% of non-carcinogens gave positive (i.e., false positive) results in at least one test in the battery. In a joint report of several EU expert committees released in 2009 and 2010, a similar opinion is expressed concerning.

- The low predictivity of in vitro chromosomal mammalian cell assays for carcinogenic activity: "the predictivity of positive results from in vitro assays responding to the clastogenic activity of chemicals in mammalian cells, i.e., the test for chromosome aberrations, the micronucleus assay, and the mouse lymphoma assay, is very limited".

- ICH guidance on genotoxic impurities (ICH M7—in preparation) already emphasizes the

focus on DNA reactivity particularly about potential carcinogenicity in its working title: "M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk".

- On the basis of the foregoing arguments, it would seem reasonable to conclude that any Ames-negative impurity should not be classified or evaluated as a GI irrespective of any evidence from in vitro mammalian cell assays (for chromosomal aberrations for example); this is not a completely universal view however since the issue is not presented with complete clarity in the current guidance.

For example, in the draft FDA guidance, on the one hand impurities that give "positive results in one or more genotoxicity assays" are a cause for concern, but on the other hand, if the initial evaluation (involving a bacterial reverse mutation assay) of the genotoxic potential of an impurity with an identified structural alert is negative, no further genotoxicity studies are recommended.

- In terms of applying quantitative limits, compounds for which carcinogenicity data are available, if Ames-positive, should be subjected to a compound-specific risk assessment. Ames-negative compounds for which carcinogenicity bioassay data are available should be considered to be outside of the scope of the EU guidance and evaluated on a compound-specific basis. This is not a universal experience in regulatory assessments however, and it may require forceful arguments to make the case.

7. Genotoxic Impurity Limits[3]:

- If an impurity meets the criteria discussed above in terms of being classed as a GI (Ames-positive or, in the absence of published or in-house data, assumed to be Ames-positive based on the presence of a structural alert), it can be controlled at the default TTC (threshold of toxicological concern) limit of 1.5 µg/day. However, there are many exceptions to this general rule including:

- Compounds with evidence for a threshold, e.g., topoisomerase II inhibitors and classical intercalating agents;

- Compounds with carcinogenicity bioassay data, e.g., formaldehyde and allyl chloride;

- "Severe" indications, such as cancer treatment (see ICH S9 guidance);

- Indications where life expectancy is <5 years; Limited duration of exposure, 1 year (applies to both clinical trials and marketing in the EU and only to clinical trials according to the draft US guidance);

- GI formed as a "significant metabolite" (examples of which are pretty rare);

- Exposure via food, e.g., acetaldehyde and crotonaldehyde. A limitless than the default TTC is recommended in the draft FDA guidance 8 for juveniles and infants, by applying additional safety factors of 3 and 10, respectively.

- However, no such provisions are made in the EU guideline because the current TTC limit is considered exceptionally conservative. Given this explanation, it is hard to understand why the EU guideline (and the draft FDA guideline) apply a group limit for GIs that are structurally similar (effectively using an additional safety factor of 2 or 3 in the case of most structurally similar GIs). Many other arguments refuting the multiple GI approach are presented by Elder and Harvey.

8. Structural Alerts and In-Silico Evaluations [2]

- It should be emphasized that in-silico systems such as DEREK are not essential for the determination of structural alerts; as indicated in the draft FDA guidance, an in-Cerebro assessment, combined with published information on representative compounds in the same structural class, can be just as effective in many cases.

- Agencies that have internal access to such in-silico systems will most likely undertake their evaluation which can throw up concerns, whereas that undertaken by the applicant did not.

- For a significant number of chemical classes, structural alerts massively over predict mutagenicity (Ames positivity) owing to numerous modulating factors including high molecular weight, hydrophilicity, high reactivity, steric hindrance, molecular symmetry, and ready metabolism.

- Such over predictions were demonstrated by Raillard et al. for several structural classes, including aldehydes, α, β-unsaturated carbonyls, and aromatic amines, that can be associated with drug substance degradation pathways.

- It may be possible to "read across" with confidence for some tightly defined structural classes, but it might be necessary to provide compound-specific data to convince some skeptical regulators.

Table No. 2: Limit of Genotoxic impurity (µg/g) =TTC (µg) /Daily dose(g)

Duration of treatment	**≤1 month**	**>1-12 moths**	**>1-10years**	**>10 years to the lifetime**
Daily intake micro g/day	120	10	10	1.5

9. Risk Assessment of Pgis and Development of Methods of Analysis[2]

- Although several articles stress the major challenges faced in developing methods of analysis for determination of parts per million and subparts per million levels of GIs controlled at a TTC-based limit, it is not clear in all cases that the decision to apply such a limit has been preceded by a thorough risk assessment. Sun et al.

- It describes the enormous effort required to develop a robust, validated assay for just one GI (dimethyl sulfate) at the TTC level.

- Dimethyl sulfate (DMS) is Ames positive and considered to be carcinogenic in rodents, although no data on oral carcinogenicity appear to be available.

- Since DMS has the same Swain Scott s constant (an index of nucleophilic selectivity) of 0.86 as methyl methanesulfonate (MMS; TD50 mouse 31.8 mg/kg/day), in theory, it may be reasonable to assume that the two compounds possess similar moderate carcinogenic potency (based on the established approximate correlation of TD50 and Swain Scott s).

- Also, it can be argued that DMS probably exhibits a threshold for carcinogenicity since the compound is hydrolyzed extremely rapidly in aqueous environments.

- In spite of such considerations, it may be prudent to assume a worst-case TTC limit for DMS since most regulatory agency assessors may be reluctant to accept evaluations based on “read across” approaches. On the other hand, for other structurally alerting potential impurities such as 4-chlorobutyryl chloride in levetiracetam, application of the TTC limit is not justified (since the PGI is reported in TOXNET to be Ames-negative).

Table No. 3: Limit of Genotoxic impurity (µg/g) =TTC (µg) /Daily dose(g)

Daily dose (mg)	Daily dose (g)	Limit (limit)
1.5	0.0015	1000
15	0.015	100
150	0.15	10
1500	1.5	1
15000	15	0.1

Table No. 4: Acceptable intake for an individual impurity.

Duration of treatment	**≤1 month**	**>1-12 moths**	**>1-10years**	**>10 years to the lifetime**
Daily intake microg/day	120	60	30	5

The concentration limits in ppm of genotoxic impurity in drug substance derived from the TTC can be calculated based on the expected daily dose to the patient using an equation

Concentration limit (ppm) = TTC [µg/day] dose (g/day]

Table No. 5: Cohort of concern[3]

Compounds	**Risk / million**
Aflatoxin-like compounds	5
Aromatic amines	5
Aromatic nitrates	2
Azoxy compounds	0
Azoxy compounds	4
Benzidine derivatives	2
Carbamates	0
Heavy metal-containing compounds	1
Highly chlorinated compounds	5
Hydrazines	2
Miscellaneous ash by alerts	2
α –Nitro furyl Compounds	1
N- Nitroso compounds	47
Organophosphorus	0
Steroids	5
Strained rings	1
Tetrahalogenated dibenzodioxins and dibenzofurans (2,3,7,8)	2
Vinyl containing compounds	2

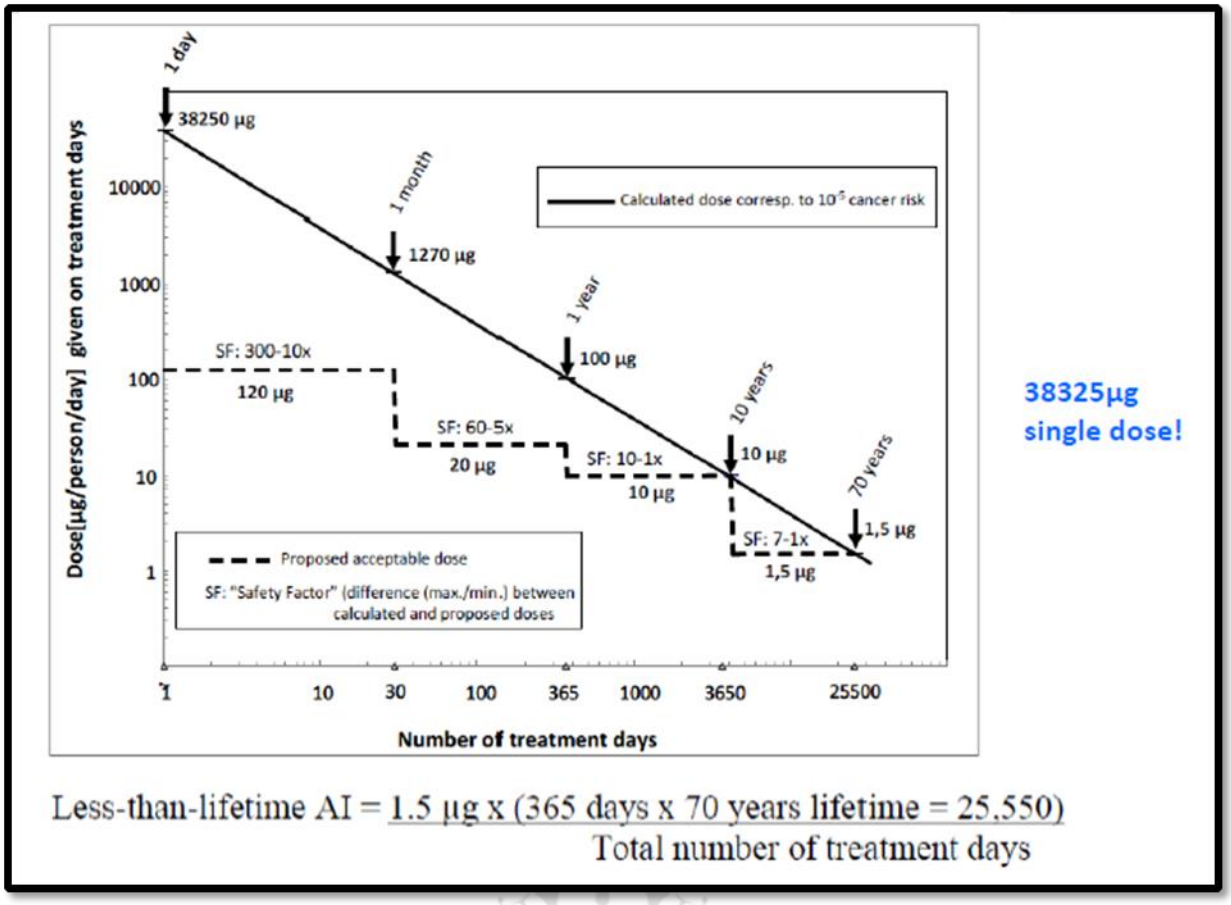

Figure No. 4: Graph between Dose Vs Number of treatment days

- Establishing Less Than Lifetime exposure limits (ICH M7 notes 6)Impurities in drug substances are defined as "any component of the new drug substance that is not the chemical entity defined as the new drug substance" according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q3A(R2) guideline In the case of drug products, impurities are defined as "any component of the new drug product that is not the drug substance or an excipient in the drug product" according to the ICH Q3B(R2) guideline .

- A subset of the impurities is genotoxic, presenting a safety concern to clinical trial subjects and patients. This chapter provides an overview of the regulatory guidelines that are relevant to impurities and genotoxic impurities.

- High-Performance Thin-Layer Chromatographic Determination of Celecoxib in its Dosage Form the ICH is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

The ICH brings together the regulatory authorities and pharmaceutical industry of Europe, Japan, and the United States to discuss scientific and technical aspects of drug registration. Since its inception in 1990, the ICH has evolved, through its ICH Global Cooperation Group, to respond to the increasingly global face of drug development, so that the benefits of international harmonization for better global health can be realized worldwide. ICH's mission is to achieve greater harmonization to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. The main focus of the ICH process is the preparation of harmonized guidelines that are adopted in the three ICH regions: the European Union (EU), the United States, and Japan. Countries outside the ICH may also use the ICH guidelines within their own countries. Generally, the ICH guidelines are accepted as the industry standard. ICH guideline topics are divided.

- **Q (quality guidelines):** harmonization achievements in the quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing, and a more flexible approach to pharmaceutical quality based on good manufacturing practice (GMP) risk management.

- **S (safety guidelines):** the ICH has produced a comprehensive set of safety guidelines to uncover potential risks like carcinogenicity, genotoxicity, and nephrotoxicity. A recent breakthrough has been a nonclinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

- **E (efficacy guidelines):** the work carried out by the ICH under the efficacy heading is concerned with the design, conduct, safety, and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better-targeted medicines.

- **M (multidisciplinary guidelines):** these are the cross-cutting topics that do not fit uniquely into one of the qualities, safety, and efficacy categories. This category includes ICH medical terminology (MedDRA), the common technical document, and development of Electronic Standards for the Transfer of Regulatory Information. The following sections provide a summary of pertinent guidelines with the focus on aspects of impurities and genotoxic impurities. In order not to change the meaning of the guidelines, the original content has been used as closely as possible. References cited in the guidelines are not included in this chapter for the sake of conciseness.

10. Impurities in New Drug Substances, Ich Q3a (R2)

ICH Q3A(R2) is intended to guide registration applications on the content and quantification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. Although this guideline is not intended to be applied during the clinical research stage of development, in later stages of development the thresholds in this guideline can be useful in evaluating new impurities observed in the drug substance batches prepared by the proposed commercial process.

Impurities in new drug substances are addressed from two perspectives:

Chemistry aspects include classification and identification of impurities, report generation, the listing of impurities in specifications, and a brief discussion on analytical procedures.

Safety aspects include specific guidance for qualifying those impurities that were not present or were present at substantially lower levels, in batches of new drug substances used in safety and clinical studies.[5]

Impurities can be classified into the following categories:

• Organic impurities (process and drug-related)

• Inorganic impurities

• Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substances. They can be following,

- Identified or unidentified, volatile or non-volatile, and include the following:
- Starting materials
- By-products
- Intermediates
- Degradation products

- Reagents, ligands, and catalysts

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

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

Other materials (e.g., filter aids and charcoal)[3]

- Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance.
- Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH guideline Q3C on residual Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH guideline Q3C on residual solvents Details of the actual and potential organic impurities most likely to arise during the synthesis, purification, and storage of a new drug substance should be summarized and included in the registration application.
- The summary should be based on a sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products.
- This discussion can be limited to those impurities that might reasonably be expected based on the knowledge of the chemical reactions and conditions involved. [3]

Table No. 6: Reporting identification and qualification thresholds for impurities in new drug substance, ICH Q3A

Maximum Daily Dose (g/day)	Reporting Threshold (%)	Identification threshold	Qualification threshold
≤2	0.05	0.10% or 1.0mg/day intake (whichever is lower	0.15 or 1.0mg/day intake (whichever is lower
>2	0.03	0.05%	0.05%

(Source: Impurities in New Drug Substances, ICH Q3A (R2), ICH Harmonised Tripartite Guideline, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.)

- Identification of impurities present at an apparent level, not more than (≤) the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold.

- Genotoxic impurities are considered to be unusually potent impurities in this respect to the documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities should be included in the registration application. Technical factors (e.g., manufacturing capability and control methodology) can be considered part of the justification for the selection of alternative thresholds based on manufacturing experience with the proposed commercial process.

- Technical factors (e.g., manufacturing capability and control methodology) can be considered part of the justification for the selection of alternative thresholds based on manufacturing experience with the proposed commercial process.

- The studies considered appropriate to qualify an impurity will depend on several factors, including the patient population, daily dose, and route and duration of drug administration. Such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate. [5]

11. Impurities in New Drug Products, Ich Q3b (R2)

- ICH Q3B (R2) guides registrations applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances.

- This guideline is complementary to the ICH Q3A(R) guideline. The ICH Q3C guideline on residual solvents should also be consulted, if appropriate. The ICH Q3C guideline on residual solvents should also be consulted, if appropriate. This guideline addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure

system (collectively referred to as “degradation products” in this guideline).

- 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. Impurities arising from excipients present in the new drug product or extracted or leached from the container closure system are not covered by this guideline. This guideline also does not apply to new drug products used during the clinical research stages of development.[5]

12. Impurities: Guideline for Residual Solvents, Q3c (R5)

- The objective of Q3C (R5) is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. The objective of Q3C (R5) is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

- 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 the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. [5]

13. General Principles[5]

Classification of residual solvents by risk assessment

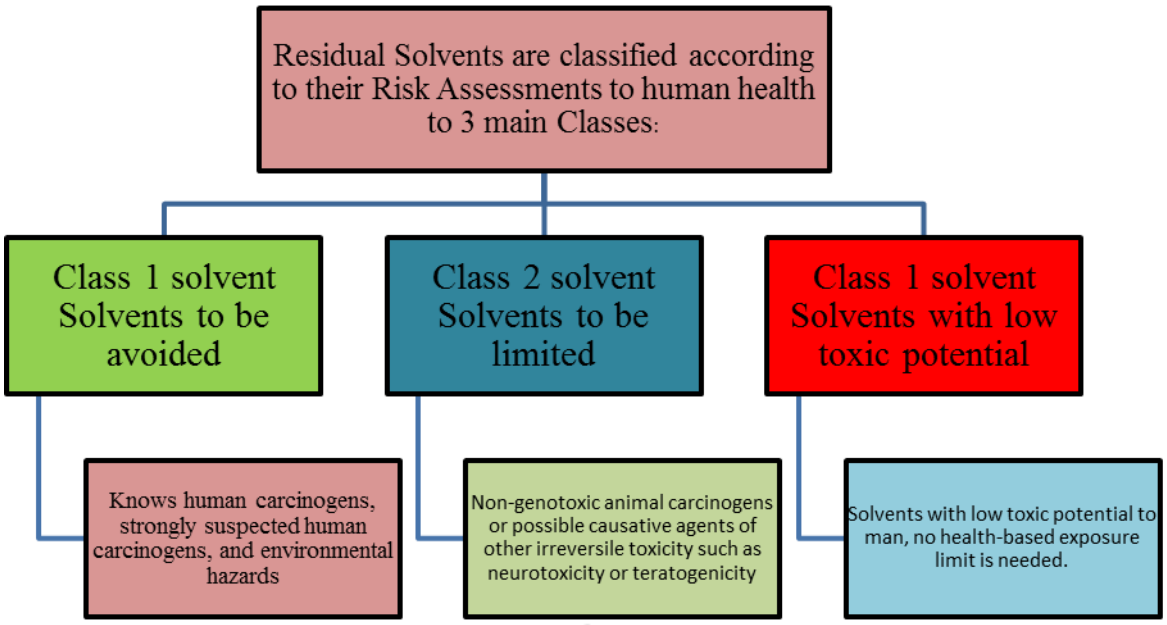

Figure No. 5: Classification of residual solvents by risk assessment

13. Analytical Procedures Residual Solvents:

Are typically determined using chromatographic techniques such as **gas chromatography?** Any harmonized procedures for determining levels of residual solvents as described in the pharmacopeias should be used, if feasible. Otherwise, manufacturers would be free to select the most appropriate validated analytical procedure for a particular application. If only Class 3 solvents are present, a non-specific method such as loss on drying may be used. Validation of methods for residual solvents should conform to ICH guidelines Text on Validation of Analytical Procedures and Extension of the ICH Text on Validation of Analytical Procedures.[5]

14. Limits of Residual Solvent[5]

14.1 Class 1 solvent

Solvents to be avoided

Solvents in Class 1 should not be employed in the manufacture of drug substances,

excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1 unless otherwise justified. 1, 1, 1-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1500 ppm is based on a review of the safety data.[5]

Table No. 7: 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 hazards
1,2-Dichloroethane	5	Toxic
1.1-Dichloroethanes	8	Toxic
1,1,1-Trichloroethane	1500	Environmental Hazard

14.2 Class 2 solvent

Solvents to be limited [5]

Solvents in Table 2 should be limited in pharmaceutical products because of their inherent toxicity. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

Table No. 8: Class 2 solvents in pharmaceutical products

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chloroform	0.6	60
Cyclohexane	38.8	3880
Formamide	2.2	220
Methanol	30	3000
N-Methylpyrrolidone	5.3	530
Tetrahydrofuran	7.2	720
Xylene	21.7	2170
Toluene	8.9	890

14.3 Solvents with Low Toxic Potential[5]

Solvents in Class 3 (shown in Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally

accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less **(corresponding to 5000 ppm or 0.5% under Option 1).**

Table No. 9: Class 3 solvents in pharmaceutical products.[5]

Acetone	**Methyl isobutyl ketone**	**Ethyl ether**
Acetic acid Heptane	Dimethyl sulfoxide	Ethyl formate
Anisole	Ethanol	Formic acid
Methyl acetate	Ethyl acetate	3-Methyl-1-butanol
Butyl acetate	Ter-Butylmethyl ether	Isobutyl acetate
1-Butanol	Methyl ethyl ketone	1-Pentanol
2-Methyl-1-Propanol	Heptane	Isopropyl acetate
2-Butanol	Pentane	1-Propanol

Table No. 10: Example of class 3 solvent should be limited by GMP or other quality-based requirements.

14.4.1 Solvents for which no adequate toxicological data was found. [5]

1,1-Diethoxypropane	**Isooctane**
Methyl isopropyl ketone	Isopropyl Ether
1,1-Dimethoxymethane	Petroleum ether
Methyl tetrahydrofuran	Trichloroacetic acid
2,2-Dimethoxypropane	

14.4.2 Options for describing limits of class 2 solvents [5]

The options are used to describe the limit class 2 solvent.

Option 1: Testing should be performed for residual solvent when production or purification process is known to result in the presence of such solvent. Option 1By assuming a product mass of 10 g administered daily

Concentration (ppm) =1000*PDE/ dose

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

No further calculation is necessary provided that the daily dose not exceed 10 g

Option 2: products that are administered

Products that are administered in a dose greater than 10g per day applied by adding the amounts of a residual solvent present in each of the components of the drug product .the sum of the amounts of solvent per day should be less than that given by the PDE.

Example of option 2

The permitted daily exposure to acetonitrile is 4.1 mg per day, thus, the option 1 limit is 410 ppm the maximum administered daily mass of drug product is 5.0g and drug product contains two excipients. The composition of the drug product and the calculate maximum content of residual acetonitrile are given in the following table.

Table No. 10: Composition of the drug product and the calculate maximum content of residual acetonitrile

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	400 ppm	0.36 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Drug Product	5.0 g	728 ppm	3.64 mg

Excipient 1meets the option 1 limit, but the drug substance, excipient 2 and drug product do not meet the option 1 limit however the product meets the option 2 limits of 4.1 mg per day and thus conforms to the recommendation in this guideline.

Specification for class 1 and class 2 residual solvent in active substance [5]

A) Class 1 solvent used as starting materials

They should be routinely controlled, either in suitable

B) Class 1 solvent present as an impurity

It should be NMT 30% of the specified limit, in a suitable intermediate or the final active substance, supporting data should be presented on 6 consecutive pilot scale batches 3 or consecutive industrial scale batches.

C) Class 2 solvents used in the last step of the synthesis

It should be routinely controlled in the final active substance

D) Class 2 solvent used before the last step of the synthesis

It should be NMT 10 % of the acceptable concentration limit (e.g acetonitrile 41 ppm) supporting data should be 6 consecutive pilot scale batches or 3 consecutive industrial scale batches [5]

Analytical procedures:

- Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonized procedures for determining levels of residual solvents as described in the pharmacopeias should be used, if feasible. Otherwise, manufacturers would be free to select the most appropriate validated analytical procedure for a particular application. If only Class 3 solvents are present, a non-specific method such as loss on drying may be used. [5]

Reporting levels of residual solvents:

- Manufacturers of pharmaceutical products need certain information about the content of residual solvents in excipients or drug substances to meet the criteria of this guideline.

- The following statements are given as acceptable examples of the information that could be provided from a supplier of excipients or drug substances to a pharmaceutical manufacturer.

- The supplier might choose one of the following as appropriate: Only Class 3 solvents are likely to be present.

- Loss on drying is less than 0.5%. Only Class 2 solvents X, Y, are likely to be present. All are below the Option 1 limit. (Here the supplier would name the Class 2 solvents represented by X, Y, ...) Only Class 2 solvents X, Y, and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5%. If Class 1 solvents are likely to be present, they should be identified and quantified. EMA/CHMP/ICH/82260/2006 Page 7/26 "Likely to be present" refers to the solvent used in the final manufacturing step and to solvents that are used in earlier manufacturing steps and not removed consistently by a validated process. If solvents of Class

2 or Class 3 are present at greater than their Option 1 limits or 0.5%, respectively, they should be identified and quantified.[5]

15. Methods for establishing exposure limits

PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL) in the most relevant animal study as follows:

PDE = NOEL x Weight Adjustment / F1 x F2 x F3 x F4 x F5

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species

F1 = 5 for extrapolation from rats to humans

F1 = 12 for extrapolation from mice to humans

F1 = 2 for extrapolation from dogs to humans

F1 = 2.5 for extrapolation from rabbits to humans

F1 = 3 for extrapolation from monkeys to humans

F1 = 10 for extrapolation from other animals to humans

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F1 takes into account the comparative surface area: body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.67} \quad (2)$$

In which M = body mass and the constant k has been taken to be 10. The body weights used in the equation are those shown below in Table A3.1.

F2 = A factor of 10 to account for variability between individuals

A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this guideline.

F3 = A variable factor to account for toxicity studies of short-term exposure

F3 = 1 for studies that last at least one-half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs, and monkeys).

F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.

F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents.

F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents.

F3 = 10 for studies of a shorter duration.

In all cases, the higher factor has been used for study durations between the time points, e.g. a factor of 2 for a 9-month rodent study.

F4 = A factor that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fatal toxicity associated with maternal toxicity

F4 = 5 for fatal toxicity without maternal toxicity

F4 = 5 for a teratogenic effect with maternal toxicity

F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the no-effect level was not established

When only a LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.[2]

PQRI Guideline:[6]

15.1 Product Quality Research Institute

• The not-for-profit, a non-stock, tax-exempt entity incorporated in Virginia

• Serves as a forum for academia, industry, and FDA to work cooperatively

• PODP Leachable and Extractable Working Group currently in operation

15.2 Highlights of PQRI Process[6]

Opportunity to collect raw data through independent experiments/studies, or through data-mining

• Scrutiny of data by scientists from diverse backgrounds

• Discussion of data outside of NDA process

15.3 History of PQRI OINDP Leachable and Extractable Working Group[7]

- Proposal to develop thresholds and examine best practices for L&E in OINDP drafted by IPAC-RS and submitted to PQRI
- Working Group formed in 2001, consisting of chemists and toxicologists from FDA, industry, and academia
- Working Group developed a hypothesis and step-wise plan to investigate per established PQRI process
- Work plan approved by PQRI DPTC and Steering Committee in 2002
- Toxicologists and chemists formed sub-groups.

15.4 History of PQRI OINDP Leachable and Extractables Working Group[7]

- Toxicologists: acquired data through extensive literature and database searches and analyses
- Chemists: acquired data by conducting extractions studies and placebo leachable study
- Developed recommendations, “Safety Thresholds and Best Practices for Leachable and Extractables Testing in Orally Inhaled and Nasal Drug Products”
- Submitted final to PQRI and FDA in summer 2006 Science and data-based recommendations to PQRI and FDA. Not a policy/regulatory document

Nasal Sprays:

- Nasal spray drug products contain therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, buffering agents) in nonpressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump or could have been premiered during manufacture. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of the formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local and/or systemic effects. Metering and spray producing (e.g., orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation, and these can be constructed of many parts of different design that are precisely controlled in terms of dimensions and composition. [8]

- The concept of classical bioequivalence and bioavailability may not be applicable for all nasal sprays, depending on the intended site of action. The doses administered are typically so small that blood or serum concentrations are generally undetectable by routine analytical procedures. Additional information will be provided in future guidance for industry on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action. [8]

Inhalers:

Definition of SCT and QT

- Safety Concern Threshold (0.15 µg/day): - Dose below which concern for carcinogenicity and noncarcinogenic toxicity is negligible – Identification of leachable below this threshold generally would not be necessary. [9]

- Qualification Threshold (5 µg/day) - Dose below which concern for noncarcinogenic toxicity is negligible - Leachable below this threshold without structural alerts for carcinogenicity or irritation would not require compound-specific risk assessment. [9]

Definition Analytical Evaluation Threshold (AET)

- The AET is the threshold at or above which an OINDP pharmaceutical development team should identify and quantify a particular extractable and/or leachable and report it for

potential toxicological assessment. The AET is based directly on the SCT but is a relative value, not an absolute value.

Example AET Calculation for a Metered Dose Inhaler

- Consider an MDI with 120 labeled actuations per canister, a recommended dose of 8 actuations per day, and a critical component elastomer mass per valve of 250 mg. For an individual organic leachable derived from this elastomer, the estimated AET would be

$$\text{Estimated AET} = \frac{(0.15 \text{ mg /day} * 120 \text{ labeled actuation /canister})}{8 \text{ actuation / day}}$$

Estimated AET~ 2.25 mg / canister

PDP (Parenteral Drug Product) Toxicology Outcome

- An SCT approach can be applied to leachable sand extractable qualification in parenteral drug products.

- Based on most Parenteral Drug Product (PDP): of 1.5 µg/day for an individual organic leachable can be used to calculate an AET.

- The QT developed for OINDP was further evaluated adapted from the Cramer

Classification to identify and qualify leachable.

- Class 1 (systemic toxicity) 50 µg/day

- Class 2 (sensitizer/irritant) 5 µg/day

- Class 3 (mutagens/carcinogens) 1.5 µg/day

Different risk factors require different approaches

Table No. 11: L & E Risk Based Assessment of Dosage Forms

	OINDP	PODP	PODP
		Parenteral	Ophthalmic
Representative Dosage form	Metered-dose inhaler (the focus of PQ RI recommendations)	• Prefilled syringe • Small and large volume	Topical solutions and suspensions (eye drop)
Formulation	• Strong solvents • "All extractable are leachable"	• Primarily aqueous • Less aggressive than MDI formulations • P^H affects matter	
Examples of Critical Packaging Materials	Elastomers (MDI valve)	• Polyolefin • Elastomers • Cyclic olefin copolymers • Polycarbonate	• Polyolefin • 2^o packaging components
Typing dosing	Pulmonary	Direct to bloodstream or tissue	Topic, ocular

OINDP (Orally Inhaled and Nasal Drug Products**) Threshold and Best Practices**

Safety Concern Threshold (SCT)

Low-Risk Leachables Not Identified

• <0.15 ug/day

• Qualification Threshold (QT)

Assessment of Identified Leachable

• Non-carcinogenic >5 µg/day

Table No. 12: SCT by therapeutic area

Drug Product	OINDP (PQRI-OINDP)	Injectables/PDP (PQRI-PODP)
SCT	0.15 µg/day	1.5 µg/day
Origin/Published	PQRI-OINDP Guideline 2006 E & L Handbook 2012 USP <1664.1>	PQRI-PODP WG Paskiet et al., PDA J. Pharm. Sci. Technol., 2013 67(5) 430-447
Comments	Used metered dose inhaler as a model; highest risk profile, most conservative SCT	PQRI-PODP guideline in the draft, anticipated in 2017

With PODP recommendation, we are evolving towards SCT's specific to therapeutic area

History of E&L in Ophthalmology

US-FDA - Ophthalmology[1]

Unpublished set of consistent practices in place for ~ 15 years

Specification limits on individual, unspecified impurities: NMT 0.1%

Higher limits negotiable for potent APIs

Avoid penalizing companies for potent drugs

Surrogate means of monitoring for unexpected leachables

For confirmed leachable:

Report in ppm, ug/mL or ug/g; % vs API is not relevant

Above 1 ppm – report

10 ppm – identification (in practice, most companies ID at 1 ppm)

20 ppm – qualify (in practice, most companies assess at 1 ppm)

Thresholds are concentration-based, not dose-based (PQRI)

Ophthalmic manufacturers continue to use this approach for US filings

These US practices have been successfully used for EU filings, but there does not appear to be a consistent practice in place

Best Practices for E&L studies

- Controlled Extraction Studies (CES)
- Analytical Evaluation Threshold (AET)
- Identification threshold

Inhalation Solutions and Suspensions:

• An inhalation spray drug product consists of the formulation and the container closure system. The formulations are typically aqueous-based and, by definition, do not contain any propellant. Aqueous-based oral inhalation solutions and suspension must be sterile (21 CFR 200.51). Inhalation solutions and suspensions are intended for delivery to the lungs by oral inhalation for local and/or systemic effects and are to be used with a specified nebulizer. Unit-dose presentation is recommended for these drug products to prevent microbial contamination during use. The container closure system for these drug products consists of the container and closure and can include protective packaging such as foil overwrap. Recommendations on overwrapping of inhalation drug products packaged in semipermeable container closure systems are provided in section III.G.[5].

• Inhalation Sprays: An inhalation spray drug product consists of the formulation and the container closure system. The formulations are typically aqueous-based and, by definition, do not contain any propellant. Inhalation sprays are intended for delivery to the lungs by oral inhalation for local and/or systemic effects. The products contain therapeutically active ingredients and can also contain additional excipients. The formulation can be in unit-dose or multidose presentations. The use of preservatives or stabilizing agents in inhalation spray formulations is

Table No. 13: Examples of Packaging concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspension	Sterile Powder and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspension; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solution and Suspensions; Topical and Lingual Aerosols; Oral Solution and Suspension	Topical powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

CONCLUSION:

Impurity assessment is very important as the regulatory requirement is concern.according to ICH, ICH Q3A and ICH Q3B this two guidelines for impurity there is the specific limit for every type of impurity and that limit should not be exceeded. Impurity should follow the qualification and quantification threshold as per regulatory. Before releasing, a product into market impurity qualification is very necessary if a product fails that test then that product not released into the market.

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