AstraZeneca

October 31, 2003

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

Re: Docket Number 2003N-0361
Response to FDA Call for Comments
Anti-counterfeit Drug Initiative

Dear Sir or Madam:

Reference is made to the August 26, 2003 Federal Register notice announcing the request for comments on the Anti-counterfeit Drug Initiative.

AstraZeneca has reviewed the information provided relative to this initiative. Our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Robert J. Timko, Ph.D., Associate Director, Technical Regulatory Affairs at 302-886-2164.

Sincerely,

Ronald Stellon
Vice President Quality Assurance
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Enclosure

2003N-0361

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FDA COUNTERFEIT DRUG TASK FORCE INTERIM REPORT

QUESTIONS RELATED TO THE POTENTIAL OPTIONS FOR IMPROVING PRESCRIPTION DRUG SECURITY.

AstraZeneca answers to selected questions.

1. GENERAL COMMENTS

We applaud the FDA for taking the initiative to address the growing problem of counterfeiting to ensure patient safety. We agree that there is no single magic bullet and that we need a multi-pronged approach.

We would encourage FDA OCI to communicate with manufacturers whose products were potentially implicated in anti-counterfeiting investigation. This would be for purposes of assisting in the investigation and mitigating the risk of future events.

We are not endorsing any technology. Manufacturers should be able to use what is best for their products and customers.

If the FDA specifies new requirements for manufacturers, it will take time to implement. We would like the FDA to work with manufacturers to determine what is reasonable and to provide manufacturers with needed flexibility.

2. QUESTIONS CONCERNING TECHNOLOGY (OPTIONS 1-9)

1. Discuss the advantages and disadvantages of unit of use packaging. Please provide any information on the economic impact of requiring unit of use packaging.

   Answer: Advantages: The patient is more likely to receive the intact manufacturer's package with all its anti-counterfeiting features present. This would also help to curb repackaging for resale, which has been problematic for counterfeiting. This would also increase the chances of determining the chain of custody, since the unit of use package would retain the manufacturer's lot number.

   Note: We believe that unit of use should be standardized as a 30-day supply and/or a 90-day supply unless the standard dosing regimen dictates otherwise. This might mean that prescription plans may need to change.

   Also we believe that unit of use can be achieved with bottles. CPSC standards are easier to achieve with a bottle than with a blister.

3. Discuss the advantages and disadvantages of using tamper evident packaging on drug products. Please provide any information on the economic impact of requiring tamper evident packaging features on these products.

   Answer: It should be noted that the foil induction seal used on bottles is a tamper evident seal.

4. What anti-counterfeiting technologies are currently being used? Are there any data on which technologies are successful?

   Answer: There are multiple technologies and solutions available. There is no technology that meets all needs.

5. What, if any, minimum number of anti-counterfeiting technologies should be utilized on packaging and labeling? Should technologies be utilized on all dosage forms (e.g., APIs, finished dosage forms) and products or just dosage forms and products at high risk of being counterfeited?

   Answer: Stipulating a minimum number of technologies will not provide manufacturers with the flexibility they need. However, as track and trace technology evolves, it may serve to replace anti-counterfeiting technologies on packaging and labeling.

6. Should any specific anti-counterfeiting technologies be utilized? Should covert technologies always be utilized? Should overt technologies always be utilized?

   Answer: We strongly believe that the FDA **should not** specify anti-counterfeiting technologies, because this will limit manufacturers' flexibility and incentive to continuously innovate. Also counterfeiters will know which technologies to adopt.

7. Should some anti-counterfeiting technologies only be identifiable by the manufacturer and/or the FDA?

   Answer: Yes, very definitely. The more people who know about a product's covert features, the more likely that a counterfeiter will copy a covert feature.

8. On what dosage forms and products should taggants, other markers, or unique characteristics be utilized? All dosage forms and products? High-risk dosage forms and products? Are there unique characteristics of products that can be utilized in lieu of taggants or chemical markers for forensic analysis?

   Answer: We see product taggants as covert features, which unfortunately may not provide real time verification of authenticity. Altering formulation is a long-term project and would require significant work resources from research and development and prior FDA approval. For this reason, we would like taggants to be used at manufacturers' discretion.

   How will the FDA ensure that taggants are not disclosed to the public?

9. What role should the FDA play in reviewing the use of (i) anti-counterfeiting technologies incorporated into the packaging and labeling, (ii) taggants, markers, and other unique characteristics incorporated into the product itself, and (iii) track and trace technologies?

Answers:

(i) FDA should authorize the use of anti-counterfeiting features on the packaging (without product contact) and labeling without prior approval. Such actions would, of course, be provided on annual reports. The presence of any covert features must not be available through Freedom of Information.

(ii) Manufacturers need to assess the risk to their products, determine whether taggants should be used, and the frequency of changing taggants. The addition of food grade or generally recognized as safe substances (GRAS) at low levels should be permissible (with appropriate justification) without FDA prior approval. This would facilitate manufacturers adding taggants to existing products and changing taggants in new products. The presence of any taggants in products must not be available through Freedom of Information.

(iii) For track and trace, everyone in the supply chain must use the same technology/platform. There must also be an infrastructure in place to transmit data from the dispenser back to the manufacturer.

10. How should "validation" of an anti-counterfeiting measure or track and trace technology be determined? Should only "validated" anti-counterfeiting measures be used? Who should do the validation?

Answer: A risk-based approach, appropriate to the technology being used, should be employed. We believe verification, not validation, is more appropriate to anti-counterfeiting measures.

11. Should a database, as described in Technology Option 5 be created? If so, who should develop the database? Where should it be housed? Who should have access to the data? Who should be responsible for updating and maintaining it?

Answer: Technology Option 5 suggests creating an electronic database with photographs of product, packaging and labeling information that should be made available to the public. . As an alternative, we, as a manufacturer, could create a web site that includes all of our overt features. Covert features are strictly proprietary and need to be kept confidential.

12. Discuss the advantages and disadvantages and the role of track and trace technologies, in particular bar codes and RFID.

Answer: See 9iii above. Advantages: In addition, bar codes requiring scanning to be read. Also tracking information cannot be added to bar codes as it can be with RFID. Track and trace should also provide real time verification of product integrity.

Disadvantages: RFID is only as good as the integrity of the package. Repackaging will render RFID useless. RFID can be copied, just like any other feature. Unless RFID is included at the unit of use level, it would be feasible to separate the RFID tag from the case or pallet and create bogus trails.

13. What are the costs and challenges involved with setting up an infrastructure for utilizing various track and trace technologies?

    Answer: The costs and the time required are unclear. Setting up an infrastructure would be a substantial undertaking, involving multiple components of the distribution chain, including pharmacies and hospitals. Also standards need to be established.

14. Tracking and tracing drugs and biologics throughout the drug distribution chain may result in the creation of a large database that includes tracking data from each entity that "handles" the product. Who should create and maintain such data? Where and how should the data be housed? Who should have access to the data? How can appropriate confidentiality be assured?

    Answer: We do not believe that the data should be owned by any one entity. Also the data needs to be secure.

15. Are there additional benefits beyond the ability to detect counterfeit product that anti-counterfeiting and track/trace technologies can provide for industry, (e.g., inventory control, facilitation of product recalls, and identification of theft and product diversion)? Give specific examples.

    Answer: Yes, you provided good examples. Track and trace technology may also reduce the incidence of medication errors. Possibly it could be used to automate pharmacy billing.

16. Discuss the logistic, economic, and public health effects of direct shipment of product to retailers and other end users.

    Answer: We believe at the present time that manufacturers should have the flexibility to decide if more direct distribution would be needed. If products at a high risk of counterfeiting are distributed directly from manufacturers to pharmacies, then the counterfeiters may very well move to those products not considered high risk.

    We also agree with PhRMA that a closed distribution system is the best way to assure the integrity of the US 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.

17. For products that are shipped directly from manufacturers to retailers, would the use of track and trace technology on those products provide any additional benefits?

Answer: Yes, see question 15 above.

18. Should all products be considered at high risk of being counterfeited? How can products at high risk of being counterfeited be identified? Which, if any, of the following criteria should be considered: (a) potential impact on public health if the product were counterfeited, (b) any history of, or the potential for, counterfeiting, tampering, or diversion of the product, (c) wholesale and retail price of the product, (d) volume of product sold, both on a unit and dollar basis, (e) the dosage form of the product, e.g., injectable, (f) approved and unapproved uses of the product, (g) current and potential misuse or abuse of the product, e.g., "street value", (h) other products in the class with a history of being counterfeited, (i) the length of remaining patent life for the product?

    Answer: No, not all products are at a high risk of being counterfeited. We believe that all criteria listed above are relevant. We believe that manufacturers should make this determination.

19. Discuss what could be included in an FDA guidance which should focus on key principles, on the use of anti-counterfeiting technologies.

    Answer: We believe that this should be left up to the manufacturer. However, we would support FDA guidance to facilitate the use of anti-counterfeiting technology.

20. Should FDA conduct research on development or evaluation of anti-counterfeiting technologies? If so what should this research focus on? How should FDA integrate its research efforts with other public and private sector efforts?

    Answer: It is important that if the FDA conducts research, this information is not available to counterfeiters.

21. Discuss what could be included in an FDA guidance on physical site security and supply chain integrity.

    Answer: We believe manufacturers are covered under GMPs for physical site security. We believe our physical site security is adequate. We believe FDA guidance on supply chain integrity should include:

    - Consistent requirements for wholesalers
    - Limit of number of wholesale transactions
    - Improved control over repackagers. If repackaging for resale is allowed, then repackagers need to provide the same level of control, track and trace, anti-counterfeiting and tamper evident measures as the original manufacturer.

- Increased FDA oversight and enforcement of counterfeiting criminal activities. Also increased FDA surveillance of vulnerable points in the supply chain.

2. QUESTIONS CONCERNING REGULATORY REQUIREMENTS AND SECURE BUSINESS PRACTICES (OPTIONS 10-13)

1. Discuss the most effective ways to achieve the goals of the wholesale distribution rule (21 CFR 203.3(u) and 203.50). Given recent or impending advances in technology, comment on the feasibility of using an electronic pedigree in lieu of a paper pedigree.

   Answer: We would like to see federal oversight of wholesalers instead of state oversight, so that there is uniform control over the drug distribution system. We also believe that any electronic pedigree should provide for authentication at the point of dispensing, but every segment in the supply chain would need to be involved and an infrastructure would need to be established.

2. Discuss the advantages and disadvantages of the new Florida and Nevada requirements for wholesale distributors, including the costs involved with compliance.

   Answer: We applaud Florida and Nevada's efforts to shut down fraudulent or negligent secondary wholesalers. The requirements listed in Option 10 seem reasonable.

   Option 10: "Continue to work with NABP to update their Model Rules for Licensure of Wholesale Distributors, using the Florida statute as a model where appropriate, in the following areas: requirements for licensure, qualifications of employees (especially those who handle drugs), storage and handling of drugs, site security (both for facilities and information), inspection and examination of drugs, record keeping, availability of records to inspectors and law enforcement personnel, due diligence with respect to business partners and contractors, administrative subpoena power, and criminal penalties; update FDA regulations under 21 CFR 205, as appropriate, to make it consistent with updates to the NABP Model Rules for Licensure of Wholesale Distributors."

3. Discuss the advantages and disadvantages of requiring a pedigree if track and trace technology is also being utilized for a given product?

   Answer: If RFID is used then the RFID chip could include the electronic pedigree. Disadvantage: The inclusion of electronic pedigree in RFID is likely to raise the cost of any RFID implementation significantly. Making pedigree inclusion a requirement might inhibit lower cost application and a limit sensible entry points for this technology.

6. Discuss the advantages and disadvantages of increased penalties for counterfeiting drugs?

   Answer: We support enforcement and penalties against those who knowingly introduce and distribute counterfeiting drugs.

7. Identify areas where business practices could be changed to prevent the introduction, and facilitate the identification, of counterfeit drugs.

   Answer: There are a variety of enhancements throughout the supply chain that could be pursued to decrease the risk of counterfeiting. For example:

   - Wholesalers purchasing only from manufacturers.
   - Pharmacies purchasing only from such wholesalers.
   - Controls over repackaging for resale.

9. Comment on the advantages and disadvantages of manufacturers sharing market data with the FDA for use in identifying counterfeit products.

   Answer: Manufacturers' market data is proprietary information. Sharing of relevant market data (by manufacturers and wholesalers alike) for specific counterfeiting incidents may be appropriate.

3. QUESTIONS CONCERNING INTERNATIONAL ISSUES (OPTIONS 22-23)

2. What global standards are needed to address the problem of counterfeit drugs? Who should develop these standards?

   Answer: We would encourage global cooperation to deal with:

   - Internet pharmacies
   - Importation
   - Other identified threats to product security.

- Common global sanction/legal redress against counterfeiters operating off-shore from the US.

- Regulatory Agencies should collaborate to ensure that there are clear global standards. This collaboration should include consultation with industry to ensure that proposals can be practically applied.