



Track D

Device Design Similarity and Testing Needed to Support Device Changes

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Device Survey

Where did it come from?

As a follow up to the PQRI Bioequivalence conference (Feb 2009) the IPAC-RS Device Working Group was asked to consider current attitudes to device changes

What is it?

The survey aims to explore the practice and perception of the required level of testing when device changes are introduced during inhalation/nasal product development or post-approval



What are its objectives?

- Establish a view on the 'as is' situation in relation to device changes
- Move towards consensus on appropriateness of in-vivo and in-vitro testing, risk management, QbD, self-regulation for device changes
- Highlight areas where regulatory requirements may differ from what is perceived to be technically required



Medical Devices vs Medicinal Products

Medical Devices are often more varied and technically complicated than Medicinal Products and yet as a rule are less prescriptively regulated

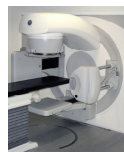
- Principle of Proportionality versus the Precautionary Principle



Elastoplast



Contact Lens



Radiation Therapy



Catheter for Angioplasty



Drug Eluting Stent



Artificial Heart Valve

Medical Device regulation is based on

- Risk Management approach to design, development and market supply
- Manufacturer taking responsibility to ensure products meet relevant safety, quality, performance or efficacy requirements
- Reduced direct oversight from Competent Authorities

Definitions



- Risk
 - Combination of the probability of occurrence of harm and the severity of that harm*

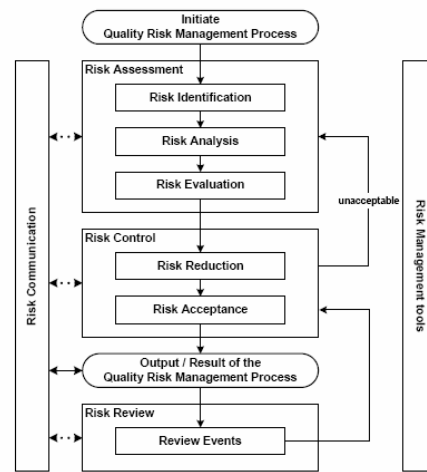
- Quality by Design
 - Systematic process to build quality into a product from the inception to final output

* ISO 14971:2007, definition 2.16

Risk Management – Convergence of Approaches



ISO 14971
(Medical Devices)



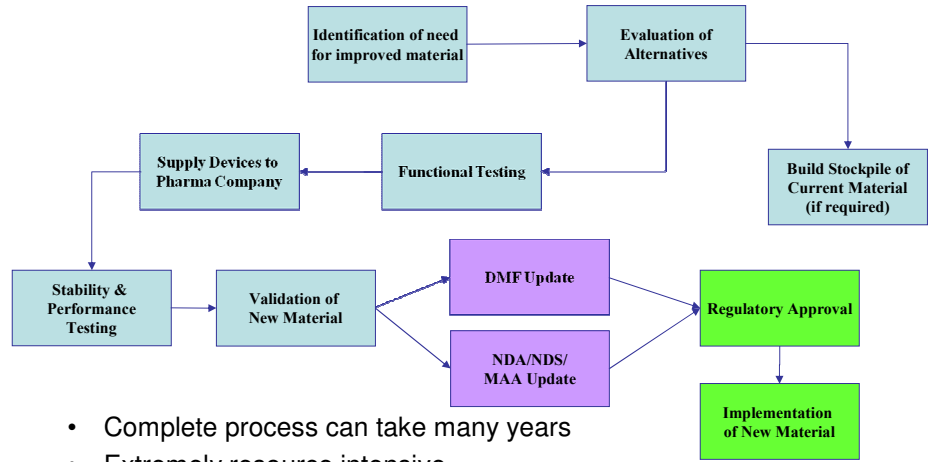
ICH Q9
(Medicinal Products)

Differences remain.....



**Change to Plastic used in Inhalation Device
(e.g. actuator in a pMDI)**

Medicinal Product



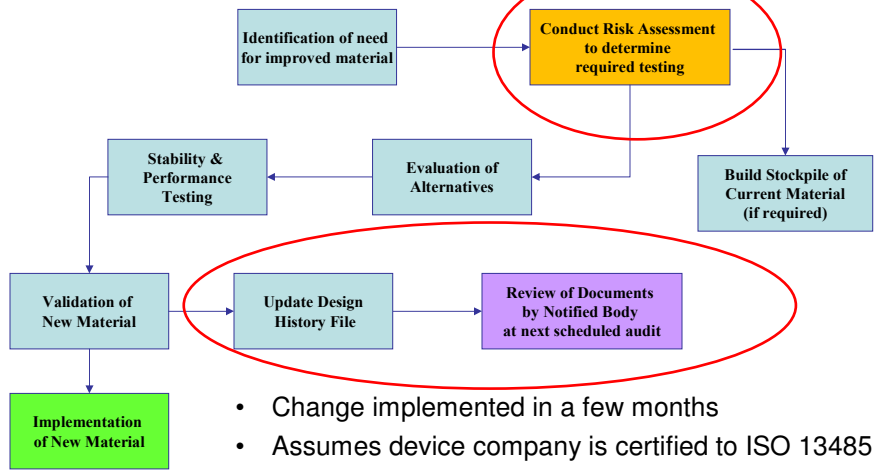
- Complete process can take many years
- Extremely resource intensive

Differences remain.....



**Change to Plastic used in Inhalation Device
(e.g. component in a refillable nebulizer)**

Medical Device



- Change implemented in a few months
- Assumes device company is certified to ISO 13485

Device Survey



Fifteen scenarios covering three main types of device changes:

- Design
- Materials
- Manufacturing process

Scenarios based on real experience derived from cross industry contributors

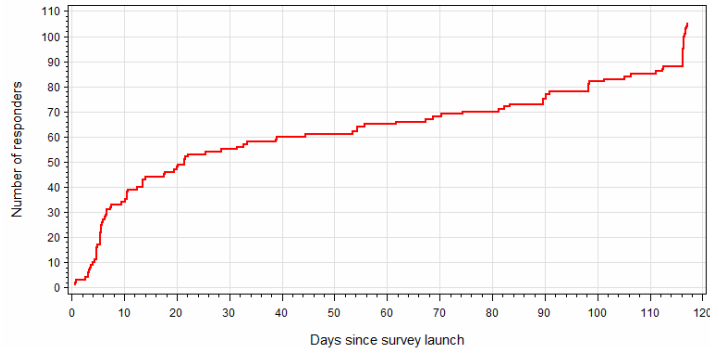
- Categorised to cover main types of device changes
- Distributed across different development phases
- Changes to Innovator vs Generic products

Device Survey



- **Basic background of respondent collected**
- **Same set of information collected for each scenario**
 - **Context (NDA/ANDA)**
 - **Filing route (CBE, Annual Report, etc)**
 - **Stability testing (condition and duration)**
- **For each of 13 non-clinical and 8 clinical tests:**
 - **Would you do this test?**
 - **For what reason (technical/regulatory/both)?**
- **Possibility to comment**

105 responses obtained



Training	N	Sector	N	Region	N	Experience	N
Pha/Bio/Med	36	Government	6	North America	43	< 1 year	4
Che/Phy/Eng	49	Pharma Comp.	67	Europe	51	1-3 years	14
Mat/Stat	4	Device Dev/Manuf.	12	Asia/Pacific	5	4-9 years	29
Reg Affairs	9	Academia/Med Inst	8	Australia	1	10-19 years	44
Other	4	Other	9	Other	2	20-39 years	10
No Answer	3	No Answer	3	No Answer	3	≥ 40 years	1
						No Answer	3

Guide to graphs



- Two graphs for each of the 15 scenarios
- One graph summarize responses to non-clinical test, and one for clinical tests
- Each bar represents the response to a particular test
- The abbreviated test name is given below the bar
- The height of the bar gives the number responders that would do the test, in percent of those answering the question
- The blue portion of the bar shows the proportion responders that would do the test for technical reason only
- The orange portion shows the proportion responders that would do the test for regulatory reason only
- The red portion shows the proportion responders that would do the test for both technical and regulatory reason

Abbreviations – non-clinical tests



MechVer	Mechanical verification
DevRob	Device robustness
Phy&Dim	Physicochemical parameters and dimensional measurements
Filling	Filling Line Trials
EmMass	Emitted Mass (Shot Weight)
DCU	Dose Content Uniformity
APSD	Aerodynamic Particle Size Distribution – ACI or NGI
LungCast	Aerodynamic Particle Size Distribution – Lung cast model
PackInt	Package integrity related tests
Spray	Spray Pattern / Plume Geometry (MDIs)
EXs	Extractables characterization
LEs	Leachables characterization
Other	Other – to be specified

Abbreviations – clinical tests



UserH	User Handling Study
DevVal	Device Validation (Function) Study
PK BE	Pharmacokinetic Bioequivalence Study
PD BE	Pharmacodynamic Bioequivalence Study
ClinEff	Clinical Efficacy Study
ClinSaf	Clinical Safety Study
FlowProf	Flow Profile Measurement
Other	Other – to be specified

Scenario 1



Scenario 1 (of 15)

Focus area	Design Change
Stage	Clinical Phase 3
Description	<p>An inhaled corticosteroid already marketed in a pMDI will be replaced by a DPI using the same active pharmaceutical ingredient (API). The pMDI actuator body is white, with a distinctive coloured mouthpiece cap. The DPI is currently all-white</p> <p>However, for this new product a marketing decision was taken to make the operating button of the DPI the same familiar colour as the pMDI cap. The DPI body and mouthpiece cap remain white. Feedback from patients on the proposed DPI showed that a small number of them thought that the coloured button was in fact the mouthpiece cap and that it was possible (by exerting significant force) to remove it.</p> <p>The desired solution is to keep the coloured button, however; the button would be modified to make it non-removable. Please assess this change in design.</p>

1: DPI operating button change

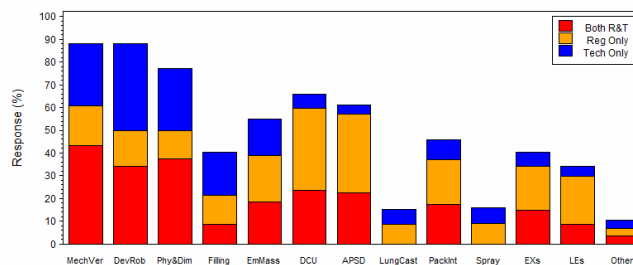


Context	N
NDA or EQ	46
ANDA or EQ	12
No Answer	47

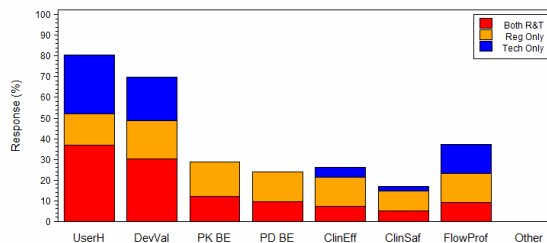
Submission	N
Update IND/CTA	23
PAS or EQ	8
Suppl. CBE30	8
Suppl. CBE	2
Ann. Rep or EQ	5
No Submission	5
No Answer	54

Months	25/60	30/60	40/75
No Test /0	20	21	20
3	7	4	10
6	2	6	9
9	1	1	0
12	5	5	2
18	2	0	0
24	8	3	2
No Answer	60	65	62

Scenario 1: Non-clinical testing



Scenario 1: Clinical testing



Scenario 2



Scenario 2 (of 15)

Focus area	Design Change
Stage	Clinical Phase 2b (dose – ranging) completed and considering a start on clinical Phase 3
Description	A pMDI containing a beta-2- agonist (SABA) is being developed without a dose counter or dose indicator. During development the company decides that such an additional technical feature will be incorporated into the commercial device. The chosen technical solution is to add a proprietary counter which is to be adhered to the base of the can.

2: Addition of MDI dose counter

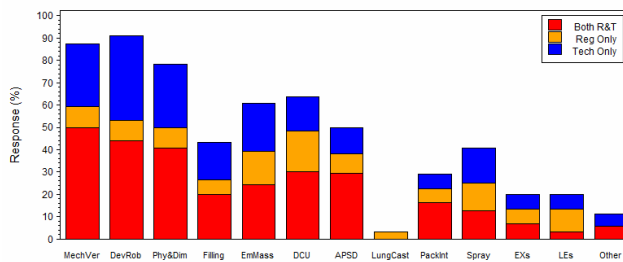


Context	N
NDA or EQ	27
ANDA or EQ	9
No Answer	69

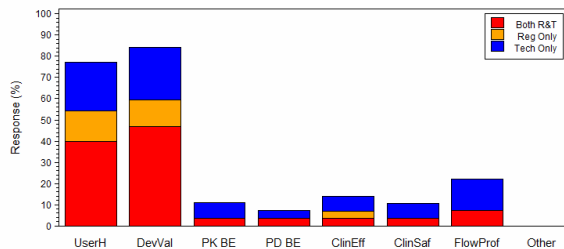
Submission	N
Update IND/CTA	20
PAS or EQ	9
Suppl. CBE30	1
Suppl. CBE	2
Ann. Rep or EQ	1
No Submission	1
No Answer	71

Months	25/60	30/60	40/75
No Test /0	16	19	15
3	3	2	4
6	2	0	13
9	0	2	0
12	3	2	0
18	0	0	0
24	7	3	0
No Answer	74	77	73

Scenario 2: Non-clinical testing



Scenario 2: Clinical testing



Scenario 3



Scenario 3 (of 15)	
Focus area	Design Change
Stage	Clinical Phase 2b (dose – ranging) completed and considering a start on clinical Phase 3
Description	A novel beta-2-agonist inhaled drug product (DPI) is under development. As a result of feedback from intended users and opinions from several focus groups, it is proposed to modify the mouthpiece to be longer and slightly wider.

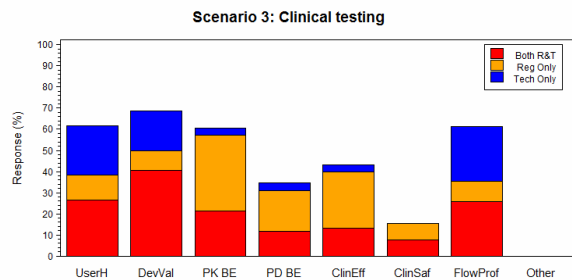
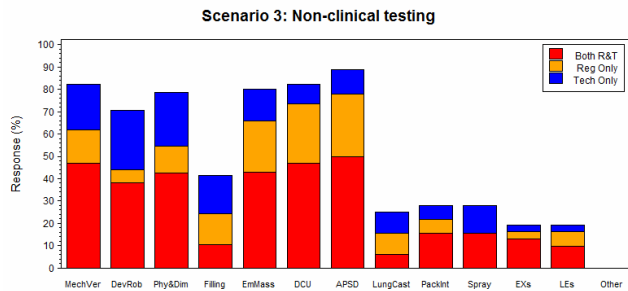
3: DPI mouthpiece change



Context	N
NDA or EQ	30
ANDA or EQ	7
No Answer	68

Submission	N
Update IND/CTA	24
PAS or EQ	4
Suppl. CBE30	2
Suppl. CBE	1
Ann. Rep or EQ	1
No Submission	1
No Answer	72

Months	25/60	30/60	40/75
No Test /0	12	12	12
3	3	3	5
6	3	2	12
9	0	1	0
12	4	6	1
18	0	0	0
24	9	3	0
No Answer	74	78	75



Scenario 4



Scenario 4 (of 15)

Focus area	Design Change
Stage	Up to and including clinical Phase 2a completed and contemplating a start on clinical Phase 2b
Description	A product containing a corticosteroid in combination with a long acting beta-2-agonist is initially developed (for ease and speed of development) as a simple capsule DPI for Phase I studies. Subsequently a multi-dose (reservoir) DPI will be used. In-vitro data shows equivalent performance can be achieved in the DPI and the company wants to minimise time and cost by 'bridging' to the earlier Phase 1 studies conducted in the simple capsule DPI. Evaluate the "bridging" from simple-capsule to multi-dose (reservoir) DPI.

4: Capsule to multi-dose DPI

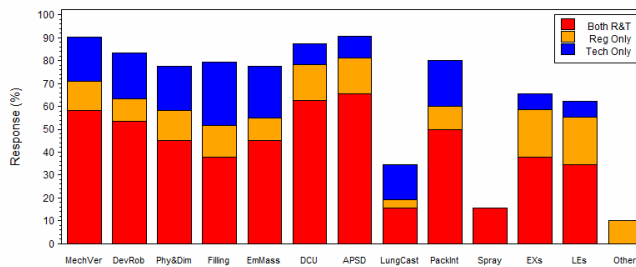


Context	N
NDA or EQ	28
ANDA or EQ	5
No Answer	72

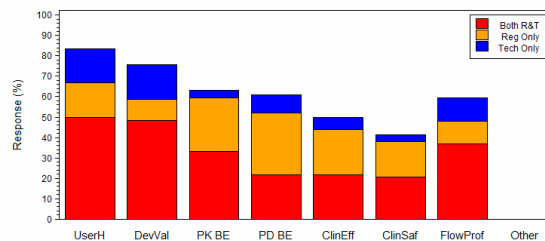
Submission	N
Update IND/CTA	25
PAS or EQ	4
Suppl. CBE30	0
Suppl. CBE	0
Ann. Rep or EQ	1
No Submission	1
No Answer	74

Months	25/60	30/60	40/75
No Test /0	0	3	0
3	4	5	6
6	3	1	17
9	0	0	1
12	3	10	1
18	1	0	0
24	20	7	4
No Answer	74	79	76

Scenario 4: Non-clinical testing



Scenario 4: Clinical testing



Scenario 5



Scenario 5 (of 15)

Focus area	Design Change
Stage	Clinical Phase 2b (dose – ranging) completed and considering a start on clinical Phase 3
Description	A novel DPI is used in the development of a new multi-dose corticosteroid drug product. As part of the industrialisation process a small number of component changes are requested by the automation provider to improve bowl-feeding and assembly. The proposed changes affect only non-patient and non-formulation contact components.

5: DPI components change for automization

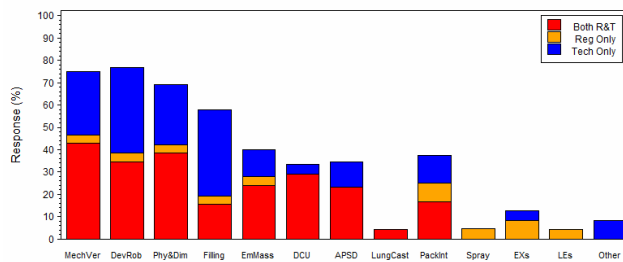


Context	N
NDA or EQ	26
ANDA or EQ	4
No Answer	75

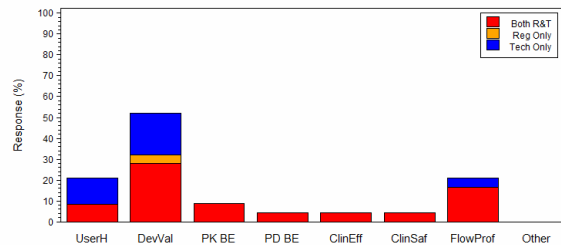
Submission	N
Update IND/CTA	8
PAS or EQ	2
Suppl. CBE30	2
Suppl. CBE	1
Ann. Rep or EQ	7
No Submission	6
No Answer	79

Months	25/60	30/60	40/75
No Test /0	14	16	13
3	2	1	2
6	0	0	5
9	0	0	0
12	0	0	1
18	1	0	1
24	4	2	0
No Answer	84	86	83

Scenario 5: Non-clinical testing



Scenario 5: Clinical testing



Scenario 6



Scenario 6 (of 15)

Focus area	Material change (MDI)
Stage	Fully commercialised product
Description	<p>A corticosteroid pMDI uses a particular design of metering valve from a certain supplier and Phase 3 clinical studies are in progress, as are ICH stability studies.</p> <p>The manufacturer of the base elastomer used to make the valve gaskets/seals makes a change to their change of site of manufacture. The manufacturer initially claims the 2 processes are equivalent hence the material should be the same.</p> <p>When test samples are received it becomes evident that the change has significantly reduced the level of a known toxic extractible and introduced a new extractible peak. After discussion with the elastomer manufacturer it becomes apparent that the differences in process can explain the change in extractible profile.</p> <p>The mechanical and other functional properties of the gaskets/seals and the metering valve are unaffected by the change.</p>

6: Base elastomer manufacturing change

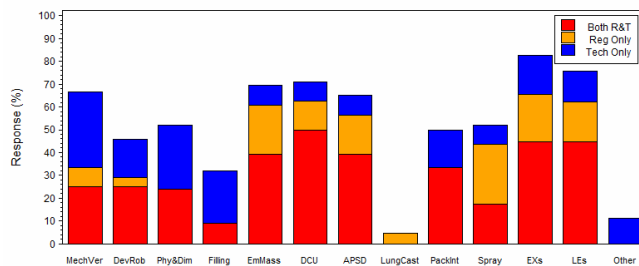


Context	N
NDA or EQ	26
ANDA or EQ	5
No Answer	74

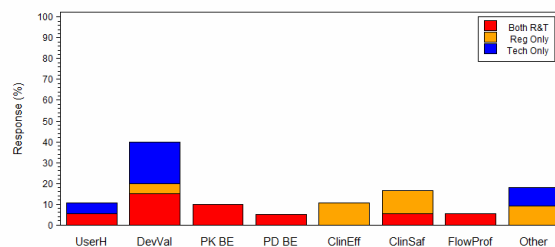
Submission	N
Update IND/CTA	14
PAS or EQ	7
Suppl. CBE30	3
Suppl. CBE	0
Ann. Rep or EQ	3
No Submission	2
No Answer	76

Months	25/60	30/60	40/75
No Test /0	2	6	2
3	1	2	4
6	5	3	16
9	0	0	0
12	5	6	2
18	1	1	1
24	12	3	2
No Answer	79	84	78

Scenario 6: Non-clinical testing



Scenario 6: Clinical testing



Scenario 7



Scenario 7 (of 15)

Focus area	Material Change (Nasal spray)
Stage	Phase 3
Description	The supplier of one of the contact polymers used in a nasal spray pump for a corticosteroid (for seasonal and perennial rhinitis) announces that the source/supplier of one of the polymer additives, the antioxidant BHT, has to be changed. The rest of the polymer manufacturing process remains unchanged and the level of this particular additive also remains unchanged, as does the specification..

7: Polymer additive source/supplier change

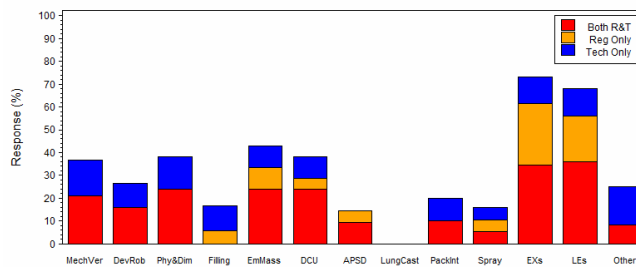


Context	N
NDA or EQ	22
ANDA or EQ	4
No Answer	79

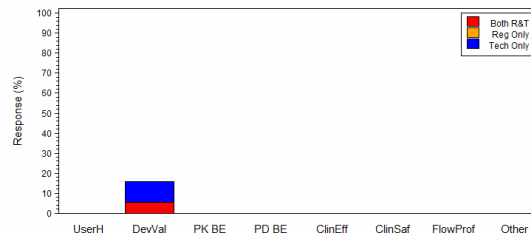
Submission	N
Update IND/CTA	0
PAS or EQ	6
Suppl. CBE30	7
Suppl. CBE	1
Ann. Rep or EQ	5
No Submission	4
No Answer	82

Months	25/60	30/60	40/75
No Test /0	9	12	6
3	2	2	7
6	2	2	10
9	0	0	0
12	2	1	0
18	0	0	0
24	10	2	2
No Answer	80	86	80

Scenario 7: Non-clinical testing



Scenario 7: Clinical testing



Scenario 8



Scenario 8 (of 15)

Focus area	Material Change (DPI)
Stage	Clinical Phase 2b (dose – ranging) completed and considering a start on clinical Phase 3
Description	DEHP, although at very low levels, ($\ll 1\mu\text{g/g}$) is a known extractable from the polypropylene mouthpiece of an inhaler used to deliver a steroid/LABA combination drug. In view of the developing regulatory guidance, there is a potential for the regulatory situation to become increasingly conservative regarding the presence of phthalates. Based on the information provided, the recommendation is to seek an alternative material and the device modified to use this alternative material.

8: Mouthpiece material change

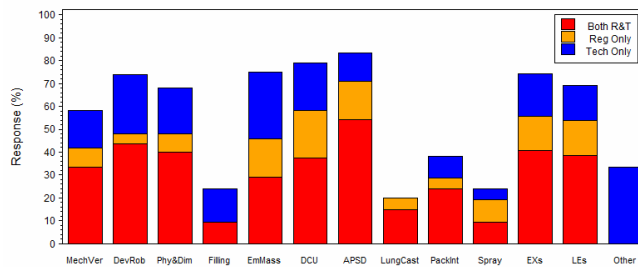


Context	N
NDA or EQ	23
ANDA or EQ	5
No Answer	77

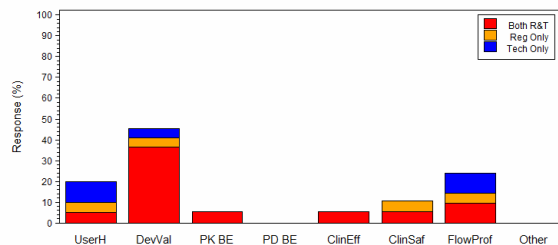
Submission	N
Update IND/CTA	15
PAS or EQ	7
Suppl. CBE30	2
Suppl. CBE	1
Ann. Rep or EQ	1
No Submission	0
No Answer	79

Months	25/60	30/60	40/75
No Test /0	8	12	6
3	3	3	4
6	3	1	10
9	0	0	1
12	1	2	2
18	0	1	0
24	10	2	2
No Answer	80	84	80

Scenario 8: Non-clinical testing



Scenario 8: Clinical testing



Scenario 9



Scenario 9 (of 15)

Focus area	Material Change (Nasal spray)
Stage	Fully commercialised product.
Description	A supplier has changed an ink that is used to print batch code and manufacturing date directly onto the body of the polypropylene bottle containing a decongestant nasal solution.

9: Ink change

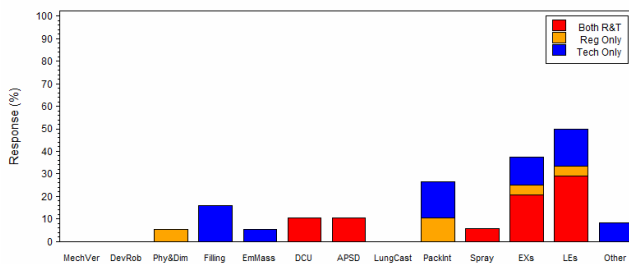


Context	N
NDA or EQ	21
ANDA or EQ	6
No Answer	78

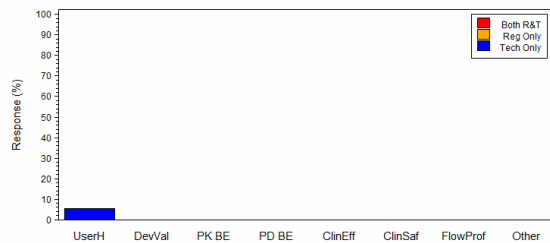
Submission	N
Update IND/CTA	0
PAS or EQ	2
Suppl. CBE30	4
Suppl. CBE	3
Ann. Rep or EQ	8
No Submission	6
No Answer	82

Months	25/60	30/60	40/75
No Test /0	11	12	10
3	2	1	4
6	1	1	6
9	0	0	0
12	0	0	0
18	0	0	0
24	5	2	2
No Answer	86	89	83

Scenario 9: Non-clinical testing



Scenario 9: Clinical testing



Scenario 10



Scenario 10 (of 15)

Focus area	Material Change (DPI)
Stage	Fully commercialised product
Description	<p>A supplier of Polypropylene for a DPI Device is to relocate its manufacturing facility and has announced a three-year project to complete its move and to generate equivalence data. The supplier confirms that it will use identical equipment and processes.</p> <p>A DPI contains this material in the form of non-drug contact components which must be very accurately moulded and also have important friction characteristics.</p> <p>The equivalence data and samples of the resin from the new site will be available six months before the original facility ceases production.</p>

10: PP manufacturing plant relocation

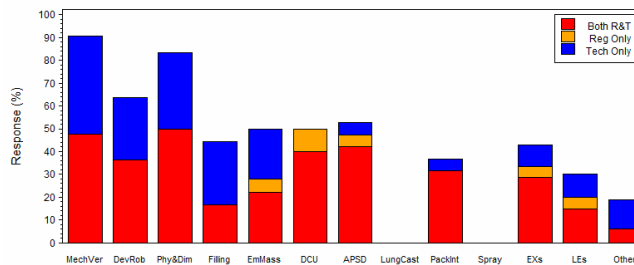


Context	N
NDA or EQ	21
ANDA or EQ	5
No Answer	79

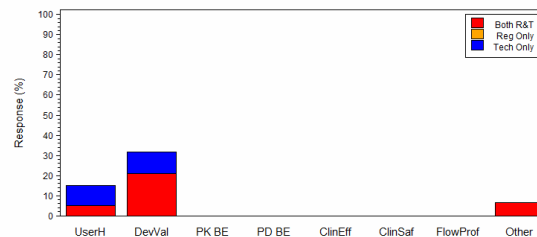
Submission	N
Update IND/CTA	0
PAS or EQ	3
Suppl. CBE30	6
Suppl. CBE	4
Ann. Rep or EQ	8
No Submission	3
No Answer	81

Months	25/60	30/60	40/75
No Test /0	9	11	8
3	2	3	5
6	4	2	5
9	0	0	0
12	0	0	2
18	1	0	1
24	6	3	1
No Answer	83	86	83

Scenario 10: Non-clinical testing



Scenario 10: Clinical testing



Scenario 11



Scenario 11 (of 15)

Focus area	Manufacturing change
Stage	Phase 3
Description	pMDI manufacture (SABA and anti-muscarinic formulations) is to be relocated from a US site to one in the EU. The new location does not have the bespoke cold filling technology used at the donating site and will operate a through-the-valve (TTV) filling process. Thus, there will be a requirement to change the valve used in the pMDI to make it suitable for TTV filling. This valve must be applicable to.

11: MDI valve & filling process change

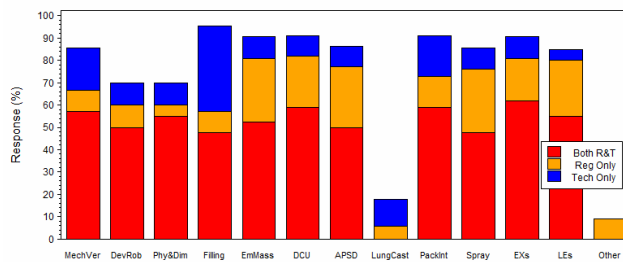


Context	N
NDA or EQ	21
ANDA or EQ	2
No Answer	82

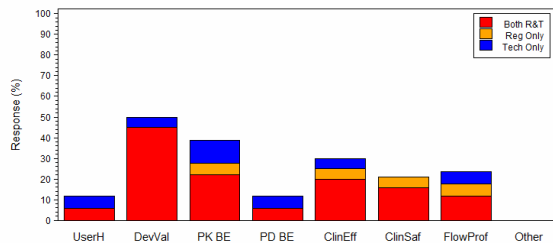
Submission	N
Update IND/CTA	13
PAS or EQ	7
Suppl. CBE30	2
Suppl. CBE	0
Ann. Rep or EQ	0
No Submission	0
No Answer	83

Months	25/60	30/60	40/75
No Test /0	1	4	1
3	3	3	4
6	2	1	13
9	0	0	0
12	2	6	2
18	0	1	0
24	13	4	1
No Answer	84	86	84

Scenario 11: Non-clinical testing



Scenario 11: Clinical testing



Scenario 12



Scenario 12 (of 15)

Focus area	Manufacturing change
Stage	Clinical Phase 2b (dose – ranging) completed and considering a start on clinical Phase 3
Description	<p>Within one year from now, a supplier of a DPI is to close the plant where it currently manufactures the device.</p> <p>The company informs you that it will relocate all of the tooling and manual assembly lines to the new plant, and that this will require minimal validation.</p> <p>However a secondary material conditioning process to reduce static <u>will</u> be completely different at the new site, although the supplier assures you that the new process will produce an “equivalent” result.</p>

12: New material conditioning process

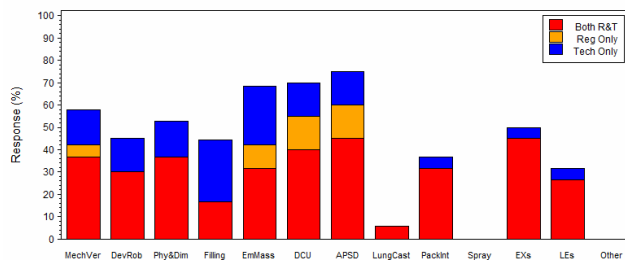


Context	N
NDA or EQ	21
ANDA or EQ	2
No Answer	82

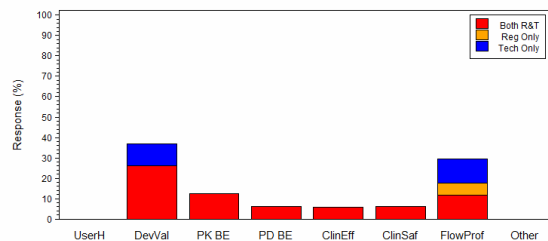
Submission	N
Update IND/CTA	12
PAS or EQ	6
Suppl. CBE30	0
Suppl. CBE	0
Ann. Rep or EQ	2
No Submission	1
No Answer	84

Months	25/60	30/60	40/75
No Test /0	6	8	6
3	3	4	4
6	1	0	5
9	2	0	0
12	2	1	1
18	0	1	0
24	4	2	2
No Answer	87	89	87

Scenario 12: Non-clinical testing



Scenario 12: Clinical testing



Scenario 13



Scenario 13 (of 15)

Focus area	Manufacturing change
Stage	Fully commercialised product.
Description	<p>A manufacturer of a pMDI valves (for a beta-2-agonist (SABA) product), which is to be marketed in the EU, has built a new set of tooling for additional volume production. The current tooling and process is validated and clinical trial devices have been used for Phase 2 trials.</p> <p>Whilst performing the validation on the new tooling they have to make significant changes to the previously validated moulding process in order to meet the components' dimensional specifications.</p> <p>The required changes have gone outside of the original process optimisation "window". How would you deal with this change?</p>

13: Moulding process change

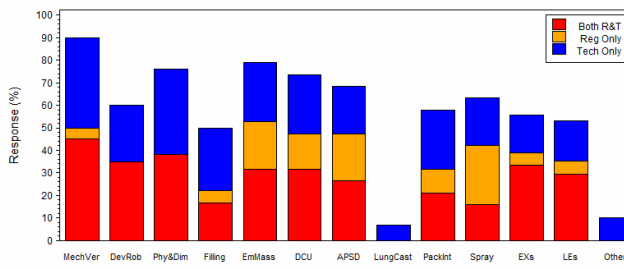


Context	N
NDA or EQ	17
ANDA or EQ	6
No Answer	82

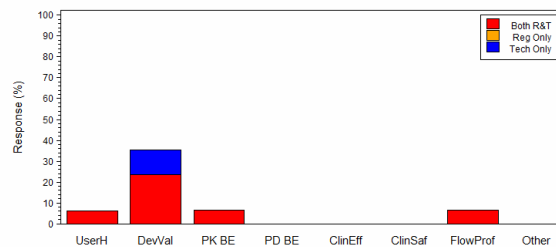
Submission	N
Update IND/CTA	2
PAS or EQ	4
Suppl. CBE30	7
Suppl. CBE	2
Ann. Rep or EQ	3
No Submission	4
No Answer	83

Months	25/60	30/60	40/75
No Test /0	7	10	10
3	4	3	3
6	1	2	6
9	0	0	0
12	3	0	0
18	0	0	0
24	3	1	0
No Answer	87	89	86

Scenario 13: Non-clinical testing



Scenario 13: Clinical testing



Scenario 14



Scenario 14 (of 15)	
Focus area	Manufacturing change
Stage	Phase 3 completed.
Description	<p>A supplier of a DPI currently pending regulatory approval has scaled-up from 2-cavity moulds to higher cavitation moulds containing 16 cavities for production readiness.</p> <p>In addition to increasing the number of cavities, the supplier has made significant technical modifications to the mould layout / design in order to improve moulding efficiency (examples: going from “cold runner” to “hot runner”; changing cooling system; modifying runner layout and design, etc.)</p> <p>These changes may potentially change the functionality and performance of the device. How would you assess this change?</p>

14: Injection mould scale-up

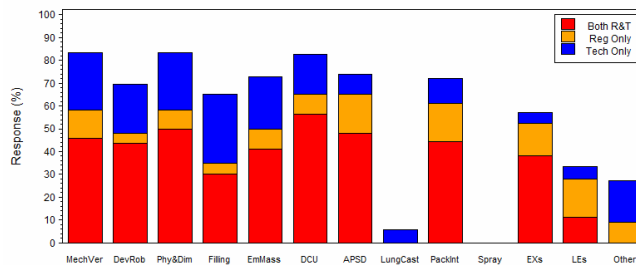


Context	N
NDA or EQ	21
ANDA or EQ	3
No Answer	81

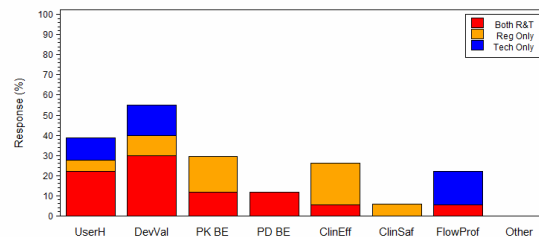
Submission	N
Update IND/CTA	8
PAS or EQ	11
Suppl. CBE30	2
Suppl. CBE	0
Ann. Rep or EQ	1
No Submission	1
No Answer	82

Months	25/60	30/60	40/75
No Test /0	3	7	4
3	4	4	4
6	2	3	10
9	0	0	0
12	3	2	2
18	0	0	0
24	9	3	2
No Answer	84	86	83

Scenario 14: Non-clinical testing



Scenario 14: Clinical testing



Scenario 15



Scenario 15 (of 15)

Focus area	Manufacturing change
Stage	Phase 3
Description	<p>A supplier of a Dose Counter for a corticosteroid pMDI which is currently marketed in the EU has had to make significant changes to the previously validated ultrasonic welding process. Ultrasonic welding is used to weld a plastic window to a Dose Counter main body.</p> <p>The changes to the process are outside of the process validation range. Neither dimensional nor functional requirements were changed and the window is still hermetically sealed to the body.</p>

15: Ultrasonic welding process change

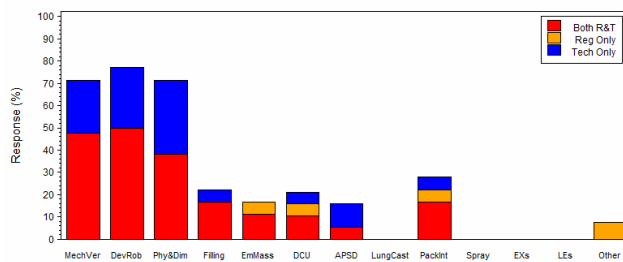


Context	N
NDA or EQ	19
ANDA or EQ	5
No Answer	81

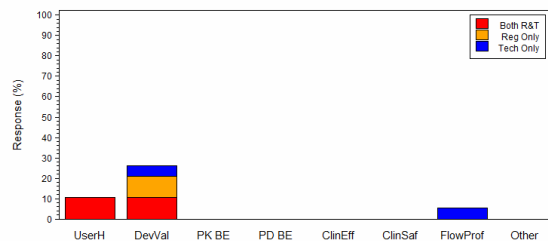
Submission	N
Update IND/CTA	0
PAS or EQ	3
Suppl. CBE30	2
Suppl. CBE	2
Ann. Rep or EQ	7
No Submission	8
No Answer	83

Months	25/60	30/60	40/75
No Test /0	12	14	12
3	1	1	2
6	0	0	4
9	0	0	0
12	0	0	0
18	0	0	0
24	4	1	0
No Answer	88	89	87

Scenario 15: Non-clinical testing



Scenario 15: Clinical testing



Topics for Discussion



Device Changes to OINDP:

- More effective balancing of innovation, customer satisfaction, continuous improvement, Public Health protection and public confidence
- Benefits of more self-regulation of activities, subject to oversight, as in the case of medical devices based on Risk Management and Quality Management Systems
- Are studies always scientifically and technically justified or are they done for purely prescriptive regulatory reasons?
- Who should decide when a scientific and technical justification is adequate and acceptable?
- Would improved Industry performance standards and quality systems provide a mechanism for transparent self-regulation?
- Would a classification system for OINDP device changes help distinguish between those changes that require regulatory approval from those that do not?
- How would you propose classifying OINDP device changes (e.g. fluid path and non-fluid path)?
- Using post-market surveillance and patient/user feedback to optimise our processes