

Current Perspectives on Rapid INDs

Mitchell N Cayen

Cayen Pharmaceutical Consulting, LLC

Topics to be Discussed

1. Definitions and historical background.
2. FDA guidance and European position paper.
3. Industry perspectives.
4. Regulatory perspectives.
5. Concluding thoughts.

Acknowledgements

- Robert Butz, MDS
- Joy Cavagnaro, AccessBio
- Jon Daniels, Cantox
- Joe DeGeorge, Merck
- Michael Graziano, Bristol-Myers Squibb
- John Lazor, FDA
- David Pegg, Pfizer
- Bob Powell, FDA
- Bill Robinson, Novartis
- Malcolm Rowland, Manchester, UK
- Fred Tonelli, Johnson & Johnson
- Phil Wilcox, Glaxo-SmithKline

1. Definitions and Historical Background

Questions we often hear

- Where is industry failing in drug development?
- What are the main causes of failure in early clinical trials?
- Where do you start in order to fix big Pharma?
- What is a better R and D paradigm?
- How do you assess risks earlier?
- Can regulators help to streamline the drug development process?

CAN RAPID INDs HELP MAKE THINGS BETTER?

What is a “Rapid IND”?

- ***Old Definition:***

What management challenges research staff to attain in an unreasonable amount of time.

- ***Current Definition:***

A regulatory acceptable approach to conduct a limited clinical study with a less than traditional amount of toxicological support.

Rapid IND Goal

**To reduce the time and resources
expended on candidate products
that are unlikely to succeed**

Other Relevant Terms

- **Microdose:**

Less than 1% of the dose calculated to yield a pharmacological effect in humans, based on in vitro and preclinical in vivo data.

- **Screening IND:**

When a microdose study comprises several compounds.

- **Exploratory IND (explIND or eIND):**

Same as “Rapid IND”.

- **Phase 0.**

FDA Guidance of 2004

“Fast Track Drug Development Programs – Designation, Development, and Application Review”

(June 2004)

- Serious life threatening conditions
- Unmet medical needs

***2. FDA Guidance and
European Position
Paper on Rapid INDs***

The FDA Guidance

***“Exploratory IND Studies”
was issued January 2006***

Both the FDA guidance and European paper are aimed more for small molecules, and may not apply for biologics.

The FDA Guidance: eIND

Three Examples

1. Microdose studies.
2. Clinical trial to study pharmacologically relevant doses. Study can last up to 7 days. Obviously, the toxicology requirements are more extensive than for a microdose study.
3. Mechanism of action related to efficacy.

FDA Guidance

- Fewer risks than standard Phase 1 studies
- More flexibility for treatment of life-threatening diseases.
- Preclinical safety studies must be GLP.
- IND is withdrawn after completion of human study described therein.
- Thus, advantage is for compounds NOT likely to succeed.

Microdose Study

The microdose can comprise several drug candidates in order to choose the best candidate based on PK profile (“Screening IND”).

FDA Guidance: Microdose

- Maximum dose: $\leq 1\%$ of PD dose for a maximum of 100 μg .
- Possible clinical goals:
 1. Early PK characterization.
 2. Receptor selectivity profile using positron emission tomography (PET) or other sensitive imaging techniques.

FDA Guidance: Requirements for Microdose Study

1. Extended Single Dose Toxicity Study:

- One species (selection based on in vitro metabolism + in vitro primary PD data), males and females
- Several doses: establish MTD.
- 14 day study period: sacrifices on days 2 and 14. No toxicokinetics required.
- Gross necropsy, hematology, clinical chemistry and histopathology.

2. No genetic toxicology study is needed.

FDA Guidance: Requirements for Pharmacological Dose Study

- Preclinical goal: Select safe starting dose and estimate human MTD.
- Two-week toxicology + toxicokinetics in relevant/sensitive species; can be the rat.
- Confirmatory toxicology study in second species:
 - Typically dogs
 - Duration: typically 4 days
 - Can be only males if clinical trials will use only males
 - Single dose level, eg rat NOAEL.

Pharmacological Dose Study Requirements (cont'd)

- Genetic toxicology - generally as per ICH:
 - Ames test
 - Chromosomal aberration
 - Mouse lymphoma or in vivo micronucleus at MTD
- Safety pharmacology:
 - CNS & respiratory systems: can be part of rat tox study
 - Cardiovascular: can be part of dog confirmatory study

FDA Guidance: Clinical Doses

- Clinical starting dose is no greater than 1/50th rat NOAEL, based on mg/m².
- After establishing the animal MTD, use allometric scaling + safety factor of 100 as an estimate of the human MTD.

Maximum Clinical Dose is Lowest of the Following:

- $\frac{1}{4}$ of rodent NOAEL based on mg/m^2 .
- $\frac{1}{2}$ the AUC from rodent NOAEL, or dog AUC at rat NOAEL, whatever is lower; thus, will need to turn around human PK.
- Dose which elicits a pharmacologic or pharmacodynamic response.
- Observation of clinical AE.

(Thus, trial terminated when any of the above occur)

European Position Paper

The European CHMP/CPMP position paper on “Non-clinical Safety Studies to Support Clinical Trials with a Single Microdose” was published in June 2004.

European Microdose Paper: Toxicology Requirements

Toxicology requirements are the same as those in FDA guidance, except:

1. Genetic toxicity studies are required.
2. MTD margin of safety = 1,000, not 100.

European Data Base (June 2006)

48 Compounds:

- 6 (13%): no rodent NOAEL
- 4 (8%): non-rodent toxicology
- 17 (35%): projected exposure less than pharmacologic
- 21 (44%): projected exposure was pharmacologic

3. Industry Perspectives

Industry Perspectives: Sources

- Drusafe public workshop: June 26, 2006
- Big and small PhRMA colleagues in drug metabolism, drug discovery and toxicology
- Other consultants
- FDA CDER colleagues
- European source
- Personal

Key Single Question: *Are Rapid INDs Worthwhile?*

- Bang for the buck?
- Does it save time?
- Does it help in selection of the best compound within or between a chemical series?
- Does it result in more rapid discarding of nonviable drugs?
- Does it save money?

Microdosing: Compelling Concept

- Clinical PK often the cause of NCE attrition.
- Multiple compounds can be tested under a single IND.
- Selection of one compound out of several with similar (discovery) properties.
- Early compound elimination.
- Rapid go/no-go decision based on single dose human PK.

Microdosing: Requirements

1. Sufficient bulk product and characterization (non-GMP).
2. Toxicology for each compound (GLP).
3. Very sensitive bioanalytical assay for each compound in human plasma.

A Big PhRMA Company

Experience: *Five Projects (05-06)*

- Goal: Compound selection or go/no go.
- Exposure, half-life, relative bioavailability and/or absolute bioavailability.
- For abs bioavailability, did oral dose with cold + iv dose with ¹⁴C-labeled compound (supporting tox: oral only).
- Result: Traditional INDs filed for three projects.

Another Big PhRMA Company Experience (Two Projects)

RESULTS (both projects complete)

Project One: Successful selection of lead candidate from several eIND candidates.

Project Two: Single candidate dropped due to human PK.

A Small Pharma Company Experience: Microdoses

- Novel antibiotic.
- Goal: determine if PK enabled once daily administration.
- Compared with two related agents.
- Result: specific question was “answered” (proprietary whether or not goal was attained).

Microdosing: Perspectives on Success Rate

- Very few “winners” to date.
- A small number of big Pharma companies (and a lesser number of small companies) have been successful in achieving the goal of early compound selection or rapid project termination.
- Thus, these companies are supportive of the microdosing initiative.
- Seems more “popular” in Europe.

Microdosing: Limitations

SCIENTIFIC

PK at microdoses may not necessarily reflect PK at therapeutic doses, and thus results can be misleading.

REALITY

There are very few programs where one compound cannot be selected/prioritized based on preclinical screening (in vitro assays and animal models)

Why microdosing is not used more

- Conceptually good idea for compound (or formulation) elimination, but its time may have passed.
- Will rarely lead to reduced attrition, where attrition due to safety or lack of efficacy, which is not used with this approach.
- Limited opportunities re PK.
- However, imaging initiatives may be more successful.

Microdosing: A Theoretical Advantage

EARLY HUMAN RADIOLABELED STUDY

- Advantage: early data on metabolism in man
- Disadvantage: May still require animal radiolabeled studies for dosimetry, and radiolabeled microdose may not reflect therapeutic dose.
- Conclusion: minimal advantage.

Microdosing Monograph

“Microdosing in Translational Medicine:
Pros and Cons” (2006)

Hermann A.M. Mucke (\$2,750)

The Pharmacological Path: A Big Pharma Company Experience

Project One: Background

- Backup to late stage compound which had low bioavailability, high variability.
- Goal: PK at PD doses.
- Tox: 2-week rat; 4-day dog qualification; genetic tox; safety pharmacology.
- Clinical: SD escalation, placebo controlled.
- Starting dose: 1/50th of rat NOAEL.

The PD Path: a PhRMA Experience

Project One: Results

- Found PD response.
- Clinically relevant doses lower than expected (half rat NOAEL).
- Plasma exposure criteria achieved.
- Conclusion: candidate deemed viable for further development.

The PD Path: a PhRMA Experience

Project Two: Background

- Large dose-exposure variability in animals.
- Wide projected human dose.
- Potential clinical issue: were plasma drug levels less than at animal MTD?
- Goal: explore potential nonlinearity at PD doses

The PD Path: a PhRMA Experience

Project Two: Results

- Did not achieve exposure targets.
- Dose escalation terminated.
- Alternate formulation being sought.
- Strategy: file amendment to current eIND and repeat with new formulation.

Why one major Pharma company will not conduct eINDs

- Conceptually good idea, but will not likely lead to reduced attrition.
 - Attrition due to safety or lack of efficacy not adequately addressed.
- Very few programs where one compound cannot be select based on preclinical screening studies.
 - More cost effective to differentiate new molecules with in vitro assays and animal models.
- Cannot readily assess target modulation in healthy volunteers for certain diseases (eg. oncology; infectious diseases)

Why one major Pharma company will not conduct eINDS (cont'd)

- Resources: takes up “slots” in early development portfolio.
- Rarely assesses tolerability (MTD not established).
- PD activity does not necessarily mean efficacy
 - Cannot fully explore dose/exposure range.
- Delayed timeline to Phase 2
 - Requires followup traditional IND.
- Estimates will do standard INDs in about 40% of programs.

The Naysayer Conclusion

“The total amount of resource savings are not enough to justify routine use of the explND strategy when weighed against the risks and opportunity costs for most drug programs”

PD Path: Industry Perspectives – Potential Benefits

- More advantages than microdosing.
- Target specific compound-related issues.
- Reduced timeframe to proof of principle.
- Safer, effective dose regimens earlier.
- Reduction in later stage attrition.
- Quicker access to patients.
- Resource savings

eINDs: Resource Savings

- Drug substance.
- Animals used for toxicology.
- Shorter toxicology studies.
- Staff (FTEs)
- Time to IND submission

***THUS THEORETICAL SAVINGS IN
COST, TIME AND STAFF***

eIND: The Reality - Toxicology

- Target organ toxicity/MTD may not be defined, thus progress to clinic based on arbitrary safety margin.
- In a short tox study, what is “toxicity” vs “finding”; “adverse” vs “non-adverse”?
- Are toxicology changes of acute consequences with clinical eIND study?

eIND: The Reality

- Need new IND for Phase 1 study, as eIND withdrawn after completion. Thus need 2 INDs for Phase 1 with single NCE.
- Inherent delay of clinical “go” decision:
 - bulk drug synthesis.
 - complete characterization of drug product and drug substance.
 - complete toxicology and TK package.

eIND: The Reality

- Cannot fully explore dose/exposure range.
- PD activity may not predict efficacy.
- What is “pharmacologic”?
- How much time does it really save if a pre-eIND discussion with FDA is advisable?
- Reluctant acceptance of new concept: needs internal champion.

eINDs: Current Status

- Seems different between big and small Pharma.
- Big Pharma: work with numerous NCEs, so goal is to kill compounds early.
- Small Pharma:
 - Work with small number of NCEs
 - Under investor pressure to get to clinic with an open IND.
 - Only occasional potential advantage over traditional approach.

What DMPK/TK is “needed” for eINDs?

- Microdosing:
 - Liver microsome metabolism similarity between toxicology species (rat) and human.
 - Enzyme inhibition (in vitro) is advisable.
 - No toxicokinetics.
- PD eIND:
 - Liver microsome metabolism comparison.
 - Toxicokinetics.
 - Enzyme inhibition is advisable.

4. Regulatory Perspectives

Regulatory Perspectives

- FDA trying to push the concept: fewer risks than traditional INDs.
- Encouraging sponsor to discuss with FDA division before submission.

Regulatory Perspectives

- FDA has no internal statistics (IND/eIND)
- There has not been a “flood” of eINDs.
- Pharmacologic path more popular than microdosing path.
- Some reviewers not recognizing eINDs.
- Heterogeneity between the 15 divisions.
- FDA thinks popularity will increase.

5. Concluding Thoughts

Many reasons not to do an eIND

1. Cost savings probably significant, but time savings are questionable.
2. No single distinct factor can make a “go”.
3. Hesitancy to use nonvalidated marker for go/no-go.
4. Early go/no-go: faster; NDA: longer.
5. Within company reluctance.

Microdosing: Where do we stand?

- Compelling approach to help select a candidate or a formulation based on PK
- What is really needed for implementation?
 - Single dose toxicology (14-day followup) for each drug candidate
 - Very sensitive assay for each drug candidate
- ***Major issue: PK nonlinearity***
- Rarely recommended, due to problematic predictability to therapeutic dose.
- More popular in Europe than in North America.

Ideal Candidates for eIND

1. High potency

- efficacy at low mg/kg doses
- limits tox and clinical drug requirements

2. Good oral bioavailability in animals

- impacts tox dose
- impacts amount of API needed

3. Fairly safe in preclinical

- large window between efficacious dose and NOAEL.

Ideal Candidates for eIND

4. Single targeted goal

- Should have single endpoint for go/no go decision.
- Lead compound with multiple backups*.

5. Readily detectable clinical efficacy marker

- PK is OK, but PD is the major driver.

6. Possible to achieve efficacy in humans within the Exp-IND

- Complicated: PK/PD in animals difficult
- Extrapolating PK/PD to man often problematic

Backup Compound Strategy

- Plan for success with lead compound, but position best backup with limited program:
 - Any toxicology flags?
 - Better clinical PK?
 - Better clinical PD?
 - Synthesis experience
- Faster than conventional IND for backup elimination, but not faster for selected backup.

Ideal Candidates for eIND

7. Resource and Project Strategy

- Too much or too little can kill expIND
- Cost to next decision point
- Cost to full development
- Outsourcing/licensing plans

8. When large scale synthesis is difficult.

9. Management understanding of issues, limitations and predictability.

- cost savings should not be overly optimistic
- needs internal champion

eINDs: Some Potential Benefits

- More rapid identification/confirmation of potential therapeutic targets.
- Reduced attrition at later development stages.
- Earlier determination of safer, more effective dosage regimens.
- May enable quicker access to patients.

Nonclinical Studies Being Conducted for PD eINDs:

- Toxicology (2 weeks) in sensitive species (rat).
- Confirmatory study in nonrodent.
- Genetic toxicology: two appropriate in vitro assays, or one in vitro and one in vivo.
- Safety pharmacology, ie CV, CNS, respiratory.
- Drug metabolism: toxicokinetics; in vitro metabolism (test species and human); enzyme inhibition.

IS THIS TOO MUCH?

eINDs: The Psychology (MNC)

- Those who have done it/planning it – they support it (must justify to management).
- Those who have not done it/plan it – they do not support it (too many caveats).
- Bottom line:
 - Microdosing: be very careful
 - PD approach: can be useful for selected programs.

eINDs: Conclusions

- Microdosing:
 - Rarely recommended for PK.
 - Imaging may be more useful
- PD-based eINDs:
 - Can weed out “losers” earlier.
 - Good approach for backup selection.
 - ***Assure PD and/or PK endpoint results in a go/no-go decision.***

eINDs: Current Perspectives

- FDA more enthusiastic than industry.
- Europe more enthusiastic about microdosing strategy than USA.
- Main value: kill compounds early.
- Currently embraced more by big Pharma.
- Small Pharma may get to clinic with traditional INDs faster (rapid decision making; infrastructure)
- May provide value for small Pharma or biotech companies with limited finances.
- Is it worth it? ***MAYBE***

Acknowledgements

- Robert Butz, MDS
- Joy Cavagnaro, AccessBio
- Jon Daniels, Cantox
- Joe DeGeorge, Merck
- Michael Graziano, Bristol-Myers Squibb
- John Lazor, FDA
- David Pegg, Pfizer
- Bob Powell, FDA
- Bill Robinson, Novartis
- Malcolm Rowland, Manchester, UK
- Fred Tonelli, Johnson & Johnson
- Phil Wilcox, Glaxo-SmithKline