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

Re: Docket No. 2003N-0361, Anti-Counterfeit Drug Initiative

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. The company has more than 5,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life and a worldwide network of pharmaceutical facilities to produce quality pharmaceutical products that are safe and efficacious. Our key marketed products span numerous therapeutic categories that include oncology, cardiovascular/metabolics, headache and migraine, infectious diseases, medical imaging, mental health, nervous system, diabetes, nutritionals, ostomy and wound care.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal to detect and prevent counterfeit pharmaceutical products in the U.S. supply chain and ultimately to help ensure the integrity and safety of pharmaceutical products for our consumers.

We commend the U.S. FDA for their effort to raise awareness of this public health issue and to bring together all parties responsible in this anti-counterfeiting initiative for achieving an effective result. Bristol-Myers Squibb appreciates the opportunity to provide comments on this docket and the *FDA Anti-Counterfeiting Task Force Interim Report.*

General Comments:

1. All regulatory and legislative actions considered for addressing the issue of counterfeit drugs and biologics should be applicable to all bio/pharmaceutical manufacturers, i.e., both generic and brand, as well as repackagers.
2. The legal penalties for those who are convicted of crimes associated with counterfeiting of drug and biological products or their diversion should be more severe to help deter this type of criminal activity.
3. All members of the supply chain should be allowed to have flexibility in determining what types of security technologies are needed on the product(s) they are responsible for distributing.

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4. Rather than mandating certain types of security technologies for all products, the amount or sophistication of security technologies employed should be guided by the identified specific risks that may indicate the potential for a product to be counterfeited.
5. There is a significant ongoing cost impact to the pharmaceutical industry in implementing security technology solutions that periodically change in order to remain effective. These additional product costs may impact consumers.
6. The Interim Report suggests a cost benefit relative to a reduced labor cost due to automation. In many cases, automation moves costs to other areas of the business and many times, these costs are not typically considered in the overall benefit model. Examples of the benefit model for reduction of labor cost would be helpful in evaluation of the security technologies.
7. The Interim Report suggests an improved inventory management and control benefit for distributors and pharmacies but not specifically for the pharmaceutical industry. Many pharmaceutical companies already have in place an enterprise wide system for inventory management and control that are highly integrated with production planning, raw materials management and quality control systems. The benefit to these pharmaceutical companies to implement another inventory management and control system may not be as apparent. Those in the supply chain that may stand to benefit the greatest from anti-counterfeiting technologies on products for inventory management and control, i.e., the distributors and pharmacies, should share in the financial impact from the technology implementation.
8. Oversight activities, such as inspection of the distribution chain members' facilities, for assuring the integrity of the country's distribution system are needed, but this oversight needs to be conducted by appropriate government authorities to ensure its independence.

Technology Comments:
(Reference: *FDA Anti-Counterfeiting Task Force Interim Report* (pdf version), p. 25-26.)

1. Package all finished dosage form drugs in unit of use packaging as appropriate for the particular product (e.g., tablet, multi-dose vial) at the point of manufacture, as is now done in many nations.

   Response:
   The concept of moving to unit dose packaging is a worthwhile concept in the battle against counterfeiting because it removes the need to repackage. However moving in this direction would have a huge impact on the industry in terms of cost, regulatory filings, stability testing and equipment and possibly increased costs for consumers.

2. Use tamper evident packaging from the point of manufacture, with labeling that notes the tamper evident feature, for all dosage forms, active pharmaceutical ingredients (API's), and bulk chemicals.

   Response:
   This practice is currently in effect for virtually all final package presentations.

3. Incorporate for all drug products at least two types of validated anti-counterfeiting technologies into packaging and labeling at the point of manufacture with at least one of these technologies being covert (i.e. not made public, and requiring special equipment or knowledge for detection) using a phased in approach starting with those products at high risk of being counterfeited and where the introduction of counterfeit product poses a serious health risk.

Response:
As previously stated, rather than mandating certain types of security technologies for all products, the amount or sophistication of security technologies employed should be guided by the product's risks. We agree with incorporating anti-counterfeiting technology with the following conditions:

- Industry is not directed to a specific technology
- Industry is not directed to the amount of security technology for each product
- Industry is given sufficient lead time to move into their selected technology
- Clarification is provided on what constitutes a validated anti-counterfeiting technology

4. Incorporate for all drug products a taggant, chemical marker, or other unique characteristic(s) into the manufacturing process that is only identifiable with the use of sophisticated analytical technologies using a phased in approach starting with those products at high risk of being counterfeited and where the introduction of counterfeit product poses a serious health risk.

   Response:
   This would require extensive investigation into compounding materials, processing methods and long term stability with impact to current drug/biological design and development processes. However going forward with pipeline products, this technological approach can be integrated. There would also be significant issues around regulatory filings in terms of timing and how proprietary information about the technology chosen is disclosed. In addition, is the identification to be conducted only by the manufacturer or are others to be allowed to perform the identification?

5. Create an electronic database of drugs and biologics for authentication purposes, which consists of photographs of the product, packaging and labeling information, and the anti-counterfeiting measures utilized in the packaging, labeling, and product itself.

   Response:
   Who would mange this database and how would it be updated? Assuming that the database would be used to determine authenticity, how would this information be secured? In addition, who are the intended users of this database?

6. Achieve the goal of the pedigree requirements by phasing in track and trace technology (i.e., electronic pedigree) for all drugs and biologics starting at a case and pallet level for products at "high risk of being counterfeited" and progressively including all products at the case, pallet, and package level. The technology should have an integrated infrastructure that is able to track and trace products at all points in the distribution chain from manufacturer to end user.

   Response:
   When the technology is readily available and standardized, we agree with the program that extends to the pallet level. In our opinion, the technology and infrastructure does not presently exist at the case or package level with regards to the management of the resulting data.

   In addition, an integrated infrastructure for track and trace technology throughout the supply chain has many significant implications including, but not limited to, constantly changing technology standards, agreement of all supply chain members to these standards, security

and control and maintenance. Achieving the goal of pedigree requirements through this integrated infrastructure may be a significant issue from the perspective of ownership of this record of information and verification of its authenticity. Patient privacy needs to be considered relative to track and trace technology, especially at the individual package level.

7. On an interim basis, because the technologies described above may take several years to implement, all drugs and biologics "at high risk of being counterfeited", should be tracked and traced either (1) By limiting the number of transactions of the product (e.g., shipping the product from the manufacturer either (a) directly to the retailer or health care entity, (b) to the retailer or health care entity through a single licensed wholesaler who would sell the product directly to retailers or health care entities, (c) identifying steps that multiple wholesalers can implement to reduce the risk of counterfeit introductions), or (2) By using available track and trace technology, identifying the drug at least at the case and pallet level, and preferably at the product level, throughout the distribution system.

   Response: Options to tighten the supply chain by limiting the number of times a product is handled after its manufacture:
   - eliminates the supply chain entities that have been shown to be responsible for the diversion of pharmaceutical products and insertion of counterfeits,
   - minimizes the need for complex and expensive security technologies, and
   - may ultimately contain product pricing and costs for our customers while increasing the assurance of product authenticity and consumer confidence.

8. Issuance of an FDA guidance document concerning the appropriate use of anti-counterfeiting technologies as well as the FDA application and review process for incorporating or changing taggants, chemical markers, or other unique characteristic(s) of the product.

   Response:
   Guidance in terms of application and validation of anti-counterfeiting technology is welcomed but "appropriate use" should be left to the discretion of the manufacturer. Technologies may be used in innovative ways that may not be readily apparent and the flexibility to use technologies based on the uniqueness of our products is essential to our competitive advantage. It is also important that guidance for the FDA application and review process provide for industry protection on proprietary information relating to anti-counterfeiting security technologies of packaging, on-product and in-product components and unique product characteristics.

9. Issuance of an FDA guidance document concerning physical site security and supply chain integrity.

   Response:
   The business practice of physical site security is currently in effect for virtually all manufacturing facilities. Guidance on supply chain integrity should focus on those supply chain members who do not manufacture product under the cGMPs.

Secure Business Practices and Regulatory Requirements Comments:
(Reference: *FDA Anti-Counterfeiting Task Force Interim Report* (pdf version), p. 26-27.)

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.

Response: See General Comments above.

11. Develop sets of "secure business practices" which would be voluntarily adopted by manufacturers, wholesalers, repackagers, and pharmacies. Best practices would be identified in areas such as: employee qualifications, security of physical facilities and information systems, package disposal, dealings with business partners and contractors, inspection and examination of products, record keeping, etc.

    Response:
    The cGMPs, 21 CFR Part 11 and other FDA guidances currently cover many of the suggested business practices for manufacturers in our industry. Any additional guidelines or practices developed should complement existing regulations, cGxP practices or guidances and not conflict or generate confusion with these existing documents.

12. Designate, by entities such as manufacturers, wholesalers, repackagers, and pharmacies, an individual or team to coordinate security and anti-counterfeiting. Such activities would include quality improvement, monitoring and use of anti-counterfeiting technologies, and regular review of the entities' security and anti-counterfeiting measures.

    Response:
    A quality system approach to coordinate security and anti-counterfeiting is inherent to the pharmaceutical industry and good business practice. Designating a team of supply chain members to foster collaboration and anti-counterfeiting improvements may be a valuable effort in combating the counterfeiting problem.

13. Timely sharing with FDA, by manufacturers, of relevant market tracking and trending data and the analysis of these data for use as a means of identifying counterfeit or diverted product in the marketplace.

    Response:
    Timely sharing with FDA is currently in practice by PhRMA members who have adopted the voluntary program for reporting counterfeit drugs to the FDA's Office of Criminal investigations within five working days of determining that there is a reasonable basis to believe that a product has been counterfeited.

    At this time, the impact of counterfeits on market tracking and trending data is not fully understood. Signals that may or may not be indicative of counterfeit product need to be verified in order to identify real counterfeit product in the marketplace. Risk management also plays a role in the timeliness and interpretation of market data for identifying attributes indicative of counterfeits.

    Reports of diverted product are currently investigated to the fullest extent and there is collaboration with appropriate law enforcement agencies for remediation. Systems for

market tracking and trending of data in identifying diverted product in the marketplace may be more appropriate to the wholesalers and distributors in providing timely sharing of this information with FDA.

Rapid Alert and Response Systems Comments:
(Reference: *FDA Anti-Counterfeiting Task Force Interim Report* (pdf version), p. 27.)

14. Enhancing the MedWatch Alert System for use as a tool to receive and disseminate timely information about counterfeit drug products, especially identification of suspect drug product.

    Response:
    Enhancing the existing MedWatch Alert System will expedite and facilitate adoption by supply chain members for their use in reporting and receiving information about counterfeit drug products. There is familiarity with the existing system and there would be essentially no impact on the supply chain members' business processes to use the system for this purpose.

15. Create a counterfeit alert network through use of existing, or newly developed, communication tools that allow reception, dissemination, and sharing of information about counterfeit drugs in a timely manner (e.g., to pharmacists, manufacturers, wholesalers, and law enforcement and public health official officials.

    Response:
    Enhancement of MedWatch Alert System is preferred over an additional alert network. See response to option 14 above.

16. Further enhance FDA's internal processes for responding to and investigating reports of suspected counterfeit products.

    Response:
    Recent industry counterfeit events indicated that a partnership with FDA is essential in responding to
    and investigating reports of suspected counterfeit product. Enhancements resulting from these
    experiences would seem appropriate and consistent with continual improvement. In addition, the FDA
    Office of Criminal Investigations is in need of an enhancement of investigating personnel to deal
    with the increasing workload relative to counterfeiting but also to terrorism.

Education and Public Awareness Comments:
(Reference: *FDA Anti-Counterfeiting Task Force Interim Report* (pdf version), p. 27-28.)

17. Increase the efforts of the FDA, other government agencies, and appropriate private sector partners to educate consumers and health care professionals on how to reduce risk of obtaining counterfeited drugs before an event occurs. Helpful messages could include: (1) what is a counterfeit drug and why U.S. consumers and health care professionals should be vigilant, (2) the dangers of buying drugs over the Internet or from other unknown entities, (3) good purchasing practices that will decrease the chances of encountering counterfeits, and (4) legitimate ways to obtain drugs (e.g. federal or state purchasing programs, private sector purchasing programs for low income consumers).

Response:
Increasing public awareness and education is essential in combating counterfeit products. It also ensures the value of efforts and resources invested in anti-counterfeiting programs and activities. Education and public awareness is a shared responsibility among supply chain members and their professional industry organizations. Example messages provided above are appropriate but need to be communicated in a manner that serves the various ethnic groups and those with physical and mental impairments.

18. Educate consumers and health care professionals on how to identify counterfeit drugs (including how to recognize anti-counterfeiting technologies on packages, labeling, and drug products themselves) and what to do when they believe they have identified a counterfeit product.

    Response:
    Education of consumers, as appropriate so as not to cause panic, is essential. This may include their understanding of the important role that their healthcare provider or pharmacist can provide in identifying counterfeit drugs (including how to recognize anti-counterfeiting technologies on packages, labeling, and drug product themselves) and their obligation in reporting them.

19. Assure flexibility as agency officials determine their outreach approach and create a set of pre-established consumer and professional outreach plans that can be utilized if deemed appropriate (based on risk analysis) after counterfeits are detected in the stream of commerce.

    Response:
    Pre-established outreach plans are essential for responding to and communicating about counterfeit situations in a timely manner to minimize damage to the public health. However, flexibility is needed for unique circumstances.

20. Provide outreach efforts appropriate for the diverse elements of the U.S drug distribution system. We find that individual strategies for educating and increasing awareness should be considered for diverse stakeholders including: consumers, pharmacists, wholesalers, repackers, doctors, nurses, the media, and public health officials. These creative strategies could take the form of public service announcements, educational fliers and communication tools that can be distributed by pharmacists and PBMs, toll-free numbers on labels; permanent messaging on appropriate industry and private group websites to establish a permanent presence, as well as many other potential tools.

    Response:
    To have the greatest effectiveness, outreach efforts must be targeted to various demographic groups in terms of the message and mechanism used to communicate. Metrics should be established to verify their efficacy, measure return on investment and provide data to make improvements in the outreach efforts.

21. Explore ways of improving and coordinating agency and industry messages and efforts to address and contain a counterfeit event. Though a drug manufacturer is not responsible for the creation of a counterfeit of its products, ensuring health professionals are well informed about the event and protecting the public from it should be a shared public policy goal.

Response:
Collaboration is essential between the agency and industry. A forum to explore ways in which the agency and industry can work together to address and contain counterfeit events should be considered.

International Issues Comments:
(Reference: *FDA Anti-Counterfeiting Task Force Interim Report* (pdf version), p. 28.)

22. Strengthen international cooperation in law enforcement efforts, identification of counterfeit products, use of anti-counterfeiting technologies, and education of stakeholders and consumers.

    Response:
    Strengthening international cooperation in law enforcement efforts should be a priority. Currently, the Pharmaceutical Security Institute (PSI) and its members work to achieve better alignment with international law enforcement entities including ways to improve international relationships for the battle against counterfeits. The 17 members of the PSI are developing and delivering training programs to law enforcement agencies, public health authorities and regulatory bodies concerning counterfeiting, theft and diversion. In addition, the PSI has formed a Technical Advisory Committee to provide the members with scientific expertise regarding technological anti-counterfeiting solutions.

    There is an increased complexity of the human dimensions for the use of anti-counterfeiting technologies and education of stakeholders and consumers from an international perspective, particularly cultural and language challenges. In addition, the geographic market and its distribution chain may lessen or increase the product risk for counterfeiting, thus impacting the type and amount of anti-counterfeiting technology needed as well as the amount and type of education.

23. Develop global standards for (a) packaging of final dosage forms and API's, (b) the use of tamper evident packaging, (c) product pedigrees, (d) the use of anti-counterfeiting measures, and (e) the use of trace/track technologies.

    Response:
    Being a global company, we support global standards for packaging related activities. However, this system needs to be flexible enough to accommodate different markets, operational practices and regulatory requirements in the global marketplace.

    Recognizing these differences we need sufficient time to develop a comprehensive yet workable system to minimize the counterfeiting problem worldwide.

BMS respectfully requests that FDA give consideration to our comments. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie F. Smaldone, M.D.
Senior Vice President,
Global Regulatory Sciences