

Three globes with grid lines are shown in the background, overlapping each other. The globes are rendered in a blue and yellow color scheme, with the grid lines in a lighter yellow. They are positioned on the left side of the slide, with the largest globe in the foreground and two smaller ones behind it.

Global Strategies & Case Reports of Developing NME Leads to Human Trials

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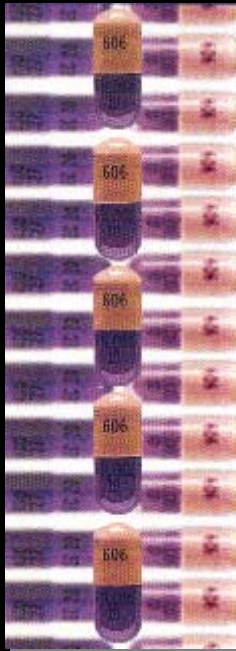
**Cost of developing a new drug
increases to about \$1.7 billion...**

Wall Street Journal, December 8, 2003



High Gain

6.26



Omeprazole

5.2



Hit
Movie

4.2



Top Ten
Artists

0.6



Jackpots &
Valuables

Pharmaceuticals are a high-gain enterprise. In the year 2000, the worldwide pharmaceutical market was about 325 billion dollars. There were forty-four drugs with worldwide sales over 1 billion dollars—a general threshold for blockbuster status—from among which omeprazole (Prilosec™) was the top moneymaker, at 6.26 billion dollars.^a

Revenue in the year 2000 from this single drug exceeded the total cash intake from the top five-grossing movies of all time (Titanic, two Star Wars movies, Jurassic Park, and Independence Day)^b as well as the combined retail value of all the known paintings of the top ten grossing artists (Picasso, Monet, Renoir, Degas, Cézanne, Chagall, Matisse, Pissaro, van Gogh, and Modigliani)^b.

Finally, the combined value of the highest prices ever paid for the most expensive diamond, coin, clock, pen, piece of furniture, sculpture, book, baseball, manuscript, plus the biggest slot-machine and lottery jackpots is only about ten percent of the single-year revenue of omeprazole.^c

^a *Med Ad News* 20 (5), 7 May 2001.

^b Ash, R. *The Top 10 of Everything 2001*, Dorling Kindersley, New York, 2000.

^c *Guinness World Records 2001*, Guinness World Records LTD, London, 2000.

Revenue (in billions)

A world map with a grid of latitude and longitude lines, rendered in a light blue color against a dark blue background. The map shows the outlines of all major continents and islands.

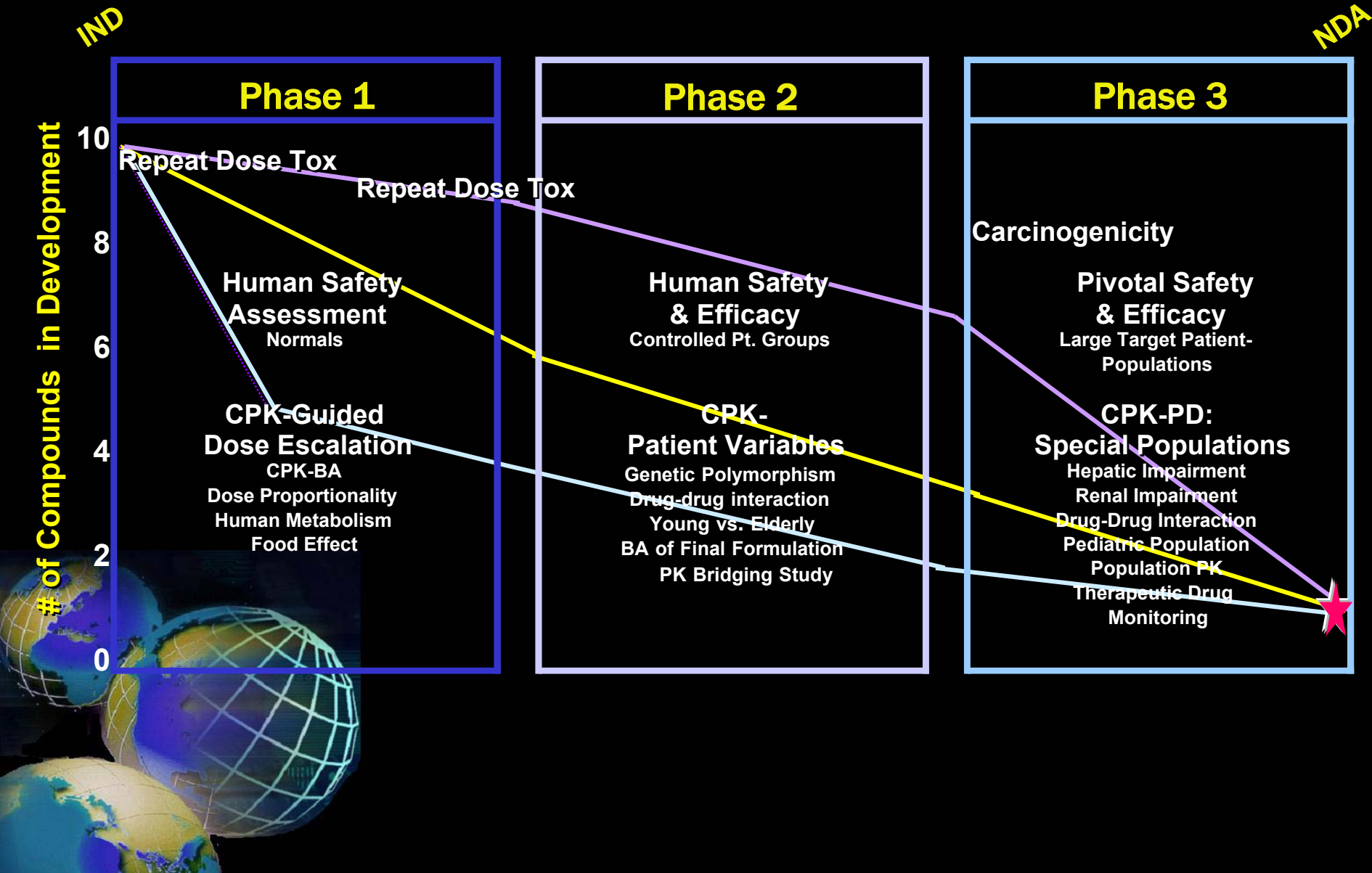
**Only 3 out of 10 marketed drugs
produce revenues that match or
exceed average R & D costs...**

**A new medical compound entering
Phase 1 testing is estimated to have
only 8% chance of reaching the
market...**

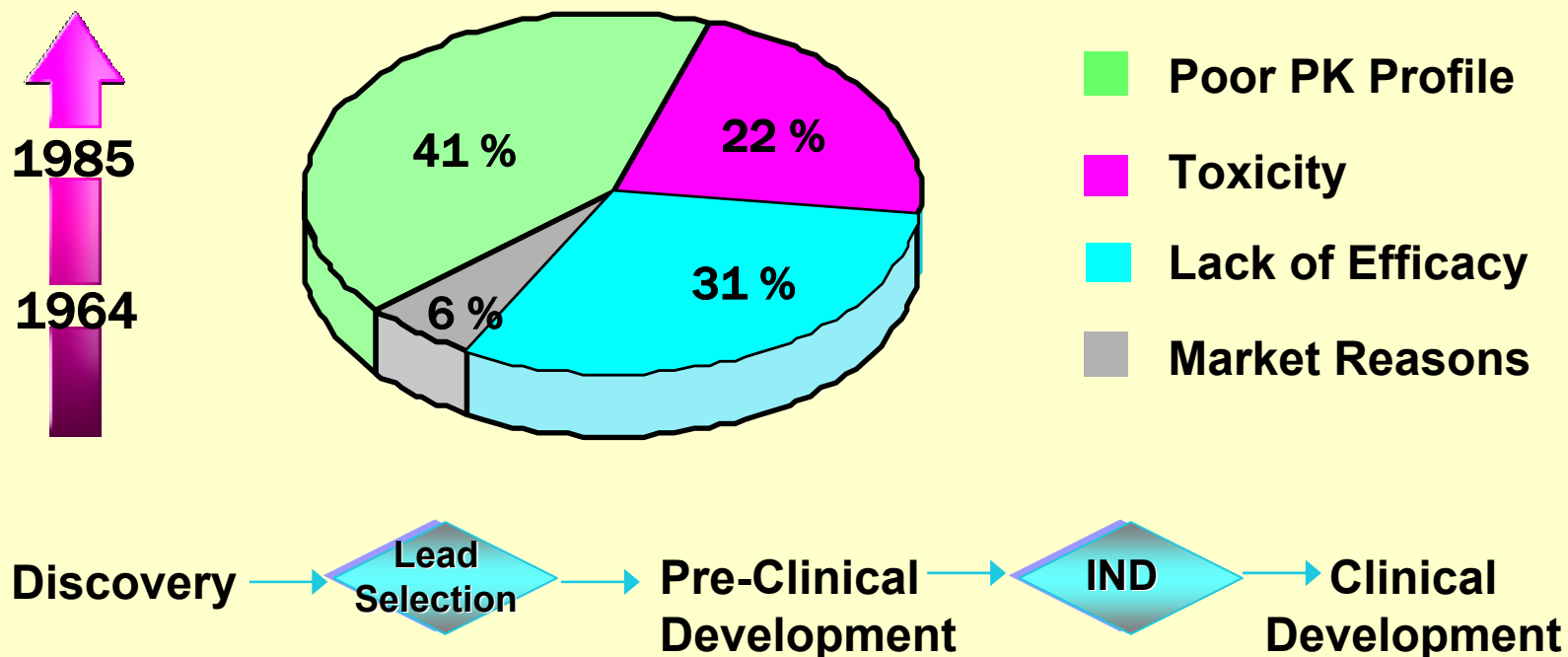
Critical Path Report, FDA, March 2004



Managing the Attrition Curve

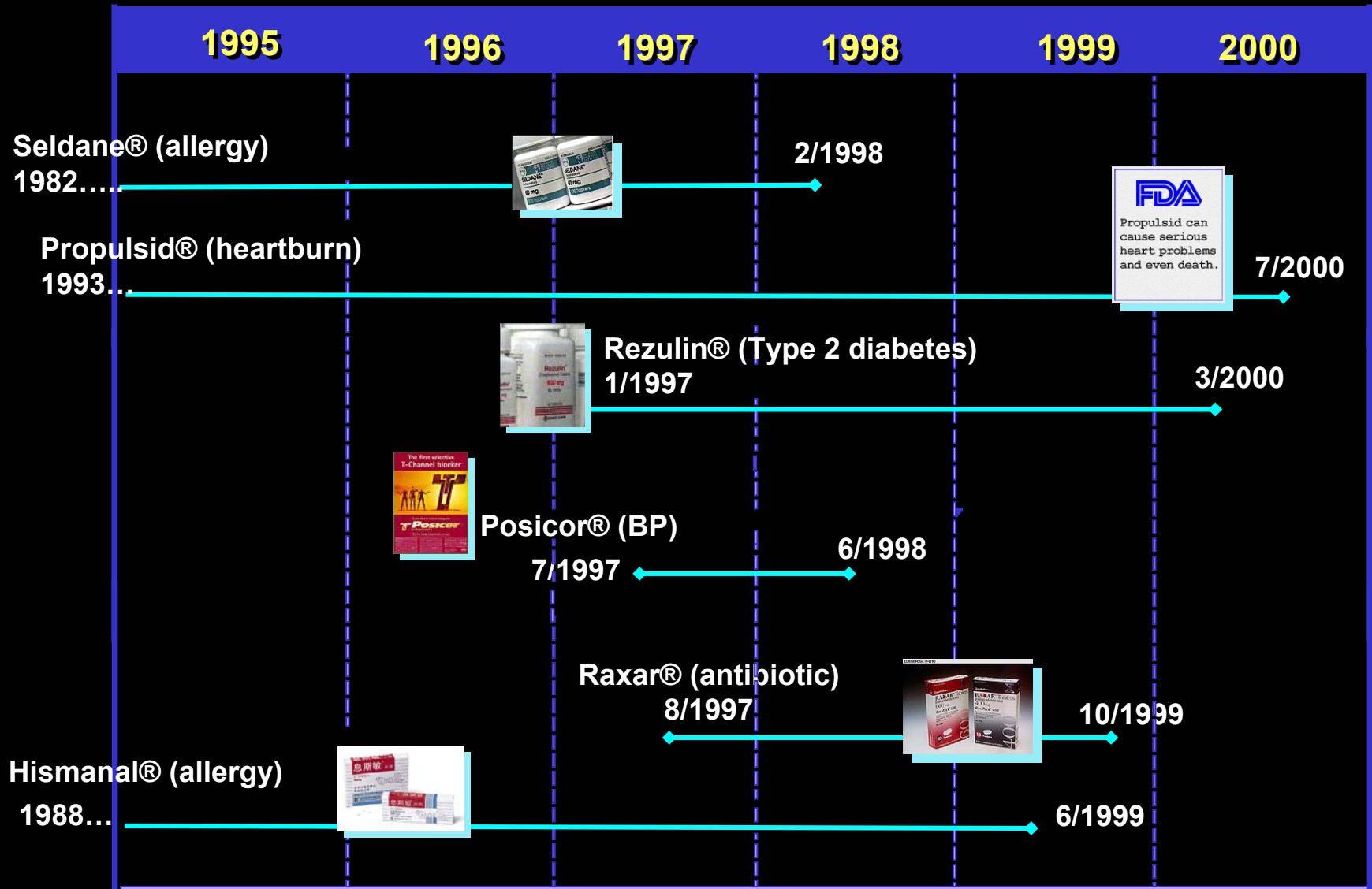


Reasons that Compounds Fail



*Prentis, et al, Br J Clin Pharmac, 25, 1988
Data on 198 failures of 319 NCEs in UK, 1964-1985*

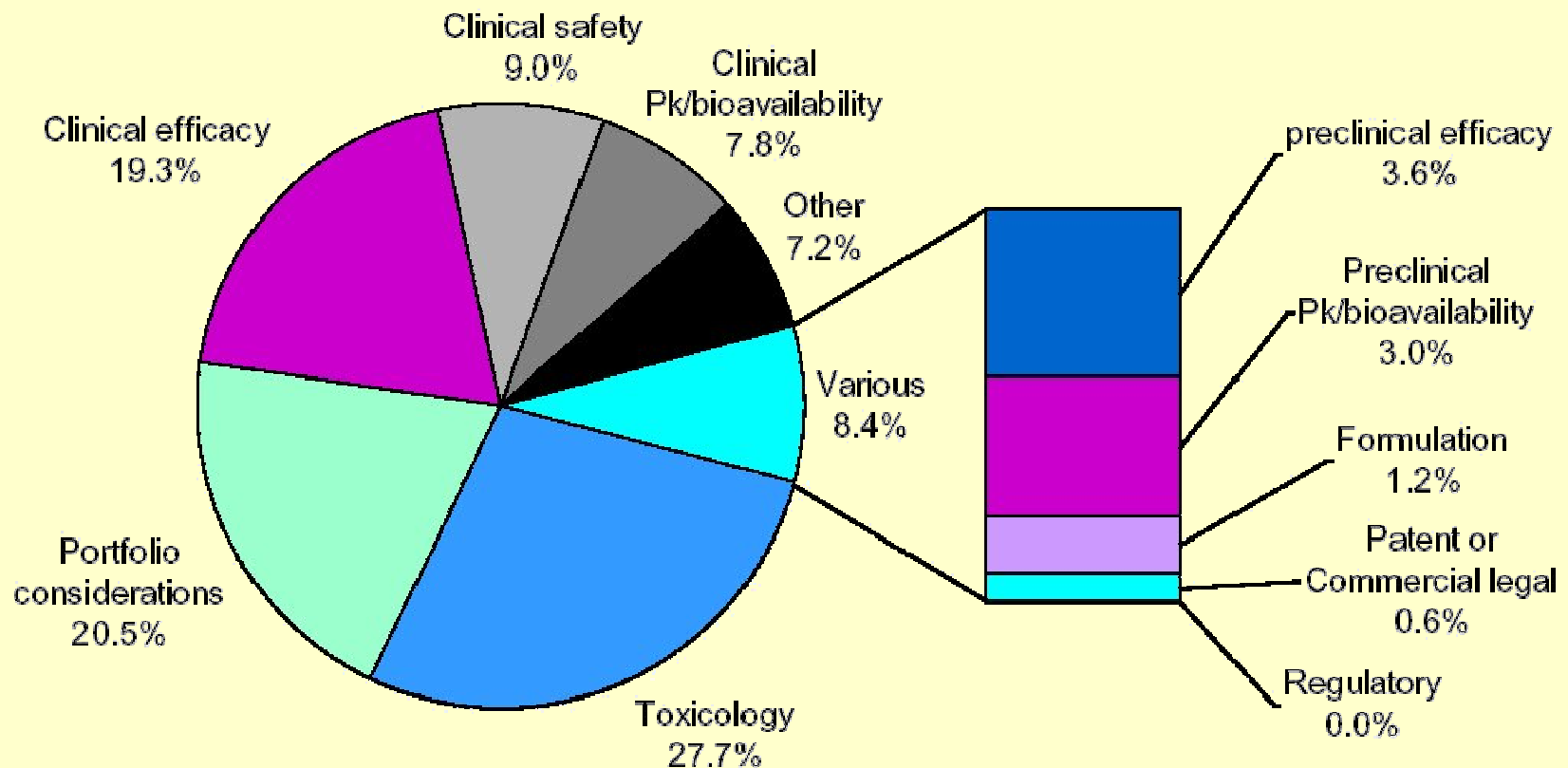
Drug Withdrawal from the U.S. Market (Due to Unfavorable Drug Metabolism Profile)





Information on polymorphic ADME genes is the most advanced area in genomic regulatory submission and a high priority for regulatory agencies...

Reasons That Compounds Fail—2001

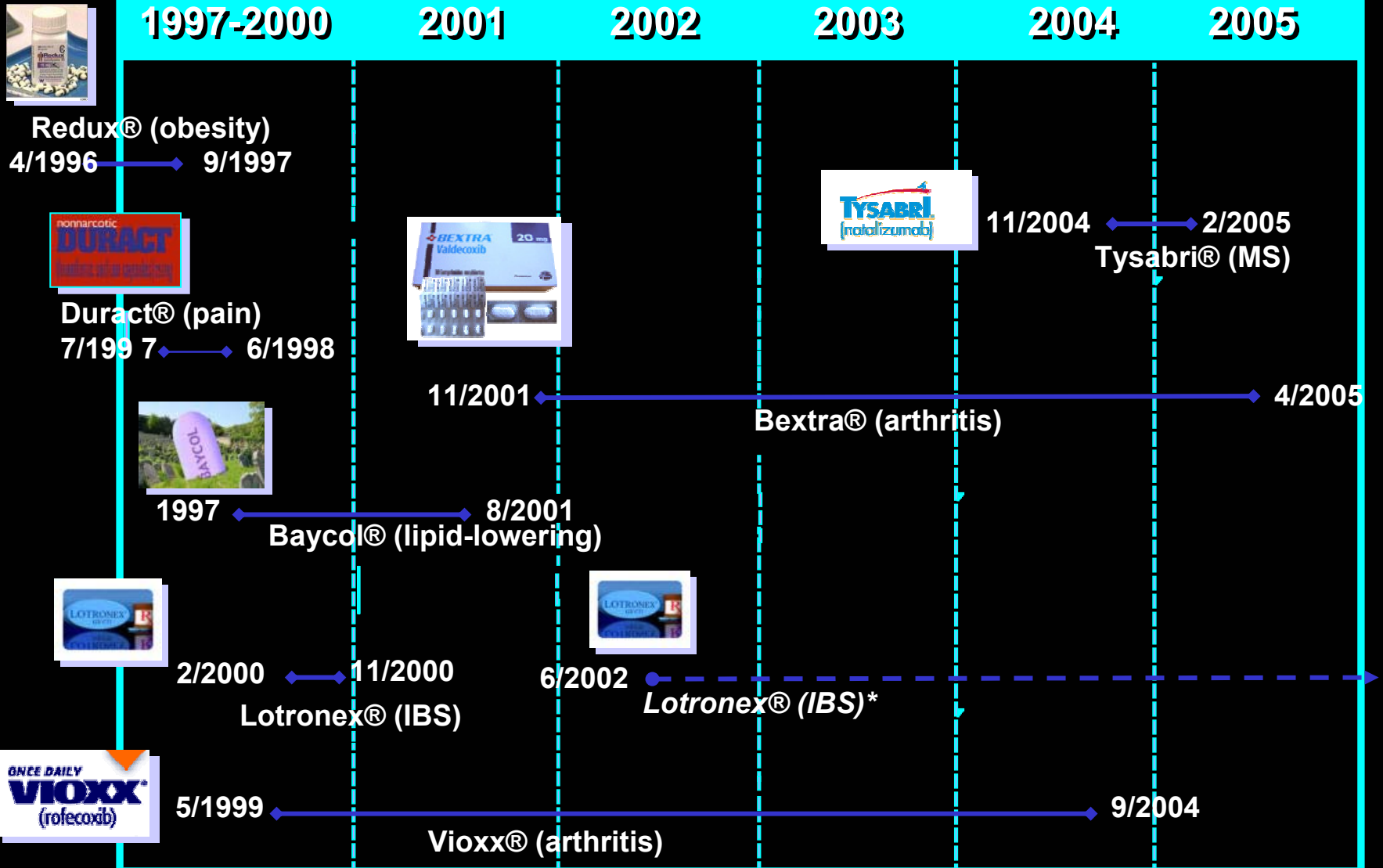


*Data provided by 25 companies
for 166 of the 189 NASS Terminated in 2001*

STRATTERA® (atomoxetine HCl)

- A selective norepinephrine reuptake inhibitor
- Attention-Deficit/Hyperactivity Disorder
- Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity [extensive metabolizers (EMs)]. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.
- Laboratory tests are available to identify CYP2D6 PMs.
- The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethyatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).

Drug Withdrawal from the U.S. Market (Due to “Safety” Issues)



*Restricted Marketing

Health Canada

- Clinical Trial Applications
- 30-day default review period
 - ➔ 7-day target for Phase 1 and comparative BA trials



The Investigational Medicinal Product Dossier (IMPD)

- IMPD, IB, and the Clinical Protocol
- The aim of this information is not the registration of the drug but rather its use in a particular clinical trial about which the EC/CA will give an opinion

Ethics Committee/Competent Authority

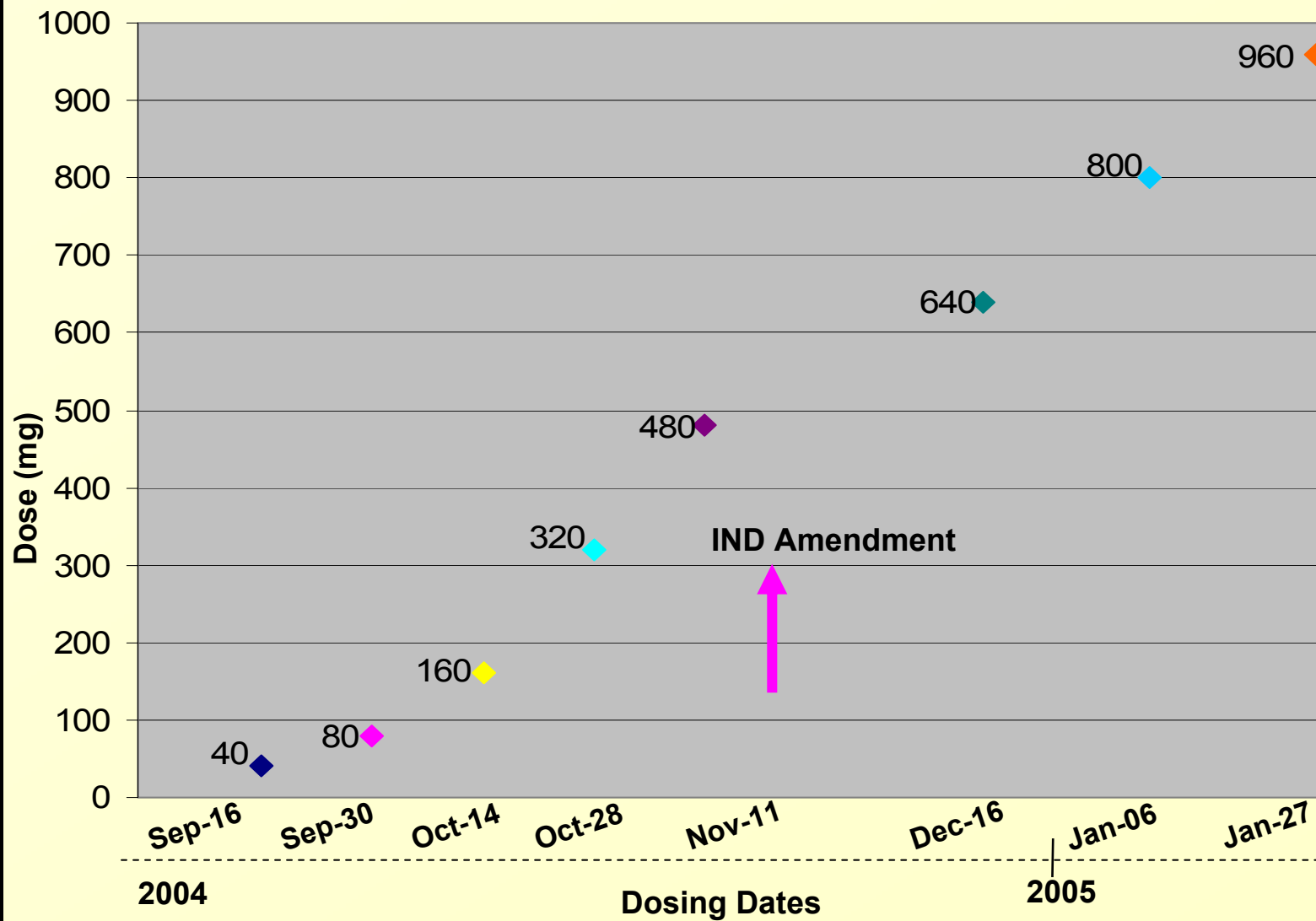


Compound A: FIM Dose Selection

- NOAEL, Rat 1000 mg/kg/d X 28 d
- NOAEL, Dog 500 mg/kg/d X 28 d
- FIM Dose per Guidance 1620 mg
- Actual FIM Dose 40 mg



Compound A: Dose Escalation



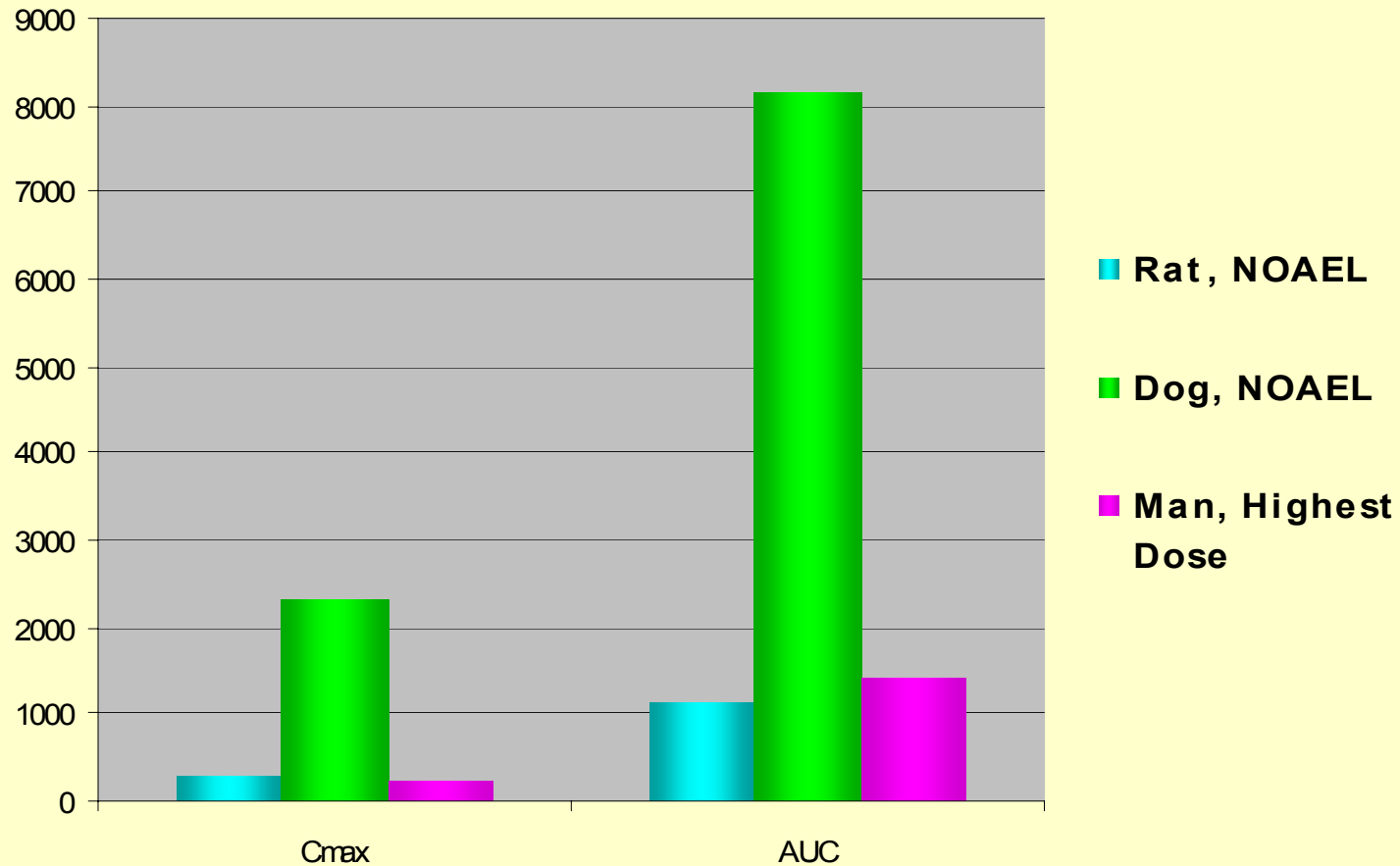
Compound A: FIM Doses

- NOAEL, Rat..... 1000 mg/kg/d X 28 d
- NOAEL, Dog 500 mg/kg/d X 28 d
- FIM Dose per Guidance..... 1620 mg
- Actual FIM Dose 40 mg

Highest Dose in FIM Study: 960 mg

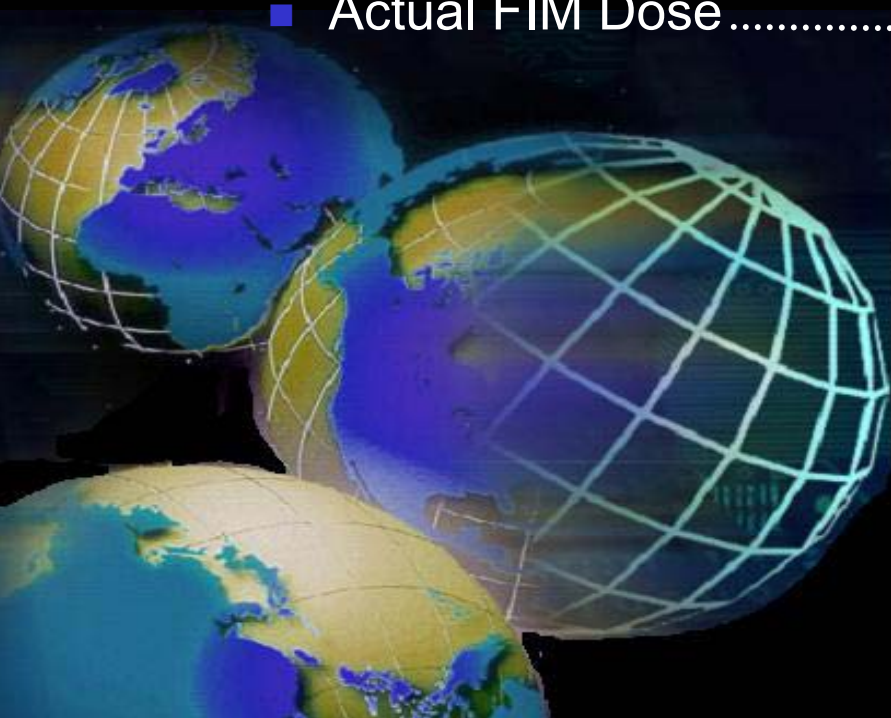


Compound A: Comparative Exposure Between Animals and Man

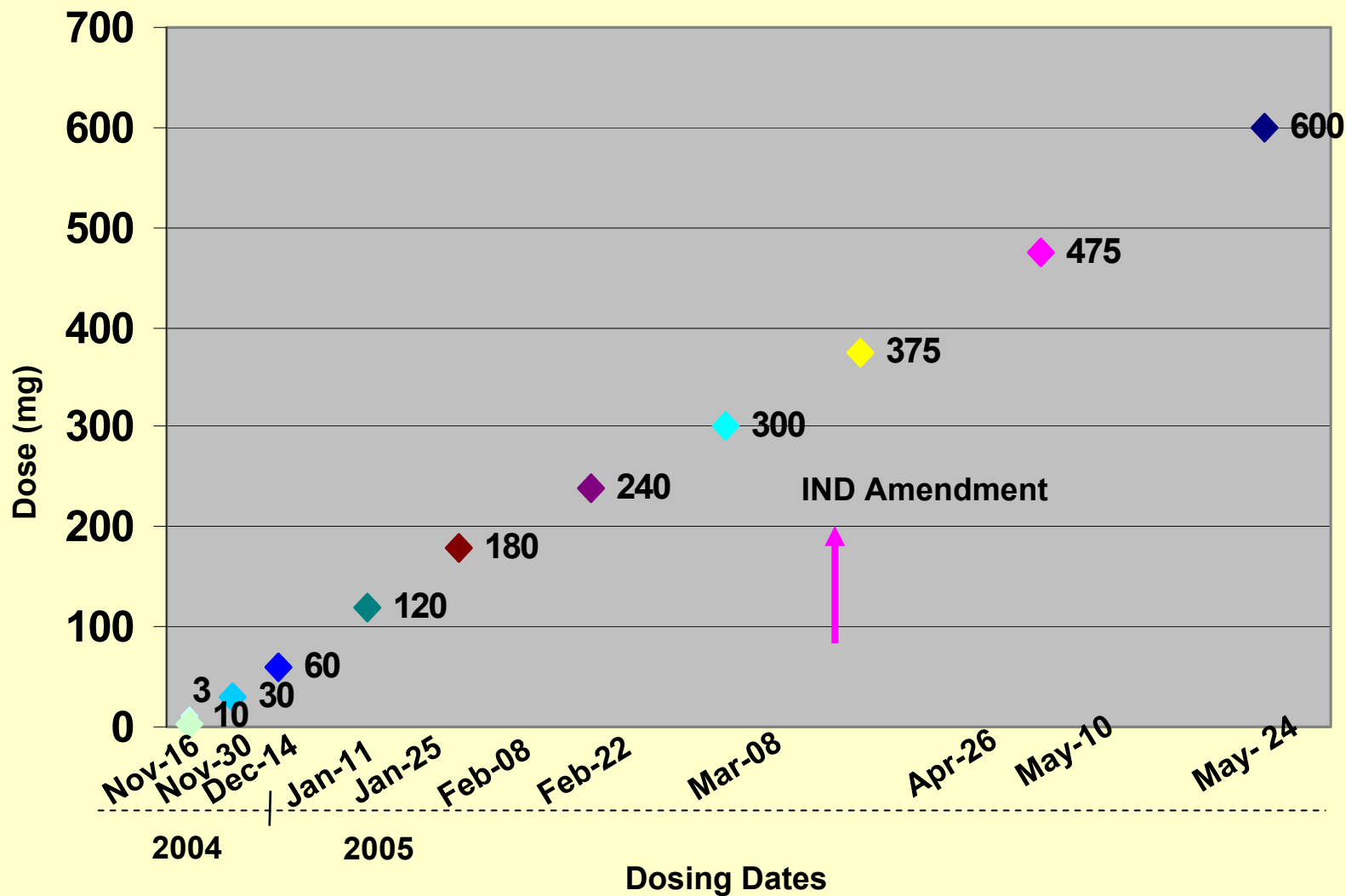


Compound B: FIM Dose Selection

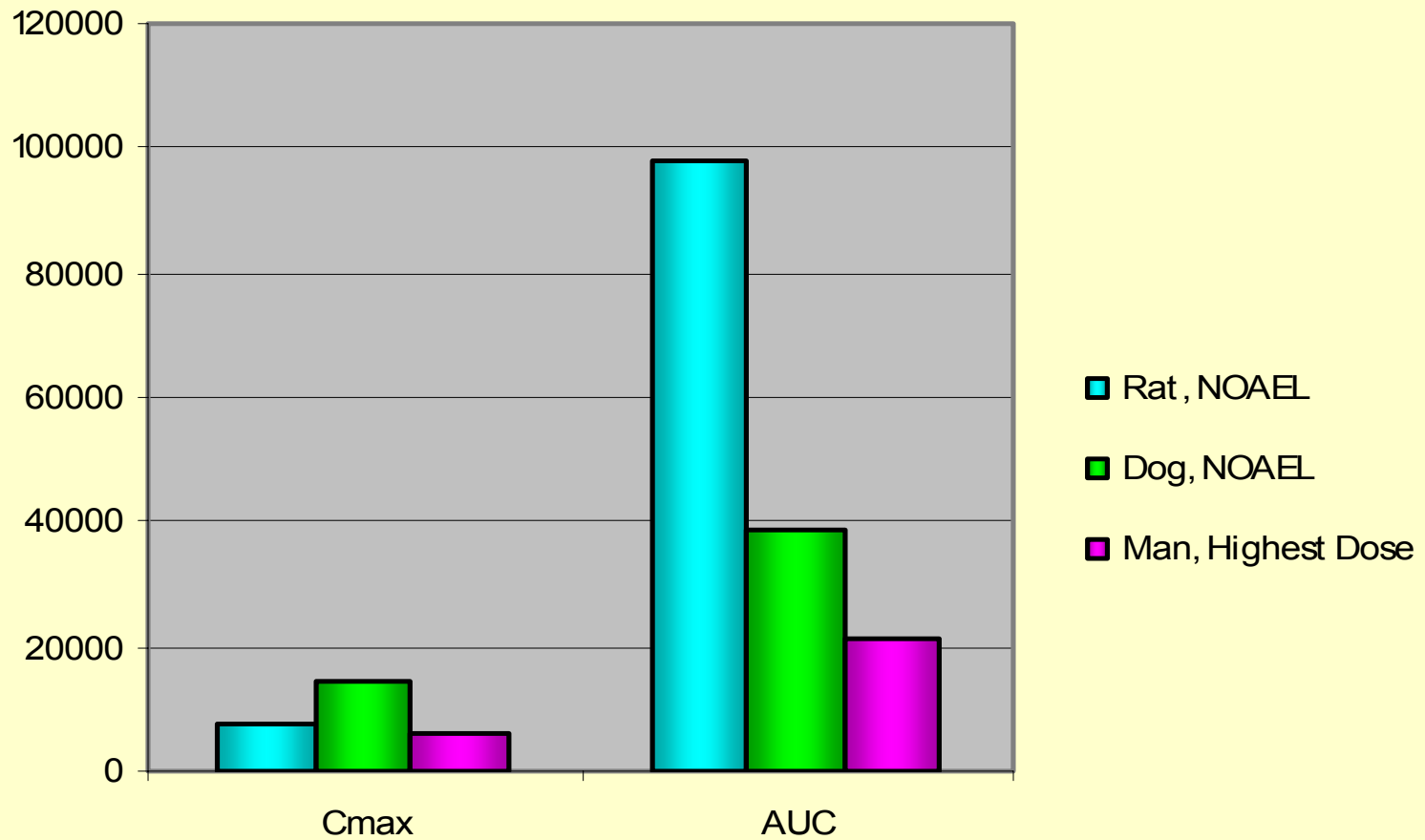
- NOAEL, Rat 60 mg/kg
- NOAEL, Dog 30 mg/kg
- FIM Dose per Guidance 3 mg
- Actual FIM Dose 3 mg



Compound B: Dose Escalation



Compound B: Comparative Exposure Between Animals and Man



Compound B: FIM Doses

- NOAEL, Rat..... 60 mg/kg
- NOAEL, Dog 30 mg/kg
- FIM Dose per Guidance..... 3 mg
- Actual FIM Dose..... 3 mg

**Highest Dose in
FIM Study: 600 mg**

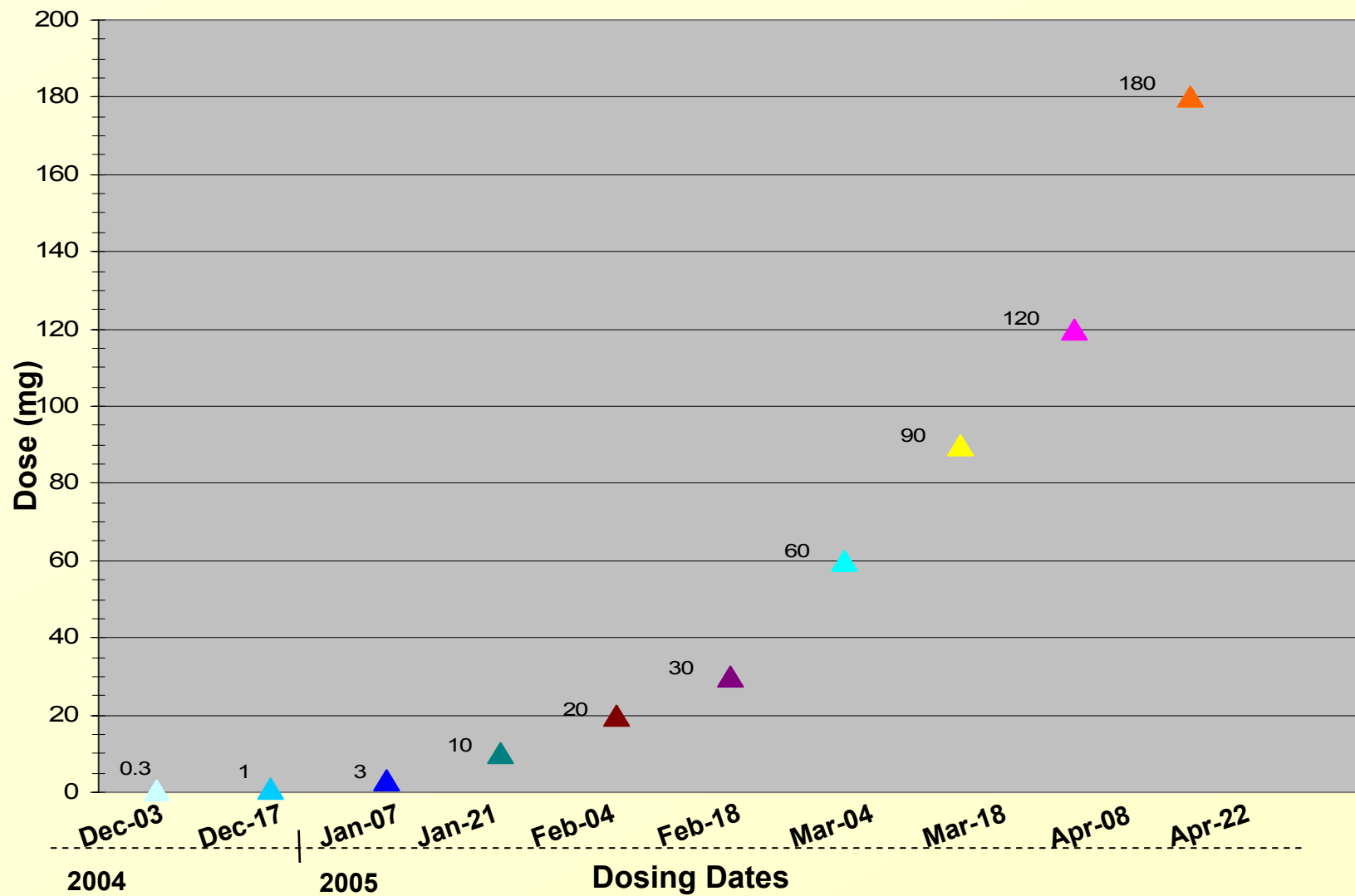


Compound C: FIM Dose Selection

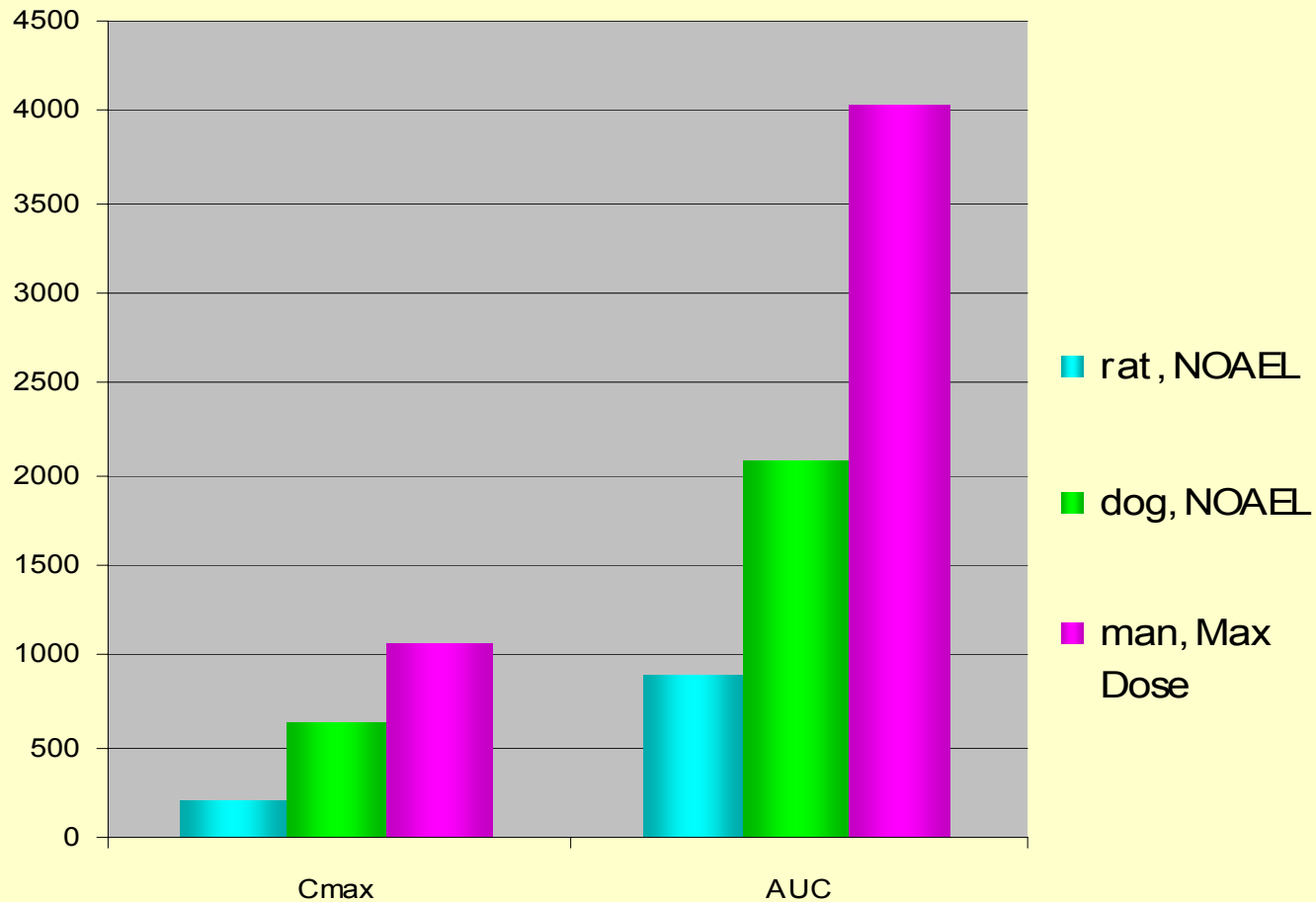
- NOAEL, Rat 1 mg/kg/d X 28 d
- NOAEL, Dog 10 mg/kg/d X 28d
- FIM Dose per Guidance 1 mg
- Actual FIM Dose 0.3 mg



Compound C: Dose Escalation



Compound C: Comparative Exposure Between Animals and Man



Compound C: FIM Doses

- NOAEL, Rat 1 mg/kg/d X 28 d
- NOAEL, Dog 10 mg/kg/d X 28d
- FIM Dose per Guidance 1 mg
- Actual FIM Dose 0.3 mg

MTD Dose: 180 mg



Compound D: FIM Doses

- STD, Rat 590 mg/m²/d X 30 d
- STD, Dog 540 mg/m²/d X 30d
- FIM Dose 60 mg/m²/d up to 99d
- Dose Limiting Toxicity in man @ 60 mg/m²/d

MTD Dose: < 30 mg/m²/d



Exploratory IND

- “The agency believes that sponsors have not taken full advantage of that flexibility and often provide more supporting information in their INDs than is required by regulations”
- Clarifies preclinical/clinical/ CMC approaches for expIND for
 - ➔ Clinical pharmacokinetic or imaging
 - ➔ Human pharmacological studies
 - ➔ Human mechanisms of action studies
- Duration of dosing in man: no more than 7 days

FDA Draft Guidance, April 14, 2005

Exploratory IND Studies:

- For investigational new drugs and biological products
 - ➔ Including recombinant therapeutic proteins and monoclonal antibodies
 - ➔ Does not apply to human cell or tissue products, blood and blood proteins, vaccines or devices
- Very early Phase 1 studies
 - ➔ Typically prior to traditional dose escalation, safety, and tolerance studies
- Very limited human exposure
 - ➔ No therapeutic intent
 - ➔ Limited dose range and limited period of time
- Assess feasibility for further development

For Human Pharmacokinetics

- A microdose: $< 1/100^{\text{th}}$ of a pharmacologic effect dose and $< 100 \text{ ug}$



For Pharmacologic Effect Studies

- A starting dose no greater than $1/50$ of the NOAEL from 2 week tox in a sensitive species on mg/m



Traditional vs. Exploratory IND

Traditional IND

A Single NME

➤ Nonclinical Safety to Address

- Selection of FIM dose
- Target organ toxicity
- Pharmacodynamics

➤ Provide Justification to Address

- Proposed clinical program and potential outcome
- Maximal tolerated dose

➤ CMC:

- Graded nature as needed

Exploratory IND

One or More Related NMEs

➤ Nonclinical Safety under GLP in general for microdosing in man:

- Extended, single-dose toxicity, one species, using intended clinical route

➤ For human pharmacology:

- 2-week tox in rat and a non-rodent
- Safety pharmacology
- Genotoxicity

➤ For human MOA:

- Pharmacologic endpoints

➤ Address

- Rationale of compound selection and investigation endpoint
- Sub-therapeutic or pharmacologic dose, thus lower risk to subjects

➤ CMC;

- Guidance in development for cGMP

The background of the slide features three globes with a grid of latitude and longitude lines. The globes are rendered in a dark blue and black color scheme, with some landmasses highlighted in a lighter, yellowish-green. They are arranged in a way that creates a sense of depth and global connectivity.

Conclusion

Innovative early clinical evaluation of one or more NMEs will generate critical information in a timely and cost-effective manner.

