Regulatory Statistics in FDA’s Center for Drug Evaluation and Research

Lisa M. LaVange, PhD
Office of Biostatistics
OTS, CDER, US FDA

Center for Drug Safety and Effectiveness
Seminar Series
Johns Hopkins Bloomberg SPH
October 28, 2013
Outline

- Introduction to the Office of Biostatistics
- Current office initiatives
- Selected topics
  - Meta-analysis
  - Biomarkers
  - Anti-bacterial trials
INTRODUCTION

Office of Biostatistics, Office of Translational Sciences, CDER, FDA
Where is the Office of Biostatistics?

US Food and Drug Administration (US FDA)

Center for Medical Products and Tobacco (CMPT)

Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Center for Tobacco Products (CTP)
Where is the Office of Biostatistics?

Center for Drug Evaluation and Research (CDER)

Office of Translational Sciences (OTS)

Office of Biostatistics (OB)
Office of Clinical Pharmacology (OCP)
Office of Computational Sciences (OCS)
Office of Biostatistics, Office of Translational Sciences, CDER, FDA

OFFICE INITIATIVES
Office of Biostatistics

• People:
  – 170 statisticians and support staff
  – Planned growth to ~190

• Metrics (2012):
  – ~250 statistical reviews (efficacy, safety, bioequivalence, TQT, abuse liability)
  – ~50 non-clinical reviews
  – ~120 consults
  – ~1,500 protocols/IND reviews
  – Participation in 40 of the 55 Advisory Committee meetings

• Special projects:
  – Guidance documents
  – Qualification of biomarkers and clinical outcome assessments
  – Regulatory research projects
Office of Biostatistics

• Vision statement:
  The Office of Biostatistics is recognized for excellence in the application and communication of statistical science in drug regulation and development. We play a central role in promoting innovative, science-based, quantitative decision-making throughout the drug development life-cycle.

• Mission statement:
  Provide CDER and other internal and external stakeholders with statistical leadership, expertise, and advice to foster the expeditious development of safe and effective drugs and therapeutic biologics for the American people. Protect the public health by applying statistical approaches for monitoring the effectiveness and safety of marketed drugs and therapeutic biologic products.
Office of Biostatistics

- Inherent in these statements is our responsibility to promote and provide strategic, quantitative thinking to medical product regulation
  - To keep unsafe or ineffective drugs from the market
  - To speed proven therapies to the market
- To accomplish these objectives, we apply problem-solving skills and state-of-the-art statistical methods in:
  - Advising sponsors about development programs and study designs
  - Reviewing clinical data submitted to the agency
  - Collaborating on regulatory decision-making with our many colleagues throughout the agency
Statistical reviews

• Key components of statistical reviews
  – Determine the accuracy of sponsor’s data and the validity of sponsor’s analyses
  – Assess the robustness of sponsor’s results, particularly when key analysis assumptions are difficult to verify
  – Evaluate results in light of evidentiary standards for confirming efficacy and safety
  – Assess risk and benefit in pre- and post-market reviews

• Consistent with the CDER Strategic Plan for 2013-2017 calling for smarter regulation by providing greater clarity and consistency,’ we
  – Strive for consistency in application of statistical methods across medical divisions while also factoring in therapeutic considerations
  – Strive for transparency and reproducibility of reviews
Office initiatives

- **Data standards and quality of submission files**
  - Facilitate statistical review work
  - Increasingly important to support integrated analyses across multiple products or sponsors (e.g., to determine non-inferiority margins or conduct safety meta-analyses)

- **21st century data management/handling**
  - Ability to monitor quality of ongoing trials and implement sophisticated methods of error and fraud detection are improved with electronic data capture and digital source documents

- **Reproducibility of analyses and program code sharing**
  - Collaboration on safety graphics through CTSPEDIA wiki: [https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome](https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome).
  - Participation in Computational Science Symposium annual meeting and collaborative working groups (informaticists in industry and academia)
Guidance documents

Issuance of CDER guidance documents is primary source of policy dissemination

Led by Office of Biostatistics:

- Non-Inferiority (Draft published in 2010; Final version forthcoming)
- Adaptive Designs (As above)
- Multiple Endpoints (Draft to be published soon)
- Carcinogenicity Studies (Draft published in 2000; final forthcoming)

Office of Biostatistics provided input to:

- Numerous disease-specific guidance documents
Office initiatives

• What about areas where guidance documents do not apply or do not yet exist?
  – Statistical Policy Council – re-established in 2012
    • Develop, establish, and recommend CDER statistical policies and procedures
    • Goal is to clarify statistical policies and to effectively disseminate, internally and externally

• Possible/probable future guidance documents
  – Meta-analysis (in progress)
  – Missing data (planned; working group active)
  – Subgroup analyses (potential; working group active)
  – Covariate adjustment (revival)
Office initiatives

- **Training and mentoring**
  - Core competencies (e.g., ICH E9) as well as new methodologies
  - Communication skills: written and verbal

- **Growth**
  - US Congress approved user fee authorization for drugs, generics, and biosimilars in 2012
  - Planned increase in manpower to support user fee initiatives
  - Challenges of recruiting statisticians in a competitive market, particularly with doctoral degrees
• 1970-1990 – steady growth of biostatistics at FDA
• Enactment of Prescription Drug Users Fee Act (PDUFA) in 1992 (re-authorizened every 5 years)
  – Pharmaceutical companies charged a fee for submissions
  – Funds enabled FDA to expand review teams (medical and statistical)
  – Shorter review times promised as a result—average review times for NDAs reduced from 2-5 years to less than 2 years
  – Accelerated reviews possible in special circumstances, with an average review time of 6 months
• 1990s to date
  – Growth continues with PDUFA II, III, IV, and now V
  – Statistical reviewers contribute significantly to PDUFA initiatives
Projects with significant Office of Biostatistics involvement:

- **Meta-Analysis**
  - Lead role

- **Biomarkers and Pharmacogenomics**
  - Co-Lead role

- **Patient Reported Outcomes (PROs)**
  - Co-Lead role

- **Benefit-Risk**
  - Supporting role
PDUFA V

Other programs that impact our work, through

- Increased communication with sponsor
- New review timelines
- New requirements for data submissions

• New molecular entity (NME) review program

• Rare diseases drug development

• Data standards

• Sentinel and drug safety
• Office of Biostatistics, Office of Translational Sciences, CDER, US FDA

META-ANALYSIS
Meta-Analysis

The Problem:

• Lack of consensus on best practices in conducting meta-analyses
• Lack of clarity on the evidentiary standards applied to published meta-analyses that call into question the safety of approved products
• Lack of resources needed to review and evaluate existing meta-analyses and/or conduct additional meta-analyses
Meta-Analysis

PDUFA V initiative:

- Build a dedicated review team to evaluate scientific methods, limitations in methods, and potential best practices
  - Add resources to strengthen existing team in Division of Biometrics VII
  - Recruitment delayed due to sequestration
- Convene public meeting on meta-analysis methods
  - To be held Nov. 25, 2013 on FDA-White Oak Campus
  - Federal Register Notice published Oct. 24, with link to concept paper
- Guidance document
  - Draft due in 2015
  - Final due in 2017
Guidance document

- Intended to address the particular requirements of meta-analyses conducted to inform a regulatory decision or action
- Not intended to review the extensive literature on meta-analyses or endorse any existing method for evaluating meta-analyses (e.g., Cochrane group)
- Focus on meta-analyses of randomized controlled clinical trials and not observational studies
- Focus on meta-analyses to address safety questions rather than efficacy
Guidance document, cont.

- Describes FDA’s role in:
  - Reacting to a published meta-analysis
  - Reviewing a submitted meta-analysis
  - Conducting a meta-analysis (using data submitted to FDA)

- Clarifies FDA’s concerns with respect to quality, potential sources of bias, multiplicity, etc.

- Provides FDA’s expectations in terms of pre-specification of hypotheses, appropriate documentation, etc.
Two recent examples (next slides):

1. A regulatory meta-analysis to evaluate risks for an entire class of drugs – antidepressants and suicidal events
2. A cumulative meta-analysis that involves an indirect comparison of two drugs – rosiglitazone and pioglitzaone
Suicidal Behavior and Ideation
Psychiatric Indications

<table>
<thead>
<tr>
<th>Age Class</th>
<th>OR (95% CI)</th>
<th>[Sample Sizes]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 24</td>
<td>2.22 (1.40, 3.60)</td>
<td>[61/2414 26/2073]</td>
</tr>
<tr>
<td>25 to 30</td>
<td>1.55 (0.91, 2.70)</td>
<td>[47/3810 21/2604]</td>
</tr>
<tr>
<td>31 to 64</td>
<td>1.00 (0.60, 1.69)</td>
<td>[41/5558 27/3772]</td>
</tr>
<tr>
<td>65 and Up</td>
<td>0.77 (0.60, 1.00)</td>
<td>[147/27086 124/18354]</td>
</tr>
<tr>
<td>Adult Overall</td>
<td>0.39 (0.18, 0.78)</td>
<td>[12/3227 24/2397]</td>
</tr>
</tbody>
</table>

* [Treat. Events/Treat. n  Plac. Events/Placebo n]
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of XXX or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. …
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND
Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS
We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer. From a clinical-trials database maintained by the manufacturer.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published Online First on June 7, 2007.
Rosiglitazone versus Pioglitazone Meta-Analysis

Results:
Placebo Controlled, All Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pioglitazone</th>
<th>Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>OR (95% CI) 0.56 (0.18, 1.67)</td>
<td>OR (95% CI) 1.53 (0.94, 2.54)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.80 (0.10, 6.14)</td>
<td>2.32 (0.78, 8.32)</td>
</tr>
<tr>
<td>MI</td>
<td>0.41 (0.09, 1.56)</td>
<td>2.23 (1.14, 4.64)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.64 (0.08, 99.71)</td>
<td>0.65 (0.27, 1.52)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.63 (0.12, 3.01)</td>
<td>1.89 (0.82, 4.73)</td>
</tr>
<tr>
<td>Serious M. Isch.</td>
<td>1.27 (0.52, 3.22)</td>
<td>2.05 (1.33, 3.22)</td>
</tr>
<tr>
<td>Total M. Isch.</td>
<td>1.02 (0.51, 2.06)</td>
<td>1.73 (1.28, 2.35)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.77 (0.62, 5.75)</td>
<td>2.20 (1.40, 3.52)</td>
</tr>
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</table>
Avandia RECORD Study Re-Analysis To Get FDA Committee Scrutiny

By Brenda Sandburg / Email the Author / Apr. 12, 2013
Word Count: 585 / Article # 14130412006 / Posted: April 12 2013 6:25 PM

Executive Summary

Two FDA panels will jointly review an independent “re-adjudication” of GlaxoSmithKline’s RECORD study of Avandia's cardiovascular risk; 12 of 33 panel members voted to withdraw the drug when they considered the RECORD data in 2010.

Three years after FDA requested an independent re-adjudication of GlaxoSmithKline PLC’s Avandia (rosiglitazone) RECORD study, the data will be presented to two FDA advisory panels.

The Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee will jointly discuss the “re-adjudication” of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial at a June 5-6 meeting.

The two advisory committees last reviewed the RECORD study and Avandia’s cardiovascular safety risks at a meeting in July 2010. At that time, 12 of 33 members voted for withdrawal of the drug ("Avandia Advisory Committee Re-Review Reflects Well On FDA” — "The Pink Sheet," Jul. 19, 2010).
Avandia AC

• Advisory Committee (AC) meeting (June, 2013) to review the re-adjudication of cardiovascular endpoints in a large, open-label outcome study of rosiglitazone versus active comparator

• AC concerned with:
  – Bias due to adverse event reporting in an open-label study
  – Apparent subgroup by treatment interactions when subgroup is defined post-randomization (e.g., increased insulin use)
  – Impact of missing data on events unable to be retrieved or adjudicated

• Statistical team addressed each issue during the course of the meeting
Avandia AC

• Meta-analysis of rosiglitazone presented at 2007 AC meeting
• Briefing package for the 2010 meeting included sensitivity analyses to assess impact of excluding trials with zero events from the meta-analysis
  – Stratified Mantel-Haenszel analysis of risk differences
  – Bayesian logistic regression model analysis
• Conclusion: results did not change
Meta-analysis

- Availability of and access to public datasets has increased the number of published meta-analyses
- Increased use of data submission standards has improved ability of regulators to conduct meta-analyses
- What statisticians bring to the table:
  - An understanding of the potential for bias to be introduced, e.g., from knowing study results when deciding what studies to include
  - An understanding of the importance of preserving randomization in a meta-analysis of clinical trials
  - An understanding of how to manage studies with zero events on one or more treatment arms
  - An understanding of how to interpret – or not – multiple p-values, as analyses proliferate
Methodological Challenges

• Bias and multiplicity
  – Assessing sources of bias and their impact, e.g., knowledge of study results prior to selecting studies for a meta-analysis
  – Multiplicity, e.g., concept of primary vs. secondary analyses; issue of early analysis results motivating additional analyses
  – Pre-specification in an RCT helps control sources of bias and multiplicity—what is the appropriate analogue for a meta-analysis?

• Random effects models for sparse events
• Time-to-event models for sparse events
• Network meta-analysis for non-inferiority margins and other situations
• Cumulative and sequential meta-analyses
BIOMARKERS
Biomarkers

The Problem:

• Pharmacogenomics and qualified biomarkers have the potential to decrease drug development time
• Qualified biomarkers can be used for clinical trial enrichment
• Regulatory submissions involving pharmacogenomics or biomarkers have increased recently
Biomarkers

PDUFA V initiative:

• Increase capacity for
  – Statistical reviews of submissions involving biomarkers or pharmacogenomics markers to guide therapeutic development and eventual labeling
  – Statistical reviews of biomarker qualification submissions

• Public meeting
  – To discuss strategies to facilitate scientific exchange
  – Planned for 2014
Biomarkers

- Draft guidance on qualification process for drug development tools (DDTs) issued October, 2010
- Draft guidance on clinical trial enrichment issued December, 2012
- FDA Statisticians review biomarkers via qualification submissions and sponsors’ applications
- Biomarker qualification submissions to date span many disease areas and marker types
- Initial statistical review includes evaluation of proposed context of use, analytical approach, and adequacy of data sources
- Need clarity on evidentiary standards for the different usage contexts
- Statistical reviews may dampen the excitement about a promising biomarker, but important to find the true signal amidst the noise
Example 1: CTNeoBC

• Collaborative project in neo-adjuvant breast cancer

• Objective: To evaluate the relationship between pCR* and long-term clinical benefit (EFS* and OS*) in neoadjuvant trials

*pCR: Pathologic Complete Response
EFS: Event-Free Survival
OS: Overall Survival
Example 1: CTNeoBC

- 12 neoadjuvant randomized controlled trials from
  - GBG/AGO (Germany)
  - NSABP (US)
  - EORTC/BIG (EU)
  - ITA (Italy)
- Total number of patients included: 12993
Biomarkers

Example 1: CTNeoBC

- Public meeting held March 2013 to discuss results
- Statistical analysis provided insight into strengths and limitations of pCR as an early endpoint
  - Evidence of prognostic biomarker – patients with pCR had better clinical outcomes, e.g., event free survival
  - Lack of evidence that treatment effects with respect to pCR predict benefit in clinical outcomes
- Implications for designing adaptive design trials using pCR as early endpoint
Biomarkers

• **pCR**
  - Absence of invasive cancer in the breast and axillary nodes with DCIS allowed

• **EFS (Event-Free Survival)**
  - Time from randomization to occurrence of one of the following events (whichever occurs first)
  - Loco/Regional recurrence (after neoadjuvant therapy)
  - Distant recurrence
  - Death

• **OS (Overall Survival)**
  - Time from randomization to death due to any cause
pCR vs EFS and OS (Responder Analysis)

Event-free Survival

- HR = 0.48 (95% CI: 0.43, 0.53)
- pCR (n = 2131) vs no pCR (n = 9824)

Overall Survival

- HR = 0.36 (95% CI: 0.31, 0.42)
- pCR (n = 2131) vs no pCR (n = 9824)
Meta Analysis Results (Trial Level)

\[ R^2 = 0.01 \]

\[ R^2 = 0.18 \]
Example 2 -- Biomarkers for pulmonary arterial hypertension (PAH)

• Need better endpoint than 6-min walk test, esp. in pediatric populations

• Change in pulmonary vascular resistance index (PVRI) looked promising
  – Used for diagnosis
  – Measure of physiological target of many PAH therapies
  – Initial pharmaco-metric analysis (trial-level correlation and regression analyses) showed positive relationship
Is pulmonary vascular resistance index predictive of exercise tolerance in adult patients with idiopathic pulmonary arterial hypertension

John P. Lawrence *, Jim Hung, Sue Jane Wang

U.S. Food and Drug Administration, Silver Spring, MD 20993–002, USA

ABSTRACT

Background: Clinical trials for adults with pulmonary arterial hypertension use exercise capacity, as measured by walking distance, as the primary endpoint to measure symptomatic improvement. In this article, we look at the relationship between walking distance and a hemodynamic variable, pulmonary vascular resistance index (PVRI), from the available trials.

Methods: Patient-level data from 16 randomized controlled clinical trials were obtained. All idiopathic subjects with a baseline and study endpoint measurement of both hemodynamic and exercise endpoints were included. Changes from baseline in both endpoints and the relationship between the endpoints were summarized. Receiver operating characteristic curves were used to investigate the predictive ability. Measures of surrogacy were also calculated.

Results: There is a weak correlation between changes in PVRI and exercise capacity. Receiver operating characteristic analysis shows a high false positive rate of using one variable to predict the other. Measures of surrogacy show the proportion of variability in exercise capacity explained by PVRI is approximately 5%.

Conclusions: PVRI should not be used as a surrogate marker to predict changes in exercise capacity.
More rigorous analysis raised doubts about the usefulness of ΔPVRI as a surrogate endpoint

- Based on 16 studies in adults
- Correlation analyses took into account randomized comparisons within study as well as study to study heterogeneity
  - Observed a small, almost negligible patient-level correlation
- ROC analyses of ΔPVRI as predictor of 6-min walk test were not positive, nor were Freedman’s test or surrogacy
- Concluded that ΔPVRI may not be a useful clinical endpoint in PAH trials
ANTI-BACTERIALS: STUDY DESIGN AND ANALYSIS
These staph bacteria are resistant to vancomycin, an antibiotic that is one of the last lines of defense.
Every day in hospitals all over America, thousands of patients die of infections that used to be curable. But the antibiotics used to treat them aren't working anymore.

It's called drug resistance, and it's largely a consequence of antibiotics overuse. The more germs are exposed to antibiotics, the faster they mutate to evade being vanquished.

To counter the growing trend, the Obama administration is moving on many fronts to speed the development of new antibiotics.

It's investing tens of millions in private drug companies to foster new germ-killing drugs. It's setting up a new research network to develop new antibiotics. And, most controversially, federal health officials are pushing to loosen up the approval process for new antibiotics targeted at patients with life-threatening infections and dwindling treatment options.

"Where we're talking about life-threatening illnesses, you can do much less study and get those drugs out there — if in fact they'll be limited to those kinds of uses," Dr. Janet Woodcock, the chief drug official at the Food and Drug Administration, tells Shots.

**Pipeline Drying Up**

Woodcock says the basic problem is that many large drug companies have abandoned antibiotics research and development in recent years for more profitable lines of business, such as drugs for diabetes, cancer and obesity.
Pressure Grows to Create Drugs for ‘Superbugs’

By BARRY MEIER

Government officials, drug companies and medical experts, faced with outbreaks of antibiotic-resistant “superbugs,” are pushing to speed up the approval of new antibiotics, a move that is raising safety concerns among some critics.

The need for new antibiotics is so urgent, supporters of an overhaul say, that lengthy studies involving hundreds or thousands of patients should be waived in favor of directly testing such drugs in very sick patients. Influential lawmakers have said they are prepared to support legislation that allows for faster testing.

The Health and Human Services Department last month announced an agreement under which it will pay $40 million to a major drug maker, GlaxoSmithKline, to help it develop medications to combat antibiotic resistance and biological agents that terrorists might use. Under the plan, the federal government could give the drug company as much as $200 million over the next five years.

“We are facing a huge crisis worldwide not having an antibiotics pipeline,” said Dr. Janet Woodcock, director of the Center for Drug Evaluation and Research at the Food and Drug Administration. “It is bad now, and the infectious disease docs are frantic. But what is worse is the thought of where we will be five to 10 years from now.”

Annually, tens of thousands of Americans die from infections, largely acquired in hospitals, that are resistant to antibiotics, experts say.
III. Comments
The draft guidance is being distributed for comment purposes only and is not intended for implementation at this time. Interested persons may submit written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m. Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

IV. Electronic Access
Persons with access to the Internet may obtain the draft guidance at either http://www.fda.gov/ohrms/dockets/cdrh/092203index.htm or http://www.regulations.gov.

Date: May 22, 2013
Leslie K. Kun,
Assistant Commissioner for Policy

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
[Docket No. FDA-2013-N-0056]

New Approaches to Antimicrobial Drug Development: Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER) is seeking input from the public on the following topics related to antibacterial drug development: Potential new study designs, proposed priorities for CDER guidance, and strategies intended to slow the rate of emerging resistance to antibacterial drugs. The purpose of this notice is to request information and comments from the public on these areas of focus.

Dated: Submit either electronic or written comments by July 30, 2013 at 5 p.m. EST.
ADDRESSES: Submit electronic comments to http://www.regulations.gov.

III. Comments
The draft guidance is being distributed for comment purposes only and is not intended for implementation at this time. Interested persons may submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5620 Fishers Lane, rm. 10-25, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:
Jesse Santiago, Center for Drug Evaluation and Research, Food and Drug Administration, 10900 New Hampshire Ave., Silver Spring, MD 20993-0002; 201-708-5246; FAX: 201-708-5299; email: jesse.santiago@fda.hhs.gov.

1. Background
Antibacterial drug development is critical to the public health and is an FDA priority. We recognize the increasing concern that antibacterial drug development has not kept pace with the increasing threat of drug-resistant and untreatable infections. To address this concern, we are seeking to explore new clinical development paradigms for antibacterial drugs. Areas of ongoing need are numerous and include new drugs for treatment of hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, complicated urinary tract infection, complicated intra-abdominal infection, and infections caused by drug-resistant organisms.

On September 14, 2012, the FDA announced the formation of the CDER Antimicrobial Drug Development Task Force, which supports new antibacterial drug development. The task force is a multidisciplinary group of CDER scientists and clinicians seeking to identify priority areas and develop and implement policies to solutions to the challenges of antibacterial drug development. This includes the use of existing partnerships and collaborations to work with other experts in the field, including academia, industry, professional societies, patient advocacy groups, and Government Agencies. Specifically, the task force seeks to:
   - Explore novel scientific approaches to facilitate antibacterial drug development (e.g., broader use of clinical pharmacology data, new statistical methods, innovative clinical trial designs, use of additional available data sources, and advancement of alternative measures to evaluate clinical effectiveness of potential new therapies);
   - Identify issues related to unmet medical need for antibacterial drugs, including the reasons for the lack of a robust pipeline for antibacterial drug development;
   - Identify new approaches for weighing risks, benefits, and uncertainties of potential new antibacterial drugs addressing unmet need;
   - Evaluate existing FDA guidelines related to antibacterial drug development to determine if review or elaboration is needed; and Identify areas where future guidance would be helpful.

II. Potential New Study Design Approaches
The task force explores novel scientific approaches to facilitate antibacterial drug development and is seeking input from the public on study design approaches with potential utility for future antibacterial drug development. Possible elements being considered include:
   - Bayesian approaches;
   - Adapting approaches;
   - Use of novel point of care diagnostics to avoid use of confounding therapies;
   - Evaluating safety and efficacy by enrolling patients in trials with infections at any one of a number of different body sites;
   - Large simple trials; and
   - Accelerated approval using either a surrogate endpoint reasonably likely to predict clinical benefit or a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit.

To advance the development of antibacterial drugs, we seek input on the listed examples as well as additional ideas regarding the design, conduct, and analysis of clinical trials.

III. Guidance Development
The task force focuses on developing guidance to address issues related to development of new antibacterial drugs.

Initial guidance efforts focused on community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, and antibacterial drugs for patients with limited or no alternative therapies (including development of drugs that have a limited spectrum of activity). As the task force works to prioritize areas of future draft and final guidance development, we seek input from the public on the following areas of priority as well as any additional areas for potential future guidance development.
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
[Docket No. FDA–2013–N–0556]

New Approaches to Antibacterial Drug Development; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER) is seeking input from the public on the following topics related to antibacterial drug development: Potential new study designs, proposed priorities for CDER guidances, and strategies intended to slow the rate of emerging resistance to antibacterial drugs. The purpose of this notice is to request information and comments from the public on these areas of focus.

DATES: Submit either electronic or written comments by July 30, 2013 at 5 p.m. EST.

ADDRESSES: Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets
Antibiotic Resistance Gets Attention Of FDA, Congress

By Sarah Karlin / Email the Author / Jun. 6, 2013
Word Count: 1272 / Article # 14130606005 / Posted: June 6 2013 11:00 PM

Executive Summary

Both FDA and Congress are taking interest in combating antibiotic resistance, but FDA likely has more power to make headway in the near term, even as industry remains somewhat wary of that particular agenda item.

FDA is seeking stakeholder feedback on how to slow the rate of antibiotic resistance and get more life out of antibacterial drugs, as well as input on new antibiotic clinical trial designs and proposed priority areas for guidance to facilitate antibiotic development.

The agency’s May 31 Federal Register notice requests comments on these three topics be submitted by July 30. The information will be used by the Center for Drug Evaluation and Research’s newly formed Antibacterial Drug Development Task Force which is helping find answers to antibiotic drug development issues and implement guidance and other regulations related to the Generation Antibiotic Incentives Now portion of the FDA Safety and Innovation Act ("FDA Antibiotic Task Force Developing Standards To Help Products GAIN Traction" — "The Pink Sheet" DAILY, Sep. 24, 2012).

“We recognize the mounting concern that antibacterial drug development has not kept pace with the increasing threat of drug-resistant and untreatable infections,” the notice says.
Anti-bacterials

• In spite of recent advances in clinical trial designs (e.g., adaptive designs) as well as advances in understanding the science of acute bacterial infections, the pipeline for new antibiotics is not keeping up with medical need

• FDA is undertaking a number of initiatives to promote anti-bacterial drug development

• One such initiative involves an external collaboration of statisticians, with kick-off meeting held in August, 2012

• Provided an opportunity for leading experts in clinical trial methodologies to discuss alternative approaches to design and analysis that may prove useful for anti-bacterial programs
CTTI Statistics Think Tank

- Clinical Trials Transformational Initiative (CTTI) convened the Statistics Think Tank for Anti-Bacterial Drug Development on August 20, 2012 in Bethesda

- Objective: *To discuss innovative approaches to the design and analysis of clinical trials in anti-bacterial drug development.*

- Participants included
  - 4 academic statisticians
  - 4 statisticians from industry
  - 4 statisticians from (non-CDER) govt agencies

- Expertise spanned clinical trials, Bayesian methods, non-inferiority trial designs, meta-analysis, missing data
CTTI Statistics Think Tank

Partial list of topics discussed:

• One-study paradigm
• Possible uses of Bayesian methods
• Trial designs for resistant pathogens
• MIC-based methods
One-Study Paradigm

• Design issues
  – Size of study, power, and representation of subgroups
  – Representativeness of study population – more sites with fewer patients per site may be more attractive

• Analysis and results:
  – Level of evidence
    • Move beyond p-values and consider totality of evidence in the form of the posterior distribution of the treatment effect
  – Consistency across subgroups
One-Study Paradigm

- Single study with p-value < 0.05
  - Chance of replication is 50:50 ➔ supportive evidence needed
- Medical device analogue: Mechanism of action plus one confirmatory trial sufficient for submission
- Pharmacologic or pre-clinical data
  - In vitro ‘kill’ studies
  - Exposure response data from animal models
- Exposure response in humans from phase 2 studies
- Differentiate between NMEs and drugs approved for other indications
Bayesian methods

• Potential for application of Bayesian methods in 3 areas:
  – Bayesian approach to meta-analyses of historical data to generate a non-inferiority margin using Dirichlet processes (Tiwari, et al., 2011)
  – Bayesian analysis of non-inferiority trials that can incorporate historical data on active control products and mechanistic data arising from PK/PD and other pre-clinical studies as prior distributions (Gamalo, et al., 2013)
  – Bayesian hierarchical modeling to evaluate efficacy of product targeting single pathogen across multiple infection (body) sites

• Issues requiring attention include exchangeability assumptions about past studies

• Research ongoing at FDA
Resistant pathogens

- Area where medical need is felt most urgently
- Also area where more short-cuts are being considered
- Important to hold onto the science as much as possible while still encouraging new drug development
- Example: consider alternative to single-arm studies
  - Design includes an active control arm with highly imbalanced randomization (e.g., 4:1 or 5:1)
  - Leverage historical control data via frequentist or Bayesian methods to increase power
- Example: nested superiority trial for patients with resistant pathogens nested within a non-inferiority trial (Huque, et al.)
Summary

• Statisticians have an important role to play in regulatory decision-making
  – We bring an ability to problem-solve and a level of rigor that is a hallmark of our discipline
  – All in all—we are a ‘value-added’ group!

• The Office of Biostatistics is a rich resource of statistical expertise and regulatory experience
  – We are well-poised to meet current and future challenges in drug evaluation and research
References

- Meeting materials for the June 5-6, 2013 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM). http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm331504.htm


• Huque MF, Valappil T, Soon G. Nested trial design for demonstrating treatment efficacy of new antibacterial drugs. Submitted for publication, 2013.