
BRIEFING

《 1083 》 **Good Distribution Practices—Supply Chain Integrity**. Because there is no information in the *USP–NF* on this subject, a new general information chapter is being proposed. This new chapter will be a part of the series of information chapters describing various aspects of the pharmaceutical supply chain. The current official chapter in this series is [Good Storage and Shipping Practices](#) 《 1079 》, with a recent proposal for revision appearing in *PF* 37(4). A workshop will be held May 22 and 23 at USP in Rockville to discuss comments on [Good Distribution Practices—Supply Chain Integrity](#) 《 1083 》 that have been received from industry.

(SM1: D. Hunt.) Correspondence Number—C102568

Add the following:

《 1083 》 GOOD DISTRIBUTION PRACTICES—SUPPLY CHAIN INTEGRITY

PURPOSE

This general information chapter describes a set of recommended practices for helping to ensure supply chain integrity for drug components (drug substances and excipients) and drug products (medicines). Worldwide efforts to help protect the integrity of medicine supply systems are ongoing and quickly changing. The nonmandatory information in this chapter is intended to contribute to the growing body of resources and best-practices information to enhance and protect supply chain integrity.

SCOPE

Supply chain integrity involves minimizing risks that arise anywhere along the supply chain, from the sourcing of the pharmaceutical raw materials to the manufacture of the medicinal ingredients, and also to the finished dosage form (medicine) itself in its packaging and its distribution to a patient or consumer. The goal of good distribution practices is to encourage sound business practices that help deter interference and manipulation by bad actors and also to provide effective means to detect adulterated drug components and drug products to prevent them from entering the supply chain. The global supply chain for pharmaceuticals and medical devices is complex, with many components of a medicine now typically arriving at the point of manufacture from other countries.

In the United States, Congress addressed supply system integrity with passage of the Prescription Drug Marketing Act in 1988. That legislation responded to the challenge of drug diversion in the wholesale distribution system and introduced the first requirement for drug pedigrees to identify prior sales, purchases, or trades of drugs by anyone other than an authorized distributor of record. That paper pedigree system proved problematic, particularly because the potential profits for bad actors grew along with the rise of the modern pharmaceutical industry and with the emergence of more complex drug reimbursement schemes (e.g., Medicare and Medicaid). Congress responded with requirements aimed at

encouraging a broader system of electronic track-and-trace pedigrees. The FDA Amendments Act of 2007 amended the federal Food, Drug, and Cosmetic Act (FDCA) with a new provision addressing pharmaceutical security. That provision, which FDA is now implementing, directs the agency to develop a standardized numerical identifier for prescription drugs and to develop standards for the identification, validation, authentication, and tracking/tracing of prescription drugs. (See final FDA Guidance for Industry on Standards for Securing the Drug Supply Chain—Standardized Numerical Identification for Prescription Drug Packages at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125505.htm>).

This general information chapter provides recommendations on how to minimize risk in international supply chains via effective partnerships and manufacturing quality systems. The chapter also gives special consideration to counterfeit medicines and provides definitions under U.S. law.

Threats to supply chain integrity are legion, encompassing such threats as the insertion of counterfeit and adulterated medicines into distribution for simple economic gain or purposes of terrorism, as well as cargo theft of regulated products and their diversion for illegal purposes. The types, medical consequences, and distribution mechanisms of counterfeit medicines are described below, followed by recommended best practices to detect and combat them. Anticounterfeiting technologies described below include the use of authentication technologies on primary packaging, and the establishment of drug pedigrees with the use of machine-readable data carriers. Best practices are provided for manufacturers to protect their products and to combat counterfeit sales through illegal Internet pharmacies. Cargo theft of medicines is increasing and guidance on good security practices is provided to assist in combating these occurrences.

This chapter may be of use to all organizations and individuals involved in the global supply chain for raw materials, drug components and medicines in their packaging, including the following:

- Manufacturers of drug substances and excipients
- Manufacturers of legally marketed drug products for human use where manufacturing operations are located at the applicant holder's facilities or at facilities belonging to the application holder's contractor
- Transportation companies involved in automobile, truck, rail, sea, and air services
- Third-party logistic providers, freight forwarders, and consolidators
- Brokers, importers, and exporters
- Packaging operations by the applicant holder or designated contractor
- Repackaging operations in which the drug product may be owned by an organization other than the primary manufacturer
- Wholesalers and distributors
- Pharmacies, including retail, mail-order, hospital, and nursing home pharmacies
- Mail distributors including the U.S. Postal Service and other expedited shipping services

DEFINITIONS

Importation

The process of importing raw materials, drug components, and drug products is at risk for opportunistic insertion of counterfeit or contaminated products, goods, and materials into the supply chain. By devoting heightened due diligence to assure proactive business practices and implementing appropriate controls and processes throughout all supply chains, the drug product manufacturer can help ensure that the product reaches the end user with its quality intact. Appropriate controls and processes also help ensure that imported drugs are treated in

a manner consistent with federal law which, under the import provisions of FDCA Title VIII, requires that, as with domestic drugs, imported drugs adhere to the following:

- Must not be adulterated [i.e., must meet any applicable compendial standards and must comply with good manufacturing practices (GMPs)]
- Must not be misbranded (i.e., must have adequate labeling and no false or misleading statements and must be manufactured in an establishment registered with FDA under FDCA Section 510)
- Must be legally marketed (i.e., subject to license either with an NDA or BLA, or other valid marketing authority)
- Must (if subject to Rx) be dispensed only upon a valid prescription
- Must be distributed with an appropriate pedigree

Importers include entities, their agents, or brokers who make an import declaration (i.e., a duty entry form that describes the products, goods, and materials acquired from another country) and who are liable for any payment of duties on the imported products, goods, and materials. Typically, the importer is named as the consignee in the shipping documents and/or the buyer in the exporter's invoice. Manufacturers, repackagers, distributors, or other entities who import products and materials for the purposes of producing and/or selling drug components, drug products, and medical devices are importers. Importers are responsible for knowing and understanding the relevant laws and requirements of both the exporting and importing countries.

Product safety and security expectations of importers are aimed at minimizing risks along the product supply chain and integrating integrity measures to secure the supply chain, as appropriate. These measures include product track-and-trace technology or chain-of-custody approaches along with verification of product suppliers, agents, or brokers. Collaborating with custom officials and other law enforcement agencies is an additional way an importer can gain a greater understanding of the strengths and weaknesses within the supply chain.

Importers should undertake three primary initiatives beyond ensuring compliance with applicable federal laws and regulations in order to help prevent and detect potential risks that could impact product safety along with product and supply chain integrity:

- A risk-based approach to supply chain management
- Development of effective and trustworthy supplier partnerships and contracts
- A quality system for the management of supply chain integrity

Each of these initiatives is discussed further below.

Supply Chain Risk Management

Importers should establish a risk-based process to assess, identify, and understand the critical areas in their supply chains and should clearly assign responsibilities. A formal, documented quality assurance program should be established for supply chain operations, along with a mechanism to disseminate supply chain information within the organization.

Drug substances and excipients may be imported directly from the manufacturer via a short supply chain or from a distributor/broker or a number of distributors/brokers involved in a long, complex supply chain that involves many countries. Importers themselves should audit the drug substance and excipient manufacturers, or use established third-party audit firms and not rely solely on a completed questionnaire from the manufacturer. Failure to know and confirm the identity of the drug substance and excipient manufacturers and their exact manufacturing locations (show factory) gives rise to the risk that the item is actually produced in another

location (shadow factory) by either the original company or subcontractors under conditions that do not satisfy GMP requirements. Recommended measures include the following:

- Confirm the name(s) and geographic location(s) of suppliers and their subcontractors
- Investigate the company's reputation, and determine if it is a subsidiary of a larger company
- Establish that the supplier is registered with its national regulatory authorities and is licensed to manufacture pharmaceutical ingredients (not bulk chemicals)
- Determine whether subcontractors are used by suppliers and for what purpose, and establish their identity
- Establish procedures to prevent tampering during shipment, e.g., tamper-evident embossed tape on boxes and drums or numbered seals on bulk materials
- Verify or test the products, goods, or materials throughout the supply chain, e.g., by verification or testing at certain supply chain stops/points
- Verify the shipping documentation associated with the imported product or material, i.e., its chain of custody
- Be alert to signals/events/disruptions in the environment or changes in the supplier's organization that may negatively impact suppliers, subcontractors, or the products, goods, or materials
- Be alert to information that could indicate counterfeiting or other fraudulent activities such as offers to sell the product at a price significantly below market value.

Development of Effective Supplier Partnerships

Spending time in advance to fully investigate, assess, and understand if a potential supplier is a suitable partner helps avoid problems that could arise later. It also provides an indication of the supplier's willingness to work with the importer in resolving unforeseen issues or complying with new requests. A supplier's cooperation and ability to comply with the importer's requirements are crucial in a contractual relationship.

An initial investigation and assessment of a potential supplier should be conducted in person and onsite where the product or material is made, as a quality audit and in accordance with appropriate regulatory requirements for the importer's country (e.g., cGMP compliance for U.S. markets). This approach helps to ensure that a robust quality system is in place and helps to gain a better understanding of the product or material to be imported. The results from the initial assessment provide the working baseline for further engagement with the supplier. Any areas of concern should be discussed and addressed with corrective or preventive action plans as needed. Recommended measures include the following:

- Investigate the supplier's reputation by reviewing its business rating (e.g., Dunn & Bradstreet rating), any intellectual property or trademark infringements, or other violations
- Research the supplier's certifications, e.g., those from the International Organization for Standardization (ISO) and those in the World Customs Organization's Authorized Economic Operator program such as the Customs–Trade Partnership against Terrorism (C-TPAT),¹ and the Customs Watch programs (EU or comparable programs)²
- Determine the supplier's experience and reputation as a vendor for the pharmaceutical industry to determine the company's commitment to the long-term viability of its business and dedication to product safety and integrity
- Check to see if the supplier has registered with a verification program
- Evaluate the supplier's regulatory compliance with the laws and requirements of both the exporting and importing countries

- Establish procedures and schedules for conducting ongoing routine supplier assessments to avoid subtle, progressive, or surreptitious loss of quality following internal cost cutting or subcontracting as a cost-saving measure (quality fade)
- Incorporate into the contract or formal agreement the results of continuous assessment of supplier requirements and expectations, thereby enhancing confidence that the supplier will provide a quality product in a safe and secure manner
- Establish procedures for corrective actions when a product does not meet specifications, when the importer's requirements are not met, or when there are changes in the supplier's business

Building a Supply Chain Quality System

Existing quality management frameworks such as ICH Q10 Pharmaceutical Quality System, ISO, or comparable guidances or standards provide a solid basis for ensuring product safety. Product and supply chain integrity, however, require going beyond the typical product compliance and control measures described in these quality frameworks. Importers can enhance their processes, policies, specifications, procedures, and documentation for product safety and supply chain integrity by meeting the requirements of the American National Standards Institute's Security Assurance Standard (ANSI/NASPO SA-2008) or other comparable standard. Recommended measures include the following:

- Establish a senior management structure that collectively focuses on product safety, product integrity, and supply chain integrity
- Establish and document well-defined roles and responsibilities for addressing product and supply chain integrity issues such as product adulteration, counterfeiting, theft, and diversion
- Ensure that staff have appropriate training, knowledge, experience, skills, and competence to perform their roles and responsibilities
- Institute mechanisms for continual improvement by facilitating communication, information sharing, and prioritization to ensure implementation of refined business processes and technological solutions.

COUNTERFEIT DRUGS AND MEDICAL DEVICES

Definitions of Counterfeit and Substandard Drugs

Legal definitions of counterfeit, falsified, or substandard drugs vary from country to country, and some nations do not have a legal definition. The European Parliament in June 2011 adopted Directive 2011/62/EU, amending Directive 2001/83/EC, to add extensive requirements to prevent entry into the legal supply chain of falsified medicinal products. The Directive included a detailed definition of "falsified medicinal product" (see Article 1 point 33) that pertains to any medicinal product with a false representation of its identity, source, or history. In the United States FDCA, 21 USC 321 §201(g)(2), defines a counterfeit drug as the following:

A drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor.

Substandard medicines are drug products whose composition and ingredients do not meet

their quality standards and specifications. *Counterfeit* and *substandard* are not interchangeable terms, but for convenience and simplicity this chapter refers to both as *counterfeit*.

Types of Counterfeit Drugs

All forms of medicine, including those that purport or appear to be branded, generic, over-the-counter, or biologic drugs, in tablet, injectable, or other dosage forms, are under threat of being counterfeit or substandard. The most common motive for producing a counterfeit drug product is commercial gain (i.e., economically motivated adulteration), achieved by providing a reduced amount of the drug substance or even totally lacking any drug substance, or by substituting another lower-cost drug substance. Similarly, excipients can be omitted, reduced, or replaced. In some cases the amount of drug substance can be greater than the labeled content (i.e., the economic motivation may be evasion of regulatory requirements, or compendial quality standards). Counterfeit drug products may contain the correct amount of ingredients but may not be manufactured according to GMPs and/or may be processed in sites that are not registered with the relevant regulatory authority. Counterfeiters often use modern packaging and printing technologies to produce fake labels and primary and secondary packaging in order to deceive pharmaceutical companies, regulators, wholesalers, distributors, pharmacies, and end users. Using these technologies, counterfeiters can duplicate or produce facsimiles of some of the authentication added by manufacturers to deter counterfeiters. Counterfeiters also can produce fake labels and primary packaging with altered expiration dates that falsely prolong the shelf life.

Although counterfeit drugs target all therapeutic categories, differences can depend on geographical location and disease prevalence. In developing countries, anti-infective drugs that treat life-threatening conditions are extensively counterfeited as well as simple analgesics, antihistamines, and vitamins. In developed countries, expensive and best-selling drugs are counterfeiters' targets. Public health officials can list the drugs at highest risk for counterfeiting, but these do not take into account unexpected opportunities such as an outbreak or threat of a pandemic disease or a sudden shortage of a widely used drug. Counterfeiters are opportunistic and quickly offer to supply such drugs and will cease doing so when the threat recedes or the shortage is remedied.

Medical Consequences of Counterfeit Drugs

The clinical outcomes for patients who take counterfeit or substandard drugs can vary widely from lack of efficacy to death and are rarely documented except in the cases of either successful prosecutions or multiple deaths. Even in the event of multiple deaths, it is difficult to obtain accurate statistics in developing countries. For example, the meningitis vaccine used in Niger in 1995–1996 contained only water and resulted in an estimated 2500 deaths. The absence or low levels of drug substance in counterfeit antimalarial drugs are believed to cause a large number of deaths annually in Africa and Southeast Asia. Toxic ingredients also can cause death or serious illness. In 2008, batches of heparin sourced from China were found to be adulterated with oversulfated chondroitin sulfate, a molecule that mimics heparin's anticoagulant effect but to a lesser degree. The adulterated product was linked to an increase in serious adverse events and deaths, resulting in the withdrawal of heparin injection and heparin-containing medical devices and diagnostic products from a number of countries.

The use of toxic excipients such as diethylene glycol-contaminated glycerin or diethylene glycol has occurred in five countries since 1990. The latest occurred in Panama in 2006 and caused at least 115 deaths. Serious side effects also can occur when an additional drug substance is added to the drug product or completely replaces the drug substance stated on the label. Patients may be hypersensitive to the additional/replacement drug substance, or the drug substance may be intended to produce a therapeutic effect that can be quite different from that of the labeled drug.

Besides their adverse effects on individual patients, counterfeit drugs pose a wider threat to the global health care system. Subtherapeutic doses of antibiotics contribute to the development of disease-resistant strains of bacteria. The failure of counterfeit or substandard drug products to provide the desired therapeutic effect can undermine public confidence and can cause patients to seek alternative drug products such as herbal medicines or traditional nonmedical approaches, especially in developing countries. In addition, markets where counterfeits are allowed to thrive can find it increasingly difficult to support legitimate producers and distributors.

Distribution and Extent of Counterfeit Drugs and Devices

Patients' access to prescription drug products and medical devices involves controlled channels such as doctors, hospitals, or registered pharmacies as well as unlicensed channels such as illegal pharmacies, street markets, criminals, etc. Another channel (pharma-tourism) involves traveling to other countries in order to obtain drug products. Yet another source is the Internet, which provides a mechanism for global sourcing of drug products and medical devices and provides criminals an almost perfect mechanism for advertising and selling counterfeit drug products and medical devices with little risk to themselves. The supplier and the recipient never meet in person because advertising, ordering, and payment take place in cyberspace. Only the delivery of the drug products or medical devices by mail is a physical transaction. The pharmacy's server may be in one country, the advertiser's server (spammer) in another country, the manufacturing site in a third, processing of credit card payments in a fourth, the banking facilities in a fifth, and the criminals running the operation in a sixth country.

Because of the paucity of information, the exact extent of counterfeit drugs either in individual countries or globally is not known. Counterfeiters do their best to hide the extent of their business practices, and so estimates generally are based on the amount of products seized by customs agents or raids on vendors followed by an in-depth investigation by law enforcement or regulatory authorities. Some general points can be made. In countries with strong regulatory oversight combined with alert and proactive law enforcement and honest pharmaceutical manufacturers, wholesalers, distributors, and pharmacists (e.g., North America, Western Europe, and Japan), the amount of counterfeit drugs entering the marketplace is low at present. The number of counterfeits reaching these countries is increasing and is predicted to continue to rise in the future. The amount of counterfeit drugs in developing countries varies from country to country but is considerably higher than in North America, Western Europe, and Japan. Strong governmental action to combat counterfeit and substandard drugs produces a sharp decrease in their availability, but such actions must be applied continuously or the levels will return rapidly to their previous level.

BEST PRACTICES TO COMBAT COUNTERFEIT DRUGS AND MEDICAL DEVICES

Combating counterfeit drugs and medical devices requires the combination of a number of strategies that involve the cooperation of stakeholders such as pharmaceutical or device manufacturers, supply-chain entities, regulatory authorities, law enforcement, and patients. No single approach or entity can be successful working in isolation—the brand holder may detect counterfeits and identify their source, but has no powers to enforce the law itself. Enforcement and apprehension require the cooperation of national authorities such as the U.S. Immigration and Customs Enforcement's Homeland Security Investigations, U.S. Customs and Border Protection, FDA, the U.S. Postal Inspection Service, and the Drug Enforcement Administration, along with multinational and global organizations such as the International Criminal Police Organization, World Customs Organization, the Permanent Forum on International Pharmaceutical Crime, the European Heads of Medicine Agencies Working Group of Enforcement Officers, and the World Health Organization's International Medical Products

Anti-Counterfeiting Taskforce.

Packaging Technologies

Packaging technologies such as tamper-evident designs, authentication technologies, and serialization are an integral part of brand protection and are applicable to both the product label on the primary packaging and/or on the secondary packaging. Although tamper-evident designs are relatively simple (e.g., perforated openings or tamper-evident seals), they can be combined with a number of more sophisticated authentication technologies in an approach described as *layering*. Authentication technologies are classified as overt, covert, and forensic. These authentication technologies are not new, and many have been used in the bank note and explosives industries. Overt technologies can be detected by eye, smell, or touch without any other assistance and are readily discernable to pharmacists, patients, and counterfeiters. Typical features include raised printing, color-changing inks, watermarks, and optically variable devices (holograms). Covert features require instrumentation such as scanners or microscopes for viewing or reading. Typical covert features include microtext and microthreads, nano-encryption, taggants, and invisible or luminescent inks that are sensitive to a specific wavelength of light (e.g., UV or black light). Information about covert features and the equipment required to detect them must be provided so personnel in any part of the supply chain can recognize them. Forensic features require sophisticated laboratory tests, and brand owners keep their presence a closely guarded secret for use in legal proceedings. From a drug development perspective, analysts should be aware of extractables and leachables from a label's adhesive, ink, etc. that can be used in the process of product authentication when their presence is known and because of their unique chemical structure. For example, this applies to the special inks used for labels of semipermeable containers.

One limitation of these approaches is that they protect the package, not the product. Physical-chemical identifiers (PCIDs) are substances that possess a unique physical or chemical property and are added directly to solid oral dosage forms. Examples of PCIDs include inks, pigments, flavors, and molecular taggants that possess established safety profiles. A substance employed as a PCID should not adversely affect the identity, strength, quality, purity, potency, or bioavailability of the solid oral dosage form. Such substances may be in use as food additives, colorants, or excipients.

Establishment of Drug Pedigrees

A drug pedigree is a statement of origin that identifies each prior sale, purchase, or trade of a drug, including the date of the transactions and the names and addresses of all parties involved. This can be recorded on paper or electronically (e-pedigree) to secure the drug supply chain against entry of counterfeit, stolen, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs and additionally can assist in product recalls. The advent of electronic pedigrees has been anticipated for many years, but has proved difficult to realize for a wide variety of reasons mostly related to the practicality and affordability of the technology, and to the logistical complexities of introducing new business and regulatory requirements across industries (manufacturers, distributors, and users in the healthcare industry) and widely diverse national regulatory jurisdictions. Most envisioned pedigree systems entail giving each prescription drug package a unique identifying code called a standardized numerical identifier (SNI) at the point of manufacture. If a drug container's contents are subdivided during repackaging or if the manufacturer's smallest unit-of-sale package (e.g., prefilled syringes) is repackaged and sold individually, then a new and unique SNI must be applied to each unit of the subdivided packaging and to each of the separated drug-filled containers. To maintain traceability, the repackager's SNIs must be linked to the manufacturer's SNI. SNIs can be created by combining the 10-character National Drug Code (NDC) for the drug with a serial number of up to 20 characters (numbers or letters and numbers). The SNI can be applied to

packaging in both human-readable and machine-readable forms. The human-readable form enables the package to be identified when electronic means are unavailable or when pedigree transactions are recorded on paper.

The implementation for e-pedigrees requires that the SNI be incorporated into a machine-readable data carrier such as a 2-dimensional bar code (2D bar code) or a radio-frequency identification (RFID) tag. A 2D bar code consists of square modules arranged within a perimeter-finder pattern that is variable in size and data capacity. The data matrix subset ECC 200 is the only version that supports the GS1 System of global standards for identification and error checking and correction algorithms. Specifications for ECC 200 have been published in ISO 16022:2006 Automatic Identification and Data Capture Techniques—Data Matrix Bar Code Symbolism Specifications. Two-dimensional scanners or vision systems can read data matrix symbology but require a direct line of sight.

RFID uses electromagnetic waves to transmit data between a terminal (interrogator or reader) containing an antenna and a tag (transponder) with an integrated circuit and an antenna. RFID tags are described as *active* if their own power source sends and receives information, *semiactive* if the power source operates the chip circuitry but does not communicate with the interrogator, or *passive* if they do not possess their own power supply and respond only when interrogated. The information received by the terminal is stored in a database. RFID tags can be read at a distance, but the range varies considerably depending on whether the tag is active or passive, the radio frequency used, the antenna size, the amount of stored information, and the local environment. For example, the presence of metal or water can significantly reduce the range for passive tags. RFID tags do not need a direct line of sight for reading and can be placed underneath a product label and still be read.

Application of Machine-Readable Data Carriers to Drug Products

To establish an electronic drug pedigree, 2D bar codes and/or RFID tags are required on the unit of sale, secondary or tertiary packaging (case), or pallets. Different carrier types can be selected for different levels of packaging, e.g., 2D bar code or RFID tag applied to the unit of sale and RFID tags used at the case and pallet level. Information can be added to the primary container itself by laser-etching 2D bar codes directly onto the glass or plastic container surface for parenteral products. Container vendors could include information such as glass batch, container lot number, manufacturer, manufacturing location, date of manufacture, and so on. Etching the 2D bar code on the container surface at the pharmaceutical manufacturing facility or adding the 2D bar code to the product label could provide drug product information. RFID tags can be added under or on the product label or on the cap or bottom of a container.

The addition of a data carrier to the primary container–closure system must not affect the safety, identity, strength, quality, and purity of the drug. Concern has been expressed about the possibility that accidental, repeated interrogation of an RFID tag may adversely affect biopharmaceuticals via nonthermal effects. Recent studies have indicated that several hormones, immunoglobulins, and vaccines are not affected by high doses of effective isotropic radiated power (EIRP) under experimental conditions. It is too early to extend these limited results to all biopharmaceuticals, and analysts should study the effects of electromagnetic radiation on these products before using RFID tags on their primary packaging. Alternatively, 2D bar codes can be used instead of RFID chips on primary packaging for biopharmaceuticals because 2D bar codes do not involve radio emissions.

An RFID testing protocol for biopharmaceuticals should include the following parameters:

- Use of a range of standard frequencies: high frequency (13.56 MHz) and ultrahigh frequency (915 MHz and 2.4 GHz)
- Power level: at least 8 W EIRP (double the level approved by the Federal

Communications Commission)

- Test chamber: dark, temperature-controlled radio-frequency (RF) anechoic chamber
- Distance of product from power source: position at which at least 90% of peak RF power is applied
- Time frame: at least 24 h
- Determination of effect of RF exposure: analyze the product by purity and stability-indicating assays

Repackaging Guidance, Information Retention, and Security

Repackaging plays an important and increasing role in drug distribution, but also presents challenging and unique issues in terms of assuring and maintaining the integrity of the medicine supply. For example, repackaging drug products can lead to the loss of security devices placed on the packaging by the manufacturer and removal of the data carrier. Repackagers should add equivalent authentication devices, along with a new data carrier programmed with the original information. In addition, procedures must be in place to ensure the destruction of the removed packaging to prevent counterfeiters from obtaining it and adding counterfeit product to the genuine packaging.

All the information collected in the drug pedigree for each unit of sale for each batch should be retained for the same period of time as all other batch records. The volume of data generated will be considerable and will require investment in data storage capabilities. The consolidation or linkage of the data generated by the various parties in the supply chain will be challenging and will be further complicated if the product is repackaged.

The presence of an RFID tag on a prescription drug product package should be clear, conspicuous, and accurate and should be indicated by either a statement or a symbol that has been developed in agreement with all parties involved in the drug supply chain. Information on an RFID tag may be read covertly at a distance without direct line of sight and without the patient's knowledge if the tag is still active on the drug product. This raises privacy concerns for the patient, and this issue should be addressed if RFID tags are used on the item of sale. If the tag will be disabled (killed) it should be done at the last step in the supply chain just before it is provided to the patient. This places an additional burden on the dispenser (pharmacy, hospital, or physician's office) and destroys information that would be required if a product recall is initiated. Currently available tags can be temporarily deactivated and then later reanimated using a special device that retrieves the information. These RFID tags are known as *zombie tags* and are one approach to allay patient concerns about privacy issues. The alternative approach is to use 2D bar codes because they cannot be covertly read at a distance and require a direct line of sight at short range.

International Standards and Global Approaches to Establishing Drug Pedigrees

Because drug products and medical devices are items of commerce, they can use current readily accepted global trade standards. The GS1 system of standards is the most widely used supply chain standards system and includes standards for both 2D bar codes and RFID (Electronic Product Code standard EPCglobal) and the Global Trade Item Number as an identifier for items in trade. GS1 standards depend on international standards such as those issued jointly by ISO and the International Electrotechnical Commission.

The European Federation of Pharmaceutical Industries has a project for coding and identification that uses a 2D data matrix bar code to demonstrate the feasibility of mass serialization of drug packs within the European Union. The project uses an existing GS1 EAN open standard and data matrix code ECC 200. This approach is supported by the Groupement International de la Répartition Pharmaceutique Européenne, an umbrella group that represents European pharmaceutical wholesalers. This group suggests that although RFID may be a

solution in the future, the current best practice is to use 2D bar codes. France has added to its packaging a 2D data matrix ECC 200 bar code and GS1-128 syntax that contains the CIP13 code, batch number, expiration date, and human-readable text. Other countries, for example, Turkey, have published requirements for the addition of 2D bar codes to the primary packaging of pharmaceuticals.

Within the European Union, the mass serialization of product packs is not envisaged to follow each step through the supply chain but to provide a way to allow authentication of prescription drug products at the point of dispensing by the pharmacist by transmitting the code electronically to a centralized data base. This would allow the pharmacist to determine whether the drug had been previously dispensed, recalled, or is counterfeit.

Combating Illegal Internet Pharmacies

Legitimate pharmacy sites on the Internet provide consumers with a convenient and private way to obtain drug products, but many illegal sites claiming to be legitimate offer approved and unapproved prescription drug products and herbal supplements at low cost. Some patients use illegal Internet pharmacies not just to minimize costs but also to avoid obtaining a legitimate prescription from a licensed physician (which evades professional supervision, the need for which occasioned FDA classification of the drug as Rx instead of Over the Counter). Accordingly, products supplied by illegal Internet pharmacies carry the threat of multiple risks to a patient's health: they may be counterfeit, may not contain the purported drug substance, may contain toxic materials, and may not have been stored, dispensed, or prescribed properly.

Guidance for selecting legitimate Internet pharmacies is available from the National Association of Boards of Pharmacy (NABP) via its on-line Verified Internet Pharmacy Practice Sites program that lists licensed pharmacies engaged in a full range of defined pharmacy practices. Listed Internet pharmacies must comply with NABP's criteria for compliance with state and federal laws. A second NABP program, the e-Advertiser Approval Program, assesses and approves Internet advertisers that offer only limited pharmacy services or other prescription drug-related services online. A review of nearly 7000 Internet pharmacy sites determined that 96% of the sites were out of compliance with NABP's patient safety and pharmacy practice standards.

Legitimate Internet pharmacy sites are characterized as follows:

- Require a prescription from a licensed doctor, usually by mail (if they accept a fax copy, they will always call the prescribing physician to verify the prescription)
- Provide a physical address or a phone contact number
- Require submission of a detailed medical history
- Clearly state their payment, privacy, and shipping fees on their sites
- Use secure or encrypted website connections for transactions.

Illegal Internet pharmacy sites are characterized as follows:

- Do not provide a physical address or a phone contact number
- Offer prices that are dramatically lower than the competition's prices
- Do not require a prescription for prescription drugs or offer access to bogus prescriptions
- Offer non-FDA approved prescription drugs
- Offer bonus supplies with an order
- Are named on the NABP's "Not Recommended Sites" list of Internet pharmacies.

Illegal Internet pharmacies rely on web hosting services, web listings, and spamming to

advertise their services, and typically they obtain payments by credit cards and services that link to the owner's bank account. More than 80,000 portal Web sites currently sell advertising space for unregulated medications and link to one or more of the 1400 anchor websites that allow customers to place orders via illegal pharmacies. The host server should have the appropriate technology, including spam blocking and automatic spam filtering, to block websites from unlicensed internet pharmacies. There should be a commitment by search engines to enforce terms and guidelines for refusing advertisements from unlicensed pharmacies. In addition, payment service providers should have in place policies that prohibit the use of their services for the purchase and sale of goods that are determined to be counterfeit under applicable law.

Best Anticounterfeiting Practices

Best practices should address threats to the overall product supply chain and not just to one part of the supply chain. Thus the application of anticounterfeiting measures, such as authentication technologies and establishing a drug pedigree for the drug product, will not alone protect the patient if the drug product has been unintentionally manufactured with a counterfeit drug substance or excipient. Similarly, a well-controlled national supply chain with established drug pedigrees will not by itself protect patients who purchase counterfeit drugs or medical devices via the Internet from illegal pharmacies. Vigilance is needed to combat counterfeiters who use the Internet to promote their products and to insert them into an established supply chain.

Pharmaceutical manufacturers should establish a dedicated team to oversee product security (brand protection), and this team should be integrated into established corporate activities, systems, and processes. The membership should be global and cross-functional, and its activities should include the following:

- Establish a formal process to implement and modify product security features
- Maintain ability to authenticate products
- Work with trade partners and understand the downstream distribution chain
- Review distribution agreements in an effort to shorten or restrict the distribution chain
- Identify, manage, and monitor a company's Internet domain portfolio
- Monitor the Internet for unauthorized offerings of company products
- Analyze threats and prepare countermeasures
- Establish a network of contacts with national and international enforcement agencies
- Establish a public awareness program to highlight the dangers of obtaining products from unauthorized sources
- Establish procedures to respond to the discovery of counterfeits.

When a counterfeit product or suspected counterfeit product is detected in the supply chain, the marketing authority should immediately implement a number of steps, including the following:

- Inform relevant regulatory authorities. In the United States, use MedWatch, the FDA Safety Information, and Adverse Event Reporting Program
- Assess the counterfeit's hazard to patients' health
- Monitor adverse drug event reports associated with the suspected counterfeit lots when patients' health has been or may be affected
- Establish whether the lot number on the counterfeit product is genuine or fake
- Recall and quarantine or destroy a genuine product that has been relabeled or repackaged with counterfeit lot numbers
- Publicize ways to distinguish the packaging of genuine vs. counterfeit products, for

example by lot number, expiration dates, packaging design, overt authentication or tamper-evident technologies, and photographic examples

- Preserve product samples as evidence, and conduct a detailed analysis of the counterfeit product, its packaging, and its route of entry into the supply chain.

DIVERSION AND THEFT

Diversion of genuine drug products or medical devices occurs when they are redirected from medical sources to illegal markets or illegal use, usually for financial gain or for personal use, and can occur within a country or internationally. Methods of diversion include doctor shopping, whereby an individual visits numerous doctors in order to obtain multiple prescriptions; forgery of prescriptions; fraudulent prescriptions written by physicians; and illegal Internet pharmacies. Diverters can obtain high-value drug products from patients and also relabel returned expired drug products. Pharmaceuticals that have been donated or sold at a discounted price to support a public health initiative can be diverted and sold for profit in the private sector.

The most commonly diverted drug products in the United States are narcotics, depressants, and stimulants. To combat prescription diversion, a number of states have established prescription monitoring programs that facilitate the collection, analysis, and reporting of information. The establishment of drug pedigrees either at a federal or state level assists in detecting and combating the reintroduction of diverted drug products into the distribution network but does not affect products diverted for personal use.

Theft of drug components, drug products, and medical devices can occur anywhere in the supply chain. This includes theft from the manufacturer during transportation by air, rail, road, or ship, from distribution centers and warehouses, and from hospitals or pharmacies. Stolen and diverted products pose a significant risk to public health because of the risks of adulteration and of storage or handling under improper conditions that have adversely affected the quality of the product before it is illegally reintroduced into the supply chain. Theft of a part of a lot could result in the recall of the whole lot from the distribution chain and from patients.

Companies that store and ship large amounts of products (pharmaceutical and medical device manufacturers, distributors, etc.) should review their security procedures for their warehouses and distribution centers and their transportation procedures, particularly for transportation by trucks and tractor trailers. Companies should give particular attention to high-value drug products or medical devices that are in short supply because of an urgent health need.

A number of factors increase the risk of theft from road transportation vehicles. These include a lack of two-way communication with the driver(s), lack of tracking or specific security SOPs as well as the use of multiple sub-contractors, shipping over a weekend or holidays, stopping or parking in high-risk areas, and drivers' leaving the vehicle unattended. The risk of theft of high-value cargoes can be reduced by the implementation of good trucking security practices such as those described below.

Security systems and devices on trucks and/or trailers should include the following:

- Tamper-evident seals
- Immobilization devices and alarms
- Two-way communication system with driver
- Monitored and/or geofenced GPS tracking system
- Covert cargo tracking device

Security procedures should include the following:

- Verify product loading and vehicle sealing at collection point
- Verify that tamper-evident seals applied to the outer door of a vehicle or transport carrier have not been broken, to demonstrate that the door was not opened during transport
- Plan schedules and routes to avoid stops or overnight parking in insecure locations
- Plan schedules to avoid delivery or arrival on weekends or holidays
- Be aware of and approve any subcontracting arrangements, and use only known carriers
- Implement screening/vetting procedures for drivers
- Plan for emergency 24-h contact and contingencies in case of accidents or unexpected events

The risk of theft from storage facilities can be reduced by the implementation of layered good storage security practices such as the following:

- Secure external perimeter, closed-circuit TV systems, and lighting
- Alarm systems on doors, windows, and skylights and appropriate use of motion detectors
- Back-up power supply for security systems
- Restricted access to loading docks
- Security procedures for all visitors and drivers
- Security awareness training with emphasis on staff being vigilant about their surroundings

License holders should have a plan in place to respond to theft, including informing law enforcement, pharmacies, regulatory authorities, and the public. After the discovery of a theft, assemble the following details as soon as possible:

- Product name and type (prescription, OTC, infant formula, etc.), samples, bulk product, drug substance, medical device, etc.
- Product form (tablets, capsules, parenteral, powders, type of device, etc.)
- Lot number(s), National Drug Code number(s), and SNI
- Description of packaging/containers, including any tamper-evident protection and authentication technologies
- Quantity of each product lot stolen
- Quantity of product lots already in legitimate distribution or secured under the license holder's control
- Evaluation of potential risks to the public that may be posed by the product if it is held under incorrect handling and storage conditions

A communications plan should inform pharmacies, the public, and regulatory authorities of the occurrence and provide instructions or guidance to show how pharmacists or patients can identify the stolen lot(s) and what steps patients should take if they have received the stolen product.

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¹ C-TPAT is a voluntary government–business initiative to build cooperative relationships that strengthen and improve overall international supply chain and U.S. border security.

² An application for a Customs Watch allows the authorities to detain a suspected shipment. The goods remain in custody until the owners and the importer have come to an agreement or a court reaches a decision. The legal basis is the EU Customs Regulation (1383/2003).