The Basis for Drug Approval in US

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Chelmsford (A 414)
Chipping Ongar A 128
Brentwood
Kelvedon Hatch A 128
Industrial Estates
Secret Nuclear Bunker

Consulting

- AAI Pharma
- Affinergy
- Astrazeneca
- Abraxxis
- Alpha Rx
- Nuvo/Dimethaid
- Neopharm
- Pfizer
- Novartis
- PLx Pharma
- Hisamatsu
- LAB Pharma
- Dr Reddys
- Biosense
- Avanir
- Cerimon
- Leerink Swann
- Alimera
- Nomura
- Luxor
- Paraexel
- Nitec
- Bayer
- Combinatoryx
- Rigel
- Chelsea
- Regeneron
- Genelabs
- Cypress
- SNBL
- Avera
- Solace
- Puretechventures
- Puretech Development
- White Mountain Pharma
- TAP
- Abbott
- Cell Therapeutics
- Omeros
- Jazz
- Shwarz
- Proethic
- Takeda
- Teva
- Zydus
- Proprius
- Savient
- Alder
- Cure
- Cellegy
- Chemocentryx
- McKesson
- Diobex
- Sepracor
- Purdue
- Serono
- Coley
- Mediimune
- Altea
- Neuromed
- polymerix
- Millenium

FD& C Act

- Prohibits interstate transportation of unapproved new drug products
- Requires substantial evidence of safety and efficacy as the basis of approval of new drugs
- Permits the FDA to grant exemptions from the FD&C Act to study new drug products

1962 Amendments

- Thalidomide and the FDA
- Requirement for efficacy

- Mechanism to conduct clinical studies
  - Goal to predict safety and efficacy when the product is marketed
  - Accomplished through carrying out adequate and well controlled trials

NDA Review (focus)

- Substantial evidence of effectiveness

  "…Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by qualified scientific experts, that proves the drug will have the effect claimed by its labeling…"

  – Kefauver-Harris Drug Amendments to Section 505(d) of Federal Food, Drug and Cosmetic Act, 1962

- Safety - FD&C Act of 1938
- Labeling - Original Food & Drug Act 1906

What is Needed For Approval: In General

- Non clinical data performed in terms of GLP
- Manufacturing practices performed in terms of GMP
- Clinical data performed in terms of GCP
  - Two replicate adequate and well controlled trials
  - One if the $p < 0.001$ (robust p value)

What is Needed for Approval

- It is critical to determine relative risk vs benefit
  - In a lethal disease these requirements are often modulated
    - Multiple myeloma, drug approval as subpart H obtained after phase II data alone with robust phase IV program defined
    - Iressa, clear subpart H approval on PFS but failed phase IV proof study leading to restricted distribution determination

Typical Development Program

- Non clinical
  - Animal data usually surrounding safety but efficacy might be added in POC
- Clinical
  - Phase I
    - Usually safety, SAD, MAD, PK/PD, very short term
  - Phase II
    - Efficacy signal studied, dose ranging, may include PK/PD
    - Longer than in phase I, some safety data accumulated
  - Phase III
    - More robust, larger numbers, and longer duration, would serve as pivotal trials for approval
- NDA/BLA

Approval

- The analysis will typically evaluate two replicate data sets as pivotal
- There will likely be other data which will serve to support
  - Randomized, blinded and well controlled
    - In some circumstances in evaluating responses in cancer, unique open lable and other trials are acceptable
  - Outcomes are defined in hierarchical fashion with primary, secondary etc; if two co primary outcomes issues of multiplicity of measures need to be considered; if primary fails, usually trial fails although for approval it is totality of evidence that wins
  - Statistical plan is defined early in course of trial
  - If a surrogate outcome, then may be required to do a link to a clinical outcome later

Approval

- The population to be analyzed for efficacy should include all patients who have received at least one dose of drug (mITT)
- Subset analyses based on demographic issues, response etc which will typically not be those pts who reflect the entire treatment population, will likely be considered hypothesis generating and require confirmation in at least one further trial
- Such a confirmation trial would be designed to include the appropriate pt population that had been identified by the data dredging exercise and what the appropriate apriori defined endpoints would be
- Exploratory analyses are always useful, but rarely lead to regulatory decisions

Hypothetical

- New drug for cancer treatment
  - Two studies with primary outcome PFS
  - First study failed for PFS
  - Second study was discontinued
  - But post hoc extensive data analysis of first study concluded that there was a subgroup of patients who benefited in terms of survival!! WOW!!
  - A third study was being conducted, with the information from the post hoc analysis of the first study, the third study was altered to address those issues

Drug Safety

- Determined throughout development
  - Phase I-III
  - Summarized in NDA
  - Phase IV/ post-marketing
- Problems
  - It doesn't appear that the data accumulated through NDA is robust enough to reflect rare events
  - Phase IV *studies* are similarly afflicted
  - Post-marketing is significantly flawed (e.g.Weber effect)

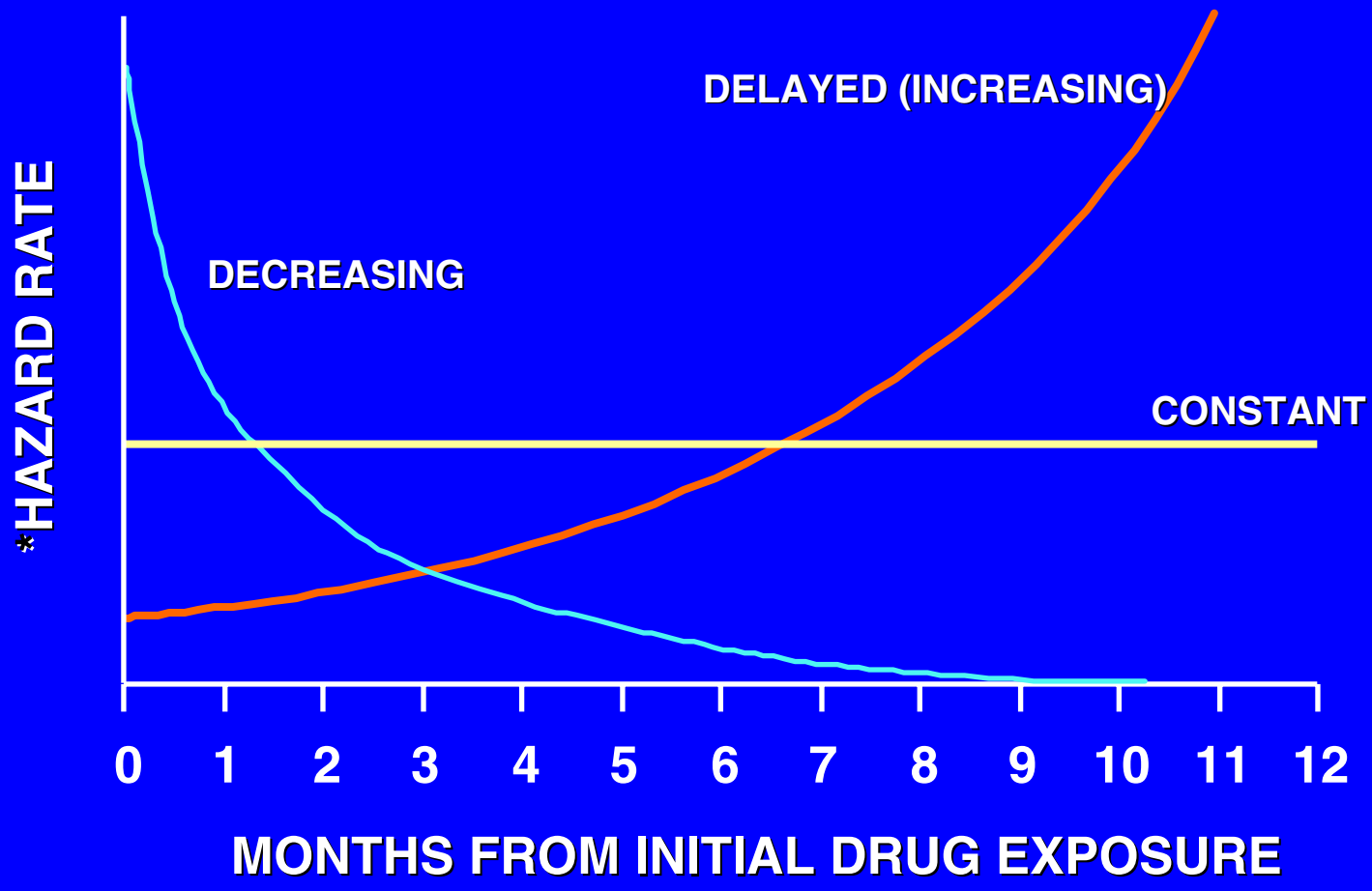
For Safety

- At present trial designs are not nearly as robust as for efficacy
- Typically observational in nature
- Recent experience with large simple trials
- Now known that understanding safety in trial universe is related to overall exposure numbers

Typical Numbers

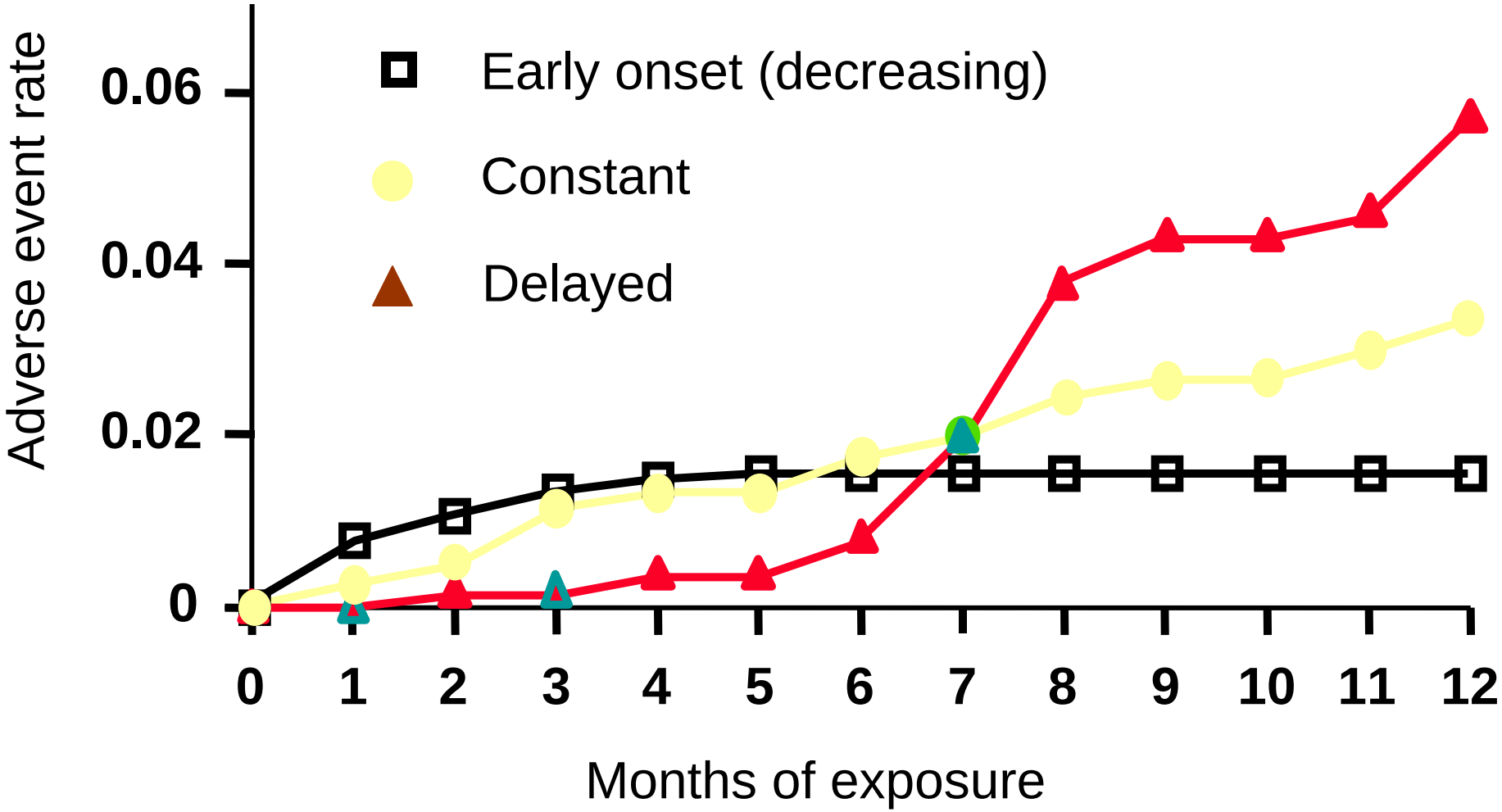
- 300 patients studied
  - Ability to detect adverse events which occur at a frequency of at least 1%
- 3000 patients studied
  - Ability to detect adverse events which occur at a frequency of at least 0.1%

HAZARD FUNCTIONS FOR THREE PATTERNS OF DRUG-INDUCED CLINICAL EVENTS



* OR RISK PER UNIT TIME

ESTIMATED CUMULATIVE ADVERSE EVENTS FOR THREE PATTERNS OF ADVERSE EVENTS OCCURRENCE

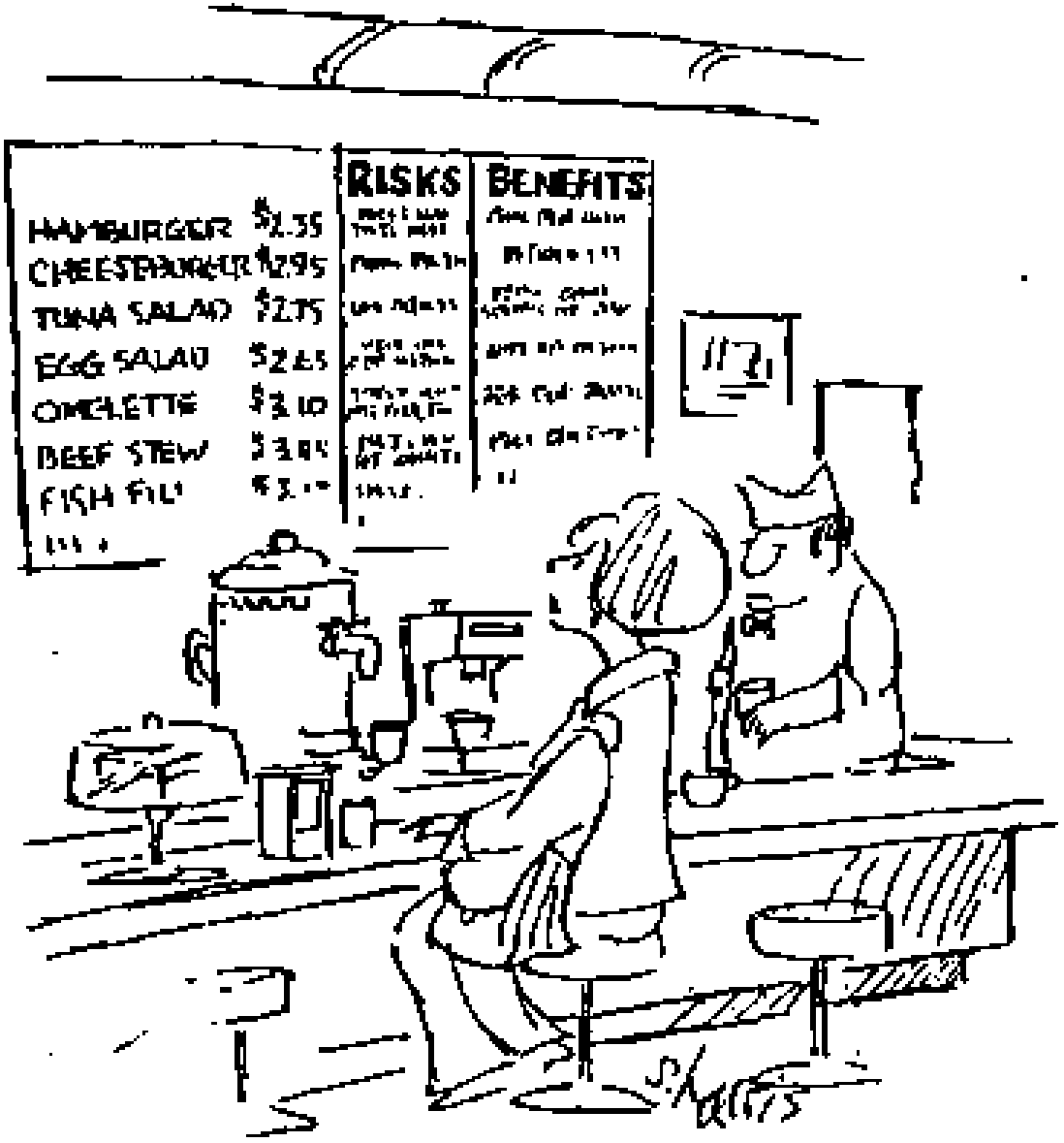


Summary

- Approvals require adequate and well controlled trials which succeed
- Analyses need to be predicated on pre defined outcomes and stat plans
- Post hoc subset analyses may be informative but are not considered for pivotal approvals since they are hypothesis generating

“Absence of evidence is not evidence of absence”

Legal Maxim



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