International Pharmaceutical Aerosol Consortium on Regulation and Science

POINTS TO CONSIDER FOR A P2 FOR AN ORALLY INHALED OR NASAL DRUG PRODUCT

IPAC-RS MODEL OINDP WORKING GROUP

Jackie Schumacher, Pfizer, **Co-Chair**
Liuda Shtohryn, AstraZeneca, **Co-Chair**
Claire D'Abreu Hayling*, Teva
Stefan Leiner, Boehringer Ingelheim
Michael Golden, GlaxoSmithKline
Steve Nichols, sanofi-aventis
Laurence Huxham, AstraZeneca+
Terry Tougas, Boehringer Ingelheim
Johan Waldeck, Novo Nordisk+

* Former Working Group member

+ Former members of the IPAC-RS Combination Products Working Group, now incorporated into the Risk Management Working Group. The Model OINDP Working Group wishes to acknowledge the contributions of the Combination Products Working Group, in particular Laurence Huxham and Johan Waldeck, to these Points to Consider.

PREAMBLE

Context for the Points to Consider for a P2 for an OINDP

The International Conference on Harmonization (ICH) Q8 Guideline on Pharmaceutical Development[1] provides guidance on what information should be considered for inclusion in the drug product development section ("P2") of a Common Technical Document (CTD) submission[2] to describe process and product understanding for all product types.

This document[3] provides points to consider for the P2 specific to orally inhaled and nasal drug products (OINDP), but is not intended to supersede specific local requirements. Nor is it intended to dictate requirements. These points to consider fully support the concepts presented in Q8, Q9, [4] and draft Q10, and cross-reference these sections. In particular, risk assessment and management (as per the ICH Q9 Guideline) are especially useful for OINDP because of the number of factors that may affect product performance and because of the interaction between the formulation and container closure system/device.

Due to the route of administration, particular attention has been given to factors that may affect delivery to the lungs or nasal passages, such as aerodynamic particle size distribution (APSD) and the composition and properties of container closure systems/devices. These topics have therefore been developed in more detail. In contrast, for topics that are not unique to OINDP, *e.g.*, formulation development, this document references Q8.

It is recognized that some of these points to consider may not be achievable for all products, *e.g.*, the correlation between clinical outcomes and the aerosol particle size distribution of the delivered dose. This document provides topics that may be considered in the documentation of a P2 for an OINDP.

The premise of this document[5] is to provide a balance between presenting sufficient detail to be useful and not being overly prescriptive. Where detailed information is included, it is intended to illustrate the types of information appropriate to include for common types of OINDP. The user of this document should consider the relevance of the content relative to the product being described. Conversely, additional studies or information beyond what is described here may be important to include for a specific type of OINDP.

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[1] Available at http://www.ich.org/LOB/media/MEDIA1707.pdf

[2] ICH has set forth a prescribed format and headings for the CTD in its M4 Guideline (http://www.ich.org/LOB/media/MEDIA554.pdf). Applicants may not modify the overall organization of the CTD as specified by ICH M4, nor may they change or add section headers. Applicants are permitted to add sub-sections or attachments to the CTD as appropriate. The Working Group has followed these conventions in this document; no new sections have been added, and no sections have been moved.

[3] This document was drafted by the Model OINDP Working Group of the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). The document is intended as a working draft to be used and commented on by the OINDP industry, and revised based on these comments.

[4] Available at http://www.ich.org/LOB/media/MEDIA1957.pdf

[5] This version of the document was disseminated to IPAC-RS companies on 3 June 2007 for their use with the intent of further revision after experience with the document has been gleaned.

Finally, this document uses a number of terms that are unique to OINDP or relatively new to pharmaceutical development. Working definitions for these terms may be found in the Glossary.

Quality by Design for OINDP: General Considerations

Throughout this document, the application of QbD concepts is described. This preamble provides some points to consider for aspects of QbD that do not fit within a particular P2 section; these aspects may be incorporated throughout the P2 as appropriate. It is recognized that not all of the points to consider are currently achievable (technically or pragmatically), but instead are aspirational goals in order to execute and describe a full Quality by Design (QbD) development. Individual companies should decide on a strategic basis how, and to what extent, to apply QbD concepts for a particular product development program and how to document these concepts.

The user of this document has the flexibility to incorporate the level of detail that is appropriate to accommodate different product types and regulatory regimes. Under QbD, inclusion of more detailed information about the pharmaceutical development program or the basis for the design space and/or control strategy may provide an opportunity for regulatory flexibility.

Under QbD, prior knowledge can be an important tool to support decisions made during the development process. In a P2 for an OINDP, prior knowledge of specific processes may be especially useful to describe (***e.g.***, MDI filling processes and knowledge gained previously that may pertain to the described development), because in many cases sponsors will have developed delivery platforms/systems.

Because of the diversity of OINDP and approaches to development, this document does not specify where in the P2 the discussion of the drug product, drug substance, and container closure system/device design spaces or the rationale for the control strategy should be placed. The applicant can best assess where to place this information for their particular OINDP. We have, however, provided some considerations for the elements to include when discussing design space or the rationale for the control strategy for an OINDP.

If an applicant has established design spaces for an OINDP, their description might include a discussion of the factors explored and an explanation of the areas of dependence between the design spaces of the formulation and container closure system/device, ***i.e.***, how they work together and affect one another. The factors in the design space can be established via the risk analysis steps accomplished during design verification and validation, which may be discussed in 3.2.P.2.4 Container Closure System. For example, for an MDI, an applicant might discuss attributes of the container closure system (e.g., orifice diameter) and formulation that influence particle size distribution, and their interaction with each other to achieve the desired particle size distribution.

An ultimate goal of QbD is to establish the relationship between the clinical performance of the product and the design spaces of the product, container closure system/device, and formulation. Descriptions of these relationships may be used to link critical quality attributes and critical processing parameters to product performance, i.e., safety and/or efficacy. Note that the establishment of such linkages has been identified as a key technical challenge that needs to be addressed not only for OINDP, but for all products.

Inclusion of the rationale for the drug product control strategy in the P2 may provide opportunities for regulatory flexibility. The specifics of the actual control strategy would be placed elsewhere in the submission, for example in the Quality Overall Summary. The rationale may reference the risk analyses conducted and the critical quality attributes and processes identified during design and development of the product and development of the manufacturing process. If online testing is used, the selection of online and end-product tests and the basis for the criteria selected may be discussed. Use of online testing for certain parameters may obviate the need for related end product test(s).

In the rationale for the control strategy, emphasis may be placed on known parameters of the OINDP that are critical to the quality of the product, as identified through risk analyses; these might include, e.g., delivered dose, particle size, and leachables and extractables. The rationale may include, e.g., the definition of critical quality attributes for the container closure system/device and their relationship to specific design attributes and process parameters, and may be based on knowledge and experience gained during the development and manufacturing scale-up phases.

Summary Remarks

As noted above, these Points to Consider are intended to provide sufficient recommendations to OINDP sponsors without being overly prescriptive. The user should consider this document in the appropriate context, including the necessity to go beyond the elements described herein. In the spirit of continuous improvement, this document is intended to be a living document; the Working Group welcomes suggestions for improvement, questions, and/or specific examples for potential inclusion in the next revision. Any such feedback should be submitted via the IPAC-RS Secretariat (dede.godstrey@dbr.com).

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

Introduction

Because of the complexity of OINDP, provide general introductory information for the product, including the extent of Quality by Design applied, and navigation information for the Pharmaceutical Development section. Provide the intended use of the drug product, taking into account the user needs and risks and how the product meets those needs and protects against the risks.

If applicable, identify unique product attributes and their relevance; identify novel excipients and/or briefly describe any unconventional process operations, container closure system/device components, or methods (inclusive of PAT and release/stability methods).

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

See ICH Q8 for further guidance.

3.2.P.2.1.2 Excipients

See ICH Q8 for further guidance.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

See ICH Q8 for further guidance.

3.2.P.2.2.2 Overages

See ICH Q8 for general guidance. If applicable, describe any overages or overfills that are required, such as overages necessary to account for losses of drug substance in the container closure system/device.

3.2.P.2.2.3 Physicochemical and Biological Properties

In addition to the information required by ICH Q8, for inhalation products, provide further detail on aerodynamic particle size of the product and particle size of the drug substance, as it relates to the physiological response to the product. Describe the rationale for selection of the drug product system, including APSD and particle size of the drug substance.

Provide a summary of the drug products evaluated in clinical studies, including the aerodynamic particle size, drug substance particle size, and any other physicochemical property that may affect physiological response. Discuss any differences between drug substance used in clinical studies and that used for in-vitro development tests. Discuss, if possible, whether the particle size influences clinical performance, especially if a range of particle size distributions was utilized in the clinic. For example, demonstrate the influence of aerodynamic particle size on PK/PD and/or bioavailability. In addition, for nasal products, include information to show that a significant portion of the delivered dose does not have the potential to reach the lungs. Provide justification for choice of particle size distribution used for proposed commercial formulations. Further, describe any changes in container closure system and/or device that effect the physicochemical properties of the drug product (e.g., aerosol properties), and describe those effects.

As stated in the preamble, it is recognized that the relationship between particle size and clinical outcomes has not been established in most cases. However, in cases where this relationship is established, this discussion might include:

- describing the rationale for the studies (in vivo/in vitro) performed to evaluate the effect of the particle size distribution as it relates to the desired product profile;
- identifying the site of deposition of different particle sizes (***e.g.***, in the oropharynx, large airways, smaller airways, and respirable dose);
- establishing a correlation or relationship between the range of particle size distributions studied and the clinical outcomes; and
- finally, justifying the acceptance criteria, if applicable, for particle size distribution based on the clinical relevance.

3.2.P.2.3 Manufacturing Process Development

See ICH Q8 for further guidance. Information regarding the container closure system/device manufacturing processes may be provided under 3.2.P.2.4 Container Closure System.

3.2.P.2.4 Container Closure System

As stated in the preamble, due to the route of administration particular attention has been given to factors that may affect delivery to the lungs or nasal passages, such as the container closure system/device; therefore, this section has been developed in more detail.

This section will discuss the development of not only the container closure system but also the delivery device, if it is distinct from the container closure system. The terminology and concepts used in this section are derived in part from the Global Harmonization Task Force's (GHTF) proposed guidance on Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)[6] and on FDA CDRH's Design Control Guidance for medical device manufacturers.[7] The use of these terms and concepts is not intended to imply a requirement or expectation that applicants adhere to either guidance. Appendix B includes a figure depicting a high

[6] Available at http://www.ghtf.org/sg1/inventorysg1/pd_sg1_n011r17.pdf

[7] Available at http://www.fda.gov/cdrh/comp/designgd.pdf; endorsed by the Global Harmonization Task Force June 1999.

level representation of design controls that may be applied to the container closure system/device.

The table below presents the content of modular sub-sections, which should be considered for inclusion, as appropriate, under 3.2.P.2.4 Container Closure System. 3.2.P.2.4 Container Closure System should follow a logical organization; e.g., an MDI with a canister, valve, actuator, overwrap, etc., may be presented in one section (container closure system), whereas a predispensed unit with a separate mechanical device may be presented in separate sections (container closure system and device). Because the formulation and the container closure system/device in an OINDP frequently interact in a significant way to affect device or product performance, the formulation and final drug product are discussed where relevant.

Per ICH Q8, sufficient information and detail should be included in this section to provide a comprehensive understanding of the container closure system, device, and their development and interaction with the formulation.

Table X

Proposed Section Title	**Content**
Intended Use	This section might describe the intended use for the container closure system/device and provide the rationale for selection of the design input requirements, *e.g.,* by addressing: • intended use of the final drug product, and • an acceptable risk profile
Risk Management	The philosophy governing the approach to risk analysis used in the container closure system/device development program may be described here. Specific risk analyses and their results may be discussed in the sub-sections below as appropriate to justify decisions made, and cross-referenced here. The level of detail in these discussions will vary depending on the complexity of the container closure system/device and the frequency and severity of the risks.
Prior Knowledge	This section could describe any relevant information from container closure systems used previously, for example, from platform systems/devices.
Design Inputs	This section might describe the detailed design input requirements for the container closure system/device components together with a rationale for their inclusion. These may be derived from: • the intended use, risk analysis, and prior knowledge described in the previous sections • compatibility and interaction of the container closure system/device

Proposed Section Title	Content
	with the formulation, and • the relevant regulations and standards.[8] Justification of any deviation from the relevant regulations and standards should be considered for inclusion in this section.
Design Outputs	This section might include a general description of the container closure system /device and describe how the container closure system/device meets the design input and protects against identified risks.
Design Verification	This section may demonstrate that the design input requirements are fulfilled by the design of the container closure system/device. The following may be considered: • a general overview of the design verification strategy, • verification methods, results and conclusions
Design Validation	This section may describe studies to demonstrate that container closure system/device requirements conform to the user needs and intended use described previously. This section may include: • description of the techniques employed to validate the design, e.g., mechanical, functional, and/or clinical studies, the rationale for their selection, and results. • any risk analyses conducted to support the rationale and/or choice of validation techniques. • drug product characterization studies used to demonstrate that the container closure system/device fulfills user needs and/or to support label instructions and the rationale for their selection and inclusion.[9]
Manufacturing Process	This section, with reference to 3.2.P.2.3 Manufacturing Process Development, might describe the manufacture of the container closure system/device and the development of that manufacturing process. This section may include: • a description of the approach to the development of the manufacturing process including major design inputs for the manufacturing process e.g., critical quality attributes, risk analyses, production specifications, etc. • a discussion of the final assembly process for the container closure system/device and how the container closure system/device assembly

[8] E.g., the relevant ICH guidelines, FDA guidances, EMEA/Health Canada guidelines.

[9] For ease of use, the current FDA, EMEA and Health Canada guidance on drug product characterization studies are summarized in Tables 1 and 2. It is not within the purview of this document to recommend specific characterization studies for OINDP. Tables 1 and 2 are not intended to be inclusive of all possible characterization studies; other studies may be more appropriate for a particular drug product. It is the responsibility of the sponsor to determine which characterization studies to conduct for a particular drug product in question.

Proposed Section Title	Content
	process and the drug product manufacturing process interact (e.g., during filling) • a discussion of any design or manufacturing process changes made during scale-up from initial to final commercial design. These may be discussed in terms of their impact on the product's quality attributes. As an example, a risk assessment for advancing from single to multiple cavity tooling may be included. • validation studies conducted to demonstrate the ability of the manufacturing process to reliably produce a container closure system/device with the appropriate quality.

Where the information described in the table above is available to regulators via other documentation (*e.g.*, DMF, 510k, CE mark), those submissions may be referenced.

3.2.P.2.5 Microbiological Attributes

See ICH Q8 for further guidance.

3.2.P.2.6 Compatibility

For a nebulized drug product, if the product is to be administered with another inhalation product, consider addressing the compatibility of the drug product to provide appropriate and supportive information for the labeling.

TABLE 1
FDA DRUG PRODUCT PERFORMANCE CHARACTERIZATION STUDIES[10]

Study	MDI	DPI		Nasal Spray	Inhalation Spray	Inhalation Solution/ Suspension
		Device-Metered	Pre-Metered			
Relevant to Label/Instructions						
Stability	X	X	X	X	X	X
Priming/Repriming	X	X		X	X	
Cleaning Requirements	X	X	X	X	X	
Use/Misuse						
Temperature cycling	X			X	X	X (suspension)
Effect of Resting Time	X				X	
Dose Build-up and Flow Resistance		X	X			
Effect of Orientation		X	X	X	X	
Effect of Patient Use		X	X			
Device Ruggedness/ Robustness	**P**	**P**	X	X	X	
General Properties						
Drug Deposition on Mouthpiece/ Accessories	X	**P**	**P**		**P**	
Effect of Storage on PSD	X	X				X (suspension)
Profile of Actuations Near Exhaustion	X	X[11]		X	X	

[10] Based on FDA Draft MDI/DPI Guidance (available at http://www.fda.gov/cder/guidance/2180dft.pdf) and Nasal Spray and Inhalation Solution, Suspension, and Drug Products Guidance (available at http://www.fda.gov/cder/guidance/4234fnl.pdf). Only studies relevant to the drug product performance (formulation, container closure system, and device if included) have been included.

[11] For device-metered DPIs that do not incorporate a locking mechanism to prevent use after the labeled number of actuations.

Study	MDI	DPI		Nasal Spray	Inhalation Spray	Inhalation Solution/ Suspension
		Device-Metered	Pre-Metered			
Plume Geometry	X			X	**P**	
Microbial Challenge	X				X (device-metered, aqueous- based)	
In Vitro Dose Proportionality[12]	X	X	X	X	X	
Effect of Varying Flow Rates	X	X	X		X	
Leachables[13]	X			X	X	X
Effect of Moisture	**P**	X	X			
Photostability[14]		X	X	X	X	X
Fill Weight		X				
Preservative Effectiveness[15]				X	X	X
Characterization of Nebulizer Specified in Labeling (Delivered Dose and PSD)						X

P = Suggestions from individuals at ONDQA, and are pending further Working Group discussions

[12] For products with multiple-strength doses

[13] While not specifically referenced in the Product Characterization section of the FDA Guidances, L&E studies as discussed in the Container Closure section of the Guidance are included in this table because they are a key study related to product performance. Note that PQRI L&E Best Practices propose that one time L&E studies be performed for DPIs only if extractables of safety concern are identified at the AET level from components that have long-term contact with the drug product. The Best Practices propose that leachables studies are not required for inhalation solutions if extractables studies performed on direct formulation contact container closure system materials yield no extractables at Final AET levels, or no extractables above final AET levels with safety concern; and if there is no potential for migration of organic chemical entities through the unit dose container into the drug product formulation.

[14] If warranted; *e.g.*, if formulation is enclosed in clear blisters or capsules.

[15] If warranted, *i.e.*, if the drug product contains a preservative.

TABLE 2
EMEA/HEALTH CANADA DRUG PRODUCT PERFORMANCE CHARACTERIZATION STUDIES[16]

Pharmaceutical Development Study	Pressurised Metered Dose Inhalers	Dry Powder Inhalers		Products for Nebulisation		Non-Pressurised Metered Dose Inhalers
		Device-Metered	Pre- Metered	Single Dose	Multi-Dose	
Relevant to Label/Instructions						
Shaking requirements	X[17]			X[17]	X[17]	X[17]
Initial & re-priming requirements	X					X
Cleaning requirements	X	X	X			X
Use/Misuse						
Actuator / mouthpiece deposition	X	X	X			X
Low temperature performance	X					
Performance after temperature cycling	X					X
Effect of environmental moisture	X	X	X			
Robustness	X	X	X			X
General Properties						
Physical characterisation	X[17]	X	X	X[17]	X[17]	X[17]
Minimum fill justification	X	X	X	X	X	X
Extractables / Leachables	X			X	X	X
Delivered dose uniformity & fine particle mass through container life	X	X	X			X
Delivered dose uniformity & fine particle mass over patient flow rate range		X	X			
Fine particle mass with spacer use	X					
Single dose fine particle mass	X	X	X			X

[16] From Joint EMEA/Health Canada Guidance for Industry on Pharmaceutical Quality of Inhalation and Nasal Products. Available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/inhalationnas_e.html#3.

[17] For suspensions

Pharmaceutical Development Study	Pressurised Metered Dose Inhalers	Dry Powder Inhalers		Products for Nebulisation		Non-Pressurised Metered Dose Inhalers
		Device-Metered	Pre- Metered	Single Dose	Multi-Dose	
Particle / droplet size distribution	X	X	X	X	X	X
Drug delivery rate and total drug delivered				X	X	
Delivery device development	X	X	X	X	X	X
Preservative effectiveness / efficacy				X[18]	X[18]	X[18]
Compatibility				X	X	

[18] If a preservative is present

APPENDIX A: GLOSSARY

Container Closure System: Primary and secondary packaging components that together contain and protect the formulation. The container closure system may serve as a delivery device, as in the case of an MDI.[19]

Critical Components: Drug product contact components and components that are critical to the delivery of the drug product. Also: primary components.

Critical Quality Attribute: An attribute of the formulation, container closure system, device, or product that is essential to achieve the desired efficacy or safety protocol of the drug product.

Critical Process Parameter: An aspect of the manufacturing process that is essential to achieve a product with the identified critical quality attributes.

Control Strategy: A system that ensures that the critical quality attributes of the product are met. This system might address variables such as incoming materials, process parameters, and packaging and storage.

Design Attribute: A qualitative or quantitative feature of the container closure system or device design, e.g., dimensions or composition.

Design Controls: An interrelated set of practices and procedures that are incorporated into the design and development process (i.e., a system of checks and balances), and that make systematic assessment of the design an integral part of development. [20]

Design Input: The physical and performance requirements of a device, product, or process that are used as a basis for the device, product, or process design.[20]

Design Output: The results of a design effort at each design phase and at the end of the total design effort. [20]

Design Requirements: The physical and performance requirements of a device that are used as a basis for device design. [21]

Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of

[19] Based on FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics (Available at http://www.fda.gov/cder/guidance/1714fnl.htm) and Joint EMEA/Health Canada Guidance for Industry on Pharmaceutical Quality of Inhalation and Nasal Products (Available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/inhalationnas_e.html#3).

[20] Adapted from FDA CDRH Guidance for Industry on Design Controls. Available at http://www.fda.gov/cdrh/comp/designgd.html

[21] FDA CDRH Guidance for Industry on Design Controls. Available at http://www.fda.gov/cdrh/comp/designgd.html

the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.[22]

Design Validation: means establishing by objective evidence that device specifications[23] conform with user needs and intended use(s).[21]

Design Verification: means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled. [21]

Device: The sum of component(s) of the container closure system responsible for delivering the drug to the respiratory tract (inhalation product) or the nasal and/or pharyngeal region (nasal product).[24]

FMEA: Failure mode effect analysis is a method that examines potential failures in products or processes and their causes. It helps select remedial actions that reduce the consequences from a systems failure. It may be applied to, ***e.g.***, a design or a process.

Intended Use: The anticipated patient population characteristics and needs, environmental conditions, and any other critical factors under which the container closure system, device, and final product are expected to function.

OINDP: Orally inhaled and nasal drug product(s).

Overage: A fixed amount of the drug substance added to the formulation in excess of the label claim to compensate for product losses.

Overfill: A fixed amount of the formulation added to the drug product in excess of the labeled content to ensure delivery of the dose.

Risk Management: The systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and monitoring risk**.**

System Risk Analysis: A procedure to identify and reduce the risks associated with the product during intended use. The risk analysis is conducted from the perspective of the user but focuses on the failure modes associated with the device. The risk analysis must also consider and include potential foreseeable misuse.

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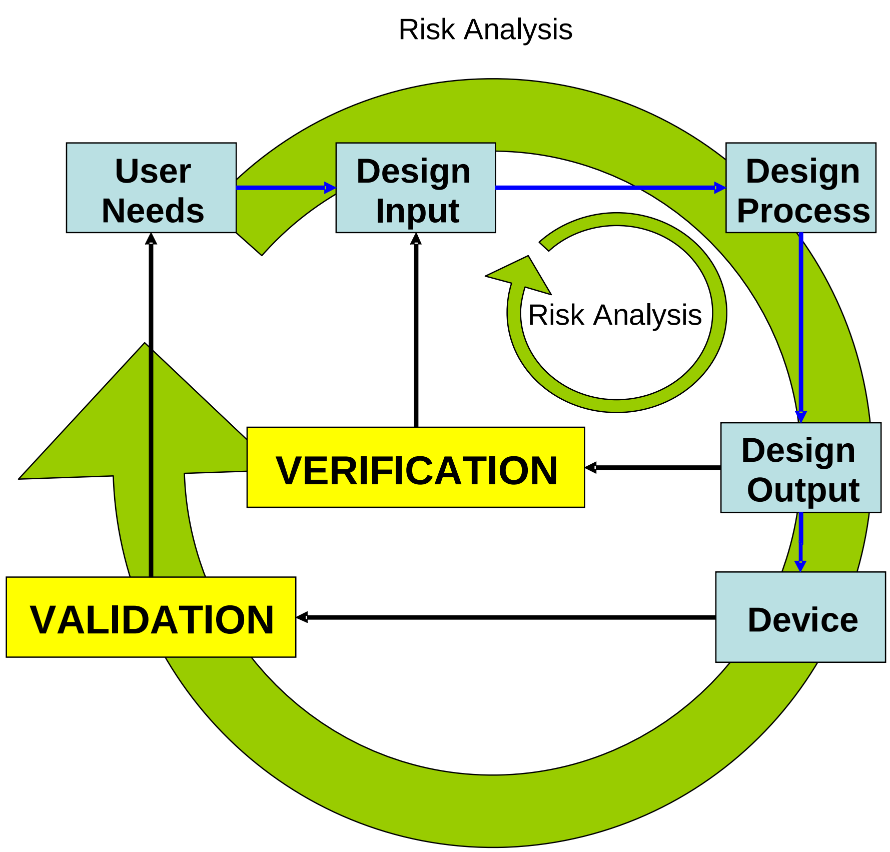
[22] ICH Q8. November 2005. Available at http://www.ich.org/LOB/media/MEDIA1707.pdf.

[23] As defined in ISO 9000:2005 Quality management systems -- Fundamentals and vocabulary (Available at http://www.iso.org/iso/en/CatalogueDetailPage.CatalogueDetail?CSNUMBER=42180&ICS1=3&ICS2=120&ICS3=10).

[24] Joint EMEA/Health Canada Guidance for Industry on Pharmaceutical Quality of Inhalation and Nasal Products. Available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/inhalationnas_e.html#3.

APPENDIX B: DESIGN CONTROLS[25]

The figure below depicts design controls, which are typically used in device development, and the role of risk analysis in this process. This figure may be helpful in understanding the container closure system/device design process. Device development is an iterative process: the user needs, or intended use, are first defined and then translated into specifications, which become the design inputs and are used to develop the device design. This design process should result in a prototype, drawing, or blueprint of the device, which is then verified to ensure that it meets the design inputs originally specified and validated against the user needs originally defined. If the deign inputs or user needs are not met, the design process, followed by verification and validation, is repeated until the design output fulfills all requirements, at which point the cycle stops. Risk analysis is a key element in every step of this process; it helps to define the user needs, identify and manage potential areas of risk, and identify key quality attributes.



[25] Adapted from Figure 1, FDA Guidance for Industry: Design Controls for Medical Device Manufacturers, CDRH, March 1997, and originally used with permission of the Medical Devices Bureau, Health Canada. FDA Guidance endorsed by the Global Harmonization Task Force June 1999. Available at: http://www.fda.gov/cdrh/comp/designgd.html