Recommended Baseline Requirements for Materials used in Orally Inhaled and Nasal Drug Products (OINDP

IPAC-RS

International Pharmaceutical Aerosol Consortium on Regulation & Science

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I. Introduction

This document describes baseline requirements for materials used to manufacture components for OINDP, and is the second revision of the original document presented in 2011.[i] The first revision was issued in 2017. This current revision is primarily driven by changes in the regulatory and standards landscape since 2017. We note that national and international guidelines and standards are continuously evolving, and that references noted in this document are not comprehensive, but do capture current expectations. As there is no single guidance for these types of materials, these requirements were compiled from a variety of international regulatory and compendial requirements. The impetus for this document was based on a clearly articulated need for a uniform set of requirements that arose out of several discussions between pharmaceutical manufacturers, regulators and multiple suppliers in meetings sponsored by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). The recommendations originally put forth by the Polymer Forum for plastics served as the foundation for several additional discussions. The baseline requirements provided in this document apply to all types of materials and although they are not the sum total of all requirements for materials used in OINDP or other products, they are the requirements that have been agreed to by the member companies of IPAC-RS. Materials that meet these baseline requirements are considered to have the quality necessary for OINDP.

It is anticipated that OINDP or other drug product manufacturers as well as manufacturers in the supply chain will use this document to guide primary packaging/device or production material selection and control; and that their chosen suppliers will be able to provide materials and information that meet these requirements. Adherence to these requirements can benefit both suppliers and drug product manufacturers by ensuring that the appropriate level of testing is conducted and thus avoid unplanned events throughout the product lifecycle. Materials that do not meet one or more of these baseline requirements may still be considered for use with appropriate justification. Risk management and assessment approaches can be used to determine whether requirements in this document need to be applied to materials not in direct contact with patient and/or formulation. The final determination of suitability for use is ultimately made by the regulatory authorities. Regulatory authorities may also, at any time, inspect supplier facilities; these requirements provide insight regarding general quality expectations with respect to some aspects of regulatory inspections (e.g., see Appendix 2 regarding quality agreements).

This document also includes a chart that provides recommendations on testing requirements for materials that are divided into four different categories (see Table 2, page 11). These categories were developed based on the chemical nature of the material and reasonable applicability of the test based on the level of completeness of component manufacture. The levels in the supply chain are described in the accompanying diagram (see Figure 1, page 12). Different categories of testing are applied to each level in the supply chain for four different component types: plastic, elastomer, metal/glass, multi-layer materials (e.g., foil). Those suppliers providing materials for dosage forms with a high degree of concern can consult these recommendations and communicate relevant requirements throughout their supply chain as appropriate.

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[i] These recommendations could be applied to container closure system materials for other drug products (e.g., parenterals, ophthalmics) where there is a high degree of concern with respect to the route of administration, as well as manufacturing process materials as appropriate.

These requirements result directly from regulatory requirements for the pharmaceutical industry. For example, both the EMA Guideline on plastic immediate packaging materials (19 May 2005 (CPMP/QWP/4359/03)),[1] and the US FDA Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999,[2] require compliance to food additive regulations and pharmacopoeias. For drug products with a high degree of concern associated with the route of administration (e.g., inhalation drug products), further toxicological evaluation based on extractables and leachables data and biocompatibility testing is required by regulatory authorities. Further guidance for OINDP is provided in the FDA Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products, July 2002;[3] the FDA Draft Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Quality Considerations,[4] and the Health Canada[5] and EMA[6] draft guidelines on the pharmaceutical quality of inhalation and nasal products. Related guidance is included in the CDRH reviewer guidance for nebulizers, MDIs, spacers and actuators.[7] While many of these regulatory requirements are focused on the finished components, a risk-based approach may be used to set applicability at lower levels in the supply chain (e.g., compounded material, fabricated component).

This document contains additional text recognizing transitions to low global warming potential propellants, and a section discussing the transition to and lifecycle considerations for lower carbon footprint materials and components.

II. Security of Supply

As shown in Figure 1, multiple organizations (e.g., raw material suppliers, converters) are involved in the supply chain of a component used in a pharmaceutical product. An organization that is the raw material supplier customer (molder) can also be the supplier of a component. Due to the complexity typically found in the supply chain for an inhalation product, management of security of supply requires dedicated management of the upstream supply chain.

The typical timeframe to implement a change to a material (e.g., plastic, colorant) in an inhalation product can be quite lengthy due to the regulatory requirements to implement the change. Due to the extended timelines required to implement a change, it is desirable to have a minimum of 36 months rolling availability of unchanged[ii] material (subject to contractual agreements for specific materials between individual suppliers and their customers). See Figure 1, Materials Manufacture Flowchart, for clarification of suppliers and customers (a customer can be a downstream supplier or pharma company).[iii] Considerations to determine how this extended period of notification to ensure supply is managed would include:

- The shelf-life of material when stored according to manufacturer's recommendations
- Adequate notice period (minimum 12 months) to qualify new material according to regulatory requirements
- *Last-call option*: notice to customers to allow bulk purchase before production discontinuation, in order to guarantee supply to patients, where practicable and legally possible. Timing of notice can be negotiated.

[ii] i.e., Unchanged ingredients, processes, or equipment. See Appendix 1 for more information on need for security of supply.

[iii] See Appendix 1: Rationale for Security of Supply

Note that the management of notification period for implementation of a change will be challenging and will depend on the complexity of the supply chain as well as the contractual agreements between the various participants therein. Business, technical, quality, and regulatory considerations will determine the actual time period to implement the change.

Suppliers are expected to utilize and have documented and auditable proof that there is a quality system that supports notification of change and change control.

Table 1 provides examples of timeframe scenarios, with Material Availability following the general equation:

Notice Period + Raw Material Shelf Life + Finished Component Shelf Life = Resulting Material Availability

Table 1. Example timeframe scenarios related to material availability

	Notice Period with Last Call Option	**Raw Material Shelf Life**	**Finished Component/Assembly* Shelf Life**	**Resulting Material Availability**
Material #1	12 months	---	24 months	36 months
Material #2	12 months	12 months	12 months	36 months
Material #3	18 months	12 months	6 months	36 months

*Assembly could be, e.g., valve, multilayer foil, inhaler

III. Change Management

Customers and suppliers should agree on change control practices including types of changes that require notification, notification period, and approval process for changes. These should be incorporated in a supply agreement and/or quality agreement that specifically provides a responsibility matrix, addresses key quality/regulatory concerns including change control for documents, materials, specifications, processes, facility and equipment (see Appendix 2). Further, suppliers should ensure that their suppliers have adequate change control programs in place.

What constitutes a change varies from product to product and from company to company and includes, e.g.,

- Product changes (e.g., materials, manufacturing processes, specification, switch to sustainable grades)
- Facility changes (those which impact product)
- Documentation changes to controlled documents that may include compliance statements, production records, methods, drawings, etc.

Change Control Procedures should include written procedures for the identification, documentation, impact assessment, appropriate review, and approval of changes affecting the form, fit, function or quality of products and/or associated processes, equipment, systems and methods. Procedures should ensure changes will be implemented in a controlled manner. An independent group (e.g., Quality Unit), should have responsibility and authority for management/approval of changes.

Impact assessment is a key component of change management. To properly evaluate impact of a change it is important to include all stakeholders. This enables proper identification of risks and their comprehensive assessment. This assessment informs the types of activities that will be required to determine if the change is feasible, implement the change and evaluate any residual risks post-change. In cases where a change is expected globally it can be advantageous to have joint discussions with pharmaceutical developers, suppliers and regulators. Examples of global changes that impact packaging/device materials indirectly or directly are MDI propellants and plastics made from bio-based feedstock.

Currently, the industry is gradually developing MDIs that incorporate low-global warming propellants, a change driven by regional and international climate change legislation and treaties. There have been several initiatives involving key stakeholders over the years to assess risks and evaluate paths forward.[8, 9] This requires the industry to review and evaluate the impact of such changes on materials compatibility, stability and leachables profiles. Although the propellants are not part of the packaging/device materials an indirect effect of a change in propellant could be physical or chemical incompatibility with a packaging/device material and result in a change of that material.

Another global change involves upstream polymer producers, who, in response to the need to reduce carbon footprints, are transitioning to use of bio-based feedstock, using a "mass balance" approach. There is currently discussion among stakeholders as to the type of regulatory change management pathway for downstream users this transition would represent. Background and current approaches to this are described in Appendix 6.

IV. Compliance Statements

Where applicable, the following certificates of compliance should be readily available to allow Pharma and companies in the supply chain to understand, mitigate and manage the regulatory risks and/or safety or quality concerns associated with the packaging or device material as early as possible in the drug development process. 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 or product quality; it also supports a robust long-term agreement between material or component suppliers and Pharma for the supply of materials and components.

1. Biocompatibility
    - ISO 10993 – 3, 4, 5, 6, 10, 11, 23
    - USP <87>, <88>
2. Food Additive Compliance:
    - US: 21CFR Parts 172-189[10]
    - EU: Commission Regulation (EU) No 10/2011 and amendments[11]
    - EU: Other materials (ceramics, gaskets, etc.)[12]

- Other food additive compliance requirements, e.g., printing inks, adhesives, paper boards, silicone, rubber[13, 14, 15, 16, 17]
- Pigments: BfR Requirements;[18] 21 CFR 178
- WHO Codex Alimentarius, General Standard for Food Additives, STAN 192-1995[19]

3. TSE (BSE, “mad cow disease”):

   ISO 22442 Medical devices utilizing animal tissues and their derivatives

   - Compliance with ISO 22442[20], EP 5.2.8[21]; guidances: CPMP/EMEA 410/01,[22]

4. Elemental Impurities:
   - ICH Q3D Guideline for Elemental Impurities[23]
   - Coatings comprised of metal, which are traditionally used for fabricating metal components, e.g., nickel coating on stainless steel, should not be included in device components that are in the drug path.

5. REACh
   - Materials should be in compliance with Regulation no. 1907/2006/EC24 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACh).
   - Consideration should be given to the substances with very high concern list, http://echa.europa.eu/web/guest/candidate-list-table. Substances from this list should not be used unless justified.

Electrical OINDP Devices

6. WEEE[25] Materials should be in compliance with EU Directive 2012/19/EU as amended, on waste electrical and electronic equipment (WEEE).
7. ROHS[26] Materials should be in compliance with the current Restriction of Hazardous Substances Directive (RoHS).

V. Additional Supplier Information

The following statements and information may be requested depending on application/use of the drug product. The information provides the customer with an initial set of data that directs strategy to assess the risk of leachables in drug products. The following information generally provides supportive data and assurance to the customer and regulators 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.

1. CMR and endocrine-disrupting substances (according to regulation (EU) 2017/745
   - Substances which are carcinogenic, mutagenic or toxic to reproduction (‘CMR’, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008),[27] or

- Substances having endocrine-disrupting properties (in accordance with Articles 59 of Regulation (EC) No 1907/2006[28] or with the criteria that are relevant to human health amongst the criteria established by a delegated act pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012[29]

not more than 0.1 % weight by weight (w/w) unless justified in devices, or parts thereof or materials used therein

The presence of those substances in a concentration above 0,1 % weight by weight (w/w) shall be labelled on the device itself and/or on the packaging.[30]

2. DEHP Content (Canadian Requirement)
    - Identifier for devices containing ≥ 0.1% w/w of Di (2- Ethyl hexyl] Phthalate (DEHP): Class II, III, and IV Medical Devices License Application form[31, 32, 33].
3. BPA Content (Canadian Requirement)
    - Identifier for devices manufactured from raw materials containing or derived from bisphenol A (BPA): Class II, III, and IV Medical Device License Application form[31, 32, 33]
4. Epoxy derivatives (BADGE, BFDGE, NOGE):
    - Does the product contain any epoxy derivatives?
      If yes: Compliance with Regulation (EC) 1895/2005[34]
    - Use and/or presence of BFDGE and NOGE is no longer permitted as from 1 January 2005 in accordance with Directive 2002/16/EC.
5. Mercaptobenzothiazole (MBT) content[35]
6. Nanomaterials content
    - Compliance with European Regulation (EU) 10/2011 as amended[9, iv]
    - For Class II medical devices (Canadian requirement): If the device contains material of a particle size of 1000 nanometers or less, please specify the type and size range: Class II Medical Device License Application form.[31]
7. N-nitrosamines
    - Compliance with Directive 93/11/EEC
    - United States Food and Drug Administration. Control of nitrosamine impurities in human drugs, Guidance for Industry.[36]
    - European Medicines Agency and Co-ordination Group for Mutual Recognition and Decentralised Procedures -- Human. Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of

[iv] Commission Recommendation of 18 October 2011 on the definition of nanomaterial (Text with EEA relevance), 2011/696/EU, defines "nanomaterial" as a "natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %. By derogation…fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials."

Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.[37]

- Health Canada. Guidance on nitrosamines impurities in medications. Evaluating and managing the risks of N-nitrosamine impurities in human pharmaceutical, biological and radiopharmaceutical products.[38]
- Further guidance can be found here: *An Overview and Discussion of N-nitrosamine Considerations for Orally Inhaled Drug Products and Relevance to Other Dosage Forms*, AAPS PharmSciTech (2023) 24:37.[39]

8. Polycyclic aromatic hydrocarbons (PAH) content.[35]
9. Latex
    - Guidance for Industry and Food and Drug Administration Staff: Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex[40]
10. Per and Polyfluoroalkyl Substances (PFAS):
    - EU Proposal for a restriction of PFAS according to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006, concerning the Registration, Evaluation, Authorization and Restriction of Chemicals, as amended, Annex XV: Restriction Report (view current status at https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/72301/term)
    - Global regulations (see review https://icrl.lexxion.eu/data/article/18898/pdf/icrl_2023_01-005.pdf)
11. Electronics
    - Conflict Minerals[41]
    - UL Standard for Safety: 1642 Lithium batteries; 2054 Household and Commercial Batteries
    - EN IEC 60086-1 Primary Batteries – General; -2 Primary Batteries - Physical and Electrical Specifications
    - EN IEC 60601-1 Medical Electrical Equipment — General requirements for basic safety and essential performance. Others in the series may also be relevant.
    - EN IEC 62133 Secondary cells and batteries containing alkaline or other non-acid electrolytes—safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications
12. Under confidentiality agreement(s), the supplier should be able to provide formulation composition, process and quality information, e.g., to allow the customer to develop appropriate acceptance criteria and to provide timely responses to health authorities.
13. Suppliers should have current Drug Master Files (DMFs) available (e.g., for USA, Canada, China) and provide Letters of Authorization.[v]

[v] Regulatory Agencies (e.g., FDA) are the only entities (other than the submitter) allowed access to the DMF. Customers can develop CDAs with their suppliers to be provided this same information.

VI. Material Testing

The following tests should be conducted on patient contacting or direct and indirect drug-contacting materials, where applicable, to further demonstrate its suitability for use within an OINDP.[vi, 42] Table 2 and Figure 1 below provide examples of what type of testing is generally expected at various points in the supply chain. For plastics and cured elastomers it is possible that testing can be performed on the materials (Category 2 or 3) as a tool for material selection. For the other types of materials testing finished components according to Category 4 is preferable. Critical components[vii] from finished devices and/or packaging can be tested according to Category 4.

Pharmaceutical manufacturers are responsible to ensure testing is performed by their suppliers (via quality and/or technical agreements) and/or within their own organizations. It is important that tests are performed according to the current standard and that test results (not just a certificate of compliance) are available as objective evidence of compliance.

Performance Criteria

- Initially, the material must meet all applicable requirements listed in the following bullets as well as the supplier's own specifications (e.g., ISO, dimensions), although certain materials may need additional requirements as specified by the customer. Note that requirements may include one-time tests or certifications.
- At the end of shelf-life, the material must meet routine extraction requirements (where applicable) and the supplier's specifications, assuming the material has been stored correctly throughout the shelf life period.

Pharmacopeias/Standards Compliance:

- Biocompatibility: based on product use (patient contact and duration), e.g., for an inhaler, mouthpiece, surface mucosal contact/limited duration, compliance with ISO 10993,[43] parts 5, 10 and 23 (to address cytotoxicity, sensitization and irritation), or USP <87> as appropriate. See also FDA guidance for industry and staff regarding application of ISO 10993-1.[44] Additionally, FDA CDRH expects adherence to ISO 18562 series for components in the breathing gas pathway.[45]
- Physicochemical testing: compliance with EP Chapter 3 and applicable sub-chapters;[46] USP <661>;[47] <381>,[48] <660>,[49] Japanese Pharmacopoeia XVIII.

[vi] Examples of direct and indirect contact materials in a drug product are, e.g., capsule in a blister where the blister material is indirect contact with the drug formulation due to the presence of a semi-permeable capsule shell; LDPE vial in overwrap, where vial is direct contact and overwrap is indirect contact. In many situations, the indirect contacting material is considered a functional barrier, and would be considered primary packaging

[vii] For OINDP, critical components are generally those that contact either the patient, i.e., the mouthpiece, or the formulation, components that affect the mechanics of the overall performance of the device, or any necessary secondary protective packaging. Manufacturers should consult with customers and/or appropriate regulatory authorities to discuss any questions regarding the identification of critical component. See Reference 35, for further discussions regarding critical components.

Controlled Extraction Studies[viii]

Controlled extraction studies should be done as a one-time test, per the PQRI recommendations. A minimum study would include the following:

- Solvents of varying polarity. Appropriate solvents with a good range of polarity include isopropanol, hexane or heptane, and water (e.g., at different pH levels).[50] Any local regulations should be considered in choice of solvent. Other solvents that provide such a range are also appropriate, and the selection should be rationalized as noted in the recommendations.
- At least one solvent extraction technique and evaluation of potential volatiles (e.g., headspace, thermal desorption).
- At least two analytical methods (e.g., gas chromatography, liquid chromatography) plus mass spectrometry to evaluate semi- and non-volatile organic compounds.
- Elemental analysis should be performed, if compositional information is not available/provided. Elemental impurities analysis should be performed on the container closure system and/or device components. However, recommendations for analysis of materials of construction can be considered, as appropriate.
- Quantification and identification of organic leachable compounds is expected at levels above the analytical evaluation threshold (AET);[35] for material evaluation purposes quantification and identification of organic compounds is acceptable at 10 ppm, but ideally should be done at 1 ppm.
- Migration from outside layers or secondary packaging to primary packaging should also be considered.
- Example protocols for Controlled Extraction Studies are available from PQRI, the Extractables and Leachables Safety Information Exchange (ELSIE) Consortium,[ix] ISO 10993-18, and USP <665>.[51] Additionally, further general guidance on extraction studies may be found in USP <1663>. Suppliers may consider these protocols and general guidance for further information on conduct of a controlled extraction study.

Routine Extractable Testing[x]

If indicated by the risk management process as an appropriate control, routine extractable testing should be conducted periodically using validated methods to monitor the material composition to ensure the extractable profile is consistent with that seen during development and that there are no chemical compounds present that may adversely impact the safety of the patient, quality of the product, or functionality of the device. See Appendix 4 for further detail on routine extractable testing.

[viii] See Appendix 3: Rationale for Controlled Extraction Studies for more information

[ix] www.elsiedata.org

[x] See Appendix 4: Rationale for Routine Testing for more information

Foreign Particulates and Particulate Matter

Introduction of particles via materials and/or processes used to fabricate components for OINDP should be avoided. For example, talc should not be used as a processing aid, e.g., during fabrication of bags used to store inhalation drugs or devices. Particulates that are not part of the drug product formulation are considered "foreign particulates." Particulates originating in component manufacturing processes may be counted as foreign particulates in the drug product, and therefore suppliers and customers should develop agreed acceptance criteria.

Alternatively, particles that reside on breathing gas pathway components may be entrained in the airpath and delivered to the patient directly. Recently limits have been established for Particulate Matter by ISO 18562-2. Support for these concepts may be found in, e.g., PS 9000:2016 GMP guideline for packaging suppliers.[52]

Table 2. Requirements for OINDP Materials Supply Chain

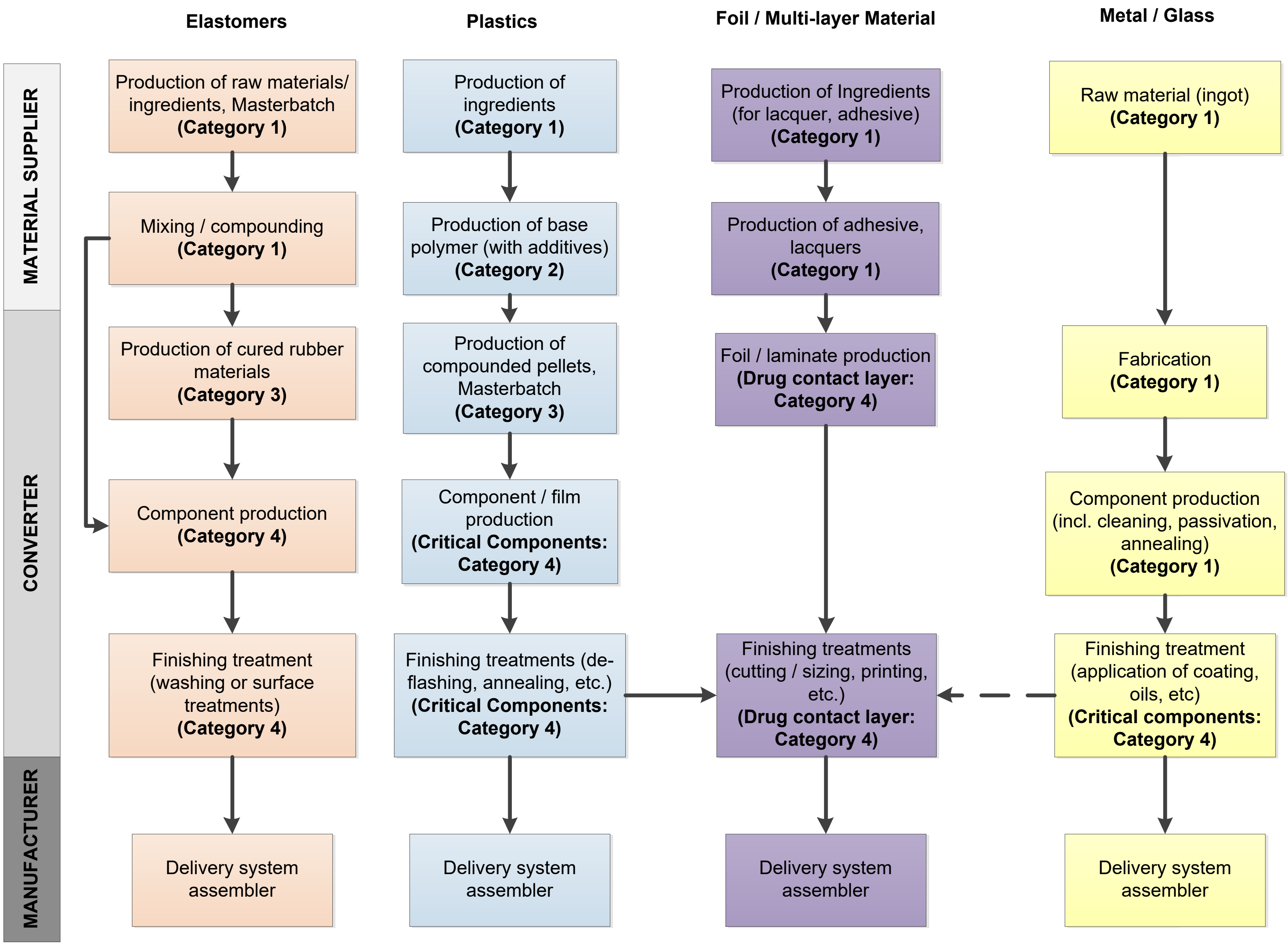
(Categories are applied in the Materials Manufacture Flowchart, page 12)

Test	Category 1	Category 2	Category 3	Category 4
Biocompatibility—based on compliance with ISO 10993 or USP <87>. ***Deliverable:*** Certificate of Compliance (required) and report with test results (upon request)		One-time test* for plastics only	One-time test* for plastics only	One-time test*
Physicochemical Testing – based on compliance with EP3, USP <661>, USP <381>, USP <660>; ISO 10993-1, JP XVIII ***Deliverable:*** Certificate of Compliance (required); Certificate of Analysis (upon request)		One-time test* for plastics only	One-time test*	One-time test*
Controlled Extraction Studies ***Deliverable:*** Report with results (complete data package)	No test Should provide composition information.	One-time test* Or, at the least, provide composition and processing aids or additives	One-time test* Or, at the least, provide composition and processing aids or additives	One-time test*
Routine Extractables Testing, if part of risk-based control strategy Periodic, Quantitative / Qualitative Validated method ***Deliverable:*** Certificate of Analysis			Routine Test.▲ Can be done at the request of customer, in connection with Category 4 routine extractables testing	Routine Test.▲ Commercial requirement may be adjusted based on product needs (e.g., no leachables of concern)

* Test once at the beginning of materials selection, or if significant change has occurred. See Appendix 5 for more information on one-time testing.

▲ Test material according to schedule developed in agreement with customer. See Appendix 4 for more information.

Figure 1. Materials Manufacture Flowchart with Testing Categories



Appendix 1: Rationale for Security of Supply

Definition of an unchanged material: A material that is manufactured using the same process, equipment and input chemicals to the same supply specification. (This excludes, e.g., parts that need preventative maintenance).

Material changes during development or on the commercialized product especially for high risk products such as Orally Inhaled and Nasal Drug Product (OINDP) are costly, complex and could have a significant impact on the supply of medication to patients. There are several circumstances that could trigger a material change:

- Unavailability of an ingredient in the material composition
- Business decision to discontinue the material
- Updated equipment and/or new facility
- New regulatory restrictions on use of material/ingredients/processing aids
- New regulatory requirements for packaging/device

Some material changes are initiated by the pharmaceutical manufacturer and others by suppliers. If a pharmaceutical company is notified by their supplier well in advance of a material manufacturing change (i.e., formulation, specification, manufacturing process or site of manufacture) or discontinuation, a strategy for managing this change can be defined. In the same way, if key stakeholders are consulted to develop a strategy for implementing new regulations an appropriate implementation date can be set to accommodate the activities necessary to ensure a smooth transition (e.g., USP <661> revision official date set for >5 years after adoption).

The extent of the change management process is dependent on the criticality of the material in the drug product and its function. The following activities may be required to manage the change and ensure it doesn't impact the safety or performance of the drug product:

- identification of candidate materials
- conduct risk evaluation and impact assessment
- selection of a demonstrably equivalent material (physical, chemical and functional)
- 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
- requalification of the mould tooling
- revalidation of production processes
- modification and revalidation of analytical methods used for release testing
- regulatory review and approval

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.

Appendix 2: Quality Agreements

Quality agreements may be established separately from or in conjunction with supply agreements and delineate the responsibilities of both suppliers and customers. They are required for suppliers who directly maintain dossiers with regulatory agencies related to supply or contract manufacturing arrangements for drugs and outsourced activities.[53, 54] In general, all relevant regulatory requirements outlined in cGMPs (21 CFR 210 and 211; EU Commission Directive 2003/94/EC; Eudralex Vol. 4 Good Manufacturing Practices; PS 9000:2016; and other relevant standards) are listed and responsibilities discussed. Typically, in regulatory guidelines, customers are referred to as “owners” or “contract givers;” suppliers are “contracted facilities” or “contract acceptors.”

The PS9000:2016 GMP guideline for packaging[55] provides general guidance on quality agreements. Guidance from this guideline is noted as follows:

Quality agreements should agree to the terms relating to key quality and regulatory systems. The following categories should be considered for inclusion in quality agreements, where applicable:

- organization and customer responsibility matrix
- definitions
- batch records
- deviations/resolutions of quality issues
- change control and notification:
- document change control
- material change control
- specification change control
- process change control
- facility and equipment change control
- cleanliness and hygiene
- complaints and impact on commercial supply
- product testing
- customer audits
- document retention
- lot approval and product release
- manufacturing environment
- material suppliers
- process validation
- qualification and/or validation of equipment
- recalls

- reference to current versions of standards and guidelines
- regulatory compliance
- regulatory contacts and audits
- requirements for raw materials and subcomponents
- retained samples
- customer samples; these may include a representation of each printed station or moulding cavity
- rework and reprocess
- subcontractor management
- supply agreements
- confidentiality
- IT security
- Transfer of artwork between customer and organization
- Management of anti-counterfeit technology, anti-counterfeit features and security arrangements, etc.
- AQLs and defect classification

Table 3. Example responsibility matrix [55]

Item	**Customer**	**Supplier**
Component Specifications		**X**
Specifications against which material is tested by the organization	**X**	
Supply/procurement projections	**X**	
Testing in-process/release		**X**
Testing on receipt	**X**	
Certification: Certificate of Analysis(CoA), Certificate of Compliance (CoC) or Certificate of Testing (CoT)		**X**
Retained samples	**X**	**X**
Supply agreement	**X**	**X**
Quality agreement	**X**	**X**
Design file	**X**	**X**

Appendix 3: Rationale for Controlled Extraction Studies

The primary role of a controlled extraction study is risk assessment/mitigation. Extractables are chemical entities that are extracted from packaging or delivery system components *under laboratory conditions*, often with application of solvents and heat. Extractables are potential leachables. Leachables are chemical entities that migrate out of the packaging or delivery system components *into the drug product* as a result of direct contact with the formulation over the shelf-life of the drug product. Only leachables have potential to impact the patient. Although the scope of this paper addresses packaging and device components, other sources of leachables should be considered, e.g., manufacturing process materials. Further consideration of potential leachables from the drug production process should be evaluated, see USP <665> for consideration in the development process.

The patient may be exposed to any compounds that leach into the drug product and this may negatively impact the drug product safety. As leachables are typically a subset of extractables, Controlled Extraction Studies allow risk assessment or safety evaluation of potential leachables at an early stage of drug product development during the material selection phase. This potentially allows for a changing of materials if toxic extractable species are detected and assessed to be a safety concern. Extraction studies can be performed independently of the drug product. For example, extraction studies could be performed by the material or component manufacturer. However, it is the responsibility of the drug product manufacturer to ensure that controlled extraction studies to characterize the material, are performed, and to evaluate results with respect to the specific drug product. Detailed information on Controlled Extraction Studies is given in the PQRI recommendations, and in USP <1663>.[56]

Extraction studies can be used to ascertain material composition or predict probable leachables depending on the solvents and conditions used. For MDI components there is little difference between the two types of studies due to the strong extracting power of the propellants used. However, for other OINDP (e.g., DPI, inhalation solution, nebulizer) packaging/device components there are significant differences. Strong solvents (e.g., dichloromethane, isopropanol, hexane) and elevated temperatures (e.g., boiling) have been used to understand material composition. Solvents that more closely mimic the properties of the formulation (e.g., water, alcohol/water mixtures) and temperatures that represent conditions of storage and use (e.g., 40C) can be used to identify and quantify species most likely to be found as leachables (see USP <1664>.[57]

Extractable identification and reporting of likely leachables for toxicological assessment is initiated when that potential leachable is at or above the safety concern threshold (SCT) of 0.15 µg/day. This specific SCT value (i.e., 0.15 µg/day) is meant for OINDP; a different threshold value (1.5 µg/day) was developed for parenterals. While this threshold is meant for the evaluation of leachables in the drug formulation, an adaptation of this threshold to analytical evaluation of the extractables has been described in the PQRI recommendations. The SCT is translated into a product specific analytical evaluation threshold (AET), which can be estimated by taking into consideration the dosing scheme and mass of the delivery system component. If a surrogate standard is used for quantification, then additional work with authentic standards will need to be performed to obtain an accurate estimate of the potential leachable. A typical calculation[xi] is as follows:

$$AET = \frac{0.15\,\frac{\mu g}{day} \times volume\ container\ [ml]}{\frac{dose}{day}\,[\mu l] \times mass\ container\ [g]} \times 1000 = \frac{0.15\ \mu g \times 1ml}{50\mu l \times 1.5g} \times 1000 = \frac{2\mu g}{g} container$$

As suppliers can only provide data specific for their material and not for specific drug products, the IPAC-RS materials working group proposes a generic AET of 1 ppm, defined as amount of the extractable, e.g., in a plastic component. This proposed AET value reflects most of the products in the market or under development. For example, for typical extractables or leachables levels of MDI drug products (in µg/can) please refer to PQRI Recommendations, Appendix 1.[xii] For some drug products a higher AET would be sufficient; however for other drug products the required AET may even be lower. An AET of 10 ppm is considered acceptable for a material that is in non-continuous contact with the drug product.

For any species detected above the AET, the aim of the analysis is to identify the chemical or to provide sufficient evidence for a toxicologist to be able to assess its safety and daily exposure limits.

[xi] Assumes a nominal set of conditions: container with a mass of 1.5 g containing 1 ml drug product with a daily dose of 50 µl.

[xii] Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, PQRI Leachables and Extractables Working Group. Product Quality Research Institute. (2006). Part 4, Appendix 1, Table 1

Appendix 4: Rationale for Routine Testing

Routine Extractables Testing may be a critical part of a comprehensive control strategy to ensure the quality and safety of the final drug product. Its utilization as an appropriate control is dependent on regulatory requirements and product risk evaluation. Routine Extractables Testing is defined according to the OINDP PQRI recommendations as, "… the process by which OINDP container closure system critical components are qualitatively and quantitatively profiled for extractables, either for purposes of establishing extractables acceptance criteria, or release according to already established acceptance criteria." Examples of critical components are, valve actuators, elastomers, springs, plastic components, canister, blister pack materials, foil overwrap etc. In addition to the PQRI recommendations, which provide a systematic approach to Routine Extractables Testing, consideration should be given to the requirements in the FDA's Guidance for Industry and EMA's Guideline documents that govern packaging/device components.[1, 2, 3, 4, 6] Drug product manufacturers will usually develop a correlation between the profiles generated by Controlled Extraction Studies and those generated by Leachables Studies. From this correlation a list of target compounds can be developed for Routine Extractables Testing. Routine Extractables Testing is therefore used to provide a reliable and robust means of monitoring the quality (and safety) of components that will be used in the drug product.

Routine extractables testing methods are based on those used in the Controlled Extraction Studies, and the component profiles generated from such routine testing should be associated with those found in the Controlled Extraction Studies. Routine extractables testing methods can include, for example, Gas Chromatography/Flame Ionization Detector (GC/FID) or High Performance Liquid Chromatography/Ultraviolet Detector (HPLC/UV) as analytical techniques.

In addition, routine extractables methods are validated to include the linear dynamic range, quantitation limit, method precision and accuracy. A robust analytical method for routine testing will ensure that analytical test results are produced with a high level of confidence allowing development of appropriate acceptance criteria for the component specification. The extractables acceptance criteria for a component are based on the following:

- Qualitative matching of the extractables profile with the reference profile
- Quantitative limits for targeted extractables
- Quantitative limits for unspecified extractables

Routine Extractables Testing may be a key part of a robust control strategy to maintain drug product quality. When indicated as a control, Routine Extractables Testing should be performed at least periodically and preferably for each lot of material used in critical components. The frequency of such testing may change, following a risk based approach based on the drug form (e.g. liquid or solid), once a sufficient amount of data is obtained to justify less frequent testing (such as skip-lot testing). However, any reduction in the testing regimen should be science-based and done in consultation with the regulatory authorities.

Appendix 5: Rationale for "One-time" Testing

"One-time" testing is a general term that is applied to a number of different tests performed on a material, the results of which provide critical quality and safety information that aids the materials selection phase of the pharmaceutical development process. (See Table 2 for examples). These various tests are identified in the testing requirements table above, and are required by the various international health authorities. Because information from these tests is needed at the beginning of the development process during materials selection and evaluation, the appropriate entity to conduct these tests is the supplier (the category of supplier may vary with the test). Further, these tests will be conducted on either the raw material or on finished components, but not on a fully assembled delivery system or product. It is the responsibility of the pharmaceutical manufacturer to collect this information and establish that the materials are qualified for their intended use.

Although this testing is termed "One-time," such testing may need to be repeated if there is a significant change to the material/component or if there is a possibility that a change could affect the safety or functionality of the material/component. The results from these tests should be shared with the customer as part of the agreed change control process. The frequency of such tests, and the circumstances under which they may need to be repeated are usually outlined in agreements (e.g., Quality Agreements) between the supplier and customers.

Suppliers should have a regular change control process in place that considers what constitutes a significant or critical change that may affect the safety or functionality of the material/component. Such change control can incorporate a risk-based approach where manufacturing processes, equipment configuration, material composition, and some supply changes are well understood such that any changes can inform the determination of significance of a change and the need for subsequent testing. It should be noted that excellent communication throughout the supply chain is required to manage and assess the changes.

Appendix 6: Use of Sustainable Plastics in Device

With the drive to make products more sustainable there have been major changes implemented by the resin suppliers to offer more sustainable grades of resins for everyday use and in medical devices.

There are 3 main areas these suppliers are looking to introduce sustainable resins into the supply chain:

- Mechanical recycling.
- Chemical recycling.
- Use of circular and biobased feedstocks rather than fossil feedstock.

The use of mechanical and chemical recycling materials in medical devices is a complex proposition to implement due to the complex nature of recycling existing material, and safely using them in the manufacture of medical devices. At the moment, the use of recycled material into medical grade resins suitable for pharmaceutical packaging/devices is in its infancy but is being implemented by some resin suppliers for medical grade resins.[58]

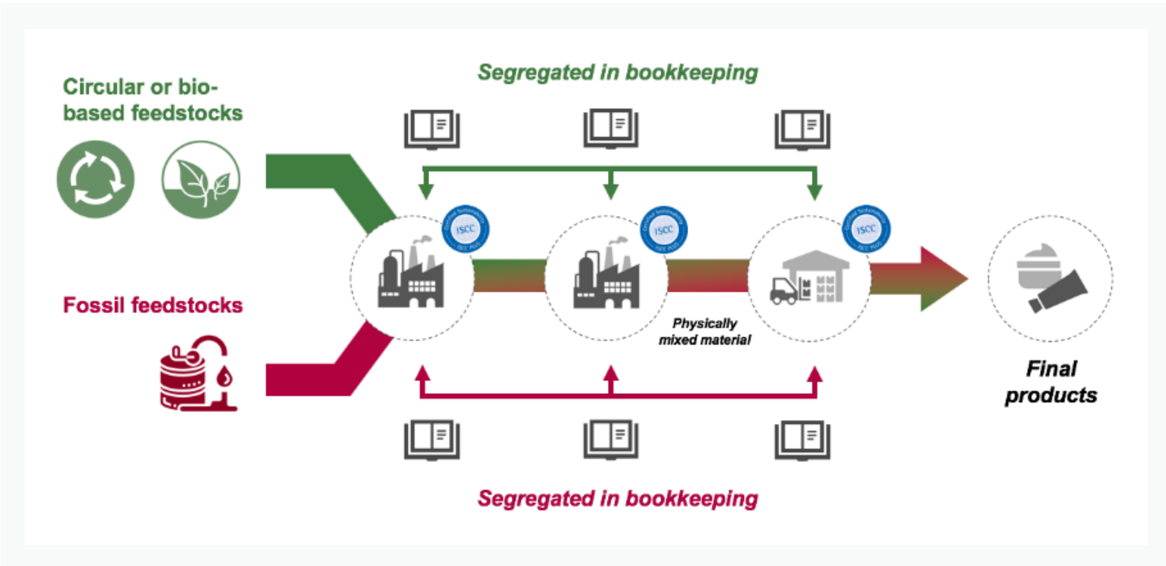
The implementation of circular and biobased feedstocks at the start of the resin supply is more readily available. Essentially this is a reduction of the use of fossil feedstocks with the use of circular and biobased feedstock to produce the initial ethane or propane, which is then heat treated (cracking) to produce the ethylene or propylene used to create the different types of resins used.

Some resin supplier are conducting development and testing to be able to show that sustainable resins produced with circular and biobased feedstocks are chemically the same as the original fossil based grades. With this approach, suppliers are then providing circular and biobased resins or fossil-based resins to the same part number and using the same DMF.

However, to implement these materials and offer them to the packaging/device manufacturer requires segregation and open bookkeeping of the sustainable grade of resin compared to the fossil-based resin. Confidence in the supply chain can be gained by having it independently audited by an organization such as International Sustainability and Carbon Certification (ISCC) or REDcert.

Figure A6.1 below summarizes a typical supply chain for a circular or biobased feedstock sourced resin. Each step of the supply chain from resin supplier, moulder and convertor (CDMO) to the license holder who ultimately own and sells the product can be audited to obtain certification.

Figure A6.1: Resin Supply Chain



Prior to switching to a sustainable grade of resin(s) for OINDP packaging/device there are some important points to consider, some of which are captured below:

- Switching to a sustainable grade of an existing resin is probably the simplest pathway
- Moving to a new resin supplier may also be of benefit due to factors such as cost, material availability, ease of shipping or supply chain security
- Currently the price of these sustainable grades is more than the existing fossil feedstock grade. Thus, understanding the impact to the cost of goods is important.
- The implementation of these types of resin changes is not fully understood from a Regulatory perspective. One could ask, “If the circular and biobased feedstock grades are really the same as the fossil feedstock grade is there a requirement to submit this type of change?”
  - This is an area of focus that IPAC-RS are trying to understand by working with FDA and MHRA in the consortium’s sustainability roundtable discussions.
- However, irrespective of the regulatory pathway, it is still important that any material switch is fully evaluated, and the new materials verified and validated prior to presentation in the commercial supply chain using a robust change management system.
- There may be a requirement for the supply chain to be audited and certified by either ISCC or Redcert. This may require new processes to be implemented at the site of the moulder and converter and at the site of packaging and release.
- On a multi component device like a DPI or pMDI with dose counter, is the change for all components from existing resins to sustainable grades, or just specific components like the actuator body for example?

- Work with existing resin suppliers to understand what work they have completed to confirm the sustainable grade is the same material in terms of characteristics, and how this has been positioned with regulatory authorities. For example assess:
- The risk impact of the change
  - What testing suppliers have done
  - Availability of equivalence data and biocompatibility to support an assessment.
  - Regulatory impact for the resin -- this the same resin DMF as the standard grade? How is the resin supplier documenting this change from a regulatory perspective?
  - What is the suppliers' certification (e.g., ISCC or Redcert)?
- Understand if the new material has the same process parameters and technical performance. The resin suppliers should have done this assessment, but this may need verifying and validating at the injection moulder. Work with the moulder or CDMO to agree level of work required to implement this change.
  - Is full qualification required?
  - Cost and time implication?
  - Regulatory impact?
- Understand how this change will impact device performance and regulatory approval of the change.
  - Consider whether to conduct mould trials and some verification of components and device design? Or repeat all design verification testing and full validation?

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