

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. 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, 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 manufacturers will use this document to guide primary packaging/device material selection and control; and that suppliers will provide materials and information that meet these requirements. Adherence to these requirements can benefit both suppliers and OINDP 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. The final determination of suitability for use is ultimately made by the regulatory authorities.

This document also includes a chart that provides recommendations on testing requirements for materials that are divided into four different categories (page 6). 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 7). Different categories of testing are applied to each level in the supply chain for four different component types: plastic, elastomer, metal, foil. It is intended that all levels in the supply chain would consult this document for an awareness of baseline requirements and take actions appropriate to the level in the supply chain.

These requirements result directly from regulatory requirements for the OINDP manufacturing industry. Both the EMEA 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 Canada⁵ and EMA⁶ 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

A minimum of 36 months rolling availability of unchangedⁱ material (subject to contractual agreements for specific materials between individual suppliers and their customers).ⁱⁱ This 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. Timing of notice can be negotiated.

Suppliers are expected to have a quality system that supports notification of change and change control.

The following table provides examples of timeframe scenarios:

	Notice Period with Last Call Option	Raw Material Shelf Life	Finished Component 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

Change Management

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 or quality)
- Documentation changes to controlled documents (batch records, methods, etc)

Change Control Procedures should include written procedures for the identification, documentation, appropriate review, and approval of changes affecting the quality of products and/or processes, equipment, systems and methods. Procedures should ensure changes will

ⁱ i.e., unchanged ingredients, processes, or equipment. See Appendix 1 for more information on need for security of supply.

ⁱⁱ See Appendix 1: Rationale for Security of Supply

be implemented in a controlled manner. An independent group (i.e., Quality Unit), should have responsibility and authority for management/approval of changes.

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.

Compliance Statements/Supplier Information

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 OINDP material as early as possible in the drug development process.

1. Food Additive Compliance:
 - US: 21CFR Parts 172-189⁸
 - EU: Commission Regulation (EU) No 10/2011⁹
 - EU: Other materials (ceramics, gaskets, etc)¹⁰
2. Pigments: BfR Requirements;¹¹ 21 CFR 178
3. Composition, process & quality information
 - Under confidentiality agreement(s), the supplier is expected to provide minimum composition, process and quality information, e.g., for inclusion in customer's dossier and to allow the customer to provide timely responses to health authorities.
4. Heavy Metals:
 - Directive 94/62/EC;¹² Pb, Cd, Cr-VI, Hg < 0.01%
 - Coatings comprised of metal, which are traditionally used for fabricating metal components, should not be included in device components that are in the drug path.
5. TSE (BSE, "mad cow disease"):
 - Compliance with 2003/32/EC,¹³ EN ISO 22442¹⁴, EP 5.2.8¹⁵; guidances: CPMP/EMEA 410/01,¹⁶ MEDDEV 2.11/1.¹⁷
6. Phthalates Content (required for labeling in EU):
 - Compliance with 93/42/EEC as amended by 2007/47/EC.¹⁸
7. DEHP Content (Canadian Requirement)
 - DEHP content (required for Canada): Notice to Manufacturers of Licensed Class II, III, and IV Medical Devices (http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/md_notice_im_avis_dehp_bpa-eng.pdf).
8. BPA Content (Canadian Requirement)

- BPA content (required for Canada): Notice to Manufacturers of Licensed Class II, III, and IV Medical Devices (http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/md_notice_im_avis_dehp_bpa-eng.pdf).
9. REACH
- Materials should be in compliance with Regulation no. 1907/2006/EC¹⁹ concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH).
10. Drug Master Files (DMFs): Suppliers should have current DMFs available and provide Letters of Authorization.ⁱⁱⁱ

Material Testing

The following tests should be conducted on the material to further demonstrate its suitability for use within an OINDP.

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.

Pharmacopeias/Standards Compliance:

- Biocompatibility: based on surface mucosal contact/limited duration, compliance with ISO 10993,²⁰ parts 5 and 10 (to address sensitization, irritation). Classification of plastics as per USP <88>²¹ is not required but is preferred.
- Physicochemical testing: compliance with EP Chapter 3;²² USP <661>;²³ <381>.²⁴

Controlled Extraction Studies^{iv}

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

- Minimum three solvents of varying polarity.²⁵ A good starting point for consideration of three appropriate solvents with a good range of polarity is those provided as examples in the PQRI recommendations: isopropanol, hexane, methylene chloride.^v Water can also be used. Other solvents that provide such a

ⁱⁱⁱ 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.

^{iv} See Appendix 3: Rationale for Controlled Extraction Studies for more information

^v 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**

range are also appropriate, and the selection should be rationalized as noted in the recommendations.

- At least one extraction technique.
- At least two analytical methods (e.g., gas chromatography, liquid chromatography) plus mass spectrometry.
- Quantification and identification is acceptable at 10 ppm, but ideally should be done at 1 ppm.
- A detailed protocol for Controlled Extraction Studies is also being developed by the Extractables and Leachables Safety Information Exchange (ELSIE) Consortium.^{vi} Suppliers may consider this protocol for more guidance on conduct of a controlled extraction study, when it becomes available.

Routine Extractable Testing^{vii}

Routine extractable testing should be conducted periodically 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, or functionality of the device.

Foreign Particulates

Materials and/or processes used to fabricate components for OINDP packaging/devices should not contain or introduce foreign particulates.

(Continued)

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

^{vi} www.elsiedata.org

^{vii} See Appendix 4: Rationale for Routine Testing for more information

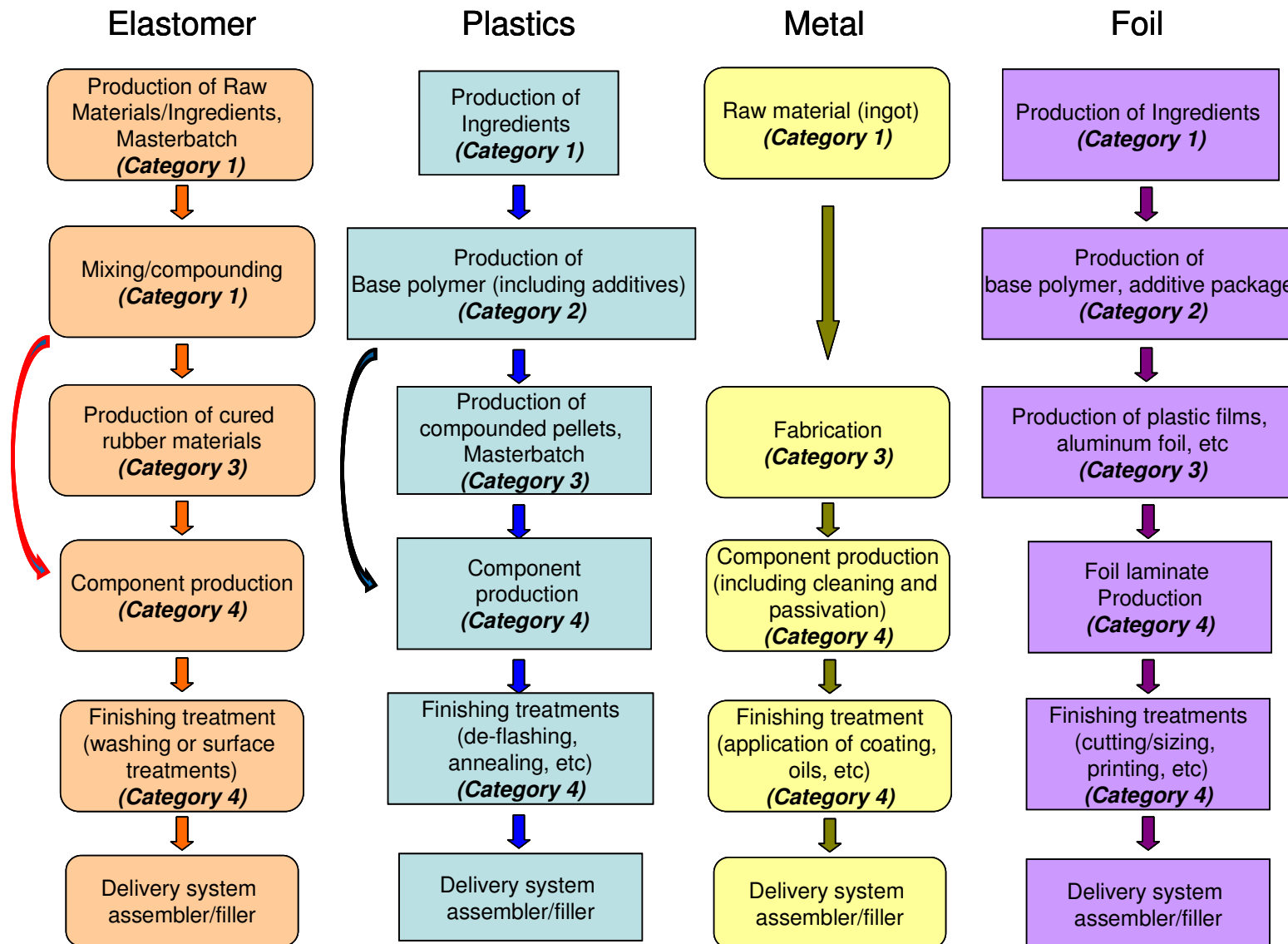
Requirements for OINDP Materials Supply Chain
(Categories are applied in the Materials Manufacture Flowchart, page 7)

Test	Category 1	Category 2	Category 3	Category 4
Biocompatibility—based on surface mucosal contact/limited duration, compliance with ISO 10993 Deliverable: Certificate of Compliance (required) and report with test results (upon request)			One-time test*	One-time test*
USP classification of plastic: USP <87>, <88>, and <1031> (Not required but preferred) Deliverable: Certificate of Compliance and report with test results (upon request)			One-time test*	One-time test*
Physicochemical Testing Deliverable: Certificate of Compliance (required); Certificate of Analysis (upon request)			One-time test* <i>Compliance with EP3.1</i>	One-time test* <i>Compliance with EP Chapter 3, USP <661>, <381>, (optional JP XV)</i>
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 Per <i>batch</i> , 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 development testing results (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

[▲] Test each batch/lot. See Appendix 4 for more information.

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.

Orally Inhaled and Nasal Drug Product (OINDP) material changes during development or on the commercialized product 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 dependant 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
- testing to verify material properties in relation to its function in the design of the device
- testing to qualify the toxicological and biological safety profile of the material or process
- requalification of the mould tooling
- revalidation of production processes
- testing to assess the stability of the drug formulation in relation to its contact with the new material
- 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 in conjunction with or separately from supply agreements. To address key quality and regulatory concerns the following elements should be considered when preparing a quality agreement (adapted from IPAC-RS GMP guideline for suppliers of OINDP components):²⁶

1. Definitions,
2. Document review, approval, retention, exchange and archival with respect to:
 - batch records,
 - deviations/investigations,
 - specifications/drawings,
 - test methods,
 - operating procedures,
 - IQ/OQ/PQ reports,
 - certificates (e.g., compliance, analysis),
 - design history file (devices).
3. Change control and notification practices with respect to:
 - document change control,
 - material change control,
 - specification change control,
 - process change control, and
 - facility and equipment change control.
4. Practices with respect to:
 - cleanliness and hygiene,
 - complaints and impact on commercial supply,
 - product testing,
 - customer audits, lot approval and product release,
 - process validation,
 - qualification of equipment,
 - recalls,
 - resolution of quality issues,
 - subcontractor management.
5. Requirements for manufacturing environment
6. Expectations regarding material suppliers
7. Requirements for components:

raw materials and subcomponents,
retained samples,
customer samples,
rework and reprocess.

8. Organization and customer responsibility matrix
9. Reference to current versions of relevant standards and guidelines
10. Regulatory compliance expectations
11. Regulatory contacts and audits

Appendix 3: Rationale for Controlled Extraction Studies

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 and delivery system components *into the drug product* as a result of direct contact with the formulation over the shelf-life of the drug product. Any compounds that leach into the drug product will be inhaled by the patient and may negatively impact the safety of the drug product. 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. These studies can be performed independently of the drug product. As such, these extraction studies should be performed by the material or component manufacturer and not by the drug product manufacturer. Detailed information on Controlled Extraction Studies is given in the PQRI recommendations.

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. 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 and an analytical uncertainty factor of 50%. A typical calculation^{viii} is as follows:

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

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 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.^{ix} 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.

Surrogate reference compounds can be used for initial evaluation of a product in order to produce semi-quantitative results for a comparison with the AET. For compounds that are above the AET, further laboratory work (typically mass spectrometry) would be necessary to tentatively identify the compound (assign a CAS number, or, at the very least, the class of

^{viii} 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.

^{ix} 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

compound). Based on the semi-quantitative results one could begin the toxicological evaluation of the compounds present to determine if there is any significant health risk from the extractables produced. Final toxicological assessment, typically performed by the pharmaceutical manufacturer, would require confirmation of the identity of the compounds above the AET and quantitative results based on authentic reference compounds.

Appendix 4: Rationale for Routine Testing

Routine Extractables Testing is a critical part of a comprehensive OINDP control strategy to ensure the quality and safety of the final drug product. Routine Extractables Testing is defined according to the 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) and High Performance Liquid Chromatography/Ultraviolet Detector (HPLC/UV) as the analytical technique.

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 provides a key part of a robust control strategy to maintain drug product quality. Routine Extractables Testing needs to be performed for each lot of material. 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 governed by the nature of the Extractables profile, the class of compounds that are being controlled, whether or not there is direct contact of the manufactured component with the drug product formulation, whether or not the extractables correlate with leachables, and in consultation with the supplier/customer.

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. 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.

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 assess 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/applc-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 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
- 12 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>
- 13 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>
- 14 Medical devices utilizing animal tissues and their derivatives
http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=51985
- 15 *European Pharmacopoeia (EP)* General Chapter 5.2.8, “Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products”.

- ¹⁶ [EMEA/410/01](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003698.pdf) 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
- ¹⁷ 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
- ¹⁸ 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>
- ¹⁹ 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>
- ²⁰ 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
- ²¹ United States Pharmacopeia (USP) <88> Biological reactivity tests, in vivo
- ²² European Pharmacopeia (EP). Chapter 3 "Materials and Containers"
- ²³ USP <661> Physicochemical Tests - Plastics
- ²⁴ USP <381> Physicochemical Tests - Elastomeric Closures
- ²⁵ 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
- ²⁶ GMP Guideline for Suppliers of OINDP Components. IPAC-RS. (2006). New version incorporated into PS 9000:2011 (Pharmaceutical Quality Group/IPAC-RS) to be launched for public use in September 2011.