[S-16]

Assessment of Drug Safety in Regulatory Toxicology

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The pharmaceutical industry currently faces tremendous challenges in drug discovery and development. There is considerable pressure from patients and business partners to both contain costs and to deliver novel and safe medicines that treat debilitating and/or life threatening diseases. To accommodate these demands the pharmaceutical industry must discover new approaches to research and development activities. Preclinical toxicology is a key component of the drug development process. Well designed toxicology studies and an effective strategy for implementing these studies to enable clinical development is critical for early identification of drug candidate liabilities and for managing the early stage pipeline. In addition to traditional preclinical toxicology paradigms, understanding mechanism based toxicity through investigative toxicology and inclusion of tools such as transcriptional profiling may be useful to accelerate attrition of drug candidates with a low probability of success and increase the efficiency of drug discovery and development.

Industry Trends in Drug Development

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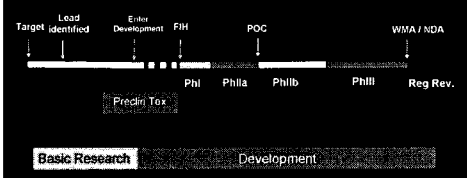
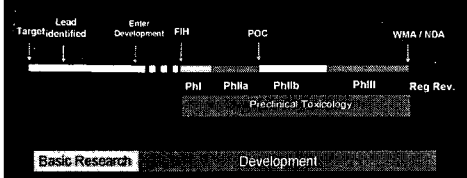
Drug Development Timeline



Early Stage Development

- FIH Enabling studies
  - Genetic Toxicology studies (ICH S2B)
    - Assess potential for compound to interact with genetic material
  - Repeat Dose Toxicology studies (ICH S4)
    - 2, 5, 14 wk oral toxicity studies
    - Identify target organs, NOAEL and safety margins
      - Provide clinical markers of the toxicity for human monitoring
  - Safety Pharmacology (ICH S7)
    - Assess potential for compound to affect the physiology of major organ systems (CV, CNS, Resp.)

Drug Development Timeline



Late Stage Development

- Timing and Design of Chronic toxicology studies (ICH S4A)
  - 6 month rodent, 9/12 month non-rodent
- Inclusion of WOCBP into clinical trials (ICH S5, M3)
  - Timing of Repro/Tox studies to assess potential effects of compounds on fetal development and on adult reproduction
- Carcinogenicity studies (ICH S1A/B/C)
  - Assess carcinogenic potential of compound
  - Timing and dose levels; often rate limiting to Regist.

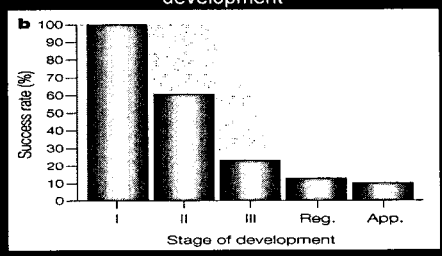
Traditional drug development paradigms are not sustainable in the face of current and future pharmaceutical development challenges.

Change is necessary for success!

To improve overall success need more FOCUS on early development candidate selection:

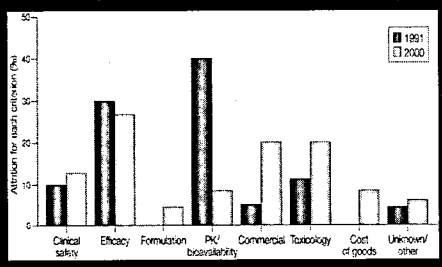
Better candidates and earlier "failure"

Percentage success of compounds entering FIM that progress through different stages of development



Ismail Kola & John Landis (2004). *Nature Reviews: Drug Discovery 3 : 711 - 715*

Reasons for attrition (1991–2000).



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Need for New Approaches to Pharmaceutical Development

- Pharmaceutical development costs approaching $1 B and average 7-10 yrs to develop
- 1 in 10-15 compounds entering clinical stage succeed
- Human genome project has yielded >3000 drug target, most unproven, with greater risk for failure
- Significant advances in chemistry and HTP screens have yielded many more drug candidates
- Public demanding safer, more effective, less expensive medicines
- Toxicology testing is a bottleneck to early human studies
- Traditional clinical "POCs" come too late in process

Industry Trends

Phase 1 *Faster* and Better

Traditional and Expanded Roles of Phase I Studies

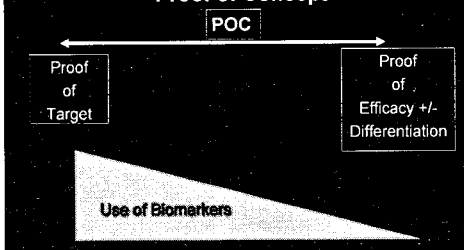
Cautiously increase doses of compound:

- Evaluate safety
- Begin to investigate PK in humans
- Serve as the basis for testing POC in Phase IIa
- Investigate "Proof of Concept"
  - Investigate "Proof of Mechanism"
  - Investigate "Proof of Target/Principle"
  - Investigate "Efficacy"
- Probe PK/PD and Biomarker relationships
- Compare PK/PD properties of multiple compounds

How to Get More Out of Early Exploratory Studies

- Novel Mechanism: Key is determine effect on Target/Disease
  - Biomarker assessment of target modulation (ideally in the disease tissue)
  - Biomarker assessment of disease process
  - Investigate PK/PD relationship
- Precedented Mechanism: Key is differentiation
  - Optimal PK (e.g. for QD dosing)
  - Better safety
  - Improved potency/activity

Value of Biomarkers in Spectrum of "Proof of Concept"



Goals of Early Exploratory Clinical Study Designs

1. Accelerate attrition (- Target, - Efficacy, - Differentiation)
2. Feedback to Discovery
3. Choose the optimal compound for Development
4. True go/no go decisions based on Biomarkers
5. Phase one studies include minimally disease subjects

Phase 1

For novel target development clinical investigation will need to undergo substantial revision to *speed* critical decisions

- Risk of failed "concept" is greater
- Risk for unknown development threats greater

Multiple Strategies and Innovations are Needed to Shorten Timelines Reduce Investments to Decisions *Without Increasing Costs*

One Approach Being Embraced in MRL and Elsewhere in Industry

Exploratory IND

Multiple Approaches Needed to Decrease Costs, Shorten Timelines and Improve Therapeutic Options

Exp-IND is one tool in a new drug development "tool box"

Goals of Exp-IND:

- Decrease time and costs to critical early clinical decisions and shift candidate failure from phase 2-3 to phase 1
- Improve the quality of pharmaceutical candidates entering later more intensive/expensive development thus, increasing later stage success
- Allow more rapid validation of potential therapeutic targets that intrinsically carry greater risk for failure

Exp-IND: A Radical PhRMA Proposal
Draft FDA Guidance April 2005

Goals of Exp-IND:

- Decrease time and costs to critical early clinical decisions
- Improve the quality of drug candidates entering later, more intensive/expensive development
- Foster rapid validation of novel therapeutic targets that intrinsically carry greater risk for failure

Based on enabling "mini" phase 1 to include normal volunteers or minimally diseased subjects

Exp IND Path to the Clinic

- Primary preclinical safety study for "each" compound is a single 2 wk tox study
  - Usually a traditional, GLP, M & F rodent
- Nonrodent study to establish the rodent as *adequately sensitive*:
  - A pilot 7 day study (3 of a single gender) at a single dose level that approximates the rodent 2wk NOAEL (mg/m² or AUC basis)
- Routine Safety Pharmacology

Exp-IND Path to the Clinic

Other Safety Studies to support Exp-IND:

- Two in vitro or 1 in vitro and 1 in vivo assay to evaluate mutagenic and clastogenic potential
- In vitro drug metabolism for test species (and for human)
- TK in both test species

Clinical Studies Under the Exp-IND

Clinical Studies Allowed:

- Clinical doses from sub/pharmacologic dosing to near non-clinical NOAEL in limited number of subjects
- Multiple dose, up to 7 sequential doses (days) with a given compound for Proof of Concept (PoC)
- Sequential testing within the same subjects with up to 5 different test articles (or formulations) for a maximum of 10 dosing days
- Normals and minimally diseased subjects allowed

Flexible clinical design allows identification of critical data for early go/no-go decisions useful in drug development

Examples of EIND

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BACK UPS