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Identifying CDER's Science and Research Needs Report

July 2011

The CDER Science Prioritization and Review Committee (SPaRC)

Center for Drug Evaluation and Research

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Dr. Margaret Hamburg, Commissioner of the FDA, stated at the RAPS 2009 Conference, "Just as biomedical research has evolved in the past decades, regulatory science — the science and tools we use to assess and evaluate product safety, efficacy, potency, quality and performance — must also evolve."

Janet Woodcock, Director of Center for Drug Evaluation and Research - Guest Commissioner's Comments, August 17, 2007, "In all cases, we look to FDA reviewers and scientists to identify the most pressing problems and scientific issues, so that we can recruit partners to help us address them."

Background

Purpose

This document is the result of an effort to identify regulatory science needs that, if addressed, would enhance CDER's ability to fulfill its regulatory mission. The FDA Critical Path Opportunities Report and Critical Path Opportunities List,[1] published in 2004 and 2006, focused on addressing scientific challenges underlying medical product development and served as a catalyst for CDER to launch this effort. In October 2010, the FDA released "Advancing Regulatory Science for Public Health," a document which incorporated the Critical Path objectives into a broad framework for advancing regulatory science.[2] FDA will soon be releasing a cross-cutting strategic plan for regulatory science. This CDER science and research needs document complements the strategic plan, providing additional details specific to CDER products. By communicating CDER's science and research needs externally, CDER hopes to stimulate research and foster collaborations with external partners and stakeholders.

The document is not intended to address the clear and compelling need to maintain a robust scientific readiness to respond rapidly to regulatory crises, such as contaminated heparin, nor does the document focus on scientific infrastructure needs being addressed through other initiatives (e.g., informatics infrastructure).

Process

The CDER Science Prioritization and Review Committee (SPaRC), which has broad representation from offices across the Center, initiated the effort to identify regulatory science needs. To begin the process, over 200 representatives from various offices were interviewed[3] to determine their perspectives on scientific questions or needs that, if addressed, would enhance scientific decision-making in CDER. Interviewees were asked to identify needs derived from (1) scientific challenges that are currently addressed on a case-by-case basis and might benefit from the development of a systematized approach, (2) recurrent science issues across teams, divisions, or offices, and (3) emerging scientific challenges.

A comprehensive set of science and research needs was compiled from these discussions, and major topics that crossed multiple disciplines were identified. Senior management from CDER offices reviewed and prioritized topics from their offices. During the process it became apparent that while computational infrastructure needs and data standards were critical for a number of these topic areas, efforts were already underway in CDER to address this important issue; therefore these needs are not included in this document.

Science and research needs were ultimately grouped into seven categories that were reviewed and endorsed by the SPaRC and CDER Senior Management.

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[1] http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm.
[2] http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228131.htm.
[3] http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm.

Results

The seven categories constitute clearly identified major themes, but do not encompass every articulated need. As presented in this document, the needs have not been prioritized. These regulatory science needs include developing, evaluating and/or improving: data and methods for the analyses of postmarket data; risk management strategies; scientific approaches to regulatory communications; product quality and performance; predictive models; design, analysis, and monitoring of clinical trials; and individualization of patient treatment. The results are intended to serve as a framework for further steps to identify gaps and prioritize needs within the categories.

Next Steps

Throughout this document, we have highlighted some ongoing activities which represent a small percentage of our overall efforts. There are additional science and research efforts that have begun to address the needs in this document; however, we would like to enhance these efforts. We have successfully partnered with academics, industry, other government agencies and nonprofits on many initiatives and would like to explore opportunities to expand these collaborations. Therefore, this document will be published in the *Federal Register* and will solicit input through a docket to (1) Gather information about ongoing external research and initiatives that may currently be addressing needs identified in this document, and (2) Identify opportunities for leveraging resources to address regulatory science needs through collaborations with external partners and stakeholders. The comments received from the FR notice will be communicated directly to those at CDER who are involved in related ongoing science and research efforts and initiatives and will create opportunities to exchange knowledge and foster collaboration. The comments will also support our current initiatives that are looking at overall existing internal and external CDER science and research efforts. The intent is to enable priorities to be established among the categories and identify gaps that could be addressed through targeted research projects. These priorities will be assessed within the broad framework of FDA's overall regulatory science objectives.

I. IMPROVE ACCESS TO POSTMARKET DATA SOURCES AND EXPLORE FEASIBILITY OF THEIR USE IN DIFFERENT TYPES OF ANALYSES

Overview:

To assess outcomes of drug therapy,[4] it is critical to determine the accuracy of available postmarket data sources and to identify additional data sources for evaluating outcomes in specific populations. There is also a need to explore the feasibility of using postmarket and premarket data in safety analyses and the evaluation of postmarket data in a number of use scenarios.

A. Accuracy and Availability of Postmarket Data

Following approval of a drug, the real-world patient population that uses that drug is rarely the same as the population evaluated in clinical trials. Even when patient populations are similar, real-world use may differ markedly from use in the highly monitored setting of a controlled clinical trial. Furthermore, clinical trials do not usually address long-term safety. Larger, more diverse postmarket randomized clinical trials may offer an unbiased approach to identifying postmarket risks and benefits, but they are not always feasible, and when required, they may be slow to produce results. Other postmarket data sources may offer an opportunity to gain more understanding of real-world use. In addition to spontaneous reporting, these sources include, but are not limited to, prescribing data, electronic medical records data, hospital discharge data, federal databases at the Centers for Disease Control and Prevention (CDC) and Center for Medicare and Medicaid Services (CMS), as well as other federal agencies and administrative claims databases. However, the content of and quality standards associated with postmarket data sources are generally established for purposes other than safety analysis (e.g., reimbursement, clinical care). Thus, these postmarket data sources should be assessed for their strengths and weaknesses for use in regulatory decisions. In addition, we also need to continue to improve the quality and quantity of postmarket spontaneous reports.

1. Accuracy of electronic health care data

The validity of exposure and outcome information, as identified in electronic health care data, needs to be evaluated for its use in regulatory assessments. For example, the accuracy of ICD diagnostic codes (commonly used in administrative claims data), used to identify patients with clinical adverse events, needs to be assessed systematically. Validated algorithms for ascertaining various safety outcomes could be used to better inform drug safety studies conducted by government, industry, and

[4] For the purpose of this document, the term "drug" includes biologics regulated by CDER, namely therapeutic proteins and monoclonal antibodies.

academia. Such efforts will improve our confidence in the validity of conclusions based on these types of data.

2. Utility of spontaneous reports

Spontaneous reporting data continue to be a mainstay of CDER's postmarket safety surveillance program. These reports from manufacturers, health care providers, and patients provide unique, useful information, particularly on rare or severe adverse events. However, CDER continues to receive reports with incomplete or otherwise limited information, which often hampers the effective use of these reports in detecting signals and making regulatory decisions. They are also subject to reporting bias. Efforts need to continue to improve the quality, quantity, and utility of these reports to enhance the detection and understanding of rare adverse events.

3. New data sources

Unmet needs still exist for data that could be valuable in supporting postmarket regulatory analyses. When additional data sources are identified, they should be systematically evaluated for their strengths and limitations prior to regulatory use. Examples of data needs include:

- Data to ascertain more accurate background rates of adverse events, including those occurring in special populations such as pregnant women, HIV and Hepatitis C-positive patients, or patients with co-morbid conditions.

- Population-based data that would help to identify use patterns suggesting abuse of pain medications such as opioids. Although we have data that allow us to examine use patterns, we do not have the needed information or evaluation methods to identify which patterns are most likely associated with abuse.

- Population-based data that would provide "cradle to grave" coverage to capture long-term use and effects (e.g., countries that have universal health care).

- Genetic/Genomic data to better understand response to drug products in specific populations.

- Detailed nationally representative data on product use in settings of care not typically described well in claims databases, such as long-term care facilities or oncology clinics, where drugs are administered in clinics or doctors' offices.

- Drug-related mortality statistics, because coded death certificates currently do not contain sufficient information.

- Utilization patterns for over-the-counter (OTC) drugs.

- Data on product defect rates or variability in product quality attributes to mine for possible correlations with specific patient complaints or adverse event reports (see III.C).

- Utilization patterns for homeopathic drugs and other alternative treatments (e.g., ayurveda).

- Health consequences of long-term use of drugs in populations with particular conditions, serious and chronic diseases (e.g., pregnant women; children with cancer, arthritis, and other immune disorders). Recently, CDER has been exploring establishment of specific disease/condition-based registries, which could be a better model for long term monitoring than drug specific postmarket exposure registries.

B. Develop Innovative Methods to Explore the Feasibility of Using Postmarket Data in Different Types of Analyses

1. Evaluation of safety using both premarket and postmarket data sources

It would be of value to explore ways to incorporate data from postmarket data sources with premarket data to help to support regulatory safety decisions. These approaches need to balance clinical judgment with statistical findings.

2. Explore feasibility of using postmarket data to assess both adverse and beneficial outcomes of drug therapy

The use of postmarket observational data for outcome measurements and comparative outcome measurements is widely discussed; however, such data do not reflect random assignment, and treatment assignment can introduce bias. Attempts to develop adequate approaches to assess beneficial outcomes using data other than randomized clinical trial data have not been successful. For example, hormone replacement therapy for postmenopausal women was thought to reduce the risk of cardiovascular events based on observational studies, but clinical trials proved otherwise. We need to investigate whether there are any feasible approaches (most likely starting with qualitative measures) that would allow the use of observational data to make an adequate assessment of beneficial outcome measurements, perhaps by examining whether observational data sources show similar beneficial effects seen in randomized trials.

The Sentinel Initiative is an FDA-wide effort to create a scalable, efficient, extensible, and sustainable system that leverages existing electronic health care data from multiple sources to actively monitor the safety of regulated medical products. This requires the development and testing of improved statistical and epidemiological

approaches to active surveillance of regulated medical products as initiated in Mini-Sentinel.[5]

There are a number of chronically used drugs about which we have concerns regarding potential long-term health consequences. The benefit of using these drugs has to be balanced with the adverse consequences of their long-term use. These concerns cannot be assessed adequately by short-term randomized clinical trials. We need to investigate whether there are any feasible approaches (most likely starting with qualitative measures) that would allow an adequate assessment of both adverse and beneficial long-term outcome measurements.

II. IMPROVE RISK ASSESSMENT AND MANAGEMENT STRATEGIES TO REINFORCE THE SAFE USE OF DRUGS

Overview:

We need to evaluate and enhance the risk mitigation strategies we employ to manage risks associated with the use of approved drug products. We also need to better characterize the risks associated with the use of drugs that have not been through the FDA approval process, such as compounded drugs, dietary supplements fraudulently containing active pharmaceutical ingredients, counterfeit versions of approved drugs, and marketed unapproved drugs that are not medically necessary. If we understand these risks better, we can focus our resources on targeted strategies to safeguard public health. We need to increase the use of different scientific disciplines, such as behavioral sciences, to maximize selection and evaluation of risk evaluation and mitigation strategies (REMS) and medication error prevention strategies. These needs relate directly to those identified in the recent FDA Strategic Plan for Risk Communication.[6]

A. Evaluate and Improve the Impact of Regulatory Actions on Patient Outcomes

To ensure the safe use of drugs, we need to evaluate whether our regulatory activities are resulting in improved outcomes for patients. We are currently developing a systematic methodological approach to judge our effectiveness, identify weaknesses, and improve our approaches. Evaluation strategies need to move from evaluations based primarily on performance of required activities measures only to evaluations based on clinical patient outcomes. This will necessitate identification of additional appropriate outcome measures, methodologies, and accompanying metrics.

1. Outcomes regarding approved drugs

How well do our risk mitigation strategies work? If at the time of approval or through postmarket surveillance, we determine that there is a safety issue regarding

[5] http://www.minisentinel.org.
[6] http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm183673.htm.

the use of a medication that can be improved by altered patient and physician awareness or behavior, the Agency often implements risk management strategies. These risk management strategies frequently involve professional labeling, packaging, Medication Guides, Dear Health Care Provider letters, and REMS. We need to identify outcomes, both process and clinical, and develop methods to evaluate the effectiveness of risk mitigation strategies on physician and patient behavior (process) and clinical patient outcomes. We need to determine what effect the risk mitigation strategies have on patient access to drugs, the consequences of patients not being treated with drugs that have risk mitigation strategies but instead with alternative therapies that do not, and the burdens that risk mitigation strategies impose on the health care system and the resultant effects on patient care. These outcome analyses will enhance programmatic evaluations and provide data that can be used to improve the effects of our actions. For example:

- How can we best evaluate the effectiveness of communication tools such as Medication Guides and Dear Health Care Provider letters in guiding prescriber, dispenser, and patient behavior? *(also see Category III)*
- What are effective clinical outcome measures for REMS, particularly when there are limited baseline data and the adverse events which we seek to mitigate are rare? Gaining insight into the effectiveness of these outcomes may enhance our recommendations for REMS. *(also see subsection B below)*
- What would be the best approaches to determine the effects, both positive and negative, of our compliance actions on public health?

As it relates to the evaluation of REMS, we need to broaden our understanding of how a drug is used once it is approved for marketing, such as if certain subpopulations might be at particular risk because of past patterns of unsafe use of a drug in a similar class. Approaches to consider include exploring the validity of using information available on the Internet, such as social media, to gain a better understanding of the public's use of drugs. Results may help us anticipate types of social behavior that might affect the postmarket use of a drug and help us to develop more effective public education campaigns for risk management.

The Safe Use Initiative[7] will create and facilitate public and private collaborations within the health care community to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use. These activities involve working with pharmacies, patient advocate organizations, manufacturers, health care professionals, federal partners, and consumers to promote the safe use of drugs. We need to identify ways to determine how these interventions affect patient outcomes.

[7] http://www.fda.gov/Drugs/DrugSafety/ucm187806.htm.

2. Understanding the use of unapproved, compounded, fraudulent, and counterfeit products

In the current health care climate, U.S. consumers may choose from a wide variety of products for the treatment of their medical conditions other than FDA approved drugs. Such unapproved products may be marketed as over-the-counter (OTC) or prescription drugs, compounded drugs, as well as dietary supplements with hidden pharmaceutical ingredients, and counterfeit drugs.

We currently rely on adverse events reports and literature to determine the risk to the public of these products. However, we prefer to take enforcement action before the public is injured. To do that, we need data and methods that predict which product could injure which population taking unapproved products.

In addition, we need data on the impact of compliance actions. Which action is faster? Which is longer lasting? What are the outcome measures: Death? Hospitalization? Illness?

Data needs include ingredients, products, and manufacturing methods as well as patient and provider behavior, and supply chains for these alternative products. If we can understand the reasons for public use of these alternatives to FDA approved products, then we may identify which enforcement tools are most appropriate.

3. Screening for contaminated, counterfeit, fraudulent and sub-quality manufactured and compounded drugs

To safeguard public health from fraudulent and economically motivated contaminated drugs, dietary supplements with hidden pharmaceutical ingredients, as well as sub-quality compounded drugs, we are exploring innovative strategies for CDER to screen drug products and ingredients and thereby assess their occurrence and accessibility in the market place. These include development of better sensitive analytical tools to screen for adulterants that may be present at low levels, because current methods in general focus primarily on intended ingredients and furthermore the technologies employed within these methods are often inadequate to detect contaminants. Many USP methods are inadequate to screen drug excipients and do not utilize the latest scientific advances in analytical technologies. Supply chain traceability would also enable the establishment and use of analytical technologies to generate forensic signatures and/or fingerprinting profiles for drug components.

4. Drug combinations

Complex chronic diseases may best be treated using more than one separate drug. Although such combinations of drugs are frequently used in clinical practice, there is often limited information on the safety and efficacy of such combined therapies. A clear scientific and regulatory approach to combination therapies will be important to

facilitate their development and safe use. For example, advancing various types of modeling, such as drug-drug interactions and systems biology, may suggest potential safety concerns that may be associated with new combination therapies.

B. Apply Behavioral Science Models to the Selection of REMS and Medication Error Prevention Strategies

A multidisciplinary scientific approach needs to be more fully developed to provide a better understanding of human factors and their impact on risk, particularly in relation to medication errors. We need to develop scientific methodologies that can incorporate the results of social science studies with known practices for dispensing medication. For example, integrating knowledge of hospital stocking, storage, and dispensing practices for drugs (by proprietary or generic name) with knowledge of human perception and behavior could help to establish ways to reduce medication errors. We could further evaluate the conditions under which bar coding, smart pumps, electronic prescriptions, and patient safety pharmacists have a positive impact on drug safety. Approaches for human factor analysis from other fields, such as in aviation research, might be helpful. These approaches are geared towards evaluating the potential risk of human errors and establishing strategies to minimize those errors.

Applying behavioral science models would help us to provide more consistent and informed guidance to industry regarding REMS and to minimize medication errors. We have already initiated internal efforts focused on REMS assessments which would be enhanced by our understanding of interactions among pharmacists, patients, and physicians and how specific interventions to influence human behavior could reinforce the safe use of drugs. These approaches may provide information on the burdens that REMS place on the health care delivery system and patient access, and may suggest ways to streamline REMS and to evaluate the effect of REMS modifications.

C. Strategies to Assess Benefit and Risk of Drugs Reviewed Under the Animal Rule

For products developed under the Animal Rule, efficacy is established by extrapolation from animal studies, while safety is evaluated under pre-existing requirements, which include human trials. When human efficacy studies are not ethical or feasible, the Animal Rule[8] allows for drug approval or licensure of a drug on the basis of efficacy data obtained in animals for countermeasures against CBRN threat agents. If the public is threatened with exposure to chemical, biological, radiological, or nuclear (CBRN) threat agents, prophylactic drugs may be given to a large, potentially diverse, healthy population, some of whom may not actually be exposed. The risk of adverse events due to drug exposure to the medical countermeasure in such a population needs to be balanced with the benefit of protection from harmful effects of the threat agent. For those not actually exposed to the threat agent, there is no benefit from the medical countermeasure, only the risk of adverse events from the product. We need to develop

[8] Animal Efficacy Rule (21 CFR part 314, sections 314.600-650, drugs; part 601, sections 601.90-95, biologics).

approaches that outline principles that may aid benefit/risk decisions when applied across the decision-making strata of products/indications.

III. EVALUATE THE EFFECTIVENESS AND IMPACT OF DIFFERENT TYPES OF REGULATORY COMMUNICATIONS TO THE PUBLIC AND OTHER STAKEHOLDERS

Overview:

CDER uses a variety of methods to communicate drug information to patients and health care providers. We need to determine whether current approaches (content, media, and format) are effective in conveying important medical information, and whether they are having an impact on patient and health care provider behavior and patient outcomes. Where possible, we should also determine how to improve the effectiveness of our regulatory communications. This need relates directly to the recent FDA Strategic Plan for Risk Communication.[9]

A. Labels and Similar Modes of Communication

We need to determine the most effective media and format for communicating with patients and providers. We also need to determine the content that most effectively conveys medical information in Medication Guides, Consumer Medication Information (CMI), labels on drug products, and package inserts. Pharmacies may not consistently provide appropriate content in CMI, and FDA will take over regulation of this communication. It is particularly important that consumers read and understand the labeling on OTC drug products, because OTC drugs are taken without the intervention of a health care professional. OTC drugs pose a problem because the public frequently does not perceive them as potentially dangerous. This misperception may lead to adverse consequences from overdosing on some ingredients (e.g., acetaminophen, which is present in various OTC medications that may be taken at the same time).

Additional understanding is needed in a number of areas, including how perception and behavior vary in response to information presented by various media, what parts of current labeling consumers and providers do or do not read and/or understand, and how accurately pediatric medications are being dispensed at home (e.g., whether directions relating to the amount and timing of doses, and contraindications are being followed). There are also questions about the presentation and comprehension of more complex information to both consumers and providers. In particular, we need more information on the ability of consumers to understand effectiveness information in tabular and graphical formats and the ability of providers to use information about patient reported outcomes, quantitative aspects of benefit/risk, graphical representations of data, components of composite endpoints, the results of pharmacokinetic/pharmacodynamic studies, and the impact of biomarkers on individual responses to certain drugs.

[9] http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm183673.htm.

Enhanced understanding of factors that influence comprehension and compliance will also affect our strategies for dispensing medications during emergency situations (discussed in more detail in subsection B below), and could be integrated into our risk mitigation strategies (see Category II), where effectiveness of communications would be assessed by evaluating changes in population-level behavior in response to a label change. The design of other types of communications including Drug Safety Communications, Dear Health Care Provider letters, and Drug Safety newsletters may also benefit (see "C", below).[10]

B. Emergency Communications

It is important to understand the best ways to communicate with the public in emergency situations (e.g., H1N1 influenza). To develop more comprehensive plans for mass communication we need to analyze the success or failure of government communications to the public in past emergencies.

An ancillary need involves improving our coordination with other government agencies and our ability to share awareness across agencies in emergency situations. Problems in this area stem not only from technological limitations, but from a need for better planning for communication and coordination with other agencies.

C. Risk Communications

It is important to evaluate both the reach and the effectiveness or impact of our risk communications. In particular, we need to more thoroughly evaluate the "Drug Safety Communication (DSC)," our primary communication tool for disseminating information about a newly identified, postmarket drug risk. Such research would include evaluations of the following factors: effectiveness of diffusion/penetration of our DSCs to the intended audiences, effectiveness of DSC format for presenting risk information, reader/audience comprehension of the DSC messages, and any impact on behavior regarding decisions to take or stop a medication.

IV. EVALUATE THE LINKS AMONG PRODUCT QUALITY ATTRIBUTES, MANUFACTURING PROCESSES, AND PRODUCT PERFORMANCE

Overview:

To ensure consistent quality of innovator and generic drug products over their lifecycle, we need to better understand the impact of variability in the drug components and manufacturing process parameters on product quality and performance. Efforts need to be continued and sustained in

[10] The Public Health Advisories, Early Communications, and Healthcare Professional Sheets have all been streamlined into a single communication vehicle, the Drug Safety Communication (DSC).

the postmarket environment to further our understanding and reassess the links between product quality, performance, safety, and efficacy as needed.

A. Develop Better Methodologies to Ensure Quality of Innovator and Generic Drug Products

For both innovator and generic products, implementation of advanced analytical technology, quality by design (QbD) and quality risk management principles, and improvements in manufacturing technology would help achieve better control over the consistency of critical product attributes, some of which may be linked to the therapeutic effect. Such approaches will lead manufacturers to develop the tools they need to monitor and control manufacturing processes in real- or almost real-time. We need to identify critical product attributes, and then improve our understanding of the key product and process design features and especially the manufacturing parameters that affect those attributes. Innovator and generic products are increasingly scrutinized for differences between them that might impact performance in patients. Each formulation of a drug product can include unique combinations of active and inactive ingredients, and this can complicate attempts to establish therapeutic equivalence between formulations of complex products.

1. New technologies to characterize complex drugs

We need to be able to more fully understand structure-function characterization of complex drug products proactively. Modern physicochemical characterization tools such as Nuclear Magnetic Resonance (NMR), mass spectrometry, various optical spectroscopy methods, and coupled techniques like LC-MS and LC-NMR along with advanced data analysis tools such as chemometric modeling may enable the Agency to make judgments about the significance of a slight difference revealed by these tools. Therefore, the capabilities of these tools need to be evaluated for their rigor and use in regulatory decisions. These analyses will be especially important for assessing manufacturing changes for biologics,[11] biosimilars, and other complex products.

2. Manufacturing issues unique to biologic products

Biologic products present unique challenges to evaluating quality. Biologics have many structural attributes and assessing the criticality of these attributes is difficult. We need to develop knowledge of the relationship between product structure and biological activity. This will facilitate the identification of physicochemical characteristics that can predict product performance. To study the relationship between structure and function, we need improved bioanalytical measurement methods, and meaningful and relevant bioassays. Understanding the mechanisms of

[11] Biologics regulated by CDER include monoclonal antibodies and therapeutic proteins.

activity and adverse events will facilitate the linkage of product structural attributes and adverse events.

In addition to structural attributes that affect activity and safety, the most relevant factors that affect the pharmacokinetic/pharmacodynamic assessment of biologics should be identified. Understanding the biology of pharmacologic parameters is important in defining these factors. For example, a variety of specific receptors can influence protein half-life and distribution (e.g., delivery of therapeutic enzymes to the correct cellular compartment). Enhanced knowledge of these factors could contribute to establishing criteria for design and interpretation of comparability studies during therapeutic protein product development and for postmarket changes in manufacturing processes and formulation.

Immune responses that neutralize biologic therapeutics have been responsible for development of some products and have been problematic following changes in manufacture after licensing. Immune responses to protein therapeutics currently cannot be predicted through physicochemical characterization alone, because definitive data correlating the two are lacking. Circulating antibody to protein therapeutics has been the chief criterion for determining immune responses to these products. To gain a more complete understanding of product and host factors responsible for immunogenicity of protein products, we need to assess the role of active ingredient attributes including 3-D structure, glycosylation, product characteristics (including aggregation and impurities), as well as host immune characteristics including cell-mediated immunity.

3. Quality factors that affect commercial-scale manufacturing

Significant failures in scale-up of the manufacturing of branded, generic, and biotechnology-derived drugs have led to product recalls and plant shutdowns shortly after approval and launch. A clearer understanding of the critical product and process factors that affect a company's ability to transition from production of development and clinical batches to high-quality drugs at a commercial scale would help to avoid such failures and maintain and increase the availability of drugs for the public. For example, raw material variability continues to be a significant cause of product quality problems. The scale-up of manufacturing often fails due to lack of understanding regarding the impact of variation in raw materials. We need a better understanding of how analytical tools can be used to predict performance of raw material and to detect possible adulterants, which could significantly reduce the number of defective products.

We need to better understand and promote the use of state-of-the-art process analytical technologies for in-line, on-line, and off-line monitoring of process streams. For example, for protein products, we could develop model systems for small-scale bioreactor production and purification and new technologies to monitor and control quality during production. To ensure pathogen-free protein products, we

need manufacturing procedures that reliably clear and inactivate viruses, and methods that monitor viral clearance and inactivation. The development of novel technologies for the sensitive and rapid detection of a broad range of adventitious agents can also play a role in ensuring pathogen free products.

B. Best Analytical Methods, Metrics, and Methodologies to Evaluate Novel Dosage Forms and Delivery Systems

Drug delivery systems increasingly involve technologies such as transdermal patches, inhalation delivery systems, topical formulations for direct application to the skin, modified release solid oral dosage forms, and intravenous dosage forms of targeted delivery systems, such as liposomes and other nanoscale platforms. We need to evaluate the reliability and performance of analytical methods for such materials or drug-device combination products, as these methods will be used to make regulatory assessments and decisions.

Methods are also needed to determine the bioavailability and bioequivalence of locally acting drug products. In addition, we need to evaluate PK approaches and parameters for bioequivalence determination other than C_{max} and AUC to improve assessment of product comparability, especially for sustained-release/modified-release and complex biopharmaceutical products. We should further examine the relationship of advanced physicochemical characterization to the standard methods now in use for making in vitro and in vivo correlations.

C. Link Between Product Attributes and Clinical Safety and Efficacy

We need to determine the types of data needed to explore the link between adverse events and product attributes and to further assess the feasibility of implementing approaches to track these data. Adverse event reports and databases used for epidemiology rarely include basic product information, such as manufacturer and lot number. We need to explore ways to enhance data capture across data sources used for epidemiological studies.

D. Analytical Methods and Methodologies to Evaluate Compounded Drug Dosage Forms

Frequently in compounding pharmacies, pharmacists incorporate active components of FDA-approved drugs into novel, alternative dosage forms for patients for whom the approved dosage form may not appropriate. However, in some cases, pharmacists prepare these alternative dosage forms without taking into consideration the physiological, chemical and biological properties of the active pharmaceutical ingredients that could impact its bioavailability and the dosage form performance characteristics. Without a suitable understanding of these properties, the compounded alternative dosage forms may result in products that release sub- or super-therapeutic doses to the drug target receptors with accompanying poor therapeutic outcomes. To

better regulate the use of compounded drugs, we need analytical methods and predictive models that would determine whether alternative, compounded dosage forms provide reasonable safety and effectiveness assurances to patients.

V. DEVELOP AND IMPROVE PREDICTIVE MODELS OF SAFETY AND EFFICACY IN HUMANS

Overview:

We need to continually improve nonclinical models and our understanding of those models to better predict risks of human exposure to drugs. For safety assessments, we need to better define nonclinical data that are most relevant for predicting human responses to biologics, juvenile indications, and for use in carcinogenicity assessments. To address various challenges in review and approval of these countermeasures, more research is needed in animal models and study designs. In addition, we need to assess and improve the usefulness of existing informatics and computational toxicology tools to predict safety in human populations.

A. Improve Nonclinical Science Testing Paradigms to Predict Human Risk

We need to continue to address the validity of extrapolating safety signals from currently available nonclinical methods and/or models and develop new models to predict risks upon human exposure. Some areas for further exploration include the following:

1. Models to assess organ-specific drug-induced toxicities

For example, models to assess drug-induced toxicities such as QT prolongation exist and their ability to predict human risk should be further defined. New animal models also need to be developed for example, for drug-induced pancreatitis or valvular heart disease, and to investigate the immune consequences of the use of Dipeptidyl peptidase-4 (DPP4) inhibitors in patients treated for diabetes. Appropriate assays and models that assess various facets of the human immune response and aid the prediction of adverse immune consequences need to be evaluated.

2. Nonclinical data to predict the safety of biologics

We need to determine the extent to which nonclinical data can help predict the safety of biologics especially for endpoints such as carcinogenicity and to predict safety in a pediatric population.

3. Models to predict allergic responses to small and large molecules

Allergic and anaphylactic responses can be difficult to predict with current techniques. The development and validation of more models that predict such responses would facilitate drug development.

B. Determine the Most Appropriate Animal Models/Study Designs for Countermeasure Indications

CDER is participating in a broader Medical Countermeasures Initiative[12]. A key component of this initiative is advancing the regulatory science needed to facilitate medical countermeasure development, including animal models. The number of drugs approved for countermeasure indications (treatment or prevention of diseases or conditions resulting from terrorist threat agents or emerging biological threats) needs to increase.[13] The challenge is to incorporate efficacy data from predictive animal models with safety data derived in humans, and other clinical and nonclinical data to approve products that treat the disease or condition caused by the threat agents. For a number of diseases or conditions caused by CBRN threat agents (e.g., Smallpox, acute radiation syndrome), definitive animal models to evaluate potential therapeutic agents have yet to be developed. Animal models must be developed for specific threat agent- induced disease or conditions that are comparable to the threat agent-induced disease/condition in humans. There is a need to understand the natural history, epidemiology, and estimates of response to therapy of human disease to facilitate study design of animal efficacy studies (e.g., identify endpoints and timing of assessment) and enable comparison to animal model outcomes. Furthermore, these animal models need to be relevant for the medical countermeasure of interest (e.g., by mechanism of action or the ability to bridge to an effective dose in humans).

1. Existing animal models for regulatory use

The National Institute of Allergy and Infectious Disease (NIAID) has already developed animal models of efficacy for a limited number of threat indications, however, these models need to be evaluated for their ability to predict the human response to the threat agent in conjunction with the investigational therapy. This information is necessary for the use of animal models in approvals or licensure under the Animal Rule or in support of an Emergency Use Authorization. We should continue to further our understanding of susceptibility to particular threat agents across species, to aid in selection of a well characterized model (e.g., species-specific receptors to a threat agent and/or receptors to a product for intervention, and their tissue distribution).

2. Currently approved drugs for use in countermeasure indications

We need to evaluate already approved drugs for use in new countermeasure indications. Approved drugs may need to be used at higher doses, for longer durations, or by different administration routes than exist in the approved labeling for other indications. Given the increased doses and/or prolonged administration needed

[12] Medical Countermeasures Initiative
http://www.fda.gov/EmergencyPreparedness/MedicalCountermeasures/default.htm(
[13] Project BioShield Act of 2004, Public Law 108-276 (S. 15, H.R. 2122).

for these new indications, additional clinical studies to evaluate potential safety concerns may be needed, especially for pediatric and geriatric populations. Further, we need to consider ways to address the potential noncompliance by pediatric populations because of, for example, poor palatability of an oral formulation, particularly if more frequent dosing or a longer duration of dosing is needed.

3. Combinations of drugs for use in countermeasure indications

For drugs reviewed under the Animal Rule, we need to establish the most appropriate regimen or combinations of drugs for treatment without the benefit of human clinical trials. We need to determine if a combination of drugs is needed to combat the effects of CBRN threats. While sponsors will seek approval for a single drug for a given countermeasure indication, informed decisions should be made on the most effective combined treatments, such as antitoxins and antimicrobials in combination for treatment of disseminated anthrax disease. For example, for studies in acute radiation syndrome, research on the appropriate use of supportive care is needed. Modeling simulations incorporating knowledge of mechanism of drug actions with in vivo models could be considered for their use as supporting information.

4. Data and approaches to extrapolate dosing between animal models and humans

More data and approaches are needed to address questions regarding interspecies dose extrapolation that focus more on the drug disposition than on a specific animal disease model. These mostly drug-specific issues include the following:

- Pharmacokinetic (PK) modeling in animals to identify countermeasure doses that result in comparable effective doses in humans.
- Determining effects of using different routes of administration (e.g., comparing bioavailability after an IM injection to an IV injection).
- Establishing which PK parameters (e.g., C_{max} or AUC) are associated with successful eradication and treatment of infections caused by certain types of pathogens. We need information beyond the MIC (minimum inhibitory concentration).
- Use of systems biology to support the validity of animal model extrapolations.

C. Develop and Evaluate the Utility of Mechanistic/Modeling Approaches

Vast amounts of structural, pharmacologic, pharmacodynamic, and safety-related drug information are now available to researchers. Coupled with accumulated knowledge of biochemical, metabolic, physiologic, and pathophysiologic processes, this information is being applied to the development of a variety of quantitative predictive models. Given the high societal and economic cost of late stage drug failures because of efficacy or safety concerns, it is important to thoroughly assess the added value of predictive modeling to regulatory decision making during drug development. More human data and trained modelers are needed to increase the strength of the predictive models.

The three types of predictive models that need to be investigated are quantitative structure-activity models, pharmacometric models, including physiologically based pharmacokinetic models and systems biology models. It is important to conduct prospective assessments of the predictive value of each of these modeling approaches and determine how best to use them in regulatory decisions.

1. Quantitative structure-activity models

Statistical models of quantitative structure-activity relationships (QSAR) have been developed that can relate structural similarities between a novel molecule and a library of known molecules which are linked to known animal toxicology and human safety information or to pharmacologic properties. Current applications include predictions of the toxicity of excipients, contaminants, or metabolites, and predictions of off-target activity and likely human adverse events. We need to assess the validity of the existing models to regulatory decision making.

2. Pharmacometric models

Pharmacometric models describe the quantitative relationship between pharmacologic parameters and drug response. Physiologically based pharmacokinetic models (PBPK) models provide predictions of drug absorption, distribution metabolism and elimination. Current approaches account for inter-individual sources of variation and are being used to predict drug-drug interactions during new drug development and design formulations during generic drug development. Pharmacometric models are being applied to the design of phase 3 trials (disease modeling, exposure-response modeling). We need to assess the validity of using these models in regulatory decision making and risk analysis (*also see Category VI.B and VI.C*).

3. Systems biology models

Systems biology models are based on linked, quantitative descriptions of biological processes at the biochemical, cellular, organ, and systems levels. Data describing the behavior of parameters in health and disease are incorporated in the models, as are responses to activation of drug targets. We need to assess whether these types of models may have value in predicting potential adverse events and identifying potential biomarkers that can be used to monitor these adverse events in late stage trials.

VI. IMPROVE CLINICAL TRIAL DESIGN, ANALYSIS, AND CONDUCT

Overview:

We need to develop better approaches to address complex issues commonly encountered during clinical trial review, such as missing data and multiple endpoints. The analysis of data across clinical trials would enable us to make comparisons providing new insights into safety and efficacy assessments. Our efforts in benefit-risk assessments could benefit from additional information on innovative approaches. We need to improve selection or definition of study endpoints, especially in disease conditions such as chronic degenerative diseases for which endpoints for progression may not be clearly defined. We need to identify and address deficiencies in clinical trial designs for areas such as pediatrics and orphan drug products. Identifying critical aspects to inspect during the conduct of clinical trials may improve the quality of clinical trial data and the safety of clinical trials.

A. Further Develop and Refine Statistical Methods to Improve Clinical Trial Design and Analysis

In many situations, we need to evaluate existing statistical methods for appropriateness of use in different types of datasets. Currently, most decisions are made on a case-by-case basis. Moving from this setting to recommending the types of methods in particular settings that arise in regulatory reviews would be valuable for consistent decision making. We also need to increase our use of simulations as related to clinical trial design and analysis to clarify our approaches to drop-outs and discontinuations, and early adverse events versus late onset adverse events.

1. Missing data

Although many methods exist for analyzing clinical trials that have missing data, there is little guidance on which approaches are the most appropriate to specific regulatory decision-making situations. Research incorporating approaches such as clinical trial simulation is needed. The performance properties, such as sensitivity analyses, and assumptions of currently available imputation techniques like last observation carried forward (LOCF), baseline carried forward (BCF), and mixed effect model repeated measure (MMRM) models need to be evaluated and compared for datasets arising from various clinical trial situations.

2. Adaptive designs

We need to further our understanding of approaches to adaptive design of randomized clinical trials for late stage development and early exploratory studies. While a released draft guidance for industry on *Adaptive Design Clinical Trials for Drugs and*

Biologics gives a high-level overview of general approaches,[14] further research will help us determine which approaches to apply under specific conditions.

Currently, little data exist on the regulatory application of theoretical approaches to adaptive design. We need to use clinical trial simulations that combine statistical and clinical aspects for a practical perspective. We need to research the performance characteristics for the approaches using hypothetical scenarios that can use data from pre-existing trials.

3. Non-inferiority trials

The recently published draft guidance for industry on *Non-Inferiority Clinical Trials*[15] presents approaches to the design and analysis of non-inferiority studies. To supplement the guidance, we need to collect and analyze our growing experience with these designs and, in particular, examine our experience in defining the non-inferiority margin in various therapeutic areas. Appropriateness of non-inferiority methods in safety analysis also needs to be further explored.

4. Multiplicity adjustments

A guidance on multiplicity adjustments is under development. We need to evaluate existing statistical approaches to multiplicity (multiple endpoints, multiple treatment comparisons) and make recommendations for their use in particular situations. In particular, additional methodologies to assess complex situations such as assessment of both primary and secondary endpoints, as well as sequential and "gatekeeper" approaches, are needed.

5. Analysis of data across multiple clinical trials

CDER reviews a wealth of clinical trial data. We need to develop and refine approaches to the analysis of data across multiple clinical trials to support more comprehensive evaluations of potential safety signals. We could potentially look across trials to ask similar questions as large clinical trials such as the Antihypertensives/lipid trial ALLHAT and Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) clinical trials. An enhanced ability to look across multiple studies could facilitate interpretation of rare adverse events in future clinical trials, allow examination of known or potential safety signals in clinical trial data that have been identified in epidemiological studies, and facilitate analyses of relationships between drug concentrations, drug effects, and adverse events.

[14] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf.
[15] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.

6. Assess benefit and risk of drugs

The feasibility of developing a framework for formally assessing the benefit and risk of drugs using randomized clinical trial data is being explored. Common elements that factor in our decisions are already being identified to enable us to build a knowledge base. These efforts should be expanded to support the assessment of whether a framework for consistent evaluations can be developed.

B. Improve Selection and Definition of Study Endpoints for Various Conditions

1. Chronic and progressive degenerative diseases

Development of disease modification claims for degenerative diseases such as Parkinson's and Alzheimer's, chronic pulmonary diseases, and osteoarthritis depends on the identification of valid study endpoints.[16] The trial designs, endpoints, and analyses currently in use are for approving drugs for symptomatic benefit, and may not be applicable for testing whether a drug produces disease modifying effects. We need to increase our knowledge of the natural history of these types of diseases. These efforts would also aid clinical trial design especially qualification of prognostic or predictive biomarkers for us to be able to adequately assess drug efficacy and affect the choice of exclusion/inclusion criteria (e.g., baseline disease severity distribution and its relation to other risk factors, disease progression and its relationship to relevant biomarkers, drug effects, and drop-out models).

2. Endpoints that rely on subjective ratings

- **Standards for readers**
  We need to establish best practices for multiple readers of endpoints employed in pathology or imaging modalities such as radiographs and CT scans. For studies that use imaging endpoints, more rigorous requirements are also needed for hardware and software standardization, calibration, and validation data to ensure that imaging data from multiple sites are comparable. These long-standing issues have led to challenges when assessing outcomes across multiple sites or readers. Results of research directed towards determining best practices could be incorporated into guidances on using histopathology, biomarker qualification, and imaging as endpoints in clinical trials. These approaches may also be appropriate for dermal conditions, such as scarring and blistering, to the extent the outcome is evaluated by subjective visual assessments.

- **Patient-reported outcomes (PRO)**
  We need to continue to develop evidence to support submissions of PRO instruments to regulatory agencies for "fit for purpose" determination in

[16] Coalition Against Major Diseases (CAMD) http://www.c-path.org/CAMD.cfm.

qualifying them for specific uses.[17] Further metrics need to be developed to help to establish when PRO instruments are sufficiently validated and when their use as primary endpoints for regulatory decision-making is appropriate.

3. Surrogate endpoints

There are indications for which appropriate clinical trial endpoints are either ethically questionable, or pose technical or logistical challenges. Surrogate endpoints have been used in certain areas such as oncology or antivirals. Identification and qualification of surrogate endpoints in other therapeutic areas would be of value. An example is the ethical dilemma posed by the use of fracture as an endpoint in placebo-controlled trials of certain drugs. We also need a better understanding of fracture healing, and ways to define the functional outcomes appropriate for fracture healing trials.

We need to develop better endpoints for infectious disease trials (antivirals, antimicrobial) for diagnosis and efficacy. Consistent approaches to qualify more endpoints in clinical trials for "special pathogens," because detection of the actual pathogen is often difficult. Also necessary are markers of disease severity caused by certain pathogens, such as *Trypanosoma cruzi*, the parasite that causes Chagas disease, where patients may appear asymptomatic while the pathogen is causing progressive cardiac damage. The need for surrogate endpoints has always outpaced drug development for orphan and neglected diseases. A current constraint is that the opportunities to "qualify" an endpoint may be limited because the patient pool available for such clinical trials is small.

C. Identify and Address Aspects of Clinical Trial Designs Associated With Failure of Trials, Particularly in Pediatric and Orphan Drug Products

Better ways to increase the success of clinical trials conducted in special populations are needed. For example, trials that evaluate pediatric treatments and orphan drug products may need alternative designs to make better use of the limited study populations. Retrospective evaluation of failed trials may identify aspects to improve prospective trials. For example, designs rarely used in drug development, but that may be valuable, include crossover studies and "n of 1" studies (multiple crossover studies). These have been used in the past in the approval for drugs for hereditary angioneurotic edema and vasospastic angina. However, the drawbacks of crossover studies, such as the carry-over effect, should be considered.

[17] Patient Reported Outcome Consortium http://www.c-path.org/PRO.cfm.

D. Ensuring the Quality of Clinical Trials and Human Subject Protection by Determining the Critical Factors to Inspect During the Preapproval Process

Flawed or missing clinical trial data contributes to uncertainty when analyzing datasets. Improving the conduct of clinical trials offers an opportunity to improve both patient safety and the quality of clinical trial data submitted to FDA for review. We need to develop approaches for prioritizing the inspections of clinical trials during preapproval.

Using preapproval Bioresearch Monitoring (BIMO) inspections effectively to improve trial conduct requires CDER to use a risk-based site selection model and to focus inspections on clinical trial parameters most critical for ensuring the safe conduct of quality trials. Retrospective analysis of preapproval data may identify the most relevant parameters to track during clinical trials for human subject protection and to ensure protocols are followed to generate high quality data. Results could also help to identify the most appropriate times to inspect. Implementation would entail developing data management approaches for real time monitoring.

Understanding variable characteristics in clinical trial sites is becoming increasingly important because of the international nature of current clinical trials. The sources of differences in efficacy results between U.S. and foreign clinical trial sites have yet to be determined, but differences rooted in the conduct of the clinical trial should be evaluated.

VII. ENHANCE INDIVIDUALIZATION OF PATIENT TREATMENT

Overview:

We need to improve our understanding of the safety and efficacy of pharmacotherapy as it applies to individual patients and patient subsets. More potential biomarkers for early intervention signals need to be identified. Early biomarker responses could also be identified to predict effectiveness and be used as preliminary response screens. More generally, we need to identify particular characteristics (genetic/genomic or proteomic) that predict favorable or unfavorable responses. In addition, we need to ensure that robust statistical methods are developed to support biomarker qualification and trials that incorporate the use of biomarkers in their design.

A. Identifying and Qualifying Biomarkers for Regulatory Use

Biomarkers are currently guiding decisions in a number of clinical domains important for pharmacotherapy, including dosing, patient selection for efficacy, and patient exclusion for safety. New biomarker development and qualification efforts are needed for a broad range of applications related to the development of new drugs, as well as to their appropriate postmarket use. We need approaches that can identify additional biomarkers that predict drug-induced organ and system toxicities and those that may predict favorable responses.

Approaches include identifying appropriate prognostic biomarkers to better define the natural history of conditions such as chronic degenerative diseases. Or, identification of predictive biomarkers may allow selection of more responsive patients in clinical trials and improve the interpretations of outcomes by using an enriched population.

In certain instances, a retrospective analysis of data from clinical trials may help to better define the use conditions and doses for certain patient populations, may lead to identification of predictors of disease response or recurrence or improve the design of future trials. It would also help in investigation of relationships between biomarkers and outcomes. For studies from submissions that contain genetic/genomic information, additional considerations would include whether the spectrum of response and genetic variability is adequate to discern patterns. Nonclinical studies could be retrospectively evaluated for related safety signals in subsequent clinical trials.

Evidentiary standards have not been fully formulated to establish guidelines for what constitutes sufficient data to qualify different biomarkers. Although biomarkers may be potentially identified through retrospective analyses, the process of qualifying new biomarkers may require prospective studies to verify their sensitivity and specificity, and to assess the predictive nature of profiles versus single markers. Additional research may be needed to incorporate findings from these analyses into clinical trial design.

Large, collaborative efforts may be required to identify and develop the evidence necessary to qualify new biomarkers for regulatory use.[18] By partnering with academics, industry, other government agencies and nonprofits we can facilitate the identification and validation of novel biomarkers.[19] As noted in Category VI, we also need to develop better approaches to subgroup analysis to support this need.

B. Better Understanding of Drug Product Behavior in Specific Populations

We need a better understanding of the pharmacokinetic and pharmacodynamic behavior of drug products with regard to differential ADME (absorption, metabolism, disposition, and excretion) properties, and drug interactions in specific populations, particularly pregnant, pediatric, and geriatric patients, and patients with organ dysfunction. Factors to consider also include genotype-based determination of the right dose and genotype-based drug/patient-selection.

In conclusion, this document is intended to serve as a launching point for development of a periodic process to identify CDER's emerging science needs, and prioritize and address them in a collaborative manner to advance regulatory science.

[18] Predictive Safety Testing Consortium, http://www.c-path.org/pstc.cfm.
[19] Biomarker Consortium, http://www.biomarkersconsortium.org.