



WELCOME!

U.S. Regional Training Workshop: ICH Q3D

**Lunch: order in the morning and it will
be ready for pickup at noon.**

Planning Committee



John Leighton (FDA), Frank Holcombe(FDA), Amanda Roache(FDA), John Bishop(FDA), Tim McGovern(FDA)

Douglas Ball (Pfizer), Mark Schweitzer (Novartis),
Kahkashan Zaidi (USP), Tim Shelbourn (Eli Lilly), Janeen Skutnick-Wilkinson (Biogen IDEC)



U.S. Food and Drug Administration
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FDA's Office of Pharmaceutical Quality (OPQ) And Q3D Implementation

Michael Kopcha, Ph.D., R.Ph.
Director, Office of Pharmaceutical Quality
CDER/FDA

**ICH Q3D: U.S. Training Workshop, Silver Spring, MD
August 22-23, 2016**

Office of Pharmaceutical Quality (OPQ)

Mission

The Office of Pharmaceutical Quality assures that quality medicines are available to the American public

Vision

The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality

Slogan

'One Quality Voice'



'One Quality Voice' Value Statements

- **Put patients first** by balancing risk and availability
- Have one quality voice by **integrating review and inspection** across product lifecycle
- Safeguard clinical performance by establishing **scientifically sound quality standards**

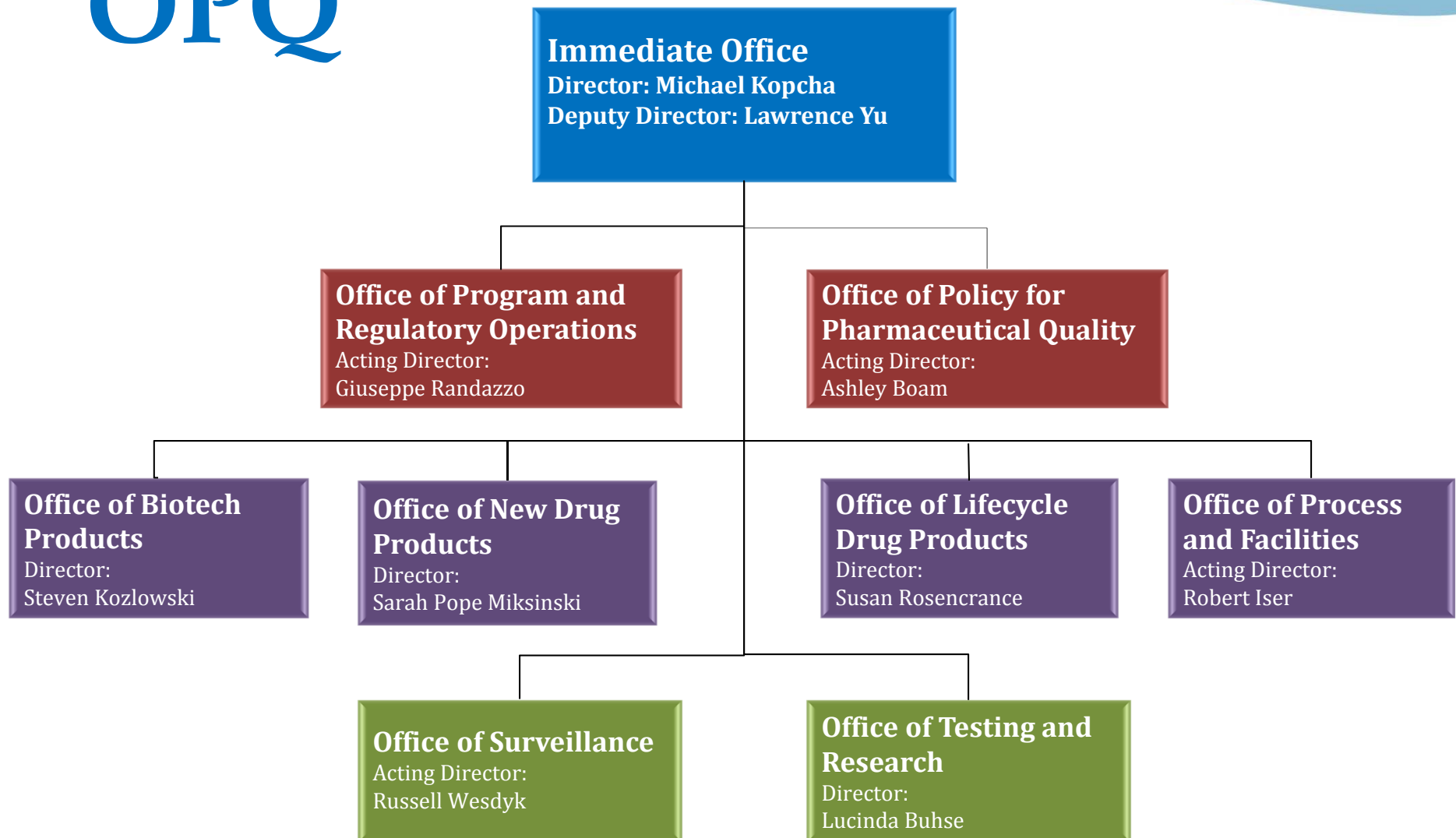
'One Quality Voice' Value Statements

- Maximize focus and efficiency by applying **risk-based approaches**
- Strengthen the effectiveness of lifecycle quality evaluations by using **team-based processes**
- Enhance quality regulation by developing and utilizing staff expertise

'One Quality Voice' Value Statements

- Encourage innovation by advancing **new technology and manufacturing science**
- Provide effective leadership by emphasizing cross-disciplinary interaction, shared accountability, and joint problem solving
- Build **collaborative relationships** by communicating openly, honestly, and directly

OPQ



**Office of Biotech
Products**

Director:
Steven Kozlowski

**Office of New Drug
Products**

Director:
Sarah Pope Miksinski

**Office of Lifecycle
Drug Products**

Director:
Susan Rosencrance

– Office of Biotechnology Products (OBP), Office of New Drug Products (ONDP), and Office of Lifecycle Drug Products (OLDP)

- Perform quality assessment of the drug substance, drug product, and biopharmaceutics portions of applications (NDAs, ANDAs, BLAs, and supplements)
 - Formulation/product design
 - Risk assessment
 - Quality standards and clinically relevant specifications
 - Control strategy related to product attributes
 - Stability

**Office of Process and
Facilities**Acting Director:
Robert Iser

– Office of Process and Facilities (OPF)

- Performs quality assessment of the manufacturing process for applications (NDAs, ANDAs, BLAs, and complex supplements)
 - Ensures successful implementation of manufacture at commercial scale
 - Advises on applied microbiological issues related to product quality and manufacture
 - Advises on inspectional and facility issues related to applications

Risk Management and Communication

OPQ Priority: Formal risk-based regulatory approaches that effectively define the scope and extent of quality assessments

- Currently OPQ employs a formal risk assessment process to best allocate resources based on product risk and patient impact
 - Maintaining structured risk assessments that focus on product failure modes and specific risks to patients
 - Developing use of the structured risk assessment as a communication tool with investigators and reviewers for more informed decision making, knowledge transfer, and good lifecycle management

Our Common Goal is Drug Product Quality

- OPQ aligns and integrates all quality functions within CDER marking a new era in FDA's quality oversight.



- Let us communicate, collaborate, and work together to deliver a high quality product that meets the patient's needs – a true partnership!



Thank you!



Introduction to the ICH Q3D U.S. Training Workshop

Silver Spring, MD

August 22-23, 2016

John F. Kauffman, Ph.D.

CDER Office of Pharmaceutical Quality

Division of Pharmaceutical Analysis

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- Overview of Guideline
- Q3D Implementation Working Group is Developing Training Modules
- Data-based expectation: elemental impurity levels in drug products and components relatively low in most cases
- FDA Expectations for Implementation
- Workshop Agenda

The ICH Q3D Expert Working Group

- Broad membership supports harmonization
 - Toxicologists and Chemists
 - FDA, EMA, MHLW
 - EFTA, WHO, Health Canada, Chinese Taipei, China, Korea
 - Pharmacopeias: USP, Ph.Eur., JP
 - PhRMA, EFPIA, JPMA
 - IPEC, WSMI, IGPA, BIO
 - At the June 2014 meeting, approximately 24 representatives participated in the deliberations.

Objectives of the Guideline

- Deliverables
 - Global policy for limiting elemental impurities in drug products
 - Harmonised, safety-based limits for elemental impurities, especially those of highest toxicological concern
 - Selection of elements to control
 - Methodology for establishing safety-based limits
 - Permitted daily exposures for specific elements
 - Appropriate risk-based approach to ensure control for elements likely to be present in drug products and ingredients.



Permitted Daily Exposures (PDEs) for 24 Elements by 3 Routes of Administration

																2 He Helium 4 G												
											5 B Boron 10.81 S 2.0	6 C Carbon 12.01 S 2.6	7 N Nitrogen 14.01 G 3.1	8 O Oxygen 15.99 G 3.5	9 F Fluorine 19 G 4.0	10 Ne Neon 20.18 G												
											13 Al Aluminum 26.98 S 1.5	14 Si Silicon 28.09 S 1.9	15 P Phosphorus 30.97 S 2.2	16 S Sulfur 32.07 S 2.6	17 Cl Chlorine 35.45 G 3.2	18 Ar Argon 39.95 G												
											19 K Potassium 39.1 S 0.8	20 Ca Calcium 40.08 S 1.0	21 Sc Scandium 44.96 S	22 Ti Titanium 47.88 S	23 V Vanadium 50.94 S	24 Cr Chromium 52 S	25 Mn Manganese 54.94 S	26 Fe Iron 55.85 S	27 Co Cobalt 58.93 S	28 Ni Nickel 58.69 S	29 Cu Copper 63.55 S	30 Zn Zinc 65.39 S	31 Ga Gallium 69.72 S 1.6	32 Ge Germanium 72.61 S 1.9	33 As Arsenic 74.92 S 2.0	34 Se Selenium 78.96 S 2.5	35 Br Bromine 79.9 L 2.9	36 Kr Krypton 83.8 G
											37 Rb Rubidium 85.47 S 0.8	38 Sr Strontium 87.62 S 1.0	39 Y Yttrium 88.91 S	40 Zr Zirconium 91.22 S	41 Nb Niobium 92.91 S	42 Mo Molybdenum 95.94 S	43 Tc Technetium [99] S	44 Ru Ruthenium 101.07 S	45 Rh Rhodium 102.91 S	46 Pd Palladium 106.42 S	47 Ag Silver 107.87 S	48 Cd Cadmium 112.41 S	49 In Indium 114.82 S 1.7	50 Sn Tin 118.71 S 1.8	51 Sb Antimony 121.75 S 2.1	52 Te Tellurium 127.6 S 2.3	53 I Iodine 126.9 S 2.7	54 Xe Xenon 131.29 G
											55 Cs Cesium 132.91 S 0.7	56 Ba Barium 137.33 S 0.9	57 La Lanthanum 138.91 S	72 Hf Hafnium 178.49 S	73 Ta Tantalum 180.95 S	74 W Tungsten 183.85 S	75 Re Rhenium 186.21 S	76 Os Osmium 190.2 S	77 Ir Iridium 192.22 S	78 Pt Platinum 195.08 S	79 Au Gold 196.97 S	80 Hg Mercury 200.59 L	81 Tl Thallium 204.38 S 1.8	82 Pb Lead 207.2 S 1.8	83 Bi Bismuth 208.98 S 1.9	84 Po Polonium [209] S 2.0	85 At Astatine [210] S 2.2	86 Rn Radon [222] G
											87 Fr Francium [223] S 0.7	88 Ra Radium [226] S 0.9	89 Ac Actinium [227] S	104 Rf Rutherfordium [261] Sv	105 Db Dubnium [262] Sv	106 Sg Seaborgium [263] Sv	107 Bh Bohrium [262] Sv	108 Hs Hassium [265] Sv	109 Mt Meitnerium [266] Sv	110 [269] Sv	111 [272] Sv	112 [277] Sv	113 Sv	114 Sv	115 Sv	116 Sv	117 Sv	118 Sv

Class 1

Class 2A

Class 2B

Class 3

58 Ce Cerium 140.12 S	59 Pr Praseodymium 140.91 S	60 Nd Neodymium 144.24 S	61 Pm Promethium [147] Sv	62 Sm Samarium 150.36 S	63 Eu Europium 151.97 S	64 Gd Gadolinium 157.25 S	65 Tb Terbium 158.93 S	66 Dy Dysprosium 162.5 S	67 Ho Holmium 164.93 S	68 Er Erbium 167.26 S	69 Tm Thulium 168.93 S	70 Yb Ytterbium 173.04 S	71 Lu Lutetium 174.97 S
90 Th Thorium [232] S	91 Pa Protactinium [231] S	92 U Uranium [238] S	93 Np Neptunium [237] Sv	94 Pu Plutonium [244] Sv	95 Am Americium [243] Sv	96 Cm Curium [247] Sv	97 Bk Berkelium [247] Sv	98 Cf Californium [251] Sv	99 Es Einsteinium [252] Sv	100 Fm Fermium [257] Sv	101 Md Mendelevium [258] Sv	102 No Nobelium [259] Sv	103 Lr Lawrencium [260] Sv

Overview of the Guideline

- Main body, references and glossary (pages 1-17)
- Appendix 1: Method for Establishing Exposure Limits (pages 18-20)
- Appendix 2: Established Permitted daily exposures (PDEs) for Elemental Impurities by oral, parenteral and inhalation routes of administration (pages 21-22)
- Appendix 3: Individual Safety Assessments for 24 elements (pages 23-67)
- Appendix 4: Illustrative Examples (pages 68-73)



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2. Scope
3. **Safety Assessment of Potential Elemental Impurities**
 - 3.1 Principles of the Safety Assessment ...
 - 3.2 Other Routes of Administration
 - 3.3 Justification for Elemental Impurity Levels Higher than an Established PDE
 - 3.4 Parenteral Products
4. Element Classification

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5. Risk Assessment and Control of Elemental Impurities
 6. Control of Elemental Impurities
 7. Converting between PDEs and Concentration Limits
 8. Speciation and other Considerations
 9. Analytical Procedures
 10. Lifecycle Management
- Appendix 1: Method for Establishing Exposure Limits

Principles for developing Q3D training materials

- Intended to provide clarity on key aspects of the guideline in order to facilitate a harmonized interpretation and implementation by industry and regulators in the ICH and non-ICH regions
- Does not provide additional guidance beyond Q3D
- Ten modules on key safety and quality topics
 - Modules 0-7 are available at WWW.ICH.ORG
 - Module 8&9 to appear soon
- Not intended to provide templates for addressing the Q3D recommendations.

Slides with this format are taken from the training material developed by the ICH Q3D Implementation Working Group.

These slides are available at
www.ich.org

Disclaimer:

This presentation includes the authors' views on Elemental Impurities theory and practice. The presentation does not represent official guidance or policy of authorities or industry.

International Conference on Harmonisation of Technical Requirements
for Registration of Pharmaceuticals for Human Use

FDA Division of Pharmaceutical Analysis Studies of Elemental Impurities

- Lead Survey, 2007: Reg. Tox. Pharm. (2007) 48, 128
- Elemental Impurities in Drug Products Survey-2010
- Small Volume Parenterals, 2013 (With ONDP)
- Excipient Survey, 2015 (Published, OpenAccess)
 - DOI: 10.1002/jps.24650
 - Search “Journal of Pharmaceutical Sciences Elemental Impurities”
 - Complete data set available in Supplementary Material

Summary of Studies: No Surprises

- Most products have low levels of elemental impurities
- Q3D/<232> Class 2B elements are only present when intentionally added
 - Critical for Risk Assessment!
- Highly refined excipients have low levels of elemental impurities
 - Cellulose based materials
 - Lactose

Summary of Studies: No Surprises – Cont'd

- Some excipients have elevated levels of elemental impurities **relative to refined excipients**
 - E.g., mined excipients and products primarily composed of mined excipients
 - Levels may still be low compared to Table A.2.2 concentrations
 - The risk assessment reveals which materials make significant contributions
- Relatively high risk
 - high dose mass, e.g., large volume parenterals
 - intentionally added reagents and catalysts
 - unrefined naturally sourced materials

FDA Draft Guidance: Elemental Impurities in Drug Products

- **Recommendations and Timelines** for risk assessment and documentation of risk assessment
- New NDA and ANDA applications submitted after June 1, 2016 should follow the recommendations of Q3D.
 - Consistent with the EMA implementation timeline
- For existing marketed products, manufactures should follow the recommendations of Q3D and/or comply with USP <232> by January 1, 2018.
 - Consistent with USP implementation timeline for <232> and <233>.
- See <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm509432.pdf> , or search FDA Guidance Elemental Impurities for details.

Ongoing Q3D EWG activities

- ICH is developing a general procedure for maintenance of impurity guidelines.
- The Q3D Implementation Working Group has requested approval to develop permitted daily exposures for the dermal route of administration.

AGENDA



Monday, August 22, 2016

Time	Topic	Speaker
9:00 AM	Opening Remarks	Dr. Michael Kopcha, Director, OPQ
9:10 AM	Introduction to Workshop	John Kauffman (FDA/OPQ Office of Testing and Research, Q3D IWG)
9:30 AM	Determining safe levels of elemental impurities	Douglas Ball (Pfizer, Q3D IWG)
10:10 AM	BREAK	
10:30 AM	Administration by other routes and other safety aspects	John Leighton (FDA/OND OHOP, Q3D IWG)
11:10 AM	Panel Discussion and Questions	John Leighton, Douglas Ball, Tim McGovern (FDA)
11:40 AM	LUNCH	

AGENDA



Monday, August 22, 2016

Time	Topic	Speaker
1:00 PM	Calculation Options	John Kauffman
1:20 PM	Risk Assessment and Control - Industry Perspective	Mark Schweitzer (Novartis, Q3D IWG)
2:00 PM	BREAK	
2:20 PM	Risk Assessment and Control - FDA Perspective	Frank Holcombe (FDA/OPQ Office of Lifecycle Drug Products, Q3D IWG)
2:50 PM	Process-introduced Elemental Impurities and Controls	Edwin Jao (FDA/OPQ Office of Process and Facilities)
3:20 PM	Panel Discussion and Questions	John Kauffman, Mark Schweitzer, Frank Holcombe, Janeen Skutnik- Wilkinson, Kahkashan Zaidi, Alison Ingham (Health Canada, Q3D IWG), Edwin Jao
4:00 PM	Wrap-up and Adjourn	

AGENDA



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Tuesday, August 23, 2016

Time	Topic	Speaker
9:00 AM	Opening Remarks	John Kauffman (FDA)
9:10 AM	USP Presentation	Kahkashan Zaidi (USP, Q3D IWG)
9:50 AM	FDA Regulatory Perspective and Expectations	Danae Christodoulou (FDA/OPQ Office of New Drug Products)
10:20 AM	BREAK	
10:40 AM	Implementation Challenges Related to LVPs and CCS	Tim Shelbourn (Eli Lilly, USP Elemental Impurities Expert Panel Member)
11:10 AM	Panel Discussion and Questions	Kahkashan Zaidi, Tim Shelbourn, Danae Christodoulou, Douglas Ball, Edwin Jao
11:40 AM	LUNCH	

Determining Safe Levels of Elemental Impurities

*FDA Elemental Impurity Workshop,
22-23 August 2016*

*Douglas J Ball, MS DABT
Research Fellow, Pfizer Inc*

Agenda

- Definitions
- Q3D process for setting elemental impurity (EI) impurity levels
 - Data Evaluation
 - Minimal Risk Level (MRL) Approach
 - Uncertainty Factor (UF) Approach
 - Limited Data Approach
- EI permitted daily exposures (PDEs)
- Establishing a acceptable limit for a non-listed EI
- Conclusions

Key Definitions

- **Permitted Daily Exposure:** The maximum acceptable intake of elemental impurity in pharmaceutical products per day.
- **Minimal Risk Level:** An estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk.
- **Modifying Factor:** An individual factor determined by professional judgment of a toxicologist and applied to bioassay data to relate that data to human safety. (ICH Q3C)
- **Safety Factor:** A composite (reductive) factor applied by the risk assessment experts to the No-Observed-Adverse-Effect Level (NOAEL) or other reference point, such as the benchmark dose or benchmark dose lower confidence limit, to derive a reference dose that is considered safe or without appreciable risk, such as an acceptable daily intake or tolerable daily intake (the NOAEL or other reference point is divided by the safety factor to calculate the reference dose). The value of the safety factor depends on the nature of the toxic effect, the size and type of population to be protected, and the quality of the toxicological information available. See related terms: Assessment factor, Uncertainty factor. (IPCS, 2004)

Safe Limit

- Certain EI are considered to have safety issues at any level (e.g. Pb)
 - Ubiquity of EI makes it impossible to eliminate from source materials
 - Limits set based on lowest level deemed to represent minimal risk for acute or chronic toxicity

Threshold of Toxicological Concern (TTC)

- ICH M7 developed a process to assess mutagenic impurities using the TTC
 - TTC Concept is based on linear extrapolation from the dose giving a 50% tumor incidence (TD50) to a 1 in 10^6 incidence, using TD50 data for the most sensitive species and most sensitive site of tumor induction
- ICH Q3D EWG determined this approach does not apply to developing EI PDEs
 - Toxicity associated with many elements do not fit linear models
 - PDEs based on linear extrapolation not feasible
 - PDE concept is based on a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime

Process for developing EI PDEs

- The factors considered in approximate order of relevance:
 - The likely oxidation state of the element in the drug product;
 - Human exposure and safety data when it provided applicable information;
 - The most relevant animal study;
 - Route of administration, and
 - The relevant endpoint(s)
- Standards for daily intake for some EI exist for food, water, air, and occupational exposure. Where appropriate, these standards were considered in the safety assessment and establishment of the PDEs
 - MRL, threshold limit value—time weighted approach (TLV-TWA), reference dose (RfD)

PDE: MRL Example

- Cadmium Oral PDE
 - A number of oral exposure studies of cadmium in rats and mice showed no evidence of carcinogenicity
 - Endpoint for oral exposure to cadmium and cadmium salts is renal toxicity
 - Therefore the renal toxicity endpoint was used to establish the oral PDE for cadmium
 - Recommendations of ATSDR, an MRL of 0.1 µg/kg for chronic exposure is used to set the oral PDE
 - This is consistent with the WHO drinking water limit of 0.003 mg/L/day (WHO, 2011).
- $\text{PDE} = 0.1 \mu\text{g}/\text{kg}/\text{d} \times 50 \text{ kg} = 5.0 \mu\text{g}/\text{day}$

Calculation of a Permitted Daily Exposure

PDE : General Methods

- **STEP 1** Hazard identification by reviewing all relevant data
- **STEP 2** identification of “critical effects”,
- **STEP 3** determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered to be critical effects,
- **STEP 4** use of several adjustment factors to account for various uncertainties (Modifying Factors)
- Process employed in ICH Q3C for developing residual solvent PDE

$$\text{PDE} = \frac{\text{NOEL} \times \text{Weight Adjustment}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}}$$

Inter species
 Inter individual
 Tox. EP vs Time exp
 Severity Tox. Effect
 NOEL not established

(50 kg) PDE
 apply for
 all
 population

PDE – Modifying Factor Example

- Cadmium Parenteral PDE
- A 12 week study in rats given daily subcutaneous injections of 0.6 mg/kg Cd, 5 days per week showed renal damage at week 7 and later (Prozialeck et al, 2009)
 - The LOAEL of this study is 0.6 mg/kg based on decreased body weight, increased urine volume and urinary biomarkers seen at this dose level. This study was used to set the parenteral PDE.
 - In a separate single dose (SC) rat, sarcomas were noted at the injection site at the two highest doses (16 and 32 $\mu\text{mol/kg}$ cadmium chloride at the end of the 72 week observation period (Waalkes et al, 1999)
- $$\text{PDE} = 0.6 \text{ mg/kg} \times \frac{5 \text{ d/wk}}{7 \text{ d/wk}} \times \frac{50 \text{ kg}}{5 \times 10 \times 5 \times 5 \times 10} = 1.7 \text{ } \mu\text{g/day}$$
- Time adjusted from 5/day/week to 7 days/week
- F1: a factor of 5 was used for extrapolation from rats to humans
- F2: a factor of 10 was used to account for individual variability
- F3: a factor of 5 was used for a 3 month study in rodents
- F4: a factor of 5 was chosen because Cd is carcinogenic by the inhalation route and granulomas were observed by the subcutaneous route. These findings are of uncertain relevance in humans
- F5: a factor of 10 was chosen because a LOAEL was used to set the PDE.

Calculation of a Permitted Daily Exposure PDE : Routes of Administration

- In the absence of data or where data are not considered sufficient for a safety assessment for **the parenteral** and **or inhalation** route of administration, modifying factors based on oral bioavailability were used to derive the PDE from the oral PDE:
 - Oral bioavailability <1%: divide by a **modifying factor of 100**;
 - Oral bioavailability $\geq 1\%$ and <50%: divide by a **modifying factor of 10**
 - Oral bioavailability $\geq 50\%$ and <90%: divide by a **modifying factor of 2**
 - Oral bioavailability $\geq 90\%$: divide by a **modifying factor of 1**.

If no bioavailability data or occupational inhalation exposure limits



Oral PDE divided by a modifying factor of 100

EI PDE

Table A.2.1: Permitted Daily Exposures for Elemental Impurities¹

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
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3



Derivation of an Acceptable Level (AL) for element impurity (EI) not in Q3D

- Needs to follow the principles to derive a PDE as outlined in the Guideline (Appendix 1)
- Literature review is needed to find safety information
- Information needs to be judged for quality and applicability
- **Note: example does not represent an ICH Q3D-derived PDE; example is for illustrative purposes only**

Example 1: Safety Qualification of an EI not in Q3D

- Drug Product in a pre-filled syringe (PFS)
- Stopper is a sulfur cured elastomer
 - Elemental sulfur (S) detected from a leachable study of the container closure system and not S from mAb
 - Based on shelf-life of DP, S level determined to be 2.3 µg/dose
- DP is a mAb that has a SC dose regimen (1 dose every 8 weeks)
- Quality attributes
 - Determined that S does not affect the quality of the mAb



Determination of an acceptable level

- **Using Q3D principles an AL for elemental S in a parenteral DP can be developed**
 - **Note: not an ICH Q3D-derived PDE; example for illustrative purposes only**
- **Limited parenteral data available – use oral study data to calculate an AL**
 - Reported human data suggests that S is relatively nontoxic but an MRL is not available
 - Rabbit iv study; single dose level, limited number of animals, non-GLP, used colloidal sulfur containing polysulfide (Greengard and Woolley, 1940; Studies on colloidal sulfur-polysulfide mixture. Toxicity J.Am.Pharmaceut.Assoc. 29: 289-292)
 - The oral bioavailability of S is unknown
 - A feed study in calves with dietary administration of 2 concentrations of sulfur (as Calcium sulfate) for 85 days showed no effects in health, body weight, Cu and Se levels and activity of Cu and Se dependent enzymes up to a dose of 16 mg/kg/day. Thus the no observed adverse effect level (NOAEL) is 16 mg/kg/day.
 - S intake (oral) = $16 \text{ mg/kg/d} \times 50 \text{ kg} \div (10 \times 10 \times 10 \times 1 \times 1) = 0.8 \text{ mg/day} (800 \text{ } \mu\text{g/day})$
 - This study was considered the most appropriate to determine an AL

Determination of an acceptable level (cont)

- Parenteral AL
- Using the most conservative modifying factor of 100 (section 3.1 of Q3D, oral bioavailability < 1%), a parenteral AL for S is:
$$800 \mu\text{g/day} \div 100 = 8 \mu\text{g/day}$$
- S in PFS DP
 - The calculated AL for S is 8 $\mu\text{g/day}$
 - PFS DP contains worst case level of 2.3 $\mu\text{g/dose}$
 - Patient dosed once every 8 weeks
 - The level of S in the DP is considered acceptable
 - ALs are subject to review and approval by regulatory agencies/authorities
- **Note: This is not an ICH Q3D-derived AL. It is an example for illustrative purposes only.**

Conclusions

- The ICH Q3D EWG toxicology team evaluated data for 24 EIs
 - Determined the most appropriate human and/or nonclinical data to set EI PDEs for the oral, parenteral and inhaled routes of exposure
 - Went through several cycles of pre-Step 2 as well as Step 2 review
 - Adjusted PDEs based on each review
- Worked in concert with USP <232> EP to harmonize EI PDEs

Acknowledgements

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- John Leighton - FDA
- Dominique Masset – ANSM
- Masayuki Mishima – Chugai
- Klaus Olejniczak - Consultant
- Anja Slikkerveer – Astellas
- PhRMA LDT
- USP <232> EP



WORLDWIDE RESEARCH & DEVELOPMENT
Drug Safety R&D

SCIENCE  LIFE-CHANGING
FOR IMPACT



Administration by other routes and other safety aspects

John K Leighton

Division of Hematology Oncology Toxicology

CDER/US FDA

Training workshop August 22/23, 2016



Disclaimer

- This presentation is the authors' view on Elemental Impurities and not ICH.
- The contents of this presentation are from the Q3D guidance and training modules 1 and 2, available at ich.org
- ICH Q3D guidance should be consulted as the source document.



Guiding principles in initiating the route dependent safety assessment

- Consider the oral PDEs in Appendix 3 as a starting point
 - Training material is available with case examples – Module 1
 - Based on a scientific evaluation, the parenteral and inhalation PDEs may be a more appropriate starting point.
- Assess if local effects are expected when administered by the intended route of administration.
 - If local effects are expected, a modification to an established PDE may be necessary.
 - If local effects are not expected, no adjustment to an established PDE is necessary.



Guiding principles in initiating the route dependent safety assessment (cont)

- If available, evaluate the bioavailability of the element via the intended route of administration and compare this to the bioavailability of the element by the route with an established PDE.
 - Information may not be readily available
 - Literature data may not be sufficiently detailed or may describe a different form
- When a difference is observed, a correction factor (CF) may be applied to an established PDE.
- It is preferred to use the term Acceptable Level (AL) for any permitted daily exposure which is not stated in the Q3D guidance.
- Assessing an EI is a 2-step approach
 - Step 1: determine the AL
 - Step 2: derive a permitted concentration



Common Pitfalls

- Data may not be available for a route specific AL
- Form of EI is not well described or not relevant
- Dose and exposure information may not be available
- If an AL proposed for the new route is increased relative to an established PDE, quality attributes may need to be considered.
- Most likely, the route specific AL will be a conversion from an existing PDE



Correction Factor

- For example, when no local effects are expected, if the oral bioavailability of an element is 50% and the bioavailability of an element by the intended route is 10%, a correction factor of 5 may be applied.
- Dermal CF = absorption oral / absorption dermal
 - If a range is available, use highest dermal absorption and lowest absorption values



Retention Factors

- The retention factor was introduced by the SCCNFP to take into account rinsing off and dilution of finished products by application on wet skin or hair (e.g. shower gels, shampoos, ...) [SCCNFP/0321/00; http://ec.europa.eu/food/fs/sc/sccp/out130_en.pdf]
- Range from 0.01 (1%, e.g., shampoo) to 1 (100%, e.g., face cream)
- Other similar terms: exposure time, duration of contact
- Available from the public literature and from government sources
 - SCCS/1501/12
 - Api, Basketter, Cadby et al, 2008
 - SCCNFP/0690/03
- Retention factor is not bioavailability!

Module 1

Developing an Acceptable Level for Other Routes of Administration

ICH Q3D Elemental Impurities

Disclaimer:

This presentation includes the authors' views on Elemental Impurities theory and practice. The presentation does not represent official guidance or policy of authorities or industry.

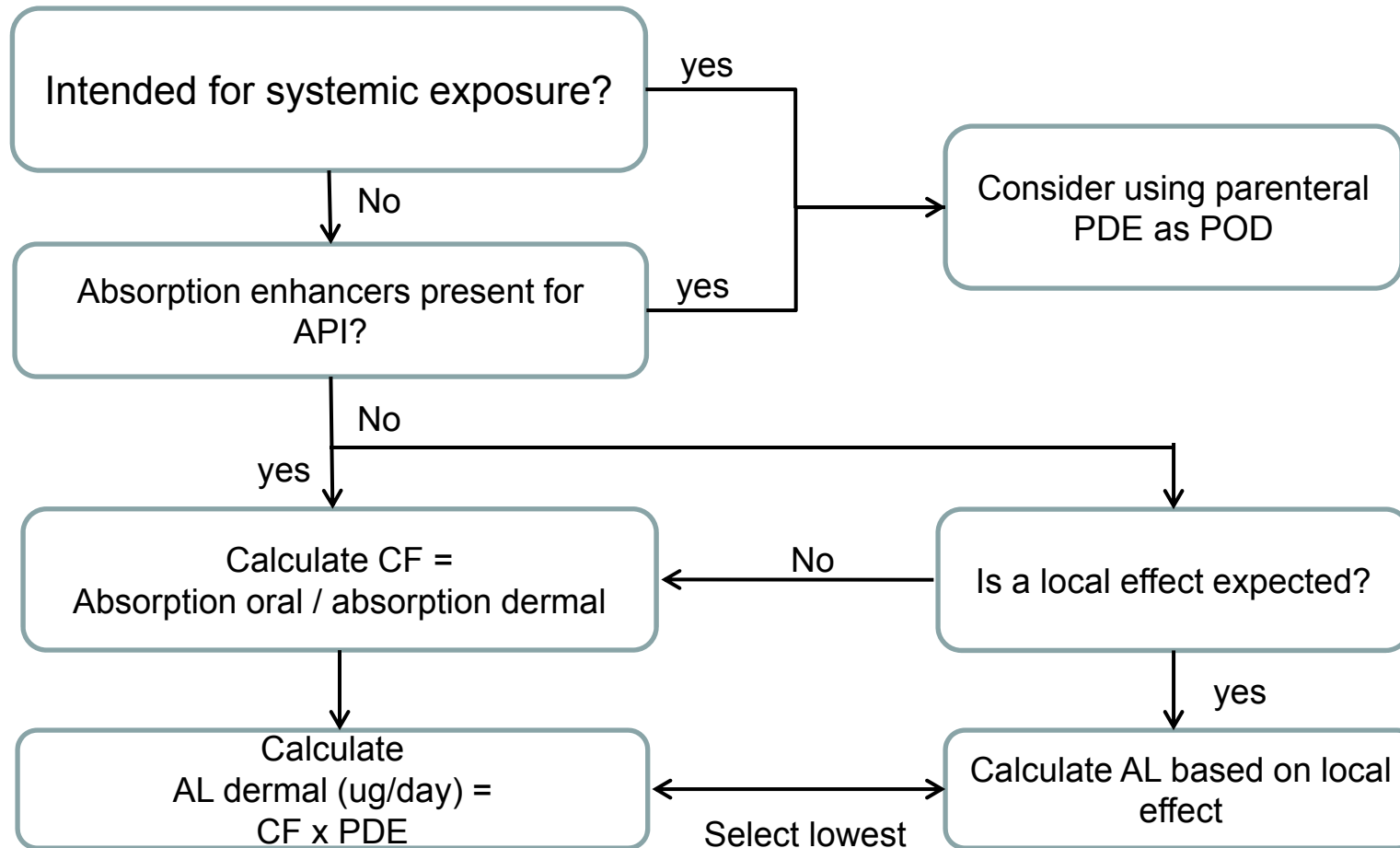
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Examples

- Examples in Module 1
 - Example 1: whole body cream
 - Example 2: whole body cream
 - Example 3: topical face cream
 - Example 4: ear drops
 - Example 5: EI with local toxicity
 - Example 6: anti-itch cream
 - Example 7: eye drop

Dermal AL Scheme





Example 1: Whole body lotion

- Whole body lotion applied at 3-4 times per day (based on surveys) for a total of 30 gm/day
- Scenario for this example:
 - Intact skin only
 - Product is designed to sit on skin surface (RF = 1)
 - No penetration enhancers
 - No systemic absorption of the API
 - No local elemental impurity toxicity reported
- This example uses an estimate of daily application (30 gm/day, 3-4 times/day) obtained from regulatory/literature sources and not a labeled dose (e.g., apply as needed).



Example 1 (cont)

- Investigate scientific literature/regulatory sources for estimates of daily exposure (e.g., SCCS1501/12, http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/scs_s_006.pdf)
- Oral PDE = 100 µg/d; oral absorption is 100% oral, 5% dermal
- Calculate Systemic Exposure = Oral PDE / Dermal absorption
- AL for EI X = $100 \mu\text{g/d} / 0.05 = 2000 \mu\text{g/d}$
- Concentration: $2000 \mu\text{g/d} / 30 \text{ g/d} = 67 \mu\text{g/g}$
- Note that the number of times applied per day is factored into the equation of total amount administered per day (30 g)



Example 3: Topical face cream

- Facial cream in a 28 gm (1 oz) tube
- Scenario:
 - No skin breaks
 - No penetration enhancers
 - No systemic absorption of the API is detected
 - For external use only for up to 7 days (1 tube)
 - Application 3-4 times per day
 - Product is designed to be stay on skin (retention factor 1)
 - Oral bioavailability 100%; dermal 5%
 - No local elemental impurity toxicity
- This example uses a label recommendations to determine the concentration of elemental impurity in the product.



Example 3 (cont)

- To set an AL, use the oral PDE and adjust for bioavailability of 5% (0.05) and Retention Factor = 1
- $AL = PDE \times CF \times RF$
- $AL \text{ EI } X = 100 \mu\text{g/day} \times (1 / 0.05) \times 1 = 2000 \mu\text{g/day}$
- According to the label, the tube of 28 gm is to be used 3-4 times per day over 7 days, or 4 gm/day
- Concentration $2000 \mu\text{g/day} / 4 \text{ gm/day} = 500 \mu\text{g/gm}$



Question 1

- Product: Drug X film-coated tablets
- Strengths: 50 mg
- Maximum daily dose: 100 mg
- Indication: chronic disease

- Risk assessment indicated that EI Z was used during synthesis of the drug substance (DS)
- EI Z in the DS is 40 $\mu\text{g}/\text{gm}$

- Question: Does this result in an acceptable intake of EI Z?

- Answer: Yes
 - Daily dose of 100 mg contains 4 μg EI Z
 - Oral PDE for EI z = 100 $\mu\text{g}/\text{day}$



Question 2

- Product: Drug X: dermal cream
- Strengths: 10%
- Maximum daily dose: 10 g
- Indication: chronic use

- EI Z in the drug substance is 40 µg/g
- Question: Does this result in an acceptable exposure to EI Z?
- Answer:
 - Permitted concentration is 300 µg/g: acceptable
 - No dermal effects in literature for inorganic salts
 - Dermal absorption ~1%; oral absorption = 30%
 - $CF = \text{oral absorption} / \text{dermal absorption} = 30 / 1 = 30$
 - $\text{Dermal AL} = CF \times \text{oral PDE} = 30 \times 100 = 3000 \text{ µg/day}$
 - $\text{Permitted Concentration} = RF \times \text{dermal AL} / \text{daily dose} = 1 \times 3000 / 10 = 300 \text{ µg/g}$



Some Sources of Reliable Assessments

- SCCS: Scientific Committee on Consumer Safety
 - http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- EFSA: European Food and Safety Authority
 - <http://www.efsa.europa.eu/>
- IARC: International Agency for Research on Cancer
 - <http://www.iarc.fr/>
- IRIS: Integrated Risk Information System
 - <https://www.epa.gov/iris>
- ATSDR: Agency for Toxic Substances and Disease Registry
 - <https://www.epa.gov/iris>
- National Toxicology Program
 - <http://www.niehs.nih.gov/research/atniehs/dntp/>

Module 2

Justification for Elemental Impurity Levels Higher than an Established PDE

ICH Q3D Elemental Impurities

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Guiding principles

- The PDEs derived under Q3D have been set to ensure that exposure to an element, which is present as an impurity in a drug product, is safe based on daily exposure over a lifetime.
- The calculations for the PDE were performed using the modifying factor approach (for detail see Guideline appendix 1).
- Typical steps are
 1. Identify the most relevant study (animal or human)
 2. Identify the most relevant starting point (SP) for the calculation (NOEL, LOAEL etc.)
 3. Select appropriate modifying factors
 4. Calculation:
$$\text{PDE} = \text{SP} \times \text{Mass Adjustment} / [\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}]$$

There is only one PDE per route

- Each element has only **one** set of established PDEs for oral, parenteral and inhalation routes of administration, which are specified in the Guideline.
- Although “Levels of elemental impurities higher than the PDE may be acceptable in certain cases”, the acceptable level (AL) is not a PDE.

Considerations for acceptance of levels higher than established PDE

- Assessment needs to be prepared on a case-by-case basis, since it depends on the element, the formulation, the clinical use of the drug product, the patient population, etc
- Needs to be justified by a science and risk-based approach
- The higher levels need to have no unfavorable impact on the risk/ benefit/ quality profile of the drug product
- Is subject to regulatory review and approval

Examples for Risk-Based approaches

- A. The subfactor approach (WHO, 2009), subdivides F2 into a subfactor for pharmacokinetics and a subfactor for pharmacodynamics
- B. Modification of modifying factors used for the established PDE, which improve the alignment with the intended use profile
- C. Replacing the study used to define the PDE with a more relevant study (based on exposure duration or route of administration)

Other approaches may be justified.

Note: all approaches will have to be supported by published references and/or proprietary data

A] Subfactor approach

- Described by the World Health Organisation (WHO)
 - WHO. Cobalt and inorganic cobalt compounds. Concise International Chemical Assessment Document. Inter-Organization Programme for the Sound Management of Chemicals (IOMC). WHO, 2006;69.
- This method allows F2 (which corrects for variation) to be written as $F2 = F2.1 \times F2.2$
 - F2.1 represents pharmacokinetics and F2.2 pharmacodynamics
 - When no specific data are available: it is assumed that PK and PD aspects are equally important then the value of both is 3.16 ($10^{1/2}$)
 - Each F subfactor can range from 1 to 3.16
- The modification of F2.1 can e.g. be based on the elimination half-life relative to the administration duration or frequency
 - After 5 half-lives, a EI is considered to have been completely eliminated

Guideline example A1: subfactor approach: modifying factor

- This example illustrates that the subfactor approach may be used to calculate ALs from oral PDEs which were developed using the modifying factor approach
- Case: oral drug product contains 350 µg of Element X
- Established PDE in Q3D: Oral PDE of 220 µg/day
 - $\text{PDE (Oral)} = 1.1 \text{ mg/kg/d} \times 50 \text{ kg} / 5 \times 10 \times 5 \times 1 \times 1 = 220 \text{ µg/day}$
- F2.1 can be modified based on the dosing interval relative to the plasma elimination half life (5 days):
 - e.g., for a dosing schedule of once a month (~ 5 half-lives) F2.1 could be decreased to 1
- Refer to Module 2 Annex for method of calculation of F2.1

Guideline example A1: subfactor approach: modifying factor (cont)

ALs for EI X can be calculated as follows:

- For once monthly dosing
 - $F2 \text{ (modified)} = F2.1 \times F2.2 = 1.07 \times 3.16 = 3.38 \sim 3$

$$AL = 1.1 \text{ mg/kg/d} \times 50 \text{ kg} / 5 \times \mathbf{3} \times 5 \times 1 \times 1 = 733 \text{ } \mu\text{g/day}$$

For practical purposes, this value is rounded to $\sim 700 \text{ } \mu\text{g/day}$.

Guideline Example A2: subfactor approach: oral MRLs

- This example illustrates that the subfactor approach may be used to calculate ALs where the oral PDEs were developed using human Minimal Risk Levels (MRLs). In the derivation of MRLs modifying factors have already been applied.
- Case: oral DP dosed once every three weeks contains EI Z
- Established PDE in Q3D: Oral PDE of 1000 µg/day
 - $\text{PDE (Oral)} = 0.02 \text{ mg/kg/d (MRL)} \times 50 \text{ kg} = 1000 \text{ µg/day}$
- Based on the dosing interval relative to the plasma elimination half-life (4 days), F2.1 can be modified from 3.16 to 1 (~5 half lives, defaults to a minimum of 1). F2.2 remains 3.16.
 - $\text{F2 (modified)} = \text{F2.1} \times \text{F2.2} = 1 \times 3.16 = 3.16$
 - $\text{AL} = \text{oral PDE} \times (\text{modified F2} / \text{original F2})$
 - $\text{AL for Z} = (0.02 \text{ mg/kg/d} \times 50 \text{ kg}) \times (3.16/10) = 1000 \text{ µg/day} \times 0.316 = 316 \text{ µg/day} \sim 300 \text{ µg/day}$

B] Modification of modifying factors

- PDEs were developed for lifetime exposure
- Modifying factors can be adjusted to consider non-chronic use:
 - The duration of the study used to set the PDE relative to the intended clinical use (Factor F3)
 - The nature and severity of the toxicity observed, and whether the toxicity was reversible (Factor F4)
- Examples:
 - B4: Intermittent dosing
 - B5: Single dose treatment



Putting it together – an FDA case

- FDA was asked whether a proposed AL for EI-X was acceptable for an oral OTC product
- The sponsor requested a waiver of EI-X levels specified in <232> as use was intermittent and not considered a safety issue; no other information provided
- FDA analysis
 - EI-X is of concern in a sensitive subpopulation
 - EI-X exceeded oral PDE by several multiples
 - Label did not indicate intermittent use only
 - The safety margin for EI-X is unknown
- Conclusion: sponsor assessment was not adequate



Putting it together – an FDA case (cont)

- Still unresolved, but based on usual approach for impurities:
 - Likely ask the sponsor to provide a rationale as to why EI cannot be reduced to oral PDE
 - Reduce EI level to PDE – additional assessment toward revision of manufacturing and formulation processes
 - Future control plans?
 - If the EI cannot be reduced, provide a scientific justification to exceed the PDE; consider
 - Bioavailability in formulation
 - Provide information about risk in sensitive subpopulations
 - Risk mitigation (restrict use in sensitive subpopulations to medical need)
 - Provide data to support intermittent use claim
 - Label changes
 - Other

Conclusions

- The intent of Q3D is to develop PDEs and a mechanism to control for EIs
- Development of ALs may be acceptable in certain cases. These cases could include, but are not limited to, the following situations:
 - Intermittent dosing;
 - Short term dosing (i.e., 30 days or less);
 - Specific indications (e.g., life-threatening, unmet medical needs, rare diseases)
- Strong rationale should be provided
 - Rationale should include, but not limited to:
 - Rationale for higher level
 - Statement on impact on DP safety, efficacy and/or quality
- ALs are subject to review and approval by regulatory agencies/authorities



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