The Role of Medical Affairs in Late Phase Product Development

Presented by:

Rick Munschauer, MD, CM
VP, Global Head, Medical Affairs
Biogen Idec

Disclaimer

The information presented represents the opinions of the speaker and does not necessarily reflect the views of the organization for whom he works
What Is Medical Affairs?

What is Medical Affairs and What do we do?

Mission of Medical Affairs

“To identify and address the unmet medical needs associated with products, therapies and disease states in order to drive improvement in patient outcomes.”
Medical Affairs Interactions

- The Providers
  - Health Care Professionals
  - Leading Clinical and Therapeutic Experts
- The Payors
  - Local (HMOs, Insurers)
  - Governmental (Medicare / Medicaid)
- The Company
  - R&D
  - Commercial
  - Regulatory
  - Compliance / Legal

Medical Affairs Activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Primary owner</th>
<th>Participant</th>
<th>Medical Affairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifying Unmet Medical Needs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-clinical trials (e.g., trials before Phase IIIa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase IIIa and IIIb (new indications)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Health Outcomes Research</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Integrated Life Cycle plan (LCM)</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Medical product strategy</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>KOL partnership / physician relationships</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-approval trials (e.g., IITs, Ph IV trials)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Hoc exploration of clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Training / Medical Excellence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuing Medical Education (CME)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSL management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promotional materials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial product strategy</td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Medical Affairs: An Overview

- Regulatory basis for a Medical Affairs department is slender
- Recent government enforcement focus on Medical Affairs activities
- CIAs require rules for field medical interactions and unsolicited requests
- Increased scrutiny of publication issues
- Recent industry guidance PhRMA and AdvaMed Codes changes the rules of engagement

Drug Development Process

**Time Line for Drug Development**

- Initial Idea
- Pre Clinical Research
- Development Phase I, II, III
- Regulatory Approval
- Market Launch
- Post Launch Development Activities

Product life-cycle management (LCM)
**Justification for Late Phase Clinical Development**

*At the time of registration, many important questions on the appropriate use of a new product remain unanswered*

Information to:

- Better define the broad safety of a product
- Establish the Risk / Benefit of the drug in special populations
  - Pediatric / Elderly / Pregnant / Ethnic
  - Concomitant medical conditions and medications
  - Side effect mitigation

---

**Justification for Late Phase Clinical Development**

- Enhance product profile
  - Dose, regimen, or delivery modification (generally conducted under IND)
  - New indications (IND)
  - Pharmacologic management of side effects
  - Promote “personalized” medicine
  - Combination therapy

---

Phase 1 | Phase 2 | Phase 3 | Phase 4
Justification for Late Phase Clinical Development

- Expand the label (Phase III and IIIb)
  - Expanded uses within indication
  - New indications

- Disease state research:
  - New outcome measures for trials
  - “Personalized Medicine” (Validation of imaging, genetic, genomic, and proteomic biomarkers)

- Comparative Effectiveness and Health Outcomes

Late Phase Clinical Development: The Process

- Identify and Prioritize the Unmet Medical Needs
- Create Tactical Plans Addressing Unmet Medical needs
- Establish Broad IIT Priorities
- Ad Boards & Consultants
- HCPs MSLs
- Registries
- Agency Regulators
- Commercial
- Phase IIIb
- Phase IV
### Addressing and Managing Unmet Medical Needs: Information Management

<table>
<thead>
<tr>
<th>Obtain</th>
<th>Manage</th>
<th>Disseminate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Publications</td>
<td>Medical Information</td>
</tr>
<tr>
<td>Phase IIIb</td>
<td>Posters</td>
<td>Request based</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Papers</td>
<td>MSL interactions</td>
</tr>
<tr>
<td>IITs</td>
<td>Presentations</td>
<td>Medical Info</td>
</tr>
<tr>
<td>Registries</td>
<td>Internal Curriculum</td>
<td>Speaker Trainings</td>
</tr>
<tr>
<td>Advisory Boards</td>
<td>Medical Training</td>
<td>Scientific Symposia (EU)</td>
</tr>
<tr>
<td>Field activities</td>
<td>Compliance Training</td>
<td>CME Support (US)</td>
</tr>
<tr>
<td></td>
<td>SOPs</td>
<td>Internet</td>
</tr>
<tr>
<td></td>
<td>Infrastructure / Process</td>
<td>Teleconference</td>
</tr>
<tr>
<td></td>
<td>Protocol review / approval</td>
<td>Live Sessions</td>
</tr>
<tr>
<td></td>
<td>Trial oversight</td>
<td>Internal Training</td>
</tr>
<tr>
<td></td>
<td>Data analysis</td>
<td>Basic</td>
</tr>
<tr>
<td></td>
<td>mPRC review</td>
<td>Advanced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topic specific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ad-Hoc Training</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Train the Trainer</td>
</tr>
</tbody>
</table>

### What Constitutes Bona Fide Research?

- Systematic investigation intended to enhance knowledge that is important to investigators in the field
- Assesses the efficacy, effectiveness, and / or safety of drug compared to placebo and / or other agents or therapies
- Unrestricted publication of results
- Approved by the FDA (EMA) and / or by a duly constituted IRB
Risks: Late Phase Development

- Does the activity have the potential to interfere with, or skew, clinical decision-making?
- Does it have the potential to undermine the clinical integrity of a formulary process?
- If the arrangement involves providing information to prescribers, or patients, is the information complete, accurate, and not misleading?
- Does the arrangement have the potential to increase costs to the federal health care programs?

Risks: Communications Surrounding Late Phase Clinical Development

- Pre-approval discussions can be considered promotional
- Off-label dissemination of reprints or abstracts
- Lack of fair balance in the presentation of benefits and risk
- Emphasis should be on education and scientific exchange involving research activity and not promotional
  - Request must be truly unsolicited
  - Response must be tailored to the question asked
  - Response must be balanced and non-promotional
- Risk arises from entire company: agents, distributors, sales, marketing as well as medical affairs
Recent Cases of Research Misconduct

**Investigations and Allegations Related to Clinical and Research Studies**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Examples of Cases</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Falsified Research     | • The Army found that Dr. Kuklo, a former Army surgeon at Walter Reed, had forged the names of four other Walter Reed doctors he claimed to be his co-authors on the study, and presented data that appeared to have been fabricated because it did not match Walter Reed patient records.  
  • Medtronic received a subpoena in May 2009 regarding its financial relationship with the surgeon.                                                                                                                                                                                                 | DOJ Investigation (still open)                                                                 |  
| Ghostwriting           | • Eli Lilly, Wyeth, Pfizer, and Merck have all faced allegations of ghostwriting, wherein these manufacturers, to a varying degree, write the paper or study and then have a medical doctor add his or her name to the publication to provide the appearance of third party objectivity.                                                                 | Ghostwriting was a factor in several multi-million-dollar settlements                        |  
| Failure to Obtain IND / IDE | • Inspection revealed that Stryker failed to obtain an Investigational Device Exemption ("IDE") prior to initiating a clinical investigation.                                                                                                                                                                                                                                                                 | FDA Warning Letter                                                                          |  
| False Claims           | • The complaint against EBI alleged that King and McNair, while implanting Ionic Spacers, "took studies that failed in laboratory animals, and then, without any reasonable basis to conclude that they would be successful, began to experiment on humans" by implementing similar surgical techniques. After the surgeries and the implantation of the Ionic Spacers, King and McNair, with EBI's full knowledge, allegedly submitted claims for payment to Medicare and Medicaid for the cost of the surgeries. | Qui Tam Action                                                                               |  
| Documented Research Needs | • Several medical device manufacturers were found to be lacking adequate documentation/substantiation for multiple research and educational grant related activities.                                                                                                                                                                      | Annual Needs Assessment is Required                                                          |  

1 Courtesy of Huron Life Sciences Advisory Services personal communication 2011

Research Requires Substantial Internal Controls and Monitoring

- Policies and procedures addressing sponsorship, funding, and disclosures relating to research and development-related activities (including Phase II-IV trials, IITs, and Registries)

- Monitoring and tracking program for all research payments with appropriate state reporting

- Monitoring research program for publications activities including needs assessment, authorship, and appropriate dissemination
### Documenting Payments: A Critical Process

<table>
<thead>
<tr>
<th>Process</th>
<th>Does the protocol reflect an independent objective and has it been approved by an appropriate approver? (e.g. IND, IRB, FDA, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose and Need</td>
<td>Why are payments necessary? Who approves the payment? What is the underlying purpose of the payment?</td>
</tr>
<tr>
<td>Payment</td>
<td>How were payments determined and who received them?</td>
</tr>
<tr>
<td>Service</td>
<td>What services were performed? What data and results were determined from the research? How is this documented?</td>
</tr>
</tbody>
</table>

### Registries: Types and Risks

**Registry Types:**
- Primarily Safety
  - Special populations
  - Specific risks
- Safety and Efficacy
  - Single drug
  - Multiple drugs
  - Standard of care
- Health Outcomes

**Registry Risks:**
- Seeding perception
  - Initial choice
  - Switching
- EMA (EU) “Directive”
  - Registries that collect efficacy measures that are not in label are considered interventional
- Pricing perceptions
Investigator Initiated Trials (IITs)

- IITs must be initiated by an investigator
- Frequently used for “Proof of Concept” in either new indications or expanded use within an indication
- Investigator may need IND for off-label indication
- Company may review proposals in terms of alignment to identified medical needs and suggest improvements but may not determine protocol
- Investigator is responsible for all aspects of study design, approval and conduct
- Investigator agrees to publish, but sponsor has no authority to require

IIT Projects Can Involve Large Sums

- $0-$50,000: 52.9%
- $50,001-$100,000: 5.9%
- $100,001-$200,000: 17.6%
- $200,001-$300,000: 5.9%
- $>300,000: 5.9%
**IIT Evaluation Process**

- Investigator Proposes Idea
- Needs More
- Not Aligned
- Yes
- MSL / MD Gives Feedback
- Notification Letter
- Request Formal Proposal
- IIT Committee Reviews Proposal

**IIT Evaluation**

- Will the study help meet the identified unmet medical need?
- Do the specific aims have scientific / clinical merit?
- Is the idea original and not addressed by other studies?
- Is the design feasible and timely?
- Is the site / investigator capable of performing the research?
  - Enough patients, institutional support, experience
Risks in IITs

- Is it **really** an *independent* investigator trial
- Questionable bona fide medical / scientific research
- MSL interaction perceived as soliciting or promotional
- Lack of investigator experience in best clinical practices, protocol execution, and AE reporting
- Lack of investigator knowledge of regulatory environment (IND)
- Seeding, kickback, or conflict of interest concerns
- Established and validated “Fair Market Value”
- Documentation for milestone payments
- Publication of findings not supported by results
- Commercial influence

Compliance Tips for IIT

- Know your IIT research portfolio and ensure it maps to unmet medical needs
- Have a transparent and documented review and approval process
- Avoid unnecessary duplication of studies
- If you intend to use the study results, ensure the proper registration on clinicaltrials.gov
- Implement appropriate language into your contracts to ensure Adverse Event (AE) reporting and regulatory compliance
- Consider terminating unproductive studies where there are significant concerns
Phase IIIb / IV Trials

- Phase IIIb / IV trials are company initiated, managed and operated directly
- Usually Phase IIIb / IV involve strong input from therapeutic experts to ensure an important medical need is addressed appropriately
- Phase IIIb are generally label expanding and therefore have strong regulatory involvement throughout
- Phase IV trials are intended to result in Level One medical information of importance to the medical community for publication and are not label enabling

Phase IV Trials

- Every Company-sponsored clinical Phase I-IV interventional study in patients must be registered (usually www.clinicaltrials.gov)
  - ICMJE member journals require, as a condition of consideration for publication, registration in a public trials registry
- Authorship must meet ICMJE criteria
  - Industry authorship for practice guidelines is inappropriate
- Obligation to publish negative studies
  - Failure to submit or publish findings because of lack of statistical significance is an important cause of publication bias
Key Compliance Issues in International Research

**U.S. Foreign Corrupt Practices Act:**
- Increasingly, pharmaceutical companies need to address unmet medical needs globally
  - This requires becoming well versed in the intricacies of both US and local laws pertinent to such interactions (e.g. FCPA).

- Certain realities shape international activities:
  - In many countries the government is inevitably the largest customer
  - Pharmaceutical companies often rely on local third party employees or agents
  - Local customs in countries where industry expansion continues

Questions?