

Regulatory Expectations For User Testing

Setting the Regulatory Scene on User Studies

P. Lucas (Pfizer) on behalf of IPAC-RS Device Working Group



IPAC-RS 2011 Conference

Regulatory Expectations- Themes

- **What regulations and standards apply to user testing ?**
- **Risk Management and User Studies**
- **How do expectations differ across patient populations ?**
- **Post-market Surveillance – The market as the true user test ?**
- **What do we understand about user testing for Generic Switching and Patient Compliance ?**




IPAC-RS 2011 Conference

The position of the user in design and regulation has evolved


User Focused Philosophy

Yesterday:
 The device, instructions and labelling have been designed to enable the user to deliver the drug and its supplies. unintentional misuse.


IPAC-RS 2011 Conference  2

Medical Device Regulation in Europe

- Medical devices regulated under Medical Device Directive (MDD) 93/42/EEC(as amended)
 - Compliance with the Essential Requirements (Annex 1) is required
- Inhalers are governed either under MDD or as Medicinal Products Directive (2001/83/EC)




Medical Device Directive
(93/42/EEC) as amended



Medicinal Products
Directive 2001/83/EC
as amended

Except for devices governed under 2001/83/EC:
 “.....the relevant essential requirements of Annex I to this Directive [the MDD] shall apply as far as safety and performance-related device features are concerned.”

Key point: Whether governed under MDD or MPD all devices shall meet the relevant Essential Requirements of Annex 1 of the MDD

IPAC-RS 



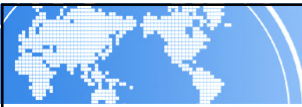
Importance of users and user testing has evolved in regulation

Yesterday:

- **Original Text from 93/42/EEC (ESSENTIAL REQUIREMENTS - Annex 1)**
*“ The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, **they will not compromise the clinical condition or the safety of patients, or the safety and health of users** or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety”.*

Today:

- **Annex 1 Revision (2007/47/EC) text above plus:**
*“.....This shall include: — reducing, as far as possible, **the risk of use error due to the ergonomic features of the device** and the environment in which the device is intended to be used **(design for patient safety)**,
and
consideration of the technical knowledge, **experience, education and training** and where applicable **the medical and physical conditions of intended users** (design for lay, professional, disabled or other users)”.*



The Role of Standards in the MDD

- Article 5 of the MDD outlines the importance of standards in assessment of conformity to the MDD and the Essential Requirements:

“Member states shall presume compliance with the essential requirements referred to in Article 3 [of the MDD] in respect of devices which are in conformity with the relevant national standards”

- For user testing this emphasises the importance of standards e.g.:

ISO 14971: Medical Devices – Application of Risk Management to Medical Devices

ISO 62366: Medical Devices- Application of Usability Engineering to Medical Devices



Labelling

Information conveyed by package leaflets is now required to meet additional requirements*

- **Key points from Article 59(3) and Article 63(2) of 2001/83/EC (as amended):**

"The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use."

"The package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals."

- ♦ **This type of user testing will answer:**

- Can the user locate information ?
- Is the language used suitable?
- Can user understand the instructions ?
- Is the text clear ?

Key Point: Correct device use cannot be assumed from instruction comprehension

* *Guideline On The Readability Of The Labelling And Package Leaflet Of Medicinal Products For Human Use Rev 1. (2009)*

IPAC-RS 2011 Conference



US Regulatory Expectations: US Code of Federal Regulations describes requirements for device design control which impact user requirements

21 CFR 820.30 Design Controls

(c) Design input: *"Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the users and patient."*

► **Impact:** *Must look at human factors during development. Best achieved through systematic consideration.*

(f) Design verification: *"Each manufacturer shall establish and maintain procedures for verifying the design input. Design verification shall confirm that the design output meets the design input requirements."*

(g) "Design validation shall ensure that devices conform to defined user needs and intended uses, and shall include testing of production units under actual or simulated use conditions."

► **Impact:** *Manufacturers should conduct human factors activities throughout the design program e.g. task/function analyses, user studies, prototype tests.*

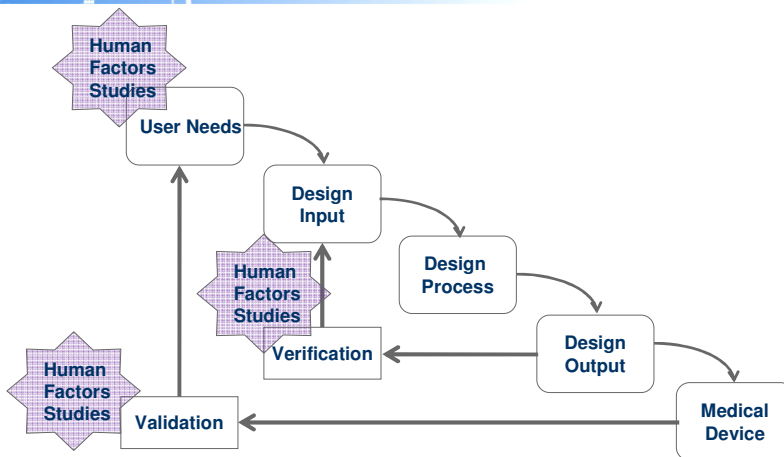
Design validation should be used to demonstrate that the potential for use error has been minimized e.g. testing the device under actual or simulated use conditions.

IPAC-RS 2011 Conference

Adapted from ANSI/AAMI HE 74



User Studies/Human Factors Studies are fundamental in Design Control

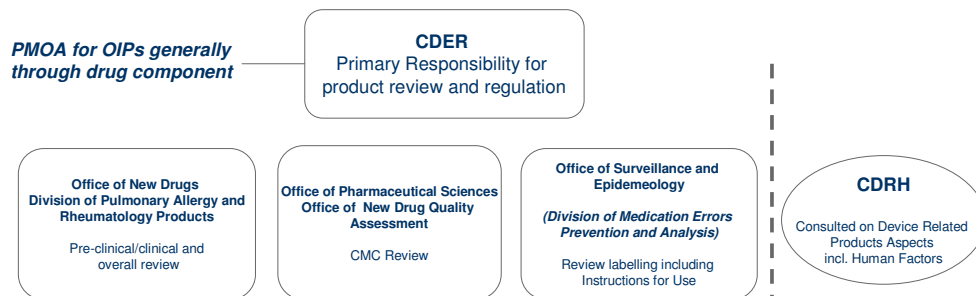


Adapted from FDA Design Control Guidance 1997

US Regulatory Expectations

- Generally OIP products will be considered as **Combination Products** as defined under 21 CFR 3.2. (e)
 - Primary Mode of Action (PMOA) determines the agency component responsible for review and regulation

Multiple Agency Functions are Involved in User Aspects of Product Reviews



With multiple agency groups involved in review of user aspects of a submission there can be challenges in sponsor understanding, co-ordination and access

Key Global Human Factors Standards and Guidance

- ISO 62366 Medical devices – Application of usability engineering to medical devices
- ANSI/AAMI HE74: 2001 Human Factors Design Process for Medical Devices
- ANSI/AAMI HE 75:2009 Human Factors Engineering of Medical Devices
- CDRH Guidance on Human Factors:
e.g. Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management

Guidance for Industry and FDA Premarket and Design Control Reviewers

Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management

Document issued on July 18, 2000

This document replaces the draft guidance document of August 3, 1999, entitled Device Use Safety: Incorporating Human Factors in Risk Management.

► *A key element of the standards and guidance is that Human Factors studies should form part of overall device Risk Management*



ISO 14971 Application of Risk Management to Medical Devices

ISO 14971 describes process for systematic management of risks including those which are use related:

e.g. User interface, use by persons with special needs, conditions of use etc.

RISK CHART	Probability of Occurrence		Hazard Classification				
			Negligible	Minor	Serious	Critical	Catastrophic
P5	Frequent	ALARP	NAC	NAC	NAC	NAC	NAC
P4	Probable	ALARP	ALARP	NAC	NAC	NAC	NAC
P3	Occasional	AC	ALARP	NAC	NAC	NAC	NAC
P2	Remote	AC	AC	ALARP	NAC	NAC	NAC
P1	Improbable	AC	AC	AC	ALARP	NAC	NAC
			Negligible	Minor	Serious	Critical	Catastrophic
			Severity of Harm				

Application of Risk Control Measures Mitigates risk

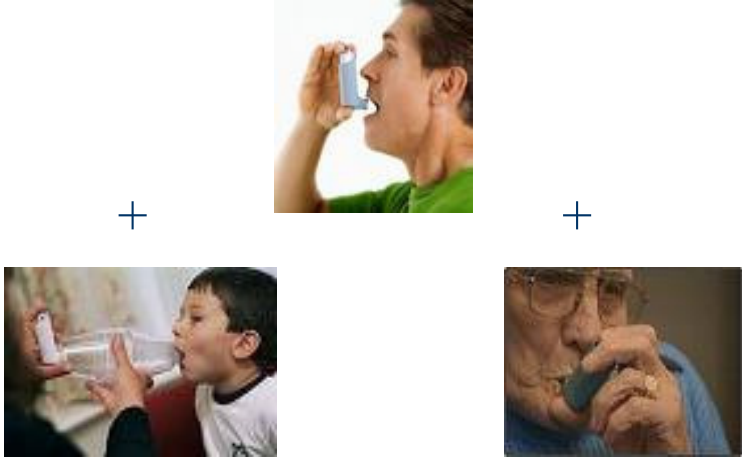
Expected priority for risk control (FDA human factors guidance):

- 1) Design Modification
- 2) User Interface Error Tolerant
- 3) Alert User
- 4) Training

Question: Is design modification always required ? Risk versus practicality ?




Who are the Users ?



+

+

IPAC-RS 2011 Conference




User Challenges for OIP Devices Common to other Devices

OIPs present user challenges common to other devices

- E.g. Can the user hold/operate the device ?
 - ◆ FDA Draft Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment (2007)
 - ◆ "...Device should be durable and within the capability of COPD Patients who may be elderly and may be co-existent arthrides"
 - ◆ "Phase 3 studies should assess durability and whether patient can follow the instructions for use and use the device effectively"
- Is the expectation to conduct Human Factors Studies or will Phase 3 clinical data be acceptable ?
- What do Phase 3 studies provide that HF studies do not ?

IPAC-RS 2011 Conference





Specific User Challenges for OIP Devices

OIPs present additional specific challenges

“...For breath-actuated delivery devices, data should be provided to demonstrate that all target patient groups are capable of triggering the delivery device. This could be evaluated as part of the clinical programme during patient handling studies.....”

CHMP/QWP/49313 Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products

“ A study should be undertaken to determine the emitted dose and particle size distribution as a function of different flow rates at constant volume.....This important study assesses the sensitivity of the device to widely varying flow rates that will be generated by patients of different age and gender and with different severity of disease....”

Draft Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (1998)

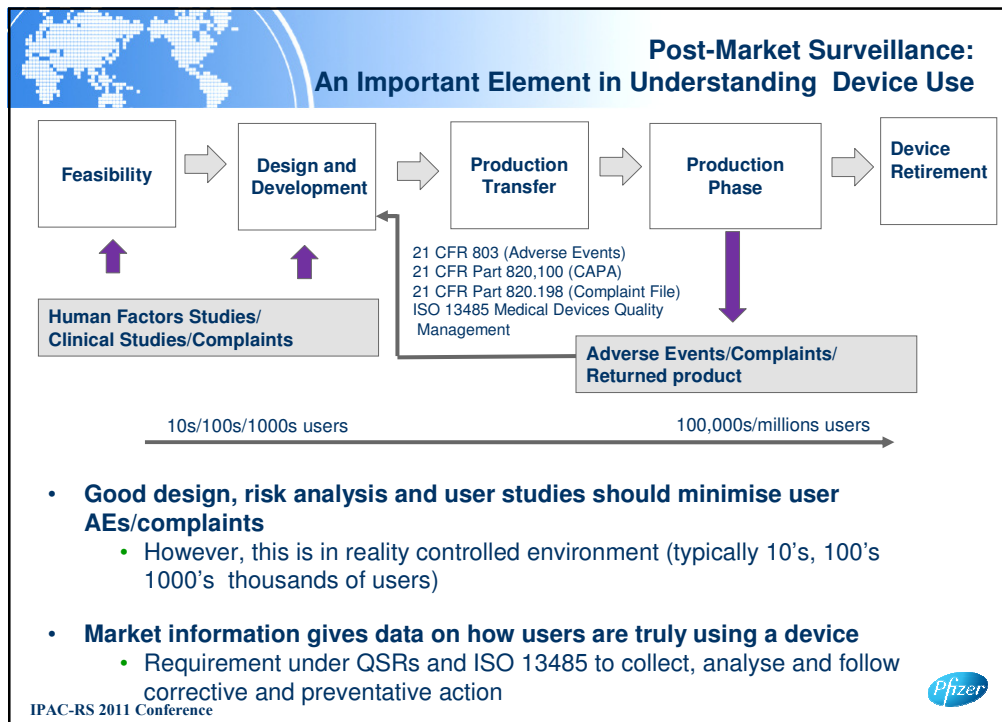


User and Product Interactions

Unlike “device studies” OIP device user studies are also required to evaluate impact of user on the product:

“Studies should be carried out for all types of DPIs to identify the effects of patient use on the characteristics of the drug product. For NDAs, it is recommended that devices used in clinical studies be sent for testing of pertinent performance”

Draft Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (1998)




User Studies for Generic OIPs

- **Increasing focus on introduction of generic OIP products resulting from patent expiries and external payer pressures**
- **Individual country legislation for generic products will differ but generally includes an expectation around “same” or “similar” dosage forms**
- **Guidance developed in the EU and Canada provides some indication of pharmaceutical aspects of similarity**
 - *HC-EMEA Joint Guidance “Pharmaceutical Quality of Inhalation and Nasal Products- App. 1.*
 - *EU Guideline on Clinical Documentation of OIPs (CPMP/EWP/4151/00 Rev. 1)*

What is the regulatory guidance for user studies aimed at assessing device similarity ?

IPAC-RS 2011 Conference




EU Requirements

- **EU Guideline on Clinical Documentation of OIPs (CPMP/EWP/4151/00 Rev. 1) outlines approval requirements**
 - ◆ In vitro data
 - ◆ PK Data
 - ◆ Therapeutic Equivalence

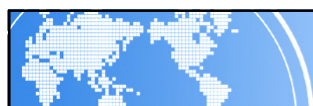
- **Where in vitro data alone is presented to gain approval:**

“Handling of the inhalation devices for the test and the reference products in order to release the required amount of the active substance should be similar.”

- **Questions- What does similarity of handling mean ? Is a comparative study required ? What type of study design ?**

 18

IPAC-RS 2011 Conference



User Studies and Generics in the US


No formal guidance provided but a key paper from authors from OGD and Pulmonary Division.

- “..the assurance of interchangeability of DPIs should take into consideration patient compliance. Similarity of the device shape and equivalence in the design and operating principles are expected to be important for ease of patient use” *

- Questions that remain to be answered
 - ◆ What types of studies/What study design would be required to confirm interchangeability ?

 - ◆ What constitutes an appropriate level of interchangeability ?

*“In Vitro Considerations to Support Bioequivalence of Locally Acting Drugs in Dry Powder Inhalers for Lung Diseases”
Sau Lawrence Lee, Wallace P. Adams, Bing V. Li, Dale P. Conner, Badrul A. Chowdhury and Lawrence X. Yu. Pharm. Res, 11 (3), 2009.

 18

IPAC-RS 2011 Conference



Key Points and Questions

- **Regulatory environment has moved from a product focused approach to a user focused philosophy**
 - Independent of region there is a regulatory expectation to ensure and demonstrate usability of a device by users.
- **The assessment of device and instruction usability by regulators can be complex and clarity to sponsors on process would be beneficial**
- **Which is the most important assessment – Phase 3 clinical studies or Human Factors Studies ?**
- **What questions can user studies answer/need to answer with respect to device similarity for generic OIPs ? What is the expectation for study design ?**



Acknowledgements

IPAC-RS Device Working Group

John Hart

Paul Lafferty