Considerations for Impurity Qualification:
ICH Q3A/Q3C/Q3D, RLD & MDD

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Abbreviation

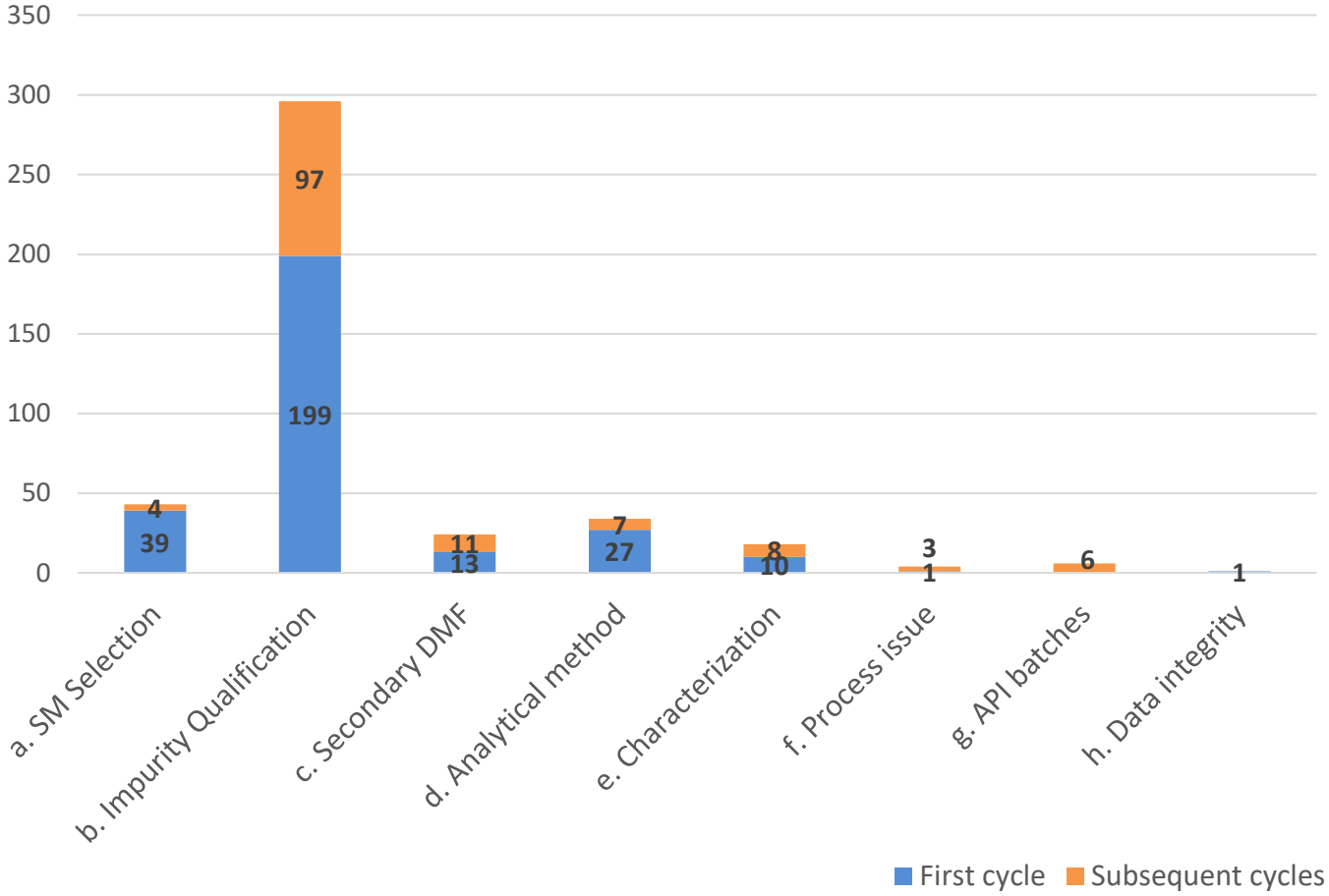
- RLD - Reference Listed Drug
- MDD - Maximum Daily Dosage
- IT / QT - Identification Threshold / Qualification Threshold
- PDE - Permitted Daily Exposure
- (Q)SAR - (Quantitative) Structure Activity Relationship
- Pharm/Tox - Pharmacology/Toxicology

Outline

- Introduction
  - Classification of impurity and applicable guidance
  - Case 1: MDD selection
- Qualification of regular impurity
  - Decision tree and qualification method
  - Case 2: Justification of impurity specification by RLD
- Residual solvent
  - Case 3: Qualification of residual solvent without established PDE
- Elemental impurity
  - Case 4: Mineral-sourced drug substance
- Summary

DMF Major Deficiencies by Category

(10/2017 – 06/2020)



- This slide is borrowed from W. Liu's presentation in 07/2020.
- 234 first cycle DMFs have major deficiencies.
- 83% of major deficiencies are "**qualification of impurity**".

➢ How to qualify impurities in drug substance?

Classification of Impurities

Impurities	Compendium or Regulatory Guidances
Regular Organic impurities	USP monograph ICH Q3A Guidance for Industry ANDAs: Impurities in Drug Substances
Residual solvents	ICH Q3C
Elemental impurities	ICH Q3D
Mutagenic impurities	ICH M7

- USP monographs are generally based on FDA-approved products.
- Discussion on mutagenic impurities will be covered by separate talks.
- Several types of drug substances such as peptides, semi-synthetic and fermentation products are not covered by ICH Q3A. The related organic impurities are qualified under the principle of clinical relevance.

Clinical Relevance

- Establishment of impurity acceptance criteria is guided by consideration of the clinical impact of impurity levels and hazard assessment, as opposed to manufacturing process capability.
- For drug substances excluded from ICH Q3A, acceptance criterion for specified impurity up to the ICH Q3A qualification threshold is generally acceptable, provided there are no toxicological, immunological, or clinical concerns at this level.
- The acceptance criteria should be informed by data derived from clinical trials, nonclinical studies (e.g., in silico modeling for evaluation of mutagenicity, in vitro, and animal studies), context of use, prior knowledge (e.g. **RLD**), publicly available information, and analytical capability, as appropriate.

Manual of Policies and Procedures, MAPP 5017.2, Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance, May 2020

Maximum Daily Dosage (MDD)

- MDD refers to the maximum amount of drug substance administered per day.
- MDD impacts the calculation of qualification threshold of ICH Q3A and permitted concentration limit of ICH Q3C, ICH Q3D and ICH M7.
- If DMF supports multiple ANDAs/NDAs with various MDDs due to different dosage form or route of administration or even clinical setting, **highest MDD is selected for the calculation**.
- How to find MDD? Find MDDs using **RLD***.

*Referencing Approved Drug Products in ANDA Submissions, Guidance for Industry, Oct. 2010

Case 1: MDD Selection

Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	RLD
MESALAMINE	DELZICOL	N204412	CAPSULE, DELAYED RELEASE	ORAL	400MG	RLD
MESALAMINE	APRISO	N022301	CAPSULE, EXTENDED RELEASE	ORAL	375MG	RLD
MESALAMINE	PENTASA	N020049	CAPSULE, EXTENDED RELEASE	ORAL	250MG	RLD
MESALAMINE	PENTASA	N020049	CAPSULE, EXTENDED RELEASE	ORAL	500MG	RLD
MESALAMINE	ROWASA	N019618	ENEMA	RECTAL	4GM/60ML	RLD
MESALAMINE	SFROWASA	N019618	ENEMA	RECTAL	4GM/60ML	RLD
MESALAMINE	CANASA	N021252	SUPPOSITORY	RECTAL	1GM	RLD
MESALAMINE	ASACOL HD	N021830	TABLET, DELAYED RELEASE	ORAL	800MG	RLD
MESALAMINE	LIALDA	N022000	TABLET, DELAYED RELEASE	ORAL	1.2GM	RLD

- Search Orange Book by name of active ingredient. Locate RLDs. Find MDDs in RLD labeling. Above table is copied from the Orange Book by searching MESALAMINE.
- Work closely with your ANDA/NDA applicants.
- Communicate with FDA by submitting a controlled correspondence.

Case 1: MDD Selection (*cont.*)

RLD	Dosage form, Route of administration	Proprietary Name	Strength	MDD	Qualification Threshold
N021252	Suppository, Rectal	CANASA	1000 mg	1 g	0.10%
N022301	Capsule, Extended Release, Oral	APRISO	375 mg	1.5 g	0.07%
N020049	Capsule, Extended Release, Oral	PENTASA	250 mg	4 g	0.05%
N022000	Tablet, Delayed Release, Oral	LIALDA	1200 mg	4.8 g	**0.05%**

- Mesalamine is used to treat ulcerative colitis.
- DMF# XYZ supports multiple RLDs due to different route of administration and clinical settings (acute, maintenance or chronic).
- Due to the multiple RLDs listed in the Orange Book, MDDs are distinct.
- Highest MDD (4.8 g) is selected for calculation of qualification threshold.
- In case that drug substance solely supports drug product with MDD other than the highest in the Orange Book, acknowledgement is needed that reference by a different product may require different impurity limits.

Qualification Threshold by ICH Q3A

Maximum Daily Dose	Reporting Threshold	Identification Threshold (IT)	Qualification Threshold (QT)
≤ 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%

If MDD =	Then…	
	IT	QT
800 mg	0.10%	0.13%
1000 mg	0.10%	0.10%
1500 mg	0.07%	0.07%
2000 mg and above	0.05%	0.05%

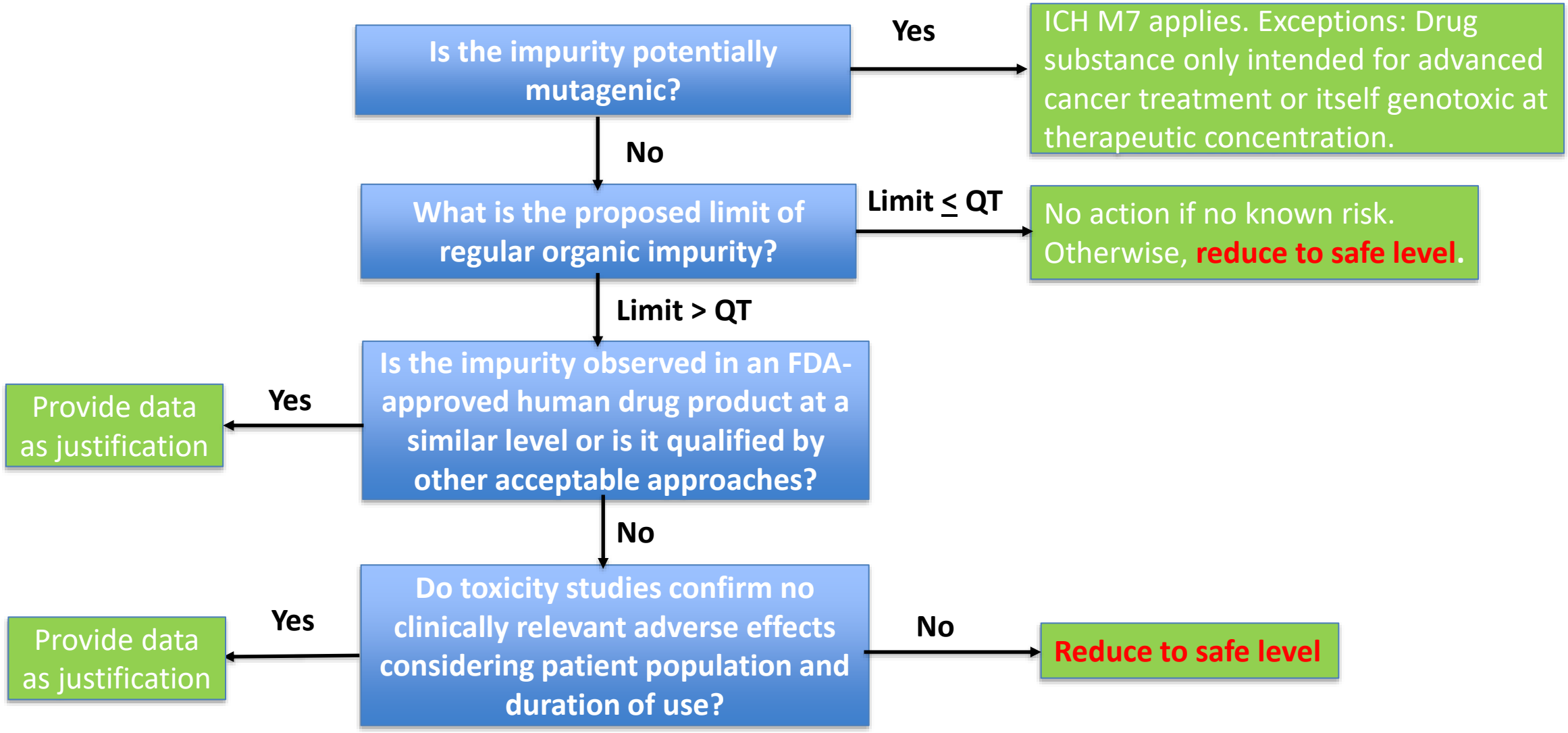
- Above table applies to regular organic impurities. For potential mutagenic impurities, refer to ICH M7.
- For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, QT should be lowered to be commensurate with the specific safety level.

Other Qualification Methods

- The observed level and proposed acceptance criterion for the impurity do not exceed the level observed in the reference listed drug product.
  - The analytical method should be validated and stability-indicating.
  - Direct comparison to RLD is the preferred method. Other options in the following would need Pharm/Tox assessment.
- The impurity is a significant metabolite of the drug substance.
- The observed level and the proposed acceptance criterion for the impurity are adequately justified by the scientific literature.
- The observed level and proposed acceptance criterion for the impurity do not exceed the level that has been adequately evaluated in toxicity studies.

Guidance for Industry ANDAs: Impurities in Drug Substances, June 2009

Decision Tree for Non-Compendial Impurity



- The above decision tree is only applicable for drug substance covered by ICH Q3A.

Case 2: Impurity Specification

Name	Origin	Observed in generic lot	Observed RLD at expiry	Proposed limit
Impurity A	Degradant (hydrolysis)	0.20%	1.5%	NMT 0.5%
Impurity B	Process impurity	0.09%	0.03%	NMT 0.15%
Impurity C	Process impurity	0.12%	Not detected	NMT 0.15%
Impurity D	Degradant (oxidation)	0.30%	1.0%	NMT 1.0%
Impurity F	Process impurity	0.30%	0.50%	NMT 0.50%
Any unspecified impurity	--	≤ 0.07%	≤ 0.05%	NMT 0.10%
Total impurities	--	1.4%	3.7%	NMT 2.0%

- Drug substance of DMF# XYZ is non-compendial and within the scope of ICH Q3A.
- MDD 64 mg/day. IT/QT is 0.10%/0.15% respectively.

Case 2: Impurity Specification (*cont.*)

Name	Proposed limit	Justification
Impurity A	NMT 0.5%	Metabolite. Also present in RLD at a level of 1.5%. The limit is set to ensure drug substance potency.
Impurity B	NMT 0.15%	Also detected in RLD. ICH Q3A qualification threshold.
Impurity C	NMT 0.15%	**Not detected in RLD.** Predicted to be negative for bacterial mutagenicity by (Q)SAR. ICH Q3A qualification threshold applies.
Impurity D	NMT 1.0%	Qualified based on RLD. Both drug substance and RLD exhibit a peak with the same retention time under **the validated HPLC method,** and present comparable mass spectra for the impurity.
Impurity F	NMT 0.50%	Same justification as Impurity D
Any unspecified impurity	NMT 0.10%	ICH Q3A identification threshold applies.
Total impurities	NMT 2.0%	Proposed limit is below the observed level in RLD and does not exceed the summation of acceptance criteria for individual specified (identified and unidentified) impurities.

Bonus: Reviewer's Checklist

Stage	Checklist on qualification of non-compendial impurity in drug substance covered by ICH Q3A
Prior to assessment	1. Search Orange Book and locate MDD in RLD labeling 2. Calculate qualification threshold of ICH Q3A 3. Confirm whether the impurity is non-mutagenic or drug substance is genotoxic or ICH S9 applies.
Assessment	1. Is the impurity qualified with ICH Q3A? 2. Is the impurity qualified with RLD? • Compare the proposed limit to the observed level in RLD • Examine analytical methods • Confirm the proposed limit is in line with RLD specification 3. Is the impurity qualified with scientific literature or toxicity studies? • Submit Pharm/Tox consult
Conclusion	1. Conclude the assessment and cite appropriate deficiency

Residual Solvents

- Solvents with known concentration limit or established PDE in ICH Q3C
  - Class 1 solvents: Solvents to be avoided
  - Class 2 solvents: Solvents to be limited
  - Class 3 solvents: Solvents with low toxic potential. PDE $\geq$ 50 mg/day.
- Solvents for which no adequate toxicological data was found
  - Manufacturers should supply justification for residual levels of these solvents.
  - ICH Q3C provides method to establish PDE (*Appendix 3*). Calculation is subjected to Pharm/Tox assessment.
- Higher levels of residual solvents may be acceptable in certain cases such as short term (< 30 days) or topical application.
  - Justification for these levels should be made on a case by case basis.

Options for Describing Limits

$$\text{Concentration (ppm)} = \frac{1000 \text{ x PDE}}{\text{dose}}$$

PDE is given in terms of mg/day and dose is given in g/day

- Two options are available when setting limits for Class 2 solvents.
- Option 1: Assuming MDD of 10 g
  - Products with MDD over 10 g should be considered under Option 2.
- Option 2: With the known MDD
  - Calculated concentration limit can be significantly higher.
  - The limit is considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum.
  - The limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process.

Case 3: Solvent Qualification

- Diisopropyl ether (DIPE) is classified as solvents without adequate toxicological data according to ICH Q3C.
- DIPE is used at early stage of manufacturing process in DMF# XYZ. Observed level is NMT 5 ppm.
- A limit of 1400 ppm is proposed by DMF holder citing NIOSH (National Institute for Occupational Safety and Health).
- MDD is 4 g, which indicates an exposure up to 5600 µg/day.
- Does the proposed limit impact review timeline?

Case 3: Solvent Qualification (*conc.*)

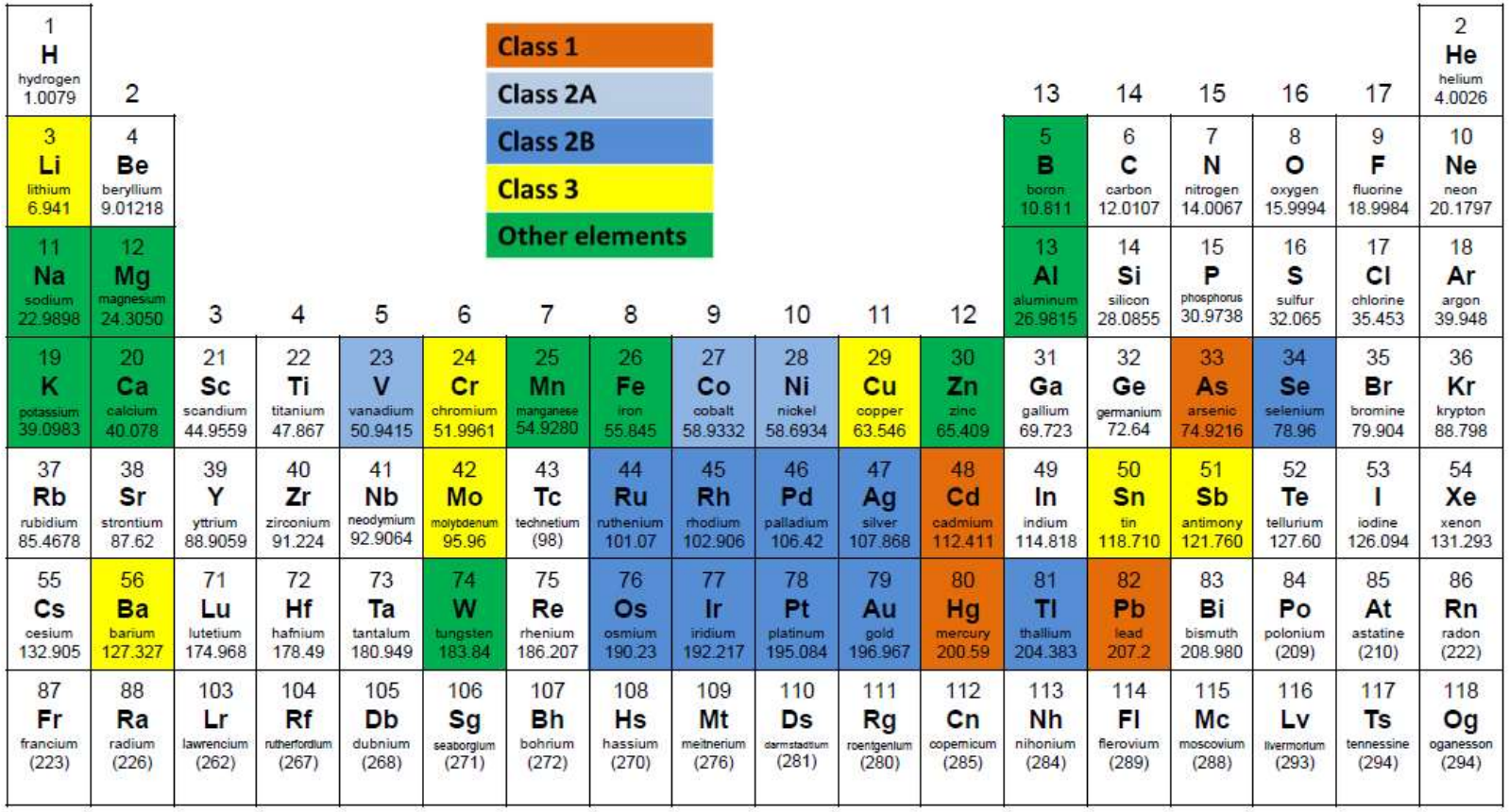
Review	Proposed limit by DMF holder	Assessment by reviewer
1st cycle	1400 ppm, citing NIOSH (National Institute for Occupational Safety and Health) report.	• An exposure of 5600 µg/day has never been accepted by a FDA-approved drug product for oral use. • Observed level is NMT 5 ppm. Request to tighten the proposed limit based on batch data, or provide the corresponding toxicological data.
2nd cycle	500 ppm, citing a literature "Permitted Daily Exposure for Diisopropyl ether as a Residual Solvent in Pharmaceuticals"	• Deemed unacceptable per Pharm/Tox consult after consideration of treatment duration and potential synergistic effect of solvent and drug substance in carcinogenicity. • Recommend to further tighten the limit.
3rd cycle	50 ppm	• Acceptable per Pharm/Tox consult

- Establishing exposure limit is evaluated by Pharm/Tox consultation (3 months).
- In absence of PDE by ICH Q3C, setting acceptance criterion in consideration of manufacturing capability might be a practical approach.

Elemental Impurities

- ICH Q3D presents a process to assess and control elemental impurities in drug product. The principles apply to drug substance.
- Element classification in ICH Q3D
  - Class 1: human toxicants that have limited or no use in the manufacture of pharmaceuticals.
  - Class 2: route-dependent human toxicants. Class 2A elements have relatively high probability of occurrence while Class 2B elements have a reduced probability of occurrence.
  - Class 3: low toxicities by oral route (PDE > 500 µg/day).
  - Other elements: low inherent toxicity but addressed by other guidelines and/or regional regulations

Periodic Table of Elements



1												13	14	15	16	17	2
H hydrogen 1.0079	2																He helium 4.0026
Li lithium 6.941	Be beryllium 9.01218											B boron 10.811	C carbon 12.0107	N nitrogen 14.0067	O oxygen 15.9994	F fluorine 18.9984	Ne neon 20.1797
Na sodium 22.9898	Mg magnesium 24.3050	3	4	5	6	7	8	9	10	11	12	Al aluminum 26.9815	Si silicon 28.0855	P phosphorus 30.9738	S sulfur 32.065	Cl chlorine 35.453	Ar argon 39.948
K potassium 39.0983	Ca calcium 40.078	Sc scandium 44.9559	Ti titanium 47.867	V vanadium 50.9415	Cr chromium 51.9961	Mn manganese 54.9280	Fe iron 55.845	Co cobalt 58.9332	Ni nickel 58.6934	Cu copper 63.546	Zn zinc 65.409	Ga gallium 69.723	Ge germanium 72.64	As arsenic 74.9216	Se selenium 78.96	Br bromine 79.904	Kr krypton 88.798
Rb rubidium 85.4678	Sr strontium 87.62	Y yttrium 88.9059	Zr zirconium 91.224	Nb neodymium 92.9064	Mo molybdenum 95.96	Tc technetium (98)	Ru ruthenium 101.07	Rh rhodium 102.906	Pd palladium 106.42	Ag silver 107.868	Cd cadmium 112.411	In indium 114.818	Sn tin 118.710	Sb antimony 121.760	Te tellurium 127.60	I iodine 126.094	Xe xenon 131.293
Cs cesium 132.905	Ba barium 127.327	Lu lutetium 174.968	Hf hafnium 178.49	Ta tantalum 180.949	W tungsten 183.84	Re rhenium 186.207	Os osmium 190.23	Ir iridium 192.217	Pt platinum 195.084	Au gold 196.967	Hg mercury 200.59	Tl thallium 204.383	Pb lead 207.2	Bi bismuth 208.980	Po polonium (209)	At astatine (210)	Rn radon (222)
Fr francium (223)	Ra radium (226)	Lr lawrencium (262)	Rf rutherfordium (267)	Db dubnium (268)	Sg seaborgium (271)	Bh bohrium (272)	Hs hassium (270)	Mt meitnerium (276)	Ds darmstadtium (281)	Rg roentgenium (280)	Cn copernicium (285)	Nh nihonium (284)	Fl flerovium (289)	Mc moscovium (288)	Lv livermorium (293)	Ts tennessine (294)	Og oganesson (294)

Values in parentheses are the mass number of the most stable isotope.

La lanthanum 138.905	Ce cerium 140.116	Pr praseodymium 140.908	Nd neodymium 144.242	Pm promethium (145)	Sm samarium 150.36	Eu europium 151.964	Gd gadolinium 157.25	Tb terbium 158.925	Dy dysprosium 162.500	Ho holmium 164.930	Er erbium 167.259	Tm thulium 168.934	Yb ytterbium 173.54
Ac actinium (227)	Th thorium 232.038	Pa protactinium 231.036	U uranium 238.029	Np neptunium (237)	Pu plutonium (244)	Am americium (243)	Cm curium (247)	Bk berkelium (247)	Cf californium (251)	Es einsteinium (252)	Fm fermium (257)	Md mendelevium (258)	No nobelium (259)

Risk Assessment

- Elemental impurities intentionally added in synthesis (e.g. catalyst, reagent) must be controlled or justified.
- Drug substance which supports multiple applications with different MDDs or routes of administration will be held to the most restrictive requirements.
- Risk assessment of elemental impurities is highly recommended for drug substance.
  - Class 1 and Class 2A elements should be included.
  - Class 3 elements should be considered in parental and inhalation routes if route specific PDE < 500 µg/day.

Qualification of Elemental Impurities

- Class 1/2/3 elements, PDEs established in ICH Q3D
  - Concentration limit calculated by assuming MDD 10 g or using known MDD.
  - For other routes of administration, the method described in ICH Q3D Appendix 1 may be used to derive PDEs. Subject to Pharm/Tox assessment.
  - Levels higher than established PDEs may be acceptable in certain cases (e.g. intermittent dosing). PDE could be derivatized on case-by-case basis by following the method described in ICH Q3D Appendix 1. Subject to Pharm/Tox assessment.
- Other elements, PDEs not established in ICH Q3D
  - Low risk unless specific quality considerations apply.
- Elements not listed in ICH Q3D
  - The proposed limit does not exceed the level observed in RLD.
  - Qualification with scientific literature or toxicity studies. Subject to Pharm/Tox assessment.

Case 4: Mineral-sourced Drug Substance

- The drug substance is usually produced from mined materials by simple production steps in aqueous systems (dissolution and precipitation or crystallization).
- Elemental impurities from natural contamination and concentration may vary widely depending on the source of the raw material.
- Risk analysis based on knowledge of the production process might be infeasible and unreliable.
- Elemental impurities should be treated like “related substances” and routinely controlled in drug substance specification.

Assessment Timeline

Impurity	Qualification Method	Assessment Timeline
Regular impurity	USP limit ICH Q3A Qualification Threshold Comparative analytical studies against RLD Scientific literature & significant metabolites Toxicity studies	Immediate Immediate Immediate Pharm/Tox consult, 3 mon Pharm/Tox consult, 3 mon
Residual solvent	ICH Q3C limit PDE derived under ICH Q3C Appendix 3, Scientific literature and Toxicity studies	Immediate Pharm/Tox consult, 3 mon
Elemental impurity	ICH Q3D limit PDE derived under ICH Q3D Appendix 1, Scientific literature and Toxicity studies	Immediate Pharm/Tox consult, 3 mon

How Can Industry Improve?

Common issue	Recommendation
Incorrect qualification threshold	• Select correct MDD in calculation of qualification threshold • Work closely with NDA/ANDA applicants
Failure to demonstrate that the same impurity is present in RLD	• Identify the impurity in RLD with validated and stability-indicating HPLC method • Confirm with specific characterization test such as LC-MS.
Proposed limit of degradant exceeding RLD limit	• Analyze RLD samples with validated and stability-indicating HPLC method • Degradant will increase if sample is not properly handled.
Proposed limit unrealistic for solvent without PDE in ICH Q3C	• Set the limit in consideration of manufacturing capability • This might be a practical approach to facilitate assessment and may avoid Pharm/Tox consult based on Agency knowledge.

Summary

- Impurity qualification has profound impact on adequacy of DMF. The proposed limit can be justified by closely following relevant guidelines.
- Impurities are qualified under the principal of clinical relevance. Maximum daily dosage is one of key factors in establishment of impurity acceptance criteria.
- Proposal of a practical limit and selection of an appropriate qualification method will facilitate the assessment process.

Acknowledgement

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Questions?

- For questions regarding the content of this presentation, please type them into the “Q&A Box” so that they can be addressed during the panel Q&A after this session.

- To submitted questions on this presentation for inclusion in the Follow-on webinar on April 9th, send them by March 19th to: DMFWorkshop2021@fda.hhs.gov.

Cross-referenced Talks/Posters

- Please refer to the following posters for cross-referenced materials:
  - ✓ *Establishing Impurity Acceptance Criteria as Part of Specifications for DMFs Based on Clinical Relevance Evaluation of Metal Impurities in Drug Substances*
  - ✓ *Evaluation of Metal Impurities in Drug Substances*

- Please refer to the following presentations on March 3rd and 4th for additional information:
  - ✓ *ICH M7(R1) – Chemistry and manufacturing control (CMC) Perspective on Hazard Assessment by Barbara Scott.*
  - ✓ *Application of (Q)SAR and Expert Knowledge for ICH M7 Impurity Classification by Naomi Kruhlak*