Chapter 5

In-Country Representation

By Michael A. Siano, MA and Heidi Feik, MSc, RAC

OBJECTIVES

- Learn the function of an in-country representative
- Understand the practical reasons for in-country representation requirements
- Gain insight into diversity of qualifications for in-country representatives among different countries
- Understand global requirements for in-country representation
- Understand pros and cons of third-party representatives versus distributor representatives

LAWS, REGULATIONS AND GUIDELINES COVERED IN THIS CHAPTER

EU/GHTF

- MEDDEV 2.5/10, January 2012, Guideline For Authorised Representatives
- GHTF/SG1/N055: 2009, Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer

Australia

- Therapeutic Goods Act 1989
- Therapeutic Goods (Medical Devices) Regulations 2002
- Australian Regulatory Guidelines for Medical Devices (ARGMD), 2011

Canada

- Food and Drug Act
- Medical Devices Regulations (SOR/98-282)
- Radiocommunication Regulations (SOR/96-484)
Chapter 5

Japan
- Pharmaceutical Affairs Law of 2002
- Yakushokuhatsu No. 0709004 of 2004
- MO 135 for GVP (good vigilance)
- MO 136 for GQP (good quality)

US
- 21 CFR 807—Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices
- 21 CFR 207—Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution

Introduction
The definition of an in-country representative differs broadly across the spectrum of jurisdictions—where one is required—ranging from an established business entity licensed as the medical device or medicinal product importer, to a natural person residing in the country.

With the notable exception of Canada, most countries require a local establishment for the commercialization of medical devices in their territories. For medicinal products, this also is a prerequisite in most countries.

The requirements for an in-country representative generally can be met in several ways. Most common among these are establishing a local branch of the parent company, assigning a distributor or importer or employing a third-party professional representative service.

Functions and Purpose of an In-Country Representative
In general, an in-country representative acts as a liaison between a foreign manufacturer and the local Competent Authority. To facilitate identification of the appropriate local entity for product questions and/or complaints, the in-country representative's name and contact information often is required to appear on the label. The in-country representative is available to receive user complaints, forward these to the manufacturer and submit the required reports to the regulatory authority.

In-country representatives also generally are expected to maintain device and/or drug technical information and compliance documentation so these can be furnished to the regulatory authority upon request.

In practical terms, an in-country representative eliminates the need for regulatory authorities to communicate with a foreign entity, possibly in a different language and time zone, about important safety and compliance information for the devices and/or drugs on their markets. In some markets, the in-country representative bears responsibility for the safety of the product, including taking any necessary legal actions.

In-country representatives bear varying degrees of legal responsibility, depending on the region and on the contract agreement with the manufacturer.

The official title of the in-country representative differs from country-to-country, with the EU and GHTF (IMDRF) term, “Authorized Representative” (AR) commonly used generically. For drugs, the term is usually “license holder” or “local representative.”

Qualifications of an In-Country Representative
The qualifications for an in-country representative vary significantly from country to country. The basic qualification, of course, is a local presence. This often can be either a real or legal person (i.e., an individual or a business entity). For business entities, normal business licenses generally are required. Additionally, many countries require the in-country representative to obtain special licenses through the Ministry of Health (or other health authority) and have specially qualified staff.

Global Examples
The following examples, taken from some of the world’s largest economies, with well-developed regulatory systems, illustrate a spectrum of requirements for in-country representation.

US
Overview
The US Food and Drug Administration (FDA) requires foreign manufacturers without a place of business in the US to appoint a US agent to represent them. Unlike many countries where only the legal medical device manufacturer is required to have in-country representation, foreign contract manufacturers also must have a US agent.

The definition of a US agent is given in Title 21 Code of Federal Regulations (CFR), Volume 8, Part 807(r) as: United States agent means a person residing or maintaining a place of business in the United States whom a foreign establishment designates as its agent. This definition excludes mailboxes, answering machines or services, or other places where an individual acting as the foreign establishment’s agent is not physically present.

In the US, unlike many other markets, market authorization (clearance/approval/exemption) is granted to the medical device manufacturer rather than the local representative, and a foreign manufacturer can submit 510(k) submissions...
In-Country Representation

or Premarket Approval (PMA) applications on its own behalf without the involvement of the local representative.

The manufacturer can change the US agent without prior agreement or authorization from the US agent, unless stipulated by prior agreement.

Foreign manufacturers (repackers, relabelers and control laboratories involved in the manufacture, preparation, propagation, compounding, processing or testing of human or veterinary drugs and human biological products, including the manufacturer of active pharmaceutical ingredients) whose drugs are imported into the US are required to register with FDA and submit a listing of every product in commercial distribution in the US (Section 510 of the *Food, Drug, and Cosmetic Act* (*FD&C Act*) and 21 CFR Part 207).

Drug products must be listed with FDA before they may be imported for commercial distribution in the US. Additionally, foreign manufacturers and importers are required to register with FDA within five days of submission of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) and to identify only one US agent. The name, address and phone number of this US agent must be submitted as part of the initial and updated registration information.

Qualifications

A US agent must be a person residing or maintaining a place of business in the US. Staff must be physically present in the US and available by phone during normal business hours. There are no special requirements for staff or facilities.

Responsibilities

The US agent must assist FDA in communicating with the foreign manufacturer, assist in scheduling establishment inspections and provide information to FDA on the products on the US market. FDA may serve documents on or supply information to the US agent, which is considered equivalent to providing said documents or information to the manufacturer itself. In the US, the medical device or drug manufacturer, rather than the in-country representative, is responsible for adverse event and pharmacovigilance reporting.

Registration

The US agent is not responsible for device or drug listing in the US, although the US agent may perform this function. Foreign manufacturers must list the name and address of their US agents in their establishment registrations.

Liability

The manufacturer maintains legal responsibility for the device or drug on the US market.

Postmarket Surveillance (Vigilance)/Pharmacovigilance

The US agent is not responsible for postmarket surveillance activities or for adverse event reporting; these responsibilities fall to the manufacturer instead.

EU

Overview


Where a manufacturer who places a device on the market under his own name does not have a registered place of business in a Member State, he shall designate a single authorised representative in the European Union.

The definition of an authorized representative according to the EU medical devices directives and GHTF guidance is: ‘authorised representative’ means any natural or legal person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer with regard to the latter’s obligations under this Directive;

The *MDD* is largely silent on specifics of the Authorized Representative’s role; however, many of the holes left by the *MDD* are filled in by MEDDEV guidance document 2.5/10.

For drugs (Directive 2001/83/EC, as amended), a Marketing Authorization may be granted only to an applicant established in the European Community. Foreign manufacturers need to appoint a legal representative in the EU to act as the Marketing Authorization Holder (MAH). The definition of such a representative is given in Directive 2001/83/EC:

The person, commonly known as local representative, designated by the marketing authorisation holder to represent him in the Member State concerned.

All foreign manufacturers must have an Authorized Representative in order to commercialize medical devices or drugs in the EU. Additionally, an Authorized Representative is required for a foreign manufacturer to undertake clinical trials in the EU. The name and address of the Authorized Representative, in addition to that of the manufacturer, must appear on the device or drug labeling.

For devices, a manufacturer may engage multiple Authorized Representatives for multiple products or product models; however, the same device model cannot be assigned
Chapter 5

to multiple Authorized Representatives. Thus, a one-to-one relationship must exist between product models and Authorized Representatives. The same requirements apply to medical devices and active implantable devices; however, this is not the case for IVDs.

The directives for devices and drugs do not define the roles and responsibilities of an Authorized Representative in detail. This, instead, is left to contractual agreements between the manufacturer and the Authorized Representative, in which a broad range of duties can be either delegated or withheld from the Authorized Representative. Thus, when engaging an Authorized Representative in the EU, it is important to clearly define the expectations of each party in their respective roles. It is also important to note that national law may include additional requirements for Authorized Representatives that reside in their territories over the requirements stipulated by the directives.

Qualifications
An Authorized Representative must be an established business entity within a member country of the European Free Trade Association (EFTA). Unlike other countries, there are no personnel qualification requirements.

Responsibilities
The Authorized Representative is required to maintain and provide upon request certain regulatory documentation to the Competent Authority for the purpose of market surveillance, including the Declaration of Conformity and Technical File for devices. Implicit in the requirement for Authorized Representatives to furnish documentation to authorities upon request is the need for the information to be up to date.

The Authorized Representative also is required to promptly communicate information from the Competent Authority to the manufacturer.

For drugs, technical files or dossiers need to be submitted for prior approval to the Competent Authority. This documentation must be kept on the premises of the legal representative.

Registration
Device registration requirements vary from one Member State to another. Where device registration is required, this can be delegated to the Authorized Representative. For drugs, registration is not required since each drug can only be marketed after issuance of a license by the Competent Authority.

Various activities require registration in the EU, including clinical trials for drugs and devices in addition to performance evaluations of IVDs and the marketing of IVDs, Class I devices, registration of Class IIa, Class IIb and Class III medical devices and custom-made devices. Intent to perform clinical investigations can be notified to the Competent Authorities by either the manufacturer or Authorized Representative; however, registration for IVDs, Class I devices and custom-made devices must be done by the Authorized Representative.

Liability
The directives are largely silent on the respective degrees of liability between the Authorized Representative and manufacturer for devices placed on the EU market. However, because the directives generally treat the manufacturer and Authorized Representative as equivalent entities (making reference to “the manufacturer or Authorized Representative”), and because the Authorized Representative is an easier target for legal action than a foreign manufacturer, the practice that has developed—and generally been supported by the courts—is one in which the Authorized Representative is fully liable for the device on the EU market.

For drugs, the MAH shall be responsible for marketing the medicinal product. The designation of a representative shall not relieve the MAH of legal responsibility.

Postmarket Surveillance (Vigilance)/Devices
The directives’ required postmarket reporting activities do not address the respective responsibilities of the manufacturer and Authorized Representative. In MEDDEV 2.12/1 (on Medical Devices Vigilance System), the manufacturer and Authorized Representative are given equal standing in most respects.

This necessitates a clear contractual understanding between the medical device manufacturer and Authorized Representative as to the respective roles in postmarket vigilance activities.

Pharmacovigilance/Drugs
For drugs, the MAH should ensure that an appropriate pharmacovigilance system is in place, assume responsibility and liability for its products on the market and ensure that appropriate action will be taken when necessary. The MAH, therefore, should ensure that all information relevant to a medicinal product’s benefit-risk balance is reported to the Competent Authorities and any other agency fully and promptly in accordance with the legislation.

When submitting a Marketing Authorisation Application, the applicant, in preparation for the role and responsibilities as MAH, should submit a description of the pharmacovigilance system and proof that the services of a Qualified Person Responsible for Pharmacovigilance (QPPV) are in place.

The MAH should have a QPPV residing in the EU, permanently and continuously at its disposal.

National regulations in some Member States require a nominated individual in that country who has specific legal obligations with respect to pharmacovigilance at a national level. One such individual may also act as the QPPV for the
whole EU. Alternatively, the QPPV for the EU may be a separate person, in addition to meeting requirements under the relevant national regulations.

**Australia**

**Overview**

To supply a drug or a medical device to the Australian market, foreign manufacturers are required to appoint an Australian Sponsor. The definition of a Sponsor, according to the *Therapeutic Goods Act* of 1989, is:

- a person who exports, or arranges the exportation of, the goods from Australia; or
- a person who imports, or arranges the importation of, the goods into Australia; or
- a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere);

but does not include a person who:

- exports, imports or manufactures the goods; or
- arranges the exportation, importation or manufacture of the goods; on behalf of another person who, at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia.

The Australian Register of Therapeutic Goods (ARTG) listing is granted to the Australian Sponsor, and the Sponsor maintains control over the market authorization in Australia.

**Qualifications**

The Australian Sponsor must be either a legal resident of Australia or a company established in the country, with a representative of the company residing in Australia.

**Responsibilities**

The Australian Sponsor is required to maintain regulatory documentation showing compliance with Australian regulations and liaise with the Therapeutic Goods Administration (TGA) on behalf of the manufacturer.

**Registration**

Listings in the ARTG must be submitted by the appointed Australian Sponsor.

**Liability**

The Australian Sponsor is considered equivalent to the manufacturer and carries a high degree of liability for the drug or device on the Australian market.

**Postmarket Vigilance**

Postmarketing vigilance requirements fall to the Sponsor. These include adverse event reporting for events occurring in Australia, recalls and maintenance of distribution records.

**Japan**

**Overview**

Manufacturers intending to manufacture drugs or medical devices in foreign countries and export them to Japan are required to be accredited by the Minister of Health, Labour and Welfare (MHLW) as an “Accredited Foreign Manufacturer,” specified in Article 13-3 of *Pharmaceutical Affairs Law (PAL)*, in the same way a Japanese manufacturer is licensed. The accreditation must be renewed every five years.

A foreign manufacturers should have either a local operating affiliate or an in-country representative in order to import and commercialize medical devices and drugs in Japan. This function is known as the Japanese Marketing Approval Holder (MAH).

Before applying for accreditation, the Japanese MAH needs to submit a “Business Number Registration Form,” with information on the foreign applicant’s business and manufacturing establishments.

A company that has a local partner with a valid importing license can be considered temporarily accredited.

**Qualifications**

The MAH must be a licensed business entity that has passed inspection for Good Quality Practice (GQP) and Good Vigilance Practice (GVP) and must be licensed by the MHLW to act as an MAH.

Staff must include a general manager, quality manager and safety manager as full-time employees. These personnel must meet minimum education requirements, depending on the class of devices with which they work.

**Responsibilities**

The MAH assumes full responsibility for the drug or device on the Japanese market. Additionally, the MAH has a role in the importing process to conduct a regulatory release assessment for each international shipment.

For many foreign medical device manufacturers, the MAH is an actual customer; this relationship is similar to a medical device company and its distributors in other countries. In many instances, the MAH is then responsible for the distribution of the medical device onto the market in Japan.

**Registration**

Drugs and medical device submissions, certifications and approvals must be submitted by the MAH.
Chapter 5

Liability
The MAH has legal liability for the drug or device on the Japanese market.

Postmarket Vigilance
All postmarket activities required fall to the MAH.

Canada
Overview
Canada is one of the few countries with a well-developed regulatory system for drugs and medical devices where a local representative is not required to market a product within its borders.

Foreign manufacturers can register and market their drugs and devices in Canada without a local representative, except in the case of devices containing wireless technology.

Manufacturers of devices containing wireless technology are subject to the requirements of the Radiocommunication Regulations (SOR/96-484) overseen by Industry Canada and must appoint a local representative in order to obtain the required wireless licenses to market in Canada as outlined in the Spectrum Management and Telecommunications—Radio Standards Procedure: RSP-100 Radio Equipment Certification Procedure (RSP-100).

Representative Types
In most markets that require in-country representation, there are three general entity types that can serve this function: a local branch (daughter company) of a foreign manufacturer, a local distributor/importer or a professional representation service. Each of these alternatives comes with various tradeoffs, which often differ by market.

Because the in-country representative generally maintains control of the drug or device approval in the market, conferring this control to a distributor or importer creates a potential for conflict of interest between the manufacturer and distributor should the relationship sour.

Where a daughter company of the manufacturer is established in a given market, the local branch can act as in-country representative and avoid the need to cede control of the product approval—and thus, market access—to a distributor or importer. In certain markets, the staff qualifications may make this approach impractical. For example, in some markets, the entity holding device registration is required to have highly qualified staff, such as a biomedical engineer.

A third alternative is the use of professional representation services. These are third-party firms who fulfill the in-country representation requirements on behalf of manufacturers without local offices. These services are available in many of the larger markets. Although these services come at a cost, they allow manufacturers to maintain control of their registrations in foreign markets without the need to establish a branch office in the country or relinquish the product approval to a distributor. An additional consideration in appointing a third-party representative over a distributor is the ability to maintain greater control over technical information, as this would not need to be supplied to the distributor.

Conclusions
The preceding examples provide a brief overview of in-country representation requirements in some of the major markets. Additionally, in almost every regulated market throughout the world, some type of local representation is required to commercialize a medicinal product or medical device.

In areas where regulatory systems are not well developed and/or not codified or transparent, there is essentially a de facto requirement for local representation since in-person interactions are often necessary for product approval and/or customs clearance.

In-country representation must be considered in any global regulatory strategy. It is important to understand the options available for representation and plan accordingly. In many cases, the local representative will hold significant power over market access for the drug or device and, thus, it is vital to identify trustworthy partners for in-country representation and establish agreements that optimize a manufacturer’s control over market authorization licenses.

It is also important to consider the ability to transfer market authorization licenses between entities, whether multiple entities can register the same device and whether multiple distributors can be authorized based on a single market authorization. The selection of a suitable in-country representative is more important in countries where one can get “locked” into a commercial relationship, e.g., in countries where it is difficult to transfer licenses and/or appoint multiple distributors.

References
1. 21 CFR 207.—Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution.