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PhRMA

November 6, 2003

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2003N-0361; Anti-Counterfeit Drug Initiative; 68 Federal Register 51270

Dear Sir/Madam:

The attached set of comments on the Food and Drug Administration's Anti-Counterfeit Drug Initiative are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2002, our members invested over $32 billion in the discovery and development of new medicines.

PhRMA welcomes the opportunity to comment on this initiative. We trust that our comments will be useful to FDA and other stakeholders as this initiative moves forward.

Sincerely,

Alan Goldhammer

2003N-0361 C38

Pharmaceutical Research and Manufacturers of America

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Comments of the Pharmaceutical Research and Manufacturers of America
on the Food and Drug Administration's Anti-Counterfeit Drug Initiative

Docket Number 2003N-0361

November 6, 2003

The Pharmaceutical Research and Manufacturers of America (PhRMA) welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) anti-counterfeiting initiative. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2002, our members invested over $32 billion in the discovery and development of new medicines.

PhRMA member companies have a strong interest in ensuring that the drugs they discover and manufacture are safe, effective and of the highest quality. This interest extends beyond the factory gates all the way to the patient, since even the most innovative medicines cannot help the patients who need them if those medicines are compromised by breakdowns in the distribution system, including diversion and counterfeiting. PhRMA member companies are committed to doing their part to protect the integrity of the American drug supply.

PhRMA applauds FDA's efforts to combat counterfeiting by establishing a Counterfeit Drug Task Force to explore available anti-counterfeiting strategies. Although the American drug supply remains the safest in the world, PhRMA believes it is prudent for FDA to seek ways proactively to strengthen the drug distribution system. As the Agency has noted, the number of counterfeit drugs discovered in the supply chain has increased in recent years, as has the apparent sophistication of the counterfeiters. PhRMA thus strongly supports the work of FDA's Counterfeit Drug Task Force in developing proactive strategies to protect the nation's drug supply before counterfeiting becomes a significant public health threat.

PhRMA's detailed comments to the Interim Report issued by FDA's Counterfeit Drug Task Force are presented below. While these comments do not attempt to address every question raised in the Interim Report, they do present PhRMA's views on the main technological and legal/regulatory issues raised in the Interim Report. Clearly, these issues are complex and will not be resolved without sustained collaboration between FDA and industry stakeholders over many years. PhRMA looks forward to working with FDA and other industry stakeholders in the coming months and years to strengthen and protect the U.S. drug supply against the threat of counterfeits.

Executive Summary

PhRMA agrees with FDA's Counterfeit Drug Task Force that there is no single "magic bullet" that will prevent counterfeiting. The only effective way to combat counterfeiting is to adopt a multi-pronged strategy that addresses weaknesses throughout the distribution system. This will require dedicated, sustained and coordinated efforts by all stakeholders, including manufacturers, wholesalers, distributors, pharmacies, physicians, patients and the FDA. PhRMA member companies are committed to doing their part to prevent counterfeit medicines from entering the U.S. drug supply.

The Federal Food, Drug, and Cosmetic Act establishes a closed distribution system in the U.S. though recent event s have identified areas where it should be strengthened. PhRMA believes that a closed distribution system is the best way to assure the integrity of the U.S. pharmaceutical supply. A closed system may be defined as one where product is shipped directly from the manufacturer to the distributor and then on to the pharmacy and ultimately, the patient. Each business transaction in the supply chain would be recorded and a pedigree, ultimately tracing each lot back to the manufacturer would be maintained. Optimally, this pedigree would be generated and maintained electronically to permit the authentication of drug products in real time at any point in the distribution system, although even a paper pedigree system would be useful. Moreover, a closed system should employ many technological and legal impediments to make it more difficult and costly for diverted or counterfeit drugs to enter into legitimate commerce. In addition, importation by anyone other than the drug's manufacturer would be prohibited. Reimportation of U.S. manufactured pharmaceuticals is already regulated under the Prescription Drug Marketing Act (PDMA).

The estimated large number of dispensing sites in the United States (approximately 80,000 by some estimates) means that the drug distribution system is complex. While three major drug distributors dominate the primary market, there are a much larger number of both licensed primary and secondary distributors. Secondary buying and selling of packaged pharmaceuticals is common as a normal part of inventory adjustment. Personal importation of small amounts of pharmaceuticals has been documented with increasing frequency, and numerous Internet sites offer consumers pharmaceuticals at deeply discounted prices even though these products are of dubious origin and quality. Repackaging of pharmaceuticals takes place at a variety of levels despite the fact the manufacturer's original container/closure system has been breached and product quality may suffer as a result. Collectively, all of the above practices create limited opportunities for counterfeit or diverted drugs to enter the system, thus potentially compromising the public health of patients.

In order to strengthen the closed U.S. drug distribution system, PhRMA believes that the following strategies must be implemented:

Facilitate Voluntary Implementation of Counterfeit Resistant Technologies. PhRMA supports the voluntary implementation of counterfeit resistant technologies on

drug packaging and labeling but does not believe these should be mandated by FDA. Counterfeit resistant technologies include overt and covert packaging and labeling features and chemical taggants. These technologies provide multiple layers of security that make drug products more difficult for counterfeiters to reproduce accurately. They also are useful for assessing the authenticity of drug products already identified as "questionable." It is important to recognize, however, that counterfeit resistant technologies do *not* provide a mechanism for identifying counterfeit drugs in real time or preventing counterfeit drugs from entering the marketplace. First, counterfeit resistant technologies can themselves be duplicated, often within 12-18 months, and thus need to be rotated on a regular basis. Second, neither pharmacists nor patients realistically can be expected to routinely check, or even be aware of, the wide variety of overt features used on the thousands of different drug products available through pharmacies, particularly if those features are rotated on a regular basis. Third, overt and covert technologies are rendered useless if a drug product is repackaged, a practice that is common in the industry and subject to only minimal regulation. Consequently, instead of mandating one or more costly packaging and/or labeling technologies that may have only limited utility in thwarting counterfeiters, FDA should seek to facilitate the voluntary implementation of counterfeit resistant technologies by, for example, clarifying and streamlining the approval requirements for these technologies.

Electronic Track and Trace. PhRMA member companies support the development of an electronic "track and trace" system (using bar codes or RFID chips for package identification) that can track drug products in real time throughout the distribution system (from manufacturer to patient) and provide an electronic pedigree vouching for the authenticity of distributed drug products. PhRMA believes that electronic track and trace will be a key element in strengthening closed U.S. distribution system. Before such a system can be implemented, however, complex technological, legal, regulatory and financial issues need to be resolved by and among FDA and all interested stakeholders. PhRMA believes it will take a minimum of five years to resolve these issues and be able to implement an electronic track and trace system in a meaningful way (i.e., to the package level). PhRMA member companies will work with FDA and industry stakeholders to assess the feasibility of implementing an electronic track and trace system.

Implement The Pedigree Requirement. While efforts to implement an electronic track and trace system are pending, FDA should immediately implement the pedigree requirement enacted by the Prescription Drug Marketing Act of 1987 (PDMA). PhRMA believes that paper pedigrees, combined with due diligence, provide the most cost-effective, currently available method for ensuring that counterfeit drugs do not enter the distribution system. FDA issued final pedigree regulations in 1999 but has stayed their effective date on four separate occasions. Those regulations, while not perfect, would significantly decrease the risk that counterfeit drug products could enter the drug supply through the so-called "shadow market." In light of the growing threat posed by sophisticated counterfeiters, PhRMA believes it would not be prudent for FDA impose a fifth stay and thereby block the pedigree regulations from becoming effective in April 2004, as currently scheduled.

Tighten Requirements For Repackagers. PhRMA believes that FDA should re-assess its policies and procedures regarding repackaging operations. Repackaging has been identified as a weak spot in the drug distribution system that can be used as an entry point and distribution center for diverted and counterfeit drug products. Repackagers remove drug products from their original packaging and labeling, thereby destroying any counterfeit resistant technologies employed by the original manufacturer. Consequently, additional oversight is necessary to ensure that repackaged drug products are authentic and are not compromised by repackaging operations. PhRMA believes that FDA could better regulate the authenticity and quality of repackaged drug products if it had authority to require prior approval of repackaging operations. At a minimum, FDA should increase its inspections of repackagers and, where appropriate, initiate enforcement action. In addition, repackagers should be subject to the same requirements regarding overt and covert counterfeit resistant technologies as original manufacturers.

Strengthen Federal Requirements for Wholesalers/Distributors. PhRMA supports efforts to strengthen the licensure requirements for wholesalers and distributors. Recent investigations, particularly by the Florida Grand Jury and the Washington Post, have identified systemic weaknesses in the oversight of the wholesale drug industry in many states. These weaknesses permit unscrupulous individuals, many with prior felony convictions, to obtain wholesaler licenses for operations that deal in diverted and counterfeit drug products. PhRMA supports efforts by Florida and Nevada to strengthen requirements for the licensure of wholesalers by, for example, requiring the posting of a substantial performance bond (e.g., $100,000) and conducting detailed pre-licensure background checks and facility inspections. PhRMA believes, however, that licensure requirements should be strengthened consistently across all states to prevent diverters and counterfeiters from re-locating to states without strong licensure requirements. This can best be accomplished through revisions to FDA's regulations at 21 C.F.R. Part 205 setting higher minimum standards for state licensing of drug wholesalers and distributors along the lines of Florida and Nevada. FDA also should review state requirement for the licensure of wholesalers to ensure that they meet these minimum federal regulatory requirements.

Increase Criminal Penalties For Counterfeiting Activities. PhRMA believes that the criminal penalties for counterfeiting prescription drug products must be significantly increased. The current penalty under the Federal Food, Drug, and Cosmetic Act (FFDCA) – a maximum of three years imprisonment – does not reflect the serious public health risks associated with counterfeit drugs or serve as an adequate deterrent to prospective counterfeiters. PhRMA thus supports increasing the maximum criminal penalty for counterfeiting drug products from three to twenty years imprisonment. PhRMA also believes that criminal penalties should be imposed against entities that create a market for diverted and counterfeit drug products by purchasing drug products without adequate due diligence into the source and authenticity of such drugs. PhRMA thus supports making it a prohibited act under the FFDCA to purchase prescription drugs from a wholesale distributor without first obtaining and verifying the information provided on a drug pedigree.

Detailed PhRMA Comments

I. Technology

PhRMA agrees that technology will play a key role in any multi-pronged strategy to combat counterfeiting. Technology, however, is not a "silver bullet" and should not be viewed as such by FDA or the public. When assessing potential technological approaches to combating counterfeiting, FDA should be sensitive to both the limitations and costs of the technology.

A. Counterfeit Resistant Technologies (Questions A.4 – A.11, A.18, A.19)

PhRMA supports the voluntary implementation of counterfeit resistant technologies on drug packaging and labeling but does not believe these should be mandated by FDA. Instead, FDA should facilitate the voluntary adoption of these technologies by clarifying and streamlining the FDA approval process for these types of features.

Companies already are beginning to employ counterfeit resistant technologies into packaging and labeling for a number of products. Such technologies include overt and covert features incorporated into the packaging and or labeling of the product and chemical taggants incorporated into the drug product itself. Overt features include holographic images, special stickers, inks of gradated colors, or threads in the container label, all of which can be used to verify that the container is authentic. Some of these approaches are similar to technologies used for document authentication. Covert features include special inks, threads or materials that are known only to the manufacturer and require special equipment (e.g., UV light source) to identify.

Covert approaches also include the incorporation of small amounts of a chemical taggant into the pharmaceutical preparation. Such chemicals can be part of the bulk formulation of active ingredient or incorporated into the gel capsule or film coating of the pill. The taggant can be verified by chemical analysis by the company. Since the presence of this agent would be part of the new drug application, FDA would have knowledge about it. Companies can also use the known analytical composition of the formulation for authentication purposes. For example, defined impurity profiles and/or amounts of different inactive ingredients as well as dissolution patterns can be tested to determine a drug's authenticity.

Counterfeit resistant technologies serve two purposes: (1) they make it more difficult and costly for counterfeiters to produce a convincing copy of a drug's packaging and/or labeling; and (2) they permit companies a means for determining whether a questionable product is authentic or counterfeit. These are important goals, and PhRMA thus supports the use of counterfeit resistant technologies on appropriate drug products. PhRMA believes it is critical to the success of anti-counterfeiting strategies to erect as many hurdles as possible for the counterfeiters.

At the same time, it is important to recognize the significant limitations of counterfeit resistant technologies. First, these technologies are merely *resistant* to counterfeiting; they are not *counterfeit-proof*. For this reason, PhRMA questions what FDA means by "validated anti-counterfeiting technology." Does the Agency mean that the technology *will* prevent the counterfeiting of prescription drugs? If so, PhRMA disagrees that any such "validated anti-counterfeiting technology" exists. Experts believe that such features must be changed at regular intervals as counterfeiters will reliably duplicate them. In fact, it is the experience of PhRMA member companies that even elaborate approaches such as holograms eventually are counterfeited and that any such feature must be rotated every twelve to eighteen months.

The experience of the U.S. Treasury is instructive. The U.S. Government employs a number of different counterfeit resistant technologies on its bank notes, including special color shifting inks, embedded threads and micro-printing. In order to stay ahead of the counterfeiters, however, the government periodically redesigns its notes every seven to ten years. The government recently introduced a redesigned $20 bill incorporating a host of new counterfeit resistant technologies; yet only three weeks after the debut of the new $20 bill, the press has reported that "a bunch of computer-generated phonies have turned up." *New $20 Not So Counterfeit Proof*, MSNBC Report, October 30, 2003.

Another limitation with counterfeit resistant technologies is that they do not provide real time verification of a drug's authenticity. Covert features and taggants typically require specialized equipment or testing to authenticate and can and should be authenticated only by the manufacturer. These tests often cannot be performed onsite or require a manufacturer's representative to travel to the site. In addition, tests for taggants may take up to several days to perform in order accurately determine whether the drug is counterfeit or not. This may be problematic if a large amount of drug is of questionable authenticity as it would have to be withheld from commerce until the testing is completed.

Although overt features theoretically can be used for real time verification, they are easier to counterfeit than covert features and thus provide the least assurance of authenticity. Moreover, from a practical standpoint, overt features are too varied and numerous to provide a for the real time verification of drug products. It simply is not realistic to expect pharmacists or patients to routinely check, or even be aware of, the wide variety of overt features used on the thousands of different drug products available through pharmacies. This problem will be exacerbated by the need to rotate overt features on a regular basis. How is the pharmacist to know which is the current active overt feature versus the previous? What should the pharmacist do if he or she questions the authenticity of the bottle and the particular feature is past date? Best practice would dictate not dispensing and sending off a sample for analysis but this may result large amounts of acceptable drug being withheld from the market.

PhRMA has strong reservations about attempting to utilize a centralized electronic database to solve this problem. Since using such a database likely would be time consuming, pharmacists likely would not use it on a routine basis for authentication

purposes. In addition, who will maintain this database? Who will have access to it? How will it be updated? As was noted earlier, overt anti-counterfeiting measures will be changed periodically. They may either replace or in some cases could augment the older measure. Thus, the database would need multiple entries for the same package. Would this not prove confusing to pharmacists or other authorized users of the database? If the database were publicly available, counterfeiters would have easy access to all of the measures currently being used. A centralized database thus could serve as a more valuable resource to counterfeiters than to pharmacists and patients.

An additional factor limiting the utility of counterfeit resistant technologies is that they are rendered useless if a drug product is repackaged, a practice that is common in the industry and subject to only minimal oversight. Repackagers remove drug products from their original packaging and labeling, thereby destroying any counterfeit resistant technologies employed by the original manufacturer. PhRMA believes it makes little sense to mandate expensive counterfeit resistant technologies if they can be defeated simply by repackaging.

The costs of implementing multiple counterfeit resistant technologies are likely to be significant. There will be a regulatory burden to both the sponsor and the FDA to address already marketed drugs that do not possess such features as part of the formulation. As FDA is aware, any change to the formulation of an already approved drug will require a change to the NDA. PhRMA requests that FDA consider, on a case by case basis, the possibility of decreased regulatory reporting categories, or requirements (such as stability data), as appropriate.

PhRMA notes that all products are potentially subject to counterfeiting and any focus should not be just on some arbitrary list of "high risk" drugs. *Any* adverse event suffered by an American patient as a result of being given a counterfeit drug is *one* too many. PhRMA urges that the choice of anti-counterfeit technology be left up to the manufacture. The manufacturer is the most knowledgeable about its products, having the benefit of the knowledge of product, formulation and packaging development to help in identifying the appropriate anti counterfeit technology to employ.

In light of the above discussion, PhRMA opposes any government requirement to incorporate counterfeit resistant technologies into prescription drug products but supports voluntary adoption of such technologies. It is clear that companies are already employing a variety of technological approaches to assuring product authenticity and no further FDA regulatory action is required. Instead, FDA should seek to facilitate the voluntary adoption and rotation of counterfeit resistant technologies by making submission requirements as clear and streamlined as possible.

A guidance in this area would be useful but FDA should take a very general role. In particular, it would be most helpful for FDA to articulate what application requirements would be required for incorporation of taggants and other chemical markers for products already marketed. FDA should not specify which technologies companies should use. The technological landscape is constantly changing, and PhRMA companies would not

want the use of new approaches limited because they were not covered in a regulation or guidance. A good example of such an approach is the one adopted by the Australians in their code of practice on tamper evident packaging, discussed further below. That code only specifies that tamper evident packaging be employed but leaves the specifics up to the manufacturer.

B. Unit-of-Use Packaging (Questions A.1 and A.2)

PhRMA supports FDA efforts to encourage increased use of unit-of-use packaging but does not believe this should be mandated. Unit-of-use packaging may help combat counterfeiting by reducing (but not eliminating) repackaging, thereby ensuring that counterfeit resistant technologies employed by the original manufacturer remain intact throughout the distribution chain all the way to the patient. There are numerous legal, economic and practical impediments, however, that prevent manufacturers from utilizing unit-of-use packaging more extensively. PhRMA believes that FDA should work to remove these impediments to the extent possible to make unit-of-use packaging more feasible.

PhRMA member companies are constantly exploring new approaches to the packaging of prescription pharmaceuticals as a way of improving product stability, preventing the introduction of counterfeit medicines into the supply chain, prevention of medication errors, and providing another avenue for the delivery of useful information to patients. Such information improves patient compliance, helps to avoid preventable errors, and results in superior health outcomes.

Most non-solid oral dosage pharmaceutical products are packaged in unit of use (e.g., ophthalmic drops, nasal sprays, inhalers, creams and ointments). Very few solid oral dosage forms are packaged in this format (the major example being birth control pills and certain other pharmaceuticals that have short, defined dosing regimens). For solid oral dosage forms it is important to distinguish "unit of use" from "unit dose" packaging so that there is no confusion regarding definition.[1] A "unit of use" can be packaged in both bottles and blister packaging for once a day therapy (e.g., thirty pills in a small bottle versus 30 pills in a blister card presentation). Unit of use packaging will permit the manufacturer to incorporate a number of counterfeit resistant features, such as overt and covert technologies and tamper evident packaging that will contribute to counterfeiting deterrence. However, decisions on packaging format are market driven based on the specific product, dosing regimen(s), safety profile (relates to Child Resistant issues) and need for compliance.

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[1] According to the United States Pharmacopeia a Unit-Dose Container is defined as a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container. A Unit-of-Use Container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

The dispensing system in the US is quite heterogeneous with over 80,000 sites including chain and independent pharmacies, hospital pharmacies, managed care organizations, mail order pharmacies, clinics, and doctor's offices. Each of these customers may have different preferences regarding package size based on dispensing practice. While many pharmacies have adjusted inventory control procedures and moved to "just in time" inventory, this may not be universal practice. Thus, there may be a need to produce a variety of package sizes even if there is a move to more unit of use packaging.

It is critical to note that both regulatory and marketing considerations raise considerable barriers against the widespread use of blister packaging. For pills where the dosage regimen is one pill a day, it is economical to design blister packs that will hold the requisite amount. For dosing regimens of two or more per day, small bottles are a more economical packaging unit.

The Consumer Products Safety Commission (CPSC) enforces the Poison Prevention Packaging Act (PPPA), and implementing regulations at 16 CFR 1700.20(a)(ii) outline the type of testing required for special packaging that meets child resistance standards. PhRMA member companies must evaluate the underlying toxicity of any unit of use packaged pharmaceutical and make decisions based on package accessibility by children and exposure to the active ingredient. This forces companies to evaluate each solid oral dosage form on a case by case basis. Recent correspondence from CPSC states that "current CPSC regulations implementing the Poison Prevention Packaging Act (PPPA) do not restrict a company from relying on child resistance test data generated by the package manufacturer or from testing of similar packaging for a different substance." PhRMA believes that there is a great deal of uncertainty about the current status of type testing and how companies approach this issue. Issues such as the child resistant feature being tested, the design and performance compliance, and the role of standards organizations all need to be discussed by stakeholders.

In order for pharmaceutical manufacturers to utilize more unit of use packaging, expeditious decisions are required during the development process. Current regulations discourage the use of new unit-of-use packaging, since it is expensive and cumbersome for companies to qualify new packaging for the launch of new products. Once a new drug is launched, commercial and manufacturing concerns may mitigate against a switch in packaging design. Thus, the type testing process needs to be more transparent than at present in terms of both the type of criteria needed to assure that children will not be exposed to harm and the timeliness of decisions to enable companies to pursue this form of packaging.

To achieve the above goal, PhRMA believes that performance and design standards can be established to facilitate type testing. Working through established standards organizations such as the American Society for Testing and Materials (ASTM) is one avenue to accomplish this goal. PhRMA believes that such a standard will have great utility. For example, a company could have the flexibility to use existing packaging designs if the new drug has a similar safety profile to a drug already packaged in blisters.

One final consideration for unit of use packaging is how to accommodate medicines where there may be various dosing regimens. It is quite common for anti-infectives to have variable dosing regimens (e.g., 7, 10, 14, 21 days; in the case of some oral antifungals, one or two pills could constitute one of the full dosing regimens). This might lead to a proliferation of unit of use packaging presentations, taking up considerable pharmacy shelf space, and causing potential confusion in filling prescriptions if the required package unit is not available.

Finally, while unit of use packaging is generally prevalent in Europe, a number of PhRMA member companies have discovered counterfeit packaging there. Thus, it should not be assumed that such an approach provides *the* single solution to preventing the introduction of the counterfeit drugs into the US.

C. Tamper Evident Packaging (Question A.3)

Over the counter medicines have required tamper evident packaging for a number of years. A number of prescription drugs have incorporated similar features. A good review of some of these approaches is in the recently issued "Code of Practice for the Tamper-Evident Packaging (TEP) of Therapeutic Goods," issued by the Therapeutic Goods Administration of the Australian Government. Examples listed there include:

film wrappers,
blister packaging,
heat shrink bands or wrappers,
bottle mouth inner seals,
tape seals,
breakable caps, and
sealed tubes.

It is important to note that pharmaceutical repackaging defeats any tamper evident features that the manufacturer includes on the original packaging. PhRMA is unclear whether the language "...with labeling that notes the tamper evident feature..." refers to the label affixed to the container, the prescription drug information that accompanies the product, or the tamper evident feature. If FDA means the direct packaging labeling, PhRMA would note that there may not be sufficient room to add more information.

PhRMA urges that dispensing sites consider adopting the practice of physically rendering any manufacturer supplied packaging unusable when the package is emptied. This practice will ensure that the packaging cannot be reused.

D. Electronic Track and Trace (Questions A.12-A.17)

Constructing an electronic pedigree system will markedly assist in assuring the authenticity of the drug supply within the U.S. However, this is a daunting technological

task that will take considerable time and resources. Constructing the infrastructure and validating the technology will take several years to fully implement.

Bar code technology has been employed for a number of years to control inventory and for product identification. Within the UCC/EAN standards system there is a Global Individual Asset Identifier that incorporates serialized identification of individual package units. This lends itself to automized track and trace. Unfortunately, bar codes require packaging to be actively scanned and at certain distribution levels this could be labor intensive. Because Radio Frequency Identification chips (RFID) emit a signal permitting passive reading, this is perhaps more amenable to an automated system. However, as PhRMA sees it this is not a fully validated technology at this point in time. As the technology becomes more robust, this may serve as a viable substitute for the use of printed bar codes.

To implement a track and trace system for assuring the authenticity of pharmaceutical products, the following must be accomplished:

1) A database that can account for each packaging unit leaving the pharmaceutical company must be constructed and maintained.
2) Each packaging unit must be labeled with a unique serial identification. The technology to do this is open to discussion. It could be a bar code or RFID as long as the symbology was robust enough to handle the number of codes.
    a. Each manufacturer would have to have their own assigned list of numbers with a leading prefix that assures that there are no duplicate numbers within the overall system. The NDC number is suitable to this task as it identifies both the product and the company that manufactures it. The remainder of the data field can be used for the serial number.
3) At every "authorized" stop along the distribution chain (this includes any transaction between secondary distributors), the code is read and transmitted back to the database along with the full information on the recipient. In this manner an electronic pedigree would be maintained and automatically updated.
4) When the bottle is opened by the dispensing site which is the final stop, the code is again transmitted and the record of this product is closed out. Thus, anyone seeking to reuse the bottle could not because the database would have a record of the bottle being "used."

In order for a robust track and trace system to evolve there must be a simple open data standard for serialized identification. This is different from the proprietary systems that UPS and FedEx use to track packages. One major unresolved question is the construction and management of the database(s). Will this be centralized or will each manufacturer maintain their own? There will also have to be a uniform communication process from trading partners to the database(s). Who will own the data, and who will have access to it? In the case of multiple databases there will have to be a standardized routing system so that information on a given product will be transmitted to the appropriate manufacturer's database.

Implementation of such a system will not be a minor undertaking. Since each transaction will have to be registered, readers of the serialized information will need to be at all distributors, pharmacies, and other dispensing sites. Manufacturer packaging lines will have to be modified to print serialized bar codes or incorporate RFID chips. Alternatively, the requirement for packaging system serialization and maintenance tracking system could be made the responsibility of the primary distributor who receives the initial shipment from the manufacturer. The full costs of such a system and the timing for its implementation are unknown. PhRMA has joined with the Healthcare Distribution Management Association and other stakeholders to study all of the aspects of a track and trace system and report the findings to the FDA.

Because the time to full implementation of an "electronic" pedigree is unknown, a complete paper pedigree must be required as part of a comprehensive systems approach to anti-counterfeiting.

PhRMA cautions FDA that simply coding packaging at the pallet or case level will not fully assure authenticity down to the individual packaging unit. In fact, it may lead to a false sense of security as countless individual packaging units coming from different cases in the same lot or different lots are bundled and shipped. At this level, the ability to track and trace is lost.

II. Regulatory Requirements And Secure Business Practices

A. Pedigree Requirements (Questions B.1, B.3, B.5)

As discussed above, PhRMA supports the development of track and trace technologies, such as bar-coding and RFID chips, that could be used to provide real-time, electronic pedigrees. These technologies hold the promise of tracking individual medications from the manufacturer through the distribution chain directly to the patient in real-time, creating a virtually closed and fully automated drug supply chain. Unfortunately, there are a host of technical, operational and legal/regulatory issues that must be resolved before any such system could be implemented. In light of these obstacles, PhRMA believes it will take at least five years, and maybe longer, to implement a system that could provide an "electronic pedigree" that is effective to the item level.

Given the serious threats to the U.S. drug supply that exist today, PhRMA does not believe that FDA and the various stakeholders have the luxury of waiting for a track and trace system to become operational before implementing a pedigree requirement. For this reason, PhRMA supports the implementation of a paper pedigree system as an interim measure while an electronic track and trace system is being developed.

PhRMA believes that implementing a pedigree requirement, even a system relying on paper records, is the single most effective action FDA could take to combat prescription drug counterfeiting in the short term. Congress recognized this in the late 1980s when it enacted a pedigree requirement as part of the PDMA. The PDMA was an important piece of consumer legislation passed as a result of Congressional concern that the integrity of

the then-existing distribution system for prescription drugs was insufficient to prevent the introduction and eventual resale of substandard, ineffective, or counterfeit drugs. The primary goal of the pedigree requirement is to ensure that the U.S. drug supply remains a closed system by preventing the introduction of counterfeit medications into the supply chain. The pedigree requirement accomplishes this goal by establishing a legal chain of custody for each pharmaceutical product that permits purchasers to assure themselves that the product originated from the original manufacturer.

While the U.S. drug supply remains the safest in the world – in large measure because of the protections enacted by the PDMA – the risks that Congress identified in 1987 have only grown in recent years. As FDA knows, the counterfeiters have become increasingly sophisticated and dangerous, and the health risks from counterfeit drugs have grown. There is even evidence that organized crime has taken an interest in the shadow market for prescription drugs and has begun establishing well-funded and sophisticated rings to manufacture phony life-saving medications, such as cancer and AIDS therapies, used by the most vulnerable patients.

Although FDA finalized regulations implementing the pedigree requirement in 1999, these regulations (which are set forth at 21 C.F.R. §203.50) have been stayed four times by FDA. As a result, this potent weapon against counterfeit drugs remains unused and in administrative limbo *fifteen years after Congress originally enacted it.* PhRMA believes that, in light of recent, serious threats to the U.S. drug supply, this situation is no longer tenable, and the pedigree requirement must be implemented immediately. In order to combat this growing public health threat, FDA should use all of the resources at its disposal, *including the pedigree requirement.*

While the existing statutory and regulatory requirements certainly can be improved (by, for instance, requiring authorized distributors of record (ADRs) to pass pedigrees), PhRMA believes that the final rule promulgated by the FDA is an accurate reflection of Congressional intent and will provide strong deterrence against counterfeiters. See 21 C.F.R. §203.50. PhRMA acknowledges that the pedigree requirement is not a "magic bullet" but believes it will throw up a powerful roadblock against counterfeit drugs, making it significantly more difficult for counterfeiters to breach the supply chain and increasing the likelihood that, if they attempt to do so, they will be identified and caught. Indeed, pedigree papers reportedly were responsible for tipping investigators off to a major counterfeiting ring operating in Florida, leading to the indictment in July of 18 members of that ring. *Salesman Fell Into A Shadow Market*, Washington Post, p. A17 (Oct. 19, 2003). Without the information provided by pedigree papers, it is likely that this counterfeiting ring would still be operating in south Florida.

The value of the drug pedigree requirement for deterring counterfeiting activities recently was examined by a statewide Grand Jury in Florida. In a comprehensive report on the safety of prescription drugs in Florida, the Florida Grand Jury reached the following conclusion with respect to pedigree papers:

> Pedigree papers, when verified through due diligence, are the cheapest, easiest and most effective way to prevent diverted or counterfeited drugs from entering the marketplace.

First Interim Report of the Seventeenth Statewide Grand Jury, Case No. SC02-2645, at 34 (Grand Jury Report). PhRMA agrees with this position and with the Grand Jury's further conclusion that a pedigree requirement should be implemented and enforced.

PhRMA acknowledges that paper pedigrees can be forged and counterfeited. However, PhRMA agrees with the Florida Grand Jury that this "is not a reason to ignore them as the [wholesaler] industry asserts; to the contrary, it is why they must be verified." Grand Jury Report, at 29-30. If a pedigree paper is forged, the prospective purchaser can detect this quickly and cheaply through routine due diligence. PhRMA believes that FDA has authority under the PDMA to require wholesalers to verify the accuracy of the information on a drug pedigree before completing a purchase. However, even in the absence of binding regulations, PhRMA believes that evolving business standards and liability concerns will force wholesalers to use due diligence to verify pedigree information.

Moreover, pedigree papers provide an additional hurdle for counterfeiters to overcome and an additional opportunity for legitimate wholesalers and law enforcement officials to identify counterfeiters. Recent events in Florida illustrate the importance of paper pedigrees in detecting counterfeit drugs. The Washington Post recently reported that a counterfeiting ring operating in Florida was initially identified when a prospective purchaser became suspicious about the information contained on a forged pedigree paper. The purchaser notified law enforcement, which seized thousands of dollars worth of counterfeit drugs and brought indictments against 18 members of the counterfeiting ring. Accordingly, the possibility of forged pedigree papers is not a valid reason for failing to implement the current regulations. On the contrary, forged pedigree papers provide an additional opportunity to identify counterfeiters and to block counterfeit drugs from entering the drug supply, especially if wholesalers exercise the due diligence contemplated by the PDMA.

Despite the clear deterrent value of paper pedigrees, FDA has failed to implement its final pedigree regulations. This is due, in part, to concerns that the PDMA does not require authorized distributors of record (ADRs) to pass pedigree information to their customers. While this clearly is a weakness in the current statute that needs to be addressed, it does not justify FDA's wholesale refusal to implement any pedigree requirement whatsoever. If FDA is concerned that secondary wholesalers will not be able to obtain information tracing the drug back to the manufacturer because of the refusal of ADRs to pass on this information, FDA can exercise its enforcement discretion in this area. In other words, FDA can commit that it will not take enforcement action against a wholesaler if the wholesaler fails to provide pedigree information back to the manufacturer as long as the wholesaler provides pedigree information back to the first ADR who received the drug from the manufacturer. PhRMA believes that this would be an appropriate exercise of FDA's enforcement discretion to facilitate a functional and

effective pedigree system while FDA works with Congress to address the weakness in the current law.

PhRMA also believes it would be appropriate for FDA to encourage ADRs to pass on pedigree information voluntarily. PhRMA believes that ADRs should not frustrate the pedigree system by refusing to pass on needed information to secondary wholesalers and calls on the wholesale industry to pass on all necessary pedigree information.

In sum, PhRMA believes that paper pedigrees, combined with routine due diligence, provide the most cost-effective approach available at this time for obtaining reliable pedigree information. Although electronic track and trace systems ultimately may prove more cost-effective, these systems realistically cannot be implemented throughout the distribution system for at least five years. In the interim, PhRMA agrees with the Florida Grand Jury that "[p]edigree papers, when verified through due diligence, are the cheapest, easiest and most effective way to prevent diverted or counterfeited drugs from entering the marketplace." Grand Jury Report, at 34. PhRMA thus urges FDA to implement its regulations immediately as an interim step while electronic track and trace systems are being developed.

B. Repackaging of Pharmaceuticals (Question B.7)

FDA should re-assess its policies regarding the repackaging of solid oral dosage drug products in light of the threat of counterfeiting. PhRMA believes that repackaging operations are a weak spot in the drug distribution system that can be used as an entry point and distribution center for diverted and counterfeit drug products. Indeed, repackaging operations have been implicated in recent high-profile counterfeiting investigations.

Repackaging is particularly problematic with respect to anti-counterfeiting technologies incorporated in drug packaging and labeling. Repackagers often remove drug products from their original packaging and pack them in new containers with new labeling. As a result, any overt or covert anti-counterfeiting technologies applied by the manufacturer to the original packaging and labeling will be removed or compromised by the repackager. Repackaging operations thus provide counterfeiters with an invaluable means of circumventing the anti-counterfeiting protections applied by the manufacturer. PhRMA notes that repackaging operations also will threaten any electronic track and trace system that relies upon bar codes or RFID chips applied to packaging by the manufacturer or authorized distributor. Indeed, the utility of overt and covert anti-counterfeiting technologies and electronic track and trace systems is severely compromised by current repackaging policies and practices. Finally, the discarded manufacturer's original packaging could be reused to package counterfeit or adulterated product.

Repackaging should also be reviewed in the context of product quality. It should be recognized that the product's approval along with its expiration dating is developed with a full understanding of the original container closure system's ability to protect and not

interact with the dosage from and is in turn demonstrated by performing stability programs. A repackager violates the integrity of this relationship by removing the product from its original container closure system and placing it into another where there is no supportive data. There are no assurances this repackaged container closure system performs as well as the original container closure system in protecting from moisture, light or oxygen. Nor is there knowledge of resins and additive packages used in the molding that container to demonstrate the repackaged container closure system does not interact with the dosage form.

While a repackager that repackages into a bottle is able to obtain the manufacturer's original expiration date with no regulatory burden, a drug product manufacturer would be obliged to either show that the proposed container closure system is equivalent to or better than the original or perform stability studies to demonstrate there is no impact to the drug quality.

The FDA should look for opportunities to reduce the level of repackaging for resale which exists today, but recognize there are various examples where repackaging pursuant to a specific need (e.g., hospital unit dose packages) adds a level of value to the drug product distribution chain.

In order to address this situation, FDA needs to exercise greater oversight over repackaging operation. One possibility is to require repackagers to obtain prior approval for each drug they repackage, though this likely would require new legislation. At a minimum, FDA must increase its surveillance and enforcement activities in the area of repackaging. Given the heightened risks associated with repackaging, FDA should significantly increase its inspections of repackaging operations to ensure that they strictly comply with all relevant cGMP and recordkeeping requirements. It must be noted that certain repackaging operations, including most owned and operated by major wholesalers, are currently subject to the same level of oversight as pharmaceutical companies themselves. However, other repackaging operations may not operate under these same regulations. PhRMA recommends that all repackagers be subject to the same, stringent regulations.

C. Strengthening Federal And State Requirements For Wholesalers and Distributors (Questions B.2, B.4)

PhRMA supports efforts by the states, particularly Florida and Nevada, to strengthen requirements governing the licensure and regulation of non-manufacturer wholesale distributors. Recent investigations have demonstrated that there are systemic weaknesses in the oversight of the wholesale drug industry in many states. In Florida, for instance, a state grand jury found that the Florida's Department of Health issued licenses to 422 instate and 977 out-of-state wholesalers – "or approximately one wholesaler for every three pharmacies." Grand Jury Report, at 8. Yet with only nine field inspectors, the Grand Jury concluded it was impossible to adequately inspect all of these facilities to ensure that they were complying with Florida's strict requirements regarding the proper storage and handling of drug products. Grand Jury Report, at 18. Moreover, the Grand

Jury determined that many wholesalers had been issued licenses without proper background checks and that some wholesalers received a permit despite one or more felony convictions. Grand Jury Report, at 14.

PhRMA thus supports strengthening licensure requirements in the following areas:

- Requiring wholesale distributors to post a significant performance bond as a condition of licensure;
- Requiring detailed background checks of key personnel;
- Requiring pre-licensure inspections to ensure that facilities are legitimate;
- Increasing penalties for violations;
- Increasing licensure fees;
- Increasing funding for state regulatory agencies to support hiring, inspections and other regulatory efforts.

While PhRMA supports state efforts to increase oversight over prescription drug wholesalers and distributors, PhRMA believes that these efforts must be consistent and coordinated. If the states address this problem in a piecemeal fashion, unscrupulous wholesalers and distributors will simply move their base of operations to those states with less rigorous requirements and/or enforcement. This phenomenon already has been observed in Nevada. After tightening its wholesaler requirements in 2001, the number of licensed wholesalers decreased the following two years from 50 to 8. Yet the Washington Post reports that "When the Nevada regulators took action, some wholesalers simply moved operations across the state line into California." *Nevada Gets Tough, With Mixed Results*, Washington Post, A16 (Oct. 22, 2003).

In order to deter this type of forum shopping by unscrupulous wholesalers, FDA should require all states to adopt the types of regulatory enhancements that Florida and Nevada have implemented. FDA can accomplish this by revising its Guidelines for State Licensing of Wholesale Prescription Drug Distributors set forth at 21 C.F.R. Part 205. These regulations establish the minimum requirements that each state must meet in order to comply with federal law regarding the licensure and regulation of wholesale distributors. PhRMA recommends that these minimum requirements be strengthened to ensure that there is uniform coverage in every state.

PhRMA also believes that FDA should actively assess each state's regulatory system governing drug wholesalers to determine whether they meet the minimum federal requirements set forth in Part 205. Indeed, it is unclear whether all fifty states meet the minimum requirements set forth in the current version of Part 205. In situations where a state does not meet those minimum requirements, FDA should work with the state to improve its oversight of drug wholesalers. While we believe most states will work with FDA to adopt increased federal standards, if a situation arises where a state's oversight remains lax despite repeated FDA warnings, FDA should consider making a formal finding that the state does not meet minimum federal requirements under the PDMA. *See* 21 U.S.C. §353(e)(2).

D. Increased Criminal Penalties For Counterfeiting (Question B.6)

PhRMA supports increasing the criminal penalties associated with counterfeiting activities in order to provide more effective deterrence. PhRMA believes that penalties and enforcement activities should be increased in two areas: (1) counterfeiting activities themselves; and (2) distributing counterfeit drugs without proper due diligence (i.e., recklessly).

The penalties under the Federal Food, Drug, and Cosmetic Act (FFDCA) for counterfeiting drug products are woefully inadequate. The maximum penalty for a felony violation – that is, one committed with the "intent to defraud or mislead" -- is three years imprisonment and/or a $10,000 fine. This is far less than the penalties associated with counterfeiting a single dime – which is fifteen years imprisonment – or counterfeiting the currency from a foreign country – which can result in twenty years imprisonment. *See* 18 U.S.C. §§ 485, 478. It also is far less than the penalties associated with distribution of illicit drugs. *See, e.g.*, 21 U.S.C. §841. These disparities make counterfeiting activities related to drug products extremely attractive to criminals, particularly organized crime.

While prosecutors often can bring additional charges against counterfeiters that carry stiffer penalties, such as mail fraud, wire fraud, and conspiracy charges, PhRMA believes there is still a significant deterrence value in substantially increasing the penalties under the FFDCA for counterfeiting drug products. Counterfeit drug products present grave public health risks, and counterfeiters often prey on the most vulnerable patient populations, such as patients suffering from cancer or AIDS who can least afford to use subpotent, adulterated or counterfeit medications. PhRMA believes that in order to send a strong message that counterfeiting activities will not be tolerated, the penalties associated with counterfeiting should be: (1) commensurate with the significant public health threat posed by counterfeit drugs; and (2) sufficient to deter counterfeiting activities, particularly by organized crime. Accordingly, PhRMA supports increasing the maximum penalty for counterfeiting drug products from 3 years to 20 years.

PhRMA also believes that stiffer penalties are appropriate for entities that create a market for counterfeit drug products by failing to conduct proper due diligence into the source of the drug products they purchase. While these entities may lack specific knowledge that the drugs they handle are counterfeit, in many cases this lack of knowledge is self-imposed. The Florida Grand Jury report and recent counterfeiting examples make clear that counterfeit drugs are able to move through the distribution system because some distributors put on blinders regarding the source of the drugs they purchase. They ignore warning signs that drugs may be counterfeit (such as unexplained, steep discounts) and fail to request pedigree papers or verify the information contained in pedigree papers because they do not want to miss a lucrative buying opportunity, particularly one involving a discount. As the Florida Grand Jury observed, "This is nothing less than a blatant example of willful blindness." Grand Jury Report, at 29.

This "willful blindness," however, creates and sustains the shadow market for diverted and counterfeit drug products. In order to deter this behavior, PhRMA believes that criminal penalties should be imposed for the reckless distribution of counterfeit drug products. In other words, entities that distribute drug products without conducting proper due diligence into the source of those drugs should be subject to criminal liability. PhRMA thus supports making it a prohibited act under the FFDCA to purchase prescription drugs from a wholesale distributor without first obtaining and verifying the information provided on a drug pedigree. Given that many of these facilitators are not hard-core criminals like the counterfeiters, PhRMA believes that increased criminal penalties for willful blindness will have a particularly strong deterrent effect in rooting out this shadow market.

III. Rapid Alert and Response Systems

PhRMA is working with pharmacy trade associations on developing an electronic drug label distribution system. When employed, every US dispensing site will have access to the most current prescribing information. The vendors that PhRMA is working with have the capacity to update this information daily. PhRMA believes such a system could also be used to disseminate timely reports about counterfeit medicines that are found in the drug supply.