Overview of exploratory INDs

Impurities in Drugs:
Monitoring, Safety and Regulation
The Israel Chapter of PDA

July, 15 – 16, 2008

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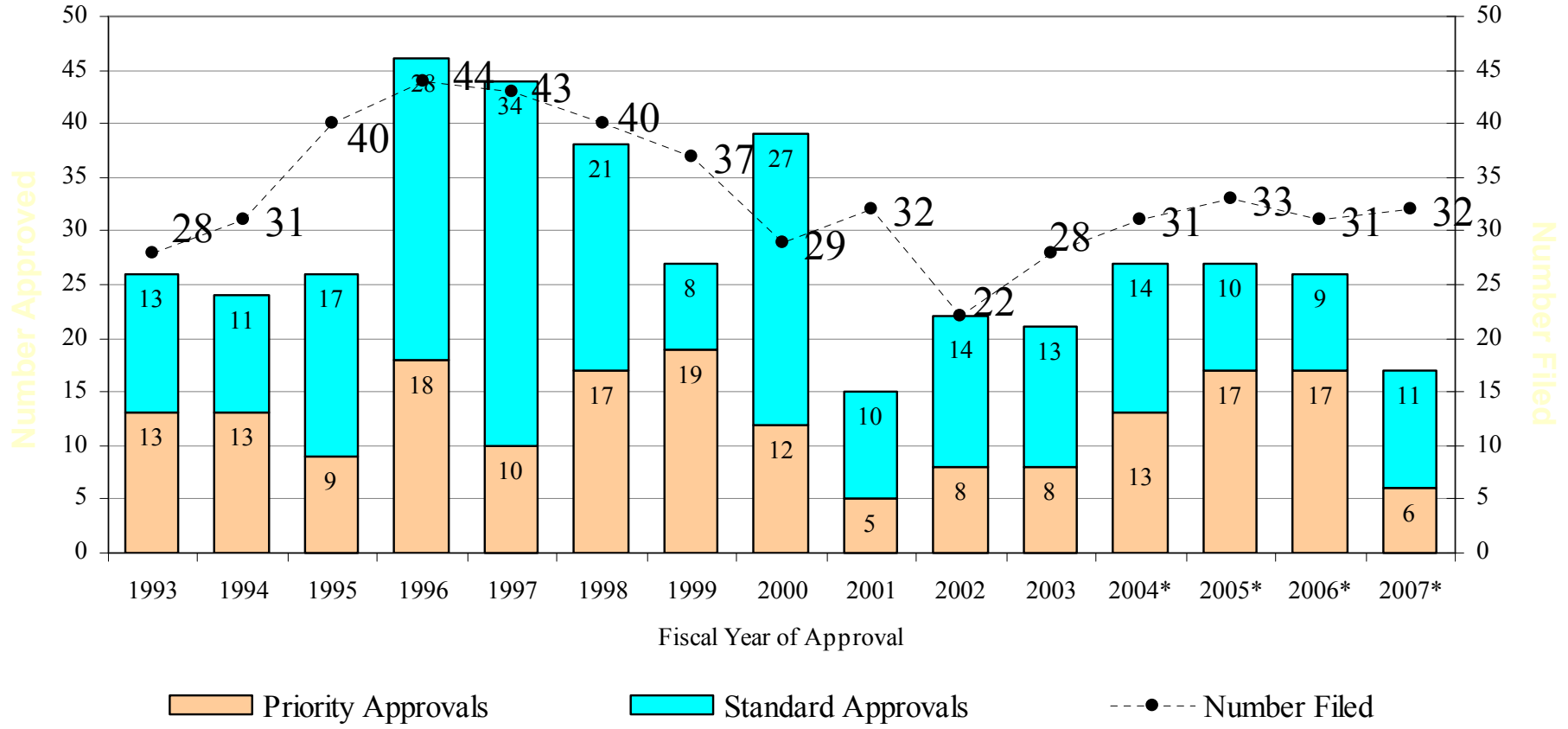
Food and Drug Administration

Challenges in Improving Efficiency of Drug Development

- NME development = **high** risk and cost
  - Extremely high failure rate before IND
  - NME IND = NDA <20% of time
  - Reported >50% failure rate in Phase 3
  - Decreased NME NDAs despite increased INDs
  - Cost per NME approved estimated at >$800M

CDER New Molecular Entity and New BLA Approvals by Fiscal Year



As of 30-Sep-07

*Includes the therapeutic biologic products transferred from CBER to CDER effective 10/1/2003.

Exploratory INDs: Guidance to Industry Investigators and Reviewers

- Draft guidance published April 2005, over 350 comments to the docket. Final published in January 2006.
- "For the purposes of this guidance the phrase *exploratory IND* is intended to describe a clinical trial that occurs very early in phase 1, involves very limited human exposure (up to 7 days of dosing) and has no therapeutic intent.
- Existing regulations allow flexibility of the amount of data that need to be submitted with an IND—depending on the goals of the investigation, the testing being proposed the expected risks.
- Viewed as pavestone on the critical path.

Use of exploratory INDs (ExpINDs) in improving efficiency of drug development

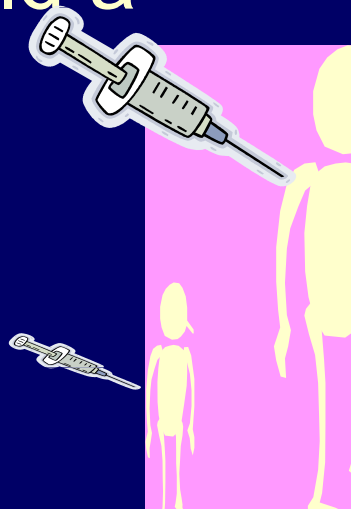
- ExpINDs allow sponsors to evaluate up to five chemical entities or formulations simultaneously
- When a lead compound has been selected, the ExpIND is closed and drug development proceeds along the traditional pathway
- ExpINDs provide opportunity to study PK and target interaction early in drug development.

Goals of expINDs

- Gain an understanding of the relationship between a specific mechanism of action and the treatment of a disease.
- Provide information on PK
- Select the most promising lead product from a group of candidates designed to interact with a particular therapeutic target.
- Explore a product's biodistribution characteristics using various imaging technologies.

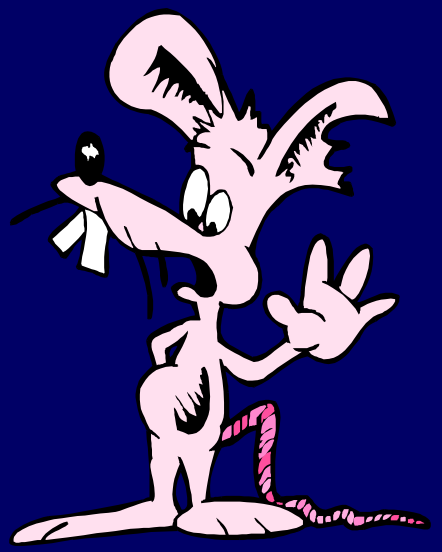
Types of studies: microdose

- Microdose studies are designed to evaluate pharmacokinetics or imaging of specific targets and are designed **not** to induce pharmacological effects.
- A microdose is defined as less than 1/100th of the dose calculated to yield a pharmacological effect and $\leq$100 micrograms.



Microdose studies

- Potential risks to subjects very limited
- Enabling study:
  - Single mammalian species
  - Clinical route of administration
  - Single dose, 14-day observation
  - Routine endpoints:
    - Clinical observations
    - Body weights
    - Hematology and clinical chemistries
    - Histopathology
- Identification of minimally toxic dose or demonstration of large margin of safety (e.g. 100X)
- Genetox not necessary.



Position Paper on Non-clinical Safety Studies to Support Clinical Trials with a Single Microdose
EMEA, June 2004

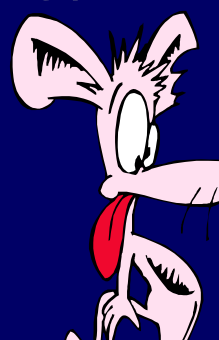
- Enabling preclinical safety studies:
- General toxicology studies using two routes of administration, IV plus clinical route.
- In vitro genotoxicity studies performed according to ICH guidance
- EMEA requires more data: two routes of administration and genetox studies.

Types of studies: Clinical Trials Designed to have Pharmacological Effects

- Paradigm first proposed by PhRMA in May of 2004
- Up to 5 compounds with a common biological target, not necessarily structurally related
- Up to 7 repeated doses in clinic in healthy subjects or minimally ill patients
- Goal is to achieve a pharmacological response but not an MTD
- PhRMA collected a data base on 106 drugs tested in two species and in phase 1 clinical trial to support preclinical safety paradigm

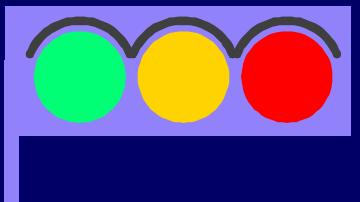
Safety Requirements for Exploratory IND designed to produce pharmacological effects

- 14-day repeated dose tox study in rodent, full clinical and histopathology
- Safety pharmacology (cv, cns, resp) as in ICH S7A
- Bacterial mutation assay and micronucleus from 14 day study
- Repeated dose study in second species (dog) at rat NOAEL. Administrations equivalent to number of dosing days in clinical trial



Clinical starting and stopping doses

- Start dose would be 1/50 the rat NOAEL (mg/m^2). If dog shows toxicity at rat NOAEL, compound not included in exploratory IND
- Stopping dose would be whichever is lowest:
  - Dose that induces pharmacological effect or target modulation
  - ¼ of rat NOAEL
  - Dose giving ½ of AUC in rat 14 day study or dog AUC if lower than rat



Evaluation of Pharma Dataset*

- **Would starting clinical trials at a dose equivalent on a body surface area basis to 1/50 the NOAEL dose in rodents be safe?**
- *Conclusion:* **Based on evaluation of 106 compounds, all trials would have been conducted safely under the expIND paradigm**

- **Would it be safe to stop trials on the basis of criteria detailed in the guidance (i.e. dose, exposure, clinical effects)?**
- *Conclusion:* **Based on evaluation of 100 compounds, all trials would have been conducted safely under the expIND paradigm**

*from PhRMA presentation Jan, 2004

The expIND will accelerate discovery and development of new pharmaceutical agents*

	Conventional IND	expIND
API	1 – 3 Kg	10 - 300 g
Preclinical Resources	➢9 – 12 studies ➢220 rodent and 38 NR ➢9 – 18 months	➢5 – 6 studies ➢170 rodent and 6 NR ➢3 – 6 months
Benefits	➢Full toxicology profile ➢Escalation to MTD in clinical trials ➢Progression directly to Ph 2	➢Predictable API requirement ➢Faster progression to clinical trials ➢Capability to evaluate candidates based on targe activity ➢Better development decisions made more quickly ➢Early and less costly attrition

*PhRMA presentation
January 2004

The expIND will accelerate discovery and development of new pharmaceutical agents*

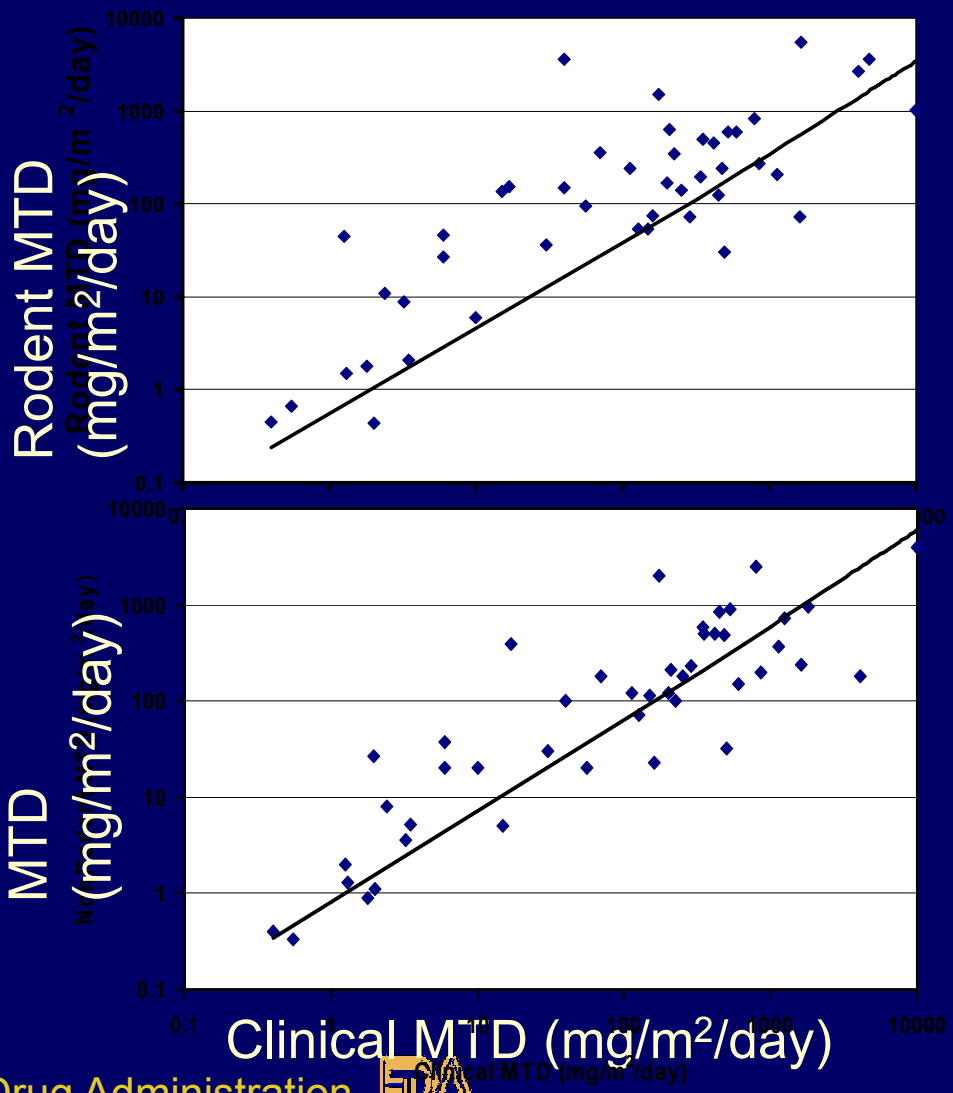
	Conventional IND	expIND
Disadvantages	➢Larger quantity of API ➢Slower decisions ➢Late and costly attrition	➢Potential delayed progression to Phase 2 ➢MTD not established

*PhRMA presentation January 2004

Viability of PhRMA-proposed paradigm

- OND has assembled results from recent submissions with 2 week or 4 week toxicology studies where the results of clinical studies are known.
- The PhRMA paradigm succeeded in identifying safe starting and stopping doses but in many cases, dog or monkey had lower NOAELs.

MTD- Rodent Human Correlation from : Smith and Tomaszewski, Preclinical and Clinical Toxicity Correlations fo Cancer Drugs Developed by NCI. , 2002.



NCI vision of expIND

PROPOSAL FOR MODIFICATION OF PRODUCT REQUIREMENTS

FOR "FIRST IN MAN" STUDIES:

FACILITATING DEVELOPMENT OF NEW ANTI-CANCER DRUGS

JOINT NCI / FDA TASKFORCE ON CANCER THERAPEUTICS

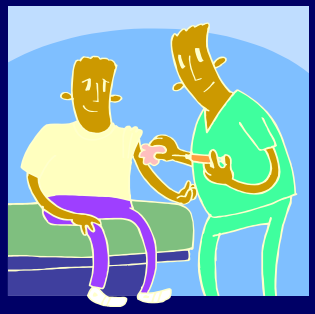
DRAFT #1: NOVEMBER 3, 2003

NCI vision for a new path for cancer drug development

- Initial clinical experience not driven by toxicity
- Pharmacological endpoints, e.g. plasma concentrations in humans
- Pharmacodynamic endpoints in surrogate or tumor tissue
- Shift in preclinical studies from toxicity to assessment of PK/PD relationships

Facilitated IND as proposed by NCI

- Used to select promising drugs for life threatening diseases
- Clinical trial populations are terminally ill patients without therapeutic options
- Up to 3 days of dosing in clinic



Success (or lack of) expINDs

- Only a handful of expINDs have been received by the FDA. Those that have been received were not for purposes initially envisioned.

Why is this tool not being used

- New paradigm, established industry, slow to adopt.
- Microdose studies may not be predictive of pharmacological dose studies.
- Protracts the time line.
- Design to kill drugs early that are likely to fail. No development team thinks their drug is a loser.

New paradigms being considered in maintenance of ICH M3R, "Timing of preclinical studies in relation to clinical trials"

- Microdose: up to 5 doses each not to exceed 1/100th the NOAEL determined in the toxicology study or 1/100th the anticipated pharmacodynamically active dose or a total dose of 100 mcg which ever is lower.

New paradigms being considered in maintenance of ICH M3R, "Timing of preclinical studies in relation to clinical trials"

- Microdose: up to 5 doses of 100mcg each not to exceed 1/100th the NOAEL determined in the toxicology study or 1/100th the anticipated pharmacodynamically active dose and with a washout of 6 half-lives between doses.

New paradigms being considered in maintenance of ICH M3R, "Timing of preclinical studies in relation to clinical trials"

- Repeat dose exploratory studies up to 14 days in the therapeutic range but not to an MTD.
- Supported by safety studies using large multiples of clinical exposure but not based on toxicity.

Bottom Line

- **CDER sees implementation of an exploratory IND guidance as an important part of FDA's commitment to improving the "critical path" to new medical products.**
- **The amount of preclinical safety data required for explNDs will generally be less or different than for conventional INDs.**
- **Reduction in safety data requirements will be scaled to the goals, duration and scope of the proposed clinical trials.**