Best Practices in Device Design for Orally and Nasally Inhaled Products (OINDP)

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Summary

Background: The design and development of the delivery device component of an orally inhaled and nasal product (OINDP) are complex, requiring the implementation of national regional and international standards to ensure compliance with increasingly rigorous regulatory requirements.

Methods: The Device Sub-Team of the European Pharmaceutical Aerosol Group (EPAG) has examined the range of guidance documentation currently applicable to the design and development of all classes of orally inhaled products (OINDPs), with the intention of providing a summary of best practices.

Results: A hierarchy of pertinent International (ISO) standards has been identified, covering quality management systems at the highest level, the design/development and risk assessment processes at the next level, followed by detailed device class-specific standards and a separate standard covering biological evaluation at the lowest level. The 'waterfall' model developed originally by the USFDA covering the design process from initial ideas through prototype development to commercial product, is enhanced to include a round of assessment post-marketing that checks if patient needs have been met. This addition is in harmony with current regulatory guidance to include human factors throughout the process. Lastly, a mind-map considering the interrelationships between patient needs /user requirements and critical aspects forming the OINDP design input has been developed.

Conclusions: The developer of the device component of a new OINDP can make use of the guidance given herein to establish best practices applicable to the user requirements specification for this particular product.

Introduction

The design and development of the delivery device component of an orally inhaled and nasal product (OINDP) are closely inter-related as the device components have to be capable of delivering the inhaled medication reliably and with high precision throughout the life of the OINDP. There is an increasing emphasis by the regulatory agencies involved with the licensure of the product on evidence being presented in the dossier that the device part has been developed following a number of national and international standards covering factors, such as failure mode analysis and prevention associated with risk assessment for potential failures. Furthermore, these agencies are expecting assessments that the device will perform effectively in the hands of the patient, using human factors analysis-based techniques. As a result, the device design team for a new OINDP is faced with a bewildering array of procedures that need to be followed in order to accumulate the evidence required for eventual approval of the product. This examination of best practices associated with device design for all classes of OINDP has been undertaken by the Devices Sub-Team of the European Pharmaceutical Aerosol Group (EPAG) to serve as a roadmap for device developers to follow.

Overview on Current Regulatory Status

The inhalation device component that enables transportation of the medicinal product to the patient is, with the exception of nebulizing systems, part of an OINDP product. However, the demarcation between drug product and medical device seems to be vague.

In Europe, orally inhaled products (OINDPs), i.e. pMDI, DPI, non-pressurised metered dose inhalers etc. are regulated as medicinal products by EC Directive 2001/83/EC. However, generally applicable devices, such as non-pressurised metered dose inhalers or pneumatic and electrical nebulizers, are covered by the Medical Device Directive (93/42/EEC) and its 2007 amendment (2007/47/EC). Although the demarcation between the two Directives is defined in MEDDEV 2.1/3 rev.3, similar design and development principles apply for all inhalation or nasal devices including e.g. nebulizers, pMDI-spacer/valved holding chamber (S/VHC) combinations, mouthpieces or nasal spray nozzles.

In the United States, most OINDPs are treated as 'combination products' in accordance with the Food and Drug Administration (FDA) definition in 21CFR3.2(e). The differentiation between drug product and medical device is made according to the primary mode of action: the CDER branch of the FDA is responsible for review if the primary therapeutic effect is by a drug whereas the CDRH branch takes the lead if the effect comes from a device [1]. A

guidance developed in 1993 applies for nebulizers, pMDI-S/VHC combinations that come under CDRH review [2]. The FDA further issued the final rule on the current good manufacturing practice (cGMP) requirements applicable to combination products in early 2013 under 21CFR4.

In Japan, Pharmaceutical Affairs Law (PAL) covers regulations on pharmaceuticals, medical devices and cosmetics. In consequence, these are regulated by the Minister of Health, Labour and Welfare (MHLW). Nebulizers for example are regarded as Class II, i.e. controlled medical devices. Thus the Pharmaceuticals & Medical Devices Agency (PMDA) requires e.g. nebulizers to be certified by a registered certification body.

Similar differentiation is established in other territories. As an effort to harmonize regulations, in particular in view of global manufacturing and supply chains of medical devices, the International Medical Device Regulators Forum (IMDRF) has been founded recently [3]. Furthermore, medical devices has become on the agenda of WHO's Global Initiative on Health Technologies (GIHT) for increasing the access of patients to high quality, safe and effective medical devices [4].

Thus the inhalation device is seen as being an "integral" part of the OINDP drug product, but relevant parts of medical device regulations have to be applied, in particular with relevance for safety and efficacy. As the burden of proof is on the drug product manufacturer, pharmaceutical companies developing OINDP products may prefer the device company to follow good management practices confirmed by ISO certification. The implementation of the ISO standards is commonly accepted as documentation system ensuring compliance with most if not all national medical device regulations, for example:

- Europe: 93/42/EC Medical Device Directive
- US: 21CFR820 Medical Devices - Quality System Regulation
- Canada: MDR/SOR98-282 Medical Devices Regulation
- Japan: Pharmaceutical Affairs Law (PAL) regulations

The most important ISO standards applicable in the development process of the device component of any OINDP are shown in Figure 1.

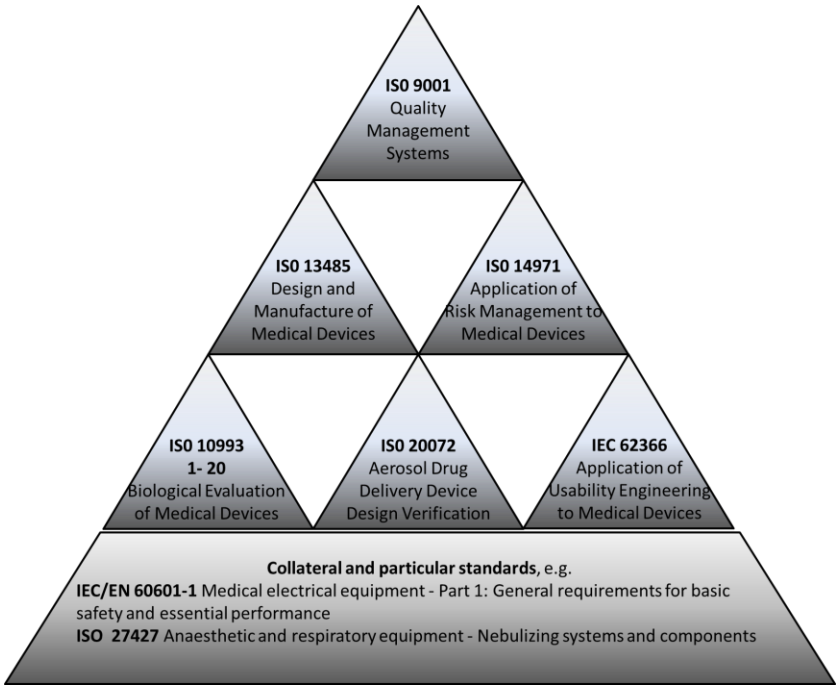

Figure 1 - Hierarchy of ISO Standards Applicable in Device Development and Manufacture

The 'Waterfall Model' of Device Development

These regulations and standards enforce the device development to be embedded in and managed by a Quality Management System (QMS) and to be pursued in a structured approach as outlined in the FDA 'Waterfall Model' of the device development process (21CFR820.30) [5].

An amended version of the FDA 'Waterfall Model' is proposed (Figure 2) to include patient use and feedback, as well as the design life cycle of OINDP products, since routine production and change controls essentially follow the same principles [6]. Furthermore, it is becoming recognized by regulatory agencies that patient feedback as well as human factors analysis form a key part governing the evolution of a given product [7].

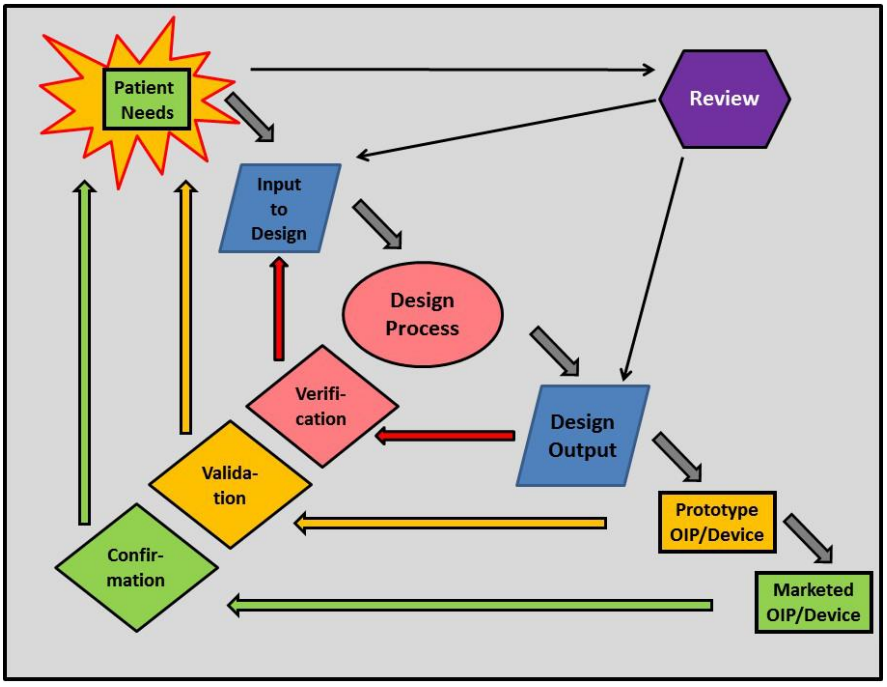

Figure 2: Amended Waterfall Model for Device Development and Manufacturing

Summary and Conclusions

This publication brings together best practices with regard to the design process for OINDP devices. This can be a complex process as illustrated by the various aspects to be considered for design input alone for inhalation devices (see Figure 3). Harmonization for regulatory submissions can be beneficial for all stakeholders and referring to and applying the various regulations, guidances and standards outlined in this publication should facilitate the device development process. The design process for OINDP products requires the device developing company to define the device aspects and requirements in view of the foreseen route of delivery. Identified patient and care giver needs (user requirements) plus company concept documents (research, marketing, IP, etc.) all form part of the documentation that leads to the development of design requirement specifications. The complexity of aspects to be considered for design input is illustrated by Figure 3.

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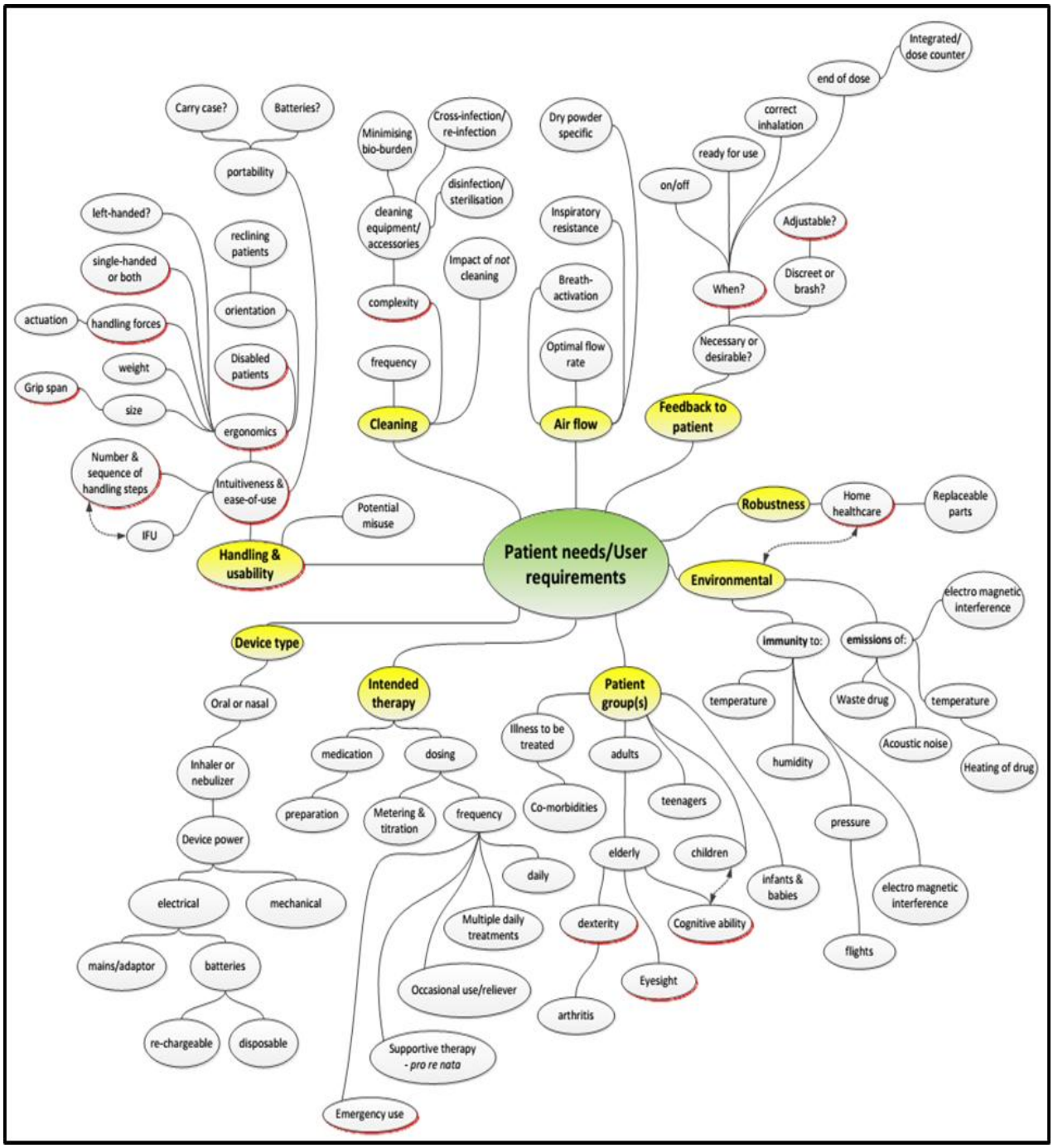

Figure 3: Aspects to be Considered for Design Input of Inhalation Devices

Inputs highlighted with a red line indicate those concerned with usability engineering and show the multi-faceted and cross-functional nature of design input.