

**European, US and International
Medical Device
Standards and Regulations
Orally, Inhaled and Nasal Drug Products**

*"Doing the Right Thing" in the Changing Culture of Design and Development of
Inhalation and Nasal Drug Products: Science, Quality, and Patient-Focus"*

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Premise:

Medical Devices are often more technically complicated than Medicines and yet as a Rule are less prescriptively regulated

[Principle of Proportionality versus the Precautionary Principle]

Topics:

- | Device-Regulation and the Drug-Device Borderline
- | "Combination" Products
- | Design and Risk Management
- | Postmarket Surveillance

Small Print

The views expressed are those of the presenters and are not necessarily the views of our respective Companies or of the IPAC-RS Membership

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Medical Technology Spectrum

IVD's	Medical Devices	Tissue Engineering	Cell Therapy	Gene Therapy	Biotech	Chemicals
<ul style="list-style-type: none"> • reagents • processors • analysers • proteomics 	<ul style="list-style-type: none"> • prosthetics • monitors • therapeutics • life-support • drug delivery • surgical instruments 	<ul style="list-style-type: none"> • xenografts • allografts • autografts • viable/non-viable 	<ul style="list-style-type: none"> • stem cells • somatic cells 	<ul style="list-style-type: none"> • genomics • vectors 	<ul style="list-style-type: none"> • bioreactors • biotransformation • transgenics 	<ul style="list-style-type: none"> • synthesisers

Advanced Therapies
(New Biotechnology)

Manufacturing Technology
Quality Assurance

Information Technology
Technical Standards

Regulation

Market Access

Medical Device Sector

Vascular implants
Hearing Aids
Intra-Ocular Lenses
Dialysis Equipment
Imaging Equipment
Stimulators
Catheters
Wound Dressings
Tongue Depressors
Heart Valves
Physiological Monitors
Sutures

Aspirators
Swabs

Orthopaedic Implants
Contact Lenses
Physiotherapy Equipment
Diagnostic Devices
Radiation Therapy Equipment
Radiation Therapy Simulators
Drug/nutrient Delivery
Cosmetic Prostheses
Contraceptives
Thermometers
Lancets
Endoscopes

Sterilisers
Filters
Surgical Instruments
Bone Cements
Spectacles
Operating Tables
Artificial Limbs
Stethoscopes
Surgical gloves
Defibrillators
Hospital Beds

Potentially > 400,000 devices on the market (> 10,000 families)

Device Development and Design Control



Device Characteristics, eg:

Intended Use

- Indications, purpose
- Patient characterisation
- Sequence of operation
- Reliability
- Environment
- Contraindications
- Disposal



Intended User

- Physician, nurse, porter, auxiliary, patient
- Ergonomics, dexterity, handling training, age, disability, intellectual acumen
- Necessary accessories
- Installer, biomedical engineering (acceptance testing)
- Service and maintenance

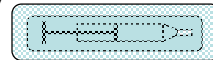
Intended Contact

- Biological compatibility
- Duration, longevity
- Bioactivity
- Bioabsorbance



Materials of Construction

- Properties of materials
- Physical compatibility
- Structural integrity
- Packaging materials
- Cleaning, disinfection, sterilisation
- Environmental compatibility



Energy / Substances

- Delivery or extraction
- Quality, quantity
- Control and duration
- Justification, optimisation and dose



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USA Medical Device Regulations

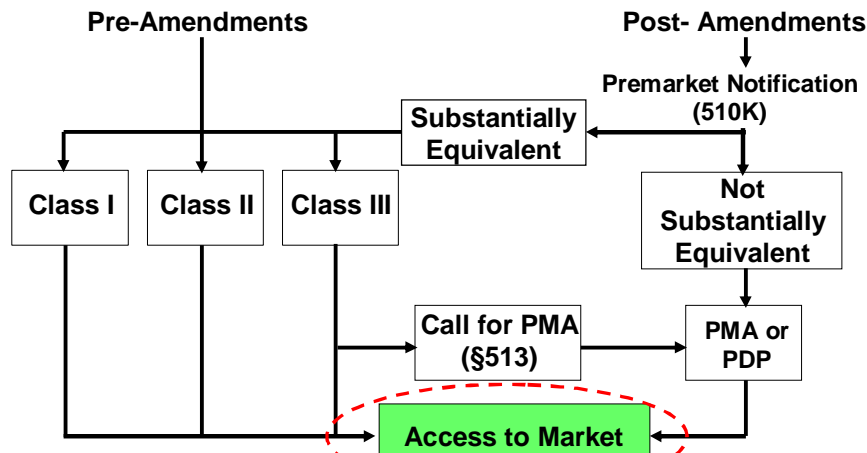


Statutory Authorities:

- I Federal Food, Drug, Cosmetic Act (FD&C Act)
- I Medical Device Amendments of 1976 (MDA)
- I Safe Medical Devices Act of 1990 (SMDA)
- I [Medical Devices Amendments of 1992]
- I [FDA Export Reform and Enhancement Act of 1996]
- I FDA Modernization Act of 1997 (FDAMA)
- I Medical Device User Fee and Modernization Act 2002 (MDUFMA)

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USA Medical Device Regulations



- Provisions for:
- exemptions from Premarket Notification
 - reclassification
 - PMAs for Pre-Amendments Class III devices

PMA = Pre-Market Authorisation
PDP = Product Development Protocol

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European Regulations



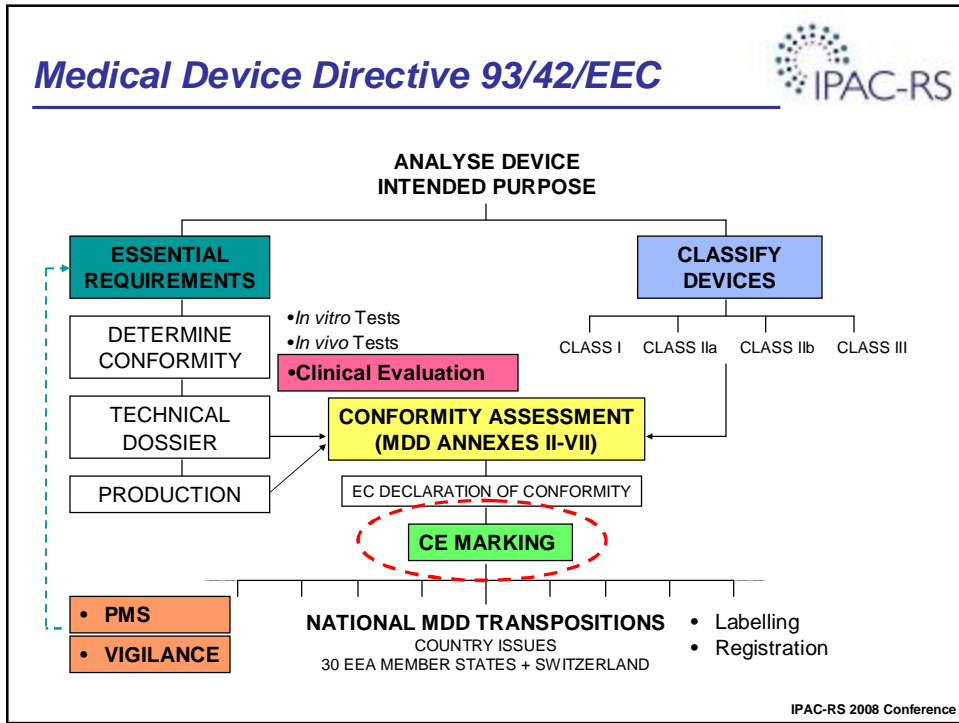
Directives:

- | 90/385/EEC Active Implantable Medical Devices
- | 93/42/EEC Medical Devices
- | 98/79/EC In Vitro Diagnostic Medical Devices
- +
 - | 2000/70/EC Devices Incorporating Human Blood Derivatives
 - | 2003/12/EC Reclassification of Breast Implants
 - | 2003/32/EC Tissues of Animal Origin
 - | 2004/23/EC Human Tissues and Cells
 - | 2005/50/EC Reclassification of total joint replacements
 - | 2007/47/EC Revision of MD, AIMD and Biocidals Directives

and, other Directives which impact on Medical Devices

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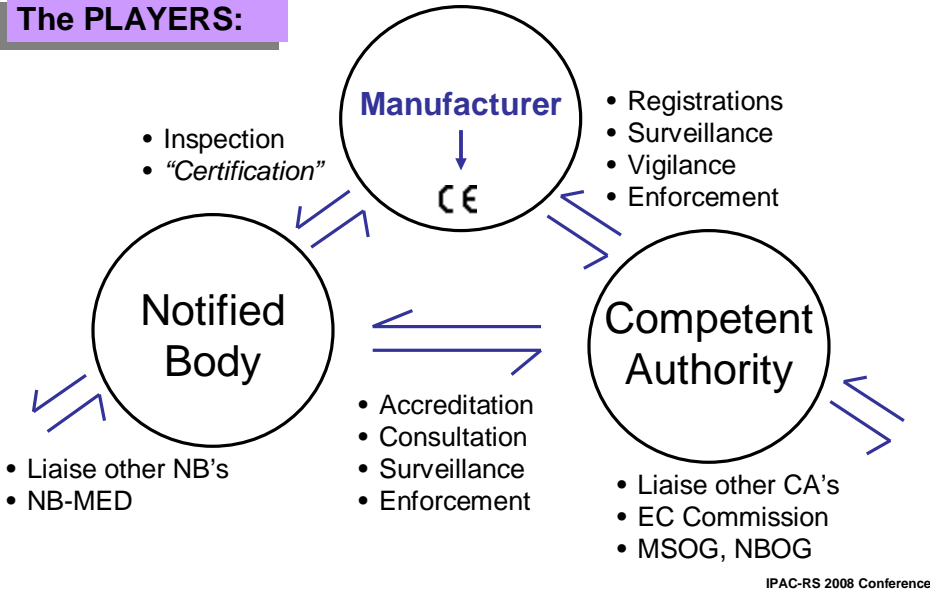
Medical Device Directive 93/42/EEC



Medical Device Directive 93/42/EEC



The PLAYERS:



USA Combination Products



Determining Legal Status

- | Must take into account **Primary Mode of Action** (PMOA)
- | “**Primary mode of action**” defined as “**the single mode of action of a combination product that provides the most important therapeutic action of the combination product.**”
- | Must take into account statutory and regulatory definitions
 - | Biologic → CBER
 - | Device → CDRH
 - | Drug → CDER
- | Must take into account FDA precedents [...or take advantage of a myriad of FDA decisions]
- | If unsure of PMOA can apply to Office of Combination Products for determination of lead FDA Centre

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EU Combination Products



Determining legal status

- | **Medical Device** does *not* achieve its **principal intended action** in or on the human body by pharmacological, immunological or metabolic means but which may be assisted in its function by such means
- | Drug - Device Combinations (*MDD Article 1.3*)
 - if intended for administration of drug then medical device (e.g. empty syringe)
 - unless drug and device are presented as integral **non-reusable** product then regulated as a drug (e.g. pMDI or pre-filled syringe)
 - relevant Essential Requirements of Annex I of MDD apply as far as safety and performance related device features are concerned
- | Drug vs Device Demarcation (*MDD Article 1.4*)
 - if action of drug is only **ancillary** then combination is a Medical Device,
 - drug aspect must be verified by analogy to methods in ICH
 - Notified Body must seek scientific opinion of Competent Authority (drugs)
- | From 2010 the test of **principal mode of action** will also apply (*MDD Article 1.5*)

Medical Devices : Guidance Document Demarcation between Directive 90/385/EEC (AIMDD) and 93/42/EEC (MDD) and Directive 65/65/EEC relating to Medicinal Products. MEDDEV 2.1/3 rev 2

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Combination Products



Examples:

- **Drug Eluting Stent**



Primary Mode of Action:

- Stent maintains patency of artery

Secondary Action:

- Drug reduces inflammation and restenosis of artery

- **Drug Eluting Disk**



Primary Mode of Action:

- Chemotherapy for brain tumor

Secondary Action:

- Localised drug delivery

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Combination Products



Examples:

pMDI



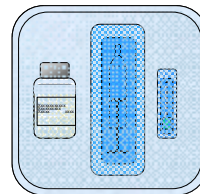
Nebulizer



pMDI with Expansion Chamber



Co-packaging






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Medical Device Regulations



Summary Comparison:

			
Regulator (enforcement)	CA's	FDA	Prefecture
Authorisation	NB's	FDA Centre	MHLW
Definitions, Classification	Ü ¹	Ü ¹	Ü
General Requirement	Safety and Performance	Safety and Effectiveness	Safety and Effectiveness
Specific Criteria	Essential Requirements	X	X
Conformity Assessment	Options	Prescribed	Prescribed
Emphasis	Self-regulation	510K, PMA	Notification and Licensing.
Full Quality System (design and production)	Optional (but not available for Class I)	Mandatory Class II+III (some Class I)	Mandatory (EO excludes most Class I)

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ICH Q-Documents (Drugs)

- Q1 Stability
- Q2 Analytical Validation
- Q3 Impurities
- Q4 Pharmacopoeias
- Q5 Quality of Biotech Products
- Q6 Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development

- Q9 Quality Risk Management**
- Q10 Pharmaceutical Quality Systems**

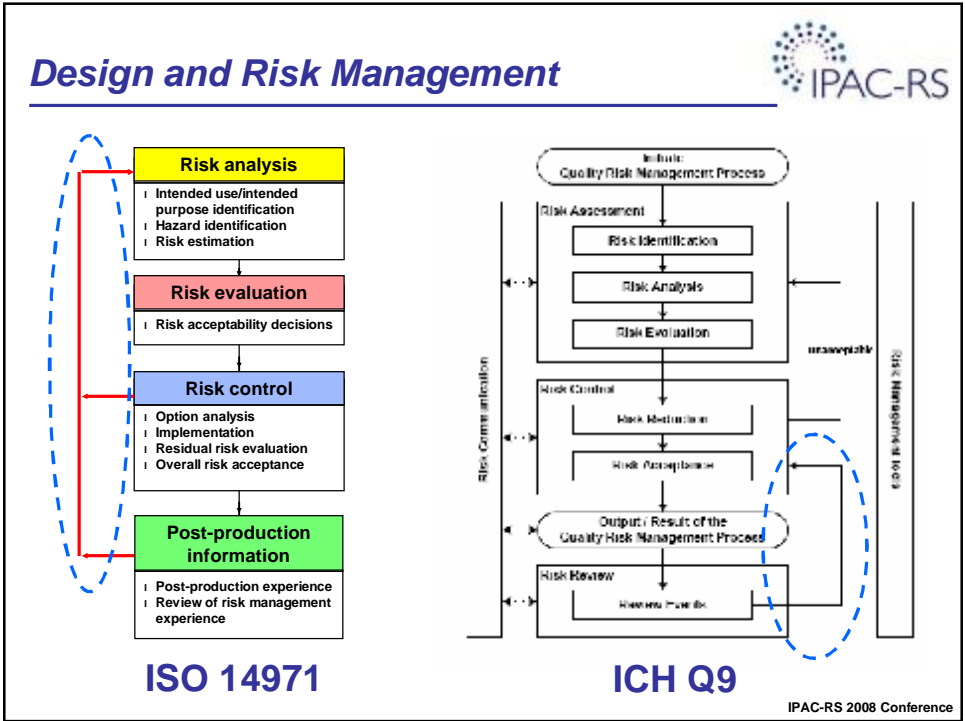
GHTF & ISO/IEC (Devices)

- SG 1 Essential Principles
- SG2 Vigilance and PMS
- SG3 Quality Systems
- SG4 Quality System Auditing Practices
- SG 5 Clinical Safety and Performance

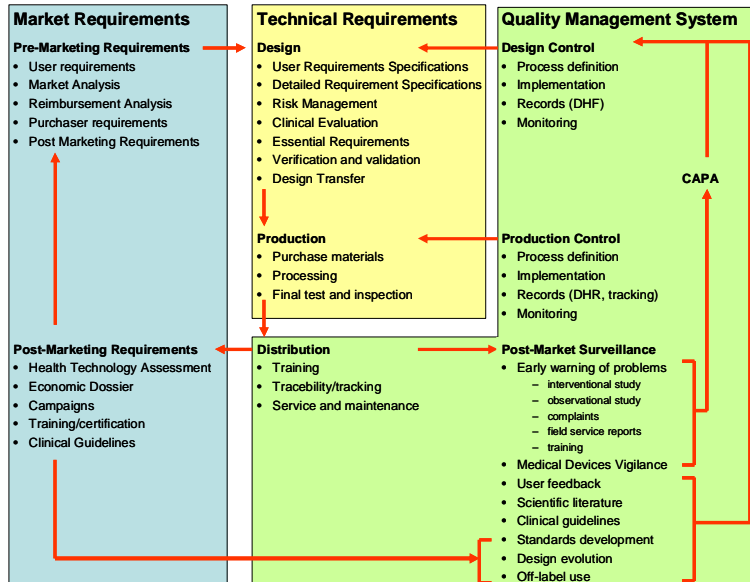
- ISO 14971 Risk Management**
- ISO 13485 Quality Management**

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Design and Risk Management



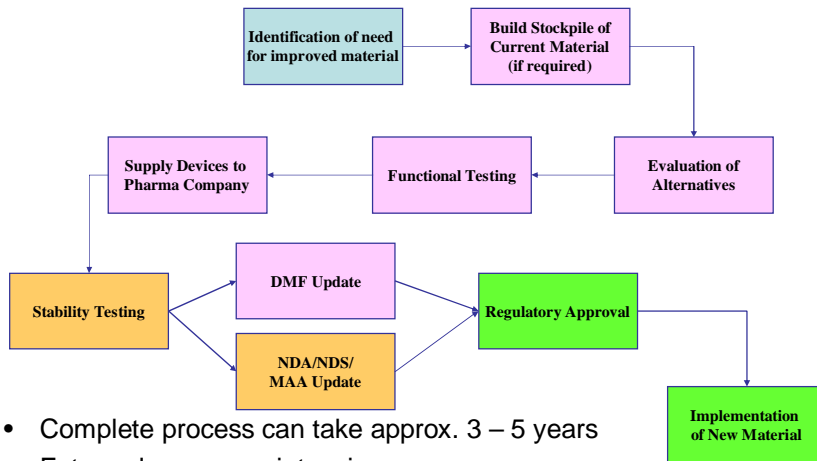
Design and Risk Management



Design Improvement – Drug Product



Change to Plastic used in Inhalation Device (e.g. valve within a pMDI)

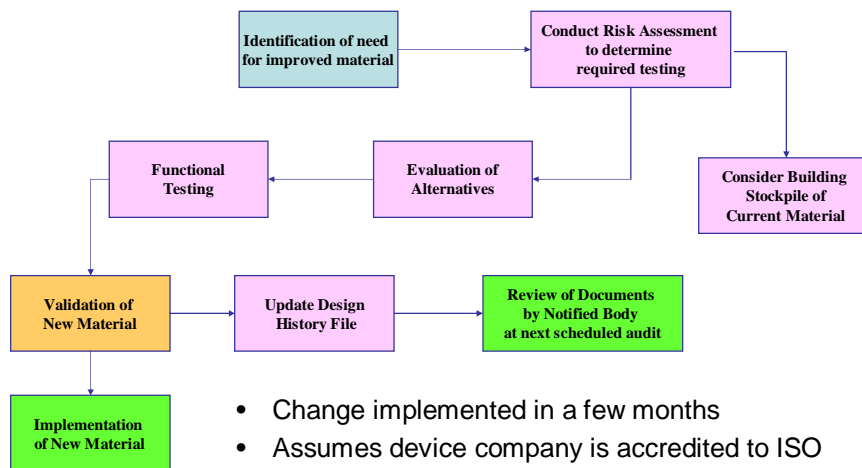


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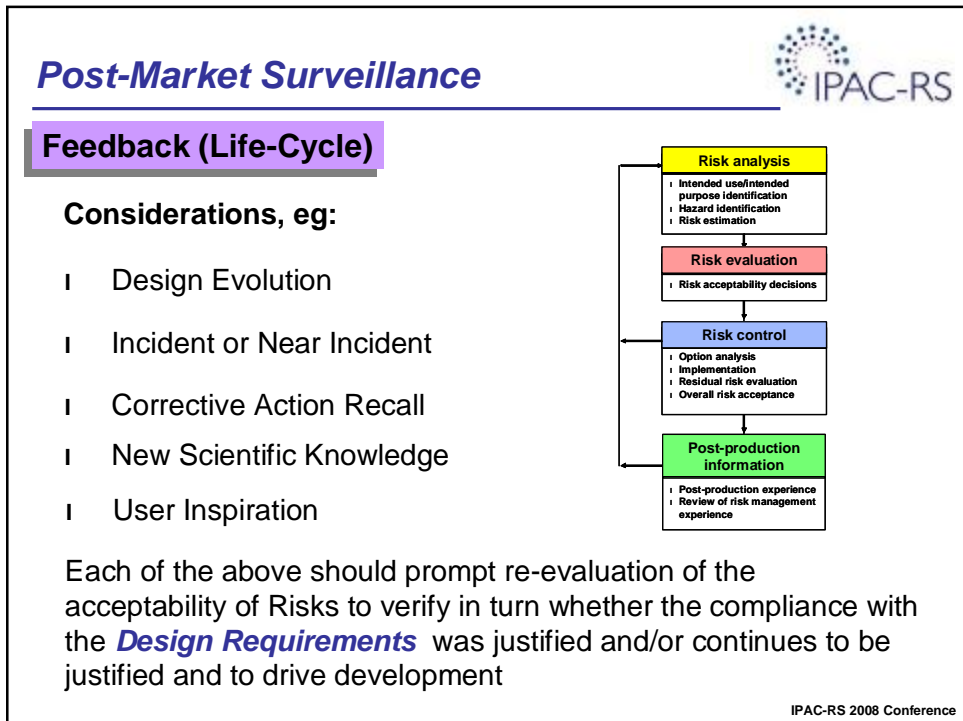
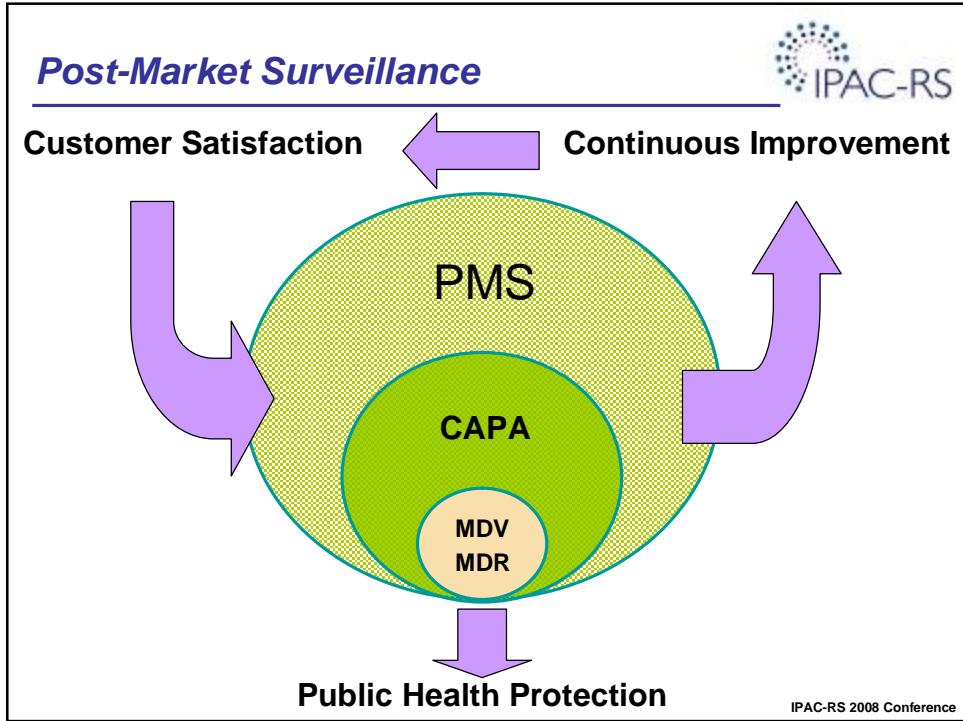
Design Improvement – Medical Device



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



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Post-Market Surveillance



Corrective and Preventive Actions (CAPA)

Requires a documented procedure for

- | | |
|----------------------------|-------------------------------|
| review of non-conformity | action taken |
| determining cause | CAPA records |
| evaluating need for action | CAPA review and effectiveness |

If required by national or regional authorities, ISO 13485 requires the **Manufacturer** to establish documented procedures to notify the regulatory authorities of those adverse events which meet the reporting criteria

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World Vigilance Reporting



MDR/MDV:	EU	USA	Canada	Australia	Japan
• Purpose		Approximately the same			
• Reporting Criteria		Approximately the same			
• Report Recipient	Competent Authority (29 +)	FDA	HC	TGA	MHLW
• Reporting Timeline	2 days (ST) 10 days (I) 30 days (NI) (MS variations)	5 days 30 days	10 days (I) 30 days (NI)	2 days 10 days (I) 30 days (NI)	15 days (I) 30 days (NI)
• Reporting Form	MEDDEV or CA Form or Web-Form	3500A	Advisory Form	Advisory Form	Initial
• Reporting Information		Approximately the same			
• Investigation		Approximately the same			
• Follow-Up Reports	Follow-up Final	3500A (Sup) 3417(Base)	Follow-up Final	As above	Monthly Final

Challenge: Evolving regulations / guidelines (eg MEDDEV Rev 5 and GHTF proposal)

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Summary

- | **Drugs and Devices are regulated very differently**
 - | **Strategically & Tactically**
 - | **Combination products present particular challenges**
- | **Drug and Device regulation is converging**
 - | **ICH vs ISO**
 - | **Opportunities to learn from each other**
e.g. Increased use of risk assessment and post-marketing feedback

Key to success – Keep talking!

THANK YOU

ANY QUESTIONS?

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