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Assessing CDER's Drug Safety-Related Regulatory Science Needs and Identifying Priorities

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The CDER Safety Research Interest Group (SRIG)

Center for Drug Evaluation and Research

Table of Contents

Executive Summary 3

Introduction to CDER's SRIG 4

A. Identifying Needs 5

B. Cataloging Projects 5

C. Identifying Gaps 6

D. Identifying Priorities 6

Conclusions and Future Steps 9

Ways to Send Comments to CDER about Research Needs 12

Additional Opportunities to Interact with CDER on Research Activities 12

Appendix 13

Executive Summary

Drug safety-related regulatory science—developing methods, tools, and data sources to better identify, predict, assess, and manage safety issues related to drug effects, drug product quality, and drug use in the marketplace—is an integral component of the regulatory science portfolio of the Center for Drug Evaluation and Research (CDER). CDER has launched an initiative to identify priority issues that need particular attention and resources. CDER currently collaborates with a variety of stakeholders to address emerging regulatory science needs; however, more focused attention is warranted given the breadth of its current activities.

CDER's Safety Research Interest Group (SRIG) identified seven major areas of safety-related needs based on research categories in the report published in 2011 entitled "Identifying CDER's Science and Research Needs." After further evaluating details of these needs in view of CDER's safety research portfolio, the SRIG used collective expertise to identify particular priority projects requiring additional resources and collaboration. To connect priority projects to resources by leveraging both internal resources and external research activities supported by other organizations, the following approaches were identified:

- For those priority safety-related research projects that would benefit from further internal collaboration, the SRIG will meet with relevant CDER staff to better understand the available data and the scope of the needed research and work to facilitate the appropriate collaborations.
- The SRIG recommends communicating priority projects that would benefit from external collaborations and resources via *Federal Register* (FR) notices, white papers, and other forms of publication to invite the outside community to partner with CDER.

The SRIG is also developing approaches to identify future priority drug safety-related research projects. CDER would benefit from an ongoing structured effort to support productive internal and external collaborations.

Introduction to CDER's SRIG

CDER, a large organization with wide ranging safety activities, would benefit from a mechanism to raise awareness of its various drug[1] safety regulatory science[2] efforts. Gaining an overall perspective on CDER's ongoing and completed projects in laboratory and clinical research, product quality, epidemiology, pharmacovigilance, and computational modeling would help CDER better understand how regulatory science can support regulatory review needs and maximize the value of those research efforts. Although CDER currently collaborates with a variety of stakeholders to address emerging regulatory science needs, more focused attention is warranted given the breadth of its current activities. In 2010, the SRIG was formed by CDER as a subcommittee of the Science Prioritization and Review Committee (SPaRC)[3]. This group embarked on a series of focused activities that are summarized in this report (Figure 1).

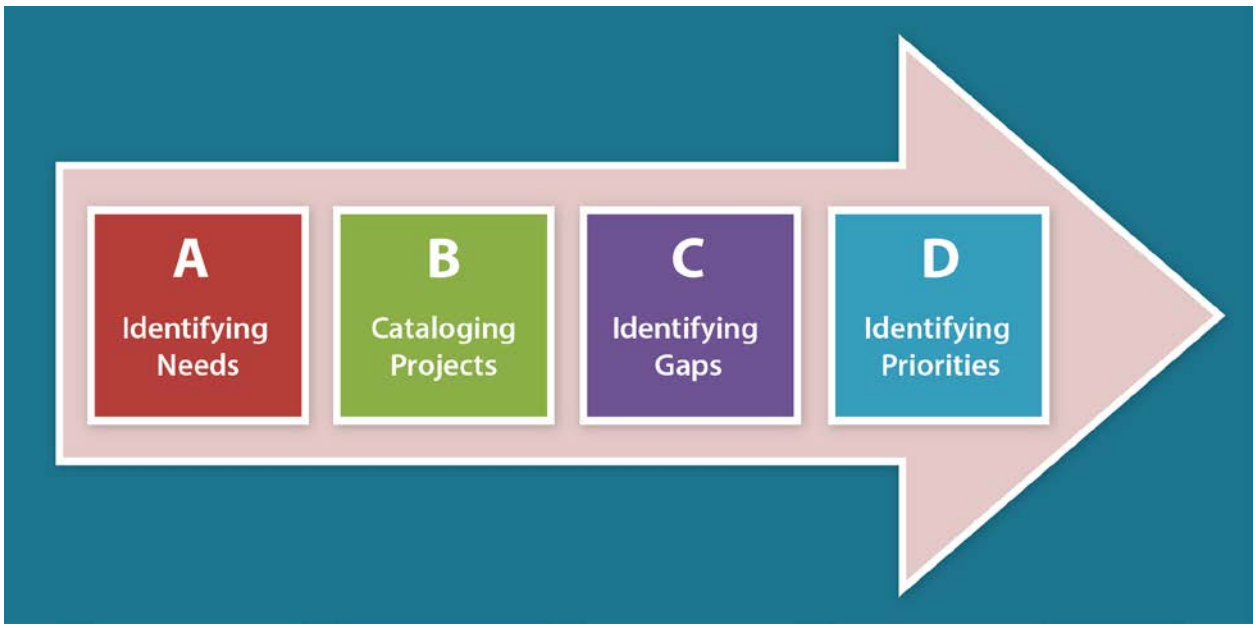

FIGURE 1. Summary of activities conducted by the SRIG

[1] For the purpose of this report, the term *drug* refers to both drugs and therapeutic biologics.
[2] For the purpose of this report, the term *regulatory science* may be used interchangeably with *research*. Some activities may not be considered strictly research but fall under the rubric regulatory science.
[3] At the request of Dr. Janet Woodcock, CDER's director, SPaRC is comprised of senior scientists from many offices in CDER.

A. Identifying Needs

CDER's Science and Research Needs Report. In 2011, the report entitled "Identifying CDER's Science and Research Needs" (CDER S&R Needs) was published.[4] That report served as a guide for CDER's contribution to FDA's *Strategic Plan for Advancing Regulatory Science.*[5]

Identifying and Elaborating on the Seven Areas of Safety-Related Research Needs. First, the SRIG identified the *drug safety-related* research areas from the seven general science and research areas described in the CDER S&R Needs (see Table 1). Second, additional details were added to these drug safety areas, based, for example, on specific legislative mandates (e.g., Generic Drug User Fee Act (GDUFA), Prescription Drug User Fee Act (PDUFA)) for new research or input from other research or working groups at CDER (see Appendix for a detailed list of identified drug safety-related research needs).

Table 1: Seven CDER Drug Safety-Related Research Needs
1. Improve access to postmarket data sources and explore the feasibility of their use in safety signal analyses
2. Improve risk assessment and management strategies to reinforce the safe use of drugs
3. Evaluate the effectiveness of risk communications of drug safety information to health care providers and the public
4. Improve product quality and design, manufacturing processes, and product performance relating to safety
5. Develop and improve predictive models of safety in humans, including nonclinical biomarkers
6. Improve clinical trial statistical analyses for safety, including benefit-risk assessment
7. Investigate clinical biomarkers of safety, including standards for qualification

B. Cataloging Projects

The SRIG compiled a list of recently completed and current drug safety-related CDER research projects. This list was derived from a database housing self-reported CDER research projects, publications by CDER authors, and direct requests for information to various CDER offices. The list included projects funded by offices whether accomplished internally or via contracts, grants or interagency agreements, or intramural research programs that involved CDER personnel and their collaborators. The compiled projects were then grouped according to the seven safety-related research needs.

[4] http://www.fda.gov/Drugs/ScienceResearch/ucm264327.htm.
[5] http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm.

C. Identifying Gaps

A modified Delphi method[6] was used to identify gaps in research efforts and to gather additional proposals for drug safety-related research. SRIG met initially with subject matter experts (SMEs) from disciplines across CDER to discuss gaps. All participants were provided with the Appendix to this report containing detailed descriptions of the seven drug safety-related research needs and the catalog of CDER's research projects. SMEs and SRIG members then consulted with their respective working groups and offices to propose detailed research activities where more collaboration and resources were needed. A report containing the Appendix, the catalog of CDER's research projects, and the list of proposed research activities was presented to CDER's senior management and the CDER-wide community for discussion and comment, and the input was subsequently incorporated into this report.

D. Identifying Priorities

Within each of the seven drug-safety related research needs, the SRIG reviewed the research activities, with particular consideration toward public health and regulatory impact, feasibility, and the need for CDER involvement. Projects were also evaluated by whether internal or external collaboration or resources were needed, given CDER's already substantial ongoing research activities in the seven areas. Based on the SRIG review, the following priority activities were identified that would particularly benefit from external collaboration and resources:

1. Improve access to postmarket data sources and explore the feasibility of their use in safety signal analyses

- Improve tools for conducting postmarketing safety surveillance using automated health care data by supporting the efforts by Innovation in Medical Evidence Development and Surveillance[7] to build a methods researchers community and data environment for methods research
- Evaluate the overall utility and practicality of product-specific registries for postmarketing safety assessment and surveillance for safety evaluation
- Determine appropriate data sources for determining suicidality in populations of interest by investigating which structured and unstructured data sources are most informative

[6] A method for gathering data from respondents within their domain of expertise (http://www.rand.org/topics/delphi-method.html).
[7] http://www.reaganudall.org/our-work/safety-and-better-evidence/imeds-program/.
[7] http://www.reaganudall.org/our-work/safety-and-better-evidence/imeds-program/.

2. Improve risk assessment and management strategies to reinforce the safe use of drugs

- Evaluate the effectiveness of the various methodologies employed as part of risk evaluation and mitigation strategy (REMS) assessments and their usefulness in determining whether REMS goals have been achieved
- Develop innovative methods to create, facilitate, and encourage research in the area of safe medication use that seeks to reduce preventable harm from drugs. Approaches could include the use of clinical studies, education, innovative messaging strategies, electronic health records, or mobile technologies
- Collaborate with local and state health departments to help identify high-risk, unapproved finished drug products and traditional medicines to establish a list of target products (for purchase or on-site sampling) for on-site screening

3. Evaluate the effectiveness of risk communications of drug safety information to health care providers and the public

- Investigate the most appropriate measures for determining the impact of CDER's Drug Safety Communications and how they are perceived by practitioners and consumers
- Investigate, analyze, and communicate the most effective approaches to reduce preventable harm from certain drugs (e.g., opioids) based on an understanding of current use and behaviors
- Determine the most appropriate way to communicate with consumers about the safety and effectiveness of generic drugs and biosimilars, given current public perception

4. Improve product quality and design, manufacturing processes, and product performance relating to safety

- Determine what data are needed to determine whether a postmarket adverse event is caused by a product quality issue, and conversely, develop an approach for predicting the clinical relevance of drug product quality issues
- Develop advanced methods to evaluate the effect of product quality factors of biosimilars on clinical pharmacology and safety
- Advance the methodology for antibody-drug conjugate products to determine the distribution of a drug and drug-linked antibody, as well as methods to monitor and control the distribution of conjugated and unconjugated species
- Further efforts to educate MedWatch reporters to include lot number by a combination of outreach efforts by FDA, key partners, and stakeholders

5. Develop and improve predictive models of safety in humans, including nonclinical biomarkers

- Develop a general framework to support a systems pharmacology approach that leverages laboratory results, published data, and computational modeling to evaluate drug safety (encompassing both dose-related and rare or idiosyncratic adverse events)
    - Systematic cross-evaluation of data/text mining tools and creation of searchable document repositories
    - "Proof of concept" integration of mechanistic modeling with current pharmacokinetic/pharmacodynamics (PK/PD) approaches and physiologically based pharmacokinetic modeling
    - Identification and use of computer modeling tools that can better integrate regulatory data with current medical knowledge and predict human outcomes
- Develop and improve quantitative structure-activity relationship models for toxicity prediction and other chemical informatics approaches relating structure to on- and off-target effects
- Develop tools and recommendations for systematic evaluation of data from clinical trials for prompt detection of outcomes often related to exposure to approved drugs (e.g., drug-induced kidney injury)

6. Improve clinical trial statistical analyses for safety, including benefit-risk assessment

- Identify scenarios where the application of Bayesian methods can enhance the content of targeted statistical safety reviews and apply these methods to safety data from randomized clinical trials
- Assess ways to define a risk margin and development of an approach/process for setting such margins for future safety outcome trials
- Review the range of methodologies currently used for treatment discontinuations in the statistical assessment of safety objectives and determine best practices
- Assess how to best analyze and design safety outcome trials for chronic indications where treatment discontinuation is likely to be encountered

7. Investigate clinical biomarkers of safety, including standards for qualification

- Explore the differences between evidentiary standards for nonclinical and clinical biomarkers
- Develop a framework for an objective cost-benefit model to evaluate and prioritize biomarkers to pursue for qualification and facilitate discussion regarding whether existing biomarkers can answer the most critical questions and whether additional biomarkers are needed
- Develop a more integrative strategy of biomarker development to:
    - Facilitate wider community participation in biomarker development, including academia and large health care organizations
    - Strengthen the link between in-depth biological research about biomarkers and use for qualification

Conclusions and Future Steps

An important outcome of SRIG activities was to bring together staff from different disciplines who are working on similar drug safety-related activities. CDER's SMEs and SRIG members were eager to discuss challenges and brainstorm about possible solutions. Possibilities for synergies across CDER groups and sharing of resources emerged, as well as the need for outside collaborations to address challenges.

The following two major conclusions can be drawn from the work of the SRIG:

(1) A number of drug safety-related research projects would benefit from further internal collaboration and support. Where a need for collaboration has been identified, the SRIG can meet with relevant CDER staff to better understand the available data and the scope of the needed research and foster activities in that area.

(2) Priority projects that would benefit from external collaborations, as well as details of the seven overall drug safety-related regulatory science needs, should be communicated to persons and organizations outside of FDA to foster further collaboration with external partners.

Furthermore, efforts can be made to connect priority research projects to resources by leveraging both internal resources and external research supported by other organizations. These efforts may include, but are not limited to:

- Communicating safety research priorities in an FR notice to elicit outside interest in collaboration
- Expanding collaborations with other FDA centers
- Identifying funded activities at other agencies that are relevant to FDA research priorities and exploring potential research collaborations (e.g., with the National Institutes of Health (NIH), the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, the Veterans Administration, the Department of Defense, and the Centers for Medicare and Medicaid Services)
- For areas that are not supported currently by external funding, communicating these priorities to the relevant NIH program officers to stimulate the development of relevant Requests for Applications (e.g., preclinical models, biomarkers, and genomics)
- Communicating priorities to the Drug Safety Oversight Board[8] to foster connections with FDA Federal Partners for collaboration opportunities

[8] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082129.htm.

- Using the FDA Broad Agency Announcement (BAA) contracts and Centers for Regulatory Science and Innovation (CERSI) grant mechanisms to address particular priorities
- Holding a yearly public meeting to solicit external stakeholder input in developing GDUFA regulatory science priorities for generic drugs
- Providing information about opportunities for those interested in drug safety research by:
    - Establishing a link to available fellowships (e.g., those supported by the Reagan-Udall Foundation, Oak Ridge Institute for Science and Education (ORISE) Fellowships, FDA Commissioner's Fellowships)
    - Inviting scientists with requisite expertise to work on sabbatical with CDER on specific areas of need

For information on FDA fellowships programs, please visit: http://www.fda.gov/aboutfda/workingatfda/fellowshipinternshipgraduatefacultyprograms/default.htm.

Drug safety-related research must be reassessed periodically. The information gathering and initial prioritization process described here are first steps, and efforts are underway to craft approaches to track progress and keep priorities current. Although the seven drug safety-related research areas may remain the same, priorities within those areas will likely change as a gap is filled leading to thoughtful reassessment of needs. Therefore, safety-related research activities would benefit from a continual, integrated, and structured review effort, facilitating productive collaborations and resource allocation (Figure 2).

FIGURE 2. Mechanisms for CDER Safety Research

Ways to Send Comments to CDER about Research Needs

In order to engage further with CDER on these areas:

- **Submit your comments and ideas to the docket**

Additional Opportunities to Interact with CDER on Research Activities

Critical Path Innovation Meeting (CPIM)

The CPIM is a means by which CDER and external scientists (e.g., from industry, academia, patient advocacy groups, and/or government) can communicate and interact on innovative product-independent topics to facilitate drug development. The goals of the CPIM are to discuss a methodology or technology proposed by the meeting requester and for CDER to provide general advice on how this methodology or technology might enhance drug development.

For more information and FDA points of contact for the CPIM, please visit http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm395888.htm.

FDA Broad Agency Announcement (BAA) or Program for Extramural Regulatory Science and Innovation (PERSI)

PERSI encourages participation of companies and educational institutions in meeting FDA goals for innovative ideas and approaches for regulatory science. PERSI-BAA identifies innovative and promising technologies for advanced development across FDA.

For information and points of contacts on PERSI-BAA, please visit the Federal Business Opportunities Web page at https://www.fbo.gov/index?s=opportunity&mode=form&id=281e9e6b5012b753dbec890ea2c5f1c4&tab=core&_cview=1.

Centers of Excellence in Regulatory Science and Innovation (CERSI)

For information, please visit the CERSI Web page at http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm301667.htm.

Appendix

Details for Seven Drug Safety-Related Research Needs

This Appendix contains references to the safety-related research needs expressed in the 2011 "Identifying CDER's Science and Research Needs" report (CDER S&R Needs). To read the needs in that Report, please refer to the specific sections indicated at the end of the headings. Additional details for safety-related research needs identified by the SRIG are included as italicized text under "In addition" in each section below.

1 – Improve Access to Postmarket Data Sources and Explore the Feasibility of Their Use in Safety Signal Analyses

A. Accuracy and Availability of Postmarket Data

1. **Accuracy of electronic health care data** – Refer to CDER S&R Needs Section I.A.1.
2. **Utility of spontaneous reports** – Refer to CDER S&R Needs Section I.A.2.
3. **New data sources** – Refer to CDER S&R Needs Section I.A.3.

In addition:

- *Investigate the role for information exchange with foreign regulators to access proprietary clinical data for trials conducted outside of an Investigational New Drug (IND) application but under the purview of the European Medicines Agency or European Union member states (such as obtaining access to EudraVigilance)*
- *Investigate whether adverse event data reported to https://www.clinicaltrials.gov for IND-exempt phase IV trials might contain additional unique information*
- *Improving ways to link specific patient complaints or particular adverse events with product defects*
- *Map molecular ontologies to organ-based toxicity, animal toxicity, and human adverse drug events via MedDRA*

B. Develop and Refine Statistical Methods for Postmarket Drug Safety Evaluation

- *Continue to refine methods for data mining of spontaneous reports and analysis of electronic health records from accessible large health care databases*

- *Investigate the feasibility of more quantitative benefit-risk modeling*
- *Develop methods to incorporate safety data analyses from both premarket and postmarket data sources*
- *Determine conditions under which meta-analysis is appropriate, including meta-analysis of observational studies*
- *Evaluate approaches to manage uncontrolled confounding in observational data*
- *Evaluate methods to reduce false positive rates and over-amplified estimates of association*
- *Investigate the appropriate use of person-time-based methods to estimate drug exposure in addition to current person-based estimates.*
- *Develop methods that allow evaluation of variables, such as dose prior to the health outcome of interest, cumulative dose, duration of dose, underlying disease, and/or concomitant medication use*
- *Develop and test additional statistical and epidemiological approaches for the Sentinel Initiative, 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*

2 – Improve Risk Assessment and Management Strategies to Reinforce the Safe Use of Drugs

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

1. **Outcomes regarding approved drugs** – Refer to CDER S&R Needs Section II.A.1.
2. **Understanding the use of unapproved, compounded, fraudulent, and counterfeit products** – Refer to CDER S&R Needs Section II.A.2.

B. Apply Behavioral Science Models to the Selection of Risk Evaluation and Mitigation Strategies (REMS) and Medication Error Prevention Strategies – Refer to CDER S&R Needs Section II.B

In addition:

- *Explore novel methods (instruments or strategies) to assess patient and prescriber understanding of risk information provided as part of REMS*
- *Regarding medical error prevention, develop scientific methodologies that can incorporate the results of social science studies with known practices for prescribing and dispensing medication in health care provider practices, hospitals, and pharmacies*
- *Develop REMS assessment methods that provide valid information on clinical patient outcomes (including rare adverse outcomes), necessitating identification of additional appropriate outcome measures, methodologies, and accompanying metrics*

- *Explore approaches that can be used to assess the burdens that REMS impose on the health care delivery system (e.g., prescribers, dispensers, hospital settings, etc.) and the impact of REMS on patient access to drugs*

C. Strategies to Assess the Benefits and Risks of Drugs Reviewed under the Animal Rule – Refer to CDER S&R Needs Section II.C.

3 – Evaluate the Effectiveness of Risk Communications of Drug Safety Information to Health Care Providers and the Public

A. Improve Labels and Similar Modes of Communication – Refer to CDER S&R Needs Section III.A.

In addition:

- *Evaluate the "generalizability" of survey responses to larger audiences when fewer than the ideal number of responses are received*
- *Evaluate and compare the performance of individual risk communication tools using already submitted assessments of the effectiveness of the communication*

B. Evaluate Risk Communications – Refer to CDER S&R Needs Section III.C.

4 – Improve Product Quality and Design, Manufacturing Processes and Product Performance Relating to Safety

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

1. **New technologies to characterize complex drugs** – Refer to CDER S&R Needs Section IV.A.1.

   In addition: *Evaluate the role of particular excipient ingredients and complex dosage forms on product safety*

2. **Manufacturing issues unique to biologic products** – Refer to CDER S&R Needs Section IV.A.2.
3. **Quality factors that affect commercial-scale manufacturing** – Refer to CDER S&R Needs Section IV.A.3.

   In addition:

   - *Develop sensitive, rapid, high-throughput methods to detect, identify, and enumerate microbial contaminants and validate their utility in assessing product sterility*

- *Develop and evaluate methods for microbial inactivation/removal from pharmaceutical products that are not amenable to conventional methods of sterilization*
- *Evaluate the impact of specific manufacturing processes on microbial contamination*
- *Develop reference materials for use by industry and academia to evaluate and validate novel methods for detecting microbial contamination*

B. Identify Best Analytical Methods and Metrics to Evaluate the Safety of Novel Dosage Forms and Delivery Systems – Refer to CDER S&R Needs Section IV.B.

C. Establish Links between Drug Product Attributes and Clinical Safety – Refer to CDER S&R Needs Section IV.C.

D. Develop Analytical Methods and Methodologies to Evaluate Compounded Drug Dosage Forms – Refer to CDER S&R Needs Section IV.D.

E. Screen for Contaminated, Counterfeit, Fraudulent and Sub-Quality Manufactured and Compounded Drugs – Refer to CDER S&R Needs Section II.A.3.

5 – Develop and Improve Predictive Models of Safety in Humans, including Nonclinical Biomarkers

A. Improve Nonclinical Science Testing Paradigms to Predict Human Risk

1. **Evaluate and promote the use of models to assess organ-specific, drug-induced toxicities** – Refer to CDER S&R Needs Section V.A.1.
2. **Develop methods for using nonclinical data to predict the safety of biologics** – Refer to CDER S&R Needs Section V.A.2.
3. **Develop and validate models to predict allergic responses to small and large molecules** – Refer to CDER S&R Needs Section V.A.1.

In addition:

- *Develop additional tools to model kidney injury similar to the algorithms to monitor drug-induced liver injury that incorporate clinical observations such as Hy's law*
- *Improve the understanding of the pharmacokinetics of biologic molecules during pregnancy (e.g., determining exposure of the fetus to biologic products)*

4. Evaluate and promote the use of cell- and tissue-based assays

- *Develop and evaluate in vitro and non-mammalian methods for assessing developmental and reproductive toxicity, based, for example, on embryonic stem cells or embryo studies in non-mammalian species such as zebrafish*

- *Develop and evaluate in vitro potency models to reduce animal use (e.g., the use of the botulinum toxin)*
- *Develop and evaluate in vitro and in vivo assays capable of identifying carcinogenicity mechanisms relevant to human cancer so that such information can be incorporated into carcinogenicity assessments*
- *Evaluate quantitative imaging (e.g., positron emission tomography, magnetic resonance imaging, computed tomography, etc.) and other advanced approaches (e.g., metabolomics) for identifying new biomarkers and predictors of safety*

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

1. **Quantitative structure-activity models** – Refer to CDER S&R Needs Section V.C.1.

   In addition:
   - *Develop and implement approaches to link chemical structures and substructures to a wide range of information about product safety, disease targets, and toxicity mechanisms*
   - *Expand in silico disease/toxicity model development and quantitative structure-activity relationship model development (e.g., for predicting bacterial mutagenicity of drug impurities) and updating of content and training sets*
2. **Pharmacometric models** – Refer to CDER S&R Needs Section V.C.2., VII.B.
3. **Systems biology models** – Refer to CDER S&R Needs Section V.C.3., IIA.4.

In addition:

4. ***Computational methods and in silico modeling***
   - *Develop simulation models for*
     - *Clinical trials that can reveal interactions between drug or device effects, patient characteristics, and disease variables that influence outcomes*
     - *Product life cycles and risk assessment*
   - *Develop computer models*
     - *Of cells, organs, and systems to better predict product safety and efficacy*
     - *To integrate pharmacokinetic, pharmacodynamic, materials science, or mechanistic safety data to predict clinical risk-benefit and to further assess postmarketing safety issues in different patient populations*
   - *Develop and apply data mining, knowledge building, and data visualization tools to inform computer model development, clinical risk prediction, and regulatory decision-making*
     - *Develop/implement semantic text mining tools for extracting hidden relationships*
     - *Develop/implement interaction mapping tools (nodes/edges, heat maps, etc.) for data visualization and exploration*
   - *Expand the cheminformatics toolkit to enable similarity searches of regulatory documents by structures and substructures*

- *Identify computational approaches for rapid search and retrieval of data*
- *Create an ontology for molecular toxic drug targets*

6 – Improve Clinical Trial Statistical Analyses for Safety, including Benefit-Risk Assessment

1. **Non-inferiority trials** – Refer to CDER S&R Needs VI.A.3.
2. **Analysis of data across multiple clinical trials** – Refer to CDER S&R Needs VI.A.5.
3. **Determine the appropriate use of meta-analysis to assess the benefits and risks of drugs** – Refer to CDER S&R Needs VI.A.6.

In addition:

4. **Further develop and refine statistical methods for safety evaluation of clinical trial data**

7 – Investigate Clinical Biomarkers of Safety, including Standards for Qualification – Refer to CDER S&R Needs VII Section A.

In addition:

- *Determine how to reduce inter-platform variability of analytical methods to measure biomarkers through identification of standards and standardized characterization*
- *Develop evidentiary requirements to demonstrate accuracy and reliability of devices that measure biomarkers using novel or innovative technologies (e.g., whole genome sequencing, new proteomics approaches, and image analysis)*
- *Evaluate how to integrate pharmacogenomic information into regulatory review*
- *Determine appropriate statistical methodology for biomarker assessment*