

Considerations when assessing  
marketing applications for orphan  
products, or  
one division director thinks about  
orphans

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# General considerations

- As you have already heard, the law and regulations make no distinction in the data standard for approval of orphans and non-orphans
- As you have also heard, the law and regulations permit considerable flexibility in interpretation and application
- The closer a disease is to a non-orphan, the more likely the typical standards (non-clinical and clinical) will apply



# Non-clinical studies

- The principle: animal studies at least as long in duration, and at exposures/doses at least as high, as those proposed for the clinical study should be available prior to the clinical study.
- Genotoxicity studies/juvenile studies as appropriate as well; CA studies for the NDA
- In certain cases, the timing of these studies can vary (may be done concomitantly, or before many patients exposed)



# Non-clinical studies

- In some cases, studies may be deferred into Phase 4 (e.g., carcinogenicity studies)
- Proposals have been made to permit studies with one member of a class to be sufficient to assess the toxicity of an entire class of “similar” mechanism; this has not been accepted, but is under discussion



# Clinical studies-efficacy

- Sponsor must submit substantial evidence of effectiveness
- Adequate and well controlled investigations, including clinical investigations
- One adequate and well controlled study and confirmatory evidence



# Clinical studies-efficacy

- Typical standard is for replication/corroboration
- If at all possible, we try to have sponsors meet this standard
- Often, sponsors claim that a second trial is difficult to perform
- Not enough patients; not enough patients with appropriate severity
- Patients have access to treatment (international)



# Clinical studies-efficacy

- Regarding insufficient numbers of patients:
  - Registries, organizations, advocacy groups may have access to patients/families and can “get the word out” and provide access to patients
  - Patients with varying severities can (should?) be studied-don’t need (desire?) absolute replication; knowing how the treatment works in a range of patients is preferable
  - Increase centers/countries



# Clinical studies-efficacy

- Literature articles
- Sometimes, the literature reports trials already performed
- If of (possibly) appropriate design, we always ask the sponsor to attempt to obtain the primary data/protocol if at all possible
- Such studies have served as the basis for drug approval



# Clinical studies-efficacy

- Outcome measures
- Sometimes, a drug effect seems to be able to be detected only on a relatively novel outcome measure
- Proposing novel outcomes is always a possibility: we would want it to reflect an effect that is clinically meaningful to a patient
- Dalfampridine is a perfect example



# Clinical studies-efficacy

- Outcome measures
- Typically, a sponsor prospectively proposes a primary outcome measure (and a primary statistical analysis plan), and the study is judged by whether or not this meets the prospective rule
- In some cases, if the rule is not met, a different outcome measure (and/or statistical analysis), can be chosen
- Such an approach must be carefully considered



# Clinical studies-efficacy

- Outcome measures
- Surrogate markers
  - Validated surrogate: A lab test that has no obvious direct relationship to how the patient feels/functions, but an effect on which predicts the clinical benefit of interest
  - Unvalidated surrogate: A surrogate, an effect on which is reasonably likely to predict the clinical benefit



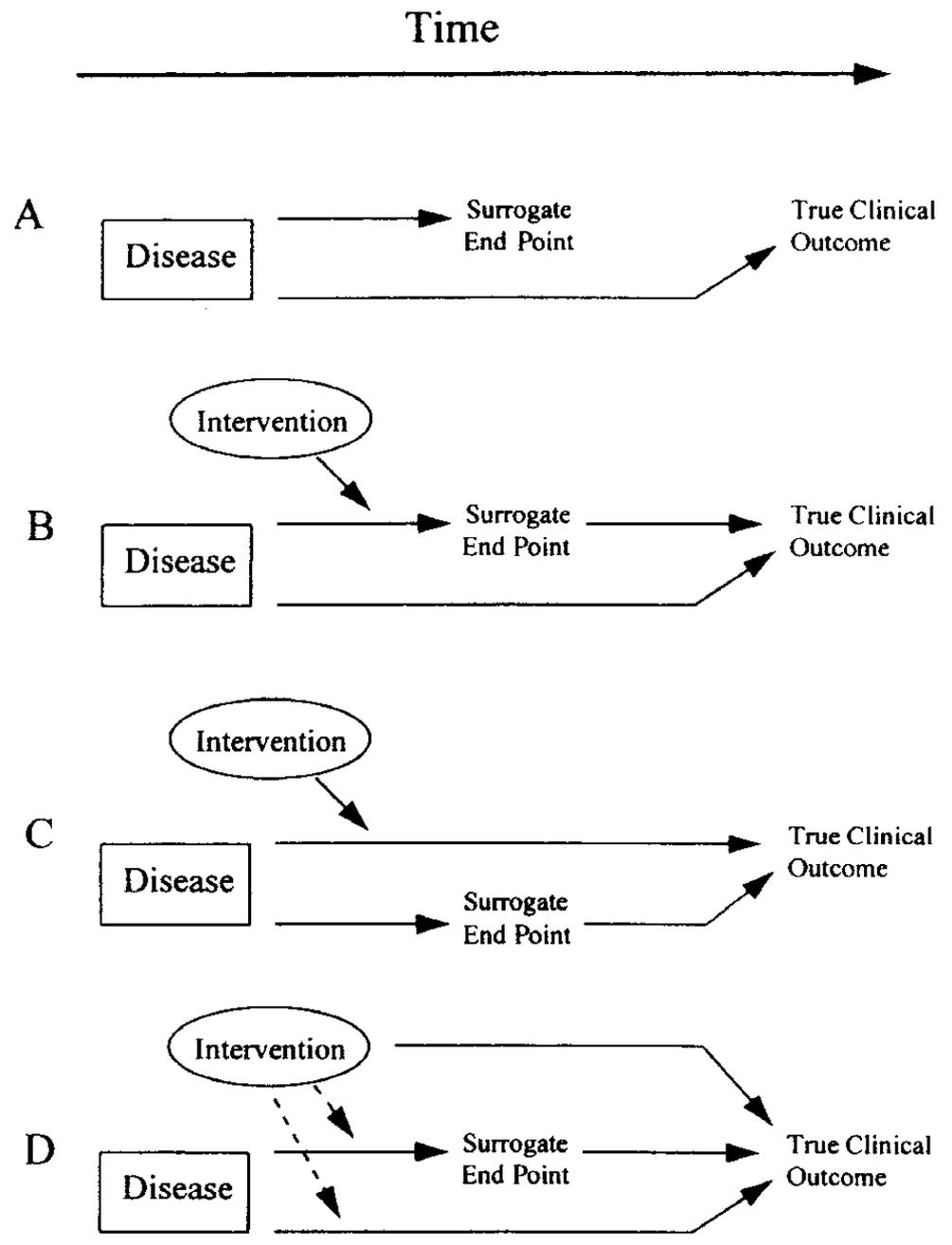
# Clinical studies-efficacy

- Unvalidated surrogate
- The Agency has the authority to approve a treatment based on an effect on an unvalidated surrogate
- This is often problematic, because the drug may have an effect on the surrogate, but not the clinical outcome of interest
- Nonetheless, we can do it

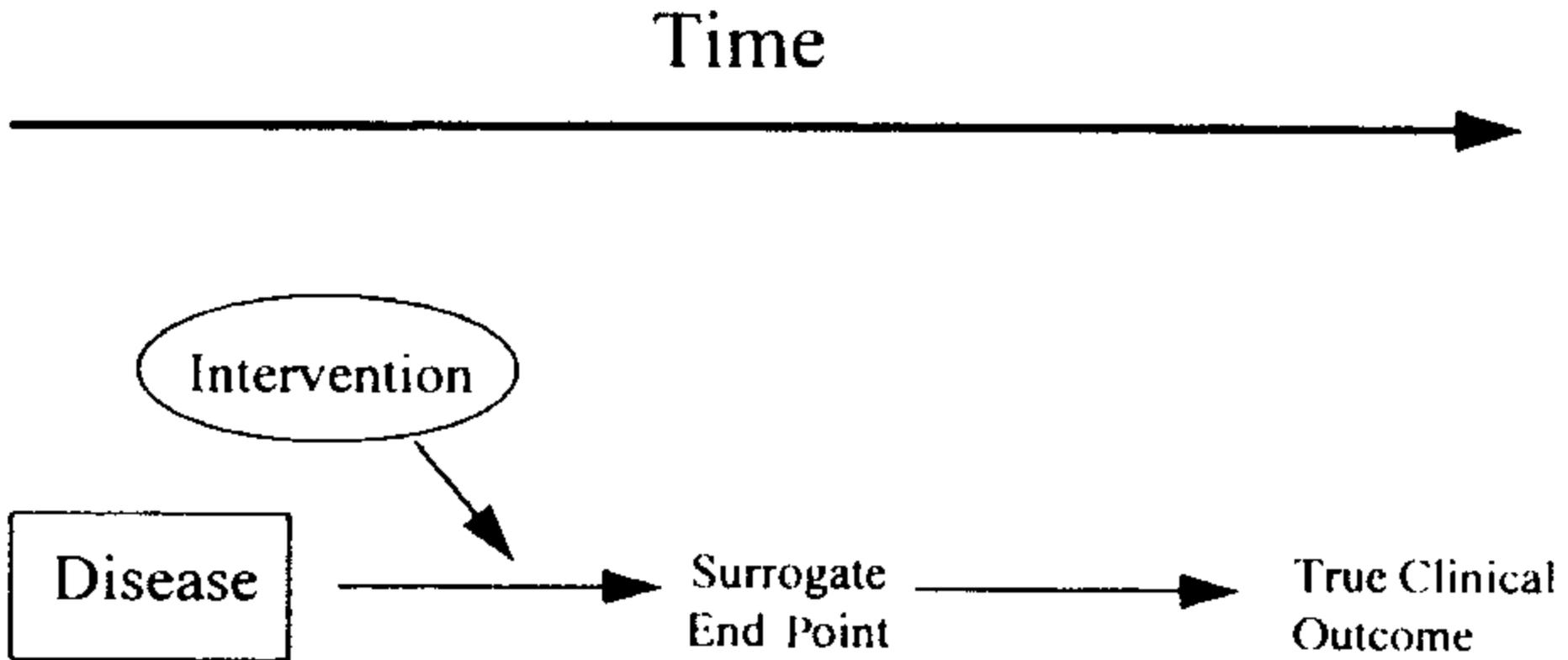


# Why do Surrogates Fail?

Fleming and DeMets,  
AIM, 1996



# Greatest Potential for a valid Surrogate



# Clinical studies-efficacy

- Outcome measures
- P-value: the probability that the outcome seen (or one more extreme) occurred by chance, given the null hypothesis
- Traditional standard is two sided p-value less than or equal to 0.05; almost always the standard
- However, this is not a formal regulatory requirement; there may be room for a different standard
- For example, a large effect, deemed important, may not reach significance in a small study



# Clinical studies-efficacy

- One study standard
- Need confirmatory evidence
- Ordinarily, the outcome in the one study should be “robust”
- That is, small p-value, multiple outcomes all move in the same direction, multiple sub-groups all move in the same direction
- This may provide confirmatory evidence



# Clinical studies-efficacy

- One study standard
- Sometimes, the one study is small, and cannot meet all of these criteria
- Confirmatory evidence can be provided by other studies (which also may be small and not reach statistical significance, but have a similar treatment effect as in the primary study)



# Clinical studies-safety

- A typical application contains data on thousands of patients/subjects, at least 300-600 treated for at least 6 months, and at least 100 for at least one year, all followed/monitored prospectively under the auspices of the sponsor
- Obviously, this standard is not applied for many orphan applications



# Clinical studies-safety

- In some cases, safety data can be obtained from “retrospective” chart review of (someone else’s) clinical patients
- These data do not meet the typical standards (much data not collected systematically), but may be acceptable (for example, if significant ADRs were captured, dropouts, etc.



# Clinical studies-safety

- More, (and better) data can, in appropriate cases, be collected in Phase 4
- This may include not only typical ADR data, but other data typically available at the time of approval (e.g., detailed metabolism data, drug-drug interaction data, thorough QT, etc.)



# Summary

- Although the rules are not different, there is considerable flexibility
- Although this is true, we try to make all efforts to have two adequate and well controlled trials and robust safety data (this is almost always required for orphans with a large prevalence)
- Only when we are convinced that this standard cannot be met do we typically rely on other means
- Don't go it alone! Meet with us

