

## **Regulatory Requirements Toolkit for Orally Inhaled and Nasal Drug Products**

### **I. What is it?**

The toolkit considers the types of Regulatory Requirements that may be applicable to Orally Inhaled & Nasal Drug Products (OINDP), either as individual materials (used in the manufacture), in-process (part-finished) products or components, or final finished products.

In particular the document gives an overview of the regulatory requirements from product development through to approval to market OINDP, as well as regulation of the materials used to manufacture them, and the use of Drug Master Files to manage specific information.

References to regulatory guidances for further information are included in the document.

### **II Who is it for?**

This document is intended to be used by those seeking a general introduction to the regulation of OINDP and the container closure or delivery system components and materials used in their manufacture. It will be specifically of interest to suppliers of components and materials for OINDP.

### **III Why use it?**

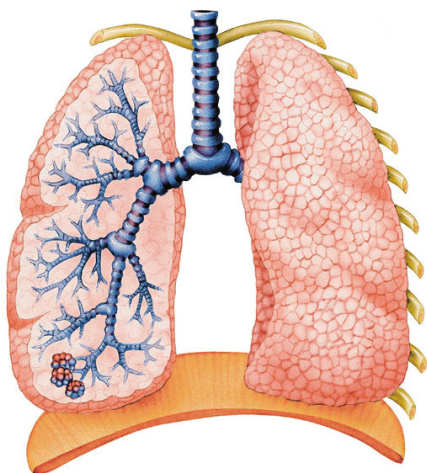
- To obtain an introduction to Regulatory Requirements for OINDP.
- To enable understanding of the development and registration phases and requirements for OINDPs.
- To identify further resources that will enable a deeper understanding of specific topics.

## Regulatory Requirements Toolkit for Orally Inhaled and Nasal Drug Products

### 1. Introduction

Orally Inhaled Nasal Drug Products (OINDP) are intended to deliver therapeutic benefit by delivery of a pharmaceutical substance to the lungs (Orally Inhaled) or nasal cavity (Nasal). Both of these routes of administration by OINDP have some common characteristics:

- Delivery of the drug as a specific range of particle sizes, which may be the drug particle alone, or bound to a carrier particle (dry powder), or dissolved or suspended in a liquid droplet
- Targeted deposition to specific membranes (for example specific point of pulmonary tract, specific mucous membrane in the nasal cavity)



OINDP are complex products which contain the drug substance with excipients as powder, solution or suspension in a container closure system which may also act as the drug delivery device. There are several types of OINDP such as nasal sprays, the pressurised metered dose inhaler (pMDI), the dry powder inhaler (DPI), nebulizers, and other novel inhaler types, such as Aqueous Droplet Inhalers (ADI). Container closure components used to manufacture OINDP include pumps, valves, cans, bottles, actuators, spray nozzles, spacer devices, dose counting mechanisms. Consideration is also given to the raw materials used to manufacture the container closure components, such as polymer materials used for moulding sub-components, rubber gasket materials used as seals.

This toolkit provides a general overview of the drug development process, regulatory filings required in the various stages of drug development, drug master file process, and material requirements. The toolkit is not intended to provide a prescriptive review of the global regulatory requirement and does not address the cGMP requirements for OINDP (Refer to IPAC-RS GMP Guideline<sup>1</sup>).

<sup>1</sup> International Pharmaceutical Consortium on Regulation and Science (IPAC-RS) Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products. 2006. The guideline can be ordered through the IPAC-RS website: <http://www.ipacrs.com/publications.htm>

## 2. Requirements for Regulatory Approvals

### 2.1 Drug Development

A new molecular entity developed as an OINDP undergoes several phases of drug development prior to being marketed. The drug development starts in discovery where a suitable candidate is identified and then progresses through clinical studies phases I-III leading to registration and marketing. Prior to its entry in phase I clinical study, appropriate animal toxicology, pharmacology and pharmacokinetic data and chemistry manufacturing and controls (CMC) information are generated to support the ‘first-in-human’ clinical study. Typically, the phase I clinical studies are conducted in healthy volunteers to establish the pharmacokinetic, pharmacological and safety effects of the drug in humans. The phase II and III studies are conducted in patients to establish the safety and efficacy of the new drug in larger patient population.

Because the container closure system is critical to the delivery of drug for OINDP, it is important to select the drug delivery system prior to pivotal clinical studies.

### 2.2 Regulatory Filings

The following table provides information on the types of regulatory submissions<sup>2</sup> that are made to Health Authorities in the life cycle of the drug (development, registration and marketing).

<b>DEVELOPMENT PHASE</b>	<b>REGULATORY FILING</b>	<b>HEALTH AUTHORITY</b>	<b>PURPOSE</b>
Clinical Phases I-III	Investigational New Drug Application (IND)	FDA – United States	Depending on the phase of clinical study, a CTA containing applicable clinical, non-clinical and CMC information is submitted to the Health Authority for approval to initiate the clinical study.
	IND Amendments		
	Clinical Trial Application (CTA) CMC Section of CTA: Investigational Medicinal Product Dossier (IMPD) Quality Substantial Amendment	EMA - Europe	Amendments are submitted to support any major change to the above described dossier content.

<sup>2</sup> The document does not intend to describe all global regulatory filings.

DEVELOPMENT PHASE	REGULATORY FILING	HEALTH AUTHORITY	PURPOSE
Registration Phase	New Drug Application (NDA)	FDA – United States	Provide clinical efficacy and safety, non-clinical, CMC and other applicable information to request authorization to market the new OINDP in the respective regions.
	Marketing Authorisation Application (MAA)	EMA - Europe	
Marketing Phase	Supplements, Annual Report	FDA – United States	Changes made to the content of NDA or MAA requires a regulatory filing. Depending on the type of change either major or minor, appropriate post-approval regulatory submissions are made to the Health Authorities.
	Variations	EMA - Europe	

### 2.3 Content of Regulatory Dossiers

The regulatory dossiers are organized in the common technical document (CTD) format.<sup>3</sup> The CTD contains five modules as follows:

- Module 1 contains administrative and prescribing information and is region specific.
- Module 2 is the summary of quality (CMC), non-clinical and clinical sections.
- Module 3 is the quality section
- Module 4 is the non-clinical section
- Module 5 is the clinical section

Depending on the country of filing and the type of dossier (clinical, registration or marketing phase), there may be variations to format, content, administrative documents, etc. The regulatory submissions could be filed with Health Authorities either in paper or electronic format (e.g., eCTD format) depending on Health Authority requirements.

As the container closure (device) information is part of the CMC section of the regulatory dossier, from this point forward this sub-section will focus on the CMC content. Below is a table which provides the typical CMC information that is required for a regulatory dossier.

<sup>3</sup> International Conference on Harmonisation. The Common Technical Document. <http://www.ich.org/cache/compo/276-254-1.html>. Accessed on 7 December 2009.

<b>MODULE 3</b>	<b>SECTIONS</b>
3.1	Table of Contents
3.2 Substance (S)	General Information (Nomenclature, structure and properties), Manufacture, Characterization, Control, Reference Standards, Container Closure, Stability
3.2 Product (P)	Description and Composition, Pharmaceutical Development, Manufacture, Control of Excipients, Control, Reference Standards, Container Closure and Stability.
3.2 Regional (R)	Additional region specific information on drug substance and drug product not included in the above S or P section are included.

Note that literature references can be included, which could support development information on, e.g., safety.

During development phases I – III, several pharmaceutical studies are conducted to establish the suitability of formulation, manufacturing process, controls, container closure system and stability for its intended use. There are several regulatory guidelines (refer to section 5) describing the specific CMC requirements unique to OINDP. Although these guidelines are applicable to registration stage dossiers, the guidelines do specify that the principles should be applied during clinical phase with consideration to the product type and phase of development.

In the regulatory dossiers, the container closure information could also be supplied using the Drug Master File (DMF). However, whilst many countries accept the use of DMFs to submit CMC information for drug substance manufacture (sometimes referred to as API), currently only the USA Food & Drug Administration and Health-Canada accept DMFs for container closure components and materials. The following section provides the details on the DMF content, process, and acceptability.

### **3. Drug Master File**

#### **3.1 Introduction**

A Drug Master File (DMF) is a method of submitting information pertaining to a Drug Product to a regulatory authority.

DMFs are mostly commonly used by suppliers of materials such as packaging materials, container closure components, excipients, drug substance. The DMF enables the supplier to:

- Give confidential information directly to the regulatory authority, where the supplier does not want to share that information with the drug product applicant. Examples of such confidential information include:
  - o Chemical compositions of materials
  - o Manufacturing process details and parameters
- Give specific critical information directly to the regulatory authority. This information may not be confidential, however this enables the supplier to manage the information directly. Examples of such information are:
  - o Material compliance certificates
  - o Analytical test methods

Only a few regulatory authorities accept the use of DMFs, because it requires the authority to have a system that is capable to manage (access, update, archive etc) the documentation. As already stated, at the time of writing this document, only the FDA and Health-Canada accept DMFs relating to OINDP packaging materials and container closure components.

A DMF is not compulsory. The Drug Product Applicant can submit the information themselves. Therefore the decision to use a DMF, and the type of information to be included, requires agreement between the Drug Product Applicant and the supplier.

#### **3.2 Contents of DMF**

The following list defines the type of information about OINDP container closures that can be submitted in a DMF (note: combined and abbreviated list from several guidance documents)

- Item numbers
- Source(s) and fabricator(s) for each sub-component
- Composition and quality of materials of each sub-component (including coating, if appropriate)
- Citations of compliance of the materials to defined regulations, pharmacopoeia etc (see section below on Material Compliance)
- Drawings of each sub-component with precise dimensional measurements
- Description of any treatment processes such as washing, coating, sterilisation

- Analysis for residual contaminants and residues of surface treatments, washings etc
- Control extraction studies for elastomeric and plastic components, also for any coated surfaces
- Toxicological evaluation of extractables and residues
- Performance characteristics of the sub-component and/or assembled finished item
- Acceptance criteria, test methods, and sampling plans

This is not an exhaustive list, but gives an idea of the level of detail that must be submitted for OINDP container closure components and materials. The DMF may contain all of the relevant information for the chemistry, manufacture and controls of the material or component being described, or it may contain only trade secret information. A combination of the application and the referenced DMFs needs to contain the complete information as described in the Container Closure Guidance.

### **3.3 Submission Process**

Once the DMF is submitted to the regulatory authority, the supplier shall issue a Letter of Authorisation (LOA) to the regulatory authority. The letter permits the authority to review the specific pages of the DMF (must be defined in the LOA) in association with the specific drug product that is being reviewed by the authority.

It must be noted that the DMF is neither approved nor disapproved. The DMF is only reviewed in association with the drug product that it is supporting. However, should the authority be dissatisfied with any aspect of the DMF, it may result in delay of issue of the marketing licence (or removal or an existing licence) until the DMF issue is resolved.

There are very specific regulations for the correct establishment and ongoing maintenance of a DMF. These include the requirement to keep all information in the DMF up-to-date. Both FDA and Health-Canada have established procedures for DMF management, and these are defined in guidelines and on their websites (see list of references).

Ongoing upkeep of the DMF to keep the information correct and current is therefore critical. The supplier and drug product Applicant should ensure careful cooperation and coordination relating to any changes, or communications from the regulatory authority.

### **3.4 Definitions**

1. Supplier: manufacturer of materials or components used in the manufacture of OINDP (Orally Inhaled & Nasal Drug Products). The supplier is not the company manufacturing or selling the final drug product. Examples of materials and components manufactured by the supplier:
  - Pumps
  - Valves

- Aluminium or steel cans
  - Glass or plastic bottles
  - Actuators, spray nozzles, DPI devices
  - Blister strips for dry powders
  - Spacer devices
  - Dose Counting mechanisms
  - Polymer materials used for moulding sub-components in the components listed above
  - Rubber gasket materials used as seals in the components listed above
2. Drug Product Applicant: the pharmaceutical company applying for the licence to market the finished pharmaceutical product.

#### 4. Materials Requirement

In the section above, the subject of ‘material compliance’ was raised.

The materials used for the manufacture of OINDP components must comply with specific regulations. The requirements are somewhat unusual in that the materials in OINDP components are often regulated as ‘Food Contact’ materials, i.e. the regulations applied to the materials are often those used for regulation of materials used in food packaging and preparation.

The table below gives some examples of the citations that are required for some plastic polymers that are commonly used for moulding OINDP components:

MATERIAL	USA FOOD CONTACT	EU FOOD CONTACT	EU PHARMACOPEIA
Polypropylene	21CFR177.1520	Food Contact EEC Directives / Framework Regulation 1935/2004/EC 2002/72/EC + amendments 2004/1/EC, 2004/19/EC, 2005/79/EC, 2007/19/EC, 2008/39/EC, REACH	European Pharmacopoeia 6th Edition 2008 + Supplements : Chemical comp. 3.1.3 – 3.1.5
Acetal (Polyoxymethylene)	177.2470 copolymer or 177.2480 homopolymer		N/A
Nylon (Polyamide)	21CFR177.1500		N/A

Although the above table only lists polymers, there are similar requirements and regulations for other OINDP component materials including steel, aluminum, elastomer (rubber), silicone oil, glass, ink.

The Food Contact regulations generally place conditions on:

- The manufacturing conditions and parameters
- The chemical composition
  - o Limitations on the types and quantities (by % of the formulation) of the input materials, additives etc

- Limitations on the residues in the finished material, such as monomers, trace elements etc
- The physical and mechanical properties

The regulation may also make reference to standard methods that must be used to verify the compliance to the regulation.

Other types of material compliance regulation that may be applicable include:

- Use of materials of animal origin, as well as regulations to assure the control of TSE/BSE
- Trace levels of Phthalates
- Trace levels of 'Heavy Metals' (cadmium, lead etc)
- Cytotoxicity
- Other pharmacopeia monographs applicable to specific types of materials

For each of the materials, the regulatory body will require documentation to assure that the materials comply with the applicable regulations. Because the regulations include criteria that can only be verified by the material manufacturer, the compliance is often assured via a certificate. It must therefore be ensured that a suitable system is in place to assure that the criteria in the regulation are maintained and therefore that the certification remains valid for all ongoing production of material. Noting that there may be a complex supply chain between the material manufacturer and the drug product Applicant who is relying on continued compliance, e.g.,

Polymer Manufacturer → Polymer Distributor → Component Moulder → Drug Product Applicant
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It should be noted that compliance to these regulations does not negate the requirement to provide other information that may be required by regulators for materials (toxicology, extractables, quality assurance activities, etc.).

It should also be noted that the material compliance regulations can differ significantly from country to country.

## 5. References

Below is a listing of some of the regulatory guidelines pertaining to OINDP from various Health Authorities. *This list is not exhaustive* and appropriate regional regulatory guidelines should be considered when developing OINDP for the global market.

### US – Food and Drug Administration

Container Closure Systems for Packaging Human Drugs and Biologics, 5/1999	<a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm</a>
Container Closure Systems for Packaging Human Drugs and Biologics – Questions and Answers, 5/2002	
Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products	<a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm</a>
Nasal Spray and Inhalation Solution, Suspension, and Drug Products	<a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm</a>
Inhalation Drug Products Packaged in Semipermeable Container Closure Systems	<a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071725.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071725.pdf</a>
<i>Federal Register Notice</i>	
INDs for Phase 2 and Phase 3 Studies	<a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm</a>
ICH M4: CTD	<a href="http://www.fda.gov/cder/guidance/4539Q.PDF">http://www.fda.gov/cder/guidance/4539Q.PDF</a>

### Europe – EMEA

Pharmaceutical Quality of Inhalation and Nasal Products	<a href="http://www.emea.europa.eu/pdfs/human/qwp/4931305en.pdf">http://www.emea.europa.eu/pdfs/human/qwp/4931305en.pdf</a>
Plastic Immediate Packaging Materials	<a href="http://www.emea.europa.eu/pdfs/human/qwp/435903en.pdf">http://www.emea.europa.eu/pdfs/human/qwp/435903en.pdf</a>

Other	
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Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. PQRI, 2006	<a href="http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf">http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf</a>
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International	
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ICH Q8 Pharmaceutical Development (R2, Step 4, August 2009)	<a href="http://www.ich.org/LOB/media/MEDIA4986.pdf">http://www.ich.org/LOB/media/MEDIA4986.pdf</a>
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<http://www.tga.gov.au/pmeds/argpmap19.pdf>

Australian Regulatory Guidelines for Prescription Medicines (Appendix 19: Metered Dose Aerosols (Pressurised And Nonpressurised) 2004

Australian Code Of Good Manufacturing Practice For Medicinal Products Annex 10: Manufacture Of Pressurised Metered Dose Aerosol Preparations For Inhalation 2002	<a href="http://www.tga.gov.au/docs/pdf/gmpcodau.pdf">http://www.tga.gov.au/docs/pdf/gmpcodau.pdf</a>
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and

Annex 10: Manufacture Of Pressurised Metered Dose Aerosol Preparations For Inhalation 2002	<a href="http://www.tga.gov.au/docs/html/gmpcodau.htm">http://www.tga.gov.au/docs/html/gmpcodau.htm</a>
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### Drug Master Files

US – Food and Drug Administration	
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Drug Master Files	<a href="http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm#guidance">http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm#guidance</a>
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Health Canada	
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Drug Master Files	<a href="http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/chem/draft_ebauche_dmf_fmm_guide_ld-eng.php">http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/guide-ld/chem/draft_ebauche_dmf_fmm_guide_ld-eng.php</a>
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Drug Master File Application Fee Form	<a href="http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/form/dmff_fmmf-eng.php">http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demanded/form/dmff_fmmf-eng.php</a>
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