Global Clinical Development and Best Regulatory Meeting Practices in US, EU, Japan and China

• Alberto Grignolo, Ph.D
PAREXEL Consulting
Factors Driving the Push to Drug Development for Global Markets

1. **Slower sales growth** in traditionally large markets (US, EU)
2. **Higher sales growth** expected in large emerging markets (China, Brazil, Mexico, India, Russia and more)
3. Growing openness of regulators to **global clinical trials** (e.g. Japan)
4. Pharma discovery pipelines are less productive than in the past
   - Each development product must be targeted at global markets in order to sustain corporate revenues
5. Drug development is long and patent life is short
   - Development should target **multiple registrations** worldwide in parallel
   - More efficient return on investment (ROI)
Clinical Development Is a Key Gateway to Global Markets

- Unmet medical need
- Local regulatory requirements
- Local medical practice
- Patient availability
- Clinical trial costs
- Bureaucracy and feasibility
- And much more!
Communication with Regulators is Essential for Clinical Development Success

- Development Planning
- Data Sharing
- Data-driven Revised Development Plans
- Registration Plan
- Problem Solving
- Benefit-Risk
- Transparency Builds Trust
Communication: Traditional Model, Staggered Clinical Development

Sponsor

- US FDA

- EU EMA

- Japan PMDA

- Australia TGA

- Health Canada

- China SFDA/CDE
Communication: Current Model, Global Clinical Development

Sponsor

- US FDA
- EU EMA
- Japan PMDA
- Australia TGA
- Health Canada
- China SFDA/CDE
Regulators Are Key Customers

• Sponsors must understand what clinical data the regulatory customers want

• Satisfying regulatory customers’ needs with an efficient global clinical program is attractive to sponsors

• Communication is essential to understanding and satisfying regulators’ needs for clinical benefit-risk information
Learning Objectives

• Learn how industry and regulators communicate with each other during the drug development process (especially clinical development), and how these communications align with their respective missions

• Understand how to maximize the value of industry-regulator interactions to promote the public health through the clinical development of effective and safe medicines

• Understand how to avoid errors that undermine industry-regulator communications and therefore impede successful clinical drug development

• Appreciate the regional differences in best regulatory communication practices and learn how to achieve the right balance between local and global clinical trials in the context of global drug development
Our Speakers Today

• 13.40
  How to Conduct Effective Clinical Development Meetings with the US FDA
  Alberto Grignolo, Ph.D
  Corporate Vice President, Global Strategy and Services, PAREXEL Consulting, USA

• 14.10
  The EU Scientific Advice Process: Roadmap for Clinical Development Success
  Michael Rozycki, PhD
  Vice President and Head, Global Regulatory Affairs Asia, Bayer HealthCare Company Ltd., China
Our Speakers Today

- **14.40**
  Effective Clinical Trial Consultations with the Japanese PMDA
  Satoshi Koike, PhD
  Director, Global Regulatory Affairs and Safety
  Amgen Development K.K., Japan

- **15.10-15.40** BREAK

- **15.40**
  PMDA Perspective on Effective Clinical Trial Consultations with Industry
  Yoshiaki Uyama, Ph.D
  Review Director, Office of New Drug III, PMDA, Japan
Our Speakers Today

• 16.10  
  **Effective Interactions Between Industry and CDE in China on Clinical Development**  
  Yang Zhimin,  
  Deputy Director, Department of Evaluation III, Center for Drug Evaluation of SFDA

• 16.40  
  **Panel Discussion and Audience Q&A**  
  Speakers;  
  Panelist: Su Ling (Sr. VP and Head Development Greater China, Novartis)

• 17.30 CLOSE
How to Conduct Effective Clinical Development Meetings with the US FDA

• Alberto Grignolo, Ph.D
  PAREXEL Consulting
Basic Organization of FDA

Office of the FDA Commissioner

- Center for Drugs Evaluation and Research (CDER)
  - Most Drugs
  - Most Biologics

- Center for Biologics Evaluation and Research (CBER)
  - Vaccines
  - Blood products
  - Cell and gene therapy products

- Center for Devices and Radiological Health (CDRH)
  - Devices
  - Diagnostics

- Center for Veteran Medicine (CVM)

- Center for Food Safety and Applied Nutrition (CFSAN)
<table>
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<th>CDER</th>
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<tr>
<td>Net gain FY08</td>
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The Two Fundamental U.S. Dossiers

- **IND**: Investigational New Drug Application
  (= clinical trial application)

- **NDA**: New Drug Application
  (= marketing authorization application)
Meetings with FDA During Early Drug Development Can Shorten Clinical Development Time

Source: DiMasi and Manocchia, DIA Journal 1997
Meeting Regularly with FDA is a Success Factor in Drug Development

- Regulatory approval is earned gradually, not in a “Final and Glorious Battle” with FDA
  - FDA Center for Drugs holds >1000 industry meetings every year
- Build and maintain ongoing relationship with this “key customer”
- Accelerate development process
- Avoid misunderstandings
- Avoid surprising each other
- Communicate new data
- Anticipate difficulties
- Highlight and jointly resolve problems before they become too large
- Monitor changes in FDA attitude or expectations of data
Key Ingredients of Successful Meetings

- Science/Medicine
- Regulatory Knowledge
- Meeting Process Management
Meetings with FDA

Discovery

Development

Commercial

Pre-IND

EOP2 or 2A

SPA

Pre-NDA

AdComm

Label

Lab

Market

Basic Research

Pre-Clinical

Clinical Testing

Marketing

1

2

3

3b

4

Product Launch

Sales

IND

NDA

SNDAs
# Types of FDA Meetings

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PURPOSE</th>
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<tr>
<td>Pre-IND</td>
<td>Verify acceptability of investigational plan</td>
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<tr>
<td>End of Phase I (rare)</td>
<td>Confirm early safety</td>
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<tr>
<td>End of Phase Ila</td>
<td>Setting adequate dose-response evaluation</td>
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<tr>
<td>End of Phase II</td>
<td>Confirm early efficacy; agree on Phase III plan</td>
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<tr>
<td>Pre-NDA</td>
<td>Agree on NDA approach</td>
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<tr>
<td>Ad-hoc Technical Meetings</td>
<td>CMC, Tox, Clinical issues</td>
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<tr>
<td>Advisory Committee Meetings</td>
<td>Address medical establishment concerns</td>
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<tr>
<td>Teleconferences</td>
<td>Discuss specific issues</td>
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<tr>
<td>Labeling Meeting</td>
<td>Negotiate final labeling (Prescribing Information)</td>
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# The Five Steps to a Successful Meeting with FDA

<table>
<thead>
<tr>
<th>STEP</th>
<th>ACTIVITIES</th>
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| 1. Request Meeting| - Letter to Division  
                      - Statement of Meeting Goals  
                      - Draft Questions |
| 2. Information Package (Briefing Document) | - Clear “story” and rationale for positions  
                                         - Final Questions  
                                         - Supporting Information |
| 3. Rehearsals     | - Anticipate FDA questions and objections; analyze written responses from FDA  
                      - Establish negotiating positions  
                      - Identify respondents |
| 4. Meeting        | - Scientific discussion  
                      - Listen carefully  
                      - Seek reasoned consensus |
| 5. Post-Meeting   | - Sponsor minutes  
                      - FDA Minutes  
                      - Follow-up |
The Target Product Profile (TPP)

Guidance for Industry and Review Staff
Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5650 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact Jeannie M. Delasko at 301-796-0950.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2007
Procedural
The Target Product Profile (TPP)

- Provides a format for discussion between sponsor and FDA
- Dynamic text, used and updated throughout the drug development process
- *Beginning with the goal in mind*
  1. Labeling goals
  2. Studies to support labeling
  3. Dialogue with FDA
- Ideally, final TPP version will be nearly identical to the annotated draft NDA labeling
Organization of the TPP: Same as the Drug Labeling

- Indications and Usage
- Dosage and Administration
- Dosage Forms and strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations
- Drug Abuse and Dependence
- Overdosage

- Description
- Clinical Pharmacology
- Nonclinical Toxicology
- Clinical Studies
- References
- How Supplied/Storage and Handling
- Patient Counseling Information
End of Phase 2 Meetings (EOP2)
Why Companies Always Need the EOP2 Meeting

- Phase 3 clinical studies have a 30-50% failure rate
  - The final path to the NDA
  - Substantial investment

- An opportunity for FDA commitment on pivotal study designs and key endpoints

- “Fine-tuning” the final development plan
  - Clinical
  - Labeling Claims
  - CMC
  - Toxicology
Guidance for Industry
End-of-Phase 2A Meetings

Additional copies are available from:

Office of Training and Communication
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10983 New Hampshire Ave., Bldg. 51, rm. 1201
Silver Spring, MD 20995-0002
(Toll) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2008
Procedural
End of Phase 2A (EOP2A) Meeting

• Objective:

To help select the dosing regimens for the next phase of drug development and to design informative dose-response and dose-selection clinical trials that will inform later phase clinical trials by best incorporating prior quantitative knowledge.
Topics for EOP2A Meeting

• Use of quantitative information for dose selection using mechanistic or empirical relationships among biomarker, surrogate endpoints or clinical endpoints

• Use of quantitative knowledge of drug effects in animals and human subjects to aid in both dose-ranging trial design and safety assessment. Examples include:
  – Placebo effect
  – Disease severity (baseline) effect
  – Disease endpoint variability and time course

• Use of available preclinical and clinical exposure-response data and discussion of implications for dose-response trial design

• Contrasting alternative trial design strategies (e.g., parallel, adaptive, randomized withdrawal)
Topics for EOP2A Meeting (cont.)

- Use of pharmacogenetic information from preclinical studies and clinical trials and discussion of the implications of genetic factors on PK, PD, or both. The discussion might include a quantitative evaluation of genetic effects on dose selection and the use of genetics to inform assessments of drug safety and effectiveness in future trials.

- Discussion of blood or DNA sampling strategies and other trial design features to optimize the usefulness of future studies.

- Discussion of the utility of PK/PD data for dosing adjustments in special populations (e.g., pediatrics).
When Should You Have the End of Phase 2 Meeting?

• When labeling claims are well articulated
  – Target indication
  – Patient population
  – Safety profile

• When effective dose seems established (Phase 2)
  – Dose-finding is satisfactory
  – PK / PD work is well-advanced

• When Phase 3 program is designed and Company is ready to present it to FDA

• When significant investment is about to be made

• When Executive Management has “publicized” the NDA submission date (and maybe even an approval date !)
EOP2: Clinical Pharmacology and Biopharmaceutics

• Consider whether PK data and concentration or dose-response data support Phase 3 initiation

• Discuss data on metabolism of the drug

• Discuss need for additional studies in special populations, food effect, or drug-drug interactions

• Discuss the linkage of Phase 3 formulations with commercial product
EOP2: Clinical/Statistical (overall plan: efficacy)

- Number of studies
- Endpoints
- Controls
- Study population
- Stage of disease
- Study duration
- Dose-response
- Dose
- Concomitant therapy
- Subsets
- Wider populations
- Stages of disease
EOP2: Clinical/Statistical (overall plan: safety)

- Total exposure (duration and dose)
- Demographic distribution
- Use with concomitant therapy
- Appropriate size of database
- Special considerations for risk management
- Immunogenicity-related issues (biologics)
Clinical/Statistical (specific to controlled trials)

- Choice and definition of endpoints (primary and secondary)
- Dosing strategy
- Rationale for choice of control group
- Randomization, blinding
- Details (e.g., handling dropouts, efforts to ensure compliance, etc)
- Detail of analyses (e.g., interim analyses, role of Data Monitoring Committee, multiple endpoints, etc)
Elements of a Successful EOP2 Meeting

- Clearly Stated Sponsor Positions
- A “Credible”, Data-Driven Phase 3 Plan
- An Effort to Cover All Issues
- No Attempt to “Hide” Problems, or to Postpone Painful Decisions
- Team Spirit on Both Sides
Guidance for Industry

Special Protocol Assessment

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 2002
Procedural
Special Protocol Assessment (SPA) Meetings

- FDA will evaluate within 45 days certain protocols and issues relating to the protocols to assess whether they are adequate to meet scientific and regulatory requirements identified by the sponsor.

- Three types of protocol are eligible for this special protocol assessment:
  1. Animal carcinogenicity protocols,
  2. Final product stability protocols, and
  3. Clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim if the trials had been the subject of discussion at an end-of-phase 2/pre-phase 3 meeting with the Review Division.
Fundamental Rules for FDA Meetings

1. Do not ask open-ended questions

2. Present specific, data-driven proposals and seek FDA agreement
Examples: EOP2 Clinical Questions for FDA

Not Very Good

“We tried several doses and a couple seem to work pretty well in some patients. Which dose do you think we should pick for our Phase III trial”?

Better

“We tried several doses, and we are satisfied that the 5mg and 10mg doses are the most promising for our Phase III trials (see background and rationale in Briefing Document). Do you agree”? 
Examples: EOP2 Clinical Questions for FDA

Not Very Good

“Should we enroll 1000 patients or 1500 patients”?

Better

Our statistical plan (enclosed in the Information Package) shows that the study is adequately powered if we enroll 1000 patients and complete 920. Do you agree that 1000 enrolled patients will be sufficient”? 
Examples: EOP2 Clinical Questions for FDA

Not Very Good
“We think this drug works great in five different diseases. Which do you want us to cure first”?

Better
“Our drug has shown preliminary evidence of efficacy in five disease conditions. We propose to conduct two Phase III trials in [Condition C] because the endpoints are unequivocal, enrollment will be rapid and there is no available therapeutic alternative. Do you agree with our selection, and is this therapeutic indication approvable”? 
Examples: EOP2 Clinical Questions for FDA

Not Very Good

“Our clinical people and our marketing people cannot agree on the target labeling claim. Can you help us decide”?

Better

“After thorough internal discussions, we have identified a target labeling claim that both our clinical and marketing people are comfortable with, and we have included it in the Information Package. Are you comfortable with it also”? 
What Can Go Wrong in an End of Phase 2 Meeting?

- FDA thinks that dose-finding is incomplete
- FDA does not think protocol or endpoints are aligned with current standards or target label (TPP)
- Safety concerns remain (CMC or Tox or Clinical)
- Formulation or stability are not satisfactory
- FDA is rigid, unresponsive, does not “hear” the Sponsor
- The Sponsor is rigid, unresponsive, does not “hear” FDA
- The parties leave the meeting without a negotiated agreement
Common Reasons that End of Phase 2 Meetings Fail

• Phase II program is not complete because meeting was requested too soon

• Phase II not well executed and there is too little information to adequately design a phase III program

• Failure to communicate plans for manufacturing changes that could affect timing of BLA or NDA submission
Risk-Mitigation for End of Phase 2 Meetings

• Have a thorough Phase 3 plan -- technically, scientifically, procedurally– well supported by Phase 2 data

• Be as open as you can about the target label (use TPP as a tool)

• Share your company’s needs and motivations as openly as possible

• Talk about problems now; do not hope that FDA will not see them or will forget them

• Instill in FDA a sense of “co-ownership” to develop an important new medicine

• “Insist” on Phase 3 commitments and adhere to them
Implications of FDA Meetings for Global Development

- FDA-EMA Communications
- FDA-PMDA Communications
- Sponsor-Driven outreach to different Regulatory Authorities
- Seeking Consensus but …
- …Sometimes Agreeing to Disagree
- Sometimes clinical development cannot be global (e.g. placebo vs active comparator)
Conclusions

• The FDA Meetings Process is well structured, rigorous, data-driven

• Good communication can shorten development time

• Clinical development discussions are key to success (but also CMC and nonclinical discussions…)