



Philosophy of Drug Development:

Genzyme Orphan Disease Perspective

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Agenda

- Background of Drug Development
- Why Orphan Drug Development is Different
- Genzyme's Pompe Experience



DRUG DEVELOPMENT

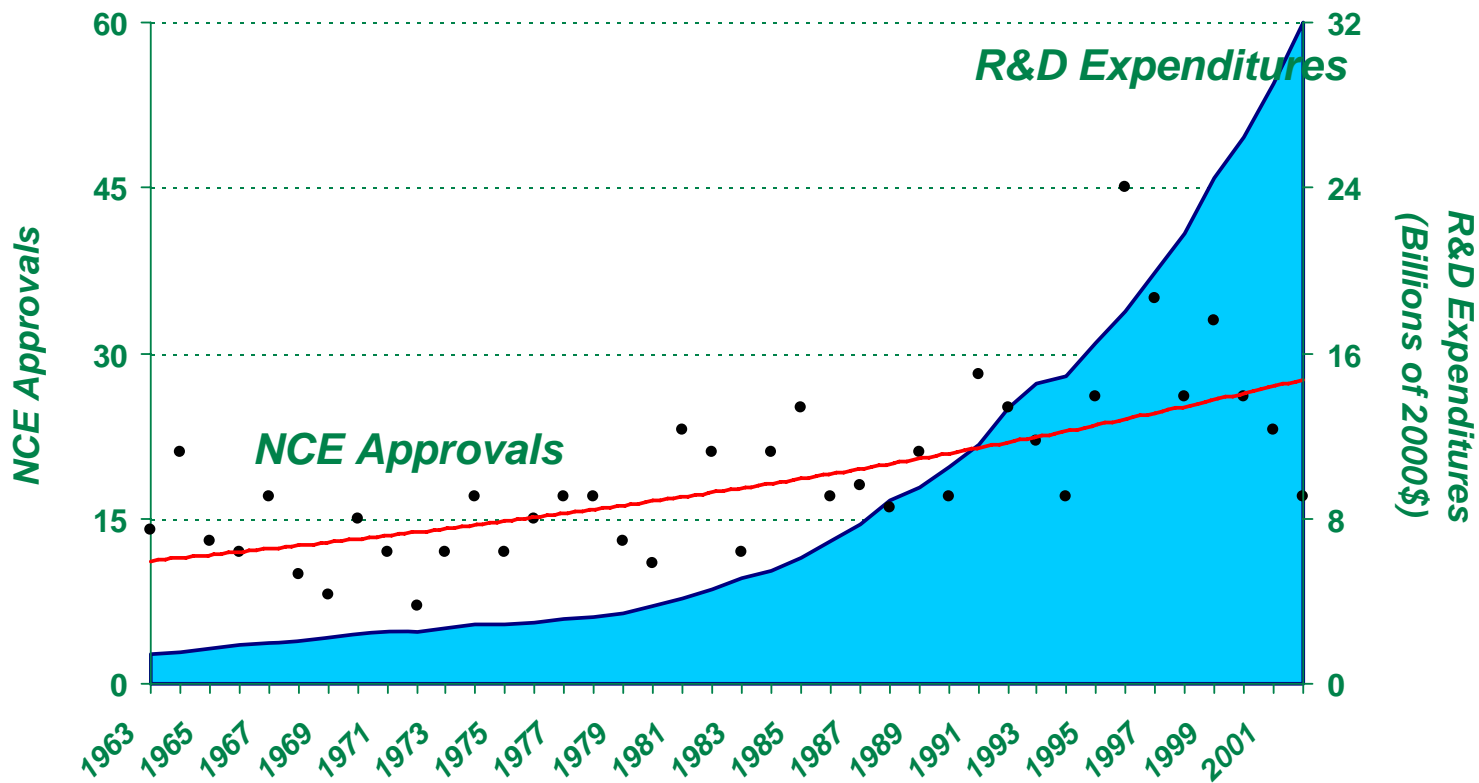
Evidence of the Challenge

Overall, costs of new drug development have risen from \$54M in 1985 to \$802M in 2002, including costs of failed compounds and capital expenditures.*

- R&D expenditures have risen dramatically in relation to filings and approvals
- Market caps for pharmaceutical industry are declining
- Capitalized Costs have risen dramatically
- Approval rate for new recombinant proteins is 17%
- Development timelines have lengthened

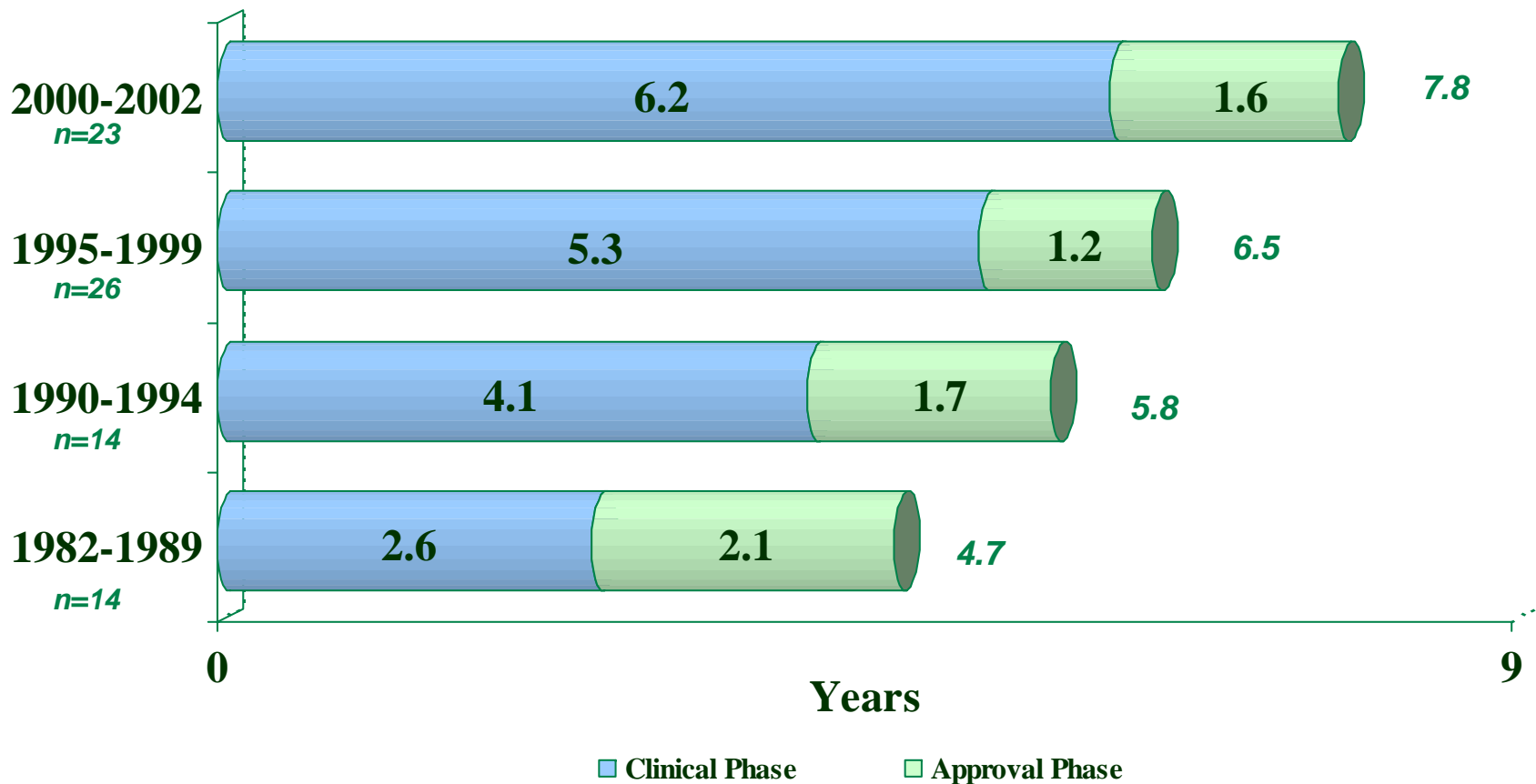
* Tufts CSDD Report, 2003 Vol 5, No2.

New Drug Approvals Are Not Keeping Pace with Rising R&D Spending



R&D expenditures are for PhRMA member firms and are adjusted for inflation
Source: Tufts CSDD Approved NCE Database, PhRMA

Biopharmaceutical Development Times, 1982-2002



Source: Tufts CSDD Impact Report, 2003 Vol 5, No 2



ORPHAN DRUG DEVELOPMENT

Orphan Drug Development: the Difference

- Small disease populations inherently contain more risk, more investment; potentially lower returns
- Increasingly complicated academic-industry partnerships
- Rarity of disease exponentially increases the complexity of clinical development, distribution and reimbursement
- Few experts, few treatment centers, few patients

Orphan Drug Development: Population Modeling in Rare Diseases

- **Seek input from experts, treaters, patients, clinical development experience**
- **Natural history?:**
 - Population dynamics (birth rate, mortality)
 - Number of patients
 - Disease incidence rates
 - Clinical phenotypes/subtypes
 - Age at Onset
 - Age at Diagnosis
 - Rate and measurement of progression
 - Age at Death without treatment
- **Augment Data with Registries**

CLINICAL TRIALS FOR ORPHAN DRUGS

- Chronic progressive disorders
 - Heterogenous
 - Reversibility vs stopping progression
- Trial design issues
 - Heterogenous vs homogenous: subsets?
 - Large treatment effect required
 - Type 2 error becomes the issue
 - Placebo use sometimes difficult
 - Endpoint selection and statistical plan
 - Duration
 - Biomarkers? validation

ILLUSTRATION OF STUDY SIZE VS TREATMENT EFFECT FOR AN 80% POWERED STUDY

