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

This document describes baseline requirements for materials used to manufacture components for OINDP, and is the first revision of the original document presented in 2011.[i] This revision is primarily driven by changes in the regulatory landscape since 2011. 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 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 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 (page 9). 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 page 10). 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 through their supply chain as appropriate.

[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, October 1998;[4] and the Health Canada[5] and EMA[6] 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).

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 manufacturer. 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 customer – 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 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

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 (materials, manufacturing, specification)
- 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.

Compliance Statements

Where applicable, the following certificates of compliance 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. 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.

1. Food Additive Compliance:
    - US: 21CFR Parts 172-189[8]
    - EU: Commission Regulation (EU) No 10/2011[9]
    - EU: Other materials (ceramics, gaskets, etc)[10]
    - Other food additive compliance requirements, e.g., printing inks, adhesives, paper boards, silicone, rubber[11, 12, 13, 14, 15]
    - Pigments: BfR Requirements;[16] 21 CFR 178
    - WHO Codex Alimentarius, General Standard for Food Additives, STAN 192-1995[17]
2. TSE (BSE, “mad cow disease”):

    ISO 22442 Medical devices utilizing animal tissues and their derivatives
    - Compliance with 2003/32/EC,[18] EN ISO 22442[19], EP 5.2.8[20]; guidances: CPMP/EMEA 410/01,[21] MEDDEV 2.11/1.[22]
3. Elemental Impurities:
    - Directive 94/62/EC;[23] Pb, Cd, Cr-VI, Hg < 0.01%
    - ICH Q3D Guideline for Elemental Impurities[24]
    - 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.
4. REACh
    - Materials should be in compliance with Regulation no. 1907/2006/EC25 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.
5. WEEE[26]
6. ROHS[27]

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. Phthalates Content (required for labeling in EU):
    - Compliance with 93/42/EEC as amended by 2007/47/EC.[28]
2. DEHP Content (Canadian Requirement)
    - DEHP content (required for Canada): Notice to Manufacturers of Licensed Class II, III, and IV Medical Devices[29].
3. BPA Content (Canadian Requirement)
    - BPA content (required for Canada): Notice to Manufacturers of Licensed Class II, III, and IV Medical Devices[30]
4. Aromatic Amines content[31]
5. Epoxy derivatives (BADGE, BFDGE, NOGE): Does the product contain any epoxy derivatives? If yes: Does the product comply with Regulation (EC) 1895/2005?
6. Mercaptobenzo thiazole (MBT) content[32]
7. Nanomaterials content[33, iv]
8. N-nitrosamines content and compliance with Directive 93/11/EEC
9. Polycyclic aromatic hydrocarbons (PAH) content
10. Latex
    - Draft 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[34]
11. Electronics
    - Conflict Minerals[35]

[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.”

- UL Standard for Safety: 1642 Lithium batteries; 2054 Household and Commercial Batteries
- EN 60086-1 Primary Batteries – General; -2 Primary Batteries - Physical and Electrical Specifications
- EN60601 Medical Electrical Equipment
- EN 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 and provide Letters of Authorization.[v]

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, 36] Table 2 and Figure 1 below provide examples of what type of testing is generally expected at various points in the supply chain. 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.

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.

[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] Examples of direct and indirect contact materials in a drug product are, e.g., capsule in a blister where capsule material is direct contact, and blister material is indirect contact; 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 43, for further discussions regarding critical components.

- 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,[37] parts 5 and 10 (to address sensitization, irritation), or USP <87> as appropriate. See also FDA guidance for industry and staff regarding application of ISO 10993-1.[38] Classification of plastics as per USP <88>[39] is not required but is preferred.
- Physicochemical testing: compliance with EP Chapter 3;[40] USP <661>;[41] <381>,[42] <660>, JP XV.

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.[43, 44] Appropriate solvents with a good range of polarity include isopropanol, hexane or heptane, and water (e.g., at different pH levels).[45] 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.
- 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 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] the bioprocess systems alliance (BPSA), and ISO 10993-18. Additionally, further

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

[ix] www.elsiedata.org

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]

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.

Foreign Particulates

Introduction of foreign particles via materials and/or processes used to fabricate components for OINDP should be avoided. Particulates that are not part of the drug product formulation are considered "foreign particulates." Particulates originating in component manufacturing processes will be counted as foreign particulates in the drug product, and therefore suppliers and customers should develop agreed acceptance criteria. For example, talc should not be used as a processing aid, e.g., during fabrication of bags used to store inhalation drugs or devices. Support for these concepts may be found in, e.g., PS 9000:2016 GMP guideline for packaging suppliers.[46]

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

Table 2. Requirements for OINDP Materials Supply Chain

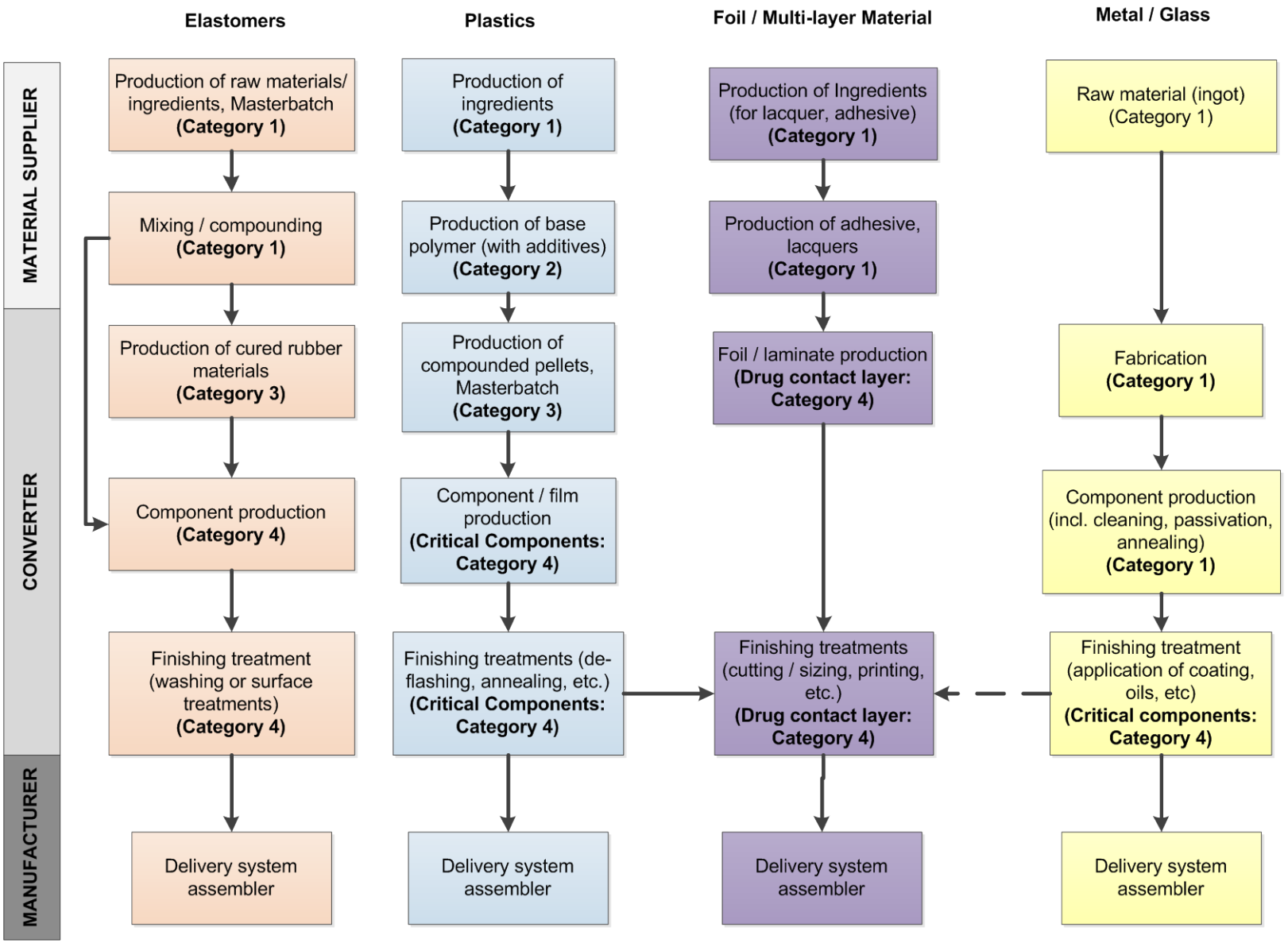
(Categories are applied in the Materials Manufacture Flowchart, page 8)

Test	Category 1	Category 2	Category 3	Category 4
Biocompatibility—based on compliance with ISO 10993 or USP <87> and <88>. ***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 XV ***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 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. 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. 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:

- selection of a demonstrably equivalent material
- 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
- 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 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.[47, 48] 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[49] 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 [49]

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 and delivery system components *under laboratory conditions*, often with application of solvents and heat. Extractables are potential leachables, which 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 extractables and leachables should be considered, e.g., manufacturing process material.

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>.[50]

Extractable identification and reporting 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; different threshold values are being 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, mass of the delivery system component. If a surrogate is being used, then additional work with authentic standards will need to be performed to obtain an accurate estimate. 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, our working group proposes a generic AET of 1 ppm, defined as content of the extractable, e.g., in a plastic component. This proposed AET value reflects most of the products

[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.

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.

[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." 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 EMEA's Guideline documents that govern packaging/device component testing.[2, 3, 4] 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, 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, see pp. 6-7). 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 needed to manage and asses the changes.

Appendix 6: References

[1] Guideline on Plastic Immediate Packaging Materials, EMA (2005). www.emea.europa.eu/pdfs/human/qwp/435903en.pdf

[2] Guidance for Industry. Container Closure Systems for Packaging Human Drugs and Biologics. Chemistry, Manufacturing, And Controls Documentation. CDER (1999) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf

[3] Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation, CDER (2002). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf

[4] Draft Guidance for Industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. Chemistry Manufacturing and Controls Documentation, CDER (1998). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070573.pdf

[5] Guidance for Industry. Pharmaceutical Quality of Inhalation and Nasal Products. Health Canada (2006). http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/inhalationnas-eng.php

[6] Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products. EMA (2006). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003568.pdf

[7] *Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators*, CDRH (1993). http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081293.pdf

[8] 21CFR Parts 172-189 CFR - Code of Federal Regulations Title 21

[9] *COMMISSION REGULATION (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food.* Journal of the European Union. 15 January 2011. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:012:0001:0089:EN:PDF

[10] Other materials – ceramics, gaskets, etc. http://ec.europa.eu/food/food/chemicalsafety/foodcontact/legisl_list_en.htm

[11] Resolution AP (89) 1 on the use of colourants in plastic materials coming into contact with food

[12] Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles

[13] Resolution AP(2002) 1 on paper and board materials and articles intended to come into contact with foodstuffs

[14] Resolution AP(2004)1 on coatings intended to come into contact with food (replacing Resolution AP (96) 5)

[15] Resolution AP(2005)2 on packaging inks applied to the non-food contact surface of food packaging materials and articles intended to come into contact with food

[16] Database BfR Recommendations on Food Contact Materials (formerly "Plastics Recommendations") http://www.bfr.bund.de/en/database_bfr_recommendations_on_food_contact_materials__formerly__plastics_recommendations__-1711.html

[17] World Health Organization (WHO) Codex Alimentarius, General Standard for Food Additives, STAN 192-1995.

[18] Commission Directive 2003/32/EC introducing detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilising tissues of animal origin http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2003L0032:20030516:EN:PDF

[19] Medical devices utilizing animal tissues and their derivatives http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=51985

[20] *European Pharmacopoeia* (*EP*) General Chapter 5.2.8, "Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products".

[21] EMEA/410/01 Rev. 3 Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003698.pdf

[22] Application of Council Directive 93/42/EEC taking into account Commission Directive 2003/32/EC for medical devices utilising tissues or derivatives originating from animals susceptible for TSE http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_11_1_rev2_bsetse_january2008_en.pdf

[23] European Parliament and Council Directive 94/62/EC on packaging and packaging waste http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1994L0062:20090420:EN:PDF

[24] ICH Q3D Guideline for Elemental Impurities. http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

[25] Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1907:20110306:EN:PDF

[26] Directive 2012/19/EU of the European Parliament and of the Council of 4 July 2012 on waste electrical and electronic equipment (WEEE) http://ec.europa.eu/environment/waste/weee/legis_en.htm

[27] Restriction of Hazardous Substances Directive 2002/95/EC, (RoHS 1), Directive on the restriction of the use of certain hazardous substances in electrical and electronic equipment. http://ec.europa.eu/environment/waste/rohs_eee/index_en.htm

[28] Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending … Council Directive 93/42/EEC concerning medical devices http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:247:0021:0055:en:PDF

[29] Health Canada. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/md_notice_im_avis_dehp_bpa-eng.pdf

[30] Health Canada. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/md_notice_im_avis_dehp_bpa-eng.pdf)

[31] Regulation (EU) No 10/2011

[32] Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. Product Quality Research Institute. 2006.

[33] Regulation (EU) No 10/2011

[34] Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex - Guidance for Industry and Food and Drug Administration Staff. US Food and Drug Administration. CBER, CDER, CDRH, CVM. 2014 http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm213055.htm

[35] 17 CFR Parts 240 and 249b; Conflict Materials, Final Rule. See also OECD (2013), *OECD Due Diligence Guidance for Responsible Supply Chains of Minerals from Conflict-Affected and High-Risk Areas: Second Edition*, OECD Publishing. http://dx.doi.org/10.1787/9789264185050-en

[36] USP <1661> Evaluation of plastic packaging systems and their material of construction with respect to their user safety impact

[37] International Organization for Standardization (ISO) 10993 Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process; Part 5: Tests for in vitro cytotoxicity; Part 10: Tests for irritation and skin sensitization http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_tc_browse.htm?commid=54508

[38] Guidance for Industry and Food and Drug Administration Staff. *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"*. CDRH, Food and Drug Administration. June 16, 2016.

[39] United States Pharmacopeia (USP) <88> Biological reactivity tests, in vivo

[40] European Pharmacopeia (EP). Chapter 3 “Materials and Containers”

[41] USP <661> Physicochemical Tests - Plastics

[42] USP <381> Physicochemical Tests - Elastomeric Closures

[43] 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). http://pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

[44] USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems, Table 1.

[45] Safety Thresholds and Best Practices For Extractables and Leachables in Orally Inhaled and Nasal Drug Products. *Part 3; Chapter II; Section C: Recommendations for Controlled Extraction Studies, Recommendation 1: Controlled Extraction Studies should employ rigorous* ***extraction with multiple*** *solvents of varying polarity. Page 85*. PQRI. 2006. http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

[46] PS 9000:2016 Pharmaceutical packaging materials for medicinal products, with reference to Good Manufacturing Practice (GMP). Quality Management Systems – Requirements; Part 8 Operation; 8.2.2.2 Specifications. https://www.pqg.org/pharma/publications/ps-series

[47] Draft Guidance for Industry Contract Manufacturing Arrangements for Drugs: Quality Agreements. May 2013. US Food and Drug Administration

[48] EudraLex. Rules Governing Medicinal Products in the European Union. Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Chapter 7, Outsourced Activities

[49] PS 9000:2016 Pharmaceutical packaging materials for medicinal products, with reference to Good Manufacturing Practice (GMP). https://www.pqg.org/pharma/publications/ps-series

[50] USP <1663> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging Delivery Systems