IMPURITIES IN NEW DRUG SUBSTANCES Q3A(R2)

CLASSIFICATION OF IMPURITIES

Impurities can be classified into the following categories:

- Organic impurities (process- and drug-related) ⇒ خلال عملية التصنيع او خاصة بالدواء نفسها
- Inorganic impurities ⇒ hydrocarbone ما فيها
- Residual solvents

Terminology

- **In-process tests**, are tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal series of tests which are conducted prior to release.

- **Degradation product:** A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.

Terminology

drug substance ال خاص فقط في → therapeutic part of drug

new مادة ما الها علاقة بال chemically من خاصية drug

- **Impurity:** (1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance. (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product.

تشمل ال both

- **Identified impurity:** An impurity for which a structural characterization has been achieved.

يعني ال chemical structure واضح، مثلا ممكن اعملها IR او mass spectroscopy تحدد ال functional group

Terminology

- **Specified impurity:** An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Organic Impurities

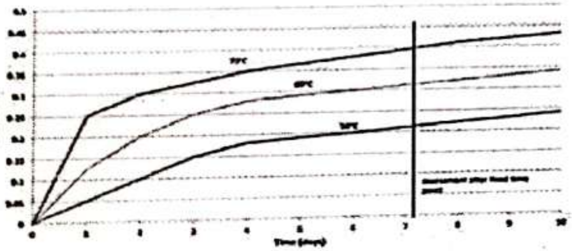
- The applicant should summarize the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance.
- In addition, the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance including results of:
  1. batches manufactured during the development process
  2. batches from the proposed commercial process
- stress testing (see ICH Guideline Q1A on Stability) used to identify potential impurities arising during storage.

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Organic Impurities

Stress testing (drug substance)

- Studies undertaken to elucidate the intrinsic stability of the drug substance.
- Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for **accelerated** testing.



RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Reporting Threshold: A limit above (>) which an impurity should be reported.

Identification Threshold: A limit above (>) which an impurity should be identified.

Qualification Threshold: A limit above (>) which an impurity should be qualified.

Qualification: The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

يكونه عن طريق الـ chromatogram احيانا الـ identification في not-feasible (غير ممكن)

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

- Any impurity (or degradation product observed in stability studies) at a level greater than (>) the identification threshold in any batch manufactured by the proposed commercial process should be identified.
- When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application.
- Where attempts have been made to identify impurities present at levels of not more than (≤) the identification thresholds, it is useful also to report the results of these studies.

application يتحاول خلال الـ في ملفات التسجيل يكونه عبارة عن كل الـ data اللي عملناها عشانه نعين هاد الـ identification

لازم الـ data بس تكونه موضحة reporting وعلى اساسها بنعمل الـ تحليل يكونه واضح تماما وبعدها بنقارنها في الـ thresholds

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Thresholds

above

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%

دائما يروح عند ال lower لانه يعطينا امان اكتر

[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

يعني لازا بدي اروح لحتى اعلى من هيك لازم يكون عندي مبرر علمي / اذا زاد ال threshold في خطورة

لـ اذا كانت الـ toxicity الها شديدة لازم نروح لـ lower

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Example 1: **0.5 g Maximum Daily Dose**

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 0.15%

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 0.15% exceeded?)
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5 0,1	None اعلى من	None
0.12	0.12[1)]	0.6	reported Yes	None[1)]
0.1649	0.16[1)]	0.8	Yes	Yes[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%

11

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Example 2: **0.8 g Maximum Daily Dose**

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 1.0 mg TDI

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 1.0 mg TDI exceeded?)
0.066	0.07	0.6	None	None
0.124	0.12	1.0	yes	None[1)2)]
0.143	0.14	1.1	yes	Yes[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%

biological safety يرتبط في ال

Qualification of impurities

- The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified. (animal + human) تشمل
- Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified.
- If data are unavailable to qualify the proposed acceptance criterion of an impurity, studies to obtain such data can be appropriate when the usual qualification thresholds given in are exceeded.
- In some cases, decreasing the level of impurity to not more than the threshold can be **simpler** than providing safety data.
- Alternatively, adequate data could be available in the scientific literature to qualify an impurity.

level احيانا ممكن نروح على ال qualification الاعلى من ال data ممكن انه ندرس ال الموجودة على الجرعة الاعلى

دائما لازم كامل نوعي اي اشي بديل بيعطي

في حل ممكن انه كاول نقلل ال impurity واحد ال ويبدل نقللها من البداية سواء من ال synthesis او ال purification

* دراسات ال safety مهمة ومكلفة خصوصا اذا اعتمدنا على ال human يعني البديل من الاصل نقلل ال level الحالي
* الحل (١) انه الدراسات تشتغل على اعلى من ال qualification
* الحل (٢) ندور في ال scientific literature

REPORTING IMPURITY CONTENT OF BATCHES

- Analytical results should be provided in the application for all batches of the new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process considering the following:
  - Quantitative results should be presented numerically, and not in general terms such as "complies", "meets limit" etc.
  - Below 1.0%, the results should be reported to two decimal places (e.g., 0.06%, 0.13%); at and above 1.0%, the results should be reported to one decimal place (e.g., 1.3%).
  - Any impurity at a level greater than (>) the reporting threshold should:
    - be reported with the analytical procedures indicated.
    - impurities should be summed and reported as total impurities.

14

٧

٢٩/٠٤/١٤٤٤

REPORTING IMPURITY CONTENT OF BATCHES

- For each batch of the new drug substance, the report should include:
  - Batch identity and size
  - Date of manufacture
  - Site of manufacture location
  - Manufacturing process
  - Impurity content, individual and total
  - Use of batches
  - Reference to analytical procedure used

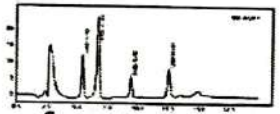
tableting mixing

development, manufacturing

artical, USP

Listing of impurities in specifications

- The specification for a new drug substance should include a list of impurities.
- Those individual impurities with specific acceptance criteria included in the specification for the new drug substance are referred to as "specified impurities" in this guideline.
- Specified impurities can be identified or unidentified.
- Specified, unidentified impurities should be referred to by an appropriate qualitative analytical descriptive label (e.g., "unidentified A", "unidentified with relative retention of 0.9").



- A general acceptance criterion of not more than (≤) the identification threshold for any unspecified impurity and an acceptance criterion for total impurities should be included.

16

Listing of impurities in specifications

In summary, 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*

Impurity limits in Pharmcopeias: e.g. felbinac

Related substances.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent) ;

— *impurity B*: not more than the area of the peak due to felbinac in the chromatogram obtained with the reference solution (0.1 per cent) ;

— *unspecified impurities*: for each impurity, not more than the area of the peak due to felbinac in the chromatogram obtained with the reference solution (0.10 per cent) ;

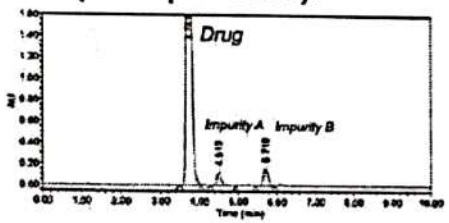
— *total* : not more than twice the area of the peak due to felbinac in the chromatogram obtained with the reference solution (0.2 per cent) ;

— *disregard limit*: 0.5 times the area of the peak due to felbinac in the chromatogram obtained with the reference solution (0.05 per cent).

Chlorides: maximum 110 ppm.

Sulfates: maximum 130 ppm.

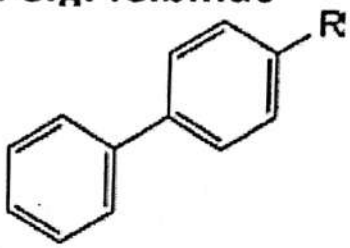
Sulfated ash (*2.4.14*) :
maximum 0.1 per cent, determined on 1.0 g.

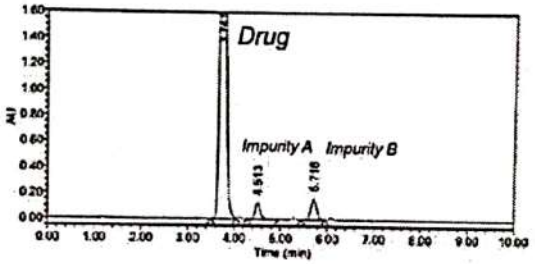


Impurity limits in Pharmcopeias: e.g. felbinac

IMPURITIES
Specified impurities : A, B.

A. R = $CO\text{-}CH_3$: 4-acetyl biphenyl,
B. R = H: biphenyl.





يمكن يكون عنا بعض الـ impurities
بعض الـ peaks الصغيرة
او الـ signals (ممكن نخربط
بينها وبين الـ noise)

Disregard limit: in chromatographic tests, **the nominal content at or below which peaks/signals are not taken into account for calculating a sum of impurities.** The numerical values for the disregard limit and the reporting threshold are usually the same.

IMPURITIES IN NEW DRUG PRODUCTS Q3B(R2)

٤٣٣١/٤

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Organic Impurities

- This guideline is complementary to the ICH Q3A(R) guideline "Impurities in New Drug Substances".
- The applicant should summarize the degradation products observed during manufacture and/or stability studies of the new drug product.
- The applicant should summarize any laboratory studies conducted to detect degradation products in the new drug product.
- This summary should also include test results of batches manufactured during the development process and batches representative of the proposed commercial process.
- A rationale should be provided for exclusion of those impurities that are not degradation products (e.g., process impurities from the drug substance and impurities arising from excipients).

RATIONALE FOR THE REPORTING

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Organic Impurities

- The rationale is similar to drug substances with regard to:
  - reporting, identification and qualification threshold concepts (but the threshold values are different)
  - the rounding of presented results
  - Chromatograms with peaks labelled (or equivalent data if other analytical procedures are used) from representative batches, including chromatograms from analytical procedure validation studies and from long-term and accelerated stability studies, should be provided.

22

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Attachment 1: Thresholds for Degradation Products in New Drug Products

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%

→ total daily intake

نروح على الاقل ⇐ عشان ال safty

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%

هون ال safety نروح على ال dose الاعلى

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Example 1: 50 mg Maximum Daily Dose

Reporting threshold: 0.1%
Identification threshold: 0.2%
Qualification threshold: 200 µg

'Raw' Result (%)	Reported Result (%) (Reporting Threshold = 0.1%)	Total Daily Intake (TDI) of the Degradation Product (rounded result in µg)	Action	
			Identification Threshold 0.2% exceeded?	Qualification Threshold 200 µg TDI exceeded?
0.04	Not reported	20	None	None
0.2143	0.2 تقريبا	100	None	None
0.349	0.3[1]	150	Yes	None[1]
0.550	0.6[1]	300	Yes	Yes[1]

24

RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

Example 2: 1.9 gram Maximum Daily Dose
Reporting threshold: 0.05%
Identification threshold: 2 mg
Qualification threshold: 3 mg

'Raw' Result (%)	Reported Result (%) (Reporting Threshold = 0.05%)	Total Daily Intake (TDI) of the Degradation Product (rounded result in mg)	Action	
			Identification Threshold 2 mg TDI exceeded? dose	Qualification Threshold 3 mg TDI exceeded?
0.049	Not reported	1	None	None
0.079	0.08	2	None	None
0.183	0.18[1]	3	Yes	None[1, 2]
0.192	0.19[1]	4	Yes	Yes[1]

REPORTING IMPURITY CONTENT OF BATCHES

- For each batch of the new drug product described in the registration application, the documentation should include:
- Batch identity, strength, and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Immediate container closure
- Degradation product content, individual and total
- Use of batch (e.g., clinical studies, stability studies)
- Reference to analytical procedure used
- Batch number of the drug substance used in the new drug product
- Storage conditions for stability studies

هل استعمل معين letriture او pharmacopya

26

Listing of impurities in specifications

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.

لـ سببه exposure حطينا الصور ---

كله رح يتحدد unspecifidr specified

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS Q3C(R6)

INTRODUCTION

- 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.
- Appropriate selection of the solvent for the synthesis of drug substance may:
  - enhance the yield, or
  - determine characteristics such as crystal form, purity, and solubility.
- Therefore, the solvent may sometimes be a critical parameter in the synthetic process.
- The ICH guideline does not address:
  - solvents deliberately used as excipients (vehicles)
  - solvates => crystal with molecule of solvent

• solvates => crystal with molecule of solvent

29

INTRODUCTION

- Drug products should contain no higher levels of residual solvents than can be supported by safety data.
- (Class 1) Some solvents that are known to cause unacceptable toxicities should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment.
- (Class 2) Some solvents associated with less severe toxicity should be limited in order to protect patients from potential adverse effects.
- (Class 3) Ideally, less toxic solvents should be used where practical.

30

SCOPE OF THE GUIDELINE

- Residual solvents in drug substances, excipients, and in drug products are within the scope of this guideline.

solvate, vehicle ما منشي ال

- It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug product.

رح نيراقب هاي العمليات اللي بتكون فيها سواء manufacture purification
او ال synthesis وعلى اساسها بقل test لهاي ال solvent

SCOPE OF THE GUIDELINE

- A cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. (drug A, excipient B, C, D, etc)
  - ➢ If the calculation results in a level equal to or below that recommended in this guideline → no testing of the drug product for residual solvents need be considered.
  - ➢ If, however, the calculated level is above the recommended level → the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount.
- Drug product should also be tested if a solvent is used during its manufacture.

SCOPE OF THE GUIDELINE

- The guideline applies to all dosage forms and routes of administration.
  سواء oral / parenteral
- Higher levels of residual solvents may be acceptable in certain cases such as **therapies** for short term (30 days or less) ① or topical application. ②
  مش ممكن يسمحوا يكون ال residual solvent نسبته اعلى في حالتين ① اذا كانت مدة العلاج قليلة او ② استخدام topical
- Justification for these levels should be made on a case by case basis.
  * لو مثلا عملت topical بمعيار معين بدي افحص مثلا رفعت ال solvent للعلاج مدته 25 يوم بدي افحص ويكون مثبت علميا
  * لازم احدد كم residual solvent في كل جزئية وآخر اشي في ال product وعلى هاد الاشي يتم عليه ال report

Options for Describing Limits of Class 2 Solvents

(Class 2) Some solvents associated with less severe toxicity should be limited in order to protect patients from potential adverse effects.

Option 1:

- The concentration limits in ppm stated in Table 2 (ICH guidelines Q3C) can be used. They were calculated using equation (1) below by assuming a product mass of 10 g

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

- Here, **Permissible Daily Exposure (PDE)** is given in terms of mg/day and dose is given in g/day.

LIMITS OF RESIDUAL SOLVENTS: Class 2

Part of Table 2 (ICH Q3C), 10 gm daily

$$\text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}} \quad (1)$$

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	*PDE (mg/day)*	*Concentration limit (ppm)*
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene[1]	0.7	70
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380

35

Options for Describing Limits of Class 2 Solvents

Options for Describing Limits of Class 2 Solvents

Option 1:

- These limits are considered acceptable for all substances, excipients, or products. ⇒
- Therefore this option may be applied if the daily dose is not known or fixed.
- If all excipients and drug substances in a formulation meet the limits given in Option 1, then these components may be used in any proportion.
- No further calculation is necessary provided the daily dose does not exceed 10 g. ⇒
- Products that are administered in doses greater than 10 g per day should be considered under Option 2.

less toxisty

Options for Describing Limits of Class 2 Solvents

Option 2:

- It is not considered necessary for each component of the drug product to comply with the limits given in Option 1.
- The PDE in terms of mg/day as stated in Table 2 can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in drug product.
- Option 2 may be 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.

صالحة

Options for Describing Limits of Class 2 Solvents

Option 2: Example 1 (acetonitrile in a drug product.)

➢The maximum administered daily mass of a drug product is 5.0 g.

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

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	*PDE (mg/day)*	*Concentration limit (ppm)*
Acetonitrile	4.1	410

- Excipient 1 meets the Option 1 limit, but the drug substance, excipient 2, and drug product do not meet the Option 1 limit.
- Nevertheless, the product meets the Option 2 limit of 4.1 mg per day and thus conforms to the recommendations in this guideline.

residual solvent

800 * 0.3 = 0.24

400 * 0.9 = 0.36

800 * 3.8 = 3.04

Comulative ≠
800+400+800 = 2000

not pass

pass excipient 1

excipient 2 not pass

عشان ال drug product انطلع على ال daily exposure

(drug product) pass

عشان هيك ال drug product كان pass مش حسب ال content هو يعني الفرق اكبر من 410

Options for Describing Limits of Class 2 Solvents

Option 2: Example 2 (acetonitrile in a drug product.)

- The maximum administered daily mass of a drug product is 5.0 g.

Component	*Amount in formulation*	*Acetonitrile content*	*Daily exposure*
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	2000 ppm	1.80 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Drug Product	5.0 g	1016 ppm	5.08 mg

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	*PDE (mg/day)*	*Concentration limit (ppm)*
Acetonitrile	4.1	410

- The product meets neither the Option 1 nor the Option 2 limit
- The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile (e.g. drying step).

Options for Describing Limits of Class 2 Solvents

Option 2: Example 2 (acetonitrile in a drug product.)

- If the level of acetonitrile was not reduced during formulation to the allowed limit, then the manufacturer of the drug product should take other steps to reduce the amount of acetonitrile in the drug product.
- If all of these steps fail to reduce the level of residual solvent, in exceptional cases the manufacturer could provide a summary of efforts made to reduce the solvent level to meet the guideline value, and provide a risk benefit analysis to support allowing the product to be utilised with residual solvent at a higher level.

اذا ماعندو بدائل في هاي الحالة لازم يعمل اي step عشانو يقللو

في حالات محدودة ممكن يسمحوا فيها

* الاصل بشوف خلال عملية الFormulation انو نقلل ال Residual Solvent اذا ماكانو في امكانية في بعض الحالات ممكن - كمي ويوضح لكن بالآخر رح يضل عندي انه ال authority هي رح تحدد شو المسموح

40

Analytical Procedures

- Residual solvents are typically determined using chromatographic techniques such as gas chromatography.
- Any harmonised procedures for determining levels of residual solvents as described in the pharmacopoeias 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 nonspecific method such as loss on drying may be used.
- (Class 3) Ideally, less toxic solvents should be used where practical.

Reporting levels of residual solvents

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:

- 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%.

٢٩/٠٤/١٤٤٤

Reporting levels of residual solvents

- If Class 1 solvents are likely to be present, they should be identified and quantified.
  - "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.

ممكن فيه عندهم في آخر manufacturing الخطوة من احتي في بداية التصنيع لكن لم يتم ازالتهم بطريقة validative (تم التحقق منها quantitivly)

Chemical structure لازم يكون محدد

الكمية

loss on drying

LIMITS OF RESIDUAL SOLVENTS: Class 1

- 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 in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified.

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

LIMITS OF RESIDUAL SOLVENTS: Class 3

- Class 3 (Table 3, Q3C) includes no solvent known as a human **health hazard** at levels normally accepted in pharmaceuticals. ⇒ GMP في الـ limit معروفة لكن toxicity ما في

- 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) would be acceptable without justification.

- Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice.

المريض مثلا بده يتعامل مع هاي الادوية لمدة طويلة مثلا ما في اي دراسات كلينيكال بتأكد الـ safety الهم

في عنا دراسات على ايام ⇒ على نفس الهاي المواد ما في تأثير على الخلايا

اذا كانه في ماشيء خلال عملية التصنيع انه تم التخلص من هاي المواد ممكن يشغل الـ Justification

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

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

GUIDELINE FOR ELEMENTAL IMPURITIES Q3D

Introduction

Elemental impurities in drug products may arise from several sources:

- they may be residual catalysts that were added intentionally in synthesis
- may be present as impurities (e.g., through interactions with processing equipment or container/closure systems
- being present in components of the drug product.

Safety assessment of potential elemental impurities

- Elements evaluated in Q3D guideline were assessed by reviewing:
  - the publicly available data contained in scientific journals,
  - government research reports and studies;
  - international regulatory *Guideline for Elemental Impurities* standards (applicable to drug products) and guidance, and
  - regulatory authority research and assessment reports.
- The available information was reviewed to establish the oral, parenteral and inhalation PDEs.

50

ELEMENT CLASSIFICATION

- **Class 1**: The elements, As, Cd, Hg, and Pb(lead), are human toxicants that have limited or no use in the manufacture of pharmaceuticals.
- **Class 2**: Elements in this class are generally considered as route-dependent human toxicants.
  - **Class 2A** elements have relatively high probability of occurrence in the drug product.
  - The class 2A elements are: Co, Ni and V.
  - **Class 2B** elements have a reduced probability of occurrence in the drug product
  - The elemental impurities in class 2B include: Ag, Au, Ir(iridium), Os(osmium), 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.
- The elements in this class include: Ba, Cr, Cu, Li, Mo, Sb(antimony), and Sn(tin).
- **Other elements:** Some elemental impurities for which PDEs have not been established due to their low inherent toxicity and/or differences in regional regulations are not addressed in this guideline.
- Some of the elements considered include: Al, B(boron), Ca, Fe, K, Mg, Mn, Na, W(tungsten) and Zn.

52

Potential Sources of Elemental Impurities

- Residual impurities resulting from elements intentionally added (e.g., catalysts) in the formation of the drug substance, excipients or other drug product components.
- Elemental impurities that are not intentionally added and are potentially present in the drug substance, water or excipients used in the preparation of the drug product.
- Elemental impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment.
- Elemental impurities that have the potential to be leached into the drug substance and drug product from container closure systems.

53

ضفناها متعمدين (عارفين انها موجودة)

غير متعمد وجودها

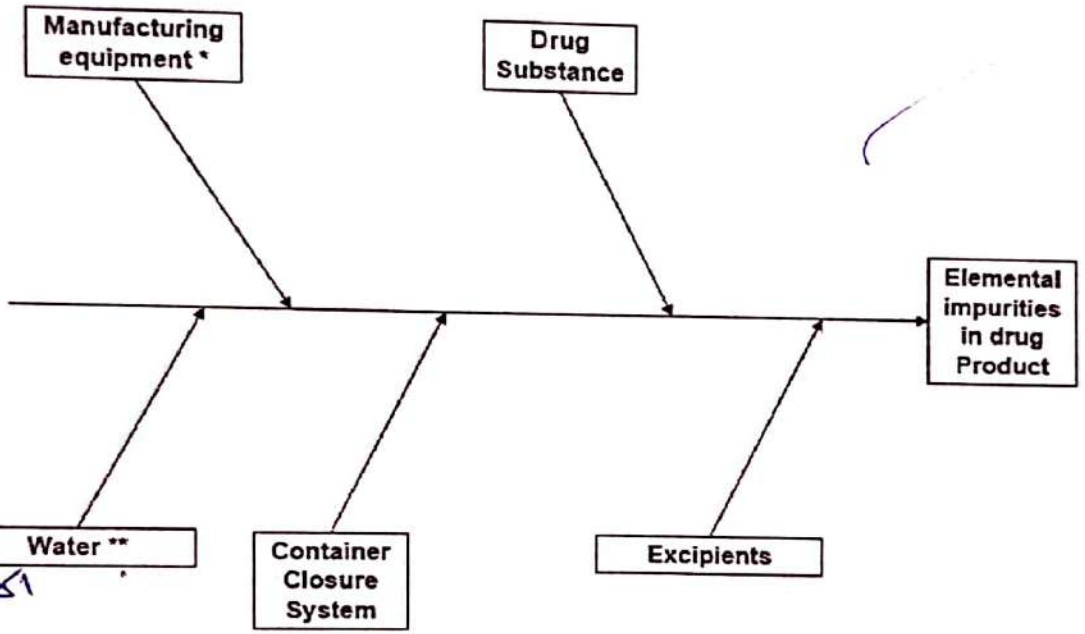
صار عندي تفاعل مع انه الاصل في صار خلاء تصنع اي interaction

صار الها migration خارجة

اذا كانة بلاستيك لانه البلاستيك مليانة impurities لانه هو من النوع مليانة product-

Potential Sources of Elemental

Potential Sources of Elemental Impurities



54

CONTROL OF ELEMENTAL IMPURITIES

- 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.
- The principles are similar to those described in ICH Q3C: Residual Solvents

CONTROL OF ELEMENTAL IMPURITIES

Part of Table A.2.1

Table A.2.1: Permitted Daily Exposures for Elemental Impurities[1]

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

56

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:**

$$Concentration(\mu g / g) = \frac{PDE(\mu g / day)}{daily\ amount\ of\ drug\ product(g / day)} \quad (1)$$

- If all the components in a drug product do not exceed the Option 1 concentrations for all target elements identified in the risk assessment, then all of these components may be used in any proportion in the drug product.

drug product في ادا
(drug + excipient 1 + ... 2)
المكونات كلوحدة بجمعها وحسب
الجدول مثلا oral ...
ادا ماوصلوا الconc الحدود
في الجدول عادي خلص

Converting between PDEs and concentration limits

- **Table A.2.2: Permitted Concentrations of Elemental Impurities for Option 1**

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
Tl	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5

Converting between PDEs and concentration limits

- **Option 1: Example**

drug + excipient

Table A.4.1: Maximum Daily Intake of Components of the Drug Product

Component	Daily Intake, g
Drug Substance	0.200
Microcrystalline Cellulose (MCC)	1.100
Lactose	0.450
Ca Phosphate	0.350
Crospovidone	0.265
Mg Stearate	0.035
Hydroxypropylmethyl Cellulose (HPMC)	0.060
Titanium Dioxide	0.025
Iron Oxide	0.015
Drug Product	2.500

Converting between PDEs and concentration limits

رح احللهم واحد كم
وبرجع للمعادلة وحسب
الارقام وبحدد كم ال
permitted con

- **Option 1: Example**

Table A.4.2: Permitted Concentrations from Table A.2.2 (assuming uniform concentrations and 10 grams daily intake)

Component	Maximum Permitted Concentration (µg/g)						
	Pb	As	Cd	Hg	Pd	V	Ni
Drug Substance	0.5	1.5	0.5	3	10	10	20
MCC	0.5	1.5	0.5	3	10	10	20
Lactose	0.5	1.5	0.5	3	10	10	20
Ca Phosphate	0.5	1.5	0.5	3	10	10	20
Crospovidone	0.5	1.5	0.5	3	10	10	20
Mg Stearate	0.5	1.5	0.5	3	10	10	20
HPMC	0.5	1.5	0.5	3	10	10	20
Titanium Dioxide	0.5	1.5	0.5	3	10	10	20
Iron Oxide	0.5	1.5	0.5	3	10	10	20
Maximum Daily intake (µg)	1.25	3.75	1.25	7.5	25	25	50
PDE (µg)	5	15	5	30	100	100	200

Converting between PDEs and concentration limits

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

ح يكون ضمن الـ table الموجودة

Converting between PDEs and concentration limits

- **Option 2b: Permitted concentration limits of elements in individual components of a product with a specified daily intake:**
- For each element identified as potentially present in the components of the drug product, the maximum expected mass of the elemental impurity in the final drug product can be calculated by multiplying the mass of each component material times the permitted concentration established by the applicant in each material and summing over all components in the drug product

الموجودة في الجدول قبل
لازم الكون محددة كل
excepient كم كمية
ولكل ingredient لازم احدد
maximum daily intake الـ

احسب كم كمية المادة وبضربه في كم كمية الـ compont
نفسه هيك بعرف انه ضمن المسموح فيه اولا

٢٩/٠٤/١٤٤٤

Converting between PDEs and concentration limits

Table A.2.2

- **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.

** ** بناءً على الـ PED ح نحسب كم الـ

نجمع كلهم ونطلع max conc الـ معنا كم الـ elemint موجود وكم في كل Componant نجمع ونحسبهم