

Impact of FDA opening offices in China and India

In November 2008, as part of its “Beyond Our Borders” initiative, the FDA opened its first overseas office in Beijing. Further offices followed in Shanghai and Guangzhou, and it is intended to open offices in further parts of the world in India, Latin America, Europe and the Middle East. Jerry Boxall takes a look at the rationale behind this initiative, and the possible outcomes.

In a fast-changing world, the US Food and Drug Administration (FDA) has had many challenges to face over recent years and has developed a number of initiatives to better deal with a new truly global marketplace. According to its mission statement, the FDA is responsible for protecting public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the United States food supply, cosmetics, and products that emit radiation. It also has responsibility for advancing public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health. There have been a number of well-publicised safety issues related to imported products, notably involving heparin, food and other products, including toys, from China. In the heparin case, a Chinese-made component contained a contaminant linked to as many as 81 deaths and hundreds of allergic reactions. These issues have highlighted the role of the FDA in the public media and heightened pressure on the United States government to ensure that the import of products from overseas is effectively policed to ensure the safety of the public. This is an increasingly difficult challenge in the current global climate, and in practice it is not possible to guarantee the safety of all imported products without bringing international trade to a standstill. What is required is an effective strategy that optimises the likelihood that unsafe products for import will be identified before they can do harm, and that sends a message to the public, and to potential exporters of goods to the United States, that adequate controls and legislation are in place. This is what the FDA is seeking to do in a number of new initiatives.

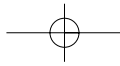
To put the challenge into perspective, the United States currently imports approximately \$2 trillion worth of products annually from more than 150 countries, and this figure is projected to triple by 2015 as demand for foreign products increases in the United States. More than half of the imports originate from five countries (Canada, China, Mexico, Japan and Germany). Imports arrive in the United States

through a complex network of more than 300 seaports, land border crossings, postal facilities and other ports of entry, and over 825,000 importers brought shipments into the US in 2006. It is clearly an impossible task to screen out all products for potential safety hazards at the point of entry, and a much broader approach including close collaboration with the countries importing goods into the United States is essential. On 18th July 2007, President Bush issued an executive order establishing an Interagency Working Group on Import Safety, chaired by the Health and Human Services Secretary, Michael Leavitt. This led to a strategic framework for continual improvement in import safety. A key element of this was a shift in focus towards a risk-based, prevention-focused approach designed to ensure that safety is built into products before they are exported to the US. The FDA has

instigated an initiative called “Beyond our Borders” designed to improve the safety of imported products regulated directly by them. A part of this initiative has been the plan to establish offices overseas. On 19th November, a milestone was reached with the opening of the first overseas FDA office in Beijing, followed by Shanghai and Guangzhou. It is intended that further offices will be opened in other parts of the world, including India, Latin America, Europe and the Middle East. The staffing in China is currently low, with a reported eight employees, and the exact role that these offices will fulfil does not appear to be entirely clear at the moment. The stated intention is to work more closely with manufacturers and other governments, better share best practices, and further ensure that quality and safety are built into food and consumer products at the point of

manufacture, according to Michael Leavitt. Clearly a presence on the ground, particularly with a mix of US nationals and local employees among the personnel, should facilitate better communications with local regulatory authorities and manufacturers, and should also enable a quicker response in the event of any safety issues emerging. The success of the overseas offices will depend heavily on good cooperation between the FDA and the local authorities. The Chinese offices have the formal approval of China, and similar approval from India has been granted. To ensure an ongoing spirit of cooperation, it may be important to ensure that the establishment and operation of overseas offices is to the mutual benefit of the United States and the country in which the office is sited, and also to remain true to the intention to “share best practices”, rather than imposing standards across the board. Within China, the opening of FDA offices has not been universally welcomed, and concerns have been expressed about

“The staffing in China is currently low, with reported eight employees, and the exact role that these offices will fulfil does not appear to be entirely clear at the moment”



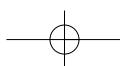
the true intentions of the United States, which have included speculation that the US is seeking to further restrict Chinese imported products, and even that it is attempting to pave the way for US products to enter the Chinese market. In addition, there is the feeling from some quarters that China has lost its authority in the field of food and drug inspections within China, and that the US does not trust China's inspection abilities anymore. China has expressed its intention that the siting of overseas inspection teams will be bi-lateral and that China will send inspectors to the US in the future, although there do not appear to be clear plans to implement this at present.

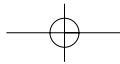
One of the potential objectives of the overseas offices is to step up inspections of foreign facilities. In practice, this may be difficult to achieve. Until this time, the FDA has sent inspection teams from the US to a relatively small number of overseas manufacturers. As an example, the Chinese facility believed to be the source of the contaminated heparin that led to many deaths of US citizens had not been subject to an FDA inspection. Only \$10 million was dedicated to overseas inspections in 2007, with \$11 million for 2008. In addition to

“The FDA has instigated an initiative called “Beyond our Borders” designed to improve the safety of imported products regulated directly by them”

this, until the opening of overseas offices, there were problems with the recruitment of volunteer inspection staff and a lack of adequate translation arrangements, in some cases relying on staff within the inspected facilities. Other circumstances that are not encountered within the US include the necessity to pre-announce inspections as well as difficulties in extending foreign inspections if problems are encountered. It is estimated that about 8% of overseas manufacturers that import drugs or drug ingredients to the US are inspected annually, and to be able to implement a biennial inspection programme overseas similar to that in place in the US would require \$70 million of investment and significantly more personnel than are now committed, according to a United States Government Accountability Office testimony in April 2008. This is unlikely to be forthcoming, so a focus on a risk-based approach is very important. To this end, the FDA has made efforts to obtain more information from foreign regulatory bodies and to work more closely with these bodies on information sharing. The FDA has also been working on improving the accuracy of data it holds on foreign establishments, which includes an electronic registration and listing system and an initiative to contract with an

Beijing Skyline





external organisation to conduct on-site verification of the registration data and product listing information of foreign establishments shipping drugs and other FDA-regulated products to the US. Up to now, inconsistent database information and a tendency for some foreign establishments that do not export to the US to register with the FDA to imply some form of FDA “approval” of their sites, has meant that an accurate count of foreign establishments exporting to the US has not been available.

In addition to the oversight of manufacturing facilities, the FDA has had to grapple with an ever-increasing volume of data generated from outside the US in its oversight of clinical trials and the approval of new drugs. According to a Tufts Center for the Study of Drug Development Outlook 2008 report, 65% of the top pharmaceutical companies’ trials will be staged outside the US, compared to 43% currently. This raises the question of how well the FDA can oversee the conduct of these trials and ensure the validity of the data, and has also led to genuine concerns about the protection of clinical trial subjects, and the potential that new drugs may be tested on poorer populations for the exclusive benefit of rich consumers elsewhere in the world. The opening of overseas offices will enable the FDA to conduct more international GCP inspections, but without a huge increase in resources, it will struggle to keep pace with the rate of increase in overseas trials.

In summary, the FDA has a significant challenge in responding to a rapidly changing global environment, as well as pressure from the media and congressional investigations as a result of a number of well-publicised safety alerts concerning foreign imports, the most notable recently being as a result of contaminated heparin from China. The sheer volume of product imports and clinical trial data coming from overseas, which will only increase, means that a targeted, risk-based approach is essential in implementing an effective strategy for ensuring the safety of US citizens. The opening of offices overseas is a part of this strategy and has a number of clear benefits. The location of the first offices in China, followed by India, reflects the rapid growth of exports from these emerging markets, and is to be followed by offices elsewhere in the world. Local resources will enable more GMP and GCP inspections to be carried out on overseas facilities by the FDA, but the greater benefit is likely to be seen in an improvement in communication and collaboration between all the interested parties, including local regulatory authorities and manufacturers. The FDA will clearly have a role in educating local stakeholders in the standards set by the FDA, and this should help to raise the quality of manufacturing and of the conduct of clinical trials and the validity of data produced. The United States remains the largest consumer of drugs globally, and the FDA is the most powerful food and drug regulatory authority in the world. However, rather than imposing FDA standards across the board,


“The location of the first offices in China, followed by India, reflects the rapid growth of exports from these emerging markets and is to be followed by offices elsewhere in the world”

the most successful long-term approach may well be to encourage sharing of information and a collaborative approach in ensuring that standards can be improved globally. The FDA cannot raise standards by itself; it can advise on the required standards and then verify whether these have been met and act accordingly. If manufacturers and those conducting clinical trials globally can be brought in to the process of harmonising and improving standards, then a more successful outcome is likely. There is inevitably a significant political element to the opening of overseas FDA offices, and as the global

economy continues to change, and as countries such as China and India experience further economic growth and prosperity, the landscape may continue to shift as local consumption of medicinal products is likely to increase within China and India as wealth is created. This could ultimately mean that the FDA’s unique position as effectively a global regulator may change in time, and a truly international effort to ensure the safety of new medicinal products and the validity of clinical trials may be more successful in the long run. To this end, the FDA has already established arrangements related to GMP inspections with Canada, Japan, the European Union and others. The FDA is also working with the European Medicines Agency and Australia’s Therapeutic Goods Administration on the oversight of active ingredients from China and India. Mutual recognition between

countries of each other’s inspection standards or the acceptance of one another’s inspections in lieu of their own should be a future objective, but may be some way off.

The opening of FDA offices overseas is one important step in the increasing challenge of keeping control over the import of FDA regulated goods into the United States. In the short term it sends a clear message that the FDA is determined to step up its efforts to prevent products of doubtful safety from entering the US. In the long term, a truly international collaboration will be required to oversee the safety of drugs and the conduct of clinical trials in the new global arena which has changed rapidly over the past decade, and which is set to change further in the years ahead ■



Jerry Boxall
Jerry Boxall, Managing Director EU of ACM Pivotal, trained as a Biomedical Scientist, Jerry has over twenty-five years of experience in this field. For the past fifteen years, he has held senior central laboratory posts both in the UK and in Europe. Jerry has been heavily involved in the establishment of both European and Global central laboratory networks and has been responsible for central laboratories in Germany, France, Denmark, The Netherlands, and the United Kingdom. Jerry joined the ACM-Pivotal team from CRL-Medinet in June 2000 as Head of European Operations, and took over as Managing Director, Europe, in January 2005. E-mail: j.boxall@acm-pivotal.uk.com

