

Minireview

Meeting the challenges of medical countermeasure development

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Summary

Despite substantial investments since the events of 2001, much work remains to prepare the nation for a chemical, biological, radiological or nuclear (CBRN) attack or to respond to an emerging infectious disease threat. Following a 2010 review of the US Public Health Emergency Medical Countermeasures Enterprise, FDA launched its Medical Countermeasures initiative (MCMi) to facilitate the development and availability of medical products to counter CBRN and emerging disease threats. As a regulatory agency, FDA has a unique and critical part to play in this national undertaking. Using a three-pillar approach, FDA is addressing key challenges associated with the regulatory review process for medical countermeasures; gaps in regulatory science for MCM development and evaluation; and issues related to the legal, regulatory and policy framework for an effective public health response. Filling the gaps in the MCM Enterprise is a huge national undertaking, requiring the collaboration of all stakeholders, including federal partners, current and prospective developers of medical countermeasures, relevant research organizations, and state and local responders. Especially critical to success are an appreciation of the long timelines, risks and high costs associated with developing medical countermeasures – and the systems to deliver them – and the requisite support of all stakeholders, including national leadership.

Introduction

The events of 11 September 2001, and the subsequent mailings of anthrax-laden envelopes within the USA,

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forever changed the way Americans view public health and national security. As recently confirmed (The WMD Terrorism Research Center, 2011), despite the investment of considerable financial and human resources since 2001, the USA does not have the range of medical countermeasures (MCMs) or established systems to rapidly and effectively respond to a deliberate chemical, biological, radiological or nuclear (CBRN) attack, or to a naturally occurring infectious disease outbreak. MCMs are the drugs, vaccines and medical devices (including diagnostic tests, equipment and supplies) that will be needed to respond to a public health emergency, including products to prevent and respond to anthrax, smallpox, radiological/nuclear agents, pandemic influenza and other emerging diseases.

In an effort to fill this gap in MCMs, product developers and the US government face particular challenges, most of which fit into two major categories: (i) problems facing eager but relatively inexperienced companies conducting MCM research and development and (ii) unique scientific and regulatory issues and uncertainties facing developers and the government arising from the fact that many MCMs cannot ethically or feasibly be tested in humans, meaning that much, if not all, efficacy data must be derived from animal experimentation.

The Federal government has a crucial role to play in facilitating MCM development and acquisition and, therefore, in addressing the associated regulatory and scientific challenges. Within the Department of Health and Human Services (HHS) the Office of the Assistant Secretary for Preparedness and Response (ASPR) leads the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE or Enterprise), a collaboration of agencies, such as the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), Food and Drug Administration (FDA), Department of Homeland Security (DHS) and Department of Defense (DoD), which is working to support and encourage the development, procurement and stockpiling of MCMs. In its role as regulator, evaluating medical products for their safety and efficacy, FDA has a unique and critical part to play.

In 2010, HHS Secretary Sebelius released the findings of an extensive review of the Enterprise and articulated a

new strategic MCM vision (HHS, 2010). The Review's recommendations contributed to the August 2010 establishment of FDA's Medical Countermeasures initiative (MCMi) to facilitate development and availability of high-priority MCMs and strengthen the MCM Enterprise. Implementation of the MCMi is being coordinated by the Office of Counterterrorism and Emerging Threats (OCET) in FDA's Office of the Commissioner. However, the MCMi involves close collaboration, both internally, among the medical product centres (i.e. Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Center for Drug Evaluation and Research) and externally, between FDA and its federal partners and other relevant stakeholders.

FDA has taken a three-pillar approach to fulfilling its overall MCMi mission: Pillar I: Enhance the MCM regulatory review process; Pillar II: Advance regulatory science for MCM development and evaluation; and Pillar III: Modernize the legal, regulatory and policy framework for an effective public health response (FDA, 2011a).

This review presents a summary of the key scientific and regulatory challenges facing MCM development, approval and use. It also describes the approaches FDA is taking through the MCMi to address these key challenges.

Key scientific and regulatory challenges to MCM development and availability

The challenges confronting MCM development and availability are more complex than the already complicated process for developing medical products. Generally, MCM development and approval must follow FDA's rigorous product review process. Yet, in many cases, such as when limited human efficacy data are available, the scientific and regulatory hurdles may be greater than the challenges inherent in *typical* drug development. In addition, medical product development is very resource-intensive, with estimates of the costs of developing a new medical product ranging from \$0.8 to more than 1.0 billion (DiMasi and Grabowski, 2007). Although the Project BioShield Act funded the creation of a government market in 2004 to acquire certain MCMs, including those that are not yet licensed or approved, the funds that are available are relatively small compared with the possible return on investment from a blockbuster drug. These challenges – and the lack of a commercial market for many CBRN countermeasures – have left most companies with extensive experience in meeting the complex regulatory requirements and a successful track record reluctant to take on MCM development. Stepping into the void have been smaller biotechnology companies (often start-ups), which, although often technically strong, have little or no experience advancing drug development through the FDA

review and approval process (Cohen, 2011). It is therefore critical that FDA provide more regulatory and scientific guidance to these companies earlier in and throughout the development process than might be the case with larger, more regulatory-experienced pharmaceutical companies. Taking such a hands-on approach with product developers is not novel to FDA. However, it is extremely resource intensive, and the MCM scientific and technical expertise at FDA who can provide this type of assistance – and ensure equity in assistance among MCM sponsors – is limited. This situation is exacerbated by the unprecedented scientific challenges and uncertainties FDA faces when reviewing and evaluating MCM submissions. It is on these scientific challenges that FDA has focused initial efforts during the first year of the MCMi.

Enhancing the MCM regulatory review process

Since the inception of MCMi in 2010, FDA has increased the human and fiscal resources it devotes to formal and informal meetings related to MCM development, including increasing pre-investigational new drug (IND) meetings and expanding the number of internal scientific and technical consultations on MCM-related issues. FDA is also working to address concerns (Gronvall *et al.*, 2007; NBSB, 2010) that FDA medical product centres may not be sufficiently consistent in their interpretation and implementation of the agency's various regulations and policy – for example in interpreting FDA's 2002 regulation New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible (animal rule) and its companion draft guidance, Essential Elements to Address Efficacy under the Animal Rule (FDA, 2009). In other instances, issues that may often be misidentified as solely regulatory in nature are actually gaps in key scientific knowledge that are hindering FDA's regulatory guidance and decision-making abilities.

To address these issues and uncertainties, FDA has created cross-disciplinary, cross-functional Public Health and Security Action Teams (Action Teams), comprising expertise from all FDA medical product centres, including staff from the centre review divisions. The Action Teams have already increased intra-agency collaboration and informational exchange, fostering more uniformity and consistency where possible. Action Teams are identifying and classifying the types of hurdles and gaps that are impeding MCM product development while providing a vehicle for harmonizing agency communications with federal partners and stakeholders.

Action Team analysis has identified some impediments as primarily scientific knowledge gaps or statutory, regulatory, or policy limitations. Scientific gaps can include limited knowledge about a threat agent's disease process

or a proposed MCM (e.g. its safety, efficacy and/or performance) being developed for a particular CBRN indication. As specific scientific gaps are identified, FDA is working closely with federal partners in the Enterprise to determine the best approach for addressing them, thus informing FDA's MCM regulatory science research agenda.

Legal, regulatory and policy limitations can include inconsistencies in interpretation and implementation of existing statutes, regulations or policies, or the lack of an appropriate framework for developing innovative MCM products and technologies. As specific limitations are identified, FDA is working internally or with HHS, Congress and other relevant partners to resolve them.

FDA has established a number of Action Teams, based on the highest research and development priorities determined by the Enterprise. Areas of focus include *in vitro* diagnostics, acute radiation syndrome, trauma and the warfighter, advanced manufacturing and development, and paediatric and maternal issues. FDA is also developing an Animal Model Qualification Program to enable a product-neutral evaluation and qualification of animal models within a context of use. The process for animal model qualification will be consistent with the process described in the guidance for industry, Qualification Process for Drug Development Tools, once it has been finalized (FDA, 2010c).

Advancing MCM regulatory science

In 2010, FDA launched the Advancing Regulatory Science Initiative, and FDA product centres established their regulatory science agendas and priorities to support more active participation in scientific research and to advance development of all FDA regulated products (FDA, 2010a). Regulatory science is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products. MCM regulatory science focuses on the development and approval of MCMs for CBRN threats and emerging infectious diseases (e.g. pandemic influenza, SARS).

MCMi's Pillar II is providing oversight and direction for FDA's overall MCM regulatory science portfolio and serves as the conduit for obtaining stakeholder input to shape the research agenda.

Initially, Pillar II activities focused on addressing centre-specific priorities identified in their respective agendas as well as on MCM priorities determined by FDA's Office of the Chief Scientist. Areas were broadly identified as research related to animal models, biomarkers, and product quality and associated assay development, among others. Pillar II has already significantly strengthened and increased FDA's intramural MCM regulatory

science research portfolio. The programme has involved extensive stakeholder input in a variety of ways. First, at MCMi's launch, FDA cosponsored with the Institute of Medicine a workshop designed to provide a broad overview of existing regulatory science efforts, review the state of the science regarding MCM product development, and identify opportunities for regulatory science collaborations (IOM, 2011). Next, a steering committee was established to peer review centre-specific regulatory science research proposals seeking FDA MCMi funding. The steering committee comprises the FDA Chief Scientist, a scientific lead from each of FDA's three medical product centres, and representatives of Enterprise partners (DoD, CDC, NIH and ASPR). Proposals are assessed for significance, alignment with Enterprise priorities, scientific feasibility and collaborative environment. It is important to note that the collaborative environment assessment includes consideration of current intra-agency collaborations, current collaborations with Enterprise partners and assessment of opportunities for potential collaboration, thereby leveraging synergies across proposals. Third, building on these efforts, FDA released a request for information that solicited further stakeholder input to enhance and refine the current MCM regulatory science research agenda and shape the Pillar II regulatory science programme (FDA, 2011b). FDA's comprehensive regulatory science programme is intended to address the scientific challenges that are slowing the progress of MCMs in the development pipeline and generate the data needed to advance products towards approval and availability.

As already noted, one of the primary scientific challenges to MCM development is the infeasibility in many cases of conducting human efficacy studies either because there are insufficient or sporadic natural occurrences of a condition or because of ethical concerns (e.g. associated morbidity/mortality). In such cases, product sponsors must pursue approval through non-traditional regulatory pathways, specifically using the animal rule. Although it provides an alternative path to approval, the animal rule raises complicated scientific and regulatory questions as animal data are applied in a new way. The animal rule created a need for robust and relevant animal models for product development and evaluation, but in many cases, models do not exist. Once models are developed that adequately represent the human condition for specific diseases, the models may need product-specific adaptation and, in some cases, may not be suitable for all products due to species-specific differences (e.g. physiology, immunology, pharmacokinetics/pharmacodynamics) or product-specific differences (e.g. immune modulator targeting receptors not present in all species). Targeted regulatory science research is needed to bridge inter-species gaps, identify acceptable correlates of protection

or develop new methods, such as *in vitro* or *in silico* modelling, that will aid in advancing MCM product development.

Three products have had indications approved under the animal rule: pyridostigmine bromide, hydroxocobalamin and levofloxacin. However, in these cases, the animal rule approval was facilitated by prior approval for another indication or information available in another country. Thus, sufficient safety and efficacy data had been developed to augment animal efficacy and other data submitted to FDA for approval under the animal rule, underscoring the fact that substituting animal data for human data is not intended to be an easier route towards approval (Gronvall *et al.*, 2007). In fact, experience has proven the contrary to be true: reliance on animal data exponentially increases the scientific complexities involved in MCM development, leading to increased regulatory uncertainties.

Modernizing the legal, regulatory and policy framework

The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives FDA various legal and regulatory authorities and mechanisms that can facilitate MCM development and regulatory review, and even allow emergency use of certain unapproved products under certain conditions. MCM development and approval must follow FDA's rigorous product regulatory review processes: for drugs and biologics, through the investigational new drug application phase and the new drug application or biologics licence application phase; or, in the case of a device, through premarket approval or notification 510(k). However, in certain situations, accelerated processes or special mechanisms (e.g. priority review; special protocol assessments; and the animal rule, as described in the previous section) are needed. Additionally, during or in anticipation of an actual emergency, FDA can facilitate use of a needed MCM through expanded access mechanisms (FD&C Act, 561, 21 U.S.C. 360bbb) or through an emergency use authorization (EUA) (FD&C Act, 564, 21 U.S.C. 360bbb-3). Some of the special legal and regulatory mechanisms for MCM development, approval, availability and use were established through emergency preparedness legislation enacted after the 2001 anthrax attacks. The animal rule was established in the Public Health Security and Bioterrorism Preparedness and Response Act (2002); the emergency use authorities are provided for in the Project BioShield Act (2004); and technical assistance teams in the event of MCM shortages are provided for in the Pandemic and All-Hazards Preparedness Act (2006).

As part of FDA's MCMi, legal and regulatory issues are coordinated and addressed through Pillar III activities, the goals of which are to support MCM development and

availability by ensuring that US laws, regulations and policies enable the application of advances in regulatory science to the regulatory review process and adequately support US preparedness for and response to CBRN agents and emerging infectious disease threats. In addition, Pillar III staff have been assessing the strengths and weaknesses of the current legal, regulatory and policy environment regarding MCM development, distribution, availability and use. Where changes are needed to better protect public health, FDA is working with federal partners and relevant stakeholders to develop and propose new approaches to improve and modernize FDA's legal, regulatory and policy framework for effective public health emergency responses. Most recently, FDA proposed changes as part of the reauthorization of the Pandemic and All-Hazards Preparedness Act, which would (i) provide enhanced clarity and flexibility for EUAs prior to a CBRN event to enhance rapid deployment, (ii) better facilitate pre-event planning and positioning of medical products, (iii) clarify FDA's authority to extend the shelf life of stockpiled MCMs and (iv) clarify that certain actions taken in preparation for or during an emergency will not violate FDA laws. Also, to support anthrax preparedness and response efforts based on stakeholder needs, FDA collaborated with federal partners to issue a mass dispensing EUA in July 2011 (FDA, 2011c) and to amend the postal model EUA in October 2011 (FDA, 2011d). In December 2010, FDA, in collaboration with federal partners, sponsored a legal and regulatory preparedness meeting to (i) inform state public health preparedness officials and legal counsel on FDA's legal authorities for MCM responses and (ii) become better informed about response challenges state and local public health officials and responders face.

As already mentioned, FDA is working to clarify and expand the agency's interpretation and implementation of the animal rule and the companion draft guidance for industry, Animal Models – Essential Elements to Address Efficacy Under the Animal Rule (FDA, 2009). FDA has created a cross-centre, multi-disciplinary team that is carefully considering the numerous comments received during the public comment period following publication of the draft guidance. Additional comments were received during and after a subsequent public meeting on the draft guidance in November 2010 (FDA, 2010b). In response to the significant revisions requested by the community and expansive scope of the comments, FDA intends to publish the guidance as a revised draft, enabling a second comment period. The revised and expanded guidance should provide additional scientific and regulatory information to support a better understanding of the specific expectations for animal data intended to support approval across the agency.

Conclusion

As identified in the 2010 Enterprise review, FDA has a crucial role to play in ensuring the success of the US Enterprise mission and vision to create a nimble and flexible system to produce the MCMs that will be needed quickly, should an attack occur. FDA's MCMi was launched to help address key challenges associated with the regulatory review process, the gaps in MCM regulatory science, and hurdles in the legal, regulatory and policy framework that may be slowing MCM development. Filling the nation's MCM gap is a long-term, complex effort that will require substantial collaboration among governmental entities at all levels, academia, industry and health professionals. In particular, success will require an appreciation of the long timelines, risks and high costs associated with developing MCMs, a significant and ongoing investment of resources, and the commitment of our national leadership.

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