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DRUG DEVELOPMENT WITHOUT ANIMAL MODELS
FDA PERSPECTIVE

Development Without Animal Models

- Regulatory Issues
- Development efficiency with no animal guidance.

Regulatory Issues

There is clearly no requirement in regulations for an animal model or even a persuasive reason to expect success, effectiveness, although such matters might be considered if animal toxicology data were of concern.

The IND rules (21 CFR 312) give no real hint of a regulatory interest in animal models of effectiveness, or more broadly, of a need for reason to anticipate effectiveness. The IND rules are focused primarily on anticipating (animal tox data) and monitoring, safety concerns (21 CFR 312.22(a), and very clearly on assuring the quality of phase 2/3 studies so that they can properly assess effectiveness.

Regulatory Issues (cont)

Animal models or other reasons for anticipating effectiveness are touched on minimally in the IND regulations, although there are repeated references to understanding and assessing the drug's pharmacologic effects.

312.21 (Phases)

The phase 1 studies are focused on metabolism and pharmacologic actions of the drug in humans, side effects with increasing doses and, if possible, early evidence of effectiveness, but most important, enough information on PK & pharmacologic actions to permit the design of well-controlled, scientifically valid, phase 2 studies. The focus on pharmacologic effects reflects a view. I believe that pharmacologic effects are the usual basis for believing a drug will do what we hope and are the usual and best basis for identifying the doses to be studied in the phase 2/3 trials.

Regulatory Issues (cont)

312.23 IND Content & Format

(a)(3)(iv) Overall investigation plan should include

The rationale for the drug or the research study. This surely could include animal data, mechanistic information.

Regulatory Issues (cont)

In sum, there is not much emphasis on the sponsor's basis or rationale for hoping the drug will be effective.

That determination is largely left to the sponsor. We rarely, if ever, refuse to allow a study because we are skeptical about the likelihood of an effect.

There is thus no FDA-imposed delay in moving to clinical trials. An exception, and I'm not aware of any examples, would be where patients in the trial are being denied known effective disease-modifying treatment, but that would be a problem even if there were a good rationale and animal model. In such cases, add-on studies may be called for.

What Replaces a Plausible Model

From the program it appears that there is interest in what outcome measures are feasible and what is the role of surrogate endpoints. I'm not sure how this relates to lack of animal models, which sometimes could be part of the support for believing in a surrogate.

To date few, if any (I can't think of one), surrogate endpoints have been proposed for approval of neurologic drugs but for an early interferon approval for MS, the MRI data were considered supportive of the clinical data and this led to an accelerated approval. MRI data alone, without a 1 year trial showing decreased exacerbation rate, would not have sufficed.

What Replaces a Plausible Model

As I'm sure you know, surrogates supporting full (as opposed to accelerated) approval are uncommon and usually need a history of relating the surrogate to clinical outcomes (HbA1c blood pressure, LDL cholesterol) or are self-evident (serum K).

But for serious disease without treatment, the accelerated approval pathway is a possibility.

Neurologic Endpoints

As I am sure you know, a drug does not have to reverse the course of a disease and can treat even a single symptom, so long as the benefit is well-documented and outweighs the drug's risk.

In MS, for example, we want to decrease both exacerbation rates and disability, but have approved drugs after showing only an effect on exacerbations.

Showing Effect When No Animal Model

I want to turn now to study efficiency, making studies more likely to succeed or smaller, a subject considered at length in our enrichment guidance (2012).

In neurologic disease, as in other areas, there are 2 distinct situations:

- Treating symptoms, generally a response that is fairly rapid, so that an early answer is available even if there is no good animal model or biomarker, as long as studies are well-designed.
- Slowing/modifying the underlying disease, usually a much more delayed effect, but conceivably one where there might be a plausible biomarker.

Showing Effect When No Animal Model (cont)

Examples where long-term data were needed, but where there were early “hints”

- CHF: acute exercise improvement (short-term) vs death/hospitalization. Acute responses are seen in days (even if interest is longer term), so that D/R and likelihood of effect can be assessed early, either by exercise test or (even faster) by cardiac output or ejection fraction. Of course, in CHF, such early effects have NOT always predicted outcome. Inotropes have generally not shown benefit but ACEs and ARBs do show both early & outcome effects. So you can get early insight into a plausible effect; i.e., did the drug have the pharmacologic/short-term clinical effect you were seeking and also get D/R. But you may still need outcome studies.

Examples

- Anticoagulants

  Good early indicators of clotting effect, effect over time, concentration-response effect, etc., but effectiveness and safety need long-term data, because outcome events are infrequent and have different C/R relationships.

  Initial dosing can be supported, perhaps, by looking at PK results, but clinical outcomes need their own assessment.

  There can be many more examples, but where the pharmacologic effects are plausible and measurable and clearly likely to be related to clinical benefit, the animal model is not really so critical once you've decided on a short-term study to assess benefit (in CHF and anti-coagulation there are animal models, of course).

  But if all effects are delayed (e.g. likely in many progressive neurological diseases) it takes a lot of time and effort before you really have any idea if the drug works.

Earlier Hints/Hopes for Effectiveness

The real problem, I think, is how to get a reasonable sense of potential effectiveness in those cases, i.e., no

- Animal model
- Plausible pharmacologic effect
- Biomarker

The only answer I can think of is more efficient study designs, notably enrichment and early use of multiple doses.

Neurological Diseases

I. Symptoms

In seizure disorders, symptoms of Alzheimer's Disease, Parkinson's Disease, treatment of depression, schizophrenia, it has not been difficult to show effectiveness, which occurs fairly rapidly (although it takes a few weeks in depression) and the community usually (not always, though) is good at early D/R. Whether animal models help (I'm sure they do in some cases) or the known pharmacologic properties are as predictive as expected, clinical trials generally give early answers (at least if dose is high enough). But suppose only certain patients respond?

Neurological Diseases

II. Changing the course of the disease

Far more difficult and few successes. How can these be made more efficient?

Possible Efficiencies

Symptomatic Conditions

Enrichment Strategies

These are discussed at length in the 2012 Draft Enrichment guidance, but steps include

A. Practical maneuvers – decreasing variability
   - Likely compliers (VA HT study)
   - Enroll people who do not get better over a short period (placebo lead in)

B. Prognostic Enrichment

   If effect size is constant for different severities of illness, choice of a more symptomatic population (frequency, severity) will enhance effect size making demonstration of effect more likely.

Symptomatic (cont)

c. Predictive Enrichment

If there are well-defined disease subsets that would be more likely to respond to an intervention, those should be studied, but even if those are not known, another possibility should be considered, especially if there is a possible early marker of response (biomarker, radiographic, clinical).

Symptomatic (cont)

If, in a randomized trial, there is no overall response, but there are what appear to be responses in some patients. This could be spurious, of course, but we do not always know what leads to a response. The "responder subset" could be re-studied in a new randomized trial or, depending on the disease, studied in a randomized withdrawal study in apparent responders. Two neuro examples of such studies follow. They were not the only studies in this case, but were confirmatory.

Patients on Xyrem for cataplexy with narcolepsy for 7-44 months randomized to continued treatment of placebo

	median attacks/2 weeks	
	Baseline	Change in Rate
Placebo (29)	4.0	+21.0
Xyrem (26)	1.9	0

$p<0.001$

Clearly demonstrated persisting long-term effect

20

Randomized WD

Patients with Huntington's Chorea on open-label tetrabenazine ≥ 2 months (mean 2 years).

Randomized to continued T (n=6) or placebo (n=12) for 3 days, at which time assessed.

Group	N	Change in Chorea Score
Continued T	6	1.7
Placebo	12	5.3 P = 0.1

Disease Changing

Disease modifying treatments are, of course, longer and harder, so that prognostic enrichment is especially critical and is almost always used in cardiac trials to increase the rate and timing of events.

- This first successful heart failure survival trial (CONSENSUS) was carried out in 253 NYHA Class IV patients. The patients had a 6 month mortality on placebo of 44% and showed a 40% mortality reduction in < 6 months on enalapril. Later studies in less ill patients needed 2000-4000 patients and often did not show survival effects.

Disease Changing (cont)

- In neurologic settings, entry criteria in MS trials have required recent exacerbations or specified MRI findings. Rates of decline, severity of illness, etc. could also be incorporated into entry criteria, seeking patients in whom a change would be recognizable more rapidly.


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