

*The National Institute of Allergy and Infectious Diseases,
The Clinical Center Office of Clinical Research Training and Medical Education
and the Food and Drug Administration*



Present...

**A Day with the FDA:
CDER and NIAID Working Together**

Friday, July 27, 2007 ★ 8:30am – 4:30pm
NIH, Building 10, Lipsett Amphitheatre

Schedule of Events:

- 8:30 Opening Remarks**
Jorge Tavel, MD Deputy Director, Division of Clinical Research, NIAID
Juan Lertora, MD, PhD Director, Clinical Pharmacology Program,
Office of Clinical Research Training and Medical Education, CC
Douglas Throckmorton, MD Deputy Center Director, Center for Drug Evaluation and
Research (CDER), Food and Drug Administration (FDA)
- 8:50 How the wheels of CDER turn: Structure and Function**
Doug Throckmorton, MD Deputy Center Director, CDER
- 9:20 Safety and Toxicology Studies**
David Jacobson-Kram, PhD, DABT Associate Director for Pharmacology and Toxicology, CDER
- 10:00 Break**
- 10:20 Emergency Preparedness, Medical Countermeasures, and the Role of
The Animal Rule**
Brad Leissa, MD Deputy Director/ CDER Emergency Coordinator,
Office of Counter-Terrorism & Emergency Coordination (OCTEC)
- 11:00 The IND Process: A Regulatory Perspective**
Dave Roeder, MS Associate Director for Regulatory Affairs,
Office of Antimicrobial Products, CDER
- 11:45 Questions/Answers**
- 12:00 Lunch (participants eat lunch on their own)**
- 1:00 Clinical Trial Design and Statistical Issues**
Bob O'Neill, PhD Director, Office of Biostatistics,
Office of Translational Sciences, CDER
- 1:40 Clinical Drug Review Process/Issues**
Badrul Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER
- 2:20 Break**
- 2:40 DSI's Role in Bioresearch Monitoring/FDA Expectations of Clinical Investigators**
Tejashri Purohit-Sheth, MD Medical Officer, Division of Scientific Investigations,
Office of Compliance, CDER
- 3:30 Pharmaceutical Quality Assessment**
Moheb Nasr, PhD Director, Office of New Drug Quality, CDER
- 4:10 Closing Remarks: Contacts and Answers to your questions**
Shirley Murphy, M.D. Director, Office of Translational Sciences, CDER

SPEAKER BIOGRAPHIES

Badrul Chowdhury, MD, PhD, Director, Division of Pulmonary and Allergy Products, CDER

Dr. Badrul A. Chowdhury is the Director, Division of Pulmonary and Allergy Products, Center for Drug Evaluation and Research, US Food and Drug Administration. Dr. Chowdhury is trained and board certified in Internal Medicine, and in Allergy and Immunology, and also has a PhD in Immunology from the Memorial University of Newfoundland, St. John's, Canada. He completed Residency training in Internal Medicine from Wayne State University School of Medicine, Detroit, Michigan in June 1991, and Fellowship training in Allergy and Immunology from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland in June 1995. From July 1995 to July 1997 Dr. Chowdhury was an Assistant Professor of Medicine at the University of Tennessee College of Medicine, Memphis, Tennessee. Dr. Chowdhury joined the FDA in August 1997. Dr. Chowdhury has published many original articles, reviews, and book chapters.

David Jacobson-Kram, PhD, DABT, Associate Director for Pharmacology and Toxicology, CDER

David Jacobson-Kram received his Ph.D. in embryology from the University of Connecticut in 1976. Between 1976 and 1979, Dr. Jacobson-Kram served as a staff fellow and then a senior staff fellow at the National Institute on Aging. After leaving N.I.H., Dr. Jacobson-Kram joined the faculty of George Washington University School of Medicine (1979 - 1984) and Johns Hopkins University Oncology Center (1984 - 1990). During this same period he served, on a part-time basis, as a geneticist in the Office of Toxic Substances at the Environmental Protection Agency and as Acting Branch Chief in EPA's Office of Research and Development.

Dr. Jacobson-Kram joined Microbiological Associates in 1988 as director of the Genetic Toxicology Division. In 1997 the company changed its name to BioReliance and his responsibilities were expanded to include oversight of the Mammalian Toxicology Program and the Laboratory Animal Health Program. Dr. Jacobson-Kram served as the VP of the Toxicology and Laboratory Animal Health Division until April, 2003. Currently, he serves as the Associate Director of Pharmacology and Toxicology in FDA's Office of New Drugs. Over the past twenty five years he has served as principal and co-principal investigator on several N.I.H. grants and government contracts. Since 1976 Dr. Jacobson-Kram has published, 58 original articles in peer reviewed journals, and 42 review articles or book chapters. The majority of these publications deal with methods and issues in genetic and molecular toxicology.

Dr. Jacobson-Kram has served as council member, treasurer and chairman of the Genetic Toxicology Association, executive council member to the Environmental Mutagen Society, Editor of Cell Biology and Toxicology, President of National Capital Area Chapter of the SOT and as a member of N.I.H. special study sections. In 1996 he became a Diplomate of the American Board of Toxicology (DABT).

Brad Leissa, MD, Deputy Director/ CDER Emergency Coordinator, Office of Counter-Terrorism & Emergency Coordination (OCTEC)

Brad Leissa received his medical degree from The Ohio State University. He received postgraduate training in internal medicine and pediatrics at The Ohio State University Hospitals. He went on to receive subspecialty training in pediatric infectious diseases from George Washington University and the Children's National Medical Center in Washington, DC. He began his career at FDA back in 1989 as a medical officer with a focus on anti-infective drug development in the Center for Drug Evaluation and Research (CDER). During the October 2001 anthrax attacks, Dr. Leissa was temporarily assigned to the Secretary's Bioterrorism Command Center at the Department of Health and Human Services. Since then he has continued to work on medical countermeasure development at FDA. He currently holds the position of Deputy Director in CDER's Office of Counter-Terrorism and Emergency Coordination (OCTEC).

Shirley Murphy, MD, Director, Office of Translational Sciences, CDER

Shirley Murphy, M.D. is currently the Director of the Office Translational Sciences in the Center for Drug Evaluation and Research at the Food and Drug Administration. Dr. Murphy joined the FDA in 2002 to start the new Division of Pediatric Drug Development and then moved to be Deputy Director of the Office of Counter-Terrorism and Pediatric Drug Development. Dr. Murphy is a board certified Pediatrician, Pediatric Pulmonologist, and Allergist/Immunologist who has had a career-long research interest in medications for children, particularly those with asthma.

From 1998-2002 Dr. Murphy was a vice-president of the pharmaceutical company, GlaxoSmithKline. Dr. Murphy also served on the faculty of the University of New Mexico School of Medicine and College of Pharmacy for 20 years, holding the positions of Director of the Division of Pulmonary Medicine and Chair of the Department of Pediatrics. Dr. Murphy has published numerous scientific articles, reviews, book chapters and books on asthma with a specific emphasis on medications for acute and chronic asthma.

Dr. Murphy served on the National Heart, Lung and Blood Institute's Asthma Expert Panel I and Chaired the Expert Panel 11, which produced the National Guidelines for the Diagnosis and Management of Asthma. In addition, she served as Chair of the First National Conference on Asthma sponsored by the National heart, Lung and Blood Institute and also chaired the FDA's Pulmonary and Allergy Advisory Committee.

Moheb Nasr, PhD, Director, Office of New Drug Quality, CDER

Dr. Moheb Nasr is the Director of the Office of New Drug Quality Assessment (ONDQA), Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA). ONDQA is responsible for quality assessments (pre and post marketing) of new drugs regulated by CDER. Dr. Nasr obtained his Ph.D. degree in Chemistry at the University of Minnesota in Minneapolis. Dr. Nasr holds a B.S. degree in Pharmacy and a Master's degree in Pharmaceutical Analysis, both from Cairo University, Egypt. After a distinguished academic career, Dr. Nasr joined the FDA in 1990, and assumed his current position in June, 2003. Dr. Nasr is leading the restructuring of the pharmaceutical quality assessment program at the FDA. Several new concepts, initiatives, and programs were developed under his leadership; including the establishment of the new Pharmaceutical Quality Assessment System (POAS), CMC Pilot Program, CMC Regulatory Agreement, and many others. Dr. Nasr serves as the FDA lead at the International Conference on Harmonization (ICH) Q8 Expert Working Group. Dr. Nasr is a member of FDA's Council on Pharmaceutical Quality.

Bob O'Neill, PhD, Director, Office of Biostatistics, Office of Translational Sciences, CDER

Dr. O'Neill is the Director of the Office of Biostatistics (OB) in Office of Translational Sciences in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration. His Office provides biostatistical and scientific computational leadership and support to all programs of CDER. Prior to October, 1998 he was Director of the Office of Epidemiology and Biostatistics responsible also for the post-market safety surveillance of new drugs. He began his FDA career in the Division of Biometrics in 1971 as a statistical reviewer of New Drug Applications in the former Bureau of Drugs. He has held successively more responsible positions in the Division of Biometrics, including Group Leader, Branch Chief, Deputy Director, and Director, a position he held for ten years before assuming his role as Office Director.

Dr. O'Neill holds an A.B. degree in mathematics from the College of the Holy Cross, and a Ph.D. in mathematical statistics and biometry from Catholic University of America and In 1989-1990, Dr. O'Neill was a visiting professor at the Department of Research, University Medical School, Basel, Switzerland where he developed and presented numerous lectures and created a course series "Topics in Therapy Evaluation and Review (TITER)" for European pharmaceutical scientists, which was the model for the European Course In Pharmaceutical Medicine (ECPM), a degree granting graduate program. He is a fellow of the American Statistical Association (1985), a member of several professional societies, a past Member of the Board of Directors of the Society for Clinical Trials, the 2002 recipient of the Marvin Zelen Leadership Award in Statistical Science and the 2004 Lowell Reed Lecture Awardee from the American Public Health Association. He has received numerous FDA and HHS awards, including the Secretary's Distinguished Service Award (1997) for developing regulations to protect the nation's children from cigarette smoking. He has published many articles and book chapters.

Dr. O'Neill was the FDA topic leader on two ICH guidance documents, E5 "Ethnic Factors in the Acceptance of Foreign Clinical Data" and E9 "Statistical Principles in Clinical Trials".

Tejashri Purohit-Sheth, MD, Medical Officer, Division of Scientific Investigations, Office of Compliance, CDER

Dr. Tejashri Purohit-Sheth currently works as a medical officer at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Scientific Investigations. She previously worked in the Division of Pulmonary and Allergy Products, where she used her medical training in Allergy/Immunology in the evaluation of the safety and efficacy of drugs for US approval.

She started her active duty service in the United States Navy. She was a Health Professions Scholarship Program recipient, whereby medical school training was paid by the US Navy. She completed her Internal Medicine Training at Portsmouth Naval Hospital, followed by her fellowship in Allergy/Immunology at Walter Reed Army Medical Center. After completion of her training, she went to become Service Chief of the Allergy/Immunology Service at National Naval Medical Center.

At the end of her obligated Navy service, she transferred her commission to the Public Health Service.

Dave Roeder, MS, Associate Director for Regulatory Affairs, Office of Antimicrobial Products, CDER

Mr. Roeder received a B.S. degree in biology at Kansas State University, followed by a M.S. in plant pathology at the University of Maryland. He worked at Meloy Laboratories in Springfield, VA and at the American Red Cross Holland Laboratories for several years prior to joining the FDA in 1990. While at the FDA, he served for ten years as a Regulatory Project Manager in the Division of Cardio-Renal Drug Products, where he managed INDs and NDAs for the calcium channel blockers. For the past seven years, he has served as the Associate Director for Regulatory Affairs in the Office of Antimicrobial Products (formerly Office of Drug Evaluation IV).

Doug Throckmorton, MD, Deputy Center Director, CDER Dr. Douglas Throckmorton is the Deputy Director in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA). In this role, he shares responsibility for overseeing the regulation of research, development, manufacture and marketing of prescription, over-the-counter and generic drugs in the US. From aspirin to cancer treatments, CDER works to ensure that the benefits of approved drug products outweigh their known risks.

Dr. Throckmorton was founding chair of CDER's Drug Safety Oversight Board and served until recently as the CDER liaison to the FDA human subjects research review board. He currently serves on the newly-constituted FDA Bioinformatics Board, and is the chair of CDER's Research Coordinating Committee, the group that helps to manage and forward the scientific mission of CDER.

Dr. Throckmorton began his career at the FDA in the Division of Cardio-Renal Drug Products in 1997, first as a medical reviewer, then as Deputy Division Director and from 2002-05, as Division Director.

Dr. Throckmorton is Board-certified in Internal Medicine and Nephrology, having received his training at the University of Nebraska Medical School, Case Western Reserve University and Yale University. Prior to coming to the FDA, he practiced medicine at the Medical College of Georgia in Augusta, Georgia.

NOTES PAGE- Opening Remarks

Jorge Tavel, MD

Juan Lertora, MD, PhD

Douglas Throckmorton, MD

Deputy Director, Division of Clinical Research, NIAID

Director, Clinical Pharmacology Program,

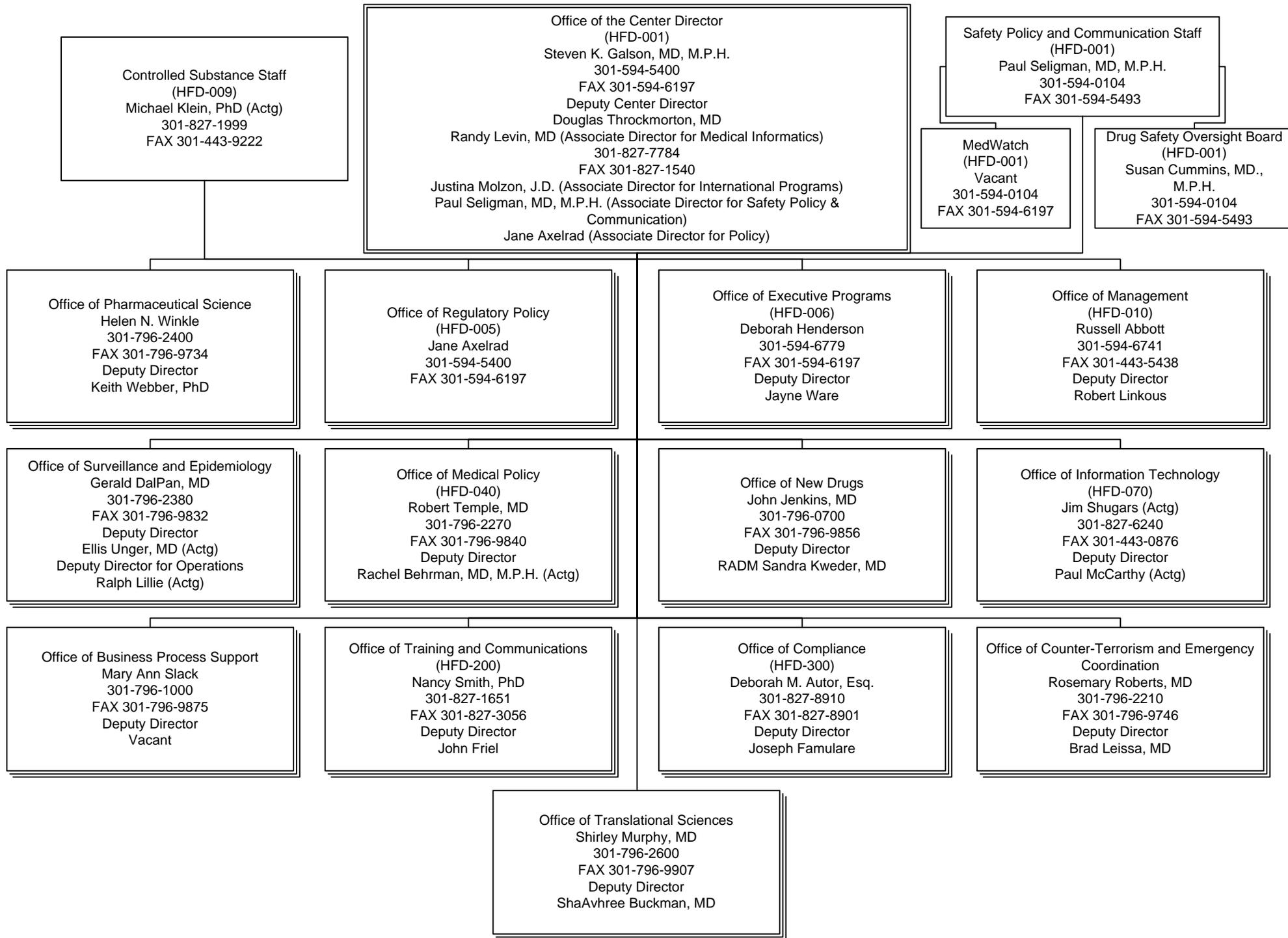
Office of Clinical Research Training and Medical Education, CC

Deputy Center Director, Center for Drug Evaluation and
Research (CDER), Food and Drug Administration (FDA)

NOTES PAGE- How the wheels of CDER turn: Structure and Function
Doug Throckmorton, MD
Deputy Center Director, CDER

CENTER FOR DRUG EVALUATION AND RESEARCH

Friday, July 06, 2007



The Wheels of CDER





Center for Drug Evaluation and Research (CDER)

Protecting and Advancing the Public Health

Douglas C. Throckmorton, MD
Deputy Director, CDER, FDA



July 2007

FDA Human Drug Program



Office of the Commissioner



Center for Food Safety & Applied Nutrition



Center for Drug Evaluation & Research



Center for Biologics Evaluation & Research



Center for Devices & Radiological Health



Center for Veterinary Medicine



Office of Regulatory Affairs



National Center for Toxicological Research

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FDA's Mission is to ensure that...

- Foods are safe, wholesome, and properly labeled
- **Human drugs and vaccines are safe and effective**
- Blood used for transfusions and blood products are safe & in adequate supply
- Medical devices are safe & effective
- Transplanted tissues are safe & effective
- Animal drugs and medicated feeds are safe & effective, and food from treated animals is safe for human consumption
- Radiation-emitting electronic products are safe
- Cosmetics are safe & properly labeled

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FDA CDER

- **Mission**
 - Ensure Americans have access to safe and effective drug products
- **Center Director**
 - RADM Steven Galson, MD, MPH

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FDA CDER Role in US Healthcare

FDA evaluates benefits/risks for the population

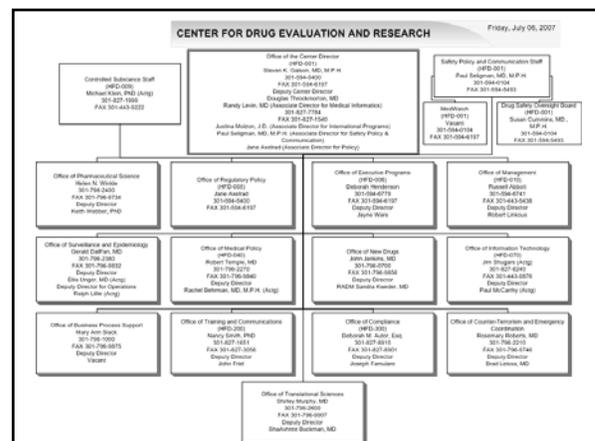
Provider evaluates benefits/risks for a patient

Patient evaluates benefits/risks in terms of personal values





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FDA Under CDER purview

- **Medicines**
 - Prescription drugs
 - Innovator – “Brand name” – drugs
 - Generic drugs
 - Over-the-Counter drugs
- **Other products that include “drugs”**
 - e.g., fluoride toothpastes, antiperspirants, dandruff shampoos, sunscreens
- **Shared responsibility for combination products that contain drugs**
 - e.g., drug coated devices

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FDA CDER Mission Critical Business Processes

- **Pre-Market Product Review** (Pre-approval processes)
 - Improve Public Health By Access And Availability Of New Products
- **Post-Market Drug Surveillance** (Product Surveillance; Consumer/Patient Safety)
 - Maximize Benefit/ Minimize Harm From Marketed Products
- **Product Safety & Compliance** (Compliance/Enforcement)
 - Minimize Harm due to Low-Quality Products

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FDA Pre-Market Product Review

New Drug Review

- **Investigational New Drug (IND) Review**
 - Process by which a sponsor (company) advances to the next stage of drug development known as clinical trials
 - Animal Pharmacology and Toxicology Studies
 - Manufacturing Information
 - Clinical Protocols and Investigator Information
- **New Drug Application (NDA)**
 - Formal application to the FDA for approval of a new drug
- **Biological License Application (BLA)**
 - Transfer of applications from CBER in FY 2002 for medicines such as:
 - Monoclonal antibodies, cytokines, growth factors, enzymes, other therapeutic immunotherapies

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FDA Pre-Approval Process

- Review Staff need to consider:
 - Chemistry, Manufacturing, and Control;
 - Samples, Methods Validation Package, and Labeling;
 - Nonclinical Pharmacology and Toxicology;
 - Human Pharmacokinetics and Bioavailability;
 - Microbiology (for anti-microbial drugs only);
 - Clinical Data – Safety and Efficacy;
 - Safety Update Report (typically submitted 120 days after the NDA's submission);
 - Statistical;
 - Case Report Forms and Tabulations;
 - Patent Information; and
 - Patent Certification

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FDA CDER Review Productivity

Priority applications represent drugs offering significant advances over existing treatments

Office of New Drugs

Office of Pharmaceutical Science
Office of New Drug Chemistry
Office of Testing & Research
Office of Biotechnology Products

Office of Translational Sciences
Office of Biostatistics

Calendar year	Filings	Actions	Percent of actions that are approvals
1996	2644	2644	66%
1997	3235	3235	57%
1998	2746	2746	54%
1999	3143	3143	65%
2000	2141	2141	49%
2001	727	727	37%
2002	1918	1918	61%
2003	1826	1826	54%
2004*	3142	3142	69%
2005*	2936	2936	61%
2006*	2638	2638	55%

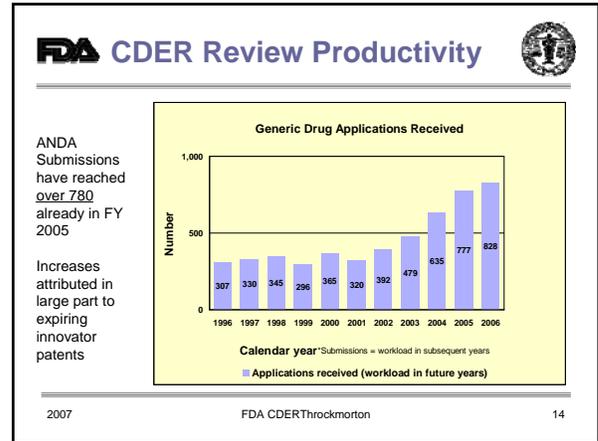
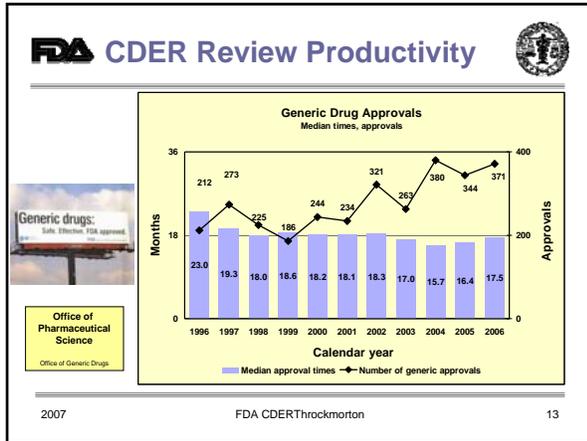
*Includes BLAs for therapeutic biologics
(A filing in one year may lead to several actions or an approval in subsequent years)

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FDA Pre-Approval Process

- **Generic Drug Review Process**
 - **Abbreviated New Drug Application (ANDA)**
 - Application for a generic version of a brand name drug
 - Generic companies are not required to repeat the extensive clinical trials required for brand name drugs
 - Must show “Bioequivalence”
 - Prove that the rate and extent of absorption of the active ingredient is the same

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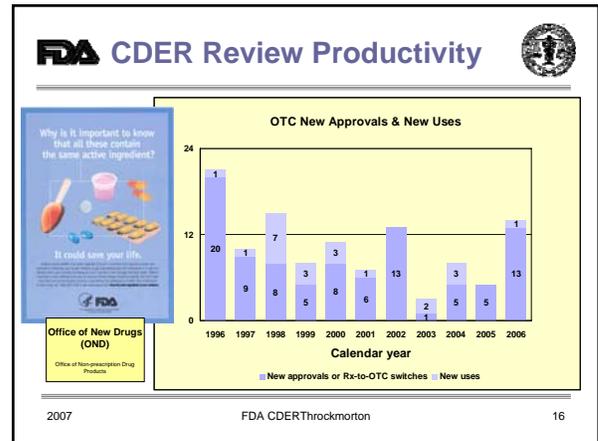


FDA Pre-Approval Process

- Over The Counter (OTC) Drug Review**
 - OTC Monographs
 - Published 'recipes' for acceptable ingredients, doses, formulations, and consumer labeling

Office of New Drugs
Office of Nonprescription Drug Products

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FDA Pre-Approval Process - Support

- Drug Promotion Review**
 - Ensure that drug advertisements and other promotional materials are truthful and balanced
 - Before drug companies launch marketing campaigns to:
 - Introduce new drugs
 - Introduce new indications or dosages for approved drugs
 - After a campaign is initiated if issues of truthfulness and balance arise

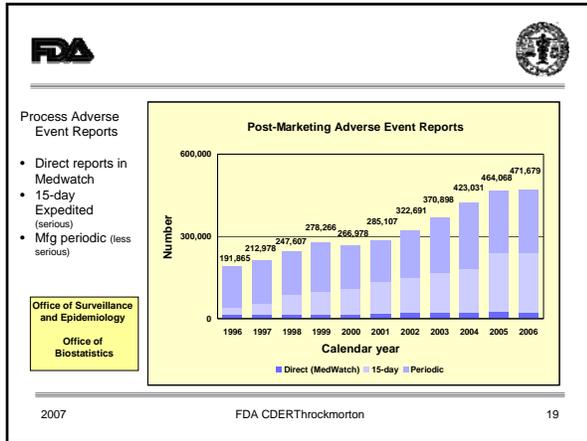
Office of New Drugs

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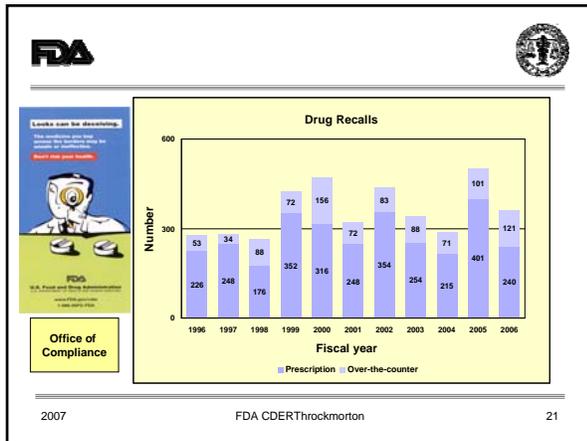
FDA Post-Market Drug Surveillance

- Product Surveillance Functions**
 - Process Adverse Event Reports
 - Identify emerging safety signals, analyze data, communicate findings
 - Medication Errors
 - Manage Drug Shortages
 - Perform Population Studies

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- FDA Compliance/Enforcement**
- **Compliance/Enforcement**
 - Enforce Quality Requirements
 - Inspect Facilities
 - Evaluate Imports/Experts
 - Manage Registration and Listing
 - Perform Internet Surveillance
- 2007 FDA CDERTHrockmorton 20



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- FDA Cross-Cutting Offices**
- **Office of Translational Sciences**
 - Lead implementation of the Critical Path Initiative for CDER
 - Interactions with outside groups
 - Oversee research and science in CDER
 - Oversee human subjects protection in CDER
 - Cross-cutting disciplines
 - Office of Clinical Pharmacology
 - Office of Biostatistics
- 2007 FDA CDERTHrockmorton 22

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- FDA Cross-Cutting Offices**
- **Counter Terrorism**
 - Identify, prepare for, and respond to
 - Biological, chemical, radiological/nuclear threats and incidents
 - Expand the availability of safe, effective medical countermeasures (MCMs)
 - For special populations (pregnant women, infants, elderly)
 - Frequent interaction with CDC's Strategic National Stockpile (SNS)
 - Participate in committees to facilitate development of MCMs and to provide recommendations for acquisition of products
- Office of Counter Terrorism & Pediatric Drug Development (OCTAP)
Division of Counter Terrorism
- 2007 FDA CDERTHrockmorton 23

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- FDA Cross-Cutting Offices**
- **Controlled Substances Staff**
 - Assess new drugs for their abuse liability
 - Make recommendations (with NIDA) on scheduling and risk management interventions of controlled substances
 - Interacts with multiple outside groups on drug abuse issues, both domestic and international
 - NIDA
 - SAMHSA
 - CDC
 - DEA
 - HHS
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FDA Support Functions



- **Support**
 - Manage Partnerships (International, Federal, State, Local Outreach)
 - Develop, Publish Industry Guidance
 - Draft Regulations, Internal Procedures
 - Provide Stakeholder Outreach
 - Manage Correspondence
 - Provide Internal Training and Professional Development
 - Perform Advisory Committee Meetings
 - Manage Program Planning and Evaluation
 - Process Regulatory Documents



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FDA Sum-up: The Wheels at CDER



- **CDER is entrusted with a huge set of critical tasks to accomplish for the US**
- **CDER has a clear mission, based on those tasks, to guide us**
- **CDER is organized to accomplish that mission**

However

- **CDER cannot accomplish everything alone: collaboration with outside groups is essential to continued success**

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FDA Conclusion



- **Understanding the processes at CDER will help with collaboration**
 - Ask until you get the answers to your questions
- **Today's healthcare environment requires that all of us question the assumptions we've used to guide our process, and that we be ready to change if those assumptions are no longer justified**

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FDA Questions?



- douglas.throckmorton@fda.hhs.gov



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NOTES PAGE- Safety and Toxicology Studies

David Jacobson-Kram, PhD, DABT

Associate Director for Pharmacology and Toxicology, CDER

Safety and Toxicity Studies

A Day with the FDA: CDER and NIAID Working Together Safety and Toxicology Studies

July 27, 2007

David Jacobson-Kram, Ph.D., DABT
Office of New Drugs
Center for Drug Evaluation and Research
U.S. F.D.A.





Food and Drug Administration


Drug Development: role of nonclinical studies

- > Overview of how drugs are developed
- > Current challenges
- > Preclinical studies
- > Genetic toxicology and carcinogenicity testing
- > The future




Food and Drug Administration

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The Future of Pharmaceuticals



- > Everyone's DNA sequence will be on file in their computer
- > Illnesses diagnosed in real time from a drop of blood
- > Drugs and dosages custom designed based on individual genetic polymorphisms, age, sex, weight etc


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Combinatorial chemistry,
thousands of chemical entities

↓

High throughput in vitro
screening, dozens of
candidates

↓

Animal models, efficacy
and safety, handful of
candidates

↓

Phase 1 clinical trial, one
drug


Food and Drug Administration

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Drug Development Paradigm

Research & Discovery		Clinical Trials			Review Process	
Preclinical Testing	IND	Phase 1	Phase 2	Phase 3	NDA	Phase 4
laboratory studies in vitro studies animal studies	20-100 healthy volunteers	100-500 patient volunteers	1,000-5,000 patient volunteers			
evaluate toxicology, show biological activity at disease target and develop formulations	assess safety and dosage	observe for effectiveness and side effects	confirm effectiveness, monitor adverse reactions from long-term use	review process and approval	Additional testing required by FDA	
YEARS						


Food and Drug Administration

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Realities of Drug Development Today

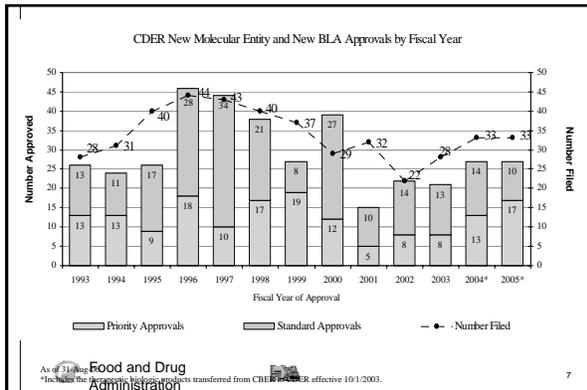
- > NME (new molecular entity) development = **high** risk and cost
 - ◆ Extremely high failure rate before IND (investigational new drug)
 - ◆ NME IND = NDA (new drug application) <20% of time
 - ◆ >50% failure rate in Phase 3 either for lack of efficacy or toxicity
 - ◆ Decreased NME NDAs despite increased INDs
 - ◆ Cost per NME approved estimated at >\$800M




Food and Drug Administration

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Safety and Toxicity Studies



Why the decline in new drugs?

- "Low hanging fruit" has been picked.
- Economics, if it's not a blockbuster, may not worth developing.
- Mergers and acquisitions in pharmaceutical industry.
- We may be becoming more risk averse, aspirin might not be approved in today's environment.
- Major diseases with unmet needs are complex and multigenic, e.g., cancer, heart disease, diabetes, Alzheimer's

Types of preclinical and nonclinical tests

- Pharmacology (mechanistic and animal models, done in discovery, nonGLP)
- Safety pharmacology
- General toxicology
- Genetic toxicology
- Pharmacokinetics
- ADME (absorption, distribution, metabolism and excretion)
- Reproductive toxicology
- Carcinogenicity
- Special studies (e.g. juvenile)

Why do we do ask for these studies?

- Determine whether it is safe to put drug candidate into humans
- Determine what constitutes an initial safe dose for human clinical trials
- Help determine a safe stopping dose
- Identify dose limiting toxicities (what should be monitored in clinical trials)
- Assess potential toxicities that cannot be identified in clinical trials

BBC NEWS March 16, 2006

Two drug test men still critical
Two men who fell seriously ill following a clinical drugs trial remain in a critical condition but four others are showing signs of improvement.

All six are still in intensive care in Northwick Park Hospital, north-west London, after falling ill on Monday.

TeGenero, which manufactures the anti-inflammatory drug, says it has apologised to the men's families.

Scotland Yard said officers are talking to the Medicines and Healthcare products Regulatory Agency and doctors.

TeGenero described the reactions as "shocking developments" and said the new medicine had showed no signs of problems in earlier tests.

CD28 Monoclonal Trial in UK

- No evidence of contamination of the product.
- Conduct of the trial appeared to have followed the protocol, e.g., no dosing errors.
- Nothing in the preclinical data predicted the overwhelming systemic reaction to the antibody. Findings of lymph node enlargement in the monkeys, but the monkeys did not demonstrate the toxicological response seen in humans.
- Dose in humans was 1/160 of the NOAEL in monkeys, so it was well within accepted safety margins.
- Adverse reaction considered to be a "cytokine" storm that was triggered by the antibody and not predicted by the animal testing.

What toxicities cannot be identified in clinical trials?



- Teratogenicity: don't want to deliberately expose pregnant women
- Carcinogenicity: long latency period and insensitivity of epidemiological studies preclude identification of this adverse effect
- Long term toxicities



Food and Drug Administration

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Nonmonitorable toxicities: teratogenicity, eg thalidomide

- Prescribed to pregnant women for nausea and insomnia.
- Resulted in over 10,000 births with severe limb malformations.
- Link between exposure and adverse effects was possible because of the potency of the drug and relatively short time period between exposure and manifestation of effects.



Food and Drug Administration

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Thalidomide-induced birth defects



Food and Drug Administration

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Nonmonitorable effects: carcinogenesis, diethylstilbestrol (DES)



- Prescribed to pregnant women to maintain pregnancies.
- Increased risk (1 in 1000) for clear cell adenomas of the vagina and cervix in female offspring.
- Link between exposure and risk could be made because of the rarity of tumor type. If exposure increased risk for a common cancer, might not have been detected.

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What preclinical safety data are required prior to giving a new chemical to human beings for the first time – and why



- Most phase 1 studies are performed in healthy volunteers. No risk vs. benefit calculation, only risk assessment.

Food and Drug Administration

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Preclinical studies define potential toxicities



- What is initial safe starting dose?
- What is a safe stopping dose?
- What organs/systems are at risk?
- Are toxicities monitorable in the clinic?
- Are toxicities reversible?
- Is the chemical potentially carcinogenic?

Food and Drug Administration

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Safety and Toxicity Studies

Minimal data set to begin a phase 1 clinical trial in healthy volunteers

- Toxicity studies in two species (rat, dog for small molecules, often nonhuman primate for biologics) with the highest dose demonstrating a "maximum tolerated dose" (MTD) and a lower dose demonstrating a "no adverse effect level" (NOAEL).
- Repeat dose toxicity study of 14 to 28 days in used most commonly.



Typical endpoints in toxicology study: in-life

- Clinical signs, behavior
- Food consumption
- Body weights
- Clinical pathology (in larger species)



Typical endpoints in toxicology study: post-life

- Macroscopic observation at necropsy
- Organ weights
- Clinical pathology
 - ◆ Hematology
 - ◆ Clinical chemistries
- Histopathology, all organs
- Toxicokinetics



Safety pharmacology

- Cardiovascular (non rodent)
 - ◆ Blood pressure
 - ◆ Heart rate
 - ◆ ECGs
 - Rhythm and morphology
 - Arrhythmia analysis
 - Interval analysis including QT interval calculation



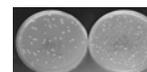
Safety pharmacology

- CNS (rodent functional observation battery, Irwin test)
 - ◆ Spontaneous locomotor activity
 - ◆ Motor coordination
 - ◆ Proconvulsive effects
 - ◆ Analgesic effects
- Pulmonary (rodent, plethysmography)
 - ◆ Minute volume
 - ◆ Tidal volume
 - ◆ Respiratory rate



Genetic toxicology

- Bacterial reverse mutation assay (Ames test, measures induction of point mutations e.g. base substitution, frame shifts)
- In vitro assay for chromosomal damage in cultured mammalian cells (metaphase cell analysis or mouse lymphoma gene mutation assay).
- In vivo test for chromosomal damage (rodent micronucleus test, not required but often performed).



Use of genotoxicity data at CDER

- > Results from carcinogenicity studies are generally not available until the time of product approval. Many people, including healthy volunteers, will have been exposed to pharmacologically active doses before carcinogenicity data are available.
- > Data from genotoxicity studies are used as a surrogate for carcinogenicity during development, i.e. during clinical trials.



A review of the genotoxicity of marketed pharmaceuticals*

- > 1999 PDR and peer-reviewed literature
- > 467 marketed drugs
 - ◆ **excluded anti-cancer, nucleosides, steroids, biologicals and peptide-based drugs**
- > 115 of 467 had no published genotox data
 - ◆ **acutely administered: antibiotics, antifungals, antihistamines, anesthetics**
- > 352 had at least one standard genotox test result.

A review of the genotoxicity of marketed pharmaceuticals

Snyder and Green, 2001

- > 101 of 352 (29%) had at least one positive assay result
 - ◆ bacterial mutation 27/323 (8%)
 - ◆ *in vitro* cytogenetics 55/222 (25%)
 - ◆ mouse lymphoma 24/96 (25%)
 - ◆ *in vivo* cytogenetics 29/252 (12%)

A review of the genotoxicity of marketed pharmaceuticals

Snyder and Green, 2001

- > 201 had both genotox and rodent carcinogenicity
- > 124/201 negative for carcinogenicity
- > 77/201 positive or equivocal for carcinogenicity
- > 100/124 noncarcinogens also negative for genotoxicity
 - ◆ 24 noncarcinogens with positive genotox data, 19 of these were *in vitro* cytogenetics positives
 - ◆ of 77 rodent carcinogens, 26 were genotox positives--many nongenotoxic rodent carcinogens!

Genetic Monitoring of Subjects in Clinical Trials

- > A number of endpoints can be easily monitored in peripheral blood lymphocytes of patients
 - ◆ chromosomal aberrations
 - ◆ micronuclei
 - ◆ mutations at the HGPRT locus
- > Such monitoring is rarely performed
 - ◆ what do you tell subjects if an effect is seen?
 - ◆ what are legal ramifications?



Is carcinogenesis testing required for approval of all drugs?

- ◆ **Drug whose continuous use is for six months or more. Drugs used frequently in an intermittent fashion for chronic or recurrent conditions (allergic rhinitis, anxiety, depression).**
- ◆ **Cause for concern:**
 - Product class
 - SAR
 - Evidence from repeat-dose studies, e.g. hyperplasia
 - Long-term retention of drug or metabolite in localized tissue



Is carcinogenesis testing required for approval of all drugs?

- Drug that is unequivocally genotoxic can be presumed to be a trans-species carcinogen and may not need to be tested. CDER rarely sees examples of such drugs.
- For patient populations with short life-expectancies, carcinogenesis testing may not be required.
- Drugs used for prophylaxis, to prevent a disease should be tested.
- Carcinogenesis testing may not be necessary for endogenous substances given as replacement therapy (insulin).
- If replacement product is different from endogenous, or results in significantly increased exposure, carcinogenicity testing may be necessary.



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Safety of healthy subjects and patients in clinical trials



- Clearly genotoxic drugs are not given to healthy subjects or patients with non life-threatening diseases.
- Pharmaceutical companies screen drug candidates early in development to eliminate frankly genotoxic molecules. Such drugs are rarely the subject of an IND.
- Subjects in clinical trials may be exposed to nongenotoxic carcinogens although this effect, like other types of toxicities, is thought to have a threshold.

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The Perfect Carcinogenicity Test Would:

- identify all materials that could potentially induce cancer in human beings.
- have 100% sensitivity (no false negatives) and 100% specificity (no false positives).
- rank carcinogens in order of potency.
- identify target organs/tissues and types of tumors, e.g. small cell carcinoma of the lung vs. squamous cell carcinoma of the skin.
- provide results rapidly and at low cost.

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State of the art: 2-year carcinogenicity studies in rodents

- Protracted, 2-year in-life, 3 month preliminary dose-range finding studies, 4 - 6 month post-life, 3 years to get answer.
- Expensive, depending on route of exposure, can cost from one to several million dollars.
- Hazard assessment is imperfect. While most human carcinogens are identified by this assay, many false positives are suspected, especially those that induce tumors in only one species, one sex and/or one site.
- Quantitative risk assessments tend to exaggerate risks to humans.
- Many animals are required. Typically, 50/sex/dose plus vehicle controls.
- Positive data provide little or no mechanistic information about the material.

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Challenges of Drug-Induced Tumorigenesis



- Drugs can induce tumors by a variety of mechanisms unrelated to DNA damage
 - ◆ Exaggerated pharmacological effects
 - ◆ Immune suppression
 - ◆ Hormonal imbalance
- Occasionally these drugs give an isolated positive genotox result, probably unrelated to actual MOA.

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Positive results: Issues to consider regarding the product



- What is the drug indication?
- Who is the target population? Geriatric, pediatric, obstetric.
- What is the likely duration of use? Approved, off label?
- Are there other drugs already serving this medical need? What is their safety profile?
- What is the margin of exposure (carcinogenic vs. clinical dose)?

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Future of Carcinogenicity Testing

- > We will learn more about activation of oncogenes and inactivation of tumor suppressor genes.
- > Techniques for detecting rare mutations *in vivo* are improving quickly.
- > In the relatively near future we will be able to detect genetic lesions in wild type animals which ultimately result in tumor formation. These will be detectable after relatively short exposures perhaps even as short as 28 days.

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How can the “omics” revolution help risk assessment for cancer

- > Shorten time required to determine if drug or a chemical is potentially carcinogenic
- > Lower cost of testing will allow more compounds to be tested
- > Improve extrapolation of animal data to humans
- > Improve extrapolation from experimental high dose to human exposure dose
- > Reduce animal usage
- > Provide insight into mechanisms of action

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Thank you for your attention. Questions?



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**NOTES PAGE- Emergency Preparedness, Medical Countermeasures,
and the Role of The Animal Rule**

Brad Leissa, MD
Deputy Director/ CDER Emergency Coordinator,
Office of Counter-Terrorism & Emergency Coordination (OCTEC)

Emergency Preparedness, Medical Countermeasures and the Role of the 'Animal Rule'



BRAD LEISSA, MD
DEPUTY DIRECTOR, OCTEC / CDER / FDA

A DAY WITH THE FDA:
CDER AND NIAID WORKING TOGETHER
July 27, 2007

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Outline

- Threats
- Medical countermeasures (MCM)
 - Product development
 - Approved MCMs
 - Approval pathways
 - 'Animal Rule'
 - Emergency access to unapproved MCMs
 - Emergency Use Authorization (EUA)
- Strategic National Stockpile (SNS)
- MCM development: NIH-CDER
- FDA websites
- Contact information

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Threats

- Biological
 - Category A: Anthrax, Plague, Botulism*, Smallpox, Viral hemorrhagic fevers
 - *Pandemic influenza, SARS*
- Chemical
 - Nerve agents (sarin, soman, VX, etc.)
 - "Blood agents" (cyanide)
 - "Blister agents" or vesicants (mustard)
 - "Choking agents" (chlorine, phosgene)
 - Toxic industrial chemicals (TICs)
- Toxins
 - Botulinum toxin, Ricin *et al*
- Radiological / Nuclear
 - Acute radiation syndrome (ARS)
 - Delayed effects of acute radiation exposure (DEARE)
 - Internal radionuclide contamination

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MCM Development *unique challenges*

- "Risky Market"
 - Market potential
 - USG
 - Stockpiles
 - Discovery → Licensure
 - "Valley of Death"
 - Push: Market share
 - Small biotech companies > "Big PhRMA"
 - Pull:
 - USG grants (NIH, DoD, DARPA)
 - USG contracts (BARDA, Project BioShield, CDC/SNS *et al*)
 - Exclusivity (Waxman-Hatch; Orphan)
 - Opportunity costs & return on investment

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MCM Development *unique challenges*

- Unique operational considerations
 - Expedited administration during mass casualty
- Human experience may derive from past armed conflicts, accidents, and terrorist attacks
 - WWI, Goiânia (Brazil), Tokyo sarin
- Classified national security information
- Shelf life / expiry (stockpiles)
- 'Animal Rule'
- Unapproved products for mass casualties (EUA)

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MCM Development *unique challenges*

- Special populations
 - 21 CFR Subpart D – 'Additional Safeguards for Children in Clinical Investigations' – greater than minimal risk
 - 21 CFR 50.52: direct benefit to subject
 - 21 CFR 50.53: no direct benefit but generalizable knowledge
 - 21 CFR 50.54: opportunity to understand, prevent, or alleviate
- Early advice is expected
 - Significant development occurs prior to IND
 - Pre-pre IND
 - Pre IND

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Establish & Maintain Public Confidence in MCMs



BioShield
"Immune Defense Formula"



Bio-SAFE



BioDefense Rx
"Cellular Protection"



BIODEFENSE

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Approved MCMs

- **Biological**
 - Ciprofloxacin, levofloxacin, doxycycline, procaine PCN G
 - *Inhalational anthrax (post exposure)*
 - Doxycycline, streptomycin
 - *Plague, tularemia*
 - *Brucellosis* (streptomycin; doxy with streptomycin)
 - Doxycycline
 - *Q fever*
 - Oseltamivir (Tamiflu®), zanamivir (Relenza®)
 - *Seasonal influenza* (prophylaxis & treatment)
 - Rimantadine (Flumadine®), Amantadine (Symmetrel®)
 - *Influenza A* (prophylaxis & treatment)

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Approved MCMs

- **Chemical**
 - Atropine, pralidoxime, ATNAA / DuoDote, diazepam
 - *Nerve agents (autoinjectors)*
 - Pyridostigmine
 - *Soman pre-treatment*
 - Sodium thiosulfate*
 - Hydroxocobalamin (Cyanokit®)
 - *Cyanide*
 - Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA)
 - *CWA barrier in conjunction with MOPP*

*No licensed manufacturer at this time

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Approved MCMs

- **Radiation / Nuclear**
 - Radioiodine
 - *Potassium iodide (KI)*
 - *Iosat™, ThyroSafe®, ThyroShield™*
 - Cesium
 - *Prussian blue (Radiogardase®)*
 - Plutonium, americium, curium
 - *Ca-DTPA, Zn-DTPA*

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Approval Pathways

- **Traditional** - Clinical Safety and Efficacy
- **'Accelerated Approval'** - Clinical Surrogates
 - Ciprofloxacin (2000) & levofloxacin (2004)
 - *Inhalational anthrax (post exposure)*
- **'Animal Rule'**
 - Pyridostigmine bromide (2003)
 - Hydroxocobalamin (2007)

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'Animal Rule'

- **"Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible"**
- **Scope:** drugs to prevent or ameliorate serious or life threatening conditions caused by exposure to biological, chemical, and nuclear/radiological substances.
- Final Rule published: 31 May 2002
 - Drugs (Subpart I): 21 CFR 314.600-314.650
 - Biologics (Subpart H): 21 CFR 601.90-601.95
- Regulatory authority of last resort.

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Emergency Preparedness...

'Animal Rule' Requirements

- There is a reasonably well-understood pathophysiological **mechanism** of the toxicity of the substance and its prevention or substantial reduction by the product;
- The effect is demonstrated in **more than one animal species** expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
 - Must be able to explain interspecies differences where they exist
 - No single animal model has been identified as the "best species" for every type of drug to treat ARS.
 - Depends on drug mechanism of action.
 - Does the animal's physiology/anatomy/metabolism significantly mimic the human for a given drug?

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'Animal Rule' Requirements

- The animal study endpoint is clearly related to the desired benefit in humans, generally the **enhancement of survival or prevention of major morbidity**; and
- The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows **selection of an effective dose in humans**.



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'Animal Rule' Requirements

- All studies subject to this rule must be conducted in accordance with pre-existing requirements under the **good laboratory practices (GLP)** regulations and the **Animal Welfare Act**...
 - GLP allows reconstruction of the experiment from start to finish
 - GLP is a quality management system.
- **Traditional safety assessments**
 - Animal toxicology
 - Human safety

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'Animal Rule'

- **How much human safety is needed?**
 - A balance of risk, benefit, and uncertainty...
 - Pre-treatment vs. therapeutic
 - Safety concerns
 - Known concern with the drug class
 - Identified during product development
 - Special Protocol Assessment (SPA) – includes pivotal animal efficacy study

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Emergency Access to Unapproved MCMs

- Emergency IND
- Treatment IND
- 'Contingency IND' – not a regulatory term
- Emergency Use Authorization (EUA)

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Informed Consent & Public Health Emergencies

- Informed consent may not be practicable during a rapidly progressive public health emergency
- Consent process may limit public health's ability to respond and contain the disease/illness

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Emergency Use Authorization (EUA)

- Signed into law 7/21/04 under BioShield Act
- Allows for the emergency use of:
 - Unapproved drugs, biologics, or devices
 - Unapproved use of approved products ("off label")
- Duration: ≤1 year
 - Can be renewed
- No informed consent

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EUA Criteria

- CBRN threat can cause serious, life-threatening disease or condition
- It is **reasonable** to believe that the product **may be** effective in Dx, Rx, prevention
 - Lower standard than 'substantial evidence'
- *Known and potential* benefits of the product outweigh the *known and potential* risks
- No adequate, approved, and available alternative
 - Includes "special populations"

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EUA Conditions

- Healthcare providers/authorized dispensers and affected individuals are informed about:
 - Risks & benefits
 - Alternative interventions
- No consent but individuals also option to accept or refuse product
 - Exception -- Presidential waiver for DOD personnel
- Monitoring and reporting of adverse events
- Recordkeeping and reporting; data collection and analysis

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EUA Misc.

- Requires Secretarial determination, declaration during an "emergency".
 - EUA cannot be "pre approved"
 - Pre-EUA submissions reviewed
- Authority to issue EUA delegated to FDA Commissioner
- EUA issuance in consultation with Directors of CDC & NIH (where practicable)

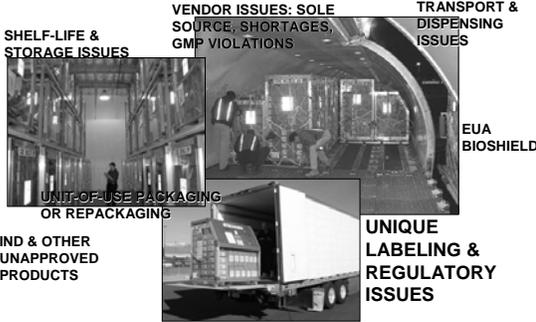
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FDA EUA Experience

- Jan 2005: EUA issued to DoD for use of anthrax vaccine (AVA) to prevent inhalation anthrax
- Jan 2006: DoD EUA terminated
- Numerous exercises

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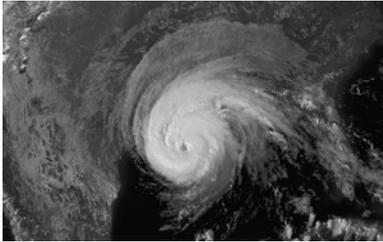
Strategic National Stockpile



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Emergency Preparedness...

EMERGENCY PREPAREDNESS: *More than Terrorism*



MCM Development: NIH-CDER

- **Pandemic influenza**
 - 'Development and Use of Antivirals for Pandemic Influenza Workshop' (Nov. 8-9, 2006)
- **Other Biothreats**
 - NIAID Biodefense Research
- **Chemical**
 - Countermeasures Against Chemical Threats (CounterACT; NINDS *et al*)
- **Radiation / Nuclear**
 - Medical Countermeasures Against Radiological and Nuclear Threats (DAIT, NCI)
- **HHS/ASPR/BARDA Interagency Working Groups**
- **PHEMC Enterprise**

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FDA Websites

- **Counterterrorism (FDA)**
 - www.fda.gov/oc/opacom/hottopics/bioterrorism.html
- **Emergency Use Authorization of Medical Products (DRAFT FDA Guidance)**
 - **HTML:** www.fda.gov/oc/bioterrorism/emergency_use.html
 - **PDF:** www.fda.gov/OHRMS/DOCKETS/98fr/04d-0333-gdl0001.pdf
- **Drug Preparedness and Response to Bioterrorism (CDER)**
 - www.fda.gov/cder/drugprepare/

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NOTES PAGE- The IND Process: A Regulatory Perspective

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The IND Process: A Regulatory Perspective

David Roeder
Associate Director for Regulatory Affairs
Office of Antimicrobial Products
Center for Drugs, FDA

July 2007

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The IND Regulations Include:

- 21 CFR 312 [Investigational New Drug Application]
- 21 CFR 50 [Protection of Human Subjects-Informed Consent]
- 21 CFR 56 [Institutional Review Boards]
- Other

2

The IND Process: A Regulatory Perspective

- When Is an IND Needed?
- Types of INDs
- Expanded Access
- The First 30 Days
- Clinical Holds
- The IND Life Cycle
- Special Programs
 - Pre-INDs
 - Subpart E
 - Fast Track
 - Special Protocol Assessments

3

When is an IND Needed?

Questions to ask

- Is it a drug?
- Is it being used in a clinical investigation?
- Is it a drug that is lawfully marketed in the U.S. for another use?

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Is it a Drug?

- “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease...” and
- “articles (other than food) intended to affect the structure or any function of the body...” (21 USC 321(g)(1)(B) and (C))
- The second prong of the definition does not apply to dietary supplements
- Note that a drug is defined by intended use, not the nature of the substance

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Is it a Clinical Investigation?

- A “clinical investigation” is “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.”
- An “experiment” is “any use of a drug except for the use of a marketed drug in the course of medical practice.”
- Not limited to commercial development

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The IND Process

Is it a Drug that is Lawfully Marketed in the U.S. for Another Use?

- 21 CFR 312.2 provides for exemptions for certain clinical studies of approved drugs for unapproved uses
- Most cases can be determined by the sponsor or investigator
- An exemption letter from the FDA is generally not necessary
- When in doubt, consult with the FDA

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IND Exemptions for Lawfully Marketed Drug Products

(must meet all criteria)

- Study is not intended to be reported as a well-controlled study for a new indication or significant labeling change
- Study is not intended to support significant change in advertising
- Does not involve a route of administration, dosing level, or patient population that significantly increases the risk (or decreases the acceptability of risk)

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IND Exemptions for Lawfully Marketed Drug Products (cont.)

- Conducted in compliance with 21 CFR 56 (IRB) and 21 CFR 50 (informed consent)
- Conducted in compliance with 21 CFR 312.7 (promotion and charging)

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Other IND Exemptions

- Certain studies with *in vitro* biologic diagnostic products
- Blood grouping serum
- Reagent red blood cells
- Anti-human globulin
- *In vitro* or laboratory research animals
- Certain bioavailability studies
- Radioactive drugs for certain research uses

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Types of INDs

- “Regular” [21 CFR 312.23 (format and content)]
- Treatment [21 CFR 312.34]
- Emergency [21 CFR 312.36]
- Emergency Care Research [21 CFR 50.24]

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Expanded Access

- Food and Drug Administration Modernization Act (FDAMA), section 402
 - Required the FDA to codify more comprehensive and consistent regulations for expanded access
 - Ensures that “opportunities to participate in expanded access programs are available to every individual with a life-threatening or seriously debilitating illness for which there is not an effective, approved therapy.”
- Proposed rule: December 14, 2006, Docket #2006N-0062
 - Proposal will replace regulations for treatment INDs and Emergency INDs

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The First 30 Days

- Study cannot proceed until 30 days from FDA receipt (new INDs and reactivated INDs only)
- 30-day safety review
- Decision: safe to proceed *or* clinical hold?

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Clinical Holds

[21 CFR 312.42]

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Clinical Holds

[21 CFR 312.42]

- Unless accompanied by a clinical hold, agency comments to an IND sponsor are advisory only
- Can be imposed at any time
- Partial clinical hold vs. full clinical hold

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Partial Hold vs. Full Hold

- Partial Clinical Hold allows limited study under an IND. The scope of the limitations can vary depending on the circumstances of the IND
- Full Clinical Hold prohibits all clinical study under an IND until issues are resolved

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Grounds for Imposing a Clinical Hold: Phase 1

- Human subjects at unreasonable and significant risk
- Unqualified investigator(s)
- Investigator brochure misleading, erroneous or incomplete
- Insufficient information to assess risk
- Exclusion by gender if for life-threatening condition

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Grounds for Imposing a Clinical Hold: Phase 2 or 3

- Any reason cited in previous slide
- Protocol deficient in design to meet stated objective

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Lifting a Clinical Hold

- Sponsor must submit a complete response to the deficiencies listed in the clinical hold letter
- FDA will respond to this submission within 30 days with its decision

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The Life Cycle of an IND

- Amendments
 - Protocol amendments [21 CFR 312.30(b)]
 - New protocols [21 CFR 312.30(a)]
 - New investigator [21 CFR 312.30(c)]
 - Information amendments (e.g., CMC, completed study reports) [21 CFR 312.31]
- Annual Reports [21 CFR 312.33]

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The Life Cycle of an IND

- IND safety reports [21 CFR 312.32]
- Meetings [21 CFR 312.47]
 - End-of-Phase 2: planning for clinical studies that will provide definitive support for efficacy and safety*
 - Pre-BLA/NDA: discuss overall content and format of BLA/NDA*
 - Other
- Written and oral communication

* These meetings are generally relevant only to commercial INDs

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Special Programs

- Pre-IND program
- Subpart E
- Fast Track
- Special protocol assessments

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The pre-IND

- NOT a regulatory application
- Valuable tool for handling reviews and communications that can not be conducted under an IND

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Common Uses of the pre-IND

- Guidance from the agency regarding difficult or novel drug development plans
- Pre-Emergency Use Authorization (pre-EUA)
- Drug development under the Animal Rule

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Subpart E

- Procedures to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists
- 21 CFR 312 Subpart E

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Fast Track

- Facilitate development and expedite review of drugs intended for the treatment of a serious or life-threatening condition and which demonstrate the potential to address unmet medical needs for such a condition.
- FDAMA sec. 112

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Special Protocol Assessments

- Protocols for pivotal efficacy studies
 - Phase 3 clinical studies
 - Pivotal efficacy studies conducted under the “animal rule”
- Carcinogenicity protocols
- Drug Stability protocols
- FDAMA sec. 119(a)

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NOTES PAGE- Clinical Trial Design and Statistical Issue

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Director, Office of Biostatistics, Office of Translational Sciences, CDER

Clinical Trial Design and Statistical Issues

Robert T. O'Neill Ph.D.

Director, Office of Biostatistics, Office of Translational Sciences, CDER

A Day with the FDA: CDER and NIAID Working Together,
Friday, July 27, 2007 NIH, Building 10, Lipsett Amphitheatre

1

Outline of talk

- ◆ Some background on the clinical trial as substantial evidence - the criteria for approving a new drug
- ◆ CDER's role in the evaluation of a protocol and feedback to sponsors
 - ◆ An example and story : the AZT - Placebo controlled trial
- ◆ CDER's role in the assessment of evidence: evaluation of randomized clinical trials in NDA's
- ◆ Principles of adequate and well controlled clinical trials
- ◆ Statistical Principles in Clinical Trials
- ◆ Some challenging areas in study design and analysis
- ◆ Guidance Development
- ◆ Concluding remarks

2

The AZT - Placebo Randomized Trial that provided the basis for approval of AZT - A Story

- ◆ FDA's role in the evaluation of the protocol
- ◆ FDA's role in the evaluation of the data
- ◆ Issues:
 - ◆ Interim analysis
 - ◆ Uncertainty in the endpoints and entrance criteria and generalization to the population benefiting
- ◆ Approved in March 1987 based upon single study
- ◆ Process for review and NIAID paradigm shift

3

Major Regulatory Events Impacting Determination of Evidence

- ◆ The 1962 Kefauver-Harris Amendments: the foundation for experimental evidence as the basis for drug approvals
- ◆ The 1970 definition of 'Adequate and well controlled investigations': the foundation for statistical principles: the concept of hypothesis testing and estimation, randomization, blinding, statistical analysis, quantifying uncertainty of conclusion
- ◆ The 1986 NDA Rewrite: the foundation for documentation of evidence, including statistical evidence and introduction of the integrated efficacy and safety section -

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Major Events Impacting Determination of Evidence (cont.)

- ◆ The 1988 Guideline for the Format and Content of the Clinical and Statistical Sections of an application
- ◆ 1992; Subpart H - Accelerated Approval of New Drugs for Serious or Life-threatening Illnesses - surrogate endpoints (AIDS crisis)
- ◆ The 1997 Food and Drug Modernization Act (FDAMA); a modification of the substantial evidence criteria
- ◆ The 1998 ICH Statistical Principles for Clinical Trials: the foundation for global understanding, harmonization and implementation of statistical principles

5

Some basics

A Successful Clinical Trial: Definition

- ◆ A trial whose observed treatment effect is clinically meaningful, (estimated precisely) and for which the statistical certainty (uncertainty) of the effect is large (small) enough to conclude that chance is not a plausible explanation for the observed effect
- ◆ The pre-specified criteria for success is met, when controlling for the multiple opportunities and or ways "to win"
- ◆ Usually, this means the p-value associated with the hypothesis(es) is less than the pre-specified Type I error, i.e. ≤ 0.05
- ◆ Bias associated with the study design, conduct or analysis is not an alternative explanation for the observed effects

6

Trial Design Considerations (1)

- ◆ Endpoints
- ◆ Screening criteria, stratifications
- ◆ Dose(s)
- ◆ Duration of trial
- ◆ Comparison groups
- ◆ Sample size
- ◆ Multiplicity - how many ways to "win" for endpoints and /subgroups
- ◆ Controlled and uncontrolled factors

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Trial Design Considerations (2)

- ◆ Parallel, crossover, multi-center, factorial
- ◆ Superiority or Non-inferiority - objectives
- ◆ Group Sequential Designs for serious irreversible morbidity/mortality outcomes
- ◆ Adaptive study designs which may change design features depending upon accumulating data

8

Planning

- ◆ Specifying the objectives of the trial
- ◆ Quantifying the objectives in terms of study population, entrance criteria, clinical outcomes, variation of critical outcomes, and number of ways for success or a 'win'
- ◆ Statistical Analysis Plan (SAP)
- ◆ Anticipating what will occur during conduct of the trial and planning how to deal with it - scenario planning / simulations

9

Major Protocol Assumptions to Enhance Chances of Successful Trial

- ◆ Quantification of endpoint incidence and variability
- ◆ Quantification of statistical risks:
 - ◆ chances of finding a treatment difference when it exists (power)
 - ◆ chances of falsely concluding a treatment effect exists when it doesn't (Type 1 error, alpha)
- ◆ Incidence rate of endpoint in the control group
- ◆ Magnitude of treatment effect ES, and the dose at which it occurs
- ◆ Homogeneity of treatment effects in important subgroups

Statistical Measures of Uncertainty

- ◆ Type 1 error - false positive rate
- ◆ Type 2 error - false negative rate (at an effect size)
- ◆ Power at a specified value of the treatment effect to show a statistically significant difference
- ◆ P-value (derived from the observed test statistic) : statistical measure of evidence against the null hypothesis
- ◆ Confidence level, e.g. 95%, 99%
- ◆ Confidence interval for treatment effect

11

Type 1 Error

- ◆ A pre-experiment statistical error rate defined as the probability of concluding that a treatment effect exists when, in fact, there is no treatment effect; usually set at 0.05 or less.
- ◆ "Statistically significant" means that the observed P-value is \leq Type 1 error .

12

Type 2 Error; Power

- ◆ The probability of not concluding a treatment effect exists when, in fact, a treatment effect of size ES, really is true.
- ◆ Power is the probability of a statistically significant (P-value less than 0.05) result when a treatment effect of size ES exists. Power is one minus the type 2 error.

13

P-value

The probability of a treatment effect of the size observed or more extreme, if, in reality, NO treatment effect exists; the p-value is a random variable, calculated on the basis of the observed test statistic, e.g. t statistic; the p-value will vary as a function of the sample size and the evidence from the data in favor of the alternative hypothesis.

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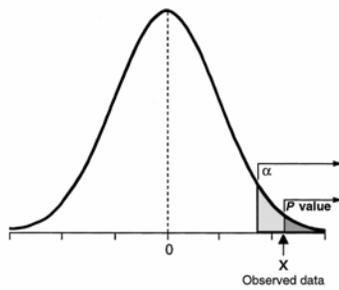


Figure 3. The bell-shaped curve represents the probability of every possible outcome under the null hypothesis. Both α (the type I error rate) and the P value are "tail areas" under this curve. The tail area for α is set before the experiment, and a result can fall anywhere within it. The P value tail area is known only after a result is observed, and, by definition, the result will always lie on the border of that area.

15

Planning the Sample Size of A Study: Statistical components

- ◆ Understanding the sample size formula and its assumptions
 - ◆ For hypothesis testing
 - ◆ For estimation of treatment effects
 - ◆ The relationship between hypothesis testing and estimation
 - ◆ Planning usually assumes a correctly specified dose and treatment effect

16

Two adequate and well controlled trials - the usual standard of evidence

Why

17

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD Context Controversy and uncertainty ensue when the results of clinical research on

JAMA. 2005;294:218-228

Results Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. Five of 6 highly-cited nonrandomized studies had been contradicted or had found stronger effects vs 9 of 39 randomized controlled trials ($P=.008$). Among randomized trials, studies with contradicted or stronger effects were smaller ($P=.009$) than replicated or unchallenged studies although there was no statistically significant difference in their early or overall citation impact. Matched control studies did not have a significantly different share of refuted results than highly cited studies, but they included more studies with "negative" results.

18

Theoretical Outcomes From a Series of 1000 Clinical Trials Assuming 1 of 10 Drugs Are Effective (the prior)

100 trials with true efficacy: H_0 is false $\beta = 0.20$ $\left\{ \begin{array}{l} 20 \text{ trials accept } H_0 \\ 80 \text{ trials reject } H_0 \end{array} \right.$

900 trials with no efficacy: H_0 is true $\alpha = 0.05$ $\left\{ \begin{array}{l} 45 \text{ trials reject } H_0 \\ 855 \text{ trials accept } H_0 \end{array} \right.$

False positive trial rate = $45/(80 + 45) = 36\%$

Simon, R., Cancer Treatment Reports, V 66, 1982, 1088-1087

The Chances of Repeating A Statistically Significant Result in a Confirmatory Study: As A Function of the Initial Observed P-Value

20

Replicating a Study Result

Probability of observing a statistically significant result (e.g. $p < 0.05$) upon repetition of a clinical trial when the effect ES observed in the first trial is assumed to be the true effect

Observed P-Value	Probability of a significant result (Power)
0.10	0.37
0.05	0.50
0.03	0.58
0.01	0.73
0.005	0.80
0.001	0.91

Source: Goodman (1992) Stat. in Med., 875 - 879 21

The Review and Evaluation of evidence from RCT's

An Example

22

Carvedilol and the Food and Drug Administration Approval Process: An Introduction

Lloyd D. Fisher, PhD, and Lemuel A. Moyé, MD, PhD
Department of Biostatistics, University of Washington, Seattle, Washington; and University of Texas School of Public Health, Houston, Texas

ABSTRACT: We discuss briefly the new drug carvedilol (Coreg®), a beta-blocker, alpha-blocker, and antioxidant. This drug was developed for congestive heart failure in a series of trials, four in the United States and one in Australia and New Zealand, briefly summarized in this document. We also summarize the classical paradigm of the U.S. Food and Drug Administration (FDA) for drug approval and the FDA's use of advisory committees. This document serves as background to the discussion of carvedilol's approval. Controlled Clin Trials 1999;20:1-15 © Elsevier Science Inc. 1999

Controlled Clinical Trials 20:1-15 (1999) 23

Carvedilol and the Food and Drug Administration (FDA) Approval Process: The FDA Paradigm and Reflections on Hypothesis Testing

Lloyd D. Fisher, PhD
Department of Biostatistics, University of Washington, Seattle, Washington

ABSTRACT: Carvedilol (Coreg®), a beta- and alpha-blocker and an antioxidant drug, was evaluated for moderate to severe heart failure patients in a program containing four United States and one Australia/New Zealand study. The data were evaluated twice by the Cardiovascular and Renal Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA). These meetings resulted in opposite decisions by the advisory committee. The crux of the argumentation was the two-positive-trial FDA paradigm. Carvedilol did not meet the usual paradigm because an exercise end point was not statistically different from placebo in three U.S. trials. Most other end points were highly significant, and death, which was monitored across the U.S. program, was different with $p < 0.0001$. Here we argue that the usual paradigm is very useful but not an absolute principle, that the usual paradigm can sometimes miss the strength of evidence even in the primary end points, and that rational decision making requires on occasion that other evidence must lead to approval. Control of the type I error rate should be taken very seriously, should rarely be violated, and serves the biomedical community well. It is not an absolute principle, however, but rather must be considered in context. Controlled Clin Trials 1999;20:16-39 © Elsevier Science Inc. 1999

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STATISTICS IN MEDICINE
Statist. Med. 2000; **19**:767-779

Alpha calculus in clinical trials: considerations and commentary for the new millennium

Lemuel A. Moyé*¹

University of Texas School of Public Health, Ross A. Stallones Building, 1200 Herman Pressler, Houston, Texas 77030, U.S.A.

SUMMARY

Regardless of whether a statistician believes in letting a data set speak for itself through nominal *p*-values or believes in strict alpha conservation, the interpretation of experiments which are negative for the primary endpoint but positive for secondary endpoints is the source of some angst. The purpose of this paper is to apply the notion of prospective alpha allocation in clinical trials to this difficult circumstance. An argument is presented for differentiating between the alpha for the experiment (experimental alpha, or α_e) and the alpha for the primary endpoint (primary alpha, or α_p) and notation is presented which succinctly describes the findings of a clinical trial in terms of its conclusions. Capping α_e at 0.10 and α_p at 0.05 conserves sample size and preserves consistency with the strength of evidence for the primary endpoint of clinical trials. In addition, a case is presented for the well defined circumstances in which a trial which did not reject the null hypothesis for the primary endpoint but does reject the null hypothesis for at least one of the secondary endpoints may be considered positive in a manner consistent with conservative alpha management. ⁵ Copyright © 2000 John Wiley & Sons, Ltd.

STATISTICS IN MEDICINE
Statist. Med. 2000; **19**:767-768

EDITORIAL

Controlling alpha in a clinical trial: the case for secondary endpoints

Ralph B. D'Agostino, Sr

Boston University, 111 Commonwealth Street, Boston, MA 02215, U.S.A.

STATISTICS IN MEDICINE
Statist. Med. 2000; **19**:767-767

Commentary on 'Alpha calculus in clinical trials: considerations and commentary for the new millennium'¹

Robert T. O'Neill

Food and Drug Administration, Center for Drug Evaluation and Research, Office of Biostatistics, 5600 Fishers Lane, Parklane Building, Room 718-01, Bethesda, MD 20892, U.S.A.

STATISTICS IN MEDICINE
Statist. Med. 2000; **19**:767-768

Discussion for 'Alpha calculus in clinical trials: considerations and commentary for the new millennium'

Gary G. Koch

Department of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, NC 27599-7000, U.S.A.

26

The Development of Guidance to industry

A Major product of the IND/NDA review process

Its impact on the efficiency and predictability of medical product development and on expectations for evidence

27

1988

Documentation and Reporting of Clinical Studies

Guideline for Industry

Structure and Content of Clinical Study Reports

- ◆ The 1988 Guideline for the Format and Content of the Clinical and Statistical Sections of a New Drug Application



1990

ICH and the Start of International Harmonization of Biostatistics Principles for Clinical Trials

29

International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use

- ◆ Began in 1990 : six parties - Japan, Europe, U.S. , industry and regulators
 - ◆ Canada, Asia, other regions
- ◆ ICH E9 Guidance would not have occurred without statistical representatives of three regions
- ◆ They were not in place in 1990
- ◆ ICH E9 was one of the last efficacy topics considered

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Guidance for Industry
E9 Statistical Principles for Clinical Trials

Additional copies are available from:
Office of Training and Communication
Division of Drug Information (DDI)-200
Center for Drug Evaluation and Research (CDER)
1401 Rockville Pike, Rockville, MD 20852-1449
http://www.fda.gov/cder/guidance/index.htm

or
Office of Communication, Training and Manufacturers Assistance (OCTMA)-010
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1449
http://www.fda.gov/cber/guidance.htm; Fax: 301-827-0807 or 301-427-1244
If using Telexphone: 300-637-5700 or 301-427-1244

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 1998
8231

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- Statistical Principles for Clinical Trials:**
Published September 16, 1998
www.fda.gov/cder/guidance
- ◆ Introduction (Purpose, scope, direction)
 - ◆ Considerations for Overall Clinical Development
 - ◆ Study Design Considerations
 - ◆ Study Conduct Considerations
 - ◆ Data Analysis Considerations
 - ◆ Evaluation of safety and tolerability
 - ◆ Reporting
 - ◆ Glossary of terms
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- Eight ICH Documents have implications for clinical trials**
- ◆ E - 3 : Clinical Study Reports
 - ◆ E - 4 : Dose - Response
 - ◆ E - 5 : Acceptance of foreign data
 - ◆ E - 6 : Good Clinical Practice
 - ◆ E - 7 : Special populations: Geriatrics
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 - E - 9 : Statistical Principles
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Draft - Not for Implementation

Guidance for Clinical Trial Sponsors
On the Establishment and Operation of Clinical Trial Data Monitoring Committees

Copy of the Draft Guidance is available from:
Office of Training and Communication
Division of Drug Information (DDI)-200
Center for Drug Evaluation and Research (CDER)
1401 Rockville Pike, Rockville, MD 20852-1449
http://www.fda.gov/cder/guidance/index.htm

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September 1998
8231

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Guidance for Industry
E 10 Choice of Control Group and Related Issues in Clinical Trials

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Office of Training and Communication
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 2001
ICH

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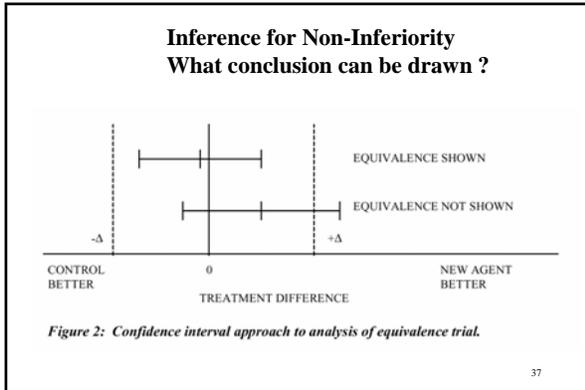
 The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 23 September 1999
CPMP/EWP/2158/99

CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) POINTS TO CONSIDER ON BIostatistical/Methodological Issues Arising from Recent CPMP Discussions on Licensing Applications: CHOICE OF DELTA

I. INTRODUCTION

Following discussions surrounding a number of recent applications, a further topic has been added to the list of statistical/methodological referred to the Efficacy Working Party by CPMP. This is the choice of the margin of equivalence or non-inferiority (delta' or Δ) in comparative clinical trials with these purposes. This issue is referred to in ICH Topics E9 (Statistical Principles for Clinical Trials) and in the Step 2 draft of ICH E10 and also in the recent CPMP position paper on Superiority, Non-inferiority and Equivalence. However, the discussion in these documents is limited.



Statistics in Medicine

Special Issue:
Non-Inferiority Trials:
Advances in Concepts and
Methodology

Volume 22, Issue 2, 2003

38

- Some challenging areas:**
Statistical concepts are critical
- ◆ Non-inferiority clinical study designs and selection of the effect size margins
 - ◆ New study designs - adaptive study designs
 - ◆ Subgroup analysis
 - ◆ Multiplicity issues
 - ◆ Quantitative safety analysis in clinical trials
- 39

Program **P/RMA**

"Clinical, Statistical, and Regulatory Challenges of Multiple Endpoints" Workshop

October 20-21, 2004

Bethesda Marriott
5151 Pooks Hill Road
Bethesda, MD 20814

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Program **P/RMA**

Adaptive Designs Workshop
Opportunities, Challenges and Scope in Drug Development

November 13-14, 2006

Marriott Bethesda North Hotel & Conference Center
5701 Marinelli Road, North Bethesda, MD 20852
Hotel Telephone: 301-822-9200

http://www.innovation.org/index.cfm/NewsCenter/Briefings/Adaptive_Designs_Workshop

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- Clarifying the terminology**
What are adaptive designs ?
- ◆ Distinguish between adaptive strategies and formal prospectively designed 'adaptive designs'
 - ◆ OUR DEFINITION:
 - ◆ An adaptive design is a prospectively designed study to allow for future planned design modifications depending upon the data accrued in the trial up to some interim time; the desire is to modify the study objective or design based on interim knowledge of and access to interim unblinded results from that trial, but to do so in a manner that appropriately controls the type 1 error (or false positive rate) for the multiple options and possibilities that the adaptations allow for. Data from each stage is intended to be combined in some manner
 - ◆ The trial needs to be interpretable at its conclusion and the operational bias needs to be minimized
- 42

The term adaptive may mean:

- ◆ Adaptive change in planned sample sizes
- ◆ Adaptive change in choice of test statistic
- ◆ Adaptive choice of hypothesis (inferiority to superiority)
- ◆ Adaptive choice of a primary endpoint
- ◆ Adaptive choice of one or more dose groups
- ◆ Adaptive allocation to treatment to achieve balance
- ◆ Adaptive allocation to treatment to assign fewer subjects to the inferior treatment
- ◆ Adaptivity to adjust statistical power on what has been observed
- ◆ Adaptivity to drop or add treatment arms
- ◆ Adaptivity to enrich subpopulations

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STATISTICS IN MEDICINE
Statist. Med. 2005; 24:329-339
 Published online 18 November 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/sim.1975

On the efficiency of targeted clinical trials

A. Maitourmam and R. Simon^{*1}

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Perspective Clinical Cancer Research Vol. 10, 6/39-6/63, October 13, 2004

Evaluating the Efficiency of Targeted Designs for Randomized Clinical Trials

Richard Simon and Aboubakar Maitourmam
 Biometric Research Branch, National Cancer Institute, Bethesda, Maryland

ABSTRACT

Purpose: Genomic technologies make it increasingly possible to identify patients most likely to benefit from a **molecularly targeted drug**. This creates the opportunity to **conduct targeted clinical trials with eligibility restricted to patients predicted to be responsive to the drug.**

Experimental Design: We evaluated the relative efficiency of a targeted clinical trial design to an untargeted design for a randomized clinical trial comparing a new treatment to a control. Efficiency was evaluated with regard to number of patients required for randomization and number required for screening.

Results: The effectiveness of this design, relative to the more traditional design with broader eligibility, depends on multiple factors, including the proportion of responsive patients, the accuracy of the assay for predicting responsiveness, and the degree to which the mechanism of action of the drug is understood. Explicit formulas were derived for computing the relative efficiency of targeted *versus* untargeted designs.

Conclusions: Targeted clinical trials can dramatically reduce the number of patients required for study in cases where the mechanism of action of the drug is understood and an accurate assay for responsiveness is available.

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Quantifying risks and harms - improving methodology

Perspective
JULY 13, 2006

STATISTICS AND MEDICINE

Time-to-Event Analyses for Long-Term Treatments — The APPROVe Trial

Stephen W. Lagakos, Ph.D.

The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial¹ compared rofecoxib with placebo in the prevention of recurrent colorectal polyps, but the researchers also collected data on adverse effects after the initiation of treatment. There are several reasons why using such windows might be desirable. First, events occurring during treatment or the subsequent window period might be

N ENGL J MED 355:2 WWW.NEJM.ORG JULY 13, 2006

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Figure 1. Hypothetical 95 Percent Confidence Band for the Difference, $I_{10}(t) - I_0(t)$, between the Cumulative Incidence Curves for the Rofecoxib (I_{10}) and Placebo (I_0) Groups, Constructed from the Results of the APPROVe Trial. Differences lying partly or completely outside the shaded region are inconsistent with the data. Differences lying wholly within the shaded region include the following: separation of the cumulative incidence curves in the two groups at times both before and after 18 months, and consistently higher or lower cumulative incidence in the rofecoxib group before 18 months.

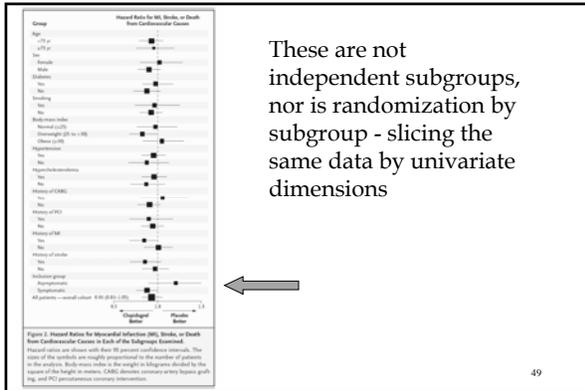
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Subgroup analysis

Discovery vs. Confirmation Promotion (Advertising) of a label claim

- ◆ Personalized medicine
- ◆ Planning for subgroups
- ◆ Searching for subgroups
- ◆ Relationship to 'enrichment' designs

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STATISTICS AND MEDICINE

The Challenge of Subgroup Analyses — Reporting without Distorting

Stephen W. Lagakos, Ph.D. N ENGL J MED 356:16 www.nejm.org APRIL 20, 2006

Related article, page 1706

In the 20 subgroup analyses conducted by Bhatt et al., only one interaction test, for symptomatic versus asymptomatic patients (see the article for the precise definitions), gives an uncorrected P value smaller than 0.05 (0.045). Had the interaction tests been assessed with a criterion of $0.05 \div 20$ (0.0025) to account for the fact that 20 were conducted, none would have come close to reaching statistical significance.

Probability That Multiple Subgroup Analyses Will Yield at Least One (Red), Two (Blue), or Three (Yellow) False Positive Results.

Concluding Remarks

- ◆ Statistical principles are essential to the design, analysis and interpretation of the modern randomized clinical trials - the adequate and well controlled trial
- ◆ Evidence based evaluation of RCT's is FDA's standard for proof of efficacy and safety
- ◆ FDA's review process has evolved to provide advice and guidance during development and study planning as well as scientific review and evaluation
- ◆ NIAID has been a major partner with FDA with the AIDS Clinical Trial Group (ACTG) structure

NOTES PAGE- Clinical Drug Review Process/Issues

Badrul Chowdhury, MD, PhD

Director, Division of Pulmonary and Allergy Products, CDER

Clinical Drug Review Process

Clinical Drug Review Process

Badrul A. Chowdhury, MD, PhD
 Director
 Division of Pulmonary and Allergy Products
 Center for Drug Evaluation and Research
 US Food and Drug Administration

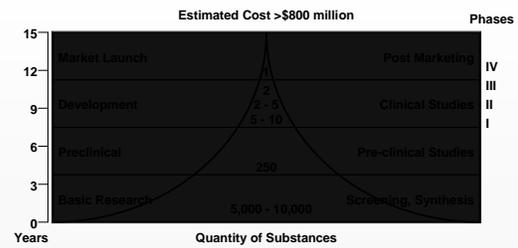
Disclaimer

- In this presentation I am relaying personal views and opinion. This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred.
- I do not have any financial interest or conflict of interest with any pharmaceutical company
- The materials presented are available in the public domain

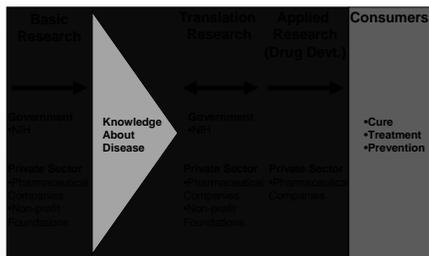
Outline of the Presentation

- Drug development and regulatory control
- New drug application (NDA) and review
- Investigational new drug (IND) application and review

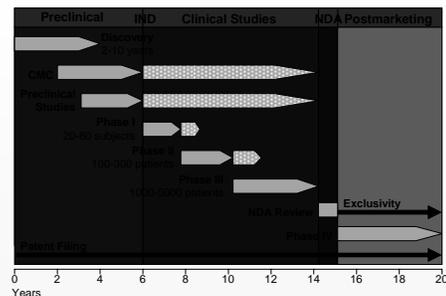
Challenges in Drug Development - Expensive and Risky



Drug Discovery and Development



Drug Development



Clinical Drug Review Process

Evolution of Drug Regulation - Milestones of Drug Safety Regulation

- The Pure Food and Drugs Act of 1906
 - Drug could only be removed from market if government could prove the drug was adulterated or misbranded
- Federal Food, Drug, and Cosmetic Act of 1938
 - Manufacturers had to provide evidence of SAFETY of new drugs before marketing
- The Drug Amendment of 1962
 - Manufacturers had to provide evidence of EFFECTIVENESS in addition to SAFETY before marketing
 - IND process clarified, and distribution of investigational drugs regulated

FDA's Authority

- Federal Food, Drug, and Cosmetic Act (FDC Act)
 - Broadly defines and describes various processes, e.g.,
 - Sec. 201 - defines "drug" and "device"
 - Sec. 503 - prescription vs OTC dispensing
 - Sec. 505(i) - human testing process (IND)
 - Sec. 505(b), Sec. 505(j) - marketing process (NDA, ANDA)
- Code of Federal Regulations (CFR)
 - Written by the FDA to instruct how the FDC Act is to be applied. e.g.,
 - 21 CFR Part 201 - drug labeling
 - 21 CFR Part 312 - IND processes
 - 21 CFR Part 314 - NDA and ANDA processes
- Guidance
 - Written by the FDA to reflect current thinking on specific issues
 - Not binding to the FDA or to the regulated industry

NDA Process

- Sec. 505 of FD&C Act
 - "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless approval of an application filed pursuant to section (b) or (j) is effective with respect to such drug"
- Sec. 505 (d) of FD&C Act
 - Adequate manufacturing and controls to ensure identity, strength, quality, and purity (QUALITY)
 - Safety under conditions of labeled use (SAFETY)
 - Substantial evidence of efficacy under conditions of labeled use (EFFICACY)

Technical Sections of NDA

- 21 CFR 314.50 (d)
 - Chemistry, manufacturing, and controls
 - Nonclinical pharmacology and toxicology
 - Human pharmacokinetics and bioavailability
 - Microbiology
 - Clinical data
 - Statistics
 - Pediatrics
 - Samples and labeling

NDA Clinical Review

- Efficacy
 - Generally supported by two adequate and well-controlled studies, each convincing on its own
 - Occasionally one well-controlled study may be adequate
- Safety
 - Exposure guidelines (ICH E1A: The extend of population exposure to assess clinical safety) require at least 1500 subjects exposed, including 300 to 600 exposed for 6 months or longer, and 100 exposed for 1 year or longer

NDA Review and Action

- FDA review
 - by various review disciplines
- File within 60 days
 - 21 CFR 314.101 describes conditions under which an application can be refused to be filed
- Advisory committee meeting, if necessary
- Action within 10 months for standard application and within 6 months for priority application
 - Approval (21 CFR 314.105)
 - Approvable (21 CFR 314.110)
 - Not Approvable (21 CFR 314.120)

Clinical Drug Review Process

Exemption of IND Requirement

- The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the IND requirements if all of the following apply (21 CFR 312.2(b))
 - the investigation is not intended to be reported to the FDA to support a new indication or significant change in labeling
 - the investigation is not intended to support a significant change in the advertising for the drug product
 - the route of administration, dosage level, patient population, and other factors do not significantly increase the risk or decrease the acceptability of the risks
 - the investigation is conducted in compliance with the requirements of an IRB (21 CFR 56) and with informed consent (21 CFR 50)
 - the investigational drug may not be represented as safe or effective for the purpose for which it is under investigation, nor it may be commercially distributed, or test marketed, or be sold

IND Sponsors

- Commercial entity or investigator
- Health care provider
 - Treatment use of investigational drugs (21 CFR 312.34)
 - Use of investigational drugs for serious and immediately life threatening diseases in patients for whom no satisfactory alternative drug is available
 - Emergency use of investigational drug (21 CFR 312.36)
 - Use of investigational drugs in emergency situation that does not allow time for full IND submission

IND Process

- Sec. 505(i) of FD&C Act
 - "... drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs."
 - Use conditioned on
 - Pre-clinical tests adequate to justify human testing
 - Investigators agree to supervise use of drug and give to no one else
 - Investigators agree to maintain records, and make reports
 - Regulations require informed consent

IND Process

- Technical contents of IND application (21 CFR 312.23)
 - Chemistry, manufacturing, and controls information
 - Pharmacology and toxicology information
 - Previous human experience
 - Investigators brochure
 - General investigational plan
 - Protocols for each planned study

CMC Information

- Assure proper identification, quality, purity, and strength of the investigational drug for safe use in the proposed studies
- Amount of information needed will vary with the scope of the investigation

CMC Information

- Drug substance
 - Description (physical, chemical, or biological characteristics)
 - Name and address of manufacturer
 - General method of preparation
 - Acceptable limits and analytical methods
- Drug product
 - List of all components
 - Name and address of manufacturer
 - Manufacturing and packaging process
 - Acceptable limits and analytical methods
 - Stability during planned clinical studies

Clinical Drug Review Process

Preclinical Information

- Adequate in vitro or animal toxicology studies on the basis of which the investigator has concluded that it is reasonably safe to conduct proposed clinical studies
- Amount of information needed will vary with the duration and nature of the proposed clinical investigation

Preclinical Study Attributes

- Aim is to select a reasonably safe dose for human use
 - Identify toxicities to be monitored in human subjects
 - Identify a no observed adverse effect level (NOAEL) that will guide human dose selection – starting human dose should provide an appropriate safety margin, e.g., 10 fold below NOAEL in most sensitive species
 - Assess reversibility of toxicities
- Study two species, at least one non-rodent species
- Assumptions in lung deposition (with appropriate particle size, e.g., MMAD 5 micron or less for man and dog, and 2 micron or less for rodents)
 - Dog: 15-20% deposited
 - Rat: 7-10% deposited
 - Human: 100% deposited

Investigator's Brochure Content

- Summary CMC information
- Summary pharmacology and toxicology information
- Summary of pharmacokinetics in animals, and human if known
- Summary of safety and effectiveness in humans from previous studies, if available
- Description of possible risks and side effects, and precautions and special monitoring plan

Clinical Study Protocols

- Protocol for each planned study
 - Phase 1 protocol should detail elements that are critical to safety
 - Phase 2 and 3 protocols should be detailed and describe all aspects of the study
- Protocols elements
 - Statement of the objectives and purpose of the study
 - Patient selection criteria
 - Description of study design
 - Method for determination of study drug dose(s) and duration of exposure
 - Description of observations and measurement to be made to fulfill the study objective
 - Description of clinical procedures, laboratory tests, etc., to monitor effects of drugs and to minimize risk

IND Administrative Actions

- IND goes into effect
 - 30 days after FDA receives the IND, unless the IND is placed on a clinical hold
 - Earlier on notification by the FDA

Clinical Holds of IND

- Grounds of imposing clinical holds of phase 1 studies (21 CFR 312.42)
 - Subjects would be exposed to unreasonable and significant risk of illness or injury
 - Clinical investigators are not qualified
 - Investigator brochure is misleading, erroneous, or materially incomplete
 - The IND does not contain sufficient information necessary to assess the risks to subjects in the proposed studies
 - The study excludes subjects of one gender for a drug intended to treat a life-threatening disease

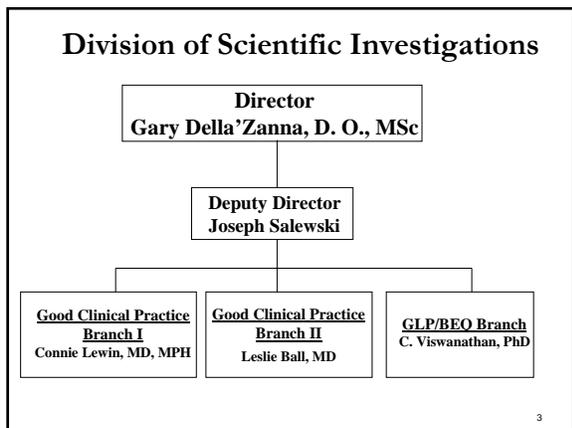
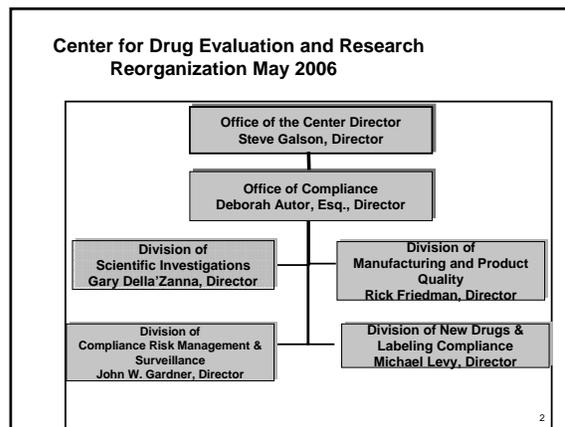
Clinical Holds of IND

- Grounds of imposing clinical holds of phase 2 and 3 studies (21 CFR 312.42)
 - For any of the condition for phase 1 study
 - The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives

NOTES PAGE- DSI's Role in Bioresearch Monitoring/FDA Expectations of Clinical Investigators
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DSI's Role in Bioresearch
Monitoring/FDA Expectations of
Clinical Investigators

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Presentation Outline

- Overview of BIMO
- DSP's Role in BIMO Implementation
- Goals of Inspections: Clinical Investigator Program
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FDA's BIMO Program

- FDA's Bioresearch Monitoring Program - A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.

Program Objectives

- To verify the quality and integrity of research data
- To ensure that the rights and welfare of human research subjects are protected

CDER's BIMO Program Responsibilities

- Ensure adherence to applicable regulations with respect to:
 - Good Laboratory Practice (GLP)
 - *In vivo* Bioequivalence
 - Good Clinical Practice (GCP)
 - Institutional Review Boards
 - Clinical Investigators
 - Sponsor-Monitors, CROs

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About BIMO Inspections

- BIMO inspections can be conducted at any point in the drug development process
- Inspections during **IND phase** are generally “for cause = directed”
- Inspections during the **NDA phase** are generally “routine”, but can be “for cause” or “directed”
- May include Clinical Investigator (CI), Sponsor/Monitoring (S/M), Contract Research Organizations (CRO), Institutional Review Boards (IRB), Good Laboratory Practice (GLP), and Bioequivalence (BEQ) inspection of FDA regulated research.

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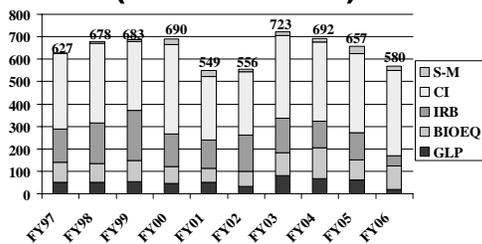
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DSI's Role in BIMO Implementation

- Directs inspections to ensure the protection of the rights and welfare of human research subjects
- Audits and verifies clinical trial data submitted to the FDA
- Ensures that investigators, sponsors, and contract research organizations (CROs) who conduct non-clinical and clinical studies on investigational new drugs comply with United States law and regulations covering GCP and GLP

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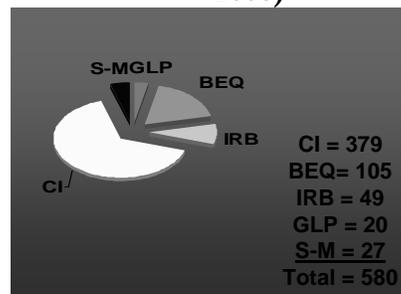
CDER BIMO Inspections (FY 1997-2006)



Based on Inspection Start Date

11

CDER BIMO Inspections (FY 2006)



Based on Inspection Start Date

12

Regulatory Authority to Conduct Inspections/Audits

- 21 CFR 312.68
 - “An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator...”

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How does DSI implement BIMO?

- Consulting service to Review Divisions
- Assigns and Performs inspections through the Office of Regulatory Affairs (ORA) to verify data submitted in support of New Drug Applications (NDAs)
- Investigates allegations of regulatory non-compliance
- Provides a scientific and medical review of Establishment Inspection Reports (EIRs) generated by ORA
- Makes recommendations regarding data to Review Divisions and directs regulatory actions

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General Goals of Inspection: Clinical Investigator Program

- Adherence to applicable regulations with respect to Good Clinical Practice
- Validity of studies in support of marketing applications
- Ensuring that rights, safety and welfare of study subjects have been protected

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Goals of Inspections

- Adequacy of the following:
 - Clinical investigator Qualifications
 - Training/Experience/CV review
 - Clinical investigator oversight of study
 - In-depth knowledge of protocol/study plan
 - Selection of competent staff for delegation of responsibilities
 - Clinical Study Center/Site
 - Informed Consent Procedures
 - IRB approval
 - Adherence to study protocol
 - Test article accountability
 - Recordkeeping

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Clinical Investigator Inspections: What do we look for during the inspection?

- The FDA Inspection (Audit) compares
 - ◊ Source Document Medical Record Data
 - vs
 - ◊ Case Report Forms
 - vs
 - ◊ Data Listing Submitted to NDA
- Verify
 - ◊ Source of subjects; Did subjects exist?
 - ◊ Did they have the disease under study?
 - ◊ Did they meet inclusion/exclusion criteria?
 - ◊ IRB Review Obtained? Consent obtained?
 - ◊ Adherence to protocol?
 - ◊ Verify primary efficacy measure
 - ◊ Adverse events?
 - ◊ Safety data: Labs, EKG etc.
 - ◊ Drug Accountability? Blinding of data?

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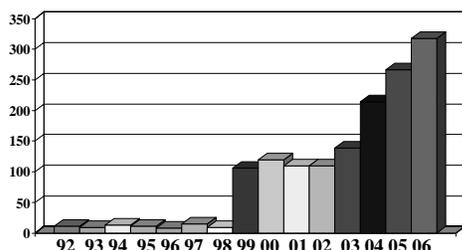
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Rationale for Inspections

- For-Cause
 - Based on complaints from any source
 - Allegations that raise concerns regarding data integrity or the rights, welfare, and safety of study subjects have been compromised
- PDUFA-Related
 - Drug is an NME
 - Pivotal studies not conducted under IND
 - Data in support of application is generated only from foreign data

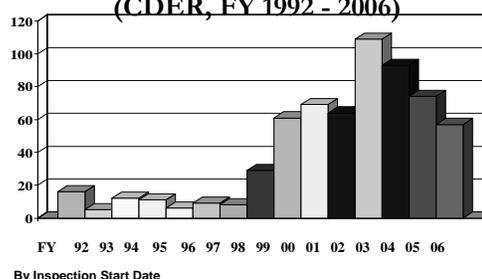
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Complaints Received: 1992-2006 by FY



21

“For Cause” Inspections Clinical Investigator (CDER, FY 1992 - 2006)



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PDUFA-Related: Selection of CIs

- Site selection is a joint process between Review Divisions and DSI
- Site selection based on:
 - A specific safety concern at a particular site or sites
 - based on review of AEs, SAEs, deaths, or discontinuations
 - A specific efficacy concern based on review of site specific efficacy data
 - Efficacy differential between sites
 - Final outcome driven by a particular site or sites
 - Efficacy outcome different than expected based on mechanism of action of drug
 - Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results
 - Previous inspectional history of specific Clinical Investigators

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FDA Expectations of Clinical Investigators

- Adherence to Code of Federal Regulations
 - Knowledge of Clinical Investigator regulations
 - Understanding Clinical Investigator responsibilities

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GCP Regulations

FDA has regulations governing the approval, conduct, review and reporting of clinical research intended for submission

- 21 CFR 312: IND regulations (rev. 2002)
- 21 CFR 50: Informed consent (rev. 2001)
- 21 CFR 56: IRB (rev. 2002)
- 21 CFR 314: NDA regulations (rev. 2002)

These are legally enforceable requirements.

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Definitions

- Investigator: an individual who actually conducts an investigation (under whose immediate direction the drug is administered or dispensed to a subject)
- Clinical Investigation: any experiment in which a drug is administered or dispensed to, or used, involving one or more human subjects

[21 CFR 312.3] 27

General Clinical Investigator Responsibilities

- Ensuring that an investigation is conducted according to the
 - Signed investigator statement (Form 1572)
 - Investigational plan
 - Applicable regulations
- Control of drugs under investigation
- Ensuring that informed consent is adequately obtained according to 21 CFR 50

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Investigator Responsibilities*

- Follow the current protocol [21 CFR 312.60]
- Personally conduct or supervise investigation(s) [21 CFR 312.60]
- Ensure that all persons assisting in conduct of studies are informed of their obligations [21 CFR 312.60]
- Ensure IRB review/approval and reporting requirements are met [21 CFR 56 & 312.66]
- Obtain informed consent of each human subject to whom the drug is administered [21 CFR 50]

*(Form FDA 1572: #9. Commitments) 29

Investigator Responsibilities*

- Notify the sponsor before making changes in the protocol [21 CFR 312.60]
- Notify the IRB and obtain IRB approval before making changes in the protocol [21 CFR 312.60 & 312.66]
- Report adverse events to the sponsor and IRB [21 CFR 312.64 & 312.66]
- Maintain adequate and accurate records
 - Disposition of drugs [21 CFR 312.62 (a)]
 - Case histories [21 CFR 312.62 (b)]
- Maintain Records for a period of 2 years following the date a marketing application is approved [21 CFR 312.62(c)]
- Make records available for inspection [21 CFR 312.68]
- Comply with all other requirements in 21 CFR 312

*(Form FDA 1572: #9. Commitments) 30

Violative Actions

- revise the protocol without obtaining the sponsor's written concurrence
- neglect to submit the revised protocol to IRB for approval
- forget to obtain written informed consent and provide oral explanation of the study
- forget to update consent forms to reflect changes in the protocol

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Violative Actions

- over-delegate to non-physicians (e.g., diagnosis that qualifies/determines eligibility for entry into the study)
- erase, white-out or obliterate original data entry either in CRFs or medical charts
- accept suggested changes to study data without checking the source documents or without justification for such changes

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Violative Actions

- backdate the consent forms and signatures
- forget to obtain IRB approval of consent form revisions
- permit changes to study data without the investigator's concurrence, especially after the investigator has "signed-off" the completed CRF
- blame anyone for inaccuracies in the CRFs

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Violative Actions

- create fake records or patients by using demographic data or using blood, urine and tissue samples from other subjects
- alter patients' diaries to reflect a positive outcome
- use your staff as subjects in a study not having the condition(s) under investigation
- destroy study records

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Inspection Procedures

- DSI submits assignment to ORA
- ORA conducts an inspection
 - FDA Form 483 may or may not be given
- ORA submits Establishment Inspection Report (EIR) to DSI
 - Inspection receives compliance classifications
- DSI reviews EIR
- DSI takes regulatory action if warranted

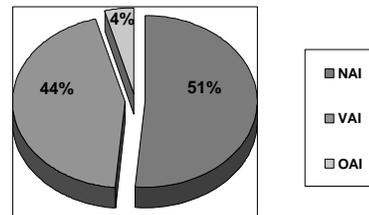
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Compliance Classifications

- NAI** - No Action Indicated
Inspected firm is in compliance
- VAI** - Voluntary Action Indicated
Deviation(s) from the regulations
Voluntary correction is requested
- OAI** - Official Action Indicated
Because of serious non-compliance
requiring regulatory or administrative
action by FDA

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Clinical Investigator Inspections Final Classification* FY 2006



Total inspections with final classification = 364
Includes OAI Untitled Letters

*Based on Letter Date

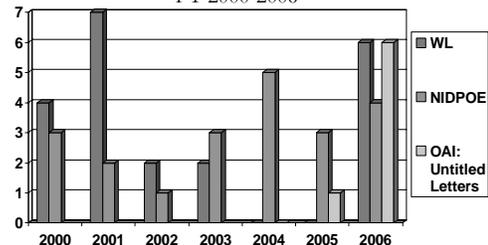
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Consequences of non-compliance (not all inclusive)

- Warning Letters
- NIDPOE Letters
- Disqualification

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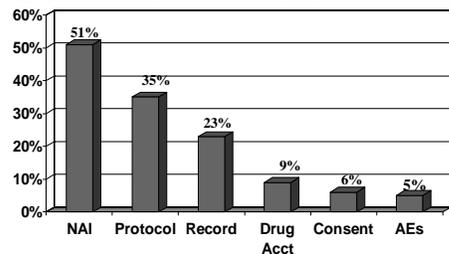
CDER Clinical Investigator OAI Actions (Warning/NIDPOE/OAI:Untitled Letters*) FY 2000-2006



*Based on Letter Date

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Clinical Investigator Deficiencies* CDER Inspections (all) - FY 2006**

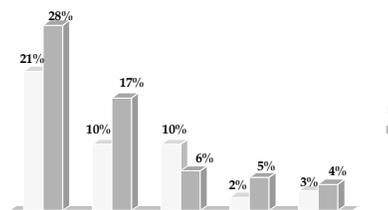


*% of total inspections with final classification in FY 2006; N=364

**Based on Letter Date

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Clinical Investigator Deficiencies CDER Inspections - FY 2006



Based on Letter Issued Date

Foreign n = 89
Domestic n = 290

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- Case Study

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Case Study: Inspection History

- PDUFA inspection request: Site identified by review division for highest enrollment (407 subjects) for study
- FDA inspectional findings: many subjects enrolled were part of a program unrelated to indication sought in application and were enrolled with questionable hx
- Referral to FDA Office of Criminal Investigations (OCI) OCI findings
 - Of 220 subjects interviewed, 201 did not participate; 15 subjects participated; 4 subjects participation unknown
 - Subject #26 was fictitious
 - Many subjects had no knowledge of being enrolled in drug study

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Results of Inspectional Findings

- DSI recommended data be excluded from NDA
- NIDPOE Letter issued

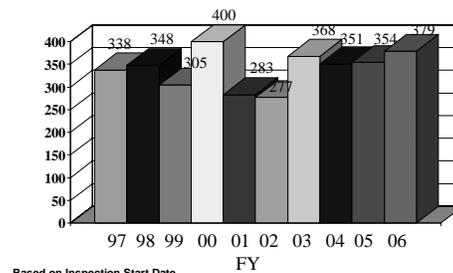
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Helpful Websites

- DSI Homepage: www.fda.gov/ohrt/biobio/biobio/bsi
Includes links to the Clinical Investigator Inspection List (NEW), Bioresearch Monitoring Information Systems (BMIS) files (NEW), Warning Letters, NIDPOE Letters, Lists of Disqualified or Restricted or Debarred Investigators, Code of Federal Regulations, etc.
- FDA Homepage: www.fda.gov
Includes links to the Federal Register Notices, FDA guidance documents.
- Compliance Programs: www.fda.gov/ora/compliance_ref/default.htm

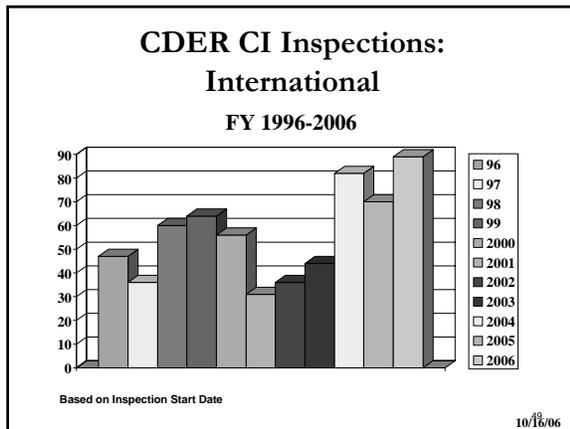
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Clinical Investigator Inspections Center for Drug Evaluation & Research FY 97-06



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10/16/06

DSI's Role in Bioresearch Monitoring



NOTES PAGE- Pharmaceutical Quality Assessment
Moheb Nasr, PhD
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Pharmaceutical Quality Assessment

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**NIAID/CDER Workshop
July 27, 2007**

Outline

- Pharmaceutical Quality Assessment
 - Types of Drug Applications Regulated by CDER
 - Office of New Drug Quality Assessment (ONDQA)
 - ONDQA Review Responsibilities
 - OGD and OBP
 - Investigational New Drug Applications (INDs)
 - CMC Expectations for INDs
 - CMC Expectations for NDAs
- FDA Quality Initiatives
 - FDA View on QbD
- Conclusion

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Types of Drug Applications Regulated by CDER

- Investigational New Drug Application (IND)
 - Section 505(i) of FD&C Act
- New Drug Applications (NDA)
 - Section 505(b) of FD&C Act
- Abbreviated New Drug Application (ANDA)
 - Section 505(j) of FD&C Act
- Biologic Licensing Application (BLA)
 - Section 351 of the Public Health Service Act and in specific sections of the FD & C Act

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Office of New Drug Quality Assessment (ONDQA)

- Review responsibilities include:
 - Review of the Chemistry, Manufacturing, & Controls (CMC) portion for:
 - Investigational New Drug Applications (IND)
 - New Drug Applications (NDA)
 - Post-approval CMC changes
 - Annual Reports
 - Compendial standards evaluation
 - Guidance and Policy development

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ONDQA Review Responsibilities (cont.)

- Drug Substance:
 - Characterization (structure, physico-chemical properties, etc.)
 - Manufacturing Issues
 - Quality Control
 - Container-Closure System
 - Stability (shelf-life)

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Drug Substance (cont.)

- Simple to very complex structures
- Complexity may arise from
 - Various sources and methods of preparation
 - Synthesis
 - Chemical, enzymatic
 - single step, multi-step, stereo-specific, etc.
 - Fermentation - Microbial (antibiotics)
 - Biotechnology - Recombinant, etc.
 - Naturally derived
 - Animal, botanical, mineral
 - Isolation, extraction, purification, etc.
 - Physico-chemical and thermal stability

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ONDQA

Review Responsibilities (cont.)

- Drug Product:
 - Pharmaceutical development
 - Formulation
 - Excipients (physico-chemical properties, performance properties, etc.)
 - Manufacturing issues
 - Quality control
 - Container-Closure System
 - Drug Delivery Systems
 - Stability (shelf-life)

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Drug Product (cont.)

- Simple to most complex
- Complexity may depend upon
 - Physico-chemical, thermal stability of the formulation components
 - Route of administration
 - Onset of action
 - Site of action
 - Dosage form
 - Drug delivery system

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Office of Biotechnology Products (OBP)

- Transferred from CBER, 2002
- Regulatory responsibilities include:
 - Review NDA & BLA applications for therapeutic protein and monoclonal antibody products
 - Conduct Research. Topics include:
 - HIV/AIDS
 - Cell Biology
 - Tumor Biology (solid tumors)
 - Humoral Immunity (Antibodies, B-cell tumors)
 - Cellular Immunity
 - Microbiology (Innate immunity, Counter bioterrorism)

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Office of Generic Drugs (OGD)

- Regulatory responsibilities include:
 - The review and approval of Abbreviated New Drug Applications (ANDA) – also referred to as generic drugs.
 - Labeling of Generic drugs
 - Citizen Petitions for generic drugs

Website: <http://www.fda.gov/cder/ogd/#Introduction>

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Investigational New Drug Applications (IND)

- Subsection 505(i) allows for an exception in the law prohibiting interstate commerce of unapproved drugs in humans
- Application for these exceptions are called 'Investigational New Drug Applications (IND)
- INDs are regulated under 21 CFR part 312 http://www.access.gpo.gov/nara/cfr/waisidx_03/21cfr312_03.html
- Can be sponsored by firms, NIH (Commercial IND) or individual investigators (Research IND)

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IND - General

- "FDA's primary objectives in reviewing an IND are...to ***assure the safety and rights of subjects***, and in Phase 2 and 3, help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety." [21 CFR 312.22]
- Unlike other drug applications, ***IND are not approved***. Rather the clinical studies are either allowed to begin or are placed on Clinical Hold.
- New INDs, unless waived, are required to have a 30-day safety waiting period.

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Types of INDs

- There are 4 general types of INDs:
 - Regular or Research IND
 - The most common type of IND
 - Used to investigate the use of a substance in humans
 - Emergency Use IND
 - Allows the use of an unapproved drug in an emergency situation (one patient, single use)
 - Treatment IND
 - Used to allow patient access to a promising new drug while it is still under review by the FDA
 - Emergency Care IND
 - Pre-approved protocol, waiver of consent

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IND Phases

- Phase 1
 - First introduction into humans to determine metabolism and pharmacological actions, side effects associated with increasing dosing
 - Includes studies of drug metabolism, structure activity relationships, mechanism of action in humans, & drugs used as research tools to explore biological phenomena or disease processes
 - Generally small numbers of patients <100 total

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IND Phases (Cont.)

- Phase 2
 - Initial evaluation of effectiveness and safety; e.g., determination of dose(s), end-points, short-term side effects to monitor
 - Generally several hundred patients in well-controlled (e.g., placebo controlled) studies
- Phase 3
 - Pivotal clinical studies to support safety and effectiveness of the drug
 - Generally large well-controlled studies.

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IND - Content

- Described in:
 - Regulations (21 CFR 312.23)
 - Many guidance and MaPPs
- INDs generally are required to contain sufficient information in the following three categories to permit an assessment as to whether the investigational drug is safe for testing in humans for the intended use:
 - Animal pharmacological and toxicological
 - Manufacture, composition, controls, and stability (CMC)
 - Clinical protocol(s) and list of investigators

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INDs - CMC Expectations

- Amount of CMC information depends upon:
 - Phase of the investigation
 - The proposed testing in humans (e.g., duration, dosage form, route of administration, type of drug)
 - Amount of info already available (e.g., new chemical vs. already marketed compound)

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INDs - CMC Expectations

- In General
 - A description of the drug substance, including its physical, chemical, or biological characterization
 - List of components in the investigational drug, including those used in the manufacture of the drug but are later removed (e.g., solvents, processing aids)
 - Description of the placebo
 - Name & place of manufacture of both the drug substance & investigational drug being administered in the subject
 - General method of preparation
 - Analytical methods and limits to assure the identity, strength, quality, and purity
 - Packaging info
 - Stability information
 - Environmental Assessment – most likely qualifies for categorical exclusion under 21 CFR 25.31

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INDs - CMC Expectations

- Must relate the investigation drug administered in humans to the drug used in animal studies to support safety.
- Changes in manufacture and formulations are expected. IND sponsors must assess the equivalency of the drug after the change. Bridging studies may be necessary.
- May reference DMF, with appropriate LOA, for this information

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IND – CMC Expectations

- Phase 1
 - Guidance for Industry – Content and Format of Investigational New Drugs (INDs for Phase 1 studies of drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (Nov. 1995)
 - Emphasis on information needed to assess safety of subjects in proposed study
 - Any unknown or impure components
 - Toxicity of the compound
 - Investigational drug characteristics of potential health hazard
 - Stability of the investigational drug throughout the proposed study
 - Methods and limits to assure ID, quality, purity, & strength of the investigational drug
 - Poorly characterized master or working cell bank
 - Detailed information on the manufacture, characterization, specifications & test methods, and long-term stability are not expected until Phase 2/Phase 3
 - Enough stability for the length of Phase 1 study to assure that the investigational drug is within acceptable chemical & physical limits for the planned clinical & toxicological studies

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IND – CMC Expectations

- Phase 2/3
 - Guidance for Industry – INDs for Phase 2 and Phase 3 Studies – Chemistry, Manufacturing, and Controls Information (May 2003)
 - More detailed descriptions of the investigational drug, method(s) of manufacture, revised methods and limits to ensure identity, quality, purity, & strength
 - Chemical structure/configuration & physical properties elucidated
 - Updated impurity information and controls
 - Representative batch formula
 - Reference standards, if needed, and tentative analytical methods & specifications established
 - More control of starting materials
 - Stability for at least the length of the clinical studies. In addition, stress studies to assess the sensitivity to pH, presence of oxygen, light, high temperatures, and high humidity.

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CMC Expectations for NDAs

- Full description of the composition, manufacture, and specifications under 21 CFR 314.50(d)(1) and, for ANDAs, 21 CFR 314.94
- Must include Chemistry, Manufacturing, and Controls (CMC) info on:
 - Drug substance
 - Drug product and excipients
 - Packaging components
- Additional information as appropriate (e.g., comparison studies)

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Drug Substance (DS)*

- Full description of the drug substance
 - Identity, physical, and chemical characteristics, and Stability
 - Method of synthesis (or isolation) and purification, including appropriate selection of starting materials
 - Manufacturing process controls (quality controls)
 - Specifications (including test methods) necessary to ensure purity and drug product performance
 - Level and qualification of impurities**
 - Container closure and stability information
- Name, address, & contact info of manufacturer
- May reference DMF, with appropriate LOA, for this information

*regulation citation: 21 CFR 314.50(d)(1)(ii)

**ICH guidance Q3a&c

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Drug Substance Stability

- Retest date or expiry assigned based upon data
- Stability testing protocol
 - Stability testing under controlled conditions
 - Accelerated 45°C/75% RH
 - Room Temperature (RT) 25°C/60% RH
 - Tests & acceptance criteria
 - Stability indicating assay
 - Testing frequency
 - ICH Q1A
- Container closure system representative of large bulk container/drum
- Submission expectations
 - For NDAs
 - 3 batches - 6 months RT and accelerated data
 - May statistically project expiry up to 6 months past RT data (trending!)
 - For ANDAs
 - 1 batch - 3 months accelerated
 - 3 months satisfactory accelerated data may permit 24 months expiry

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Drug Product*

- The marketed dosage form designed to consistently deliver the drug substance at the desired rate
- Complexity may depend upon:
 - Physico-chemical, thermal stability of the formulation components
 - Route of administration
 - Onset of action
 - Site of action
 - Dosage form
 - Drug delivery system

*Regulation citation: 21 CFR 314.3(b)

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Drug Product (DP)*

- Description & composition/formulation of the DP
 - A list of all components used in the manufacture of the DP, even if removed during manufacturing (e.g., solvents)
 - Composition of the drug product
 - Quantitative composition of drug product
 - List sub-formulations separately (e.g., tablet coating, mixture of IR and MR granules)
 - List tracers
 - Proprietary mixtures such as colors or flavors can be listed by their proprietary name (e.g., DMF)
 - Excipients on the "inactive ingredient list" for the amount and dosage form used do not need to be qualified

*Regulation citation: 21 CFR 314.50(d)(1)(ii)

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Drug Product (cont.)

- Name, address, & contact info of the DP manufacturer(s)
- Description of the manufacturing & packaging processes, including process controls
- Container closure system
- Sterility assurance for sterile products
 - Guidance:
 - <http://www.fda.gov/cder/guidance/ohd031fn.pdf>
 - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
- Drug Delivery Systems, if appropriate
 - Modified release dosage forms
 - Transdermal patches
 - Oral inhalation drug products
- Environmental Assessment
 - Regulation citations: 21 CFR 25.30, 25.31, & 25.40
 - Guidance for Industry for the submission of Environmental Assessment for Drug Applications and supplements (Nov. 1995)

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Drug Product Stability (shelf life)*

- To establish expiry based upon data
- Stability Protocol
 - Storage Conditions
 - Room temperature (RT) (25°C/60% relative humidity)
 - Accelerated (40°C/75% relative humidity)
 - Tests & acceptance criteria
 - Stability indicating assay
 - Testing frequency
 - ICH Q1A
- Submission expectations
 - For NDAs
 - 3 batches - 6 months RT and accelerated data
 - May statistically project expiry up to 6 months past RT data (trending!)
 - For ANDAs
 - 1 batch - 3 months accelerated
 - 3 months satisfactory accelerated data may permit 24 months expiry

*see ICH guidance Q1

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Drug Product - Specifications

- Specifications are the quality standards (i.e., tests, analytical procedures, & acceptance criteria) provided in the application to ensure the quality and performance of the DS, DP, intermediates, raw materials, reagents, container closure systems, etc. in order to assure safety and efficacy
- Examples for solid oral dosage forms may include:
 - Appearance
 - Assay/potency
 - In-vitro dissolution or disintegration test
 - Impurity profile
 - Content uniformity
 - Other critical quality attributes, as appropriate
- USP monograph/public standards are considered minimum requirements
 - Additional specifications may be needed (e.g., impurities)

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Additional considerations

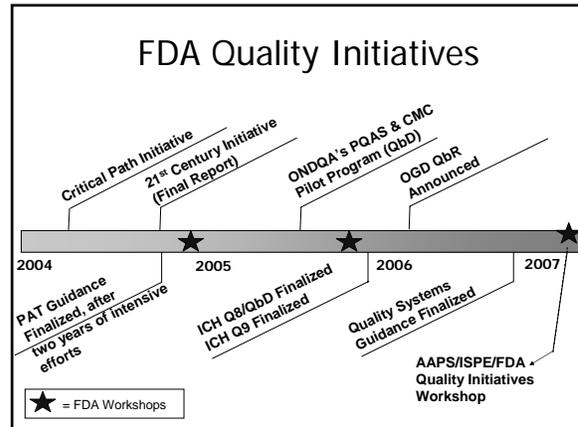
- All facilities used in the manufacture of the drug (i.e., DS, DP, packagers, testers) should be ready for inspection upon submission of the application
- Facilities should operate under Current Good Manufacturing Practices (CGMPs)
 - CGMP Regulations 21 CFR 210 & 211
 - CGMP Guidances
 - <http://www.fda.gov/cder/guidance/index.htm#CGMPs-Eff>
 - Inspection will evaluate conformance to CGMPs

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References

- Content and format of an application – 21 CFR 314.50
- Guidances (including ICH):
 - <http://www.fda.gov/cder/guidance/index.htm>
- MaPPs: <http://www.fda.gov/cder/mapp.htm>
- GMPs: <http://www.fda.gov/cder/regulatory/applications/compliance.htm>
- Additional helpful information: <http://www.fda.gov/cder/regulatory/default.htm#Regulatory>

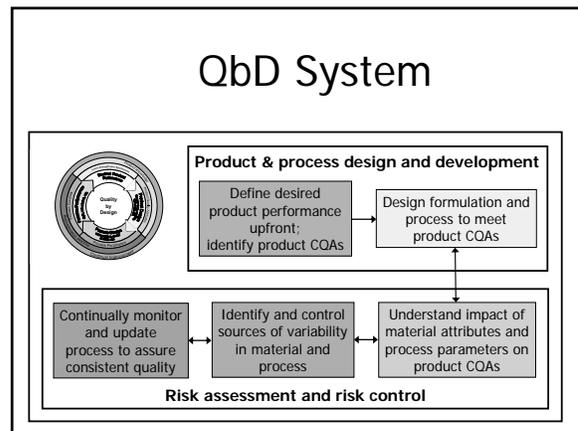
31



FDA View on QbD

- Quality by Design is:
 - Scientific, risk-based, holistic and proactive approach to pharmaceutical development
 - Deliberate design effort from product conception through commercialization
 - Full understanding of how product attributes and process relate to product performance
- **QbD information and conclusions should be shared with FDA**

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Quality by Design (QbD) – A Comprehensive Systematic Approach to Pharmaceutical Development and Manufacturing

Aspects	Traditional	QbD
Pharmaceutical Development	Empirical; typically univariate experiments	Systematic; multivariate experiments
Manufacturing Process	Fixed	Adjustable within design space; opportunities for innovation (PAT)
Process Control	In-process testing for go/no-go; offline analysis w/ slow response	PAT utilized for feedback and feed forward at real time
Product Specification	Primary means of quality control; based on batch data	Part of the overall quality control strategy; based on desired product performance (safety and efficacy)
Control Strategy	Mainly by intermediate and end product testing	Risk-based; controls shifted upstream; real-time release
Lifecycle Management	Reactive to problems & OOS; post-approval changes needed	Continual improvement enabled within design space

Why QbD?

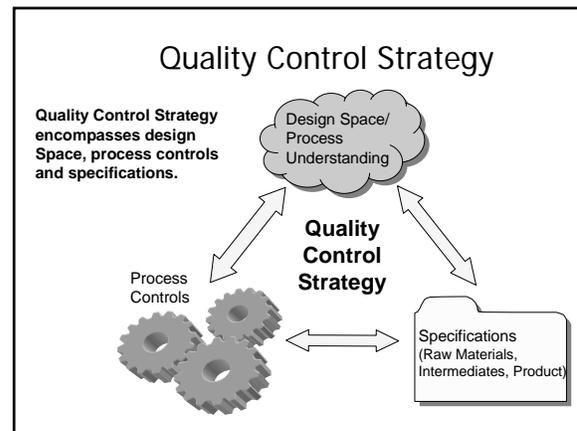
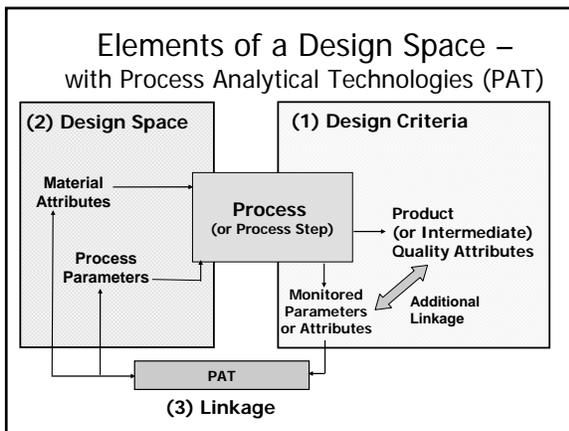
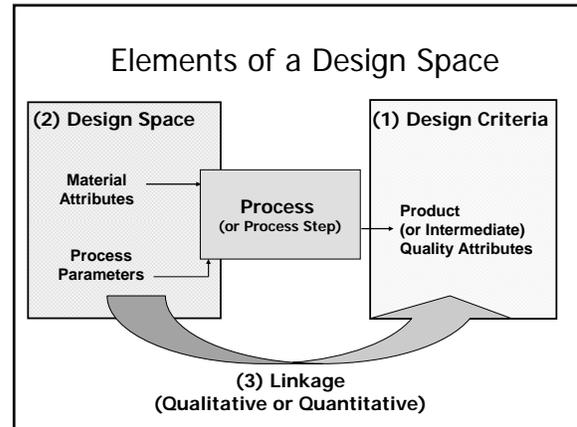
- Higher level of assurance of product quality
- Cost saving and efficiency for industry and regulators
 - Facilitate innovation to address unmet medical needs
 - Increase efficiency of manufacturing process and reduce manufacturing cost and product rejects
 - Minimize potential compliance actions, costly penalties and recalls
 - Enhance opportunities for first cycle approval
 - Streamline post approval manufacturing changes and regulatory processes
 - More focused PAI and post approval cGMP inspections
 - Opportunities for continual improvement

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Design Space

- Definition
 - The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality
 - Traditional one dimensional process range doesn't meet Q8 definition and will not lead to "regulatory flexibility"
- Regulatory Significance
 - Working within the design space is not considered as a change
- Important to Notice
 - Design space is proposed by the applicant and is subject to regulatory assessment and approval.

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Conclusions

- **The current system is adequate for regulatory submission**
 - Quality is assured by testing and inspection
 - Considerable regulatory oversight
- **However, QbD is the desired approach**
 - QbD principles should result in a higher level of assurance of product quality
 - Additional product and process understanding may result in regulatory flexibility
- **Focus remains on availability of safe, effective and high quality pharmaceuticals**

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NOTES PAGE- Closing Remarks: Contacts and Answers to your questions
Shirley Murphy, M.D.
Director, Office of Translational Sciences, CDER

How to find FDA information fast

Shirley Murphy, M.D.

- Much of what FDA does is in the public domain
- www.fda.gov has a wealth of information
 - Drugs – product information and reviews
 - Advisory Committees – transcript and slides
 - Guidance Documents – how FDA communicates it's best thinking with the outside world

1

www.fda.gov

The screenshot shows the FDA website homepage with the following sections:

- Search:** A search bar with a 'GO' button and 'Powered by Google' text.
- A-Z Index:** A link to 'Site Map'.
- Products FDA Regulates:**
 - Food: Foodborne Illness, Nutrition, Dietary Supplements...
 - Drugs: Prescription, Over-the-Counter, Generic...
 - Medical Devices: Pacemakers, Contact Lenses, Hearing Aids...
 - Biologics: Vaccines, Blood Products...
 - Animal Feed and Drugs: Livestock, Pets...
 - Cosmetics
- Consumer Health Information:**
 - Criminal Investigations at FDA
 - All Consumer Health >>
- Food Industry:**
 - Register a Facility
 - Prior Notice of Imports
- Hot Topics:**
 - New! Chili Products (Botulism) Recall
 - DCG in Toothpaste from China
 - Pat Food Recall
 - Buying Medicines Online
 - Counterfeit Drugs
 - Counterfeitism
 - Botulism Act
 - More Hot Topics...
- FDA Activities:**
 - About FDA
 - FDA FY 2008 Budget
 - Advisory Committees
 - Clinical Trials
 - Consumers
 - Professionals
 - Field Operations
 - Freedom of Information
 - Imports
 - International
 - Manufacturing
- FDA NEWS:**
 - FDA Nanotechnology Report Outlines Scientific, Regulatory Challenges
 - FDA Expands Its Nationwide Warning about the Risk of Botulism Poisoning From Certain Castileberry's Food Products and Dog Food
 - FDA Issues Nationwide Warning to Consumers About Risk of Botulism Poisoning From Hot Dog Chili Sauce Marketed Under a Variety of Brand Names
 - FDA Approves First of a Kind Medical Device to Treat Central Degenerative Disc Disease
 - FDA Approves First Molecular-Based Lab Test to Detect Metastatic Breast Cancer
- Subscribe to Multimedia News:**
 - RSS Feeds: [Human Health](#), [Press Releases](#), [Recalls & Alerts](#), [All RSS Feeds](#)
 - Podcasts: [What is a podcast?](#), [Patient Safety News](#), [Cosmetics](#), [Drug Safety](#)

How to find Drug information

This screenshot is identical to the one above, but includes a black arrow pointing to the 'Drugs' link under the 'Products FDA Regulates' section.

The screenshot shows the CDER Human Drugs page with the following sections:

- CDER Home | About CDER | Drug Information | Regulatory Guidance | CDER Calendar | Specific Audiences | CDER Archives**
- CDER Human Drugs** (with a search bar)
- News from CDER:**
 - July 5: FDA approves the first generic versions of prescription Lamal (lornoxicam hydrochloride) tablets, used to treat nail fungus infection (onychomycosis). [FDA News](#)
 - July 2: FDA issues a safety alert foromalzumab (marketed as *olaris*) Smallmolecule Information
 - June 28: FDA issues a Public Health Alert and Healthcare Professional Sheet for Colistimethate Drug Information | Podcast
- Drug Safety:**
 - About FDA's Drug Safety Initiative
 - For Patients and Healthcare Professionals: Safety Information for Specific Drugs
 - Consumer Education/Information: Resources to help you make informed decisions about using medicines.
 - FDA Drug Safety Podcasts
- Quick Info Links:**
 - Drugs@FDA:** Brand and Generic Drugs, Labels, Approval Histories, and more
 - Drug Information Database
 - Drug Shortages
 - Inactive Ingredient Database
 - MedWatch
 - National Drug Code Directory
 - Orange Book
 - Postmarketing Study Commitments

The screenshot shows the Drugs@FDA search page with the following elements:

- Navigation:** [FAQ](#) | [Instructions](#) | [Glossary](#) | [Contact Us](#) | [CDER Home](#)
- Search by Drug Name, Active Ingredient, or Application Number:**
 - Enter at least three characters: [Advanced Search](#)
- Browse by Drug Name:**
 - A B C D E F G H I J K L M N O P Q R S T U V W X Y Z 0-9
- Drug Approval Reports by Month:**
- Disclaimer:**
 - [CDER Home Page](#) | [CDER Site Info](#) | [Contact CDER](#) | [What's New @ CDER](#)
 - [FDA Home Page](#) | [Search FDA Site](#) | [FDA A-Z Index](#) | [Contact FDA](#) | [Privacy](#) | [Accessibility](#) | [HHS Home Page](#)

The screenshot shows the Drugs@FDA drug details page for AVANDIA with the following information:

- Drug Name(s):** AVANDIA (Brand Name Drug)
- FDA Application No.:** (NDA) 021071
- Active Ingredient(s):** ROSIGLITAZONE MALEATE
- Company:** SB PHARMCO
- Original Approval Date:** May 25, 1999
- Chemical Type:** 1 New molecular entity (NME)
- Review Classification:** P Priority review drug
- Additional Information:**
 - There are no Therapeutic Equivalents
 - Approval History, Letters, Reviews, and Related Documents
 - Label Information
 - Other Important Information from FDA
- Products on Application (NDA) #021071:**
 - Click on a column header to re-sort the table:

Contacts and Answers

Endocrinologic and Metabolic Drugs Advisory Committee

Executive Secretary: Cathy A. Miller, MPH, RN, (HFD-21), (301) 827-7001

July 30, 2007

- Notice of Meeting [TEXT] [PDF] [PRE-PUB]
- Nature and Basis Statements of Conflict(s) of Interest for July 30, 2007 Meeting (htm)

June 13, 2007

- Notice of Meeting (pdf) (htm)
- Draft Agenda (pdf)
- Draft Meeting Roster (pdf)
- Draft Committee Roster (pdf)
- Briefing Information (htm)
- ERRATA to Briefing Information for June 13, 2007 Meeting (pdf)
- Final Questions (ppt) (htm)
- Draft Questions (pdf)
- Slides for June 13, 2007 Meeting (htm)
- Final Minutes (pdf)
- Transcript (Index.pdf), (Part3.pdf), (Part2.pdf), (Part3.pdf), (Part4.pdf)

Guidance Documents

FDA Guidance Documents

Guidance documents represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.

If you believe an FDA employee is not following FDA's Good Guidance Practice regulations (21 CFR 10.115) or the Office of Management and Budget's Bulletin No. 07-02(M 07-07) Final Bulletin for Agency Good Guidance Practices (January 18, 2007), you should contact the employee's supervisor in the issuing office or Center. If the issue is not resolved, contact the next highest supervisor or the Center's Ombudsman. If the issue is still not resolved, contact the FDA's Office of the Ombudsman at:

FDA Office of the Ombudsman
5600 Fishers Lane, Rm. 138-07
Rockville, MD 20857
Phone: 301-827-3390
Fax: 301-486-8039
Email: Ombuds@oc.fda.gov

Guidance Documents from FDA's Centers:

- Center for Biologics Evaluation and Research
- Center for Devices and Radiological Health
- Center for Drug Evaluation and Research
- Center for Food Safety and Applied Nutrition
- Center for Veterinary Medicine
- Office of Regulatory Affairs

Office of the Commissioner:

- Exports Under the FDA Export Reform and Enhancement Act of 1996 (PDF, 233 KB)
- Computerized Systems Used in Clinical Trials (PDF) (May 10, 2007)

Guidance Documents

Newly Added Guidance Documents: Guidance Documents will be retained in this section of the page for a period of three months. The most recently added appears first and they are in the order of the date they were issued.

* Note: Draft guidances are undergoing finalization. Please contact the relevant division for the most up-to-date Agency perspective on an issue. For information on how to electronically submit a comment on a draft guidance, please see <http://www.fda.gov/oc/acm/backrounders/voice.html>

Search for Guidance Documents:

CDER Guidance Documents [Search] [Clear]

Enter words or phrases. (See Help for search tips)

Guidances Arranged by Subject

- Advertising
- Biopharmaceutics
- Current Good Manufacturing Practices (CGMPs)
- Chemistry
- Clinical Antimicrobial
- Clinical Medical
- Clinical Pharmacology
- Combination Products
- Compliance
- Good Review Practices
- Industry Letters
- International Conference on Harmonisation - Efficacy
- International Conference on Harmonisation - Joint Safety/Efficacy (Multidisciplinary)
- International Conference on Harmonisation - Quality
- International Conference on Harmonisation - Safety
- Industry Letters
- Labeling
- Microbiology
- Modernization Act
- Over-the-Counter
- Pharm/Tos
- Procedural
- Small Entity
- Compliance Guides
- User Fees

Contacts and Answers

A Day with the FDA: CDER and NIAID Working Together

TITLE OF PAGE	URL ADDRESS
CDER Homepage	http://www.fda.gov/cder/
CDER Organization Charts and Directories	http://www.fda.gov/cder/cderorg.htm
Pharmacology and Toxicology Contacts	http://www.fda.gov/cder/PharmTox/contact.htm
Pharmacology and Toxicology Guidances	http://www.fda.gov/cder/guidance/#Pharmacology/Toxicology
Counterterrorism	http://www.fda.gov/oc/opa.com/hottopics/bioterrorism.html
Investigational New Drug (IND) Application Process	http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm
Clinical Trials	http://www.fda.gov/oashi/clinicaltrials/default.htm
Office of Biostatistics: General Information	http://www.fda.gov/cder/Offices/Biostatistics/default.htm
Division of Scientific Investigations	http://www.fda.gov/cder/Offices/DSL/goodLabPractice.htm

A Day with the FDA: CDER and NIAID Working Together

TITLE OF PAGE	URL ADDRESS
Office of New Drugs and Quality Assessment	http://www.fda.gov/cder/Offices/ONDQA/default.htm
Index to Drug-Specific Safety Information	http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm
Medication Errors	http://www.fda.gov/cder/drug/MedErrors/default.htm
Drug Database	http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
Bioresearch Monitoring Information System	http://www.accessdata.fda.gov/scripts/cder/bmis/
Clinical Investigator Inspection List	http://www.accessdata.fda.gov/scripts/cder/cihl/
CDER Pre-IND Consultation Contacts	http://www.fda.gov/cder/ode4/preind/Pre-INDConsultationList.pdf
Guidance for Industry E6 Good Clinical Practice : Consolidated Guidance	http://www.fda.gov/cder/guidance/959fnl.pdf
Drug Approval Application Process	http://www.fda.gov/cder/regulatory/applications/default.htm

“You will never work at a more interesting place than the FDA”

**Jane Henney, M.D.
Personal communication 2002**

USEFUL LINKS

TITLE OF PAGE	URL ADDRESS
CDER Homepage	http://www.fda.gov/cder/
CDER Organization Charts and Directories	http://www.fda.gov/cder/cderorg.htm
Pharmacology and Toxicology Contacts	http://www.fda.gov/cder/PharmTox/contact.htm
Pharmacology and Toxicology Guidances	http://www.fda.gov/cder/guidance/#Pharmacology/Toxicology
Counterterrorism	http://www.fda.gov/oc/opacom/hottopics/bioterrorism.html
Investigational New Drug (IND) Application Process	http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm
Clinical Trials	http://www.fda.gov/oashi/clinicaltrials/default.htm
Office of Biostatistics: General Information	http://www.fda.gov/cder/Offices/Biostatistics/default.htm
Division of Scientific Investigations	http://www.fda.gov/cder/Offices/DSI/goodLabPractice.htm
Office of New Drugs and Quality Assessment	http://www.fda.gov/cder/Offices/ONDOQA/default.htm
Index to Drug-Specific Safety Information	http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm
Medication Errors	http://www.fda.gov/cder/drug/MedErrors/default.htm
Drug Database	http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
Bioresearch Monitoring Information System	http://www.accessdata.fda.gov/scripts/cder/bmis/
Clinical Investigator Inspection List	http://www.accessdata.fda.gov/scripts/cder/cliil/
CDER Pre-IND Consultation Contacts	http://www.fda.gov/cder/ode4/preind/Pre-INDConsultationList.pdf
Guidance for Industry E6 Good Clinical Practice : Consolidated Guidance	http://www.fda.gov/cder/guidance/959fnl.pdf
Drug Approval Application Process	http://www.fda.gov/cder/regulatory/applications/default.htm