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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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15 December 2025

Submission of comments on <Guideline for Extractables and Leachables Q3E> (EMA/CHMP/ICH/236669/2025) <document reference>

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.
When completed, this form should be sent to the European Medicines Agency electronically, in Excel format (not PDF), to the following address:
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All the cells with an asterisk (*) should be filled in prior to completing the columns "Comment and rationale" and/or "Proposed changes / recommendation".
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Name of organisation or individual*	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science)	20	22	2.	Devices may be registered separately and used with a drug, where the device has a fluid path and/or container that holds/delivers DP to the patient. It seems unclear if this is subject to ICH Q3E requirements as well.	Propose to align with Figure 5 and e.g., lines 822-823 to clarify scope.
IPAC-RS	35	39	2.	Guideline is not intended for products used during clinical research stages of development but may be applicable in cases of high risk to patient. A further definiton of "high risk to patient" would be helpful e.g., type of application, treatment, indications etc.	Propose to include reference to ELSIE white paper "Leachables Risk Assessment Framework": https://elsiedata.org/el-concepts/
IPAC-RS	52	53	3.1	Figure 1 flow chart, does not show a logical sequence: After "Integrated risk evaluation" two branches should originate "risk acceptable" or "risk unacceptable". Following the branch "unacceptable" the next field should be "risk reduction" and after that back to "risk assessment". Following the branch "acceptable" the next field should be "Output/ Result of the Quality risk management process" Furthermore "review events" should be connected to "Risk Assessment" as life cycle changes should trigger a "new risk assessment".	Propose to adapt Figure 1 accordingly
IPAC-RS	60	61	3.1.	Sentence is somewhat unclear on requirements for products in clinical trainls	Propose to add " for approved products"
IPAC-RS	83	85	3.2	Figure 2. Not very clear. There seems to be an arrow line missing between DP stored frozen and Low quantity of extractables. In addition, low quantity of extractables doesn't mean lower risk. Risk is dependent on the level and toxicological evaluation. Same for high quantity extractables, i.e., extractables can all be below AET and have low risk.	Figure 2 needs updating and clearification
IPAC-RS	83	83	3.2	Figure title requires adjusting due to typo - suggested amendment in red text	Figure 2: Overview ~~on~~ of Aspects to Consider for Risk Matrix
IPAC-RS	83	85	3.2	Consider adding a note in Figure 2 or the corresponding section that the physical dimensions of components (e.g., small parts with low surface area to volume ratios) may significantly influence the leachables risk. This aspect should be explicitly considered in the risk matrix.	It is recommended to include a note in Figure 2 or the corresponding section that components with very small physical dimensions—referred to as “small parts”—should be explicitly considered in the risk matrix. These components, such as gaskets, O-rings, connectors, sensors, and valves, often exhibit low surface area-to-volume ratios and may not contribute relevant amounts of extractables and leachables due to their small size.
IPAC-RS	84	85	3.2	Should consideration be included in this figure for the known presence of Class 1 compounds	

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IPAC-RS	85	85	3.2	Exposure time is deemed a relevant factor to be considered in the risk matrix. Suggest to add exposure time to Figure 2, e.g., for a fluid path of a medical device	e.g. for a fluid path of a medical device; short / long contact time
IPAC-RS	89	94	3.2	Why restrict this statement to "polymeric" manuf. and CCS. Why not include glass or other materials?	Consider other materials to be included in this statement.
IPAC-RS	151	155	3.4	"For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 leachables are observed (see Section 5). The analytical procedures used in extraction studies should comply with the criteria provided in Section 4.3." Can this be clarified?	Provide clearer explanation; consider clarifying in this section as well as Section 5 and Section 4.3
IPAC-RS	158	158	3.4	"an identification of those extractables and quantification of the concentrations **may** be conducted to mitigate the leachables risk…" Revise "may" to "must," as without identification the risk cannot be mitigated.	Change the "may" to "must"
IPAC-RS	160	161	3.4	"compounds with a similar analytical response can be employed". If no authentic reference standard existh, you don't know the response of the extractable/leachable. Suggets to use a compound with similar structural related properties.	"similar compound with structural related properties can be employed"
IPAC-RS	163	165	3.4	"As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed."To be clarified	Provide clearer explanation
IPAC-RS	166	172	3.4	"For a packaging component/system an **abbreviated data package** may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6). Table A.1.2 (Appendix 1) provides examples where the overall risk is considered low, in relation to Figure 2 (Section 3.2), and an abbreviated data package may be warranted with adequate justification." Please clarify what it is meant by abbreviated data package	Provide clearer explanation of "abbreviated data package"
IPAC-RS	166	174	3.4	COMMENT: Would it be possible to explore the extension of the option to include an abbreviated data package not only for the final drug product content but also for the drug substance final manufacturer or even the manufacturing system, where technical justification based on similarities with other studies can be provided? RATIONAL: If technically feasible, this approach could offer greater flexibility and ensure alignment across different manufacturing steps, fostering consistency and efficiency in the overall process.	
IPAC-RS	166	172	3.4	This is an example for an **abbreviated data package**: When patient safety risk can be adequately mitigated via prior knowledge, e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation, or no/few extractables detected above the AET and below their applicable safety threshold	Add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
IPAC-RS	186	187	3.4	"Although minimal leaching occurs in the frozen state, the potential for leaching from storage component/system should be evaluated before freezing and after thawing." Is it possible to have the same consideration for freeze dried product or powder after reconstitution with liquid?	Have an additional clarification for reconstituted solid products.
IPAC-RS	198	227	3.5	General comment to section 3.5: It is not clear why ICH Q3E provides detailed instructions regarding the content of initial MAA. Content requirements for initial MAA are established in ICH M4Q R1/R2	Propose to provide only general expectations as bullet-point list and reference ICH M4Q for details for initial MAA

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IPAC-RS	198	227	3.5	General comment to section 3.5: It requires very detailed information to be submitted in an initial MAA, e.g., detailed descriptions of analytical procedures and validation, all detailed study reports etc.. The concern is an increased regulatory workload for HA and industry to prepare, review and manage the information.	Propose to provide only general expectations as bullet-point list. The regulatory application should only include summaries of asessments, conclusions, control strategy. Detailed information should be available in the background, e.g., in case of HA questions due to concerns and should be routinely covered by GMP inspections.
IPAC-RS	198	198	3.5	From the text in chapter "3.5 Documentation and compliance" it is understood that the information is focused on registration/submission requirements. If this is correctly interpreted, it is proposed to clarify this in the heading. If this is not correct, it is proposed to clearly separate registration documentation requirements and to create a separate sub-section.	Propose to change the chapter heading to "3.5 Documentation for initial MAA" if the focus is on registration documentation requirements
IPAC-RS	199	201	3.5	Is the expectation being set that all associated study reports are presented for all manufacturing components and CCS materials studied. Some of these may be sourced from suppliers.	Replace "the associated study reports" with "details of the extractable/leachable studies conducted"
IPAC-RS	200	200	3.5	This should be the SCT, not the AET. The AET defines compounds to be identified so that they can be accurately quantified and assessed against the SCT. See lines 488-490	the safety assessment of substances above the ~~AET~~ SCT
IPAC-RS	205	207	3.5	COMMENT: The current ICH text could be interpreted to mean that whenever complete studies are not available, prior agreement with the regulatory authority is always required. However, in practice, prior consultation does not always take place, and in some cases, companies may take the risk of submitting data up to a certain time point (TP) and agree on the commitment to provide updated result at later stage. Could we propose a rewording to indicate that consultation with authorities is "recommended" rather than mandatory? This approach would also align with the footnote to Table A.1.2 on lines 337–338. RATIONAL: Adjusting the wording to suggest consultation as "recommended" rather than strictly required would provide greater flexibility while still encouraging engagement with regulatory authorities where appropriate. This approach reflects the balance between regulatory compliance and practical decision-making in situations where data may be incomplete.	"It is recommended to seek prior concurrence with the relevant regional regulatory authorities, where appropriate."
IPAC-RS	205	207	3.5	If the leachables studies are considered to be part of the stability program they should be subject to the same regulatory requirements including post-approval amendments and Health Authority interactions.	Propose to commit continuation of leachables studies as part of the stability program and report unexpected results or results necessitating additional risk mitigations or controls instead of periodically reporting the results.
IPAC-RS	210	211	3.5	"semi-permeable packaging". What is defined as semi-permeable packaing? Can expamples be provided?	Provide example for semi-permeable packaging.
IPAC-RS	210	211	3.5	"For semi-permeable packaging materials, secondary packaging should also be evaluated as applicable." is it possible to have the same consideration for Varnish and Ink that are part of the Primary packaging (when semi-permeable	Update to add clarification about the varnish, ink or adhesive on semi-permabale primary packaging

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IPAC-RS	212	220	3.5	Details being requested seem excessive and not aligned with current experience Revisions are suggested to make the text appropriate to all dosage types/formats and enable the applicant to define the appropriate details included within these documents Please clarify if a list of extractables and leachables studies shall be included as per line 212 or the studies themselves as per line 201-203. Why is this requirement repeated? Missing part of sentence - would be beneficial to mention to include the information in a regulatory filing (red text suggested in following column)	Consider revising this section to describe more clearly at a high level what is being recommended regarding documentation. For example, describe generally what is meant by "assessment report." We recommend that full reports are excessive and not needed. Summaries, with for example, tables should suffice. Additionally, consider referring to ICH M4Q for any details. Please also ensure that the examples provided in the parentheses do not become a check list for regulatory reviewers -- these can be shortened or put into context of what is meant by "assessment report." This approach will also help make the text more applicable to all dosage types/formats and provide more flexibility, e.g., the following may also be revised to read, "assessment report which ~~will~~ may typically include analytical method and extraction condition selections along with justifications ~~(solvents, temperature, duration, surface/volume ratio, etc.)~~ for extractables studies and a description of the sample preparation and analytical procedures for leachables studies Also, consider revising: "A list of extractables and leachables studies conducted should be included in a regulatory filing along with...."
IPAC-RS	216	218	3.5	Documentation and Compliance: This paragraph is speaking about quantification and not limit test. See suggested revision.	As the paragraph is speaking about quantification and not limit test, our recommendation will be to remove the reference to the LOD (Limit Of Detection). ICH-Q2(R2) requires quantitation limit for quantitative test and detection limit for limit test.
IPAC-RS	218	221	3.5	"All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level. " I do not feel that structure elucidation may be necessary for all extractables above the AET if they are not observed in the leachable study. This could be a significant burden to the safety assessment team with minimal value added.	Revise to include "All leachables peaks...."
IPAC-RS	219	219	3.5	This should be the SCT, not the AET. The AET defines compounds to be identified so that they can be accurately quantified and assessed against the SCT. See lines 488-490	extractables and leachables peaks above the ~~AET~~ SCT (see Section 5)
IPAC-RS	225	227	3.5	the text here is not applicable to all formats, so may be beneficial to indicate this rather then the reader be under the impression that this may be the case	adequacy of any proposed mitigation measures (for example prewashing of the packaging and delivery components/system or pre-flushing of the manufacturing components/systems) should be demonstrated by data collected before and after implementation, where this is appropriate for the container closure system and dosage format.
IPAC-RS	228	260	3.6	General comment to section 3.6: While submission requirements for initial MAAs are excessively detailed in 3.5 there is no guidance on regulatory lifecycle management at all in 3.6. It is not clear what level of documentation is required for regulatory submission of post-approval variations and currently, there is no clear guidance in the country specific post-approval variation guidelines either.	Propose to reference local post-approval variation guidelines and to consider updating those before implementation of ICH Q3E step 5

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IPAC-RS	249	250	3.6	Relation to existing information is not explicitly mentioned and is unclear. Propose to include "…., outside previously tested worst case conditions" for clarity.	It is proposed to adapt to: "Changes to process conditions, **outside previously tested worst-case conditions,** may cause different leachables or different amounts of leachables from the existing formulation contact material."
IPAC-RS	278	290	4.2	General comment to section 4.2: It seems beneficial to include more details on responsibilities of (material) manufacturer/ supplier / product manufacturer and license holder regarding extractables studies and data.	
IPAC-RS	312	312	4.3	Extractable Study: Analytical procedures are mandatory, we should make a distinction between different route of administration, for example for inhalation non volatile are not relevant	Current wording : Key characteristics of an adequate extraction study include : appropriate analytical procedures for volatile, semi-volatile, and non-volatile organic extractables and elemental extractables. Comment: please be more precise rather than using the word "appropriate," or add wording saying that "appropriate" has to be defined according to the product. For example, with regards to a delivery system using a powder formulation, testing non-volatile compounds is not relevant for components without any contact to the patient mucosa, whereas it makes sense to analyse volatile compounds. The 4 categories should be assessed, and the assessment can be that no testing is required for a specific category and this should be justified
IPAC-RS	313	313	4.3	"elemental Extractables" is set out of scope in chapter 2 (Line 25, 26)	It is proposed to delete "and elemental extractables" or refer to ICH Q3D
IPAC-RS	326	326	4.3.1	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
IPAC-RS	342	343	4.3.2	Clarify the meaning of „qualified" analytical procedures. Typically extractables procedures should be suitable, fit for purpose, e.g., adequate detection and quantification limit covering the AET.	Proposal: Methods for extractables studies need not to be validated but should be suitable for their intended use.
IPAC-RS	344	346	4.3.2	If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. The other way round if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted.	It is proposed to add a sentence that if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Propose to add these examples to Annex 1, table A.1.2 and integrate these mitigation possibilities to the workflow in Annex 1, Figure 5
IPAC-RS	350	353	4.4	Inhalation products such as DPI, pMDI and inhalation solution/suspensions for nebulization, where in-use stability involves the removal of secondary packaging (as described in Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations Guidance for Industry, draft Apr 2018), should not require a leachable study during in-use testing since the primary container is not affected during the in-use period.	Propose to add further clarification as to when in-use stability is required to be assessed as part of leachable studies.
IPAC-RS	355	356	4.4	"For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product."	Could 1 or 2 examples for an alternative approach be included, since the guideline has also C&GT in scope, this scenario of very limited batch numbers might not be so rare.

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IPAC-RS	359	359	4.4	Leachables Study: It is recognized that it would be helpful to use the same lots for extractables and leachables studies. However, it is (in most cases) not feasible, because extractables studies have to be performed at least several months before any leachables study. It needs some time to perform the extractables studies, to identify the extractables and perform a toxicological assessment to inform leachables studies on the target analytes. Subsequently leachables methods have to be developed and their suitability have to be demonstrated before starting a leachables sudy. In addition, extractables studies can be performed product independently. So they can be performed long time before any planned leachables studies. Most components do not have this long shelf life to be available for both extractables and leachables studies.	Current wording : Use of the same lots of components used in extractables assessments potentially enables a more meaningful correlation between extractables and leachables. Proposal: The lots of components used in extractables studies should be representative for the component type enabling a meaningful correlation between extractables and leachables. Where possible the same lots of components should be used.
IPAC-RS	365	367	4.4	Leachables need to be reported when they exceed SCT, not AET, unless they cannot be definitively identified and quantified.	"The non-targeted screening study should include the application of an AET (See Section 5) to indicate a level above which leachable chemical entities should be identified, quantified, and potentially be reported for toxicological review."
IPAC-RS	393	395	4.5	Simulated leachables need to be assessed for safety if they exceed SCT (not AET)	Thus, the simulated leachables detected above the simulation study's drug product specific ~~AET~~SCT should be identified, quantified, and assessed for safety.
IPAC-RS	402	402	4.5	"the simulated manufacturing process should be performed using worst-case conditions" "As the goal pf the simulation study is …….closely match the drug product manufacturing/storage conditions… line 395-400. "worst-case" and "closely match" doesn't align. Can this be clarified?	remove "and the simulated manufacturing process should be perfrmed using worst-case conditions" line 402
IPAC-RS	406	408	4.5	Clarify the meaning of "qualified" test procedure. Should the procedure be validated as described for leachables studies in section 4.4 lines 361-363?	Propose to add which parameters should be tested during test procedure qualification. Use either the term suitable for intended use or validated.
IPAC-RS	421	421	4.5	This is the SCT not AET, as in multiple other locations in the document. See comment in row 61.	Revise to, "Once the E&L profiles above ~~AET~~SCT are available,…."
IPAC-RS	432	432	4.6	Extractable and Leachable Correlation: The external environment such as secondary packaging could also be considered as a potential source of non-identified leachables	Suggest to mention awareness of secondary packaging as a potential source of non-identified extractables, during the ICH training sessions (no need to include in the written guideline).
IPAC-RS	435	436	4.6	It is stated that "the leachables profile that ultimately drives patient safety risk evaluations and component acceptability." However, at several sections of this guideline other approaches are described that allow component qualification without leachables testing (abbreviated data package): In Section 3.4: "For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g., established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold" . In section 4.3.2: Only in this case a leachables study is required: "If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. " In other cases if the amount of an adequately identified and quantified extractable is below its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study can be omitted. Appendix 1, Figure 4: For extractables above the AET, one option is to identify and quantify those extractables and if the amounts of the extractables are below the applicable safety threshold, the component is qualified.	Propose to align approach across the guideline, that although the leachables profile would ultimately drive the risk evaluation and component acceptability, abbreviated data packages may be sufficient.
IPAC-RS	446	448	5	We disagree with this definition of AET. Safety assessments should be triggered by SCT, not AET. The definition of AET should align with the definition from PQRI: 'The AET is defined as the threshold at or above which an analytical chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.' The SCT will drive whether the toxicological assessment is undertaken.	The AET is not a control threshold, but rather a threshold corresponding to a concentration above which extractables or leachables should be identified, quantitated, and reported for potential safety assessment, forming the foundation of the overall E&L risk assessment and control strategy.

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IPAC-RS	457	460	5	"For a leachable study, the AET is established at a concentration above which compounds should be identified and quantitated to enable appropriate safety assessment. For Class 1 leachables (See Appendix 4, Table A.4.1), the compound-specific safety limit, instead of a product-specific SCT, should be used for quantification." Please clarify how would it be feasible to define AET before knowing from analythical data that Class 1 leachables could be present (for instance, BPA)? Does supplier need to inform in advance about materials potentially leaching Class 1 compounds?	Provide clearer explanation
IPAC-RS	461	462	5	"Derivation of the study-specific AET depends on dosing considerations (e.g., maximum dose level, frequency of dosing, and duration of treatment)."Does this mean that Less Than Lifetime (LTL) considerations should be taken into account? Would this be applicable also for vaccines?	Provide clearer explanation
IPAC-RS	481	482	5.1	"Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5", this approach is adequate for some analytical methods but has been demonstrated as not fully adequate for some others like LC/MS. There is a need to clearly mention in the doc that the UF must be scientifically justified in associatetion with the analytical methods used	We note that a UF of 0.5 is not suitable in all cases. For example, some analytical methods require lower values. Consider clarifying that other values, including lower values, can be used and justified.
IPAC-RS	481	481	5.1	The choice of words can be improved - perhaps 'utilise' an uncertainty factor rather than 'multiply'	Under certain circumstances an acceptable approach is to ~~multiply~~ utilise an uncertainty factor (UF)
IPAC-RS	504	506	6.1	Could you provide a list or reference of reviewed 330 potential leachable permitted daily exposures (PDEs) ?	Kindly include in the reference list
IPAC-RS	513	515	6.1	Provide additional context that the QT values for dermal/transdermal may be higher as the QT is a systemic toxicity threshold. Application of bioavailability can adjust this value based on product specific knowledge	Consider inlucding in line 515 additional statement (the QT values may be adjusted based on product specific/compound specific knowledge on bioavailability).
IPAC-RS	513	513	6.1	Need to have additional clarification on how to calculate the exposure duration for example for antibiotics (liquid) that can be taken more than oone time per year. How do we calculatez the LTL for these elements. Idem for other treatment where the number of treatments sudring lifetime is not define in the posology	Is it possible to have additional information on the way to calculate the LTL and associated exposure duration when the treatment can be taken more than one time during the lifetime.
IPAC-RS	513	513	6.1	QT proposed are higher than the 5 µg/day describe in PQRI for the sensitizer. How this is justified ?	Need justification to apply a value higher than 5 µg/day for sensitizer
IPAC-RS	513	513	6.1	Table 1: Systemic and Local Toxicity Thresholds: In case you have a systemic toxicity thresholds and a local toxicity thresholds.	In case of both (systemic and local), which toxicity threshold should be used ?
IPAC-RS	513	513	6.1	Table 1: Systemic and Local Toxicity Thresholds: The route of administration "Nasal" is not written in the Table. We note that the nasal or mucosal route is very different from the inhalation route.	We suggest adding "nasal" or "mucosal" to Table 1.
IPAC-RS	513	514	6.1	Table1 Parenteral: seems complex and difficult to use/ interpret: How is it possible that the QT is stricter than the TTC for exposure duration < 1 year? --> According to the text SCT is the lowest value of either TTC or QT (line 503-504), hence an addtion of SCT in Table 1 would be helpfull to illustrate/ reinforce this to the reader. Subcutaneous injections are a parenteral application type. Are they considered under parenteral or under local toxicity threshholds subcutaneous? --> For clarfication add comment to local toxicity threshholds " Only applicable for certain scenarious - see chapter 6.4"	An addtion of SCT in Table 1 would be helpful to illustrate/ reinforce this to the reader It is proposed to give an example: e.g., a parenteral DP with an exposure of > 10 years the SCT is 1,5 µg/day, while for an exposure of 1-10 years it is 10 µg/day, for an exposure of 1 month to 1 year it is 12 µg/day
IPAC-RS	530	534	6.2	Substances classified as class 3 in ICH Q3C can also be regarded as class 3 leachables	Add also substances classified as class 3 in ICH Q3C as class 3 leachables in addition to the substances in Appendix 5.