



March 14, 2007

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Food and Drug Administration
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RE: Docket No. 2006N-0062 (RIN 0910-AF14): Comments on the Proposed Rule on "Expanded Access to Investigational Drugs for Treatment Use" (Federal Register 71: 75147-75168, December 14, 2006)

Dear Sir or Madam:

We read with interest the new proposed rule on "Expanded Access to Investigational Drugs for Treatment Use", as published in the Federal Register on December 14, 2006 (Volume 71, pages 75147-75168). The purpose of this correspondence is to provide comments in response to this proposed rule.

GlaxoSmithKline is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture, and distribution of medicines and vaccines that enable people to lead longer, healthier, and more productive lives. We appreciate the opportunity to comment on this draft guidance, as GSK has a long history of working with FDA, healthcare professionals, patients, and other stakeholders to provide appropriate access to investigational and marketed prescription drug products.

GSK maintains that achievement of regulatory approval for a new product, based on appropriate evidence of safety and efficacy, with subsequent market-based distribution of the product is the ultimate means of expanded access to the product by healthcare professionals and their patients.

Historically, with respect to the topic of this proposed rule, in the last 20 years, GlaxoSmithKline and its heritage companies have designed and sponsored a variety of "expanded access" or "compassionate use" protocols as a means to provide particular investigational drugs for treatment of appropriate patients, in situations when the available data showed that the benefits of treatment were reasonably likely to exceed the risks of treatment. Since the 1980s, our organization has experience with emergency use of an investigational drug for individual patients, compassionate use protocols for patients with immediately life-threatening illnesses (e.g., severe infection due to a drug-resistant

bacterium), expanded access protocols for patients with life-threatening diseases (e.g., HIV), treatment protocols, and treatment INDs. GSK's experts have drawn on these experiences to formulate our comments to this docket. We appreciate the opportunity to contribute to the rulemaking process.

Major Comments

1. **General Comment:** We applaud FDA's effort to consolidate, clarify, and update the regulations pertaining to all means of access to an investigational drug product for treatment use. From GSK's perspective, the proposed rule is compatible with the relevant amendments to the Act emanating from the FDA Modernization Act of 1997. More clearly articulated procedures for treatment use of investigational drugs will be helpful to all stakeholders.
2. **Safeguards:** Access to investigational drugs for treatment use has been, and must continue to be, regulated in a manner consistent with protecting the rights and welfare of patient candidates for the investigational drug, ensuring that treatment use can be designed and conducted with an appropriate margin of safety with appropriate monitoring of patients, and also ensuring that treatment use does not impair the ability to complete the adequate and well-controlled trials that will provide the key evidence of safety and effectiveness in the New Drug Application or Biologic License Application. As stated in the proposed rule, allowing expanded access to investigational drugs before they are reasonably evaluated for safety may have adverse consequences for the seriously ill patients who receive them. The safeguards in the proposed rule may be inadequate to appropriately balance the competing drivers for access. We recommend that FDA actively seek input from representative US-based institutional review boards, academic medical centers and other medical practices with substantial experience with expanded access studies, and key professional associations (e.g., American Society for Clinical Pharmacology and Therapeutics) to learn their perspectives on the proposed criteria for expanded access by patients and investigators to an investigational drug for treatment use. These stakeholders can also provide important perspectives regarding any special considerations for use of institutional review and informed consent processes to accompany increased expanded access to investigational drugs.
3. **Evidence Standard under an IND:** We encourage FDA to incorporate explicit statements into the rule regarding the standards of evidence for efficacy and safety in order to initiate treatment use of an investigational drug for patients with an immediately life-threatening disease, as well as the standards of evidence for efficacy and safety in order to initiate treatment use of an investigational drug for patients with a serious disease. Historically, the leadership of former Commissioners Frank Young and David Kessler were particularly instrumental, in our view, in helping to clarify for pharmaceutical companies and other stakeholders the expected evidence needed for

FDA, sponsors, physicians, and other stakeholders to justify treatment use of an investigational drug. With respect to a patient with an immediately life-threatening disease, we support continued use of FDA's stated standards of evidence in 21 CFR 312.320(a)(3), i.e., the standard of evidence for efficacy that there should be a "reasonable basis to conclude that the drug may be effective" for the proposed treatment use; with respect to safety, we support continued use of the standard of evidence that there should be a "reasonable basis to conclude that the drug would not expose the patient to an unreasonable and significant drug-associated risk of injury or additional illness". We also support FDA's previously stated standards of evidence when access is considered for patients with a serious disease.

4. Indication for Use in Expanded Access: The indication for use of an investigational drug in expanded access should be the same indication being assessed in controlled clinical trials, where these controlled clinical trials are part of the body of evidence intended to lead to product registration in the US. Absent this provision, there is no assurance that effectiveness for the treatment use will ever be vigorously evaluated in accordance with regulatory standards.
5. Reporting results: The preamble and the proposed rule state the sponsor's regulatory obligation to submit IND Safety Reports and Annual Reports to the IND containing an expanded access protocol [see proposed 21 CFR 312.305(c)(5)]. In addition to fulfilling these obligations, we encourage FDA to revise the proposed rule to explicitly inform sponsors, investigators, patients, and patient representatives that any safety and efficacy data collected in expanded access are expected to be reported in the initial NDA seeking approval for the drug or biologic product. It is important for all stakeholders to be aware that, historically, FDA has expected that all safety and efficacy data (as of a cut-off date between with the sponsor and FDA) be in the initial NDA so that it can be part of the review that determines whether or not the product meets the standards for approval. FDA should be transparent with sponsors and other stakeholders in the preamble to the final rule that conduct of an expanded access protocol, like any other protocol conducted under an IND, places a burden on the sponsor to ensure that the results are reported in the initial NDA, that safety data are appropriately captured and reported, and to recognize that this information will be part of the total body of data on the drug that may affect the labeling for the product.
6. Drug Supplies: We encourage FDA to revise the preamble and proposed rule to state that the sponsor must carefully assess the adequacy of supplies of the investigational drug or biologic prior to a proposal to initiate or increase the sample size of an expanded access protocol. The proposed rule incorrectly makes the assumption that the manufacturer would have adequate current and continuing supplies of the investigational drug available for expanded access by individual patients and intermediate-size expanded access. Sponsors should be encouraged to speak with FDA

about any questions or issues pertaining to appropriate chemistry, manufacturing, and controls information during the IND stages of development. Patients and other stakeholders will not have the potential to be well served by this new regulation unless expanded access is focused on those products for which the sponsor can ensure that the investigational product will be available in a quantity appropriate to meet likely demand of an initial expanded access protocol; similarly, the sponsor should ensure that sufficient product is available to sustain treatment of patients who start on the investigational drug and may require its ongoing, chronic use. Further, FDA is aware of the practical reality that sponsors of some prior expanded access programs have had to utilize an allocation program to distribute the limited available quantity of an investigational drug to patient candidates in a fair manner. These and other supply considerations must be carefully assessed before the sponsor can commit to provide the investigational product for use in expanded access. Otherwise, the sponsor and physician-investigators may be in the unacceptable situation of over-promising, but under-delivering, an investigational product to patients.

7. Labeling: FDA should inform stakeholders in the preamble to the final rule that, historically, FDA has seldom allowed any efficacy information from expanded access studies to be included as evidence of efficacy in an NDA or Supplemental NDA. FDA's effort to update the regulations governing expanded access protocols comprises an opportunity for FDA to proactively state its position on inclusion of safety or efficacy information in labeling; this is an information gap. From GSK's perspective, it is reasonable and appropriate for the applicant to include a summary of safety and efficacy information from an expanded access protocol in draft labeling submitted in the initial NDA when the patient population included in the expanded access protocol is within the scope of intended use of the product. Historically, FDA's general unwillingness to include efficacy information from an expanded access protocol in labeling has been a disincentive for some companies to make a product available for expanded access. In this environment, the company bears the unfavorable impact of safety observations in expanded access (often focused on patients likely to be very ill, non-responders to prior treatments, and not representative of the targeted population assessed in controlled clinical trials) with no potential to benefit from favorable efficacy observations in expanded access.

Additional Comments on the Proposed Rule

1. Requirements for All Expanded Access Uses (§312.305): Definitions of Immediately Life-Threatening Disease and Serious Disease:

The proposed 21 CFR 312.300(b) provides an explicit definition of "immediately life-threatening disease". This definition is reasonable and practical, from our perspective. As FDA is aware, the agency has previously defined the term "life-threatening" as (1)

diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and (2) diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival [21 CFR 312.81(a)]. We encourage FDA to confirm our view that the proposed definition of "immediately life-threatening" in 21 CFR 312.300(b) is consistent and compatible with this prior definition of "life threatening".

The proposed rule does not, itself, include a definition of "serious disease". Since the proposed rule requires that patient candidates have a serious or immediately life-threatening disease (along with other criteria), we recommend that the rule incorporate by reference or reiterate in the preamble the definition for completeness. Inclusion of this definition will also encourage consistency across different applicants and different parts of FDA. As stated in the preamble to the proposed rule, FDA's *Guidance for Industry: Fast Track Drug Development Programs - Designation, Development, and Application Review* (July 2004) has previously provided FDA's criterion for determining whether a condition is "serious", as quoted below.

"1. Whether a condition is serious

As discussed in the preamble to the proposed accelerated approval rule (57 FR 13234, April 15, 1992), determination of the seriousness of a condition:

... is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes [such as] ... inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses, and many other diseases.

For a condition to be serious, the condition should be associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient but the morbidity need not be irreversible, providing it is persistent or recurrent."

We support use of this same definition for this proposed rule.

2. Evidence Needed Prior to Initiation of Expanded Access for Patients with Immediately Life-Threatening Illness

Page 75151: The preamble to the proposed rule (on page 75151) states that an investigational drug may be used to treat a patient with an immediately life-threatening illness in the absence of any relevant clinical data in some circumstances; specifically, "In some cases, however, there may be no relevant clinical experience, and the case for potential benefit may be based on preclinical data or on the mechanism of action." This situation should be extremely rare, and we question the appropriateness of conducting (essentially) a first time in human study via a treatment protocol of patients with an immediately life-threatening illness. We recommend that the final rule state that proceeding with treatment use in such a rare circumstance requires, at a minimum, that the sponsor submit to FDA (a) robust evidence from nonclinical studies to show that it is reasonably safe to proceed with the proposed treatment use and (b) information forming the basis from nonclinical toxicokinetic studies and nonclinical pharmacology studies for selecting the dose, dosage interval, and duration of treatment for use in patients.

3. Expanded Access for Individual Patients (Proposed §312.310)

For an individual patient with an immediately life-threatening condition, the evidentiary burden could be viewed by some readers of this proposed rule as very low to initiate expanded access of an investigational drug. Indeed, the proposed rule implies that little if any clinical evidence is needed to suggest a potential benefit for an individual patient; in some rare situations, nonclinical data alone may be an acceptable basis for initiating treatment of individual patients. GSK recommends specific revisions of this aspect of the proposed rule (please see our previous comments). We support continued use of the evidence base stated in current regulations (21 CFR 312.34) for initiation of treatment use of an investigational drug for a life-threatening or serious illness. Also, the proposed rule for charging for expanded access to investigational drugs for treatment use does not support this situation as there may be no clinical trial ongoing or planned that would support marketing approval [see proposed rule in 21 CFR 312.8(c)].

4. Expanded Access for Intermediate-Size Patient Populations (Proposed §312.315)

Part 312.315(a)(1) of the proposed rule states that an expanded access program may be needed for an investigational drug that is not being developed for particular reasons. This provision is counterintuitive. Although the drug may be perceived as a promising therapy by some stakeholders, if it is not being developed in the United States because the disease is so rare that it is not possible to recruit patients to a clinical trial, the sponsor would not ordinarily maintain an active IND nor would the sponsor be manufacturing investigational drug supplies. The amount of available safety and effectiveness data in such a small patient population would be minimal, yet the language of this section of the proposed rule implies that this is an open-ended commitment to expanded access. GSK recommends that §312.315(a)(1) be deleted so that realistic expectations are set for FDA, healthcare providers, patients, and manufacturers; surely none of these stakeholders would expect to

regularly provide expanded access to an investigational drug that is not being developed for registration in the United States. In addition, the proposed rule for charging for expanded access to investigational drugs for treatment use does not support this situation as there may be no clinical trial ongoing or planned that would support marketing approval [see proposed rule in 312.8(c)].

Part 312.315(a)(3) of the proposed rule states that an expanded access program may be needed for a drug product that is no longer marketed due to safety reasons. In such situations, we recognize that there may be a subset of patients for whom the benefits of treatment are believed to outweigh the risks of treatment, where such patients lack satisfactory alternative therapies. Under the proposed §312.315(a)(3)(i), in the preamble on page 75154, it states that such patients could "continue to receive the drug" under an intermediate-size patient population IND for expanded access. We offer the following comments:

- §312.315(a)(3)(i) and (ii) are for an intermediate size population (i.e., 10-100 patients). These situations described in the proposed rule could easily involve much larger numbers of patients, thereby rendering the Expanded Access methodology inappropriate.
- Use of the word continue implies that the patients are already receiving the drug when marketing was halted. Assuming the drug was being prescribed for an approved indication, there will likely be situations where the sponsor may continue to provide the drug to these patients via a program agreed with FDA. If it is intended that new patients would begin therapy after the drug is withdrawn from the market, the word continue should be deleted.
- A drug that is no longer marketed to a broad patient population for safety reasons may still be appropriate for distribution to a targeted patient population where benefits exceed risks. In such a situation, we recommend that the final rule clarify that some situations of this type can be addressed through a restricted distribution program of the FDA-approved product in accordance with 21 CFR 314 Subpart H.
- In situations where continued access to the product is provided under this new proposed rule, the Expanded Access program is investigational. Charging for the investigational drug according to the proposed rule 312.8(c) is not allowed in this situation as the criteria would not be met. Stakeholders should be aware that this may result in providing drug free of charge for an extended period of time with the added expense of monitoring and complying with other IND regulations.

Part 312.315(a)(3)(i) of the proposed rule is intended to allow uninterrupted therapy when an approved drug is not being manufactured in a manner consistent with the specifications on which the approval of the NDA was based (GMP violations) and therefore cannot continue to be marketed under the NDA. Under proposed §312.315(a)(3)(i), the drug could be made available to patients for whom the drug is a medical necessity until the GMP violations are addressed (assuming that, despite those violations, the product does

not pose a risk that is unreasonable in the context of the disease or condition to be treated, per proposed §312.305(a)(2)). We offer the following comments:

- §312.315(a)(3)(i) is for an intermediate size population (i.e., 10-100 patients). The situation described here could involve a much larger number of patients. Who would determine whether the risk is unreasonable or acceptable? If this is evaluated by FDA via an Expanded Access protocol under an IND, please specify. The IND would have to cross refer to the NDA for CMC information and also describe the GMP issues. Again, charging for the now investigational use of the product is not supported in the new proposed rule 312.8(c).
- If the product does pose a risk because of GMP concerns, proposed §312.315(a)(3)(ii) could be used to make available an unapproved drug product containing the same active moiety (e.g., a drug product approved in another country). The comments above apply to this situation, as well.

5. Monitoring

The proposed rule in 312.310(c)(3) states that FDA "may require sponsors to monitor" an individual patient expanded access if the use is for an extended duration. Similarly, 312.315(d)(2) states that "The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators" for intermediate-size patient populations. Also, 312.320(c) states that the "sponsor is responsible for monitoring the treatment protocol . . ." These aspects of the proposed rule clearly require monitoring by the sponsor of two of the three types of expanded access and may require monitoring even for individual patient use. GSK recommends that FDA revise the proposed rule to include more realistic provisions for monitoring.

- In GSK's experience, it is impractical and burdensome to consider monitoring by the sponsor for individual patient use in view of the potential nationwide access to treatment by patients in virtually any medical care setting. In addition, there is often very little advance notice of the investigator's request to treat an individual patient; this limited time comprises a temporal barrier to monitoring by the sponsor. We encourage FDA to delete monitoring from this aspect of the proposed rule.
- With respect to intermediate-size patient populations and treatment use, GSK recommends that the final rule state that monitoring (in the sense of the word for controlled clinical trials under the IND regulations and ICH Good Clinical Practice guideline) is not required. We recommend that the final rule under "Safeguards" state that the sponsor's submission to the IND should include (1) a description of the sponsor's criteria for selection of investigators as qualified by appropriate training and experience, (2) a description of the sponsor's method for data collection by investigators or a copy of the Case Report Form for use by investigators, (3) information on whether, and under what circumstances, a commercial IRB may provide IRB oversight for investigators who practice in a setting with or without its

own IRB, and (4) the sponsor's prospective plan for demonstrating diligence in obtaining data (completed CRF) from investigators for each patient.

6. Mode of Submission

GSK suggests that reviewing divisions at FDA, as well as companies, will benefit from a shared understanding with respect to the nomenclature for use on Form FDA 1571 when a sponsor submits a Protocol for expanded access use of an investigational drug or a new Treatment IND. Standardized nomenclature should facilitate rapid recognition of these types of submissions.

- With respect to a new Treatment IND, we suggest that the sponsor make two entries in Item 11 of the Form FDA 1571, i.e., (1) check the box for INITIAL INVESTIGATIONAL NEW DRUG APPLICATION and (2) enter "OTHER: Treatment IND" on the blank line.
- With respect to a Protocol for expanded access use of an investigational drug under an existing IND, we suggest that the sponsor make two entries in ITEM 11 of the Form FDA 1571, i.e., (1) check the box for PROTOCOL AMENDMENT: NEW PROTOCOL and (2) enter "OTHER: New Protocol for Expanded Access" on the blank line.

7. Analysis of Impacts

Page 75158 of the preamble states that the proposed rule "attempts to minimize the potential administrative burdens for physicians, sponsors, and FDA". From GSK's perspective, this proposed rule is unlikely to reduce, and more likely to increase, the sponsor's substantial administrative, medical, and regulatory burdens associated with expanded access use of an investigational drug. The proposed rule foretells the likelihood of increased communication among investigators, patients, and the sponsor to explore the potential role for expanded access to the investigational drug in the care of the patient. For some investigational drugs, this need for increased communication will have substantial impact on the sponsor. The sponsor also bears the burden to provide resources for an expanded access program. These resources are used to address a wide variety of expenses, including the cost of the investigational drug, clinical laboratory tests, study monitoring, data processing, data analysis, preparation of reports, and other activities.

8. Charging for drug

Based on the proposed rule for charging for investigational drugs (proposed 312.8(c), *Charging for expanded access to investigational drugs for treatment use*), sponsors would not be allowed to charge for drugs in the categories in this proposed rule on expanded access for intermediate-size patient population, for a drug not being developed §312.315(a)(1) in the US, and an approved drug product that is no longer marketed §312.315(a)(3). Lack of the option to charge for these categories may impede availability of some drugs for expanded access. It is recommended that consideration be given to

revise the proposed rule for charging to be more inclusive of situations created by the changes to the proposed rule for Expanded Access.

9. Typographical error

The proposed rule in 21 CFR 312.305(d)2) states that ". . . may begin as described in § 312.30(a)", which should be corrected to refer to §312.305(a).

GSK is submitting these comments, in electronic format, to the agency's internet site (<http://www.fda.gov/dockets/ecomments>). Thank you for this opportunity to provide comments on this proposed rule.

Please contact Robert S. Watson (phone: 919-483-6972) or David M. Cocchetto (phone: 919-483-5127) for any matters regarding this submission. If you want clarification or further discussion of our comments, we would be pleased to schedule a teleconference or meeting in follow-up. Thank you.

Sincerely,



Robert S. Watson
US Regulatory Affairs



David M. Cocchetto, Ph.D.