Workshop on the Development of Broad Spectrum Therapeutics

The National Institute of Allergy and Infectious Diseases (NIAID), through the Division of Microbiology and Infectious Diseases (DMID), sponsored a Workshop on the Development of Broad Spectrum Therapeutics. The workshop was organized by the Office of Biodefense Research Affairs (OBRA) and the Office of Regulatory Affairs (ORA) of DMID, and was held on April 18, 2006 at the Bethesda North Marriott Hotel and Conference Center. Participants included scientists from academic institutions, biotech and pharmaceutical companies, as well as program staff from the NIAID, the Department of Health and Human Services (DHHS), the Department of Defense (DoD), and the Food and Drug Administration (FDA).

The development of broad spectrum therapeutics is of increasing priority, especially as focus is placed on the development of countermeasures for biodefense. The speakers, panelists and participants contributed to interactive discussions on the regulatory requirements for licensure of broad spectrum therapeutics and challenges to industry and academia with the development of broad spectrum drugs.

The workshop was divided into two sessions.
Session 1 included three key speakers from the FDA, and focused on the regulatory issues and requirements for pursuit of multiple pathogen indications. In Session 2, one large pharmaceutical company representative and one small biotech company representative discussed their experiences with broad spectrum antimicrobial development and highlighted their lessons-learned, successes, and challenges to their companies. Each session was followed by an interactive panel discussion that enabled all of the audience members to provide feedback, comments and questions to the panel.

Posted on this site are the slides from the presenters.
All are encouraged to review these slides, as they are filled with valuable information. An agenda and brief description of the talks from Session I and II are as follows:

Session I

- Three speakers from the FDA
    - Dr. Mark Goldberger MD, MPH
      Director, Office of Antimicrobial Products, FDA, CDER
      Dr. Goldberger provided an overview of the regulatory aspects of broad spectrum therapeutic development. In this overview, he spoke of relevant microbiology information *in vitro* and *in vivo*, clinical trial design, and the animal rule.
    - CDR William H. Taylor, PhD, DABT
      Pharmacology/Toxicology Team Leader, FDA, CDER
      Dr. Taylor spoke on the regulatory path for nonclinical studies to support development of broad spectrum therapeutics. In his talk, he spoke of preclinical safety and the various studies that an investigator may pursue. His slides depict what studies may be expected during the development path, the reasons for such studies, and at what point they should be performed.
    - Dr. Fred Marsik, PhD

Microbiologist, FDA, CDER
Dr. Marsik spoke of non-clinical microbiology studies to support the development of broad spectrum therapeutics. In his talk, he walked the audience through the *in vitro* development of an antimicrobial and the points to consider in determining the spectrum of activity. He also pointed out types of data that will help the FDA develop an understanding of the drug in the application, as well as factors to consider when choosing animals for experiments.

The three talks were followed by an interactive panel discussion. The panel consisted of seven FDA staff scientists and Dr. Lydia Falk, the Director of DMID's Office of Regulatory Affairs, whose expertise covered nearly all aspects of drug development, as it is regulated by the FDA. There was a great deal of dialogue between the panelists and the workshop participants. The panel members are listed following this summary.

During session 1, participants noted some points during the discussion:

- FDA participants advised that it is extremely valuable to seek FDA guidance early and often. Drug development can be facilitated through formal and informal communication between the applicant and the FDA, and it is recommended that the sponsor submit protocols to the FDA before initiating certain studies. The FDA can advise whether studies are needed, may require an FDA waiver, or may be needed concurrently with, or replaced by, other studies.
- The Food, Drug and Cosmetics Act (FDCA) and Title 21 Code of Federal Regulations regulate most drug development. There are over 30 guidance documents (ICH and CDER documents) available on the FDA website that will guide an investigator toward understanding what types of information is expected by the FDA for preclinical and non-clinical pharmacology and toxicology and when in the development path it is relevant.
- The safety and effectiveness requirement for approval requires substantial evidence from adequate and well-controlled studies so that a physician qualified on the basis of training and expertise could reasonably conclude that the drug has the effect claimed in the labeling.
- Although there is no requirement to do so, performing preclinical studies, such as pharmacokinetics, in both healthy and diseased animals may be of value. This could possibly maximize efficiency when understanding the clinical pharmacology in disease when there may be clear differences in the two.
- The "Animal Rule" addresses efficacy and it should be applied when definitive human efficacy trials cannot be conducted and field trials are not feasible. To employ the "Animal Rule" the pathophysiology of the disease, toxicity of the substance, and the mechanism of prevention or reduction of severity must be reasonably understood. The "Animal Rule" does not specifically address safety, and human safety data is still required.
- In cases where the "Animal Rule" will be used, the FDA will likely want to see data from safety studies in the same species as the animal model chosen for efficacy studies, however, earlier developmental work can be done in a variety of laboratory animals.

- The number of animal efficacy models needed for broad spectrum drugs is on a case-by-case basis because the number would depend on many factors, especially the pathogens and disease entities and the similarities thereof. Factors to be concerned with may include antimicrobial susceptibility, target organs, syndrome presentation in the animal compared to people, preclinical data and clinical syndromes. Animal efficacy for each indication may be the path forward.
- In choosing an animal efficacy model, particular attention should be paid to the choice of species with respect to their susceptibility to infection, disease progression and tolerance to treatment. Variation may exist even within closely related genera and species.
- There is no substantial overall difference in the preclinical studies to support broad spectrum therapeutic product development.
- One must demonstrate their ability to be able to reproducibly manufacture a product of acceptable quality.
- The preclinical and clinical safety and pharmacology studies needed depend on whether a sponsor is starting with a de novo product or a product that is already approved for use in humans. Existing knowledge of its safety profile, PK, PD, and so forth may preclude repeating these studies for a new indication.
- Discussions addressed the use of combination therapies. Participants discussed the potential value of combination treatments, although they are not frequently evaluated. Clinical trial design must be established to clearly show the benefit of a combination over a single therapy. Such a design must evaluate product A as a mono-therapy, product B as a mono-therapy and product A plus B to determine if A plus B is superior for efficacy and/or safety to either alone.
- Each product is specific and guidance must be sought from the FDA on a case-by-case basis.

Session 2

- Two speakers from Industry

  - Dr. David Pompliano, PhD
    Vice President, Biology, GlaxoSmithKline
    Dr. Pompliano spoke on behalf of a large pharmaceutical company. He spoke of GSK's experience with antibacterial discovery and their commitment to a field that is well-needed, however comes with many pitfalls and obstacles that can cause a change in direction.
    Dr. Pompliano's slides depict the challenges faced by GSK in this arena, and the decisions that ensued to overcome those challenges.

  - Dr. M.R.K. (Dickon) Alley, PhD
    Head of Discovery Biology, Anacor Pharmaceuticals, Inc.
    Dr. Alley presented the perspective of a small biotech company. He spoke of Anacor's experience with broad spectrum antibiotic development. The audience was led through the drug development pathway as Dr. Alley presented how Anacor overcame some of the challenges that arose during drug development.

This was followed by an interactive panel discussion with a great deal of dialogue between the audience and the panel. There were five industry members for Panel Session II that provided an area of expertise. The panel members were representatives from Anacor Pharmaceuticals Inc., GlaxoSmithKline, Apath LLC, NexBio Inc., and Paratek Pharmaceuticals. The panel members are listed following this summary.

During Session 2, participants noted some points during the discussion:

- Due to the rapid development and spread of antimicrobial resistance, it is important to identify novel structures for evaluation in clinical trials.
- The development of broad spectrum antivirals has been considered to be more technically challenging and less economically appealing. It was discussed that this trend might be changing.
- Participants noted that partnering at appropriate times during their drug development program was necessary.
- There are resources available to link discoveries from academic laboratories to development in industry, as well as connecting academics with entrepreneurs.
- Antibacterial research involves a great deal of chemistry and biology commitment.

In summary, the workshop was very informative with reference to the issues that industry and academia face in the development of broad spectrum therapeutics, as well as the regulatory issues that will need to be taken into account during drug development.

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