

# ***Current FDA Activities, Future Concepts & Barriers***

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**FDA**

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# Sharing Data and Models to Improve Clinical Drug Development and Regulatory Decisions

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*Join leaders from industry, FDA, and academics in an open forum to discuss the "whys" and "hows" of sharing data/models of diseases, drugs, placebo, baseline, and dropouts.*

**OVERVIEW** Clinical trial failure in late development (Phase 3) is a risk that companies cannot afford, particularly if the failure is predictable. The FDA Critical Path Opportunities List recognizes several joint development paths that could improve pharmaceutical productivity and reduce failure rates. These paths include:

- Better understanding of prior information in making current drug development and approval decisions
- Better understanding of disease through biomarkers
- Application of modern bioinformatics to mine prior knowledge (e.g., NDAs) sources

Oftentimes, useful prior clinical trial information that could improve drug development efficiency is lost within companies and at the FDA. This information could help us to better understand the biomarker relationship to primary disease endpoints, disease change over time, placebo effect, and drug effect on disease. These quantitative relationships can help employ biomarkers (e.g., biochemical, imaging, genomic) in dose finding, the creation of new surrogate markers, planning of effective clinical trials, and making better clinical development and regulatory decisions.

## CONFERENCE HIGHLIGHTS

- ▶ How to routinely and effectively share clinical trial information
- ▶ Information on specific disease models (Parkinson's disease, Type 2 diabetes, depression, non-small cell lung cancer)
- ▶ Experiences of prior industrial consortiums
- ▶ Breakout sessions to explore desirable attributes for a disease model library and the post-meeting actions needed for progress

## TARGET AUDIENCE

- ▶ Physicians
- ▶ Pharmacometricians and PK/PD scientists
- ▶ Biostatisticians
- ▶ Regulatory affairs professionals
- ▶ Clinical pharmacologists

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# ***Implementing Change at CDER***

## **Personal thoughts**

- **Scope of projects**
- **Organizational challenges**
- **2 Cases**
  - **QT- centralized**
  - **EOP2a- decentralized**
- **Suggestions to facilitate change**

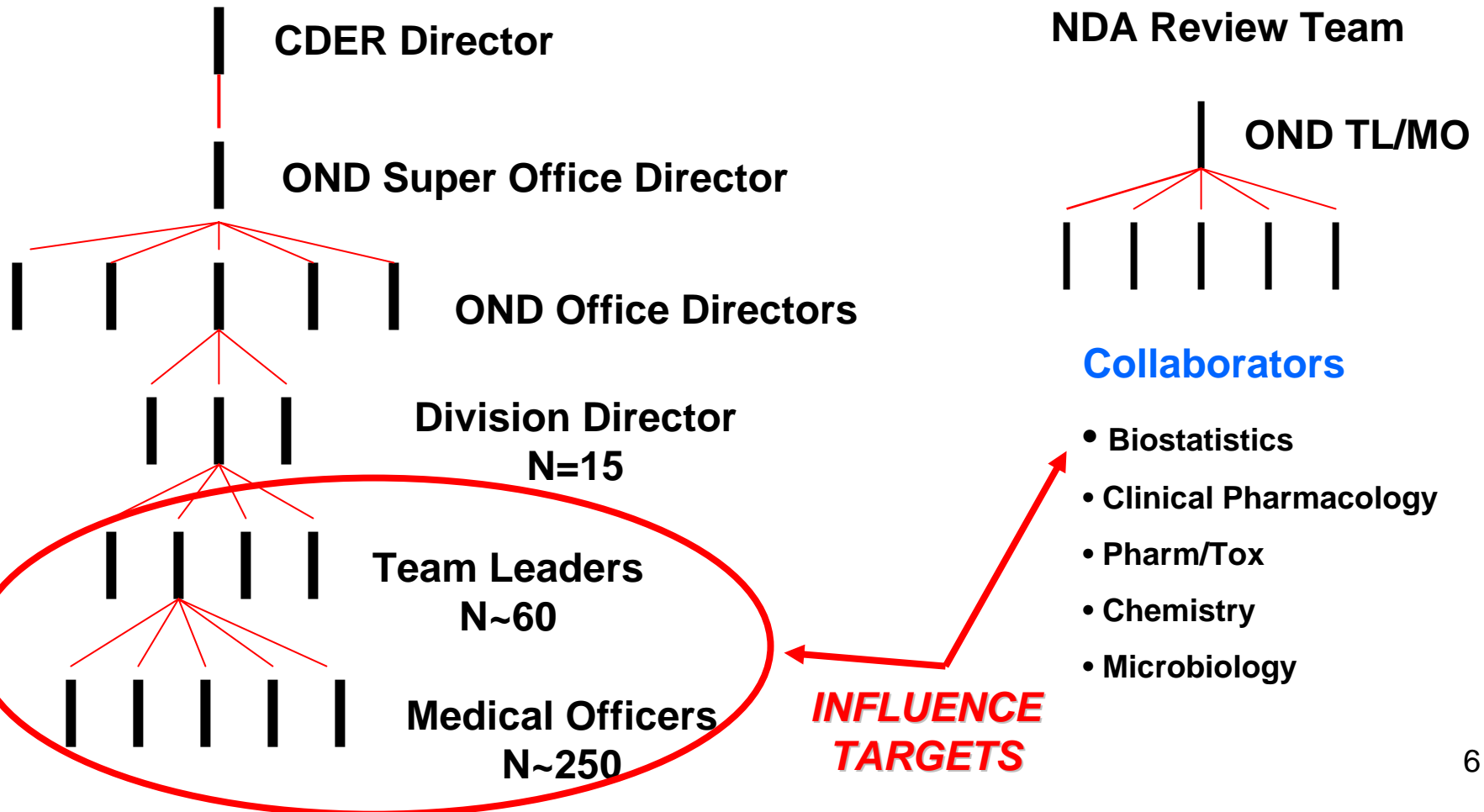
# ***A Few Change Initiatives at FDA***

- **Qualification concept paper**
- **Microarray stds consortiums**
- **Drug-diagnostics co-development guidance**
- **Oncology biomarkers**
  - **Imaging**
  - **Molecular assays**
  - **Clinical trial designs**
  - **Data mining**
- **Efficacy surrogates of cardiac drug eluting stents**
- **Imaging clinical protocol standards for clinical trials**
- **Multicolor flow cytometry**
- **CDISC**
- **Predicting nephrotoxicity**
- **Predicting hepatotoxicity**
- **ECG data warehouse for more efficient clinical trials**
- **Genetics of adverse events**
- **Mumps vaccine-predict minimally effective Ab response**
- **HIV vaccine-assay to measure efficacy**
- **Disease models-data mining**
- **eIND**
- **CGMPs**
- **EOP2a**
- **Multiple endpoints**
- **Adaptive trial designs**
- **Enrichment designs**
- **Non-inferiority designs**
- **Handling missing data**

# ***CDER Challenges to Change***

- **Many initiatives with fixed resource**
- **Decision making process**
- **Decentralized organization**
- **PDUFA time metrics**
- **Regulatory culture-inherent skepticism**

# ***CDER Structural & Decision Making Considerations (NCE NDAs)***



# **Case 1: *QT Consult Team Implementation***

- **Drivers for change**
  - **Problem: QT strategy, trials, data analysis for all NCE NDAs across 15 OND divisions**
  - **Science evolving**
  - **Aggregate data to learn (endpoints, design)**
  - **Expensive trials: need to get it right 1<sup>st</sup> time**
  - **FDA recommendations influence sponsor decisions & product value**
  - **Variable expertise across CDER**

**Sponsor**

**CDER Governance  
(Board, Division Head)**

Protocol, Final report  
↓  
↑  
Recommendations,  
Risk/benefit  
interpretation

- Charter
- Plan
- Routine reports

- Approve plans & reports
- Resources
- Conflict Resolution

Protocols, Final Reports

**OND Divisions &  
Teams (N=15)**

**QT Services & Research Team  
(MD, Stats, CP, P'col)**

Recommendations

- Risk/benefit interpretation
- Label judgment & text

- Deliverables:**
- Consultations (Internal)
    - QT Protocols
    - Final Studies (quantitative assessment & report)
  - Maintain databases for
    - QT trial data
    - Consultations & labels
  - Routine report to Board & Customers
    - Metrics, consults, literature update
  - Research focus
    - Mine database to improve standards & interpretation
    - Preclinical to clinical prediction value

# **Case 2: *End of Phase 2a Meetings***

- **Drivers for change**
  - High rate of Phase 3 trial failure
  - Root causes thought to be predictable in part
  - Share information & expertise inside FDA

## **Case 2: *End of Phase 2a Meetings***

- **Phase 1-2a data analyzed for dose selection & Phase 2b/3 trial design**
- **10 meetings total over past 2 years (e.g., antivirals, endocrine, neuro, repro, analgesia)**
- **4-6 weeks of work, several inside meetings & sponsor meetings**
- **Post-meeting evaluation (1=worthless, 5=pivotal)**
  - **Sponsors average 4.3**
  - **FDA average 3.2**

# ***Contrast Between 2 Cases***

<b>Dimension</b>	<b>QT</b>	<b>EOP2a</b>	<b>Adaptive Design</b>
<b>New, Innovation</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>Required</b>	<b>Yes</b>	<b>No</b>	<b>Evaluation: yes Approval: no</b>
<b>Time consuming</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>Less work for FDA Division</b>	<b>Yes</b>	<b>No, more</b>	<b>No, more</b>
<b>Value added FDA/Industry</b>	<b>Yes/Yes</b>	<b>?/Yes</b>	<b>?/?</b>

# ***Recommendations***

- **Buy-in**
  - Synchronize implementation & change with FDA
- **Focus**
  - Phase 1-2a seamless adaptive higher priority for learning
    - Within company control, can study it, develop tools, then move to Phase 3 when & where it makes sense
- **Resource**
  - Phase 2-3 seamless adaptive has FDA resource implications. Who owns solution?
- **Trial design justification**
  - Begin dialogue on plan & simulation conditions 1 year before
  - Simulate trial design alternatives (parallel vs adaptive)
- **Metrics**
  - Pre-specify likely impact metrics, measure & report publicly
- **Communication**
  - Case studies
  - Public meetings
  - Publications

# *Alternatives*

## CHAOS



# *Diffusion of Innovations* Peter de Jager

## ORDER

