

Office of Information and Regulatory Affairs,
FDA OMB
Attn. Bonnie M. Lee

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December 17, 1999

Dear Madam,

Find bellow my comment on FDA proposed rule:
New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New
Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies
in Humans Ethically Cannot Be Conducted
21 CFR Parts 314 and 601
RIN 0910-AA89
[Docket No. 98N-0237]

While I acknowledge the necessity of a new legislation for products aiming to prevent or cure illnesses caused by different agents where human testing is impossible and/or unethical I ask the FDA to take into account the following remarks:

The most important concern I have regards the efficacy of drug to be approved by this legislation. Clinical trials show that a considerable portion of drugs that have been proven to be effective based on animal research and therefore tested on Humans at least in phase I will never be approved and used as a therapeutic measure. A small fraction of the failed therapies are withdrawn due to commercial considerations of the sponsors, however, the rest of the research drugs are withdrawn due to unfavorable benefit/toxicity ratio or simply because they are not efficacious. This means that the predictive value of animal studies has serious limitations when applied to the human organism. Consequently, even if we use the best scientists and physicians to predict the efficacy of the proposed drug our knowledge is very limited and the value of prediction is probably hardly greater than a simple gut-feeling. While this is acceptable since there is no other way to test our hypothesis regarding the efficacy I would argue against labeling this drug as FDA approved drug. When FDA approves a drug there is a common sense that to our best knowledge this is efficacious and safe. Given a standard approval even with the restrictions FDA plans would be misleading and confusing for clients. They might falsely believe that the drug has proven efficacy. I suggest to find a middle way to define the status of these kind of drugs. Approval should not be granted by the FDA for use as an approved drug, instead, waivers should be implemented to avoid obstacles a standard research drug would pose. This could avoid misbeliefs regarding the efficacy of the drug but facilitate of the drug in emergency situations at the same time. We could call it "investigational drug approved for use without IRB approval", or so.

According to the proposal this approval process can be applied only if "reasonably well understood pathophysiological mechanism of the toxicity of the substance and its prevention by the product" (p.53965). I would omit this phrase since it is very hard to say when do we understand something reasonably well, and if yes, on what level (cellular, subcellular, molecular, submolecular, etc).

I think advertising of these drugs is very controversial if not unethical. To avoid serious conflict of interest I suggest forbidding the advertisement of the drug unless lay individuals might use it. Save the latter scenario it is probably wise to have the drug distributed to emergency centers on a mandatory basis and inform the public about the existence of this drug. If individuals can apply he approved measure the advertising should be enormously cautious, it should not include any kind of direct or indirect incentive for the public to by the drug. All proposed advertisement should

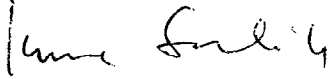
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be reviewed by a committee of ethicists, media and communication experts to avoid unethical information disclosure.

By the selection of the dose I would add a requirement of research on human cell lines of the safe dose if this is feasible and reasonable (p. 53965)

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Imre Szezik".

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