OINDP device regulation

International approaches to regulation and quality standards for orally inhaled and nasal drug products

Tim Chesworth, Paul Lafferty, Svetlana Lyapustina, Guillaume Brouet, David Christopher, John Hart
IPAC-RS Device Working Group

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Regulatory authorities generally divide medical products into either devices or drugs, with different sets of regulations for each type of product. Devices usually exhibit characteristics that are repeatable and transferable, and their effects on patients stop as soon as the device is withdrawn, making codification of safety requirements possible for most devices through a series of standardized *in vitro* tests, sometimes supplemented with short-term *in vivo* studies. The effects of drugs, on the other hand, may depend strongly on patients' conditions and other factors, and always require tests on living systems involving appropriate numbers of subjects over longer periods of time to determine safety.

These differences have led to different approaches in the regulation of devices and drugs, in requirements for approval, and in procedures for post-approval modification to marketed products. For drugs, most regulators take a precautionary stance that assumes a need for long-term assessment in order to demonstrate safety and efficacy. For devices, a risk-based classification of devices has evolved with a graduated approach to regulation; however, the US emphasizes pre-market assessment through FDA review, while the EU provides comprehensive guidance intended to permit companies to conduct their own risk assessments, with certification of conformance to the guidance provided by independent organizations.

Drug-device combination products such as OINDPs that share both drug and device attributes present particular challenges in the application of regulations by various authorities around the world. An understanding and awareness of the approaches to these types of products by various authorities can facilitate design development and control of OINDPs and can help companies evaluate the benefits of marketing a product first in one region or another.

Determining whether a product is a device or a drug

The US and EU have differing regulatory approaches and, therefore, differing methods of determining whether a product should be considered a drug or a device for regulatory purposes. In Japan, where the Ministry of Health, Labor, and Welfare (MHLW) regulates both drugs and devices, the system continues to evolve in ways that differ from both the US and EU systems (Table 1).

In the US, the FDA distinguishes between devices and drugs based on the principle of primary mode of action (PMOA), defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product" [1]. For example, a drug-eluting stent is a device since its primary function is to maintain the structure of an artery, but a drug-eluting disc is defined as a drug because its primary mode of action is direct drug therapy. Sponsors must submit applications to the appropriate center within the FDA, either the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), or the Center for Devices and Radiological Health (CDRH).

Historically, the FDA has treated OINDPs such as pMDIs as drugs regulated by the CDER. Nebulizers and spacers sold independently of inhalers are considered devices and are regulated by the CDRH, even though they may administer the same drug as an MDI. In cases of uncertainty, the sponsor may submit a request for designation (RFD) to the FDA's Office of Combination Products (OCP).

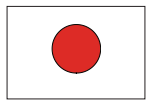
The EU has no equivalent office for combination products, and sponsors currently choose whether to submit an application for a product as a device or as a drug. According to the European definitions, a drug "achieves its principal intended action in or on the human body by pharmacological, immunological or metabolic means," while a device "achieves its principal intended action by physical action on the body and not pharmacological, immunological or metabolic means." Beginning in 2010, applications may also use PMOA as support to justify the manufacturer's designation of a product as either a drug or a device. Under the current scheme, a nebulizer that can be purchased separately from a drug is considered a device, whereas an MDI is considered a drug.

The US regulatory approach

The US FDA requires demonstration of both safety and effectiveness of drugs and devices prior to marketing. Combination OINDP products such as inhalers and nasal sprays require the submission of either a new drug application (NDA) or, for generics, an abbreviated new drug application (ANDA). NDAs require the submissions of significant amounts of data including, but not limited to: clinical trial results, pre-clinical study results, and stability data, as well as manufacturing, processing, and packaging information. ANDAs usually substitute bioequivalence (BE) data for the clinical and preclinical data used to establish safety and efficacy for new drugs; however, many inhaled drugs lack acceptable BE correlations. The NDA process can take as long as 3-5 years before a company can market a combination product.

Table 1

Comparison of regulatory approaches for devices in US, EU, and Japan

					
Regulator (enforcement)	CAs		FDA		Prefecture
Authorization	NBs		FDA center		MHLW
Definitions, classification	4	≠	4	≠	4
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		510(k), PMA		Notification and licensing
Full quality system (design and production)	Full quality system required but registration is optional (but not available for Class 1)		Mandatory Class II + III (some Class 1)		Mandatory (Enforcement ordinance excludes most Class 1)

International Standards for Drugs and Devices

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
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)

In addition to its responsibility for approving drugs, the FDA has pre-market review authority and a 3-tier device classification system in which drug delivery devices such as nebulizers fall under the Class II (medium risk) designation, which requires a pre-market authorization (PMA). For medium risk and some low risk devices, a pre-market notification, called a 510(k) application, requires manufacturers to demonstrate that a device is substantially equivalent in performance and safety to a previously classified device. While 510(k) applications also require pre-clinical and clinical data, as well as a risk assessment, the process generally takes significantly less time than for an NDA.

The FDA may or may not require post-marketing studies for either drugs or devices. Regardless of such commitment, a manufacturer who receives an adverse event report must inform the FDA. The Quality System Regulations (QSR) for devices require that manufacturers implement a system for complaints handling and procedures for corrective and preventive action (CAPA system) that provides for investigation, analysis, identification, verification, and validation of actions to prevent recurrence.

The EU regulatory approach

European regulators generally focus on the safety and technical performance of devices prior to authorization without specific requirements for demonstrating efficacy prior to marketing. In practice, approval depends on demonstrating a clinical benefit that is acceptable compared to risk, based on clinical data.

The European Medicines Agency (EMEA) has responsibility for pre-market approval of many drugs and has the authority to approve combination products. Biotechnology drugs and drugs for the treatment of certain conditions such as autoimmune diseases, cancer, and diabetes must be approved through the centralized procedure. However, the EMEA does not require review of all types of medications through its centralized procedure, so manufacturers of certain drugs may choose to submit a new drug application to an individual country for marketing approval as an alternative to the centralized procedure if they wish.

Unlike the FDA, the EMEA does not approve devices as well as drugs, except in the case of combination products filed for approval as drugs. In those cases, the manufacturer asserts that the device complies with the essential requirements listed in the Medical Device Directives (MDD), Annex 1. Submission of the documents supporting the declaration of conformity is not mandatory, but the EMEA may request the information to supplement its review of the device. The declaration provides regulators with assurance that credible risk management practices have been followed and that development work has been thorough. It should be noted that ISO or other appropriate independent certification of a company's development and manufacturing systems is seen as a significant advantage.

For other devices, the manufacturer must contract with a private certification and testing company authorized by a particular country's regulatory agency as a "Notified Body" (NB) to review the manufacturer's declaration that its product conforms to the essential requirements listed in the MDD. The device manufacturer may submit its declaration to the NB of its choice, though not all NBs have the expertise to deal with OINDP devices. No pre-authorization from the appropriate regulatory agency, known as the "Competent Authority" for the country, is required. Once the NB has certified the procedures adopted by the manufacturer for assessment of conformity, the manufacturer must place a "CE" mark on the device before marketing. Devices approved by the EMEA as part of a combination product should not display the CE mark.

Because the MDD belongs to the group of New Approach directives issued within the European Union, demonstrating adherence to an applicable interna-

tional harmonized standard such as ISO 13485 establishes a legal presumption that the device complies with the relevant essential requirements. Although the use of international harmonized standards is not mandatory, medical device manufacturers generally refer to those standards to compile a checklist demonstrating how the device complies with each requirement (see sidebar).

Post-marketing surveillance drives the lifecycle management and continuous improvement of devices in the EU, and manufacturers regulate their activities according to conformity assessment procedures subject to NB inspections. For those manufacturers that implement a quality management system, the NB will undertake periodic inspections at least once a year 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.

International standards and combination products

As is the case with regulatory agencies, international standards organizations designed to promote consistency in drug and device quality and risk management procedures around the world have approached drugs and devices separately and with varying strategies. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which focuses on drugs, emphasizes Quality by Design (QbD). ISO guidelines for devices allow for product improvement based on market feedback, which is not included in the ICH Q9 approach.

However, there are signs that drug and device regulations are converging, and efforts are under way to align international approaches via ICH and ISO. Doing so would present opportunities for the 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, would likely enhance drug development efforts, especially for drug-device combinations.

Tim Chesworth (AstraZeneca), Paul Lafferty (Quintiles Consulting), Svetlana Lyapustina (Drinker Biddle & Reath), Guillaume Brouet (Valois), David Christopher (Merck), and John Hart (Pfizer) are members of the Device Working Group of IPAC-RS. Contact Svetlana Lyapustina, Drinker Biddle & Reath, 1500 K Street, N.W., Washington, DC 20005-1209. Tel. 202 230-5179. svetlana.lyapustina@dbr.com