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# How the Critical Path Initiative Addresses CDER's Regulatory Science Needs: Some Illustrative Examples

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**Abstract**

Since 2008, the Critical Path Initiative has supported FDA's program of intramural research projects in regulatory science, with the goal of improving translation of advances in emerging sciences to the development of safe and effective medical products. Since 2011, the research of FDA's Center for Drug Evaluation and Research (CDER), including the work supported by the Critical Path Initiative, has been guided by the regulatory science needs identified in the CDER science and research needs report. In this review, the authors highlight a few of CDER'S Critical Path Initiative research projects, each addressing a different regulatory science need, to illustrate the diversity of regulatory science at CDER. They also describe elements common to these research projects, including broad collaboration with external partners, an increasing dependence on large data sets and computational models, and requirements for resources or perspectives specific to FDA.

**Keywords**

regulatory science, critical path initiative, drugs, CDER's science and research needs, research

## Introduction

The US Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) undertakes a wide-ranging program of research to help ensure that human drugs are safe, effective, and of consistently high quality. For the past decade, the Critical Path Initiative[1] (hereafter, Critical Path) has fostered collaborations among government, industry, and academia and supported FDA's intramural regulatory science research.[2] Within CDER alone, the Critical Path program has funded more than 100 separate research projects since 2008.

CDER's Critical Path program is guided by the center's regulatory science needs. To systematically identify these needs, in 2010, more than 200 of its staff, including multiple reviewers of various disciplines, were asked to identify scientific impediments with respect to regulatory decision making. On the basis of these interviews, a comprehensive list of regulatory science needs were compiled and organized according to 7 major topics by CDER's Science Prioritization and Review Committee. The 7 topics[i] and associated science and research needs were published in July 2011[3] and used to represent the center's specific needs in FDA's strategic plan for advancing regulatory science.[4]

To ensure the quality and relevance of research funded by the CDER Critical Path program, proposals are submitted annually for peer review by CDER staff. Proposed projects are selected for funding based on scientific merit, relevance to CDER's scientific needs, potential impact, feasibility, and the skills and experience of investigative teams. In the course of formal periodic assessments of each project's progress, impediments to completion are identified and, where possible, solutions implemented.

A comprehensive review of the research funded by CDER's Critical Path program is beyond the scope of this report. Rather, a selection of projects that address 5 of CDER's regulatory science needs are highlighted to demonstrate the program's diversity and to illustrate some common characteristics of regulatory science at CDER.

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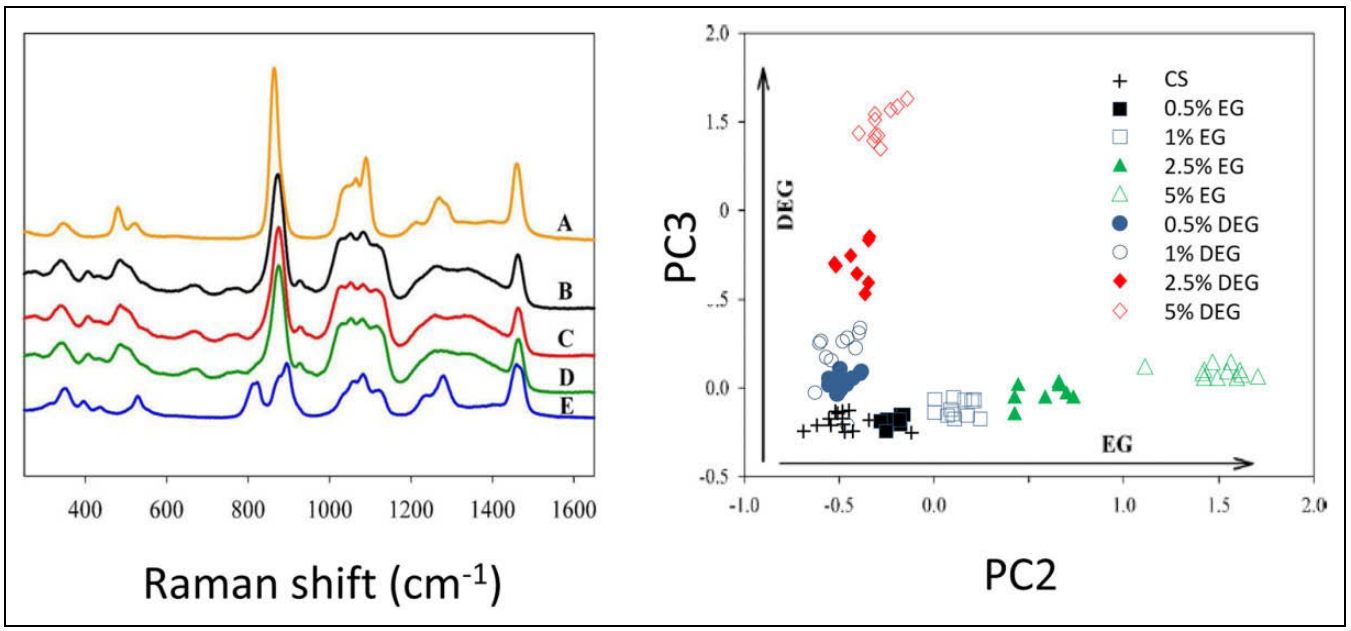


**Figure 1.** Drug inspectors working at remote locations need to rapidly identify adulterated drug samples, even when contaminants are present at low levels. Portable Raman spectrometers can be used to screen for contaminants, but the spectra of drug ingredients are complex, and changes caused by adulterants may be subtle. At left are the highly similar Raman spectra of sorbitol (C), which is a common component of many drug and personal care products, and sorbitol containing 5% of ethylene glycol (B) or diethylene glycol (D). Diethylene glycol contamination of toothpaste and medicinal syrups has caused scores of fatalities in children. Critical path investigators are exploring a variety of statistical approaches to separate signals of contamination from noise. Right, using a mathematical technique (principal component analysis), FDA scientists identified linear combinations of parameters (principal components) obtained from the Raman spectra that could be used to reproducibly separate contaminated samples according to contaminant and contaminant concentration. DEG, diethylene glycol; EG, ethylene glycol; PC, principal component. From Gryniewicz-Ruzicka et al.[6] Reprinted with permission.

## *Five Examples of CDER Critical Path Research That Address CDER's Science Needs*

> 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.
>
> —*Identifying CDER's Science and Research Needs Report*[3(p8)]

## *Screening Drugs in the Field Using Portable Spectrometers: Developing Consistency*

The volume of drug ingredients and drug products entering into the United States at border crossings, mail facilities, and import centers has more than doubled in the past decade, challenging the capacity of the import-testing process. Because they do not require investigators to be in a central laboratory to perform inspections, several types of portable spectrometers can cut inspection times dramatically and may revolutionize product monitoring.

The spectral patterns obtained in an inspection on a portable Raman spectrometer can be compared to a master library of spectra previously obtained on a master instrument to identify the substance in question. However, there are many makes of instruments in current use worldwide, and for a given substance, each instrument will record a slightly different spectrum. The differences are subtle, but they can significantly compromise drug identification. With Critical Path support, FDA scientists have developed and validated mathematical procedures for systematically standardizing spectral data across instruments in terms of the position along the *x*-axis (wavelength), intensity of the recorded radiation, resolution or width of the observed spectral lines, the frequencies at which each instrument measures emission, and baseline effects. Use of these standardized spectra has allowed for much more reliable identification of drug products in the field.[5]

Portable Raman spectrometers also have the potential to greatly improve the capacity of drug inspectors to identify products to which harmful adulterants have been added intentionally or inadvertently during manufacture. Because these adulterants may contribute relatively subtle changes to complex spectra, FDA researchers are developing and evaluating a variety of analytic procedures based on principal component analysis and soft independent modeling of class analogy to maximize the sensitivity and specificity with which the portable devices can detect adulterants such as diethylene glycol (Figure 1).[6] The work is only one component of a

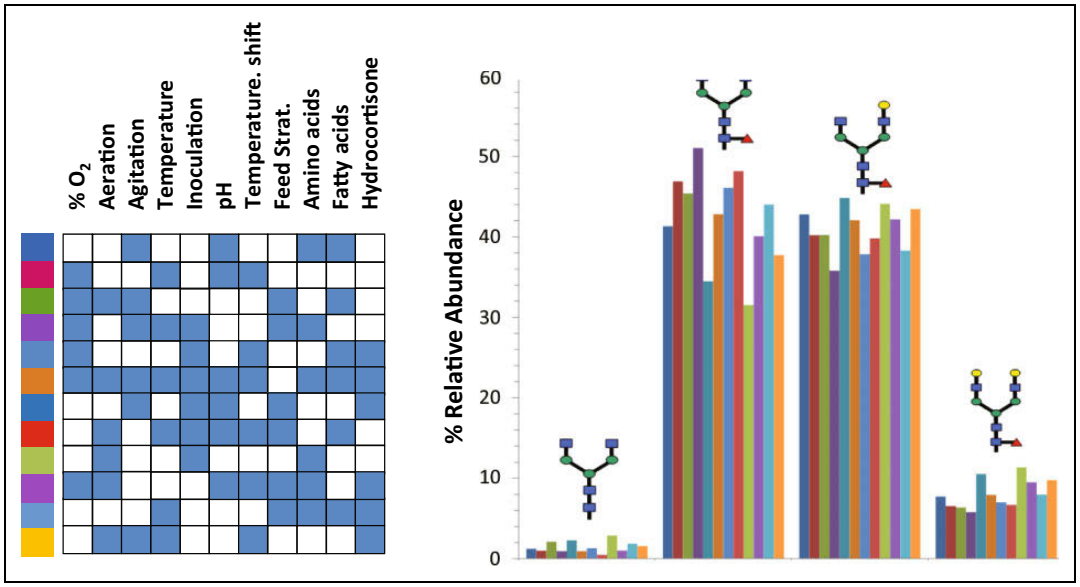


**Figure 2.** FDA researchers used 12 bioreactors (designated by different colors at left) to grow an antibody-producing cell line. Eleven parameters were varied between 2 levels, low or absent (white squares) or high or present (blue squares), according to a specific pattern (Plackett-Burman design) to reveal effects of changes in each parameter (upper left). When the runs were completed, the researchers removed the polysaccharides from the antibodies, purified them, and quantified the different chemical species from each bioreactor using mass spectroscopy (right). Statistical analyses allowed the researchers to assess the influence of each parameter on specific kinds of antibody modifications (assuming that there were no significant interactions between parameters). Fucose addition (red triangles), which is required for some anticancer effects of targeted antibodies, was enhanced to a statistically significant extent by growth at higher temperatures. Adapted from Agarabi et al. Bioreactor process parameter screening utilizing a Plackett-Burman design for a model monoclonal antibody. Submitted for publication. Reprinted with permission.

long-standing effort in which FDA is investigating a variety of spectroscopic approaches (eg, near infrared, ion mobility, X-ray fluorescence) to streamline drug inspections using portable instruments.

## *Controlling Glycosylation in a Class of Biologics*

> 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.
>
> —*Identifying CDER's Science and Research Needs Report*[3(p12)]

Biologics pose formidable challenges in the area of product quality and manufacturing: they are produced by cell-based systems sensitive to many external conditions; they may contain problematic impurities; and they are typically highly complex molecules in which subtle variations in biochemical structure may have important implications for quality and performance. Critical Path researchers are developing approaches to meet the challenge of ensuring the quality of these products.

For therapeutic monoclonal antibodies that target epitopes on a tumor cell, cytotoxic activity is influenced by glycosylation in bioreactor culture. These chemical modifications are therefore critical quality attributes that must be controlled in production. Using a "design of experiments" approach, a cross-office team of FDA researchers grew an antibody expressing cell line in 12 parallel bioreactor cultures. Eleven parameters were varied between 2 levels across the cultures according to an experimental plan designed to efficiently identify key parameters (Figure 2).[7] Mass spectroscopy was used to identify and quantify the various glycosylated forms of the antibody expressed in each culture.

The pattern of glycosylation was found to be dependent on several bioreactor culture parameters: temperature, the presence or absence of a temperature shift, and amino acid addition. In particular, higher temperature increased addition of the sugar fucose to the antibody, a modification critical for the natural killer cell–mediated cytotoxic function of monoclonal antibodies targeting cancer.

To advance research in this critical research area, FDA has initiated partnerships with industry when expertise or resources can be leveraged—for example, important work to develop new control methods for antibody quality has been done in collaboration with a nuclear magnetic resonance laboratory at Eli Lilly and Company used to evaluate production cell cultures. The array of antibody-based biologics now available to treat cancer and other diseases that rely on complex manufacturing engineering makes such collaborative efforts a key priority in the coming decade.

## Determining the Safe Dose of a Commonly Used Pain Medication in Children

> Physiologically based pharmacokinetic (PBPK) models provide predictions of drug absorption, distribution metabolism and elimination. . . . We need to assess the validity of using these models in regulatory decision making and risk analysis.
>
> —*Identifying CDER's Science and Research Needs Report*[3(p18)]

A common scenario in drug development involves a drug approval based on safety and efficacy data in adults, but there may still be a need to determine if a drug can be safely used in pediatric patients or other populations. Drug developers and regulatory agencies have increasingly come to rely on physiologically based pharmacokinetic (PBPK) models to predict drug exposure in these understudied populations and to inform clinical study design.[8] These mechanistic models use available information on anatomy, physiology, and biochemistry to develop a system of differential equations predicting the absorption, distribution, metabolism, and excretion of drugs in various compartments (eg, organs or tissues). Recently, Critical Path researchers constructed a PBPK model to predict the metabolism and exposure of acetaminophen in children, given that overdosing (and even approved doses in certain populations) can lead to liver damage caused by the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI).[9]

Jiang and coworkers incorporated information on acetaminophen's physicochemical properties (in its various formulations) and its elimination pathways (including pharmacogenomic data and in vitro data bearing on the drug's metabolism by various liver enzymes), along with extensive anatomic and physiologic data into a PBPK model in adults. After qualification with external pharmacokinetic data, the model was modified for children by incorporating data on growth and maturation processes. The predictions of this modified model were then compared with available pediatric data on the drug's plasma pharmacokinetics and urine concentrations of metabolites of the detoxification pathway. The pediatric model's predictions of plasma concentrations of acetaminophen agreed closely with reported clinical data from neonates, infants, and children and adolescents for several different formulations (intravenous, injection, tablet, solution, syrup). In addition, when information was incorporated on the maturation of the pathways involved in the acetaminophen's metabolism (eg, from pharmacogenomic studies and in vitro enzyme kinetics studies with neonatal and pediatric liver microsomes), there was comparability with previously reported urinary concentrations of various metabolites of acetaminophen and NAPQI (Table 1). These results have provided a better understanding of processes affecting the parent compound (ie, acetaminophen) and have formed the basis for other studies focused on detoxification processes for NAPQI.

**Table 1.** Pharmacokinetic modeling prediction of acetaminophen metabolite concentrations in children.[a]

| | Ratio | |
|---|---|---|
| Treated Group | Clinically Observed | Predicted |
| Neonates | 0.60 | 0.54 |
| Infants | 0.97 | 1.11 |
| Children | 1.38 | 1.34 |
| Adolescents | 1.24 | 1.43 |

[a]Data are the ratios of plasma concentrations of 2 acetaminophen metabolites (glucuronide and sulphate), clinically observed or predicted from the physiologically based pharmacokinetic model discussed in the text. Adapted from Jiang et al.[9]

This PBPK model is just one example of how FDA uses modeling and simulation approaches—in situations where clinical data are incomplete—to provide a conceptual framework that can inform the design of additional studies or, in some cases, to provide a basis for regulatory decision making.

## Predicting Cardiotoxicity Based on a Dedicated Database of Electrocardiogram 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.
>
> —*Identifying CDER's Science and Research Needs Report*[3(p20)]

Over the past several decades, a diverse set of drugs has been shown to cause a change in the electrical activity of the heart that manifests as a prolongation of the QT interval on an electrocardiogram (ECG). QT prolongation is associated with a heart arrhythmia, torsade de pointes (hereafter, torsade), which can result in ventricular fibrillation, a sometimes fatal event. For new drugs, FDA and other regulatory agencies recommend a thorough QT study that clinically examines a drug's effects on the QT interval on an ECG. Although drug-induced QT prolongation is a sensitive marker of torsade risk, it is not a specific one—many drugs prolong the QT interval with little-to-no risk of this adverse event. The lack of specificity can result in drug developers prematurely abandoning compounds.

FDA Critical Path researchers are seeking to develop measures based on ECG data that are better predictors of risk for torsade and subsequent arrhythmias. The research proceeds in part from an understanding of the drugs' effects on the ion channels in the heart that directly mediate its electrical activity and indirectly mediate contractile activity. Drugs that cause torsade almost invariably inhibit a specific potassium channel (encoded by the hERG gene), and that inhibition results in

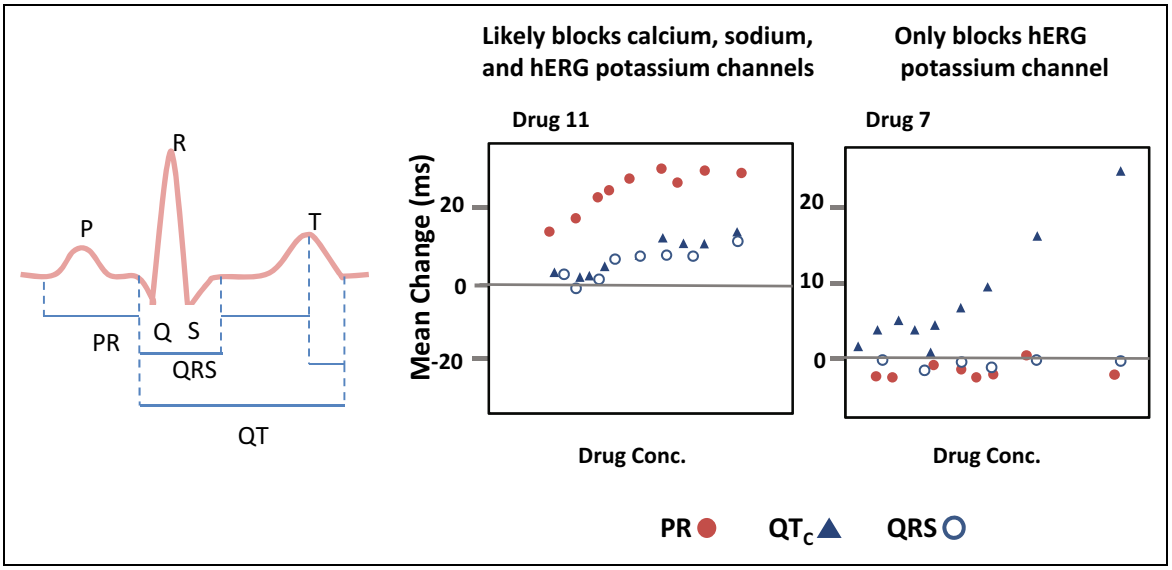


**Figure 3.** Drug-induced torsades de pointes is mediated by inhibition of the hERG potassium channel in the heart, but calcium channel and sodium channel blockage concurrent with hERG inhibition is believed to lower the risk. Critical Path researchers hypothesized that calcium channel block would prolong the PR interval on an electrocardiogram (ECG) and that sodium channel block would lengthen the QRS interval (these parameters are shown on the ECG trace at left). Of 6 drugs known to block calcium channel concurrently with potassium channels, all caused PR prolongation. Similarly, of 8 drugs known to also block sodium channels, 7 caused QRS prolongation. Concentration-dependent changes in ECG parameters are shown for 2 multichannel blockers (middle) and a drug that is selective for the hERG channel. Since many drugs that inhibit hERG prolong the QT interval regardless of whether they act on sodium or calcium channels, a drug signature consisting of the QT interval and the additional ECG parameters may more accurately predict the risk of torsades and prevent inappropriate termination of promising drugs. For full details see Johannesen et al.[10]

QT prolongation. But some drugs with this property also block specific sodium and calcium channels, and their inhibition reduces the risk of torsade. Critical Path researchers hypothesized that certain ECG parameters other than the QT interval would respond selectively to inhibition of these channels (Figure 3).[10] The researchers found that changes in these parameters corresponded closely to the drugs' inhibitory effects (Figure 3, bottom panel), raising the possibility that among drugs that prolong the QT interval, one could reliably distinguish between those that affect hERG exclusively and are torsadogenic and those that effectively stabilize heart contraction by simultaneous blockage of sodium and/or calcium channel. Results from their prospective randomized clinical trial also support the hypothesis that ECG measures of early and late repolarization can differentiate pure hERG potassium channel block associated with a high torsade risk from combined hERG potassium channel and inward current block (which may lower torsade risk).[11]

FDA's efforts to assess the cardiotoxic potential of drug candidates in this area have been strongly supported by modeling and simulation approaches. Critical Path researchers are performing extensive simulations using models of action potentials in the heart—and the "action potential to body surface" ECG model, by which action potentials can be translated to ECGs—to gain further insight into the relationship between a drug's effect on the heart and ECG parameters. With continued development of its vast collection of standardized data in its ECG Warehouse, FDA is uniquely positioned to advance research in this area.

## *Adjusting Dosing Recommendations for Renally Impaired Patients*

> We need a better understanding of the pharmacokinetic and pharmacodynamic behavior of drug products . . . in specific populations, particularly pregnant, pediatric, and geriatric patients, and patients with organ dysfunction.
>
> —*Identifying CDER's Science and Research Needs Report*[3(p24)]

Millions of patients with impaired renal function[12] require dose adjustments of systemic drugs according to the degree of their impairment. To guide clinicians, labels for approved drugs frequently contain recommendations for specific dosing according to how a patient's kidneys are functioning and other factors. Because measuring kidney filtration directly requires considerable time, resources, and technical expertise, it is more common to measure clearance of a naturally occurring endogenous substance creatinine (the clearance is determined by urine flow rate and the concentrations of creatinine in the collected urine sample) or estimate creatinine clearance or

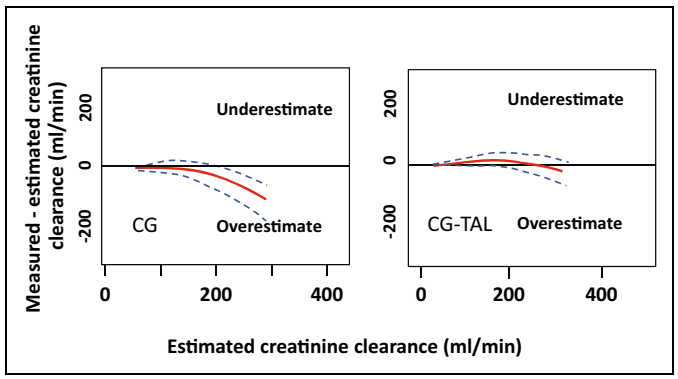


**Figure 4.** Like all formulas used to estimate kidney function, the Cockcroft-Gault (CG) formula was found to be imperfect. The fitted data—where data below the dotted line represent an overestimate of the measured filtration rate—show that for patients with higher creatinine clearance (this group would tend to include larger patients), CG tended to overestimate kidney function and therefore could lead to a higher-than-optimal drug dose. Using a more complex formula (CG-TAL; ie, Cockcroft-Gault with total, adjusted, and lean body weight) led to less bias and less difference across levels of estimated kidney function. Adapted from Park et al.[13] Reprinted with permission.

glomerular filtration with various formulas based on creatinine serum concentrations. Various formulas (eg, the Cockcroft-Gault equation, the Modification of Diet in Renal Disease equation) have been used to estimate kidney function based on creatinine clearance, and each incorporates information on age, sex, and, in some cases, patient size, albeit somewhat differently.

Given clinical data submitted to FDA, Critical Path investigators systematically investigated how well these formulas estimated kidney function when compared to direct measurements of creatinine clearance where urine was collected in the monitored setting of a clinical trial.[13] For a majority of patients, the various formulas led to the same dose recommendations. However, all formulas were inaccurate for certain categories of patients based on body mass and degree of kidney impairment, and the results indicated that modifications to the prediction formulas could lead to better prediction of the true filtration rate and, thus, improved dosing (Figure 4). For example, there was a significant improvement in accuracy and bias with the use of "lean body weight" rather than actual body weight in the Cockcroft-Gault formula for morbidly obese patients, and incorporating body surface area in the Modification of Diet in Renal Disease formula improved prediction for obese patients. The results also indicated that no simple adjustment (eg, use of an alternative descriptor of body size) of any equation was sufficient to improve estimation across all categories of patients. Despite the complexities of the results, the investigation constituted a key step forward in an ongoing attempt to understand and improve clinical estimation of kidney filtration for the purpose of determining optimal drug doses for patients with impaired renal function.

## Conclusion

The projects described here exemplify common characteristics of regulatory science research at CDER. In particular, each project addresses questions whose resolution is critical to regulatory decision making by FDA. The issues addressed are typically ones that are not tackled unilaterally by drug developers and others in the scientific community, either because they do not have the necessary incentives or the resources or because much of the data on which the research would depend are proprietary. For example, although a drug developer would have strong incentives to ensure that its product is manufactured in a way that consistently meets certain quality criteria, the company may not have the resources or incentives to study (or publicly disclose) how elements of manufacturing processes might affect an entire class of drugs (see description of the work by Agarabi et al[7] above). Or, in another scenario, a drug company may conduct research so that its product meets a current regulatory standard, but it may not engage in research that would ultimately promote safety and effective treatment for a broader class of patients (eg, by developing a better estimator of impaired kidney function, the goal of Park et al[13]), especially when such research would require access to proprietary clinical data. The differing perspectives and interests of regulators, drug developers, and those in the academic community can be accommodated through collaboration, and in the examples of research that we have presented here, FDA researchers, drug developers, and scientists in the academic community are leveraging expertise and resources to accelerate development and approval of drug products. For example, the identification of biomarkers based on ECG data (Johannesen et al[11]) was made possible by a partnership with the Duke Clinical Research Institute and Mortara instruments.

Integral to much regulatory science at CDER and at FDA as a whole is the development and availability of large structured data sets. For example, to further the development of predictive safety biomarkers, the ECG warehouse is a centralized repository of more than 6 million annotated, proprietary ECG recordings submitted to FDA, and the work of Kauffman et al[5,6] on portable Raman spectrometry for drug product inspection is based on a central master library of chemical spectra for comparison with spectra obtained on field inspections. Statistical and computational sciences are also a core component of FDA's research program, and modeling and simulation (eg, the work of Jiang et al[9] above) are increasingly used by regulatory scientists at CDER to conceptualize key relationships in complex systems and develop testable hypotheses (eg, relating to drug exposure and toxicity).

Finally, these research projects are examples of often sustained efforts, with FDA seeking to continually improve the certainty and consistency of regulatory decision making in a

variety of areas.[ii] With the increasing pace and complexity of drug development, the regulatory science challenges that FDA must address will continue to proliferate rapidly. In a time when funding for scientific research programs is somewhat constrained, it is critical that the challenges for regulatory science in the area of drug development and drug safety are widely understood in the broader scientific community and that resources that are brought to bear are leveraged through highly collaborative efforts.

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## Notes

i. The 7 topics from the CDER report are as follows: (1) improve access to postmarket data sources and their use in different types of analyses; (2) assessment and management strategies to reinforce the safe use of drugs; (3) evaluate the effectiveness and impact of different types of regulatory communications to the public and other stakeholders; (4) evaluate the links among product quality attributes, manufacturing processes, and product performance; (5) develop and improve predictive models of safety and efficacy in humans; (6) improve clinical trial design, analysis, and conduct; and (7) enhance individualization of patient treatment.

ii. A list of CDER Critical Path projects is available at http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/default.htm

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