



**International Academy
of Compounding Pharmacists**

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November 20, 2000

Jane Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration
5630 Fishers Lane
Rockville, Maryland 20852

Re: Response of the International Academy of Compounding Pharmacists to
Inquiries Made During the October 27, 2000, FDA Part 15 Hearing on the
Prescription Drug Marketing Act; Docket No. 92N-0297.

Dear Ms. Axelrad and Members of the Panel:

This responds to questions asked of the International Academy of Compounding Pharmacists ("IACP"), during the October 27, 2000, Food and Drug Administration ("FDA") Part 15 Hearing regarding FDA's December 3, 1999, final rule implementing the pedigree provisions of the Prescription Drug Marketing Act of 1988 ("PDMA"). The information presented below demonstrates that there is no reason to change the current industry practice regarding the distribution of bulk drug ingredients to compounding pharmacies.

At the outset, it is important to briefly reiterate the role of drug compounding in United States health care. Each day over 40,000 prescriptions are compounded - roughly one percent (1%) of the total prescriptions dispensed in the United States. Compounding is a necessary medical option for many patients. For example, some patients, because of allergies or other sensitivities, simply cannot tolerate standard drug formulations. If a patient is allergic to a preservative or a dye in a manufactured product, the compounding pharmacist, working with the treating physician, can prepare a dye-free or preservative-free dosage form. Other patients need drug formulations that manufacturers have discontinued

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for economic reasons. Drug companies do not, and cannot, provide the same type of patient-specific drug therapies as compounding pharmacists.

Hospice patients who have difficulty swallowing a capsule can instead be prescribed pain medications, anti-emetics and antibiotics in compounded lozenges, lollipops, skin patches or suppositories. For example, phenytoin sodium USP is an anti-convulsant used in suppository form for terminal cancer patients who can no longer swallow. Through compounding, pharmacists can fill a physician's prescription for a suppository form with effective dosage strengths which are not commercially available. For such patients to obtain the same relief through a commercial product would require the insertion of 2-3 suppositories at a time.

As demonstrated below, as well as in the attached copy of my written statement from the October 27 hearing and the comments previously filed by IACP, adequate safeguards already exist to protect the public from damaged prescription medications, including those compounded from bulk drug ingredients. The FDA's final rule will not further Congress' or FDA's stated purpose of protecting the public health and safety. Instead, it can only serve to harm the public by disrupting the supply of bulk drug ingredients required to provide patients with medically necessary patient-specific drug therapies available only through compounders.

A. Sources of Supplies of Bulk Drug Ingredients to Compounding Pharmacists

The FDA panel for the October 27, 2000 Part 15 hearing ("the Panel") asked about the number of companies in the United States that supply bulk active pharmaceutical ingredients ("APIs") to compounding pharmacies and the sources of supply for these companies. There are an estimated 15-20 companies that supply bulk drug ingredients to compounding pharmacists.

One large supplier of bulk active pharmaceutical ingredients to pharmacies for use in compounding drugs distributes 415 different APIs. According to this supplier approximately 90% of all bulk APIs are procured from domestic sources. The remaining 10% of APIs are obtained from sources outside of the United States. Fifty percent of bulk APIs come directly from manufacturers, while the remaining 50% is obtained through secondary suppliers. On average the secondary suppliers carry a greater variety of bulk APIs than individual manufacturers. For example, one secondary supplier distributes 75 of the different APIs stocked by the company. These secondary suppliers of bulk APIs are the most vulnerable under the rule and are likely to be forced out of business if FDA implements the final rule and changes the past 12 years of industry practice.

B. Quality Control Procedures for Bulk API Suppliers

The Panel asked for information about quality control procedures used by repackagers of bulk drug ingredients sold to compounding pharmacists. Congress has recognized the important health benefits of compounded therapies, as demonstrated most recently by the passage of the Food and Drug Administration Modernization Act ("FDMA") of 1997. Under FDMA, licensed pharmacists compound medications pursuant to specific requirements implemented to ensure quality assurance and to safeguard the public. One such protection includes the use of bulk drug substances that comply with the standards of an applicable United States Pharmacopoeia ("USP") or National Formulary ("NF") monograph. Moreover all establishments must be registered under the Federal Food, Drug, and Cosmetic Act, including foreign establishments. Further, all bulk drugs received by repackagers must be accompanied by certificates of analysis. 21 U.S.C. § 353(b).

Prior to purchasing any bulk APIs from any source - foreign or domestic - the large API distributor requests proof of registration with the FDA and/or labeler codes from that source. Further, as a repackager of bulk APIs, the company has implemented additional quality control procedures, as detailed below, which provide safeguards for bulk APIs obtained through either domestic or international sources and distributed to compounding pharmacies. These procedures adequately protect the public from the threat of counterfeit, damaged or adulterated bulk drugs.

This distributor requires certificates of analysis from all of its suppliers. To promote consistency in format, the company is creating standardized certificates of analysis and making them available on the company web site for all of its customers. The certificates of analysis are made available to the compounding pharmacists.

The following procedures ensure quality control of the APIs and to comply with Good Manufacturing Practices ("GMPs"):

1. Upon receipt, all chemicals are visually inspected for product and container integrity and put into quarantine.
2. The chemical's documentation is examined for completeness and accuracy.
3. A sample is taken to the Quality Control laboratory where the physical properties of the chemical are compared with the chemical's description given on the Certificate of Analysis, USP, NF or other reference document.

4. The chemical is then put through a variety of tests to confirm its identity. Depending on the substance, tests may include IR spectra, UV-VIS spectra, meltpoint, specific gravity, and various chemical tests.
5. Once the chemical meets the necessary criteria, the lot number is activated and it is released from quarantine.
6. Prior to repackaging, the bulk container's barcode is scanned against the package labels to verify the information.
7. After the repackaging process is complete, a random sample is pulled and its identity is again confirmed.
8. While filling an order, the chemical's barcode is scanned which ensures that the correct part number, size, and lot number has been pulled for the corresponding order.
9. A final quality control audit is performed by again scanning all barcodes to validate order completeness.

In light of these quality control procedures, imposing a pedigree requirement would provide no additional protection. The controls established by repackagers to meet GMPs assure product quality.

C. Recalls of Bulk APIs

The Panel also inquired about the ability of suppliers of bulk APIs to compounders to track drugs in the event of a recall. For example, this large distributor has successfully completed recalls regarding bulk drug ingredients. One recall of an API was initiated by a vendor. After receiving the recall letter from the vendor identifying the lot number of the substance, the company was able to pull the corresponding lot numbers for the API obtained from that vendor, identify specific purchasers and amounts of the substance ordered, and issue a recall on the same day. IACP is aware that other API distributors can also track shipments.

D. Impact on health care

As demonstrated in my written statement from the October 27 hearing, along with the statements of the American Pharmaceutical Association, the Pharmaceutical Distributors Association and Purity Wholesaler, the pedigree requirements of FDA's

December 3, 1999 final rule will result in a disruption of supplies of both finished prescription drugs and bulk drug ingredients to pharmacies. The inability of compounding pharmacists to purchase bulk drug ingredients will risk the health of patients whose access to vital compounded medications would be seriously disrupted. Taking into account the numerous areas in which drugs are routinely compounded - such as home-health centers and hospitals - this will affect approximately 10,000 pharmacies resulting in tens of thousands of patients who will not be able to obtain medical treatment necessary for quality health care. Any benefits that could be gained through this rule would be substantially outweighed by the public health costs, preventing patients from receiving the prescribed medications.

CONCLUSION

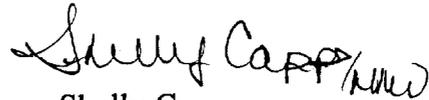
The burdensome pedigree requirements for the distributors of bulk drug ingredients are unnecessary and will not further Congress' intent in protecting the public from unsafe drugs. Sufficient quality control and antidiversion safeguards and penalties exist under current FDA record keeping, licensing and GMP regulations pertaining to initial manufacturers, repackagers and pharmacies to ensure that damaged, adulterated or counterfeit bulk drug ingredients are not processed into compounded medications for distribution to consumers. The PDMA legislative history did not discuss a single instance of any injury or adverse event associated with adulterated, damaged, subpotent or counterfeit bulk drug ingredients used in compounded drugs. Nor has FDA, through the course of this rulemaking or during recent Congressional hearings regarding FDA's monitoring of imported bulk pharmaceutical chemicals, provided any evidence of adulterated, damaged, counterfeit or subpotent bulk drug ingredients that were subsequently used in compounded drugs or any adverse events reported from patient use of such compounded drugs. There is no evidence whatsoever that requiring pedigree information would provide any benefits for APIs used in compounding.

Accordingly, we again urge that the FDA final rule be amended so that it is consistent with Congressional intent to clearly indicate that the pedigree requirements apply only to distributors of finished form prescription drugs, not to the distribution of bulk drug ingredients. If FDA chooses to ignore the will of Congress, the rule should at least be consistent with industry practice over the past 12 years and allow authorized distributor status to be demonstrated by two or more transactions with a manufacturer or other authorized distributor during a 24 month period, and require that unauthorized distributors only go back to the last authorized distributor for pedigree information.

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Thank you for the opportunity to present the position of the IACP on this crucial final rule.

Sincerely,

A handwritten signature in cursive script that reads "Shelly Capps". To the right of the signature, there are some initials that appear to be "NW".

Shelly Capps
Executive Director

cc: FDA Part 15 Panel
Docket Manager 92N-0297



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**FDA Public Hearing; Docket No. 92N-0297
Prescription Drug Marketing Act of 1987
October 27, 2000**

**Testimony of Shelly Capps
Executive Director, International Academy of Compounding Pharmacists**

I appreciate this opportunity to speak before the FDA on behalf of compounding pharmacists and the many patients who benefit from compounded medications. The International Academy of Compounding Pharmacists ("IACP") represents the interests of over 1,300 compounding pharmacists. We are very concerned that FDA's December 3, 1999 final rule, if implemented as written, will have a devastating impact on the ability of compounding pharmacists to obtain the bulk drug ingredients necessary to make compounded medications. The lack of supply of drug ingredients will seriously affect the well-being of the tens of thousands of patients who require custom-tailored medical therapies - treatments that can only be obtained through compounding.

There are two critical points that I want to make. First, the FDA's new requirements impose an unnecessary and unreasonable burden on wholesale distributors and compounding pharmacists without furthering Congress' intent of safeguarding the public. Congress' objectives can be met through monitoring and enforcement of the existing regulatory safeguards, without the burden of repetitive record keeping and tracking which will not protect the public but will increase costs to distributors, pharmacies, and ultimately consumers. My second point is that Congress did not intend that the requirements set forth in FDA's final rule apply to bulk drug ingredients.

HEALTH CARE BENEFITS OF COMPOUNDING MEDICATIONS

The pharmaceutical industry began with the compounding of drugs and treatments by individual physicians and pharmacists. During the past century, manufacturers have made giant leaps forward in developing new treatments for a myriad of patient ailments. However, despite the many technological advances in the pharmaceutical industry, compounding remains a vital element of quality patient care. Compounding fills the gaps in treatment left by mass-produced drugs and chain drug stores.

The importance of compounded drug therapies to patient health is well documented. Each of us - as individual patients - reacts to medicines differently

depending upon our own physical make-up. Some people, through allergies or other sensitivities, simply cannot tolerate standard drug formulations. Some patients need drugs that manufacturers have discontinued for economic reasons.

Compounding allows physicians and pharmacists, working together, to provide custom-tailored medications that are not commercially available to meet individual patient needs. For example, if a patient is allergic to a preservative or a dye in a manufactured product, the compounding pharmacist can prepare a dye-free or preservative-free dosage form. Children often refuse to take many medicines because of the taste. Compounding pharmacists can introduce flavoring ingredients into such drugs as antibiotics and anti-seizure medications, to make these necessary medical treatments palatable for children. Similarly, individuals such as hospice patients who have difficulty swallowing a capsule can instead be prescribed a compounded lozenge or a lollipop.

Compounding is also important in developing medical treatments that require individualized dosage strengths and product formulation. For example, compounded treatments are often used to develop safe and effective hormone replacement therapies for women, through the ability to alter strengths and product formulations (pills, topical gels, patches), for each individual woman's physical requirements. Drug companies do not, and cannot, provide the same type of patient-specific drug therapies.

Congress has recognized the important health benefits of compounded therapies, as demonstrated most recently by the passage of the 1997 Food and Drug Administration Modernization Act ("FDMA"). FDMA formally recognized the benefits that compounded medications play in treating the unique medical needs of patients. Through this legislation Congress specifically acknowledged that pharmacists will need to use bulk drug ingredients in compounding. Without bulk drug ingredients, most compounding is not possible.

IMPACT OF THE FINAL RULE ON WHOLESALE DISTRIBUTORS OF BULK DRUG INGREDIENTS

FDA's final rule will implement provisions of the Prescription Drug Marketing Act of 1987 ("PDMA"). Congress passed PDMA for two principal reasons: to protect American consumers from mislabeled, adulterated or counterfeit prescription drugs; and secondly, to protect fair competition in the pharmaceutical industry. To prevent the commercial distribution of damaged prescription drugs, Congress created a drug "pedigree" requirement. Those wholesale distributors of prescription drugs who are not deemed to be "authorized distributors" must provide a statement which details the distribution history - or pedigree - of the drug. An authorized distributor is defined as a distributor "with whom a manufacturer has established an ongoing relationship."

For the past 12 years the pharmaceutical industry has relied on an FDA guidance letter which interprets the PDMA pedigree provision as follows:

(1) an “ongoing relationship” can be established by demonstrating two transactions in any 24 month period to be evidence of a continuing relationship; and

(2) that an “unauthorized” distributor only has to trace the pedigree back to the last “authorized” distributor, not all the way back to the original manufacturer.

This guidance has served the public well. Over the past 12 years there has been no evidence of an increase in diversion of prescription drugs stemming from industry’s following this guidance letter. Further, there has been no intervention by Congress to change the direction of this guidance letter - nor any indication from Congress that the current practice does not serve the public interest.

FDA now seeks to depart from 12 successful years of agency and industry practice by altering these two interpretations of the PDMA pedigree provision to: (1) require a written agreement between a manufacturer and distributor to establish an “authorized” distributor; and (2) require that any unauthorized distributor obtain a drug pedigree which traces a drug all the way back to the original manufacturer.

FDA’s new requirements will create an insurmountable administrative burden for many wholesalers, and particularly for small wholesale distributors. FDA’s final rule does not require authorized distributors to provide pedigree information to unauthorized wholesale distributors. This places small secondary wholesale distributors at distinct economic and competitive disadvantages by having to construct the pedigree of the drug back to the original manufacturer - which in many cases may not be possible. Under FDA’s rule, an authorized distributor who chooses not to furnish this information can effectively put secondary distributors out of business.

The small wholesale distributors of bulk drug ingredients are left entirely at the mercy of manufacturers and major wholesalers. While the large manufacturers and wholesalers will engage in occasional transactions with small distributors for small amounts of selected products sufficient to satisfy FDA’s present criteria for establishing an “ongoing relationship,” those same companies are not likely to take on the additional paperwork, disclosure requirements, and regulatory burden imposed if separate written agreements are mandated for numerous products and numerous customers. The FDA final rule will allow large scale distributors to “cherry pick” which small distributors get to be “authorized distributors.” Allowing the large manufacturers to have such a competitive advantage will not further Congress’ goal of preventing the sale of damaged prescription drugs to American consumers. Rather it will thwart Congress’ intent in leveling the competitive playing field for drug companies.

Further, the final rule will disrupt the already complex balance which exists between the large drug manufacturers and the small wholesale distributors and pharmacies. This can only adversely affect the supply of bulk drug ingredients to such small operations and to compounding pharmacists. Given the intense public concern over the costs of drugs, it is inexplicable why FDA would now initiate this anti-competitive, cost-increasing measure. Indeed, FDA appears to have done no meaningful analysis of the economic impact of this rule, or assessed its impact on small businesses.

IMPACT OF FINAL RULE ON COMPOUNDING PHARMACIES

FDA's application of the PDMA's pedigree requirements to the wholesale distribution of bulk drug substances and FDA's requirement of a written agreement to demonstrate an "ongoing" relationship between distributors will greatly restrict pharmacists' access to bulk drug ingredients used to compound individualized medications. The Small Business Administration's Office of Advocacy, in its comments to the rule, has pointed out that the implementation of FDA's final rule will adversely affect approximately 4,000 small wholesale distributors. The vast majority of bulk drug ingredients purchased by pharmacies come from small repackagers who in turn purchase these ingredients from small distributors. Because of these relatively small purchases, many wholesalers are unlikely to be listed as authorized distributors. This will trigger the need for pedigree information for each shipment, which they will get only with great effort or not at all.

Large manufacturers traditionally will not supply bulk drug ingredients directly to pharmacies. The sale of bulk ingredients to compounding pharmacists is typically a miniscule component of the typical "authorized distributor's" business. These manufacturers and wholesalers have no direct economic interest in ensuring that pharmacists continue to have access to bulk drug ingredients to compound medications. Further, the final rule requirements will increase the administrative burden of larger manufacturers if required to make separate documentation sufficient to confer authorized distributor status on a wholesale distributor. The increased administrative burden will raise the fixed costs for drug manufacturing - again resulting in an increase in overall drug prices.

The inability of these distributors to purchase bulk drug ingredients would risk the health of patients whose access to vital compounded medications would be seriously disrupted. Imposing pedigree requirements will mean the loss of more than 70% of the bulk drugs currently used in compounding. Taking into account the numerous areas in which drugs are routinely compounded - such as home-health centers and hospitals - this will affect 10,000 pharmacies and tens of thousands of patients will not be able to obtain medical treatment necessary for quality health care. Any benefits that could be gained through this rule - and IACP believes the benefits are illusory - would be substantially

outweighed by the public health costs, preventing patients from receiving the prescribed medications.

FDA'S FINAL RULE IS NOT CONSISTENT WITH CONGRESSIONAL INTENT

FDA's final rule does nothing to advance Congress' objective of preventing the diversion or damage of drugs in the chain of distribution for finished form prescriptions drugs. In fact, FDA's final rule is inconsistent with Congress' intent on three points

(1) Congress did not intend to include bulk drug ingredients;

(2) The impact of the final rule on small distributors of bulk drugs will effectively destroy the practice of compounding which is inconsistent with Congress' mandate in passing the 1997 FDMA;

(3) FDA's interpretation of the pedigree requirements will create a redundant layer of regulation which will not increase competition, as intended by Congress. Instead, it gives more power to the large manufacturers and will increase drug prices for consumers - both at the pharmacy level through lack of supply and from the large manufacturers through increased paperwork and regulation.

The final rule will have a devastating effect on pharmacy compounding, an effect which is entirely avoidable while still realizing the true intent of Congress. The legislative history is clear that Congress intended only that PDMA prevent diversion in the chain of distribution of finished prescription drugs - not bulk drug ingredients. This is evidenced throughout the legislative history of the PDMA which expressly references only problems associated with the distribution of finished form prescription drugs, and never mentions the diversion of bulk drug ingredients. FDA's application of the pedigree requirements of the PDMA to bulk drug ingredients is contrary to Congress' expressed intent in passing the PDMA.

In addition, FDA's burdensome requirements for the distributors of bulk drug ingredients are unnecessary. Sufficient quality control and antidiversion safeguards and penalties exist under current FDA record keeping, licensing, and GMP regulations to ensure that damaged, adulterated or counterfeit bulk drug ingredients are not processed into compounded medications for distribution to consumers.

CONCLUSION

FDA's application of these requirements to bulk drug ingredients is a significant and unwarranted departure from FDA and industry practice. The agency's interpretation of the PDMA's pedigree requirement to apply to bulk ingredients is contrary to

Congress' intent to apply the law to finished dosage form drugs. Most importantly, if the final rule is implemented as written, it will have a devastating effect on the patients who rely on compounded medications. The inability of pharmacists to compound drugs threatens the health of patients who require individualized therapies.

In closing, on behalf of the IACP, I request that the FDA final rule be amended so that it is consistent with Congressional intent to clearly indicate that the pedigree requirements apply only to distributors of finished form prescription drugs, not to the distribution of bulk drug ingredients. If FDA chooses to ignore the will of Congress, the rule should at least be consistent with industry practice over the past 12 years and allow an authorized distributor to be demonstrated by two or more transactions with a manufacturer or other authorized distributor during a 24 month period, and require that any pedigree information required of unauthorized distributors only go back to the last authorized distributor.