

# DEVICE DEVELOPMENT AND DESIGN CONTROL FOR COMBINATION PRODUCTS: STANDARDS, REGULATIONS AND CURRENT PRACTICES FOR ORALLY INHALED AND NASAL DRUG PRODUCTS

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## ABSTRACT

This article contrasts and compares the US, European and international standards and regulations, as well as current industry practices regarding device design development and control, focusing on orally inhaled and nasal drug products (OINDPs). The review of regulations revealed both similarities (e.g., amount of regulation proportional to perceived risk) and differences (e.g., classification principles for devices) among world regions. Current practices were assessed using an interactive audience survey during a 2008 conference hosted by the International Pharmaceutical Aerosols Consortium on Regulation and Science (IPAC-RS). The survey revealed that nearly half of the audience have experienced a non-trivial change to the device between clinical phases 2 and 3 or their equivalents, which typically extended the development timeline by more than a year. In addition, nearly half of the audience experienced a non-trivial change to the device post-approval, and such changes typically required more than a year to justify and implement. The results suggest that device design and optimization is an important component of the OINDP development. Gaining an early knowledge and understanding of the relationships between a particular formulation and a particular device will therefore help minimize the need for changes or streamline implementation of changes in late product development and post-approval. Additionally, simplifying regulatory pathways for post-approval changes may stimulate continuous device improvements based on accumulated users' experience.

**Key words:** design, combination, quality, inhaled, nasal, medical device

## INTRODUCTION

Legislation addressing medical products generally divides them into drugs or medical devices according to their different modes of action. For a medical device, the primary mode of action is physical and ceases once the medical device is withdrawn from a patient. The characteristics of devices are

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generally predictable from basic scientific principles, repeatable and transferable between different types of devices. This makes it possible to codify safety requirements for most devices through a series of standardized in-vitro tests.

By contrast, the effect of drugs on organs, especially in repeated doses, can only be roughly predicted from prior knowledge and may strongly depend on the patient's condition and for some products (such as OINDPs) may depend on the patient's inhalation maneuver while using the product. True safety of drugs can only be demonstrated by tests on living systems (cells, animals and humans) involving appropriate numbers of subjects.

These general differences have led to very different approaches in the regulation of devices and drugs, in requirements for their approval, and in the freedom allowed post-approval to make changes to a marketed product. For devices, a graduated approach to regulation has evolved, according to the risk-based classification of a device. For drugs, a precautionary principle is predominant, which presumes that there are always unknowns and uncertainties that will require long term assessment to demonstrate safety and efficacy. Many device-drug combination products, however, such as OINDPs, share both drug and device attributes, which may prove challenging in the application of appropriate regulations in a given world region. A systematic consideration of similarities and differences of the existing approaches, which is presented in this article, should facilitate understanding and awareness of these approaches, as well as optimal design development and control of such combination products.

## **METHOD**

The existing regulations were reviewed and analyzed using publicly available information. The data on current OINDP industry practices was collected during the IPAC-RS conference entitled << 'Doing the Right Thing' in the Changing Culture of Design and Development of Inhalation and Nasal Drug Products: Science, Quality, and Patient-Focus>><sup>1</sup> using individual voting units and software provided by Option Technologies Interactive, LLC. The survey questions<sup>2</sup> addressed the audience demographics, experience with non-trivial changes in the OINDP device in late development and post-approval, and utilization of purposeful design principles, such as those promulgated by the US Food and Drug Administration (FDA) Quality-by-Design (QbD) initiative<sup>3 4, 5, 6, 7</sup> and the International Conference on Harmonization (ICH) Q8-10 guidelines<sup>8,9,10</sup>.

## **RESULTS**

The direct results of the survey are available online<sup>2</sup> and are summarized here for convenience. There were 135 individuals participating in the real-time survey. Of those responding, 62% worked in the USA, 35% in Europe, 3% in Canada and 1% in India. Most of the responders were educated as chemists (50%), pharmacists (22%) or engineers (13%); the others had their professional training in regulatory

affairs (8%), math/statistics (3%), biology (3%) or physics (2%). The majority of responders worked in a pharmaceutical company developing, manufacturing or marketing OINDPs (70%), 11% worked in a device company developing or manufacturing OINDP devices or device components, 10% worked in the government. The smaller fractions, totaling 2% each, were from non-OINDP pharmaceutical companies, non-OINDP device companies, academia and consulting. The remaining 1% answered “other” with regard to occupation. Most of the audience had worked in their field for many years, had experience with many types of OINDP, and had multiple job responsibilities.

One portion of the survey aimed to explore the audience experience with non-trivial changes to an OINDP device between clinical trial phases 2 and 3 or their equivalents (recognizing that the concept of a clinical trial may not directly apply to a device manufacturer). By “non-trivial” the audience was asked to assume such changes that required significant investment of time or other resources.

Of those responding, 49% had had experience with such a non-trivial change. The reasons for non-trivial pre-approval changes to the device varied as follows (the examples in parentheses were included in the question rather than specified by the responders):

- 42% = Mechanical reliability or robustness of the device (e.g., issues with the dose counter).
- 18% = External influences (e.g., changes in regulations, results of clinical trials, changes in the market place, change of suppliers of raw materials or components).
- 11% = Manufacturability (e.g., need to optimize the device for high-speed assembly).
- 11% = Changes to the drug product’s formulation (e.g., change in the excipient or co-solvent, which in turn may have changed the leachables profile or other aspects of the formulation-device interaction).
- 9% = Complications during scale-up between phase 2 and 3 (e.g., particle size growth during mixing and filling on the new equipment).
- 9% = Ergonomic, i.e., changes to the device to improve device usability in the hands of a patient (e.g., optimized valve or actuator design).

In the experience of those who had worked through such a pre-approval change, that change in the device design extended the development timeline by more than a year (59%), or at least several (3-12) months (37%), with only 4% of cases resolved within 3 months.

Even with the best possible development program, changes to the device post-approval may be unavoidable, due both to uncontrollable business factors (e.g., exit from the market of a material supplier) and to the knowledge acquired from product use by a large number of patients. Almost half (47%) of the audience had had experience with a non-trivial post-approval change to an OINDP device. Reasons for change varied, as follows:

- 30% = Changes in raw material suppliers
- 17% = Changes with the supplier of device component(s)
- 15% = Mechanical reliability or robustness of the device (e.g., issues with the dose counter)
- 11% = Manufacturability (e.g., need to optimize the device for high-speed assembly)
- 11% = Changes with the supplier of formulation ingredients
- 9% = Ergonomic improvements to the device
- 6% = Changed market conditions
- 4% = Retroactive changes of regulatory requirements

For such post-approval device changes, the time it took to conduct studies to justify the change, obtain regulatory approval and implement the change, was over a year (78%), or at least several (3-12) months (17%), with only 6% of cases resolved in less than 3 months.

Prior to the FDA QbD initiative (2004), 26% of the audience had been including ICH Q8-10/QbD-type information in regulatory submissions for OINDPs, 36% did not, and 38% either did not know the answer or were not from a pharma or device company.

Of those who had included ICH Q8-10/QbD-type information in regulatory drug product submissions pre-2004, 14% indicated that it generally facilitated the regulatory review, 9% said that it did not, and the remaining 77% either did not know the answer or were not from a pharma or device company.

For those who had not included ICH Q8-10/QbD-type information in regulatory drug product submissions pre-2004, the primary reasons included the following:

- 26% = Potential complications during review and delay of approval
- 21% = It was not encouraged by FDA or other regulatory agency
- 12% = No clear public guidance as to how to include such information
- 42% = All of the above equally important

The survey also showed that risk assessment and user requirements play a large part in device development. Surprisingly, a high proportion of the respondents (41%) felt that Failure Mode and Effects Analysis (FMEA) is the predominant tool driving risk reduction during development, while other tools played a lesser role: regulations and regulatory guidelines (24%); ICH Q9 Quality Risk Management (7%), ISO 14971 Quality Risk Management (6%), technical standards such as ISO and IEC (3%), and others.

## DISCUSSION

The medical devices industry is characterized by highly innovative and entrepreneurial companies that constantly re-invent themselves. Development times for stand-alone devices (typically 1-2 years) are short in comparison with development times for OINDP device-drug combination products (5-15 years<sup>11</sup>), and access to markets is relatively rapid. The USA began a separate regulatory oversight of devices with the 1976 Medical Device Amendments (MDA) to the federal Food, Drug and Cosmetic Act (FDCA)<sup>12</sup>, followed by similar regulations worldwide and more recently by the European Communities medical devices directives<sup>13</sup>. The regulations are constantly being amended to accommodate the changing perspectives on safety, risk and benefits. Engineering approaches to developing devices are also evolving, taking advantage of technological advances as well as continuously improving understanding of patients' needs. Table 1 summarizes the characteristics that are typically considered key during design of a device.

**Table 1. Key characteristics to be considered during device design.**

<i>Aspect to consider</i>	<i>Characteristics to consider</i>
Intended Use	Indications, purpose Patient characterization Sequence of operation Reliability Environment Contraindications Disposal Stability Robustness
Intended Users  (Physician, nurse, porter, auxiliary, patient, installer, service and maintenance staff)	Ergonomics Dexterity Handling training Age Disability Intellectual acumen Necessary accessories
Intended Contact	Biological compatibility Durability Longevity Bioactivity Bioabsorbance
Materials of Construction	Physico-chemical properties of materials Physical and chemical compatibility Structural integrity

	Packaging materials Cleaning, disinfection, sterilization Environmental compatibility
Energy / Active Substances	Delivery or extraction Quality, quantity Control and duration Justification, optimization and dose

### ***US Regulatory Approach***

Prior to 1976, medical devices in the US were regulated under the general provisions of the FDCA. Enforcement was through post-marketing actions for misbranding and adulteration. The MDA Act empowered the FDA with pre-market review authority over all devices and introduced a three tier classification system for clearing and approving the entry of new medical devices into commerce:

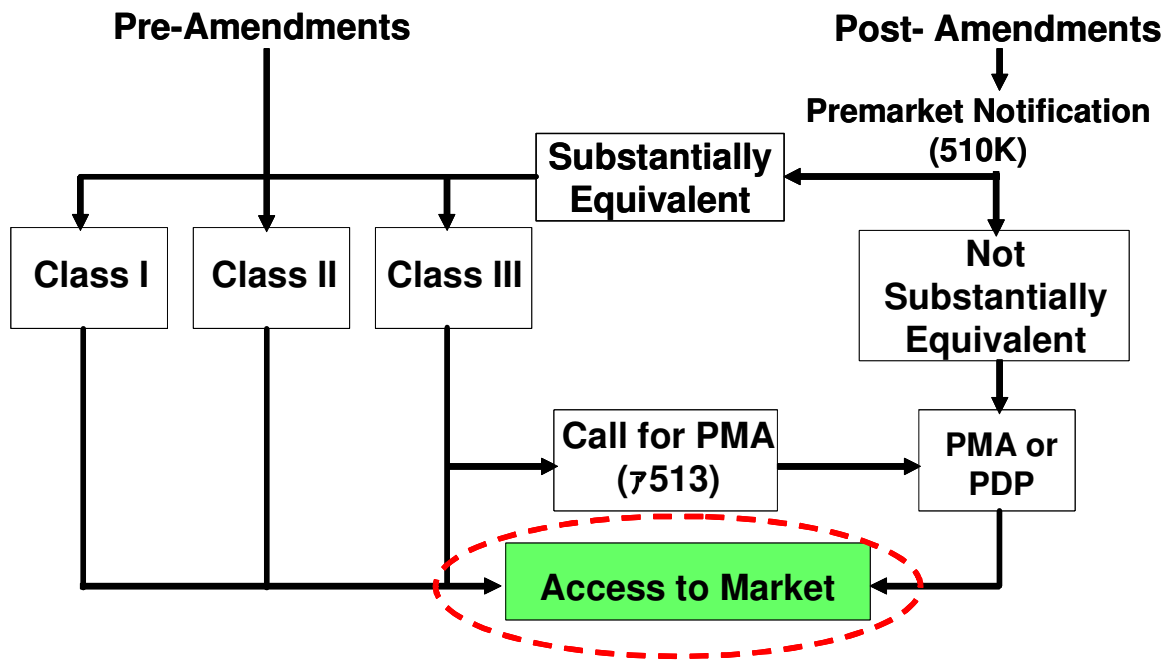
- Class I (low risk) devices for which "general regulatory controls" are sufficient to provide reasonable assurance of the ***safety and effectiveness*** of the device;
- Class II (medium risk) devices for which compliance with special controls, eg performance standards and post market surveillance, along with the general regulatory controls are sufficient to provide reasonable assurance of the ***safety and effectiveness*** of the device;
- Class III (high risk) devices being those where compliance with performance standards and general controls is insufficient to assure their ***safety and effectiveness*** and are for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury.

Section 510(k) of the FDCA provided for the notification of all devices and data so that devices could be classified prior to introduction into interstate commerce. The Act also provided for:

- monitoring the compliance of medical device manufacturers [enabled by the **Good Manufacturing Practice** (GMP) Regulation 1978, since superseded by the Quality System Regulations (QSR) 1997];
- obligation to make available information about the behavior of devices in service and specifically any death or serious injury or malfunction which could lead to death or serious injury if the malfunction were to recur (enabled by the **Medical Device Reporting** (MDR) Regulations 1984).

Figure 1 shows how a medical device may be classified by FDA taking into account the impact of the Acts promulgated since 1976 to the present.

**Figure 1. USA Medical Device Regulations. (PMA = Pre-Market Authorization; PDP = Product Development Protocol)**



The 1976 Act provided for the initial classification of pre-amendments devices but included statutory provisions for reclassification (e.g., from Class III to Class II upon acquisition of new data which suggests that **safety and effectiveness** can be secured by special controls) and the FDA Modernization Action (FDAMA) 1997 provided for de novo reclassification of devices which had been found not to be substantially equivalent. The Class a device is assigned to determines, among other things, the type of premarketing submission/application required for FDA clearance or approval to market. If the device is classified as Class I or II, and if it is not exempt, a pre-market notification (a so-called 510(k) submission) is required for marketing. For Class III devices, a Pre-Market Authorization application (PMA) is required unless the device is a **substantially equivalent** to a pre-amendment Class III device and a PMA has not been called for per section 513 of the FDCA. In that case, a 510(k) will be the route to market.

The detailed requirements that underpin device compliance with the FDCA, as amended, are codified in Title 21 Code of Federal Regulations (CFR) parts 800 to 1299 which include the following key regulations:

- Labeling; Part 801
- Medical Device Reporting (MDR); Part 803
- Establishment registration and device listing for manufacturers and importers; Part 808
- Investigational Device Exemptions (IDE); Part 812
- Premarket Approval (PMA) of Medical Devices; Part 814
- Quality System Regulation (QSR); Part 820
- Medical Device Tracking; Part 821
- Post Market Surveillance; Part 822
- Banned Devices; Part 895
- FDA Classification determinations; Parts 862-900

One of the key features of the US regulatory system is the possibility for suppliers of drug and device components or ingredients to file Drug Master Files (DMFs) or Device Master Files (referred to by FDA as MAFs) containing information about chemical composition, manufacturing process, quality controls, etc. of the ingredient or component. DMFs and MAFs are not required, are not necessarily reviewed and are not approved by the FDA. Rather, they can be referenced by a drug or device applicant who have reference rights and may be reviewed by the FDA in the course of the drug or device application review. If FDA has any questions on the DMF or MAF, the agency will communicate directly with the DMF or MAF holder without necessarily informing the drug or device applicant.

To ensure the continuing safety and reliability of the device after cleared for commerce the QSR requires that there be a system for complaints handling and procedures for corrective and preventive action. Such procedures must provide for investigation, analysis, identification of action to prevent recurrence and verification/ validation of the corrective and preventive action to ensure that it is effective and does not adversely affect the finished device;

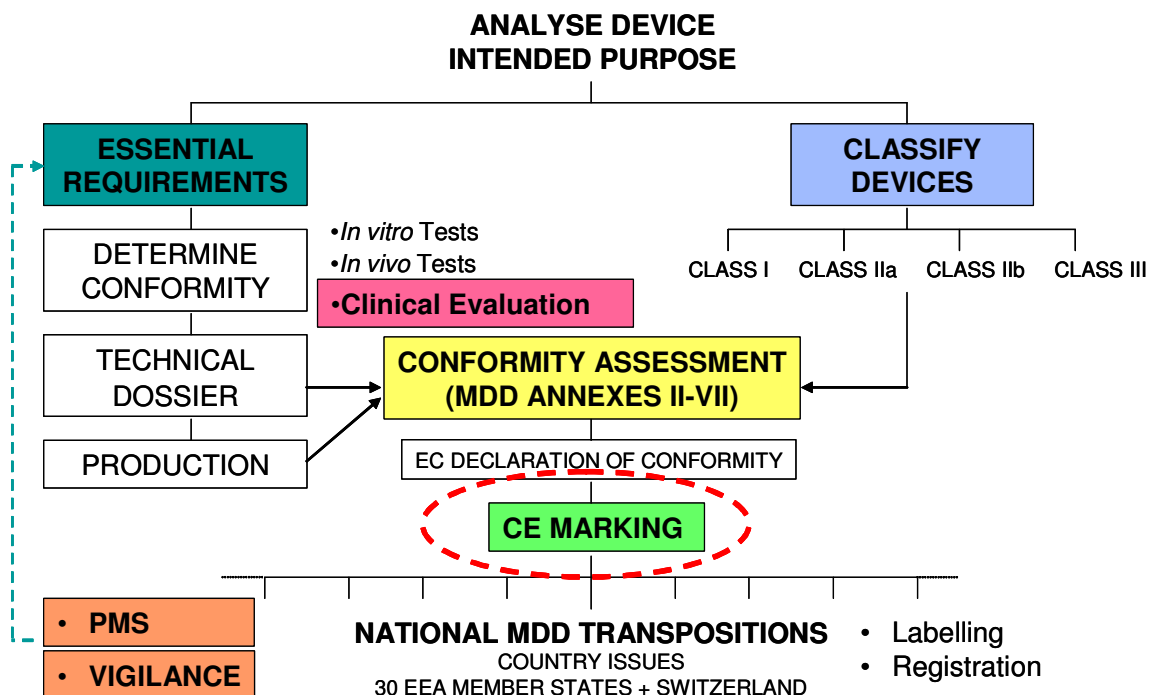
### ***EU Regulatory Approach***

In the European Union (EU), the following key directives apply to medical devices:

- 90/385/EEC           Active Implantable Medical Devices
- 93/42/EEC           Medical Devices Directive (MDD)
- 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 Medical Device, Active Implantable Medical Device and Biocidals Directives

The key features of the Medical Devices Directive are identified in Figure 2.

Figure 2. Requirements of the Medical Devices Directive (MDD) 93/42/EEC



To gain access to the EU market, a manufacturer declares compliance with the relevant essential requirements via the process of conformity assessment. Except for Class I devices (non-sterile or non-measuring), this declaration is reviewed by the Notified Body (NB) to confirm compliance. Following this review, the manufacturer must place a “CE” mark on the device before it can enter into commerce. No pre-authorization from the Competent Authority (CA) is required – all responsibility remains with the manufacturer.

To affix the CE Marking the manufacturer must pay particular attention to the following key features of the Directive:

- Essential Requirement (Article 3, Annex I);
- Harmonized Standards (Article 5);
- Clinical Evaluation (Annex X);
- Labeling and Languages (Article 4.4, Annex I.13);
- Technical Documentation (Annexes II, III, VII);
- Classification (Article 9, Annex IX);
- Conformity Assessment (Article 11, Annexes II, III, IV, V, VI);
- Notified Bodies (Article 16);
- Vigilance and Post-Marketing Surveillance (Article 10, Annexes II, IV, V, VI, VII);
- Authorized Representative (various Articles);
- National Issues.

The conformity assessment options open to the manufacturer depend on the classification of the medical device. The classification is determined using the MDD classification rules and is based on risk, with lowest risk devices designated as Class I. The classification determines the type of conformity

assessment that is permissible (e.g., Full Quality Assurance, Type Examination, Product Verification, Production Quality Assurance, Product Quality Assurance, internal production control.)

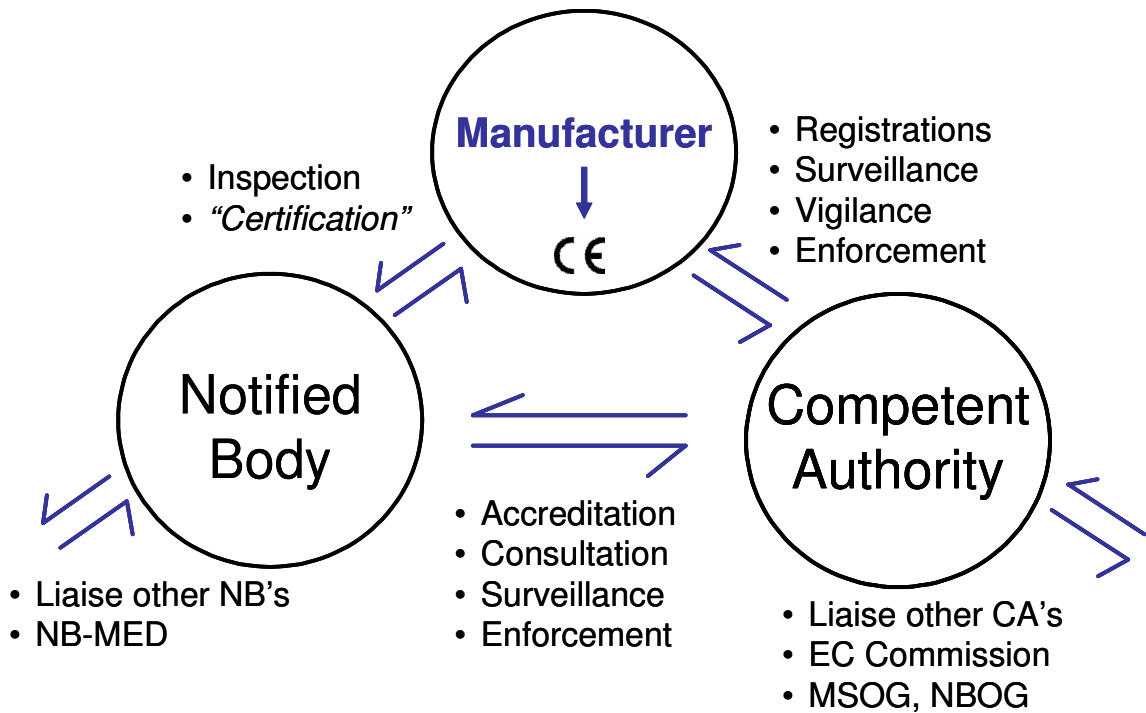
All devices must comply with the relevant essential requirements. Medical device manufacturers usually compile a checklist to show how compliance with each requirement is achieved. International harmonized standards are vital to this process although their use is not mandatory. If a manufacturer can demonstrate adherence with an applicable international harmonized standard then this establishes legal presumption that the device is compliant with the relevant essential requirements. This is as a result of the MDD being part of the group of New Approach directives issued within the European Union.

Post-marketing surveillance is an important aspect of the EU regulatory system for devices, as it drives the lifecycle management and continuous improvement of devices. Except for pre-market clinical investigations and post-marketing surveillance, manufacturers have little interaction with EU Competent Authorities for devices. Instead, manufacturers regulate their activities according to Conformity Assessment procedures subject to NB inspections (except for class I devices).. For those manufacturers that have implemented a full Quality Management System, the NB will undertake periodic (at least annual) inspections to verify the fitness of the system and the manufacturer's ability to self-regulate design and production of all devices that fall within the scope of the Notified Body approval. The only exception is Notified Body approval of Class III devices by Design Dossier examination or the Type examination. However, it is always the manufacturer that authorizes affixing of the CE Mark and release to market. The roles of the mentioned entities are illustrated in Figure 3. The abbreviations used in Figure 3 refer to non-statutory assemblies that the NBs and CAs have established to align their interpretations and methodologies:

- NB-MED is the association of Notified Bodies that seek to achieve a common consensus in their inspection activities to better create a level playing field. They issue recommendations and consensus statements many of which have been adopted as European guidelines
- NBOG is the Notified Bodies Operations Group established by the CAs to harmonize their acceptance, surveillance (auditing) and enforcement over Notified Bodies;
- MSOG is the Market Surveillance Operations Group established to ensure uniformity between the CA's in their market surveillance activities.
- MDEG (not shown here) is the Medical Devices Expert Group which is a very important assembly of CAs, NBs, industry and other stakeholders. The MDEG prepares guidelines (MEDDEVs) intended to achieve a uniform application of the Directive across all of the Member States.

The output of these groups are available via the Commission's Medical Devices website<sup>14</sup>.

**Figure 3. Roles of device manufacturer, notified body and competent authority in the EU. (See text for abbreviations.)**



### ***Drug-Device Combination Products***

The increasing complexity of products that combine aspects of devices and drugs (such as OINDPs, pre-filled syringes, drug eluting stents, etc.) challenges the regulators and other stakeholders who must develop the regulations to protect the public and yet meet the rising expectation of the public for new therapies and diagnoses.

To distinguish between "devices" and "drugs" the FDA developed a definition based upon the **primary mode of action (PMOA)**. This definition is the tool FDA uses to determine how a product with device and drug attributes should be regulated and which FDA Center should take the lead in regulating the product. The regulation became effective 23 November 2005<sup>15</sup>. "Primary mode of action" is defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product". For example, a drug eluting stent is a device (Primary Mode of Action: Stent maintains patency of artery. Secondary Action: Drug reduces inflammation and restenosis of artery). By contrast, a drug eluting disc is a drug (Primary Mode of Action: direct drug therapy. Secondary Action: sustained localized delivery). Combination Products are regulated predominantly as drug or device or biologic. For such products, one FDA Center will have jurisdictional responsibility for processing the submission, i.e., either the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) or Center for Device and Radiological Health (CDRH) or other Center.

Previous FDA decisions may be consulted to determine a product's designation. In case of uncertainty, the FDA Office of Combination Products (OCP)<sup>16</sup> may be consulted for determination of the lead FDA center by submission of a request for designation (RFD).

Historically, OINDPs have been regulated by FDA as a drug (lead center CDER). A spacer sold separately but used in a combination with a pressurized metered dose inhaler (pMDI) is regulated as a device (lead center CDRH). Nebulizers are devices regulated by CDRH. All three products above are regulated differently but can be used to administer the same drug, e.g., corticosteroid or beta-agonist. When products are co-packaged as kits (e.g., a drug vial + empty syringe + needle; or a screw-cap bottle with nasal drops + spray pump), a regulatory designation can get even more complex.




In the EU, the notion of a 'combination product' does not exist; a product is either a drug or a device. In addition, the European regulations focus on safety and technical performance of devices, and do not directly address efficacy, however the clinical benefit must be acceptable compared to the risk and be based on clinical data elicited from the scientific literature and/or results of clinical investigation. Market experience will typically demonstrate efficacy or lack thereof, e.g., health technology assessment as a prerequisite for reimbursement qualification under local health insurance.

In Europe, a Medical Device is something that 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<sup>17</sup>. Drug - Device Combinations (MDD Article 1.3) are recognized (1) if intended for administration of drug then medical device (e.g., an empty syringe); and (2) unless drug and device are presented as integral non-reusable product then regulated as a drug (e.g., a pMDI or pre-filled syringe). In this case, relevant essential requirements of Annex I of MDD apply as far as safety and performance related device features are concerned. The MDD Article 1.4 furthermore clarifies the Drug vs Device Demarcation: if the action of the drug is only ancillary then the combination is a Medical Device; the drug aspect must be verified by analogy to methods in ICH; and the Notified Body must seek scientific opinion of Competent Authority for the drug component<sup>18</sup>. From 2010, the test of principal mode of action will also apply (MDD Article 1.5).

### ***Japanese Regulatory Approach***

A Japanese system is still evolving and is different from either that of the US or EU, as illustrated in Figure 4. Both drugs and devices are regulated in Japan by the Ministry of Health, Labour and Welfare (MHLW).

**Figure 4. Summary Comparison of Regulatory Approaches for Devices in US, EU and Japan.**

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

### **International Standards for Drugs and Devices**

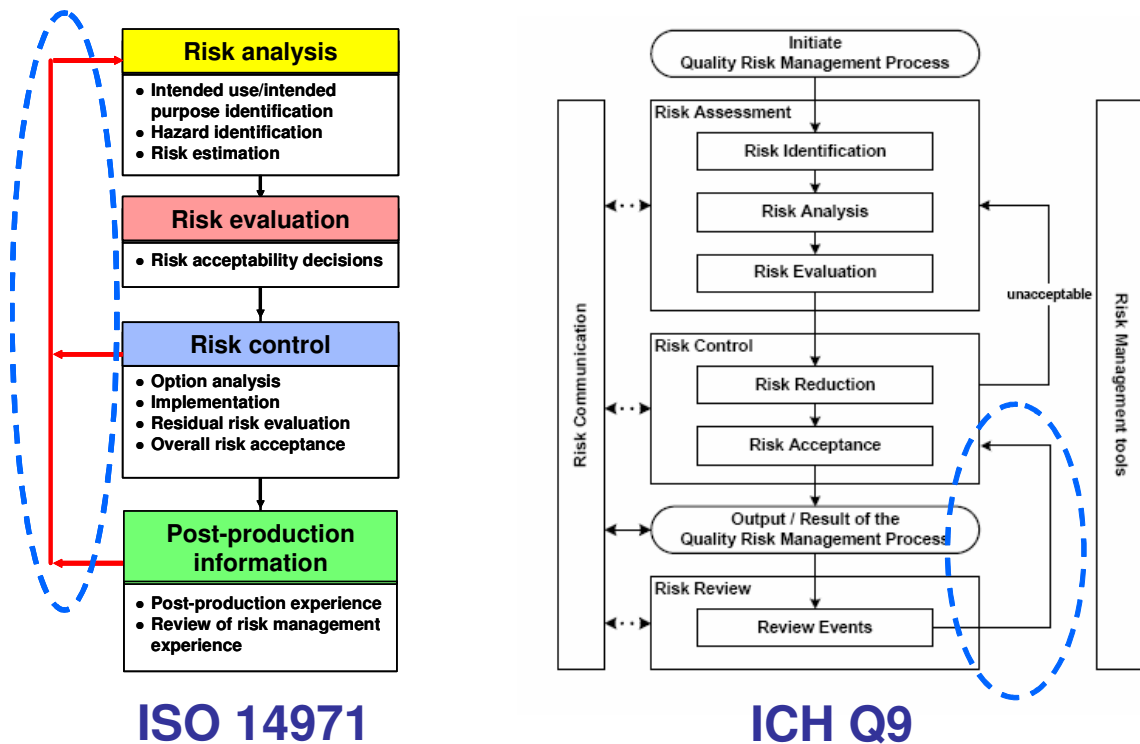
International standards and guidelines that may be helpful in the development of drugs, devices and drug-device combinations are summarized in Table 2. ICH guidelines of the Quality (“Q”) series are addressing ways to ensure quality of drugs. Documents issued by the Global Harmonization Task Force (GHTF), ISO and IEC are focused on quality issues of devices.

**Table 2. International Standards for Drugs and Devices**

<b>ICH Q-Documents (Drugs)</b>	<b>GHTF &amp; ISO/IEC (Devices)</b>
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	SG 1 Essential Principles SG 2 Vigilance and PMS SG 3 Quality Systems SG 4 Quality System Auditing Practices SG 5 Clinical Safety and Performance  ISO 14971 Risk Management ISO 13485 Quality Management  ISO 27427 Nebulizers (at final draft stage) ISO 20072 Aerosol Drug Delivery Devices (at final draft stage)

A comparison of the risk-management approaches for drugs and devices is shown schematically in Figure 5. This illustration shows that the overall processes are broadly similar, but it also highlights the key difference between the approaches for drugs and devices. In the ISO model for devices, product improvement is possible based on market feedback, leading back to the risk analysis. This is not the case with the ICH Q9 approach for drugs.

**Figure 5. Comparison of Drug and Device Approaches. The left panel is per ISO 14971 (devices) while the right panel is per ICH Q9 (drugs). The blue ovals illustrate the extent of influence of the post-approval events review.**

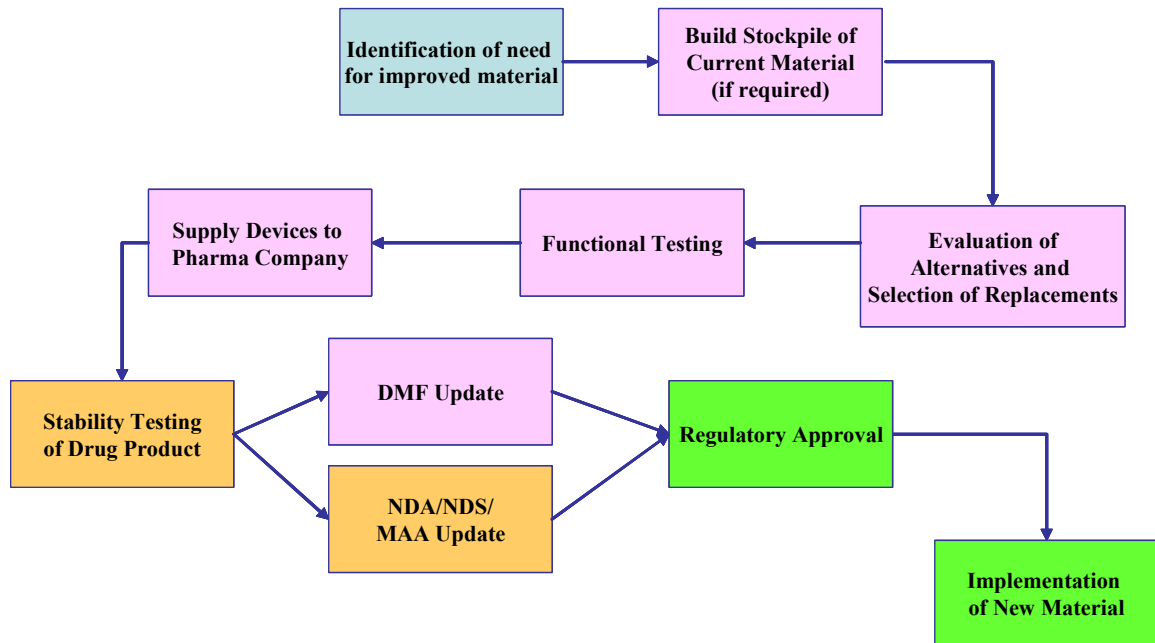


Devices rely on appropriate and robust quality assurance (QA) system and less on batch release quality control (QC) testing. This attitude has only recently started to attract attention of drug regulators and has found its realization in the FDA and ICH guidelines focused on quality-by-design and risk management systems (Table 2). Additionally, devices can more easily accommodate initiatives such as Process Analytical Technologies (PAT) and parametric release. Drug-device combination products could take advantage of the existing device design practices but in order for the benefits to be realized, strong cross functional interaction is needed.

### **Example of Implementing a Change**

Figure 6 presents a highly simplified overview of a process required to make a change in the plastic used in an inhalation device regulated as a drug (e.g., a valve within a pressurized metered dose inhaler), focusing only on key steps.

**Figure 6. Process to implement a change in the plastic used in an inhalation device regulated in the US as a drug ([DMF=Drug Master File; NDA=New Drug Application (US); NDS=New Drug Submission (Canada); MAA=Marketing Authorization Application (Europe)]).**

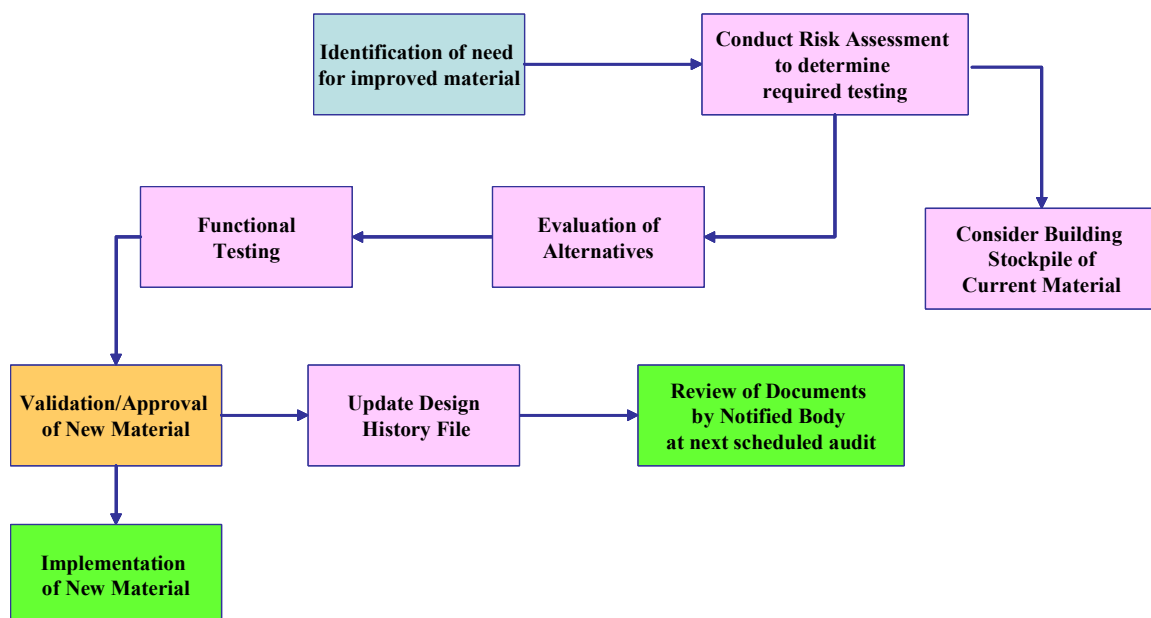


This process is time consuming and resource intensive (it can take approx. 3 – 5 years). This procedure would apply for any forced material changes, including situations when that change is an improvement to the existing device.. The key problems are:

- Regulatory approval required prior to implementation.
- Stability testing is most time consuming element.
- High barrier to change, therefore little incentive to improve products.

By contrast, a process to make a change in plastic used in an inhalation device regulated as a device (e.g. a refillable nebulizer), is illustrated in Figure 7.

**Figure 7. Process to implement a change in the plastic used in an inhalation device regulated as a device.**



These changes can be implemented in a few months [assuming that the device company is accredited to a recognised quality standard ISO 13485 or Quality System Regulations (QSR)]. This process allows opportunity to improve products based on a risk assessment approach. Barriers to change are decreased and therefore improvement is encouraged. Implementation is underpinned by the quality system and regulatory oversight is still present but handled by the Notified Body (EU) or CDRH (US). The underlying principle is that marketing a product is the beginning of a process and not the end – change will happen and should be encouraged as a means of achieving better products.

### ***Role of Post-Marketing Surveillance in Medical Device Improvement***

Post-marketing surveillance (PMS) covers a multitude of activities including testing and developing market acceptance, customer led clinical development, corrective and preventive action (CAPA) and engaging with the regulatory authorities in the event of adverse device related incidents. The feedback lifecycle may include considerations such as:

- Design evolution.
- Incident or near incident.
- Complaints separate from incident.
- Corrective action recall.
- New scientific knowledge.
- User inspiration manoeuvres.

Each of the above factors should prompt re-evaluation of the acceptability of risks to verify in turn whether the compliance with the **Design Requirements** was justified and/or continues to be justified and to drive development.

The feedback system provides the primary input into the corrective and preventive action (CAPA) processes. Quality problems, including non-conformities and customer complaints, must be systematically documented and processed. CAPA represents no small undertaking and entails:

- Review of quality problems, non-conformities and customer complaints;
- Determining the causes of nonconformities;
- Evaluating the need for action to ensure that nonconformities do not recur;
- Determining and implementing the action needed;
- Recording of the results of any investigation and of action taken; and
- Reviewing the corrective action taken and its effectiveness.

Compliance with ISO 13485 further requires that there be documented procedures to notify the regulatory authorities of those adverse events which meet the reporting criteria.

The similarities and differences in the vigilance reporting requirements in different regions of the world are summarized in Table 3. Challenges to harmonization continue, as regulations and guidelines evolve (e.g., MEDDEV Rev 5 and GHTF proposal).

**Table 3. Medical Device Vigilance (MDV) and Medical Device Reporting (MDR) requirements in different world regions. [EU may have Member State (MS) variations]. (Note: ST = Serious Public Health Threat; I = Incident; NI = Near Incident).**

MDR/MDV:	EU	USA	Canada	Australia	Japan
• Purpose	<b>Approximately the same</b>				
• Reporting Criteria	<b>Approximately the same</b>				
• 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	<b>Approximately the same</b>				
• Investigation	<b>Approximately the same</b>				
• Follow-Up Reports	Follow-up Final	3500A (Sup) 3417(Base)	Follow-up Final	As above	Monthly Final

These comparisons demonstrate that drugs and devices are regulated very differently from each other, and differently in various world regions. This may affect companies' development plans both strategically and tactically. Combination products present particular challenges. At the same time, there are signs that drug and device regulation is converging, and efforts are under way to align international approaches (e.g., via ICH and ISO). There are opportunities for drug and device sectors to learn from each other. For example, a systematic use of risk assessment and post-marketing feedback which is common practice for devices, could enhance drug development efforts, especially for drug-device combinations.

### ***Reflections on the Survey Results***

For products which necessarily combine a drug with a delivery device, such as orally inhaled and nasal drug products [e.g., pMDIs, dry powder inhalers (DPIs), etc.], the delivery device is often an important factor determining product performance characteristics as the medicinal formulation containing the active pharmaceutical ingredient. For such drug-device combination products, using purpose-driven design principles is both more natural and more complex compared to conventional drug products. On the one hand, device engineering naturally incorporates rational design approaches starting from defining desired performance parameters and risk assessment. On the other hand, the interplay between the device and drug components of the combination product requires that physico-chemical properties of the drug formulation be included in the engineering considerations of the device, and such integration may

not be straightforward. In addition, there currently exists little quantitative information about the relationships between mechanical, chemical and other in vitro characteristics and the clinical outcomes. This incomplete knowledge makes it difficult to determine in advance the desired performance specifications which could guide the device and formulation development prior to clinical trials. As a result, formulation development usually progresses in parallel with building an understanding of the device development options. Integrating the drug and device development under the Quality-by-Design paradigm may require additional efforts and iterations for combination products compared to drugs alone or devices alone. However, the benefits of this holistic approach to the patient as well as to the manufacturer (when looking at the overall lifecycle of the combination product) are significant and would almost certainly justify the effort.

The survey showed that FMEA is perceived as a key tool in risk reduction during design of a device. Ideally, however, designing a device should begin with defining user requirements, and only after a device concept has been defined, should FMEA be applied, and re-visited regularly throughout the product development program. Some of the previous knowledge about the device with a different formulation (e.g., MDI cans with a CFC propellant) may be incorporated into a new product development (e.g., HFA-based MDIs) but as a rule, risk assessment for the device should be specific to the product and formulation. This underscores the importance of the device and drug developers working closely together, starting as early in the development process as possible.

The survey results suggest that late-development and post-approval changes to the device are both very likely and time-consuming. This suggests that an early exploration of the Product Design Space would be worth the investment. For drug-device combination products, establishing the Product Design Space should include exploration of ‘subspaces’ for the device, formulation, and the interaction of the device and formulation. Consequently, it is critically important to have a two-way exchange of information and alignment of strategy between device developers and formulation developers throughout development, preparation of regulatory submission, and support of post-approval changes.

## **CONCLUSION**

Changes to a medical device are not uncommon in late development and post-approval, due to a number of factors ranging from the need to improve mechanical robustness during scale-up to the need find alternate suppliers of raw materials. The results also show that such changes typically take more than a year to justify and implement, suggesting that an early exploration of the product “Design Space” and understanding of the formulation-device interactions would be particularly beneficial for drug-device combination products.

## ACKNOWLEDGEMENTS

The authors are grateful to Richard Boschen, III (Option Technologies Interactive, LLC) for technical support in preparing and conducting the survey; to the IPAC-RS members whose responses to the preliminary draft helped refine the survey; and to the IPAC-RS Conference Organizing Committee as well as the IPAC-RS Board of Directors for supporting this project. Special thanks to Johan Waldeck who was one of the initiators of, and an early contributor to this effort.

## ABBREVIATIONS

CA	Competent Authority.
CAPA	Corrective And Preventive Action.
CBER	(FDA) Center for Biologics Evaluation and Research.
CDER	(FDA) Center for Drug Evaluation and Research.
CDRH	(FDA) Center for Device and Radiological Health.
CE	Conformité Européenne ("European Conformity").
CFC	Chlorofluorocarbon.
DMF	Drug Master File.
DPI	Dry Powder Inhaler.
EC	European Commission.
EEC	European Economic Community
EU	European Union.
FDA	Food and Drug Administration (US regulatory authority).
FDCA	Food, Drug and Cosmetics Act.
FMEA	Failure Mode and Effects Analysis
GHTF	Global Harmonization Task Force.
GMP	Good Manufacturing Practice.
HC	Health Canada.
HFA	Hydrofluoroalkane.
I	Incident.
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use).
IEC	International Electrotechnical Commission
IEEE	Institute of Electrical & Electronics Engineers.
IPAC-RS	International Pharmaceutical Aerosols Consortium on Regulation and Science.
ISO	International Organization for Standardization.
MAA	Marketing Authorization Application.
MAF	Device Master File (as referred to by FDA).
MDA	Medical Device Amendments.
MDD	Medical Device Directive.
MDR	Medical Device Reporting.
MDV	Medical Device Vigilance.
MHLW	Ministry of Health, Labour and Welfare (Japanese regulatory authority)
NDA	New Drug Application (US FDA).
NDS	New Drug Submission (Canada).
NI	Near Incident.
OCP	(FDA) Office of Combination Products.
OINDP	Orally Inhaled And Nasal Drug Product.
PAT	Process Analytical Technologies.
PDP	Product Development Protocol.
PMA	Pre-Market Authorization.
(p)MDI	(pressurized) Metered Dose Inhaler.
PMS	Post-marketing surveillance.

QA	Quality Assurance.
QbD	Quality by Design.
QC	Quality Control.
QSR	Quality System Regulations.
SG	Study Group (within GHTF).
ST	Serious Public Health Threat.
TGA	Therapeutic Goods Administration (Australian regulatory authority).
US	United States.

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