Challenges of the Development of Pain Therapies & Intersection with HEAL

Industry Considerations for Development of Assets

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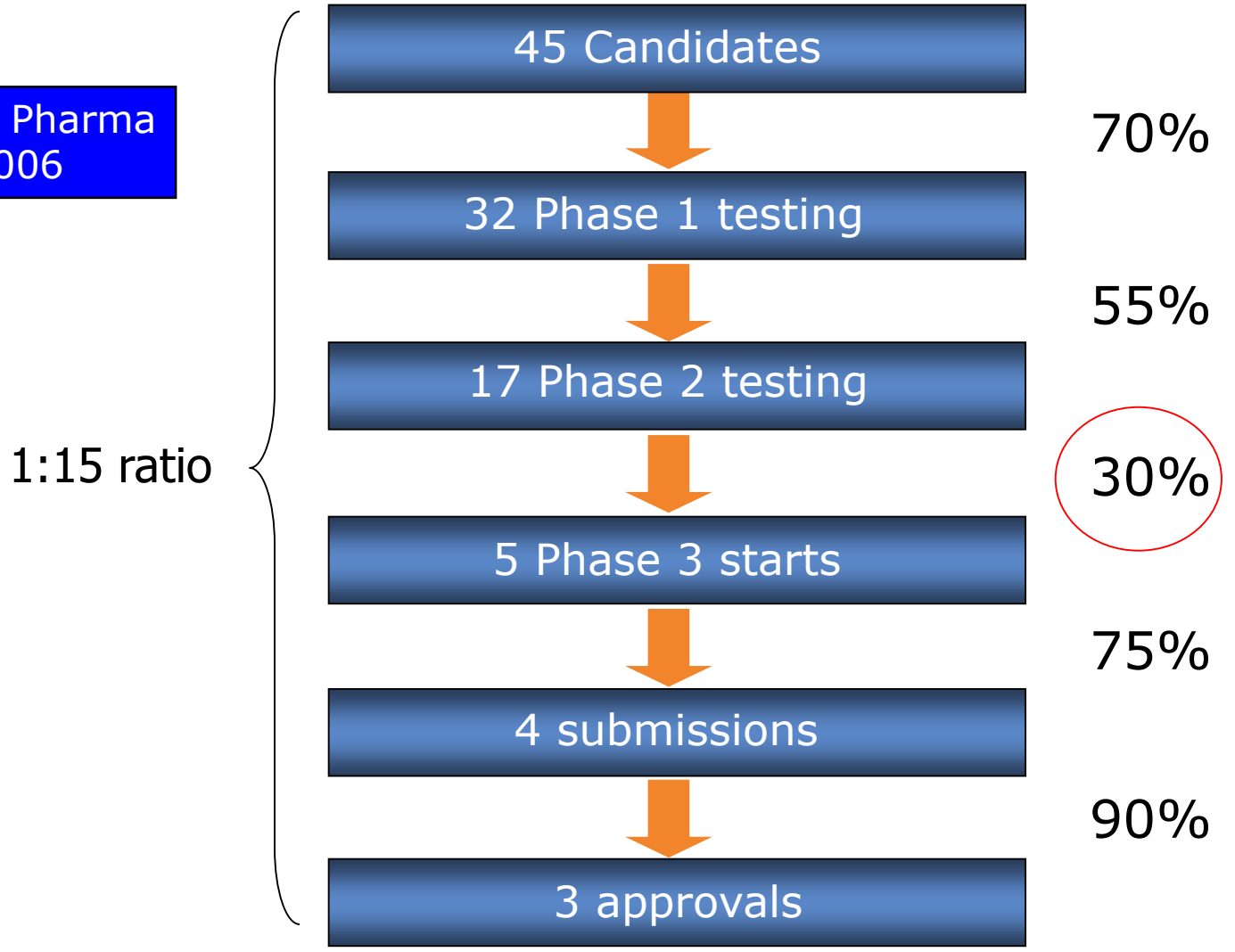
Survival of Development Candidates

NME Survival for Big Pharma
Average 2001-2006

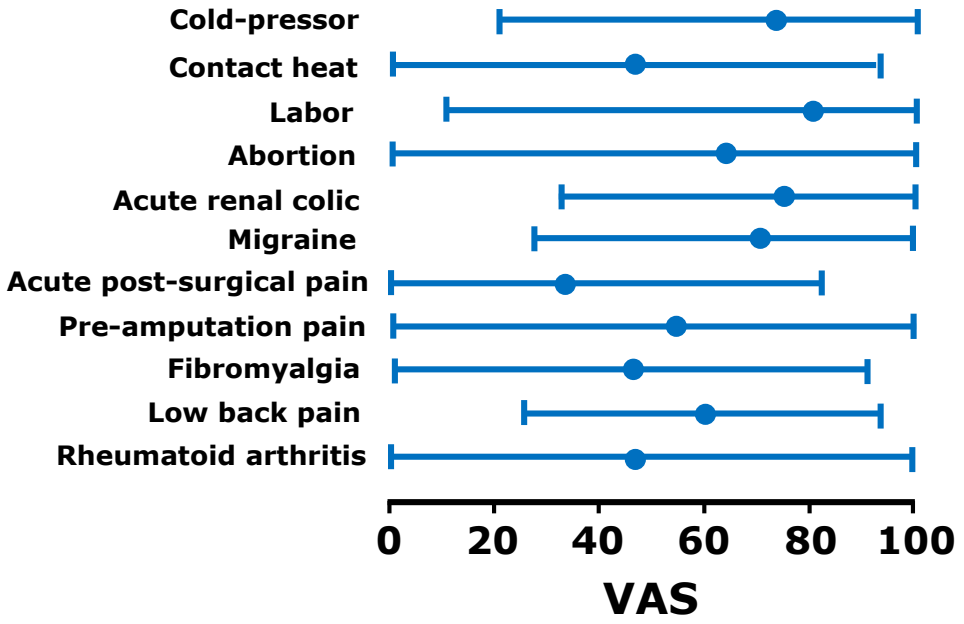


Phase 2 Survival Rates

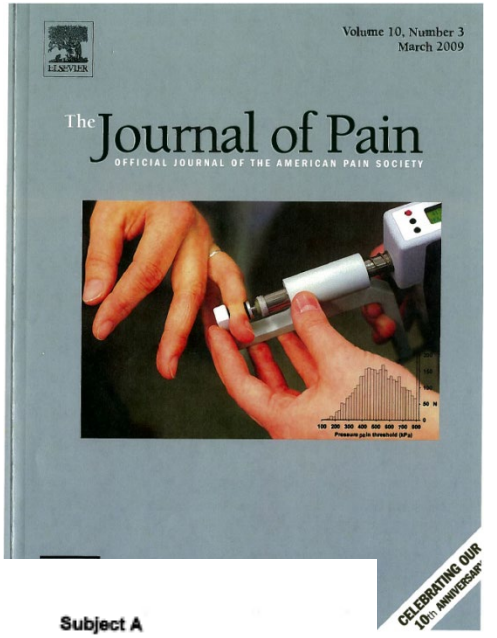
- Pharmacologic activity in animal models is not translating to positive outcomes in the clinic
- Balancing on the tightrope of minimizing investment and getting to the "killer" experiment is difficult and not easily generalized
  - The early development portal is very narrow based on the chronic pain conditions used in the testing schemes
- Good and bad compounds declare themselves early. Weak signals of clinical efficacy do not get stronger with repeated testing
  - A positive first Phase 2 study indicates a 50% probability of Phase 3 success
  - A negative first Phase 2 study indicates a 3% probability of Phase 3 success
  - Even roadkill looks good to a hungry person
- Evidence for (1) exposure at target site (2) binding to target and (3) pharmacology (proof of mechanism) in early clinical work increases the odds of survival

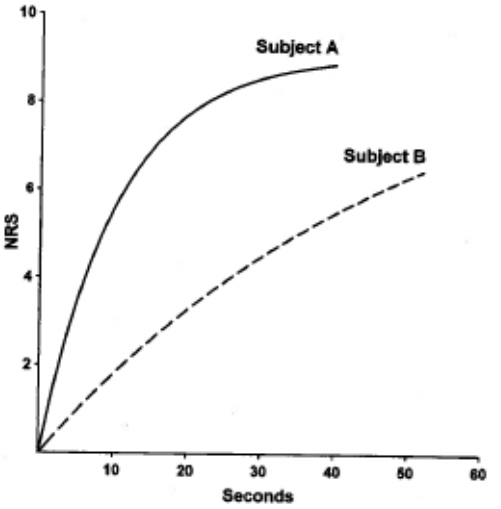
Acute, Chronic and Experimental Pain

Although some conditions may be more painful, the variation between individuals with the same condition is far greater than the degree of pain across conditions



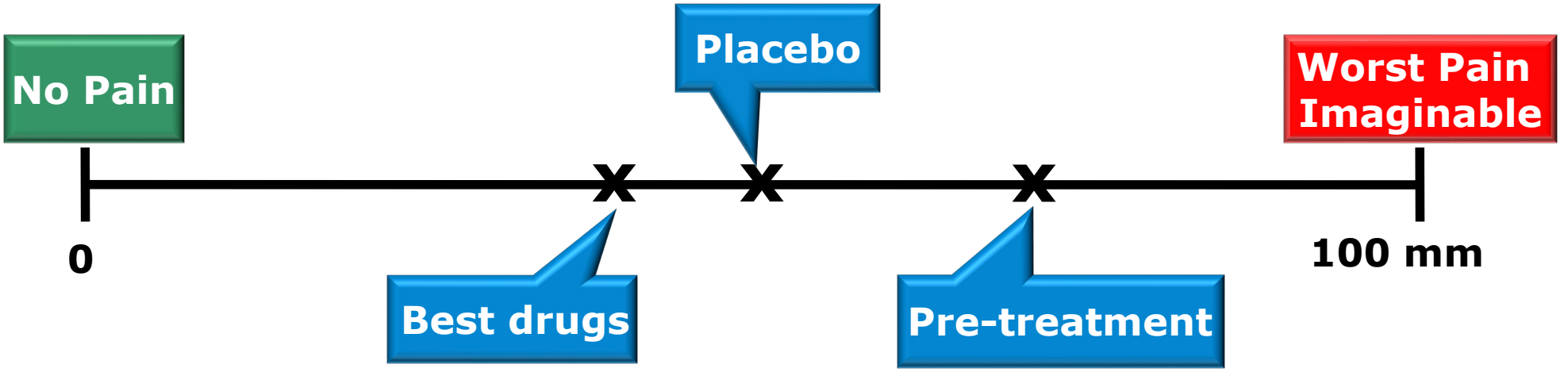
Median and range; prior to analgesic treatment



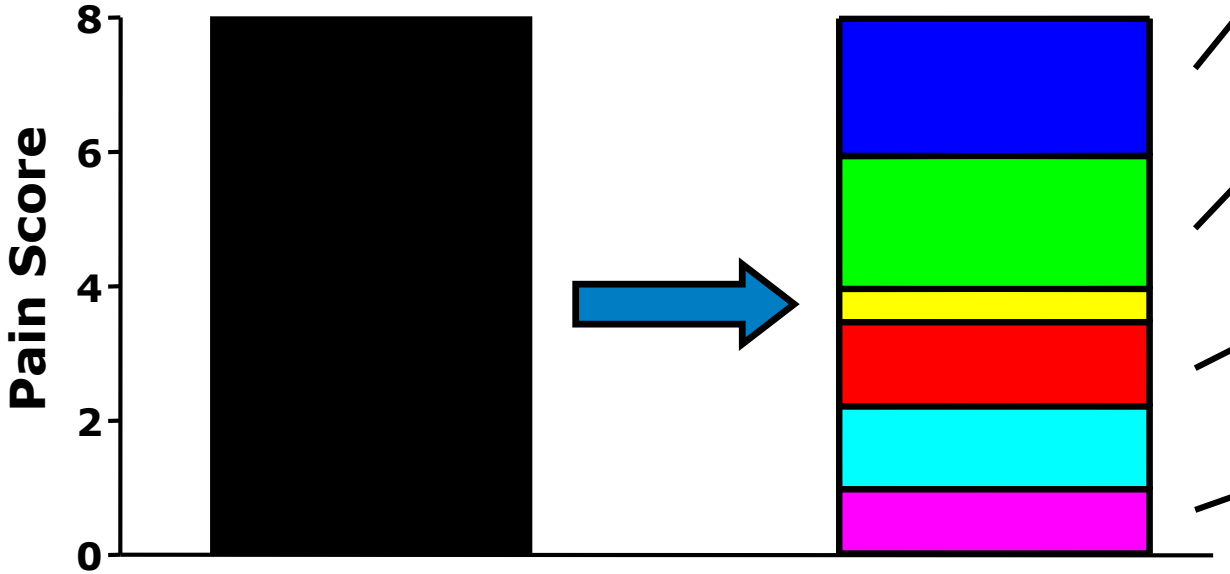


Nielsen CS, et al. Individual differences in pain sensitivity: measurement, causation and consequences. J Pain 2009;10:231-37.

Current Drugs Produce Modest Analgesia



Simple Pain Score Underlies Complex Condition



Ongoing Pain
- Burning
- Lancinating
- Stabbing

Allodynia
- Punctate
- Dynamic
- Cold
- Heat

Hyperalgesia
- Mechanical
- Thermal

Functioning
- Anxiety
- Depression
- Sleep disturbance
- Cognitive

Registration Endpoints

- Drug development in many therapeutic areas relies on:
  - objective endpoint(s) alone, or
  - combination of objective endpoint(s) and patient-reported outcome
- Drug development in pain (and many neurological disorders) relies entirely on patient-reported outcomes to demonstrate benefit
  - It is not a coincidence that these therapeutic areas suffer from the greatest number of failed studies (lack of assay sensitivity)

Generalization of Drug Responses

- Mechanisms of pain differ across clinical diagnoses based on responses to existing therapeutics
  - Many drugs are effective in musculoskelelal pain or neuropathic pain – but usually not both conditions

- Uncertainty even within general diagnoses of neuropathic or musculoskeletal pain whether responses to a drug are similar;
  - e.g., is the therapeutic response (or lack thereof) to an analgesic in patients with with post-herpetic neuralgia representative of the response of patients painful diabetic neuropathy?

- What is the impact of differences in pain severity across various clinical diagnoses of pain on the level of analgesia provided by a therapeutic agent?

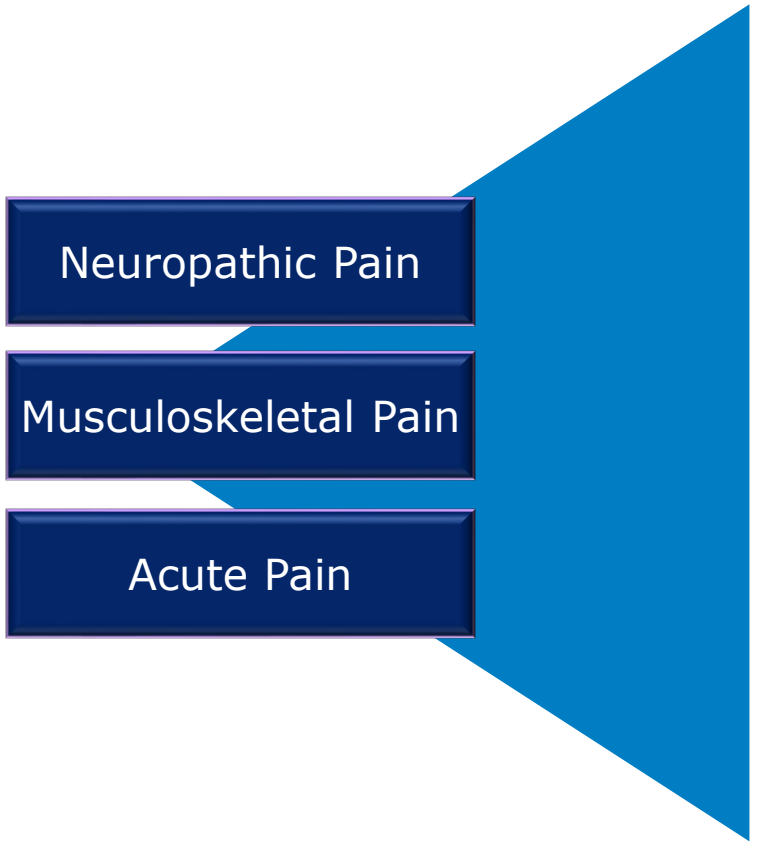
- Does the chronicity of pain (acute vs chronic) or severity affect analgesic response?

Indications Hierarchy

Investment, Speed, & Risk for Optimal Labeled Indication & Patient Access

- Migraine
- Management of Pain
  - Management of Acute Pain
    - Post-surgical pain
      - Orthopedic & Abdominal
    - Non-surgical pain
      - Sprains, strains, fractures, renal colic, trauma
  - Management of Chronic Pain
    - Nociceptive (Musculoskeletal) pain
      - Osteoarthritis
      - Chronic low back pain
      - Chronic tendonitis
      - Repetitive strain injury
    - Neuropathic pain
      - Peripheral Neuropathic pain
        - PHN, PDN, PTNI, HIV neuropathy
      - Central Neuropathic pain
        - Spinal cord injury, post-stroke pain
    - Visceral pain
      - Chronic pelvic pain
        - Interstitial cystitis, prostatitis, endometriosis
      - Chronic pancreatitis
    - Other Chronic pain
      - Cancer/cancer treatment
      - Fibromyalgia
      - Sickle cell
      - Tension headache

Experience in Pain Development



- Oral surgery
- Bunionectomy
- Hernia repair
- ACL repair
- CABG surgery
- Total knee replacement
- Total hip replacement
- Abdominal hysterectomy
- Major general surgery
- Laparoscopic cholecystectomy
- Acute low back pain
- Primary dysmenorrhea
- Renal colic
- Ankle sprain

- Osteoarthritis
- Rheumatoid arthritis
- Chronic low back pain
- Fibromyalgia
- Ankylosing spondylitis
- Psoriatic arthritis
- Tendonitis/bursitis
- Cancer pain
- Post-herpetic neuralgia
- Painful diabetic neuropathy
- Spinal cord injury
- Post-traumatic nerve injury
- HIV neuropathy
- Migraine
- Prostatitis
- Interstitial Cystitis
- Endometriosis

Probability of Seeing an Adverse Event

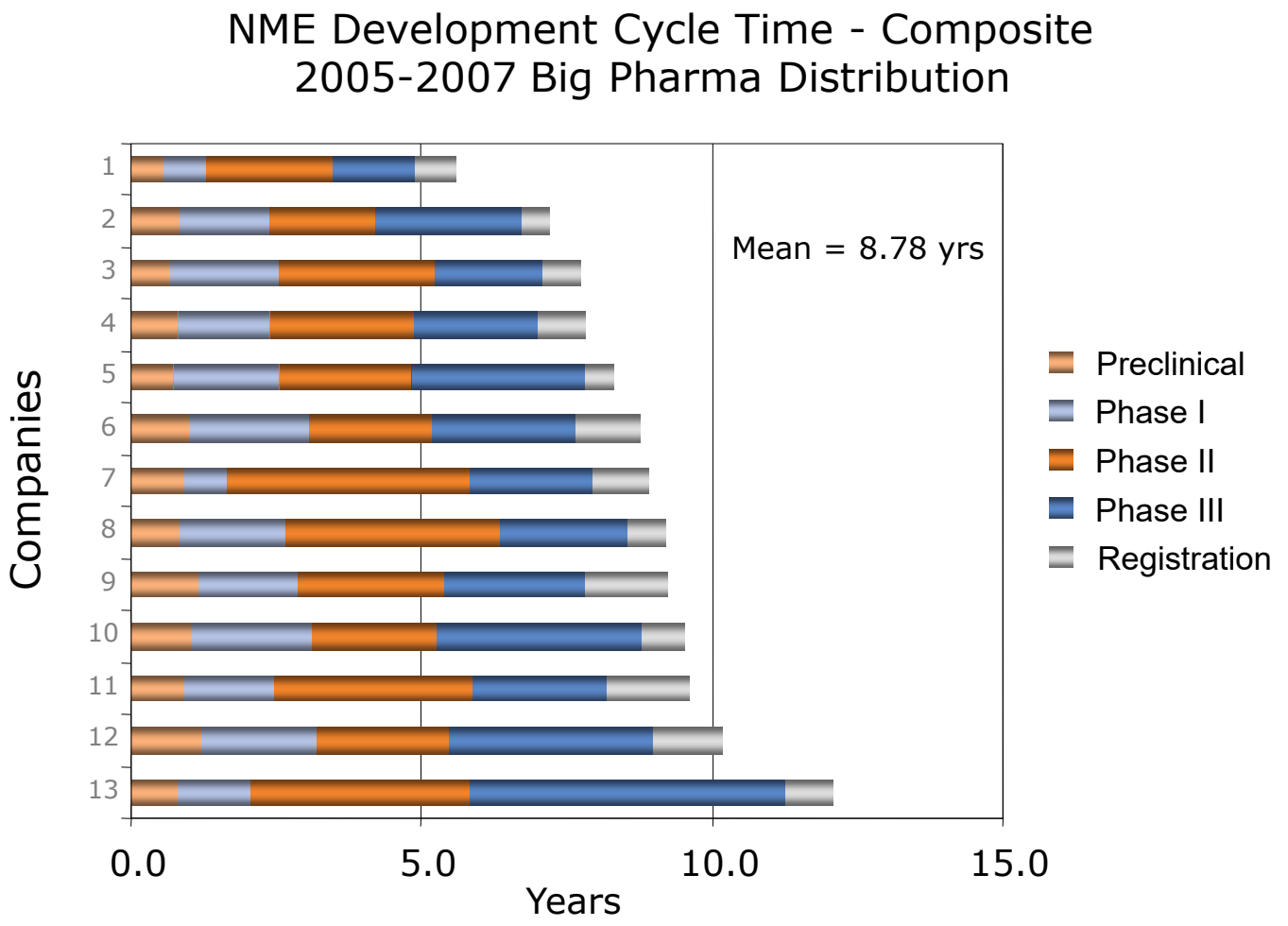
Frequency and the Size of the Clinical Safety Database

Frequency of the event rate	Size of Safety Database	Probability of seeing the event at least once	Probability of seeing the event at least twice
1% →	500	0.993	0.96
0.50%	500	0.918	0.713
	1,000	0.993	0.96
0.10%	1,500	0.777	0.442
	3,000	0.95	0.801
0.01% →	6,000	0.451	0.122
	10,000	0.632	0.264
	20,000	0.865	0.594

Note: This table does not address whether the event is caused by the drug or just chance. It only addresses that the event will be observed.

Much larger numbers are needed to see whether the event rate is higher than expected if it is an event that occurs naturally in a non-study drug treated population

Development Cycle Time



NME Development Composite Cycle Time: Entry into GLP Toxicology through Approval