NOVEL APPLICATIONS AND PRODUCT DESIGNS: DRIVING NEW REQUIREMENTS FOR ASSESSMENT AND SELECTION

IPAC-RS SUPPLIER AND PHARMA WORKSHOP ON DEVICE AND CONTAINER CLOSURE SYSTEM QUALITY

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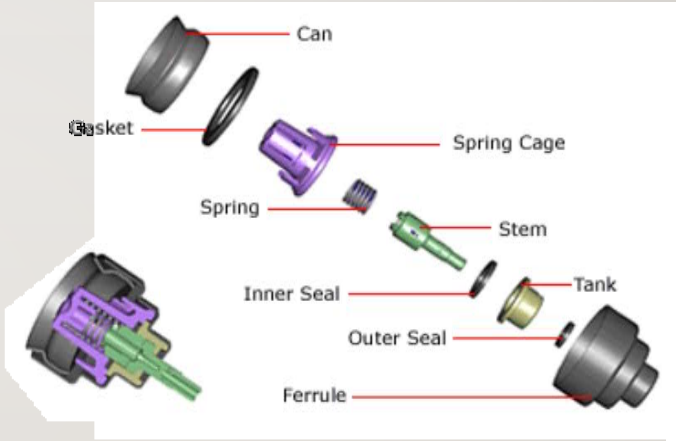
AGENDA

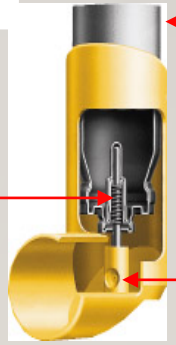
- What is Novel?
- Relevant Guidelines
- Application of risk management tools to OINDP

3 WHY THESE MATERIALS MATTER

- High degree of concern regarding route of administration with the likelihood of packaging component dosage form interactions, e.g. inhalation
- OINDP/Complex component quality plays a critical role in many pharmaceutical final product tests
  - Can be as high as 60%
- OINDP/Complex component supply chains can be:
  - intricate
  - composed of many interconnected parts

•Directly affects patients





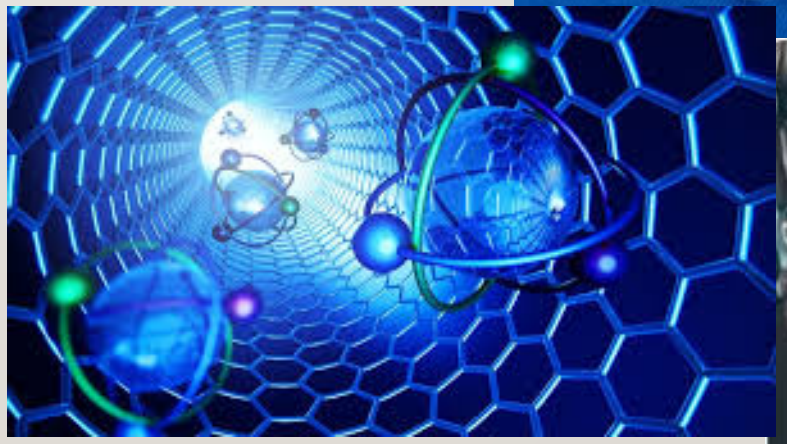
4 NOVEL DEFINITIONS

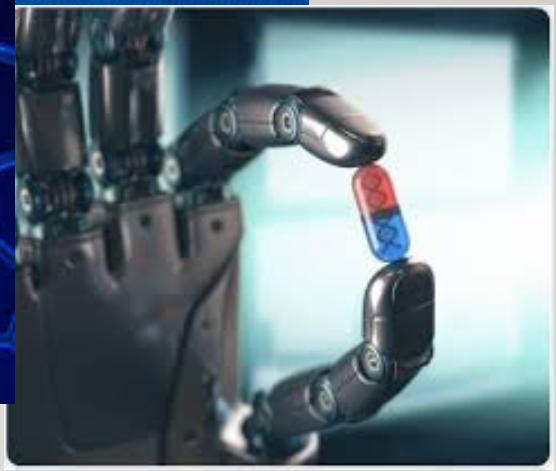
- A material or a composition that has not been previously used in an approved drug product in the US – IQ & IPEC Americas
- A material that has not previously been used in any legally US-marketed medical device – Office of Device Evaluation

- According to current EU guidelines a new or novel excipient is a substance that is used for the first time in a drug product, or for the first time in a new route of administration
- It may be a new chemical entity or it can be a well established one that has not previously been used in pharmaceutical product in or outside the EU
- pharmaceutical excipients that are used for the first time in a product for a particular drug administration pathway are considered new

5 HOW NOVEL?

- Has the material been used in approved drug products in the US/globally?
- Is it a mixture/combination of 2 or more previously approved materials?
- Is it the same route of manufacture?
- Approved material, new design?





FDA - ADVANCING REGULATORY SCIENCE INITIATIVE

- Coordinate regulatory science for emerging technology product areas:
  - Enhance the collaboration of multidisciplinary scientific expertise within the Agency when evaluating emerging technology product areas; and
  - Develop mechanisms to promote cross-disciplinary regulatory science training and research to address scientific gaps and challenges posed by novel products.
- Enable development and evaluation of novel and improved manufacturing methods
- Promote two state-of-the-art manufacturing strategies – Process Analytical Technology, and Quality-By-Design approaches – for impact on manufacturers' ability to maintain consistent quality

ISO 10993-1:2009 BIOLOGICAL EVALUATION OF MEDICAL DEVICES — PART 1: EVALUATION AND TESTING WITHIN A RISK MANAGEMENT PROCESS

- **conduct risk evaluation and impact assessment**
- testing based on results of risk evaluation and impact assessment. For example, to **verify material properties in relation to its function in the design of the device**; to assess the **stability** of the drug formulation in **relation to its contact with the new material** to qualify the **toxicological and biological safety profile** of the material or process
- For complex changes, the **change management process can take several years**, and may have a significant impact on the pharmaceutical company's business and supply to patients. The security of supply is a critical aspect of material selection and is continually monitored throughout development and commercialization to ensure supply chain risks are mitigated.
- As such**, it is proposed that a 36 month rolling availability of material** should allow pharmaceutical manufacturers sufficient time to manage changes or source alternative materials.

ISO 10993 BIOCOMPATIBILITY STANDARDS, PART 18 "CHEMICAL CHARACTERIZATION OF MATERIAL AND DEVICES" AND PART 19, "MORPHOLOGICAL AND TOPOGRAPHICAL CHARACTERIZATION OF MATERIALS AND DEVICES

- Includes consideration of:
  - device design, material components and manufacturing processes
  - clinical use of the device including the intended anatomical location
  - frequency and duration of exposure
  - potential risks from a biocompatibility perspective
  - information available to address the identified risks
  - information needed to address any remaining knowledge gaps, such as new biocompatibility testing or other evaluations that appropriately address the risks

ISO 10993 LEVERAGING EXISTING INFORMATION

- It may be possible to leverage previously conducted biocompatibility information if:
  - The previously tested device has similar indications, type, and duration of contact;
  - An explicit statement is provided regarding any differences in materials or manufacturing between the new and leveraged devices under consideration; and
  - Information is provided to explain why differences aren't expected to impact biocompatibility.

ISO 10993 TOX IMPLICATIONS

- The materials of manufacture, the final product and possible leachable chemicals or degradation products should be considered for their relevance to the overall toxicological evaluation of the device
- Any change in chemical composition, manufacturing process, physical configuration or intended use of the device should be evaluated with respect to possible changes in toxicological effects and the need for additional toxicity testing

TECHNICAL CONSIDERATIONS FOR ADDITIVE MANUFACTURED MEDICAL DEVICES DOCUMENT ISSUED ON DECEMBER 5, 2017. THE DRAFT OF THIS DOCUMENT WAS ISSUED ON MAY 10, 2016

- FDA has developed this guidance to provide the Agency's initial thinking on technical considerations specific to devices using **additive manufacturing**, the broad category of **manufacturing encompassing 3-dimensional (3D) printing**.
- Additive manufacturing (AM) is a process that builds an object by sequentially building 2-dimensional (2D) layers and joining each to the layer below, allowing device manufacturers to rapidly produce alternative designs without the need for retooling and to create complex devices built as a single piece.
- Rapid technological advancements and increased availability of AM fabrication equipment are encouraging increased investment in the technology and its increased use by the medical device industry. The purpose of this **guidance is to outline technical considerations associated with AM processes**, and **recommendations for testing and characterization for devices** that include at least one additively manufactured component or additively fabricated step.

DESIGN CONTROL GUIDANCE FOR MEDICAL DEVICE MANUFACTURERS

- Design controls are an interrelated set of practices and procedures that are incorporated into the design and development process, i.e., a system of checks and balances.
- Design controls make systematic assessment of the design an integral part of development. As a result, **deficiencies in design input requirements, and discrepancies** between the proposed designs and requirements, **are made evident and corrected earlier in the development process**.
- Design controls increase the likelihood that the design transferred to production will translate into a device that is appropriate for its intended use.

FDA CRITICAL PATH INITIATIVE
NOVEL MATERIALS AND MANUFACTURING

- **Novel materials** with **unprecedented design freedom** in both geometric complexity and chemical properties present both **advantages and challenges** in the creation of medical devices.
- The materials which make up **medical devices and combination products undergo many physical and chemical changes during their total product life cycle** (TPLC), comprising their formulation, manufacture, storage, deployment and use. From the selection of raw materials, to the implantation of a device in the clinical setting, to the long-term biological responses they inspire, materials may be subjected to some or all of the following:

MATERIALS MAY BE SUBJECTED TO SOME OR ALL OF THE FOLLOWING:

- chemical reactions
- separation/purification temperature excursions
- phase and microstructure changes
- molding/extrusion
- weaving
- 3D printing
- imparting of anisotropy
- creation of functional interfaces
- Washing
- surface treatments
- packaging/sterilization
- degradation during storage
- preps in the clinical setting
- *in vivo* degradation

15 SUPPORTIVE GUIDELINES

- ISO 14971 *Medical devices - Applications of risk management to medical devices*

- Quality Management Systems - Process Validation Guidance - The Global Harmonization Task Force
  - This process validation guidance is intended to assist manufacturers in understanding quality management system requirements concerning process validation and has general applicability to manufacturing (including servicing and installation) processes for medical devices. The guidance provides general suggestions on ways manufacturers may prepare for and carry out process validations.

MDR ANNEX I GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

- Manufacturers shall establish, implement, document and maintain a risk management system.
- Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles, including wear debris, degradation products and processing residues, that may be released from the device.

10.4: SUBSTANCES CONTAINED IN AND RELEASED FROM THE DEVICE

- The most **significant new text is the requirement for certain substances of concern** that invasive devices or devices administering/storing substances must contain a **concentration below 0.1 per cent by weight** (stated in 10.4.1) unless justified with reference to10.4.2. This includes:
  - Carcinogenic
  - Mutagenic
  - Toxic to reproduction (in total referred to as 'CMR') substances
  - Substances with endocrine-disrupting properties. T
- The section makes reference to substances categorized per EU Regulation 1272/2008 (Classification, Labelling and Packaging of Chemicals) and substances identified in EU Regulation 1907/2006 (REACH: Registration, Evaluation, Authorisation, and Restriction of Chemicals) or EU Regulation 528/2012 (Market and Use of Biocidal Products).
- A justification as per SPR 10.4.2 must be made if the CMR or endocrine-disrupting substances (for example: lead compounds, other heavy metals, phenols) are present above 0.1 per cent by weight in these device types. This subsection, 10.4.2 lists the aspects to be included in the justification for inclusion of these substances.

A RISK-BENEFIT ASSESSMENT OF PHTHALATES AS WELL AS OTHER CMR AND ENDOCRINE-DISRUPTING SUBSTANCES

- 10.4.3 and 10.4.4 state that the European Commission shall provide the scientific committee provided for in the Regulation with a mandate to prepare guidelines including a risk-benefit assessment of phthalates as well as other CMR and endocrine-disrupting substances. Phthalates are currently addressed in MDD ER 7.5 and not specifically addressed in the AIMDD.
- There is no immediate action required for manufacturers at present; however, manufacturers of devices including phthalates, CMR substances, or endocrine-disrupting substances must keep these forthcoming guideline reports in mind and account for this in plans to meet the MDR requirements. Manufacturers may reference as examples similar opinion reports from the scientific committee on emerging and newly identified health risks (SCENIHR).
- SPR 10.4.5 addresses labelling requirements for devices which include substances as referred to previously, in concentrations above 0.1 per cent by weight. This information must be disclosed on the label, and specific information on treatment of vulnerable groups including children and pregnant and breastfeeding women must be included in the IFU. This section is cross-referenced from the labelling requirement, SPR 23.2(f).
- The text and requirements for substances in the device, and especially substances of toxicological concern, are greatly expanded in the MDR. A threshold and reference for substances of concern are now specifically defined, and considerations for justification are outlined if these substances are included in a medical device. Manufacturers should be aware of what substances are present in their devices. The specific requirements will further increase the need for careful characterization of device substances and materials going forward.

19 COMPONENT CQA & RISK PROCESS

- Focus on the CQA that impact:
  - Dose delivery
  - Product integrity
  - Product purity
- Is component necessary for proper functioning of delivery system or mucosal/drug contacting?
- Are polymers or processing aids used in the component manufacturing process
- Perform chemical hazard risk analysis
  - ✓ **Does the data exist from a previous medical device?**
  - ✓ **If not determine the tests required to get the data**

- Early in the development process of an MDI or DPI, the applicant should develop a list of potential CQAs (Critical Quality Attribute) for the combination product.
- A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8(R2) Pharmaceutical Development

MATERIAL & PROCESS INFORMATION NEEDED TO PERFORM THE COMPONENT RISK ASSESSMENT

- The base material(s) of construction of the component
- The additive composition of the material
- The component fabrication process
- Any material or component pre/post-treatment
- If no compositional data are available, the data from component extractables studies or at least a list of potential extractables from the material supplier could assist with the risk evaluation.
- Extractables studies and risk assessment can guide the need for leachables studies.
- The information provides the customer with an initial set of data that directs strategy to assess the risk of leachables in drug products

- Phthalates Content (required for labeling in EU
- DEHP Content (Canadian Requirement)
- BPA Content (Canadian Requirement)
- Aromatic Amines conten
- Epoxy derivatives (BADGE, BFDGE, NOGE)
- Mercaptobenzo thiazole (MBT) content
- Nanomaterials content
- N-nitrosamines content and compliance with Directive 93/11/EEC
- Polycyclic aromatic hydrocarbons (PAH) content
- Latex
- Electronics
- Conflict Minerals

RISK MITIGATION STRATEGIES FOR MATERIALS AND COMPONENTS

- Component selection
  - **Attempt to use components already used in OINDP**
  - Additionally, information provided by the vendor(s) of plastic packaging systems and their associated materials or components of construction can facilitate suitability assessments, as such information may be appropriate additions to or surrogates for the results obtained by performing the tests.
- If several components have the same specific source of chemical harm (e.g., made from the same material) the **cumulative effect should be evaluated**
- Controlled extraction (simulation) study: Worst-case controlled extraction (simulation) study to determine the extent to which extractables may become probable leachables (for additional information, see *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery System* <1663>).
- Product assessment: Actual-case measurement of confirmed leachables in the therapeutic product in the pharmaceutical packaging/delivery system intended for the commercial market (for additional information, see *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* <1664>

22 SELECTION OF SUPPLIERS OF RAW MATERIALS AND COMPONENTS

- Engage the Quality/Supplier Qualification team early in the process
  - Quality risk management activities are usually, but not always, undertaken by **interdisciplinary teams**. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.
- **If possible choose suppliers that already supply to the OINDP community**
  - It is often not possible for suppliers to predict the interaction of a material with the final drug in all cases. What packaging material suppliers can do is an extractables study.

SUPPLIER MATERIAL INFORMATION THAT SUPPORTS THE RISK ASSESSMENT

- Where applicable **documentation should be readily available** to allow Pharma to understand, mitigate and manage the regulatory risks and/or safety concerns associated with the packaging or device material as **early as possible** in the drug development process including:
  - Certificate of Compliance
  - Safety Data Sheets
  - Technical Data Sheets
  - Component manufacturing records
  - Component specifications
  - Supplier extraction studies

- This information provides reassurance that the material meets recognized standards and is suited for use within a pharmaceutical application. It provides supportive data that the material selected for pharmaceutical application, in the first instance, **is fit for purpose**, **meets the design intent criteria** and **presents negligible risk** to patient safety; and supports a robust long-term agreement between material vendors and Pharma for the supply of materials/components

RECOMMENDED BASELINE REQUIREMENTS FOR MATERIALS USED IN ORALLY INHALED AND NASAL DRUG PRODUCTS (OINDP) – IPAC-RS 2017

- The chemical risk evaluation process is viewed as an integral part of the overall product risk management process.
  - How will the Final Product be Used
  - Identification of hazards
  - Risk evaluation based upon product use and hazards – High, medium , low (an also assign numerical values)
  - Risk mitigation to limit hazards to the patient
  - Risk assessment

CASE STUDY – CHEMICAL RISK ASSESSMENT OF MATERIALS RISK MITIGATION

- Based upon risk evaluation a component exceeds the company established threshold
- Risk mitigation is required
  - Perform additional tests on the material
    - ✓ Physicochemical (compendial)
    - ✓ Extractables
    - ✓ Leachables
    - ✓ Biocompatibility
  - Change the material in question – if there is toxicity or unacceptable patient impact
  - **Establish controls around the material**

KEY TAKE AWAY POINTS

- Choose your components/materials and their suppliers wisely
- Develop a strong partnership/relationship with your suppliers
  - Educate your suppliers about your product and the CQA
  - Learn from your suppliers about the CQA of their materials
- Have a strong Quality Agreement that outlines the change management process in detail
- Understand the risks of the material – chemical, physical etc.
- Understand the intended use of the material/device and its impact on toxicology etc.
- Follow the IPAC-RS Recommended Baseline Requirements for Materials used in Orally Inhaled and Nasal Drug Products (OINDP) for the chemical risk evaluation process

27 CLIMB THE MOUNTAIN ONE STEP AT A TIME

THANK YOU.....

DO YOU HAVE ANY QUESTIONS ?