



BAYBio 2010

Life Science Innovation: Drivers and Barriers

A Fresh Look at Regulatory Strategy – Innovating for Success

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Moderator

Jason Rock
CTO

GlobalSubmit

Jason.Rock@GlobalSubmit.com

215-253-7474



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Overview

- Discussion
- 5-10 minutes slides per speaker

Learning Objectives

- Balancing expectations
 - regulators and budget
- Get buy in from regulators
 - Regular discussion and pre-IND meeting
 - Format your analysis for your audience
- Differentiate products
 - through novel indications or label claims
- Working with novel therapies

Its all about communication

- Same page as agency
- Starts from pre-IND
- Throughout lifecycle of product
- Work within limitations
- Present your case every step of the way

Presentations

- Regulatory Innovation
 - Michelle Rohrer, PhD VP, Regulatory Genentech
- Working with the FDA
 - Janne Wissel, Chief Regulatory Officer Jazz Pharmaceuticals
- A Fresh Look at Regulatory Strategy
 - Erik O. Berglund, MD, PhD, RAC (US & EU), Sr. Regulatory Scientist, Associate Managing Director. Cato Research South San Francisco
- Introducing Novel Cell and Gene Therapy Products to EU Regulatory Agencies: Strategic Groundwork Behind a Formal Application
 - Shirley M. Clift Vice President, Regulatory Sangamo BioSciences, Inc.



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Regulatory Innovation

Michelle Rohrer, PhD
Vice President, Regulatory
Genentech

A member of the Roche Group

FDA Current Context

- 38% of CDER and OND staff have < 2 yrs experience on the job
 - Safety First initiative impacts decision making
 - Dedicated OSE staff in divisions
 - FDAAA legislation provided FDA expanded authority
 - REMS, post-marketing studies, safety-related labeling
- FDA's decision-making is slowed and appears more conservative

Genentech Research and Early Development Experience

- Submit ~10 New Molecular Entity INDs per year
- Pre-IND meetings not held routinely
- 0 – 10% Clinical Hold rate
- Elements of success
 - Strong science behind first in human studies
 - Follow ICH guidelines
 - Quality documentation
 - Strong emphasis on safety
 - Apply lessons learned across IND filings

Constant Calibration During Development

- Use EOPI, EOPII, pre-Phase III, pre-NDA/BLA meetings to probe on expectations for unknowns around REMS, labeling, indication statement
- Ask for new players (OSE) to be included in meetings
- Expect change
- Respect their chain of command
- Reach up into FDA management if what you are hearing does not make sense

Draft Labels and Negotiations

- Draft labels submitted with a rationale document
 - Brief “white paper” explaining rationale behind decisions made in creation of the label
 - Could explain text, placement, table
 - Gives reviewers context and a roadmap for how draft label was created
- Rationale documents accompany each version during negotiation
- Be a strong negotiator with a solid rationale
- Assume nothing is final until you have “the letter”
- ✓ *Great, game-changing data helps*



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What does and what does not work in interactions with FDA

Janne Wissel

Chief Regulatory Officer

Jazz Pharmaceuticals

Note: All comments and opinions expressed are those of the speaker and do not necessarily reflect the views of Jazz Pharmaceuticals.

What does and what does not work in interactions with FDA

- What works: using the Pre-IND meeting to cover your entire investigational plan in general as well as specifics of next steps
 - Create well thought-out questions that address the key aspects of your program
 - Ask questions in ways that FDA can answer
 - Durability of your response from FDA directly correlates to the precision of information provided for FDA to review prior to the meeting
 - Do your homework so that you know what FDA has said about similar questions
 - Take only the essential experts to the meetings
 - Be prepared to discuss options if FDA disagrees with you
- What doesn't work: expecting the Pre-IND meeting to give you definitive answers

- How to approach FDA to ask for something different
 - FDA will listen and evaluate alternate proposals
 - Find out who the right group is to talk to about your proposal—think about how broadly the proposal will impact FDA
 - Put together the right data to make your case

- How to develop a REMS
 - You can never start too early--initial concept development should consider the potential product risks
 - Incorporate risk mitigations into your development program
 - Keep good design history files to document the potential risks and mitigations
 - Involve the right players in the REMS process
 - It's a process, and it needs to evolve as you learn more



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What does and what does
not work in interactions
with FDA

Questions?

Contact information:

Janne Wissel

Chief Regulatory Officer

Janne.wissel@jazzpharma.com



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A Fresh Look at Regulatory Strategy Innovating for Success

Erik O. Berglund, MD, PhD, RAC (US & EU)
Sr. Regulatory Scientist, Associate Managing Director
Cato Research South San Francisco

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Do the right thing and do it well

1. Diligence – the necessity of giving sufficient attention to detail to avoid error and prevail against obstacles
2. Do right – ...human professions...forever troubled by human failings like avarice, arrogance, insecurity, and misunderstanding
3. Ingenuity – thinking anew...often misunderstood...not a matter of superior intelligence but of character...
 - willingness to recognize failure, to not paper over the cracks, and to change. It arises from deliberate, even obsessive reflection on failure and a constant searching for new solutions.

From "Better" by Atul Gawande

“Sometimes obtaining exceptionally good results is not due to a ‘lightning bolt’ insight or genius, but the result of merely doing everything that is already known but doing it well and thoroughly”

Do the right thing and do it well

- Planning upfront is key
- Research the area and related topics
- Integrated development plan from Pre-IND through Phase 3
- Communication technique with regulatory agencies
- Be prepared to negotiate and determine back-up plans and fall back positions in advance
- Be open to new team and fresh look at strategy and results
- Know what drives FDA and what their limitations are
- Good scientific rationale and solid data can override published guidance

- Sponsor received non-approvable letter for their NDA
- At an Advisory Committee Meeting (ACM), the vote was unanimous to not approve the drug
- Board called CATO for regulatory advise:
 1. scrap the drug,
 2. perform additional studies, or
 3. reanalyze by different team and resubmit?
- CATO analyzed the data and concluded that the drug was efficacious but that the ISS and ISE needed reworking
- Confounding information with the active control not being approved for certain indications

Case Study #1 (cont.)

- New AE's were not properly compared to baseline and therefore raised questions about safety in FDA's review
- CATO produced novel graphical displays and additional safety analyses
- ISS: was reanalyzed and rewritten. After the reanalysis there were no safety signals
- ISE: subpopulation was identified, for which the active control was FDA approved and analysis demonstrated that the study drug was more efficacious
- CATO presented analysis to ACM as well as FDA and drug was approved

Case Study #2

- Sponsor with limited experience of interacting with FDA
- Developing a fully human mAb with a unique human target – no cross reactivity in any normal tox species, only in very closely related non-human primates
- Strategy established to request “pre-pre-IND” feedback to receive recommendation of viable path forward without suitable tox species
- After verbal FDA agreement to review, a 2-page summary with scientific rationale was submitted via email

Case Study #2 (cont.)

- ~30 days after submitting, a response with non-committal guidance was received
- Prepared pre-IND briefing document, including:
 - studies describing specific receptor binding
 - overall mAb affinity and general PD
- Successful pre-IND meeting where FDA agreed to limited tox studies:
 - only needed supporting pharmacology studies
 - commitment to start P1 PK study at very low dose and dosing one subject at a time
- IND submitted successfully and P1 is being conducted



We bring your projects
to a higher level

Questions?

Contact Information:
Dr. Erik O. Berglund
Cato Research
eberglun@cato.com



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Introducing Novel Cell and Gene Therapy Products to EU Regulatory Agencies: Strategic Groundwork Behind a Formal Application

Shirley M. Clift
Vice President, Regulatory
Sangamo BioSciences, Inc.

Groundwork Preparation

- Develop awareness of country specific issues
 - Although attempts at harmonization have been made, each country views the cell and gene therapy field quite differently
 - Best to have US pre clinical and clinical data going in-a help but not a guarantee
- Get the best Regulatory consultant you can afford
 - Assess timing of reviews; add at least 2 to 3 more months to standard review times
 - Thorough understanding of standard clinical practice in the indication to be addressed
 - Engage KOLs in clinical research area who are aware of standard clinical practice—likely to have connections with the Competent Authority (CA) or regulatory agency

Groundwork Preparation – Country Specific Issues

- Assess potential understanding of the scientific technology by the CA
 - Engage scientists who are prominent in the field and are likely to have already interacted with the agencies
- Find out whether CAs use in house expertise for review and assessment of CMC materials or seek outside expertise
 - Learn particular “fears” of cell and gene therapy technology that the country harbors
- Understand country specific raw material issues as much as possible; ie HSA, Bovine Serum

- Consideration of Scientific Advice meeting prior to filing a CTA
 - Cost
 - Time
 - Potential Outcome

If at first you don't succeed...

Follow up effort and persistence—does it work or should you try someplace else?

- Example of inconsistency between CAs from different countries
 - Classification of a replication incompetent gene therapy agent as a GMO or Genetically Modified Organism, needing review by agricultural agencies and a complete risk assessment for potential to adulterate soil and the environment is “yes” in 4 out of 8 countries, the other 4 don’t even mention it