Approaches to Reducing Phase II Attrition

Allan B. Haberman, PhD

Phase II is the critical development stage in which most clinical attrition occurs. This report focuses on approaches to improving R&D productivity in the pharmaceutical and biotechnology industries and considers:

• Leading-edge strategies being pursued to improve success rates of therapeutic candidates in clinical development

• The use of translational medicine studies and early clinical trial protocols designed to reduce Phase II attrition

• Survey results and expert interviews on efforts to improve R&D efficiency.
Approaches to Reducing Phase II Attrition considers examples of leading-edge strategies being pursued to improve target selection and other aspects of drug discovery. These include development of multitargeted therapies, whole-pathway approaches, biology-driven drug discovery, analysis of multigenic complex diseases, and network pharmacology. Strategies for improving early-stage clinical studies are discussed, including the use of Phase 0 and adaptive trials, and employing early proof-of-concept trials. Ways in which some companies have adopted new corporate structures designed to increase innovation or make R&D more “biotech-like” are described.

Poorly predictive animal models constitute a major cause of drug attrition. We present two case studies in CNS and cancer, two therapeutic areas in which animal models are notorious for being poorly predictive. The CNS case study focuses on attempts to improve animal model efficacy studies, and the cancer case study focuses on industry’s adoption of improved animal models developed in academia. In these discussions, we indicate how these particular case studies may have lessons for efficacy studies in most therapeutic areas.

Well-designed translational studies may enable drugs that do not work in humans to fail early. We examine various aspects of translational studies, including definition of responder versus non-responder populations, and optimal dosing regimens; and identification of early and sensitive markers of efficacy, and of those patients who are likely to experience adverse effects. Examples of ways in which translational medicine is changing the organization of clinical trials in some companies are discussed. We also study the roles that various types of biomarkers play in translational medicine, as well as the current state of biomarker science. Case studies on stratification biomarkers in cancer are presented.

Approaches to Reducing Phase II Attrition analyzes results from a survey of current practices and views toward improving the efficiency and effectiveness of drug development. Finally, the complete transcripts of interviews conducted with experts in the field are provided.

### Do You See Phase II Attrition as a Major Issue in Your Company?

<table>
<thead>
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<th>Category</th>
<th>Count</th>
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<tbody>
<tr>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td>No, we use a “Learn and Confirm” drug development strategy</td>
<td>7</td>
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<tr>
<td>No, we have reduced our rate of Phase II attrition in recent years</td>
<td>6</td>
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<tr>
<td>No, we mainly acquire drug candidates in mid-stage or late-stage development via partnering or acquisition</td>
<td>6</td>
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Source: Insight Pharma Reports

About the Author: Allan B. Haberman, PhD, is Principal of Haberman Associates, a consulting firm specializing in science and technology strategy for pharmaceutical, biotechnology, and other life science companies. He is also a Principal and Founder of the Biopharmaceutical Consortium (www.biopharmconsortium.com), an expert team formed to assist life science companies, research groups, and emerging enterprises to identify and exploit promising, breakthrough technologies. He is also the author of numerous publications on the pharmaceutical and biotechnology industries, their technologies and products, and on the major therapeutic areas for drug discovery and development. Formerly the associate director of the Biotechnology Engineering Center at Tufts University, he received his PhD in biochemistry and molecular biology from Harvard University.

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- What aspect(s) of the drug development process do you work in?
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- Do you see Phase II attrition as a major issue in your company?
- What do you see as the major reasons for low productivity and high cost of drug development?
- Has your company adopted a program of translational medicine aimed at improving the efficiency and effectiveness of early drug development?
- If you have adopted a translational medicine program, has it been helping you to accelerate movement of promising drug candidates into mid-stage clinical trials and to weed out unpromising candidates?

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References

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A.1. Charles Gombar, PhD, Vice President, R&D Strategy and Business Improvement, Wyeth
   Evan Loh, MD, Vice President, Clinical R&D, Wyeth
A.2. Peter Lassota, PhD, Divisional Vice President, Imaging Biology & Oncology, Caliper Life Sciences
A.3. Bruce H. Littman, MD, President, Translational Medicine Associates, LLC
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