ISO 10993-1 BIOLOGICAL EVALUATION – THE RISK MANAGEMENT OF UNSTUDIED EXTRACTABLES AND LEACHABLES (E&L) IMPURITIES IN MEDICAL DEVICES AND COMBINATION PRODUCTS

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OUTLINE

- FDA guidance (2016) on use of ISO 10993-1
  - Highlights
  - Risk management framework
- Biologics in delivery device systems
  - Challenges with risk management framework
  - Toxtree for pragmatic decision analysis
- Case study - a theoretical prototype wearable device
- Points to consider

HIGHLIGHTS OF THE NEW FDA GUIDANCE

- During development of the new guidance, FDA received 300+ comments from 36 groups/individuals including device companies, trade associations, drug companies
- Significant comments:
  - More focus on risk assessment
  - More considerations in lieu of biocompatibility testing
  - Chemicals of concern

HIGHLIGHTS OF THE NEW FDA GUIDANCE – CONTINUED-

- Goal
  - To develop risk management framework to reduce certain biocompatibility testing requirements
- Previous guidance on biocompatibility
  - What testing is needed?
- New focus:
  - How to use risk management to address biocompatibility
  - Leverage existing data, if possible

RISK MANAGEMENT FRAMEWORK - DEFINITIONS

- Biocompatibility is the ability of a device material to perform with an appropriate host response in a specific situation
- Direct contact: Device (and/or component) comes into physical contact with body tissue
- Indirect contact: There is no direct physical contact of device/component with body tissue. However, device (and/or component) contacts fluid or gas prior to the fluid or gas coming into physical contact with body tissue.

RISK MANAGEMENT FRAMEWORK
BEFORE TESTING, CONSIDER….

- The clinically relevant attributes:
  - Device design, components/materials/manufacturing processes
  - Intended clinical use and exposure (anatomical location, frequency, contact duration)
- Justification can be made for no new testing if:
  - Device and components have a long history of safe use
  - Device and components have been well characterized chemically and physically
  - There are no new biocompatibility concerns

RISK MANAGEMENT FRAMEWORK: TOXICITY ENDPOINTS VS TESTS

- Use risk management framework to reduce unnecessary testing
- Determine what toxicity information is available (prior testing, literature)
  - Cytotoxicity
  - Local irritation/sensitization
  - Acute to chronic systemic toxicity
  - Genotoxicity/carcinogenicity
  - Reproductive/developmental toxicity
  - Implantation
  - Hemocompatibility
- Conduct only studies that address the gaps

When the material composition and extractables/leachables (E&L) impurities are known, literature is often used for safety assessment

RISK MANAGEMENT FRAMEWORK: OPPORTUNITY TO ADVANCE CHEMICAL CHARACTERIZATION AND SAFETY ASSESSMENTS

- Extracts prepared for biocompatibility testing is poorly characterized
  - Vehicle interference with analysis of leachables
  - Leachable substances are unlikely to reach sufficiently high levels for toxicity endpoints
- Chemical characterization of materials can improve safety assessment
  - Leachable substances are identified
  - Semi-quantitative or quantitative profile allows for worst-case exposure estimates
  - Literature reviews can be leveraged for data-rich compounds
  - In silico tools can be used to predict toxicity

WHAT DOES THE NEW FRAMEWORK MEAN FOR DELIVERY DEVICES FOR BIOLOGICS?

- Biologics are often administered IV/SC by delivery device systems
- Biocompatibility testing of a delivery device system typically follows ISO 10993-17: Establishment of allowable limits for leachable substances
- Chemical characterization of the device components/materials typically follows ISO 10993-18: Chemical characterization of materials
- Safety assessment of leachables impurities in the pharmaceuticals typically follows the principles and methods of ICH guidance, namely, ICH M7, Q3A(R2), Q3B(R2), Q3C(R6) and Q3D

The challenge lies with the appropriate approach to assess leachable impurities in a biologic

The key takeaway box is also commonly called a "tombstone"

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SAFETY ASSESSMENT: CURRENT ISO VS ICH APPROACH

Guideline/Standard	Scope	Description
ISO 10993-1	Medical devices	Biocompatibility evaluation and testing
ISO 10993-17	Medical devices	Establishment of allowable limits for leachable substances
ISO 10993-18	Medical devices	Chemical characterization of materials
ICH M7	Pharmaceuticals	DNA reactive (mutagenic) impurities
ICH Q3A(R2)	Pharmaceuticals	Impurities in new drug substances
ICH Q3B(R2)	Pharmaceuticals	Impurities in new drug products
ICH Q3C(R6)	Pharmaceuticals	Impurities – residual solvents
ICH Q3D	Pharmaceuticals	Inorganic impurities including metals

What would be the most science- and risk-based approach for assessing leachables impurities in biologics?

DRUG DELIVERY DEVICES ARE OFTEN STERILIZED…

- Sterilization by gamma radiation, steam or ethylene oxide leads to formation of degradation products
  - Fragments of polymeric materials
  - Reactive compounds of intentional additives
- These degradation products are often reported as Tentatively Identified Structures (TIS)
  - TIS may be detectable only under experimental conditions (dependent on solvent type, extraction conditions, analytical techniques)
  - There are no reference standards to verify identification or quantitation

TIS are often reactive, unstudied chemical compounds with insufficient information for toxicology assessments

TIS PRESENT CHALLENGES TO SAFETY AND QUALITY ASSESSMENTS FOR BIOLOGICS

- Protein therapeutics are susceptible to interactions with reactive compounds
  - Leading to structural modifications of the protein
  - Impact on product quality attributes (protein adducts, aggregates)
  - Impact to safety (e.g. anti-drug antibodies, immunogenicity)
  - Reduced efficacy (e.g. neutralizing antibodies, surface adsorption)

SAFETY ASSESSMENTS ARE RELATIVELY STRAIGHT FORWARD

Cancer risk*

- SAR classes of aflatoxin-like, azoxy- or N-nitroso-compounds (Compound specific toxicology assessment)
- Other SAR classes (TTC: 1.5 µg/day, 10^{-5} cancer risk)

Non-cancer risk**

- Cramer Class I: low order of toxicity, easily metabolized, endogenous compounds (TTC: 1800 µg/day)
- Cramer Class II: structures that are slightly more complicated, but do not exhibit the toxicity of Class III compounds (TTC: 540 µg/day)
- Cramer Class III: structures that have reactive functional groups (TTC: 90 µg/day)

*ICH M7
**Cramer et al 1978; Kroes et al 2004; Benigni & Bossa 2008; Patlewicz et al 2008 and FDA CFSAN 2011

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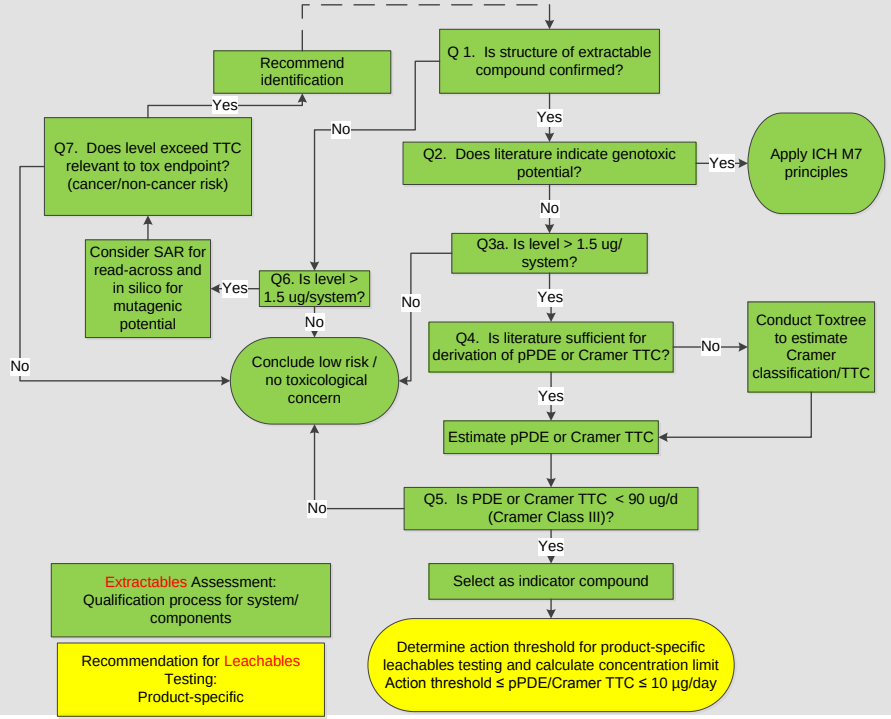
QUALITY ASSESSMENTS ARE MORE CHALLENGING

- Requires relating the Cramer Class III structures to the Adverse Outcome Pathway
- Presence of reactive functional groups that lead to significant toxicity (Kroes et al 2004)
  - Examples: cyano, N-nitroso, diazo, trazeno, quarternary N, lactones, epoxides and ethylenimines
- The molecular initiating event leading to toxicity is the interactions of a reactive chemical with critical cellular targets (Adverse Outcome Pathway) 
- The most critical and prevalent targets are macromolecules, especially DNA and proteins.
- There is ongoing efforts to refine Cramer classification (SOT-FDA Colloquium, 2016)

AOP references: Villeneuve D.L. et al. (2014a,b)

Source: Li, 2017

E&L ASSESSMENTS: DECISION ANALYSIS



Source: Li et al 2015

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SOME TIS MAY TRIGGER QUALITY/SAFETY CONCERN

- Assessment of TIS as an extractable is important for screening and selection of device and components
- Monitoring the TIS as a potential leachable is important to demonstrate stability of a drug product at recommended storage conditions

Safety assessment of data-rich compounds is straight forward. TIS are data-poor compounds with challenges.

ASSESSMENT OF TIS – A PRAGMATIC APPROACH

Mutagenicity

- Is structure a relevant metabolite of a well-studied parent compound?
- Do in silico predictions show structural alert for mutagenic activity?
- Is exposure level below ICH M7 TTC for the clinical use scenario in question?

Systemic Toxicity

- Does structure allow for read-across to a known category?
- Can structure be classified into Cramer classes?
- Does structure show reactive functional group (Cramer Class III)?

Protein modification

- Are there reactive functional groups that may form covalent binding with protein?
- Classify structures based on mechanism of protein interaction, e.g. Michael acceptors, Schiff base formers, acylating agents, nucleophilic substitutions

PRAGMATIC APPROACH: FOCUS ON DEVICE COMPONENTS/MATERIALS OF HIGH RISK

- Those that come into physical contact with the patient
  - Route of exposure
  - Duration of contact
- Those that come into contact with the drug product
  - Transient
  - Recommended storage conditions

E/L profiles are chemically complex with a mix of data-rich and data-poor compounds

Image from Google

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SAR TOOLS FOR DATA-POOR COMPOUNDS

- Free downloads / open access software:
  - IdeaConsult Ltd. (2015). Toxtree (Estimation of Toxic Hazard - A Decision Tree Approach) v.2.6.13. from http://toxtree.sourceforge.net/
  - OECD (2015). QSAR Toolbox v.3.3.5. http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm
- Compared for predicting mutagenicity
  - Stavitskaya, L., Minnier, B. L., & Kruhlak, N. L. (2014). Benchmarking Assessment of Open Source and Newly Released *Salmonella* Mutagenicity (Q)SAR Models for Potential Use Under ICH M7. Abstract # 2273B. Society of Toxicology Annual Conference, Phoenix, AZ. 2014
- Reviewed for covalent protein binding relevant to toxicity
  - Enoch, S. J., Ellison, C. M., Schultz, T. W., & Cronin, M. T. (2011). A Review of the Electrophilic Reaction Chemistry Involved in Covalent Protein Binding Relevant to Toxicity. *Critical Reviews in Toxicology*(9), 783-802

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APPLYING TOXTREE WITH RISK MANAGEMENT FRAMEWORK

- Toxtree can be used to predict the key toxicity endpoints:
  - Mutagenicity
    - In vitro mutagenicity (Ames test) alerts by ISS
    - References: Benigni and Bossa (2011); Benigni et al (2013)
  - Systemic toxicity
    - Cramer rules with extensions
    - References: Cramer et al (1978); Munro et al (1996); Patlewicz et al (2008)
  - Covalent binding with protein
    - Protein binding alerts
    - Reference: Enoch et al (2011)

CASE STUDY - A THEORETICAL PROTOTYPE WEARABLE DEVICE

- Product contact components with fluid path attached
  - Glass, septum, plunger, tubing, connectors
- Extraction conditions
  - Solvents: water; aqueous organic solvent
  - Temperature/duration: 70º C for 4 days
  - Orthogonal analytical techniques: HPLC/ELSD; GC/MS, LC/UV/MS, ICP/MS
- Decision analysis on organic extractable profile
  - Identified compounds (range: < 0.1 to 40 µg/device)
  - Tentatively identified structures (range: <0.6 to 50 µg/device)

CASE STUDY – ORGANIC EXTRACTABLES PROFILE

Number of compounds	Identified structures	Tentatively identified structures
Total: 25	12	13
20 compounds with estimate > 1.5 µg/device	10	10
5 compounds with estimates <1.5 µg/device	2	3
11 compounds with sufficient data to derive PDE	10	1
9 compounds requiring Toxtree screening	0	9

CASE STUDY - TOXTREE ANALYSIS

- None of the 9 tentatively identified structures with estimates above 1.5 µg/device were predicted to have structural alerts for mutagenicity
- Cramer classifications
  - Cramer Class I: 6 structures predicted with low toxicity (TTC: 1,800 µg/day)
  - Cramer Class II: 2 structures predicted with medium toxicity (TTC: 540 µg/day)
  - Cramer Class III: 1 structure predicted with high toxicity (TTC: 90 µg/day)
- Protein binding alerts (Toxtree with chemist expert interpretation)
  - Michael acceptors: 2 structures
  - Acylating agent: 1 structure
- Recommendation
  - Based on exposure estimate, Cramer classification and risk of covalent binding with protein, the next stage of device development should examine the critical components to mitigate the risk of high risk structure (Cramer Class III, acylating agent)

POINTS TO CONSIDER

- For biotechnology products, E/L evaluation must consider both patient safety and product quality.
- Toxtree is a useful *in silico* screening tool for predicting mutagenic activity, severity of systemic toxicity and alerts for covalent binding with proteins, which are key safety and quality endpoints for biologics.
- Robust chemical characterization and toxicology assessments are useful for development of delivery devices for use with biologics.
- The science- and risk-based approach may be used as justification to reduce biocompatibility testing requirements.

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