Session 9 – Developing a Robust Regulatory Strategy: Setting the Stage for Success

1. Regulatory Strategy in Context – Rosalie Cull
2. Regulatory Plan: The Foundation for Success – David Harrison
3. Drug Development Strategies and Planning – William Sietsema

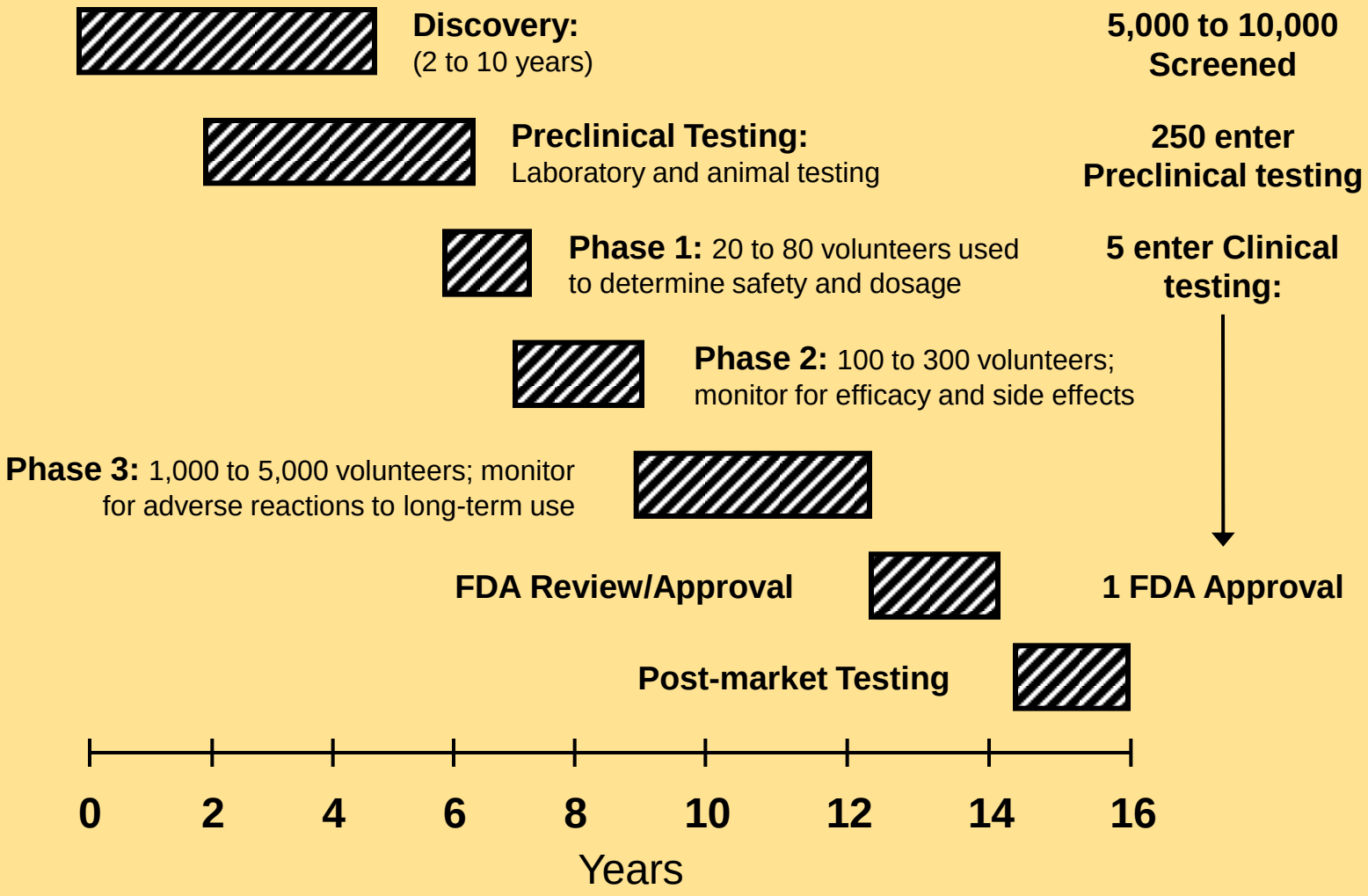
Drug Development Strategies and Planning

William Sietsema
Vice President, Global Regulatory Strategy, Consulting, and Submissions
INC Research
and
Adjunct Professor of Pharmaceutical Sciences,
University of Cincinnati, College of Pharmacy

The best map is one that points to which way is North and shows you how much water is in your way

From Stephen King's *Danse Macabre*

Development Phases



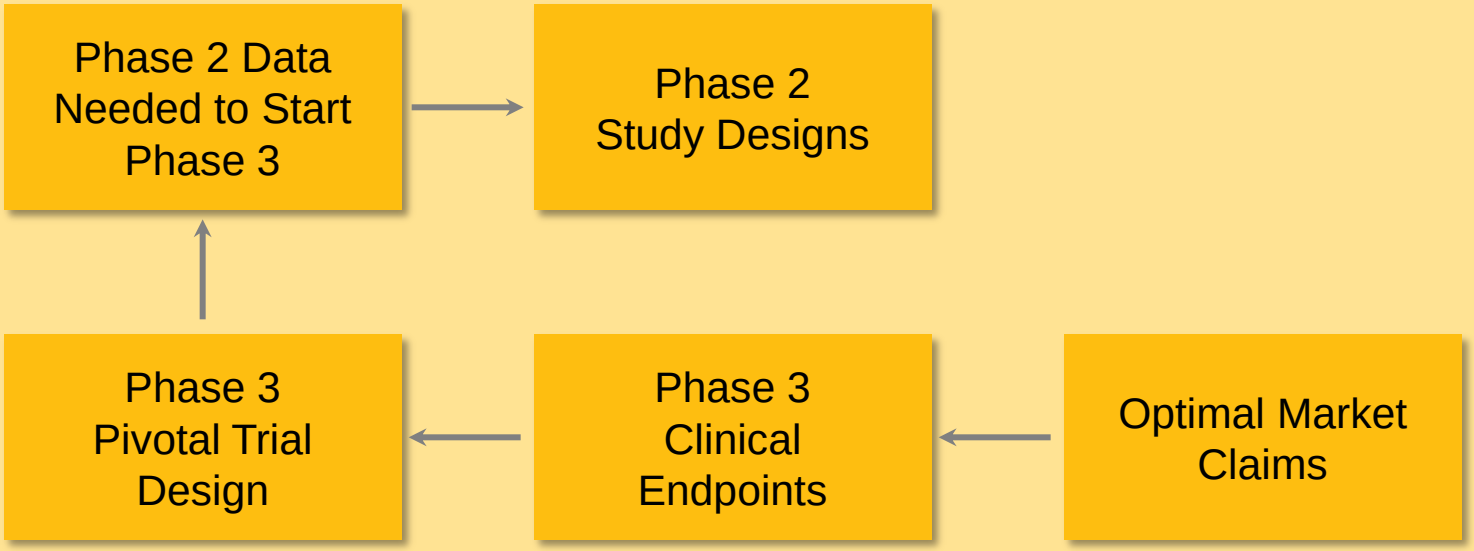
Why Plan?

- You get what you plan for
- Faster development times
- Better focus
- Lower development costs
- Lean, mean development machine

Planning Steps

- Identify potential label claims
- Research development plans for similar products
  - TGA AusPARs
  - EMA EPARs
  - FDA medical reviews for recently approved products
  - FDA advisory committee transcripts
  - Labels from each approved country
  - Publications
  - FOI requests
- Write draft label (TPP), defining desired claims
- Design Phase 3 trials to deliver those claims
- Design Phase 2 trials to give information needed for Phase 3
- Design Phase 1 trials
- Plan Phase 4 activities

Reverse Engineering Registration



- Begin with the end in mind
- Encourages efficient design
- Generate just the necessary data and avoid un-needed studies
- Shortens timelines
- Avoids rework

Elements of Plan

- Background pharmacology & device aspects where applicable
- Target Product Profile
- Phase 1 standard studies
- Phase 2 dose-ranging studies
- Phase 3 pivotal studies
- Drug-drug interaction
- Organ impairment
- Pharmacokinetic, bioavailability, metabolism
- Phase 3b and 4 studies
- Study outlines for individual studies
- Time for individual studies and whole plan
- Cost for individual studies and whole plan
- Regulatory timelines and milestones
- Discussion of issues, risks, alternatives

Phase 1 Studies

- Microdosing study?
- Single rising dose
- Multiple rising dose
- Generally in normal volunteers unless drug carries risk of toxicity not acceptable to normal volunteers
- Often great pressure to demonstrate efficacy (biomarkers?)

Phase 2 Studies

- Opportunity to develop or test clinical model for Phase 3 studies
  - Patient population(s)
  - Control group(s)
  - Efficacy endpoints
  - Statistical treatises
  - QoL instruments
  - Safety
  - Method of blinding
- Can be thought of as “practice” for Phase 3

Dose-Ranging Studies

- Sufficient dose levels in 1 or more studies to establish:
  - Ineffective dose (may come from Phase 1 studies)
  - Lowest effective dose
  - Optimal dose
  - Maximally effective dose
  - Maximally tolerated dose (may come from Phase 1 studies)
- Separate dose-ranging may be needed for elderly or children

Pharmacokinetic Studies

- Single dose pharmacokinetics
- Multiple dose pharmacokinetics (steady state)
- Population pharmacokinetics (outliers; from Phase 3 studies)
- Special population pharmacokinetics
  - Elderly
  - Children
  - Organ impairment
  - Fast/slow metabolizers

Metabolism Study

- Generally only one required
- Well-informed by metabolism studies in animals
- Define routes and amounts of metabolism
- May lead to toxicity studies of key metabolites

Organ Impairment Studies

- Needed in cases where a drug is substantially metabolized and/or eliminated via a specific organ (>20% or if narrow therapeutic index)
  - Hepatic impairment
  - Renal impairment
- Primarily evaluate pharmacokinetics and metabolism
- Often difficult populations to engage
- Small numbers of patients
- Must define and classify degree of impairment
  - Child-Pugh score for hepatic
  - Creatinine clearance categories for renal
- Key influence on label

Drug-Drug Interaction Studies

- Expected for any major concomitant medications
- Defined, in part, by similar metabolism pathways or competition for serum binding sites
- Common examples:
  - Digoxin (altered serum binding by many drugs)
  - Phenobarbital (liver enzyme inducer)
  - Cimetidine (liver enzyme inhibitor)
  - Warfarin (CYP2C9 metabolism)
  - Ketoconazole, midazolam, buspirone, felodipine, simvastatin, or lovastatin (CYP3A4 metabolism)
  - Theophylline (CYP1A2 metabolism)
  - Quinidine, desipramine, or metoprolol (CYP2D6 metabolism)

Pivotal Efficacy Trials

- Generally, 2 are required per indication
  - Controlled (some indications require placebo control)
  - Statistical proof of efficacy ($p < 0.05$)
- Single pivotal efficacy trials
  - For new dose forms of drugs whose efficacy already established
  - When substantial data exists in other geographies
  - If efficacy established definitively ($p < 0.001$)

Efficacy & Safety in Elderly

- If drug intended for use in elderly
- If elderly subjects not included in Phase 3 trials
- Can avoid if not restrictive in Phase 3 trials
- Regulatory agencies define elderly as >65
- For some indications, may need to encourage subjects >80 or >90 in order to not have wording in the labeling

Efficacy & Safety in Children

- Required in the US and EU unless disease is exclusive to adult and elderly
- Pediatric studies may carry a benefit in marketing exclusivity
- Data needed to support pediatric studies will come from adult studies
- Pediatric studies sequence with (and follow) comparable adult studies
- Accordingly, placebo control groups often avoided as pediatric studies do not form the definitive proof of efficacy

Other Studies

- Patients with intercurrent illnesses
  - If likely to be a significant portion of treated population
  - Can avoid if not restrictive in Phase 3 trials
- Open label studies to collect exposure and safety data
- QT interval prolongation
- Usability studies for devices

Exposure Guidelines

- From ICH E1A
- Drugs intended for chronic use
- Suggest at least:
  - 1500 patients exposed
  - 300 to 600 for 6 months or more
  - 100 or more for 1 year or more
- For major drugs, FDA expects much more than this
- Statistical considerations for pivotal trials frequently overshadow this

Summary

- Rigorous planning is the key to a successful and efficient program
- Prepare a “stretch goal” TPP
- Prepare a robust clinical development plan with contingencies
- Make certain the pharm/tox and quality strategies are consistent

Bibliography

1. General considerations for the clinical evaluation of drugs; FDA, 1976
2. ICH E8 General Considerations for Clinical Trials, December 1997
3. ICH E4 Dose-Response Information to Support Drug Registration, November 1994
4. ICH E10 Choice of Control Group and Related Issues in Clinical Trials, May 2001
5. Guideline for the study of drugs likely to be used in the elderly, FDA; November 1989
6. ICH E7 Studies in Support of Special Populations: Geriatrics, August 1994
7. General considerations for the clinical evaluation of drugs in infants and children; FDA, September 1977
8. General considerations for pediatric pharmacokinetic studies for drugs and biological products; FDA, November 1998
9. ICH E11 Clinical Investigation of Medicinal Products in the Pediatric Population, December 2000
10. Developing medical imaging drug and biological products. Parts 1, 2, and 3; FDA, May 2003
11. In Vivo drug metabolism/drug interaction studies – Study design, data analysis, and recommendations for dosing and labeling; FDA, November 1999
12. Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling; FDA, May 2003
13. Pharmacokinetics in patients with impaired renal function: Study design, data analysis, and impact on dosing and labeling; FDA, May 1998
14. Draft Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function; EMEA, March 19, 2003
15. ICH E1A, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions, March 1995
16. Draft ICH S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals, June 2002
17. Clinical Studies Section of Labeling for Prescription Drugs and Biologics-- Content and Format, FDA, July 2001
18. Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics, FDA, June 2000
19. A Guideline on Summary of Product Characteristics, EMEA, December 1999

Session Summary

- Whether developing a drug, device, well-thought out and vetted product concept and regulatory strategy are critical elements for success of your project
- The regulatory strategy and product concept must be agreed first so that the development strategy can be designed to fit the vision
- These plans are dynamic and must be re-examined each time there are changes in the environment or changes in strategic elements
- Understanding global regulations and designing a program which satisfies needs of many different regulators can be very challenging
- Success in the marketplace will ultimately be dependent on claims you make in the package insert or instructions for use, so design the clinical program to give you the best possible positioning