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

Re: Docket Number 2003N-0361

Ladies and Gentlemen:

In response to the request for comments related to the potential options presented in the *FDA's Counterfeit Drug Task Force Interim Report,* West Pharmaceutical Services, Inc. (West) wishes to respond to applicable questions. It should be noted that the West responses are specific to injectable dosage forms.

A. Questions Concerning Technology (Options 1-9)

Question #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.

Response:

Converting from multi-dose vials to single use vials for injectable products could be a costly measure. Each single dose vial would most likely require a percentage of overfill resulting in either an increase in batch size or additional batches as well as additional packaging and labeling materials. From a regulatory perspective, this might require additional stability studies and the filing of supplemental applications if the new size is not already in the packaging matrix for the dosage form.

Question #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.

Response:

Advantages:

Tamper evident packaging is particularly critical for use with injectable products. The route of administration and rapid onset of therapeutic activity is of significant concern particularly when dealing with acts of terrorism.

Economic Impact:

The economic impact could be considerable if redesign of the package is required; however, some of the current packaging for injectable drug products already contains tamper evident features. Most manufacturers of injectable drug products are already using a Flip-Off seal on their parenteral vials that is tamper evident by design. The seal consists of an aluminum shell and plastic button. When the button is removed, the aluminum shell and the target area of the rubber stopper are exposed. The button cannot be reapplied or replaced; if it were re-assembled after tampering, the health care professional would notice a change of "feel" and "sound" when removing an adulterated flip-off button since this packaging component has been used extensively in the pharmaceutical industry for over 50 years. The financial impact of incorporating anti-counterfeiting technologies into a standard tamper-evident Flip-Off seal is minimal – one to a few pennies per vial in most cases.

The Flip-Off seal components are able to be customized with additional security features. West, the manufacturer of the Flip-Off button, has developed the D-I-D™ (decoration-identification-differentiation) system that provides additional opportunities for incorporating anti-counterfeiting technologies into the current packaging system. This system utilizes several technologies that include: overt and/or covert printing with ink on either the plastic button or the aluminum shell; molding text or logos into the plastic button; and/or stamping (impressing) text on the aluminum shell. The economic benefits of employing this process include:

1. No change in tooling for the packaging line equipment.
2. Function and performance of the closure system are not impacted.
3. Changes can be easily implemented; printing changes average about 13 weeks and molding changes require approximately 26 weeks.
4. Incremental costs depending on the level of D-I-D system attributes incorporated range from approximately one to 10 cents per vial.

Question #5:

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?

Response:

At first thought, the tendency is to think of applying or adding more security to drugs that are expensive – the logical choice for counterfeiters. However, drugs that could be easily utilized to execute acts of terrorism should also be considered. These include vaccines (childhood and influenza) and high volume drugs that are widely prescribed such as generics.

Question #6:

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

Response:

West believes that a combination of overt, covert and forensic technologies be used at a minimum for injectable drug products.

Question #7:

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

Response:

If the product is classified as high risk or has the potential for being a target for an act of terrorism, yes.

Question #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, a (iii) track and trace technologies?

Response:

(i) Since FDA resources are currently limited especially in the review divisions and field operations, it may not be necessary for FDA to review the use of the technology employed for packaging and labeling as long as it is an acceptable, validated technology. The technology being used could be "registered" with FDA on the database that FDA speaks to establishing. This would provide investigators with information that could be used for review during CGMP inspections.

(ii) If the technology employed (e.g. taggants, markers incorporated into the product) has the potential for affecting the quality and/or purity of the dosage form (particularly biologic products), then FDA would certainly be required to play a role in the evaluation of the technology being utilized.

(iii) No comment

For the purpose of the review of anti-counterfeiting technologies, a team of reviewers/investigators should be established similar to the Pharmaceutical Inspectorate or Team Biologics. They should have knowledge of the various technologies/systems used and developed and "hands on" experience in the application of the technology in the manufacturing, packaging and labeling areas. They should be dedicated to the evaluation of these technologies and where necessary, advising industry (especially small businesses that lack resources) on best practices for implementation and compliance.

Question #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?

Response:

(1) How should "validation" of an anti-counterfeiting measure or track and trace technology be determined? This would depend on the technology being employed and validation would most likely have to be a cooperative effort between the supplier of the technology, the packaging component supplier that is incorporating the anti-counterfeit technology into their component and the dosage form manufacturer.

(2) Should only "validated" anti-counterfeiting measures be used? Yes; otherwise, how will there be assurance that the technology will consistently perform as described or purported to work?

(3) Who should do the validation? As noted in the first response to this question, it would have to be a collaborative effort between the manufacturer of the technology/product, the packaging component supplier that is incorporating the anti-counterfeit technology into their component and the dosage form manufacturer. Each would have to validate their portion of the process. The roles should be clearly defined in a development agreement or a quality agreement of responsibility.

Question #12:

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

Response:

The fact that many counterfeiters are well funded, international organizations that are able to defeat many anti-counterfeiting measures within 18-24 months after the measure is implemented underscores the need for multiple track and trace technologies that are:

(1) Continuously evolving to more sophisticated applications

- For injectable dosage forms, RFID microchips could be molded into the plastic button part of the Flip-Off seal. Incorporating the RFID chip into the tamper evident plastic button offers protection against reuse of the packaging since the plastic button is removed from the vial at the time of administration of the drug. The microchip could be programmed with information specific to the product such as unit number, lot number or some other unique identification code or information specified by the dosage form manufacturer.

- Bar codes can be imprinted on the plastic button with a variety of inks.

- Other evolving technologies that could be used as anti-counterfeiting tools include:
  a) Molding unique decoration(s) or labeling into the plastic Flip-Off button; the decoration or labeling is fused into the substrate of the button.
  b) Imprinting with inks that fluoresce, and absorb ultraviolet light (D-I-D System). Application of inks can be in the form of alpha numeric text, 2 dot matrix and/or barcodes.

(2) Capable of being changed in a relatively short period of time

- The information programmed into a microchip could be changed as needed to accommodate the dosage form manufacturer's requirements
- The same would be true for imprinting technologies
- The technology affords a great degree of flexibility to the dosage form manufacturer with a minimum amount of change

(3) Technology is not prohibitive in cost to the dosage form manufacturer.

- The cost is reasonable since there would be no changes to the tooling, equipment or process for packaging the product
- Vision systems could be reprogrammed for new text or other attributes being assessed
- Cost effective in that the technology could be applied to the existing unit dose being produced; no need to change packaging configuration

(4) Other considerations:

- There is potential for the application of these technologies throughout the entire supply chain (manufacturer to end user)
- The component manufacturer has the ability to validate the processes
- Multiple approved sources of materials of construction
- Controlled manufacturing environment (Vision systems, complete traceablity and compliance with applicable CGMPs);
- Product history with regard to processing (e.g. sterilization)
- Secure production site
- Printed or embossed seal systems available only through direct purchase from manufacturer; no distributors used for this product.

Question #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 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 the 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 life of remaining patent life for the product?

Response:

- Should all products be considered at high risk of being counterfeited? Not necessarily.
- How can products at high risk of being counterfeited be identified? Establish categories of risk based on agreed to evaluation criteria; assign numerical values to the criteria based on impact on public health and other critical factors; develop scoring system; evaluate each class of dosage form or specific products and assign numerical values; based on score, assign to appropriate risk category.
- Which if any of the criteria should be considered:

  (a) Potential impact on public health if the product were counterfeited – yes

  (b) Any history of, or the potential for, counterfeiting, tampering, or diversion of the product - yes

  (c) Wholesale and retail price of the product – yes

  (d) Volume of the product sold, both on a unit and dollar basis - yes

  (e) The dosage form of the product, e.g. injectable, - yes; bioavailability of the dosage form and ease of manufacture (clear liquids are less distinguishable than tablets) are considerations

  (f) Approved and unapproved uses of the product – yes; it would be easy to prey on patients with serious diseases with products not approved in the US but used in other parts of the world to treat the condition.

(g) Current and potential misuse or abuse of the product, e.g., "street value" – yes; high demand and high potential for illegal income,

(h) Other products in the class with a history of being counterfeited - yes

(i) The length of remaining patent life for the product? – yes

Question #19:

Discuss what could be included in an FDA guidance on the use of anti-counterfeiting technologies?

Response:

The guidance needs to include not only manufacturers of the dosage form but also manufacturers of anti-counterfeiting packaging and labeling. The guidance should address:

- Control of raw materials, manufacturing process and finished products
- Inspection and validation of technologies employed
- Reconciliation practices
- Traceability
- Written agreement of responsibility or development agreement between the component or technology provider and the dosage form manufacturer that defines who is responsible for each part of the process

Question #21:

Discuss what could be included in an FDA guidance on physical site security and supply chain management?

Response:

The guidance needs to include not only manufacturers of the dosage form but also manufacturers of anti-counterfeiting packaging and labeling. The guidance should address:

- Security of manufacturing site and warehouse facilities
- Control of materials of construction or auxiliary materials, equipment used
- Disposal of rejected materials
- Security of sales and distribution channels and shipping

B. Questions Concerning the Regulatory Requirements and Secure Business Practices (Options 10-13)

Question #10:

Comment on the need for FDA guidance dealing with site security and supply chain integrity in light of the importance of drug treatment for bio-terrorism incidents.

Response:

The FDA has an established program at CBER and almost two years experience in evaluating and designing systems and processes to combat and prevent bioterrorism incidents. Their insight and guidance on site security and supply chain integrity would be helpful and could possibly expedite the implementation of necessary systems in applicable areas of the private sector.

D. Questions Concerning Education and Public Awareness (Options 17-21)

Question #2:

What role should the private sector, professional/trade associations and consumer representatives play in educating consumers and health care professionals? Are there other groups that FDA should solicit for help?

Response:

Companies that have developed specific technologies could educate health care professionals and consumers regarding the specific role their technology plays, or the critical attributes of the anti-counterfeiting system that they should be aware of when administering, dispensing or using the dosage form. For example, the Flip-Off cap has certain "feel" and "sound" attributes that the end user should be aware of; the end user should also be made aware of overt and covert markings on the product used to protect its integrity.

This information could be conveyed directly to the end users by training seminars through the pharmacy and medical professional organizations, videos supplied to hospitals, etc. or by training the professional sales staffs of the dosage form manufacturers; they could then train the healthcare professionals and patient population.

E. Questions Concerning International Issues (Options 22-23)

Question #2:

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

Response:

The questions posed in the *FDA's Counterfeit Drug Task Force Interim Report* should be addressed globally as well. There have been several conferences held in Europe to address this concern. A starting point in establishing an international coalition to address this matter would be to establish a committee or task force in conjunction with the International Conference on Harmonization (ICH). Because of their proximity to the US, Canada, Central America and South America should be invited to participate in this effort. The *FDA's Counterfeit Drug Task Force Interim Report* is an informative, comprehensive assessment of the issues and questions germane to this issue. However, West would like to request that two other areas pertinent to this matter be considered. They are:

1. The matter of assessing the applicability, compatibility, potential for validation and integration of developing or emerging technologies into the dosage form manufacturers' current system(s) has not been addressed. West believes that this is a critical factor that needs to be considered since it could have a significant time and cost impact on the anti-counterfeiting effort being proposed for implementation. West would like to participate in the assessment process, if FDA deems this possible.

2. The United States Pharmacopeia has proposed a revision to General Chapter <1> "Injections" that would restrict the printing on caps and ferrules of all injectable drug products to cautionary statements only. This proposed revision was based on a 1999 recommendation from the National Coordinating Council for Medication Error Prevention (NCCMERP) to "help reduce errors in which product labeling and packaging have been identified as contributing factors". In conjunction with this, USP is proposing that injectable preparations of neuromuscular blocking agents (NMBAs) bear a cautionary statement "Warning: Paralyzing Agent, or Paralyzing Agent" in a contrasting print (black or white) on ferrules and cap overseals.

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Pharmaceutical Systems Division

West believes that restricting the printing on caps and ferrules of all injectable drug products to cautionary statements is not in the best interest of the healthcare provider, pharmacist and patient because it would restrict the use of a practical, flexible and cost effective anti-counterfeiting technology that could be easily and widely used as a deterrent throughout the healthcare industry to a few limited situations.

Restricting the printing on caps and ferrules is not necessarily sufficient action for preventing medication errors. While it is an additional measure to call attention to the drug, the potential for administering the wrong drug still exists, especially in the case of multiple products in a therapeutic class of drug. The only way to prevent such an error is by reading the label to verify that the correct drug is being administered. The two other recommendations proposed by the NCCMERP to prevent medication errors, namely, that (1) IV drug names be visible on both sides of the container and (2) drug names be printed as large as company names and logos would accomplish this.

West Pharmaceutical Services wishes to thank the FDA for the opportunity to comment on the *FDA's Counterfeit Drug Task Force Interim Report* and requests that our comments are included as part of docket number 2003N-0361. If there are any questions regarding our comments or additional clarification is required, please contact the undersigned at (610) 594-3105 or via email at Maxine.Gallagher@Westpharma.com.

Sincerely,
West Pharmaceutical Services, Inc.

FOR

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