

Regulatory “Obstacles”

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March 2, 2006

Problem Definition

- Developing molecular targeted therapy
- Indication: heritable skin disease
- Fundamental skin defects known
- Miniscule size of market

Key Questions

- What prevents having these therapies?
- How to overcome these “obstacles”?

Thesis: Regulatory “Obstacles” are:

- Underestimating the informational needs, and the timing for such informational needs, for drug approval.
- Overestimating the contribution from those helping you meet these informational needs.
- Underestimating toxicity signals.
- Overestimating efficacy signals.

Underestimating the Informational Needs

- “Targeted” therapies often have “collateral damage”, i.e., side effects not anticipated from known pharmacologic mechanism of action.
- Assurance that fundamental defects in skin disease are known is no guarantee for syllogistic logic; empiric data still needed (e.g., encainide & flecainide).

Academic Logic

- Higher rate of mortality post-MI in patients with arrhythmias.
- Encainide and flecainide suppress arrhythmias in post-MI patients.
- Logic: E & F will lower mortality rates in post-MI patients with arrhythmias.
- Observed: E & F associated with higher mortality rates in post-MI patients with arrhythmias.

Empiricism vs Logic

- Echt DS, Liebson PR, Mitchell LB, et al.
- Mortality and morbidity in patients receiving encainide, flecainide, or placebo, The Cardiac Arrhythmia Suppression Trial.
- N Engl J Med 324: 781-788, 1991.

Attitude to Overcome “Obstacles”

- Look beyond the “targeted” nature of drug.
- Seek empiric evidence and don’t rely on “logic”.
- Most heritable skin disorders are chronic and not life-threatening; thus, the need for chronic safety data.
- Regs, Guidance Documents, and FDA meetings/communications give direction.

Seeking Support

- FDA orphan drugs grants
- NIH grants
- FDA orphan drug – marketing exclusivity
- Investors, venture capitalists
- Frequent meetings/communication with FDA
- Hire/outsource proven quality

Required Viewing

- The Producers (1968)
- Directed by Mel Brooks
- Screenplay by Mel Brooks
- Zero Mostel as Max Bialystock
- Gene Wilder as Leo Bloom

FDA Review Disciplines

- Chemistry, Manufacturing, and Control (= “Chemistry”, “CMC”)
- CMC Microbiology
- Pharmacology/Toxicology (= “PharmTox”)
- Clinical Microbiology (=“Micro”)
- Clinical Pharmacology and Biopharmaceutics (= “Biopharm”, “PK”)
- Clinical
- Biostatistics (= “Statistics”, “Stat”)

Observations

- Many not-approvable (NA) issues in CMC.
- Many IND hold issues in CMC and PharmTox.
- Topicals are more complex than oral dosage forms.
- Systemic exposure and safety concerns exist for topicals.

Guidance Documents on INDs

- www.fda.gov
- Click on “Drugs”
- Click on “Regulatory Guidance”
- Click on the first bullet: “Guidance Documents Web Page”
- Click on “IND” in left column
- Click on first bullet

Guidance for Industry: Content
and Format of Investigational
New Drug Applications (INDs)
for Phase 1 Studies of Drugs,
Including Well-Characterized,
Therapeutic, Biotechnology-
Derived Products
November 1995

Phase 1 Investigational Plan

First human studies simply characterizing

- 1) early pharmacokinetic properties (oral)
- 2) early pharmacodynamic properties (oral and topical)
- 3) irritancy potential (topical)

Detailed plans contingent on the outcome of such studies not needed

Investigator's Brochure

- Full and balanced discussion of nonclinical toxicity
- Balanced description of the therapeutic potential: both safety and efficacy

Protocols (Part I)

- Estimate of the number of subjects
- Description of safety exclusions
- Description of dosing plan
 - 1) duration of dosing
 - 2) dose – amount of product & frequency
 - 3) method of determining dose

Protocols (Part II)

- Specify in detail those elements of the study that are critical to subject safety, e.g.,
 - 1) necessary monitoring of vital signs and blood chemistries and
 - 2) toxicity-based stopping or dose-adjustment rules

Chemistry, Manufacturing and Controls for Phase 1

Stability data to show that drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation

CMC Concerns - Examples

- Product made with unknown or impure components
- Product possessing chemical structures of known or highly likely toxicity
- Product that cannot remain chemically stable throughout testing program proposed
- Product with an impurity profile indicative of a potential health hazard or insufficiently defined to assess a potential health hazard

CMC Link to Nonclinical Studies

Relate drug product being proposed for use in clinical study to the drug product used in animal toxicology studies that support the safety of the proposed human study

Pre-IND Meeting

- 21 CFR 312.47 Meetings seems to imply that meetings might ordinarily begin at the End-of-Phase 2.
- Use Pre-IND Meeting to ascertain what specific pieces of information and nonclinical studies are needed to support the proposed dosing regimen in the proposed clinical trial.

Obstacles

- From Latin *obstaculum* > *obstare*, *ob-* in the way, *stare-* to stand.
- Something that impedes progress or achievement.
- Something to get around or over.

Regulatory Requirements (Part I)

- Best viewed as “informational needs”, not “obstacles”.
- Get to know the regs and guidance documents.
- Best to seek regulatory elegance by defining the necessary and sufficient information and when it is needed.

Regulatory Requirements (Part II)

- Hire, or outsource to, those who can provide the regulatory elegance, and avoid “the producers”.
- Communicate with FDA (best in writing), meet with FDA often (you will get written minutes), and submit Special Protocol Assessments when eligible (you get written comments).

Conclusion

- Successful drug development is mostly about getting the right information at the right time.
- Obstacles are mostly poor planning, underfunding, the wrong personnel and advisors, and overvaluing “logic”.
- There are promising therapeutic agents and patients with heritable skin diseases who need them. Meet this important public health need through regulatory elegance.

