



Millennium Pharmaceuticals, Inc.

40 Landsdowne Street
Cambridge, Massachusetts 02139
617 679 7000

30 August 2004

Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852

Re: Proposed Rule: 21 CFR Part 312 – Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application. [Docket No. 2004-N-0018, 69 *Federal Register*, 32467 - 32475, June 10, 2004]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc. (“Millennium”), a leading biopharmaceutical company based in Cambridge, Mass., co-promotes INTEGRILIN® (eptifibatide) Injection, a market-leading cardiovascular product, markets VELCADE™ (bortezomib) for Injection, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in three disease areas: cardiovascular, oncology and inflammation. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, Millennium is seeking to develop breakthrough personalized medicine products.

Millennium develops its products for global markets and has several aggressive development programmes with numerous multicentre clinical studies. Some of these studies are conducted at centres in foreign countries and may be initiated or completed before we have filed an Investigational New Drug (IND) application for the investigational drug under study. Therefore, the Proposed Rule is directly relevant to our business. We welcome the opportunity to comment on this important regulation.

Broadly, we strongly support FDA's action in regulating foreign studies not conducted under an IND under the same regime of Good Clinical Practice (GCP) as is applied to studies conducted within the US. This brings logical symmetry to what was a somewhat anomalous situation, and ends the need to comply with the strict wording of the Declaration of Helsinki which, we agree, speaks in broad principles without the level of specific detail needed to describe usefully the intended compliance.

2004N-0018

C2

Specific Comments

1. Independent Ethics Committee (IEC)

FDA proposes to define an IEC for the first time in 21 CFR 312.3 as “*a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection.*” Consequently, at proposed §312.120(b)(6), sponsors will be required to submit, *inter alia*, the names and qualifications of the members of the IEC that reviewed the study. There is a clear implication that, if the constitution of the IEC is judged unsatisfactory or the qualifications of its members are deemed inadequate, FDA may invalidate a study for regulatory decision-making. We believe this raises two issues that should be addressed.

a. Meaning of “Adequately Constituted”

The Proposed Rule gives no explicit guidance on the meaning of “*adequately constituted*” in the definition of an IEC. However, it is stated that, “*An institutional review board (IRB), ... is one type of IEC.*” Part 56, Subpart B¹ contains fairly detailed requirements for the composition of an IRB. We submit that it would clarify the definition of an IEC if the following sentence were added: “*An IEC is adequately constituted if its composition and membership complies with §56, Subpart B of this chapter.*” Alternatively, we note that the definition of an IEC in the guidance on Good Clinical Practice (GCP) (E6) of the International Conference on Harmonization (ICH), which is similar to the proposed definition in §312.3, contains no reference to an IEC being “*adequately constituted*”. Therefore, it may be acceptable to omit the requirement for “adequate constitution” from the proposed definition. Regardless, we believe that some clarification of the issue is required.

b. Qualifications of IEC Members

As noted above, proposed §312.120(b)(6) will require sponsors to report to FDA the qualifications of IEC members. However, it is not clear what is meant by “qualifications”. Clearly, this could (and would) include professional degrees, diplomas and certificates, but we would suggest that it will often be difficult or impossible to assess meaningfully the true qualifications of IEC members to evaluate study protocols and other aspects of the conduct of a study, simply by review of their formal professional qualifications. First, in many countries, members of an IEC may have no formal qualifications, or those that they have may be quite unfamiliar to both the sponsor’s staff and to FDA. Second, even though a formal qualification may seem familiar (e.g., MD), there is no assurance

¹ 21 CFR 56.107

that the described individual has necessarily received any training in, for example, research bioethics or the principles of GCP².

FDA's requirement that sponsors list the qualifications of IEC members is only relevant if the listed qualifications testify to the members' competence to protect clinical trial participants and otherwise ensure that the study is truly conducted under GCP. For FDA to require the bald listing of qualifications alone implies that the agency is not much concerned as to whether the IEC is actually competent in these respects. Therefore, we recommend strongly that FDA should clarify that "*qualifications*" means not only formal academic certifications but also evidence that the IEC members, individually and as a group, are competent to protect trial participants and ensure that the study is run in compliance with GCP. We believe that this means that sponsors should be required, in addition to listing IEC members' formal qualifications, to provide evidence that the members of the IEC have received training in bioethics and the principles of GCP, and are in other ways competent to protect trial participants. This evidence could be provided as citations of the specific training in bioethics/GCP received by each member of the IEC (type of training, date trained, training body or organisation) or as a citation of accreditation (type of accreditation, date of last accreditation, accreditation body) of the IEC by an independent accreditation body.

2. Waivers

Proposed §312.120(c)(2) states, "*FDA may grant a waiver if it finds that doing so would be in the interest of the public health*". On its face, this could be construed as placing *the public health* – presumably, the health of American citizens – ahead of the need to protect trial participants in foreign countries. We do not believe that this is what FDA intends, but we suggest that the point should be clarified by indicating that no waiver would be granted if this would compromise the sponsor's obligation to show that trial participants had been protected at all times, even though the waiver might be in the interest of the public health.

We appreciate the opportunity to comment on this important report and look forward to working with FDA to realise its potential.

Sincerely,



Robert G. Pietrusko, Pharm.D.,
Senior Vice-President, Worldwide Regulatory Affairs and Pharmacovigilance,
Millennium Pharmaceuticals, Inc

² Indeed, there would be many MDs in the US who would not be qualified to join an IEC without specific training in GCP, etc.