Overview of the Exploratory IND: Differences from the Traditional IND

Improving the Quality of Cancer Clinical Trials
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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 31 Aug-06
*Includes the therapeutic biologic products transferred from CBER to CDER effective 10/1/2003.

“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 pavingstone 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 explINDs

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 $1/100^{th}$ 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/m²). 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*

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<thead>
<tr>
<th>Benefits</th>
<th>Conventional IND</th>
<th>expIND</th>
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<tr>
<td>Preclinical Resources</td>
<td>1 – 3 Kg</td>
<td>10 - 300 g</td>
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<tr>
<td>API</td>
<td>9 – 12 studies</td>
<td>5 – 6 studies</td>
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<tr>
<td>220 rodent and 38 NR</td>
<td>220 rodent and 38 NR</td>
<td>170 rodent and 6 NR</td>
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<td>9 – 18 months</td>
<td>9 – 18 months</td>
<td>3 – 6 months</td>
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<td>Full toxicology profile</td>
<td>Escalation to MTD in clinical trials</td>
<td>Predictable API requirement</td>
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<td>Escalation to MTD in clinical trials</td>
<td>Progression directly to Ph 2</td>
<td>Faster progression to clinical trials</td>
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**PhRMA presentation January 2004**

*Food and Drug Administration*
The explIND will accelerate discovery and development of new pharmaceutical agents*

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Conventional IND</th>
<th>explIND</th>
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<tr>
<td></td>
<td>Larger quantity of API</td>
<td>Potential delayed progression to Phase 2</td>
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<td>Slower decisions</td>
<td>MTD not established</td>
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<td>Late and costly attrition</td>
<td>*PhRMA presentation December 2004</td>
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*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 for Cancer Drugs Developed by NCI, 2002.
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 timeline.
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 1/100\textsuperscript{th} the NOAEL determined in the toxicology study or 1/100\textsuperscript{th} 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 expINDs 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.
Are there agreed components to phase 0 designs?

Yes, the level of preclinical safety data required is gauged to the design of the clinical trial.

Minimal data for microdose studies, more data for clinical trials at pharmacologic doses.
How will phase 0 trials affect the design of subsequent (later stage) trials?

It should not. These studies are designed to select the optimal candidate.
How will phase 0 trials affect the overall cost and efficiency of cancer clinical trials?

The goal of exploratory IND studies is to ensure that the most promising drug candidates are taken forward into development.

By eliminating ineffective or unacceptably toxic compounds early in development, resources will be conserved.
How can we obtain more data regarding a drug’s effect on its target molecule or pathway in early stage clinical trials?

This is precisely the goal of exploratory INDs!
What would be the practical results if this approach succeeds?

Few drugs will fail in later stage clinical trials.
Unpromising candidates will be eliminated earlier.
Reduction in late stage failures will save valuable resources.
More effective and safer drugs will be available to oncology patients.