October 13, 2003

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398

Tel. 919 483 2100
www.gsk.com

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

Re: Comments on Proposed Safety Reporting Requirements for Human Drug and Biological Products
68 FR 12406, March 14, 2003
Docket No. 00N-1484

Dear Sir or Madam:

GlaxoSmithKline (GSK) is a research-based pharmaceutical company engaged in the discovery, development, manufacture, and sale of prescription and over-the-counter pharmaceutical products and vaccines. We appreciate the opportunity to provide comments on the proposed safety reporting requirements for human drug and biological products.

GSK wholeheartedly supports the stated aims of the proposed rule, particularly those related to international harmonization of safety reporting requirements and increasing the quality and usefulness of post-marketing safety reports. However, we believe that a number of the proposals introduce concepts and requirements that are not supportive of the stated aims of the proposed rule. Detailed comments on the specific proposed regulations are attached; the following are general comments on our major points of agreement and concern.

1. International harmonization:

We strongly support adoption of a common adverse event terminology, MedDRA, across all clinical safety activities. We also support FDA's endorsement of the ICH E2C guidelines (and the Addendum) regarding periodic reporting, particularly adoption of the International Birthdate (IBD) and data lock point. All of these initiatives are consistent with the stated aim of international harmonization.

However, several of the proposed regulations appear to be contrary to the stated intent of international harmonization, including:

- The definition of a suspected adverse drug reaction (SADR), particularly with regard to clinical trial reports. Interpretation of "reasonable possibility" to mean that a relationship cannot be ruled out, while technically in agreement with the ICH E2A definition, does not take into account the entire concept espoused by ICH, which includes the statement "reasonable causal relationship is meant to convey that there are facts or arguments to suggest a causal relationship." This is a well-established interpretation, is also supported by CIOMS, and has been incorporated into the European Clinical Trial Directive guidelines.
- Addition of numerous US-only appendices to the PSUR will serve to eliminate any efficiencies and cost-savings realized by adoption of the PSUR for FDA periodic reporting.
- FDA proposes to eliminate the line listings from PSURs; instead they will require semi-annual submission of individual case safety reports on Form FDA 3500A. As the line listings are an integral part of PSURs, it will actually be more work to eliminate them from the report that is submitted to FDA. FDA acknowledges this fact, and states that they are willing to accept line listings; therefore, there is no need for the semi-annual individual case report submissions, which are not required by any other regulatory authority.

- FDA introduces several new expedited and periodic reports that are not internationally recognized; including the 30 and 45-day follow-up reports, expedited reports for specific SADRs whether expected or not, and 7.5 and 12.5-year Interim Periodic Safety Reports. These will create additional work for both industry and FDA, with no additional public health benefit.
- The requirement for active query (direct verbal follow-up) with the initial reporter does not take into account variations in local medical culture and regulation, where such activities are not the norm, and may, in fact, be prohibited. For example, under the provisions of Italian Legislative Decree No 95, follow-up on suspected adverse reaction reports may be undertaken only by the Pharmacovigilance Responsible Person of the local health department or a representative of the Ministry of Health. Similarly, it will be impossible to comply with the requirement to submit death certificates, autopsy reports and hospital discharge summaries for SADRs that occur in certain countries, due to local practice and regulation.

2. Increased quality of post-marketing adverse event reports

We strongly support FDA's aim of increasing the quality of post-marketing SADR reports, and placing emphasis on serious reports, and those adverse events most likely to result in patient harm. We also agree with the proposals regarding definition of solicited reports separate from spontaneous reports, and elimination of reports arising from class action lawsuits from expedited reporting.

Again, however, a number of the proposed regulations appear contrary to these stated aims, and would deflect resource from monitoring and analysis of important safety information by imposing new reporting and compliance requirements without enhancing public health, including:

- Expedited reporting of medication errors and potential medication errors. While preventing patient illness and injury associated with medication errors is certainly a worthy goal, medication errors are primarily related to the practice and dispensing of medicine, and not to actions of the pharmaceutical industry. We agree that applicants should report medication errors that result in SADRs to FDA, but question the rationale for submitting these as expedited reports, particularly if the error was due to factors other than labeling/package instructions or product name. We also question the justification for submission of potential medication errors as defined in the proposed rule, since these involve neither a patient nor an SADR.
- Addition of other new types of expedited reports, including "always expedited" reports, reports with "unknown outcome", and requirements to document reasons why complete information cannot be obtained in expedited reports. The new 30/45-day follow-up reports also fall into this category. It is not clear how submission of these reports in an expedited manner will increase the quality of the reports or patient safety, particularly reports of expected SADRs, and follow-up reports that add no new safety information, but merely describe the applicant's unsuccessful follow-up attempts. This information is already available to FDA on request, as all manufacturers must maintain records of their follow-up attempts.
- Submission of copies of supporting documentation (e.g., hospital discharge summaries, autopsy reports, death certificates, etc.), translated into English, and inclusion of a list of all other relevant documents maintained by the applicant in the case narrative are also unnecessary and onerous requirements. The information contained in these documents is summarized in the narrative and other fields in the individual case report. This should be sufficient for evaluation of the significance of the report; copies are available to FDA on request.
- The requirement for exchange of safety information between contractors, licensing partners, etc. within five days of receipt, and submission of all safety data to FDA by the applicant (rather than by a contractor, licensing partner, etc.) is overly restrictive, and does not take into account the variety and complexity of these arrangements and contracts. We suggest that the intent of the proposed rule can be accomplished in other, more flexible ways.

3. Estimation of benefits and costs

As described in detail in our attached comments, we believe that FDA has considerably over-estimated the benefits and under-estimated the costs of implementing the proposed rules.

4. Implementation period

FDA proposes that the final rule requiring use of MedDRA become effective 12 months after publication, and that all other provisions become effective 180 days after publication of the final rule. Assuming that the final rule is not significantly modified from the proposed rule, we do not believe that 180 days is sufficient time to implement the provisions of the regulation. Full implementation will require significant changes to safety databases to meet the new reporting requirements, along with validation of the changes. In addition, new processes will need to be developed, along with extensive training of employees, investigators, contractors, licensing partners, etc. We suggest that FDA revise the implementation schedule to allow at least 12 months following publication of the final rule for implementation.

In addition, we note that FDA plans to finalize the draft guidance for industry that was published in the Federal Register of March 12, 2001 prior to publishing the final rule, and then update the guidance to incorporate the requirements of the final rule. Many of the concepts outlined in the draft guidance have been incorporated into the proposed rule, apparently without consideration of the comments on the draft guidance submitted to FDA in 2001. We suggest that FDA finalize both the proposed rule and the draft guidance for industry at the same time, to ensure that they are consistent, and that there is a regulatory basis for the expectations outlined in the guidance document.

5. Other

A. Implementation of the proposed rules will have significant impact on stakeholders outside the pharmaceutical industry. It is important that FDA actively engage these other interested parties (e.g., investigators, health care providers and their professional organizations, etc.) in dialog regarding development of the final rule and its impact on their activities. In addition, the Agency should ensure that the final rule is aligned with other ongoing initiatives within the Agency (e.g., risk management), and with other Agency functions (e.g., Review Divisions, Division of OTC Drug Products, etc.).

B. Several items associated with adverse event monitoring and reporting were not addressed in the proposed rule, and we suggest that they be incorporated into the final rule, including:
   - Electronic submission of individual case safety reports – As discussed in our specific comments, GSK currently submits the vast majority of our expedited reports to FDA electronically using ICH E2B elements, rendering many of the proposed requirements for full data set and submission of supporting documentation largely irrelevant to us. Although we note that the proposed rule states that electronic submissions are beyond the scope of the proposed rule, we request that FDA include in the final rule information regarding how compliance with requirements of the final rule is achieved when reports are submitted electronically.
   - As noted above, although many of the concepts included in the proposed rule were originally proposed in the draft guidance for industry issued in 2001, FDA does not appear to have taken the comments submitted on the draft guidance into account when drafting the proposed rule. Specifically, comments concerning the following items appear to have been ignored:
   - Use of the term "outcome" when "seriousness" is meant;
   - Active follow-up with health care professionals, without any mention of patient consent;
   - Direct verbal follow-up for all reports;
   - Inclusion of a chronological description of follow-up efforts in the case narrative;

- Highlighting of new information in follow-up reports;
- Attaching copies of hospital discharge summaries, autopsy reports and death certificates.
- There is no mention of provision of safety information received directly by FDA to sponsors/applicants. We believe that it is important for FDA and the sponsor/applicant to be working with the same data when evaluating potential safety issues. The current MedWatch to Manufacturer program is limited to reports received within the first three years after approval, and our experience with this program indicates that it provides only a very small number of reports to manufacturers. Although reports are available via the Freedom of Information (FOI) Act, these provide very limited information, and often do not allow for identification of reports submitted by the manufacturer. Other regulatory authorities routinely provide all reports that they receive directly to sponsors on both expedited (serious reports) and periodic schedules. We suggest that FDA consider implementing similar procedures for the reports that they receive directly.

Detailed comments on the specific proposed regulations are attached, organized by CFR section.

Thank you for your consideration of these comments on this important regulatory initiative.

Sincerely,

Ronald Krall, MD
Senior Vice President
Worldwide Development

Trevor Gibbs, MD
Senior Vice President
Global Clinical Safety & Pharmacovigilance

Attachment

Comments on Specific Sections of the Proposed Rule

Comments on changes to 21 CFR 312.32

312.32(a) Definitions:

Life-threatening suspected adverse drug reaction (SADR) means any SADR that, in the view of the investigator or sponsor, places the patient or subject at immediate risk of death from the SADR as it occurred. It does not include an SADR that, had it occurred in a more severe form, might have caused death.

Comment: We agree with the proposed addition of "or sponsor" to this definition. However, in section III.A.2 of the proposal, FDA indicates that if the investigator and sponsor have differing opinions regarding whether an SADR is life-threatening, the reasons for any differences in opinion should be included in the IND Safety Report. We do not think that this is appropriate or useful, and note that this statement does not appear in the proposed regulation itself.

Minimum data set means the report includes an identifiable patient, an identifiable reporter, a suspect drug, and an SADR.

Comment: With regard to the "suspect drug" component of the minimum data set, FDA notes that exceptions to breaking the blind for a study usually involve situations in which mortality or certain serious morbidities are the clinical endpoint of the study. FDA requests comment on whether the blind should be broken in other situations in which serious SADRs are not the clinical endpoint but occur at a rate high enough that the overall study blind would be compromised if each such case were individually unblinded. With the proposed revisions to the definition of "a reasonable possibility" to include all events for which a relationship cannot be ruled out, the likelihood of compromising the overall study blind for all studies will be increased (see comments below). In studies where serious SADRs are expected to occur with sufficient frequency that unblinding would compromise the integrity of the study, the sponsor and FDA should define in advance the nature of such serious SADRs that would not be subject to routine expedited reporting and unblinding. Ideally, this same agreement would apply to the entire clinical program, barring new safety information. Use of a Data Safety Monitoring Board should be considered in these situations.

Suspected adverse drug reaction (SADR) means a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out.

Comment: We have serious concerns about FDA's interpretation that "reasonable possibility" means a relationship cannot be ruled out. Although this definition is technically consistent with the ICH E2A definition, it does not encompass all of the concepts associated with the ICH definition, nor does it agree with the EU Clinical Trials Directive on ADR reporting. Both of these documents also include the concept that "reasonable causal relationship" is meant to convey that there are facts, evidence, or arguments to support a causal relationship. Such facts, evidence or arguments would include temporal relationship, a pharmacologically predictable event, or positive dechallenge or rechallenge. Confounding factors such as concomitant medications, concurrent illness, or relevant medical history should also be considered. Lack of consistent definitions and interpretations of causality between FDA and other major regulatory authorities will lead to confusion among investigators and will significantly impede our ability to manage the safety of our products on a worldwide basis.

As described in the proposed rules, use of FDA's definition would result in almost every serious unexpected adverse event being reported to FDA and investigators as an IND Safety Report, since a relationship could very rarely be totally ruled out. The example given by FDA in the

proposal (an event most probably related to the patient's underlying disease, but for which a relationship with the investigational drug cannot absolutely be eliminated) underscores this point. Unless the event occurred before the drug was administered, it is unlikely that a relationship could ever be completely ruled out.

One impact of this interpretation will be a significant increase in the number of IND Safety Reports submitted to FDA and to investigators and IRBs. This increase will make the detection of true safety signals more difficult due to the increased background "noise". Investigators and sponsors should be allowed to apply their professional/scientific/medical judgment to case causality assessments. This is consistent with other sections of the proposed rule, which require that a licensed physician be responsible for the content and medical interpretation of all expedited and periodic reports.

Investigators and IRBs have complained about the current abundance of uninformative IND Safety Reports, and the proposed change will increase their administrative burden without adding any true value. Since one of the stated objectives of the proposed regulations is to harmonize with international initiatives, we would urge the Agency to consider the EU Clinical Trial Directive and CIOMS VI proposals regarding reports to investigators. These documents recommend submission of periodic (e.g., quarterly) line listings to investigators during Phase I-III, instead of individual expedited reports. These periodic summaries should be accompanied by a summary of the evolving safety profile of the investigational product. Although the Agency would continue to receive individual reports in an expedited fashion, periodic summaries of safety information from clinical trials would be more informative for investigators and IRBs, and would be easier for them to manage administratively.

As mentioned above, a potentially more significant impact of the revised definition of "reasonable possibility" relates to the need to unblind all serious unexpected SADRs, potentially compromising the integrity of clinical trials that have a large number of serious adverse events. The Agency suggests that protocols could be written to exclude certain disease-related events that are study endpoints from expedited reporting, which we currently do for certain products. However, this is a rather unwieldy approach when applied to other common serious events that may not be study endpoints. A recent review of one clinical program indicated that of 3693 SAEs, 847 (23%) were considered "unlikely" by the investigator; 305 (8%) were possibly, probably or definitely related; and 2385 were classified as not related (data were missing for the remaining 156 cases). With the proposed interpretation of "reasonable causal relationship", all of the 847 "unlikely" cases, and depending on how rigorously "ruled out" is applied, at least a portion of the "unrelated" cases would be considered related. A review of the events reported in the 847 "unlikely related" cases found that 650 involved unexpected events that would have required the cases to be unblinded. This would have increased the number of IND Safety Reports and the number of unblinded cases from 305 (8%) to 955 (26%) without any real benefit to patient safety.

312.32(b) Review of safety information:

FDA proposes adding a clarification that review of foreign commercial marketing experience applies only to drugs that are not marketed in the United States.

Comment: GSK agrees with this clarification, but seeks additional clarification regarding the definition of "drugs that are not marketed in the United States". We propose that this apply to the active moiety, so that foreign marketing experience for the same active moiety as a US marketed product, but in a different formulation, would not be subject to expedited reporting under 312.32. These reports would be submitted to FDA under the post-marketing reporting regulations. For example, if fluticasone propionate is marketed in the US as a multidose inhaler, and a Diskus formulation is under investigation in the US but marketed elsewhere, foreign spontaneous reports for the Diskus would not need to be submitted as expedited reports to the IND, but would be submitted to the NDA for the multidose inhaler.

312.32(c)(1)(i) Written reports - Serious and unexpected SADR

The proposed rule notes that IND Safety Reports must be submitted for any SADR that either the sponsor or investigator considers serious and unexpected. The sponsor must identify all IND Safety Reports previously filed with similar SADRs, and must include an analysis of the SADR in light of previous similar reports.

Comment: In practice, investigators are not usually required to make expectedness assessments; this is the sponsor's responsibility. We request that the Agency clarify that investigators will not be required to assess expectedness, but that this remains a responsibility of the sponsor.

Safety reports previously filed with the IND concerning a similar SADR are a limited subset of information for the product. It does not include events that were not considered drug-related and once a product is marketed, does not include information reported only to the NDA. To adequately summarize this more comprehensive information for most marketed products within a 15-day time period is unreasonable. The assumption is that this proposed rule was written for purely investigational products. If so, this should be clarified in the regulations. If the regulations were changed to require periodic aggregate summaries of safety information as previously suggested, a more comprehensive and informative summary could be generated as a sponsor comment.

In section III.B.2.b of the proposed rule, FDA states that sponsors should include in any written IND Safety Reports subsequently filed with FDA a chronological history of their efforts to obtain the minimum data set if there is a delay in obtaining this information.

Comment: The value of including this information in an IND Safety Report is questionable. According to GCP, attempts to follow-up a poorly documented case should be maintained internally within a case file. Rather than requiring the inclusion of follow-up attempts in individual case reports, it would be more appropriate for FDA to reinforce the need to conduct follow-up activities and to audit industry for compliance. We also note that although this requirement is stated in the introductory section of the proposed rules, it does not appear in the proposed rule itself.

312.32(c)(1)(ii) Written reports – information sufficient to consider product administration changes

With regard to interpretation of the phrase "information that would be sufficient to consider changes in product administration", the gist of this section implies that this means information that would require major changes in the investigational program. However, it could be construed to mean something much more minor, such as a change in dose or dose schedule, which should certainly not require expedited reporting. In addition, the word "consider" is too vague; many of these considerations occur as part of routine ongoing safety data review, and the outcome may be that no change is required. We request that FDA clarify the meaning of this phrase, and to require expedited reporting only for information that results in a significant change in the investigational program.

We agree with the Agency's deletion of the ICH recommendation for expedited reporting of increased frequency of serious expected SADRs. However, we question the utility of including this information in the IND Annual Report as proposed by FDA. A more valuable assessment would include review of the incidence of all adverse events within a clinical program, whether serious or not. This may be difficult to do in an IND Annual Report, given the timing of various clinical trials relative to the IND annual reporting cycle. We suggest that rather than requiring increased frequency analysis of serious SADRs in IND Annual Reports, sponsors should routinely

review incidence rates within their program and report any significant changes in reporting rates in the IND Annual Report, when detected.

312.32(c)(4) Investigations of marketed drugs

FDA is proposing to clarify that sponsors of clinical trials filed to an IND for a drug marketed in the United States need to submit IND Safety Reports for only those SADRs that occur in the IND-filed studies.

Comment: We agree with this clarification, but, as noted above, we request clarification from FDA regarding the definition of "drug marketed in the United States". We propose that this apply to the active moiety, so that spontaneous and other reports for the same active moiety as a US marketed product, but in a different formulation, would not be subject to expedited reporting under 312.32. These reports would be submitted to FDA under the post-marketing reporting regulations. For example, if fluticasone propionate is marketed in the US as a multidose inhaler, and a Diskus formulation is under investigation in the US, foreign spontaneous reports for the Diskus would not need to be submitted as expedited reports to the IND, but would be submitted to the most appropriate NDA for the active moiety.

Comments on changes to 21 FR 314.80 (and 310.305 and 600.80)

314.80(a) Definitions (also 310.305(a) and 600.80(a))

Active query means direct verbal contact with the initial reporter of an SADR or medication error by a health care professional representing the applicant/manufacturer. For SADRs, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product and the SADR, including, but not limited to, baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

Comment: We agree with the concept of active query to capture essential information concerning serious unexpected SADRs and those selected SADRs for which Risk Management Programs are in place. However, the level of active query required by the proposed rule could have a negative impact on the willingness of HCPs to report SADRs and to provide additional information on those SADRs that they do (however inadvertently) report to industry. We do not think active query is necessary for all serious SADRs or for non-serious SADRs or medication errors, and we question the wisdom of requiring this to be accomplished solely through direct verbal contact with the initial reporter. Often, it is more effective to collect this information via other means, such as e-mail or faxing of a targeted follow-up questionnaire to the health care professional. Busy health care professionals (HCPs) often do not have time to spend discussing a single patient's case on the telephone during the business day, and other options for collecting relevant information should be allowed. In addition, the initial reporter is often the patient or other consumer, not a health care professional, and the value of direct verbal contact in this situation is questionable. In most cases, one would want to collect this sort of detailed clinical information from the patient's treating HCP. Our experience has been that, although adverse event reporting is exempt from HIPAA authorization requirements, many HCPs require written authorization from the patient before they will provide the patient's medical information to the company. In these situations, written communication with the initial reporter is required. In addition, as these rules apply to all reports, foreign and domestic, they need to take into account the various cultural differences around the world, where direct verbal contact with the initial reporter by the manufacturer may not be culturally acceptable or legally allowed.

We also question the requirement that only health care professionals should conduct active query. Appropriately trained non-health care professionals can also effectively collect this information. We suggest that the proposed rule be modified to indicate that those engaged in active query have the appropriate education, training, and experience to enable them to carry out this function (wording similar to that contained in 21 CFR 211.25).

These proposed rules also apply to over-the-counter (OTC) medications with approved NDAs, and issues noted above related to consumer initial reporters are even more relevant to adverse events related to OTC products. With OTC medications, the patient's HCP may not even be aware the patient took the product, or that they experienced an adverse event. In addition, a substantial proportion of adverse event reports involving OTC products are received by letter or e-mail from the consumer, adding further complexity to the use of active query. It is common industry practice to obtain a minimum data set for non-serious reports involving OTC products, and to not initiate further follow-up, as it is unlikely that a consumer consulted with a HCP regarding a non-serious adverse event. For serious events, additional follow-up information is sought from HCPs if the consumer provides consent to do so. Active query as defined by the proposed rule is impractical for the majority of OTC adverse event reports. It may be appropriate in the OTC setting if the HCP is fully aware of the purpose behind the inquiry and if there are specific areas of interest regarding the adverse event reported. However, to impose this approach on all serious SADRs for all OTC products is considered to be of questionable value. As noted above, an alternative to active query is the use of targeted questionnaires for specific SADRs. This approach allows focused information gathering on areas of particular safety interest for specific products and could be used by both the customer call center personnel and Safety Department staff when in contact with either consumers or HCPs.

In section III.A.6. of the proposed rule, FDA indicates that use of active query during the initial contact with the reporter of the SADR would provide all the required information, and would eliminate or reduce the need to conduct follow-up activities. This points out an underlying problem with considering every mention of an adverse event to be a report of a suspected adverse drug reaction. In an ideal world, this would be true, but in the real world, very few people call a pharmaceutical company specifically to report a suspected adverse reaction; they call to obtain information, and in the course of requesting this information, it is noted that a patient experienced an adverse event, thus setting in motion the company's adverse event reporting procedures. In our experience, most health care practitioners who call the company do not have the patient's information readily available when they call us, and do not have the time to discuss the patient's case in detail even if they did.

Full data set means completion of all the applicable elements on FDA form 3500A (or VAERS form for vaccine reports or CIOMS I form for reports of foreign SADRs), including a concise medical narrative of the case (i.e., an accurate summary of the relevant data and information pertaining to an SADR or medication error).

Comment: GSK currently submits most post-marketing expedited reports electronically, making the proposed definition of full data set largely irrelevant to us. We request that FDA provide a more detailed definition of full data set, perhaps based on ICH E2B elements, rather than one based on completion of fields on a paper form that may soon become obsolete. In addition, it is unclear which elements would be considered applicable for potential medication error reports, since by definition, no adverse event occurs in these cases, and neither the FDA form 3500A, the VAERS form, nor the ICH E2B elements are designed for reporting potential medication errors.

Medication error means any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Comment: We request that FDA clarify that "inappropriate medication use" in this definition does not include medically appropriate use of a product outside of its approved labeling (e.g., prescribing a product only approved for patients aged 12 and above to a patient who is 8 years old). We also request that OTC products be excluded from medication error expedited reporting requirements, as these products generally have a larger therapeutic index and higher safety margin than most prescription products.

Actual medication error means a medication error that involves an identifiable patient whether the error was prevented prior to administration of the product or, if the product was administered, whether the error results in a serious SADR, nonserious SADR, or no SADR.

Comment: We recognize that medication errors are an important public health issue, and we understand the need to identify and report situations where patients receive the wrong medication, dose, etc., whether or not the error results in an SADR. However, defining situations where the error was recognized and prevented before the patient received the product as "actual" errors does not seem reasonable or logical. These situations are more logically described as "potential" errors.

Potential medication error means an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a patient.

Comment: Since these reports involve neither an identifiable patient nor an SADR, they should be outside the scope of this rule. As noted above, we suggest that the term "potential medication error" is better used to describe situations where errors are identified and prevented before the patient received the product.

SADR with unknown outcome means an SADR that cannot be classified, after active query, as either serious or nonserious.

Comment: The word "outcome" is usually used to denote the clinical outcome of the patient (e.g., resolved, improved, resolved with sequellae, died, etc.), not whether seriousness can be determined. We request that FDA reconsider use of "unknown outcome" when they really mean "unknown seriousness".

Spontaneous report means a communication from an individual to a company or regulatory authority that describes an SADR or medication error. It does not include cases identified from information solicited by the applicant or contractor, such as individual case safety reports or findings derived from a study, company-sponsored patient support program, disease management program, patient registry, including pregnancy registries, or any organized data collection scheme. It also does not include information compiled in support of class action lawsuits.

Comment: We support FDA's distinction of the various types of solicited information from true spontaneous reports. GSK particularly applauds FDA's efforts to exclude class action information and the acknowledgment that these reports are usually duplicative. However, the proposed rule should be extended, as it is currently limited solely to class action information. GSK urges FDA to exclude all information compiled or received in support of litigation claims, regardless of whether they are asserted in a class action, mass tort litigation, or an individual lawsuit, for the following reasons:

- The underlying rationale of the rule (i.e., that litigation SADRs are usually duplicative and therefore will not enhance signal detection), applies regardless of whether the claim is asserted in an individual litigation or a class action. In either event, most SADRs will have already been reported by either the patient or the HCP before litigation is commenced, and duplicative reporting will not promote patient safety.

- Mass tort cases become "class actions" only after a court certifies the class. This process often takes months or years. By that time, a reporting obligation for information received in the purported class action would already have been triggered, and SADR reports submitted, rendering this new rule largely worthless.
- Most personal injury claims are not asserted in class actions but in individual lawsuits. As written, the rule will be of only limited applicability, even though the rationale for the rule applies equally to any SADR received through litigation.

Suspected adverse drug reaction (SADR) means a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out.

Comment: As FDA points out in section III.A.1. of the proposed rule, the changes in the definition regarding causality will not significantly increase the number of spontaneous reports submitted to FDA. However, we have significant concerns that the use of the term "suspected adverse drug reaction" instead of adverse event (as in the current regulations) could discourage HCPs or consumers from reporting adverse events to manufacturers, due to the perception that this could implicate them in a product liability action, regardless of any disclaimers provided by FDA.

The current disclaimer printed on the FDA 3500 and FDA 3500A forms could possibly be expanded to include language such as: "Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event. Moreover, due to the inherent limitations of the data provided in this report, it shall not be construed as reliable scientific evidence for purposes of assessing causation".

FDA has always required submission of spontaneous reports regardless of causality, based on the assumption that a reporter would not have contacted the company unless they had at least some suspicion that the adverse event was related to the drug. This is reemphasized in the proposed rule (314.80(c)(1)(i)(B)). While this assumption may be true for some spontaneous reports, there are many cases where a reporter initially mentions one adverse event that they may attribute to the drug, and in the course of further investigation, provides information on other adverse events not thought to be caused by the drug. Under current practice, these are all considered to be adverse events, and are reported to FDA accordingly, but by no means are they "suspected adverse drug reactions". If FDA insists on referring to spontaneous adverse events as SADRs, we strongly recommend that they also consider the concept of incidental events, as discussed in the CIOMS V report.

314.80(b)(1) Review of safety information (also 310.305(b)(1) and 600.80(b)(1))

FDA proposes to include animal and in vitro studies to the list of example of data sources that must be reviewed by applicants, on the basis that many of these studies report relevant safety-related information.

Comment: This requirement seems most relevant for investigational compounds. If it is intended to apply to marketed products as well, we request that the Agency clarify that it applies only to animal and *in vitro* studies conducted by the applicant, not to all such studies reported in the published literature. A requirement to review all published animal and *in vitro* studies would require a substantial increase in resource devoted to literature review, for very little, if any, increase in patient safety. It would also be difficult for an applicant to evaluate the study conduct or data integrity for studies that they did not conduct.

In this section, FDA also proposes to include electronic communications via the internet (e.g., e-mail) as a source of spontaneous reports.

Comment: GSK agrees that e-mail communications from reporters should be reviewed for spontaneous SADRs. We also agree with FDA's assertion in section III.C.2. of the proposal, which states that an applicant would be required to review information received via internet sites that it sponsors, but would not be required to review internet sites that it does not sponsor. However, we disagree with the statement that requires an applicant to review such non-sponsored sites once they become aware of safety information on that site. This would require significant resource expenditure for little, if any, increase in patient safety, as the information on these sites is often unreliable and duplicative, and it is difficult to impossible to obtain follow-up information. If the Agency includes this requirement in the final regulations, we request that they also include guidance regarding what would be considered an identifiable reporter and identifiable patient for reports received via internet chat rooms. In addition to these significant elements, it would also be interesting to know FDA's thoughts on how active query and follow-up could be carried out in a confidential manner for these "reports".

314.80(c)(1)(i)(A) Determination of outcome, minimum data set, and full data set – initial determinations (also 310.305(c)(1)(i)(A) and 600.80(c)(1)(i)(A))

Among other things, FDA is proposing that active query must be used if the minimum data set is not immediately available, or if outcome (seriousness) cannot be immediately determined.

Comment: As noted previously, the word "outcome" is usually used to denote the clinical outcome of the patient (e.g., resolved, improved, resolved with sequellae, died, etc.), not whether seriousness can be determined. We request that FDA reconsider use of "unknown outcome" when they really mean "unknown seriousness". In section III.C.5., FDA states that the requirement for active query is being included to stress to applicants that timely acquisition of this information is critical to determine whether an SADR or medication error without an SADR must be submitted to FDA as an expedited report. We disagree that active query is necessary in all cases where the reporter does not initially provide a seriousness assessment. As noted below, most pharmaceutical manufacturers developed methodology for determining medically serious events when the concept of "important medical events" was introduced into the definition of serious in 1997.

314.80(c)(1)(ii) Determination of outcome, minimum data set, and full data set – SADRs with unknown outcome (also 310.305(c)(1)(ii) and 600.80(c)(1)(ii))

This section would require manufacturers who are unable to immediately determine the seriousness (outcome) of an SADR to continue to use active query to attempt to obtain this information within 30 days after initial receipt of the SADR, and maintain records of these efforts.

Comment: We disagree with FDA's contention that manufacturers will have difficulty determining whether an SADR is serious or not, regardless of whether the outcome is known. Most manufacturers previously determined the events that are considered serious when the concept of "important medical events" was added to the definition of serious in 1997.

314.80(c)(1)(iii)(A) Determination of outcome, minimum data set, and full data set – Minimum data set for SADR reports (also 310.305(c)(1)(iii)(A) and 600.80(c)(1)(iii)(A))

Reports without a minimum data set would not be submitted to FDA.

Comment: We question whether absence of an identifiable reporter should delay or eliminate submission of an SADR report that otherwise is complete. Often reporters, particularly consumers, prefer to remain anonymous, and refuse to provide their names or addresses, but do provide fairly complete information concerning their adverse event. On occasion, a similar

situation also arises with published literature. Obviously, in these cases, active query is not possible, and we would like clarification from FDA regarding whether these reports should be submitted.

A similar comment would apply to reports of medication errors without an identifiable reporter (314.80(c)(1)(iii)(B)).

314.80(c)(1)(iv) Determination of outcome, minimum data set, and full data set – Full data set (also 310.305(c)(1)(iv) and 600.80(c)(1)(iv))

If the manufacturer is unable to obtain a full data set for expedited reports, they must provide the reasons for this and documentation of their efforts to FDA.

Comment: Manufacturers are already required to follow-up all expedited reports, to submit all follow-up information to FDA within 15 days of receipt, and to maintain documentation of their follow-up efforts. These records are available to FDA on request. We see no need to submit a follow-up report to FDA detailing why follow-up efforts were unsuccessful and documenting efforts to obtain a complete data set. This is an inefficient use of the applicant's resources and will divert attention from the more important goal of obtaining complete reports, with little or no benefit to patient safety. Review of these extra expedited reports is also a waste of FDA resources, as the reports contain no new safety information. In section III.C.5. of the proposed rule, FDA notes that in some cases they have received incomplete safety reports for serious SADRs, making their interpretation of their significance difficult. This is an inevitable consequence of the spontaneous reporting system, and similarly affects the ability of manufacturers to evaluate the significance of the reports. It is unclear how requiring submission of a chronology of follow-up efforts will improve completeness of expedited reports. If FDA has difficulties with certain companies regarding their due diligence efforts, the Agency should address this with the individual companies on an as needed basis, not through creation of unnecessary reporting requirements for all companies.

314.80(c)(1)(v) Determination of outcome, minimum data set, and full data set – Serious SADRs not initially reported by a health care professional (also 310.305(c)(1)(v) and 600.80(c)(1)(v))

This section requires manufacturers to contact the patient's treating HCP using active query to obtain a full data set for the report. If the manufacturer is unable to contact the HCP, the manufacturer must provide the reasons for this and documentation of their efforts to obtain HCP confirmation to FDA.

Comment: Manufacturers are required to maintain records of all follow-up efforts, and to make these records available to FDA upon request. As in the comment directly above, the requirement to submit reports to FDA documenting the reasons HCP confirmation cannot be obtained and a chronology of the efforts taken to obtain this information is an inefficient use of resources for both the manufacturer and FDA, with little or no benefit to patient safety. It is common practice to request permission to contact a patient's HCP for all serious SADRs received from consumers. In the light of current privacy considerations, HCPs are often reluctant to discuss a patient's medical history without written permission from the patient. It is highly unlikely that a HCP will take the company's word that they have the patient's permission for the HCP to provide detailed medical information over the telephone. In this situation, it is far more likely that the HCP will provide the information in writing, following receipt of the patient's consent form, than via the telephone.

As noted above in our comments on active query, this requirement is even more onerous for OTC products. With OTC medications, the patient's HCP may not even be aware the patient took the product, or that they experienced an adverse event. In this situation, it is unlikely that the HCP

will be able to provide any additional information regarding the SADR. Unless the SADR is particularly alarming, mandatory follow-up of OTC reports with the HCP via telephone is not warranted. Written follow-up should be sufficient for most serious OTC cases.

314.80(c)(2)(i) Postmarketing "expedited reports" – Serious and unexpected SADR (also 310.305(c)(2)(i) and 600.80(c)(2)(i))

If a full data set is not available at the time the initial expedited report is submitted to FDA, the information required under paragraph (c)(1)(iv) should be submitted, and a 30-day follow-up report submitted as required by paragraph (c)(2)(vi).

Comment: See comments under paragraphs (c)(1)(iv) above, and (c)(2)(vi) below.

314.80(c)(2)(ii) Postmarketing "expedited reports" – Information sufficient to consider product administration changes (also 310.305(c)(2)(ii) and 600.80(c)(2)(ii))

This section requires expedited reporting of information from any source that would be sufficient, based on appropriate medical judgment, to consider changes in product administration.

We request that FDA clarify the meaning of the phrase "information that would be sufficient to consider changes in product administration". The gist of this section implies that this means information that would require major changes in the product labeling. However, it could be construed to mean something much more minor, such as a change in dose or dose schedule for an individual patient, which should certainly not require expedited reporting.

314.80(c)(2)(iii) Postmarketing "expedited reports" – Unexpected SADR with unknown outcome (also 310.305(c)(2)(iii) and 600.80(c)(2)(iii))

Requires expedited submission of unexpected SADRs for which the applicant cannot obtain the outcome, and documentation in the expedited report of the reasons why this information is unattainable.

Comment: As noted in our comment on the definition of "SADRs with unknown outcome:" above, the word "outcome" is usually used to denote the clinical outcome of the patient (e.g., resolved, improved, resolved with sequellae, died, etc.), not whether seriousness can be determined. We request that FDA reconsider use of the term "unknown outcome" when they really mean "unknown seriousness". In addition, we disagree with FDA's contention that manufacturers will have difficulty determining whether an SADR is serious or not, regardless of whether the outcome is known. Most manufacturers, including GSK, previously determined the events that are considered medically serious when the concept of "important medical events" was added to the definition of serious in 1997, and have used this principle without problem since that time. The fact that an applicant was unable to obtain a definitive assessment of seriousness from the reporter should not automatically make the report expeditable. For example, suppose a consumer reports a 2-day history of diarrhea that is ongoing at the time of the report, and does not respond to any attempts to obtain additional information via telephone or in writing. It is difficult to see how either the Agency's or the applicant's pharmacovigilance efforts would be served by submitting this as an expedited report. Medical judgment should be allowed in cases such as this.

We also question the usefulness of documenting in the expedited report the reasons for not being able to determine seriousness. The same narratives are used to report individual case safety reports worldwide, and this sort of information is not appropriate for worldwide reporting, especially since "unknown outcome" (seriousness) is not an internationally accepted concept. If

this requirement is retained in the final regulations, we request that FDA provide guidance regarding which box, if any, should be checked in section B.2 of the FDA 3500A form.

314.80(c)(2)(iv) Postmarketing "expedited reports" – Always expedited report (also 310.305(c)(2)(iv) and 600.80(c)(2)(iv))

This section would require expedited submission of certain SADRs, regardless of whether they are expected and regardless of whether they are serious. It would also allow FDA to add to the list at any time.

Comment: Several components of this section are of serious concern, as follows:

- This requirement will result in a tremendous increase in expedited reports, with questionable value. For example, seizures are currently an expected adverse event for bupropion (Wellbutrin® and Zyban®), and are well-described in the product labeling. In the period from July 1, 2002 through June 30, 2003, GSK received approximately 250 spontaneous reports of seizure in association with bupropion. Approximately 50 of these cases were submitted to FDA as expedited reports, due to unlabeled adverse events that were reported in addition to the seizures. Under the proposed rules, an additional 200 expedited reports involving seizures would have been submitted to FDA. It is difficult to determine what public health benefit, if any, will be gained by this additional expedited reporting.
- We question the value of submitting expedited reports for expected SADRs, since these are already described in labeling, and FDA will receive information related to these reports in periodic submissions. We suggest that FDA change this category to "always serious" reports, as all the terms qualify as "medically important". That would ensure that all such reports would be submitted to FDA in an expedited manner if they were unexpected.
- If FDA retains the concept of "always expedited" reports in the final rule, we request that they also consider whether this requirement should apply to all drugs regardless of how long they have been on the market, or only to those that have been marketed for less than a specific period of time (such as ten years).
- This section would also require expedited reporting of events that are the indication for the drug (e.g., seizures in association with an anti-epileptic product such as Lamictal (lamotrigine)). These are essentially "lack of effect" reports, which otherwise would be reported only in the aggregate in periodic reports. If FDA includes an "always expedited" category in the final rules, it should exempt events that are the indications for use from this reporting requirement. Using the same time period as described above, GSK would have submitted an additional 75 expedited reports involving seizures that occurred in epileptic patients who were taking lamotrigine. Again, it is difficult to understand what public health benefit the Agency expects to derive from this additional expedited reporting.
- We also strongly object to the part of this section that allows FDA to modify this list of terms through revising a guidance document, rather than going through formal rule-making. GSK believes that adding new terms through a guidance document violates the Administrative Procedures Act (APA) and the FDA's own regulations, in that it would permit FDA to engage in rulemaking without the opportunity for public notice and comment. Any changes to this list of terms should require future public notice and comment, consistent with, and as mandated by, the APA.

314.80(c)(2)(v) Postmarketing "expedited reports" – Medication errors (also 310.305(c)(2)(v) and 600.80(c)(2)(v))

This section would require expedited reporting of each domestic actual and potential medication error, regardless of whether an SADR occurred or was serious.

Comment: We recognize that medication errors are an important public health issue, and that the pharmaceutical industry has a role to play in identifying and minimizing the potential for these

errors, but this is not a problem that can be solved by just one part of the health care system. Most medication errors are related to practices surrounding the prescribing and dispensing of medications, not to factors that the pharmaceutical industry can control. According to the Institute for Safe Medication Practices, the four major causes of medication error are:

- Miscommunication of drug orders, which can involve poor handwriting or oral communication, drugs with similar names, misuse of zeros and decimal points, confusion of metric and other dosing units, use of non-standard or otherwise inappropriate abbreviations, or ambiguous or incomplete orders;
- Poor distribution practices;
- Complex or poorly designed technology;
- Access to drugs by non-pharmacy personnel.

We urge FDA to involve stakeholders from other sectors of the health care system (e.g., patients, pharmacists, other HCPs, and their institutions and professional organizations) in the Agency's efforts to reduce or prevent medication errors and improve patient safety. This appears to be the approach taken in other countries, including Australia. According to a recent article in Scrip (September 11, 2003), the National Medication Safety Breakthrough Collaborative Project, developed with the Australian Council for Safety and Quality in Health Care, will bring together up to 100 healthcare bodies to redesign their medication systems, share expertise, and develop innovative responses to common medication problems.

We agree that manufacturers should identify and report situations where patients receive the wrong medication, dose, etc., whether or not the error results in an SADR. However, we question the rationale for expedited reporting of all medication error reports, particularly if the error was due to factors other than labeling/package instructions or product name, which are the factors over which we have some control. In our experience, most reports of medication error involve either no adverse event, or events that are non-serious. Rather than requiring expedited reporting of all reports of medication errors, we recommend that FDA and industry focus their resources on those that are serious, and those that industry could potentially take action to prevent or minimize in the future, as follows:

- Expedited reports should be required if the medication error resulted in a serious SADR;
- Expedited reports should be required if the reason for the medication error was related to labeling/package instructions or product name, even if no SADR was reported;
- Medication errors that result in non-serious SADRs or no SADRs should be reported and discussed in the aggregate in periodic reports (TPSRs, PSURs).

FDA states in section III.D.5 of the proposed rule that for reporting purposes all reports of medication error would be considered unexpected. Our proposed reporting scheme incorporates this concept, and more closely follows the established procedures for "standard" SADR reports (i.e., expedited reporting of serious, unexpected SADRs and periodic reporting of non-serious SADRs).

As discussed in our comments on the definitions of actual and potential medication errors, we suggest that medication errors that are identified and prevented before the patient received the product are more logically classified as potential medication errors. These should also be reported and discussed in periodic reports, and not submitted as expedited reports.

We also do not see the need for expedited reporting of potential medication errors as defined in the proposed rule, and we question the appropriateness of including this category of report in regulations dealing with adverse event reporting, as by definition, they involve neither an adverse event nor an identifiable patient. If the Agency thinks that mandatory expedited reporting of these potential errors is necessary to protect the public health, this requirement should be directed to the HCP, and not the pharmaceutical industry.

314.80(c)(2)(vi) Postmarketing "expedited reports" – The 30-day follow-up report (also 310.305(c)(2)(vi) and 600.80(c)(2)(vi))

This section mandates submission of a follow-up report 30 days after submission of an initial expedited report that does not contain a full data set. If the full data set is still not available after 30 days, the report must include the reasons the full data set was not obtained, and documentation of the applicant's efforts to obtain the information. In addition, all new information must be highlighted.

Comment: As mentioned in several of the previous comments, the introduction of this new expedited report does not appear to serve any useful function. Manufacturers are already required to follow-up all expedited reports, to submit all follow-up information to FDA within 15 days of receipt, and to maintain documentation of their follow-up efforts. These records are available to FDA on request. We see no value in submitting a follow-up report to FDA detailing why follow-up efforts were unsuccessful and documenting efforts to obtain a complete data set. This represents an inefficient use of resources and will divert attention from the more important goal of obtaining complete reports, with little or no benefit to patient safety. Review of these extra expedited reports is also a waste of FDA resources, as the reports contain no new safety information.

In addition to creating extra work for both FDA and industry, with no obvious benefit, the creation of yet another new type of expedited report with a different timeframe for submission will create additional confusion and potential compliance liabilities. The 30-day report is not an internationally recognized report, and it is unclear how it will mesh with the existing 15-day follow-up report, which is required internationally. It would appear that FDA does not want 15-day follow-up reports to be submitted unless additional follow-up information is received after submission of a 30-day report. However, if a full data set was available at the time of the initial report, and further information is received, that information would be required to be submitted within 15-days of receipt. The additional classification and tracking mechanisms that companies will need to set up to accommodate these requirements are extremely complex, and detract resource from proactive pharmacovigilance activities, with little or no benefit to patient safety. And, as noted above, as these requirements apply equally to worldwide SADR reports, they have broad implications for international companies that have non-US case handling facilities.

The proposal includes a requirement for highlighting new information in follow-up reports. Highlighting all new follow-up information is almost impossible in automated electronic systems used for production of FDA 3500A forms, especially if the new information is combined with relevant information from the initial report. In addition, there is no provision for highlighting new information when reports are submitted to FDA electronically using the ICH E2B format. We request that FDA delete this sentence.

314.80(c)(2)(vii) Postmarketing "expedited reports" – The 15-day follow-up report (also 310.305(c)(2)(vii) and 600.80(c)(2)(vii))

This section mandates submission of a follow-up report within 15 days of receipt of additional information for certain types of expedited reports.

Comment: As noted directly above, creating follow-up reports with different timeframes for submission, depending on the nature and content of the initial report will only lead to confusion, and the potential for error, and does not serve a useful purpose. We recommend that FDA retain the internationally accepted 15-day timeframe for all follow-up reports, and eliminate the proposed 30-day report.

314.80(c)(2)(viii) Postmarketing "expedited reports" – Supporting documentation (also 310.305(c)(2)(viii) and 600.80(c)(2)(viii))

This section requires submission of: (A) death certificates and/or autopsy reports for all patients who die, and the hospital discharge summary for all patients who are hospitalized. All documents not in English must be accompanied by an English translation. (B) a list of all other relevant documents (e.g., medical, records, laboratory results, data from studies) maintained by the applicant.

Comment: While not clearly stated in the proposed rule, we assume that the requirement for death certificates, autopsy reports, and hospital discharge summaries relates to SADRs that are otherwise submitted as expedited reports, not to all patients who die or are hospitalized. We request clarification from the Agency on this point.

This requirement is onerous, and full compliance may not be possible. For example, autopsy reports are not generally part of the hospital medical record, and the reporter may not have access to it. The same holds true for death certificates, which are often not issued until months following the death. This requirement also raises issues regarding patient medical record confidentiality in the US and internationally. It is often not possible to obtain these documents in other countries due to local privacy regulations, and with the implementation of the HIPAA rules in the US, it will inevitably become more difficult to obtain them here as well. Although adverse event reporting is exempt from HIPAA authorization requirements, this is not well-understood by many HCPs and others in the health care field, and we have seen an increase in the number of HCPs, hospitals, etc. who refuse to provide copies of these records without the patient's written consent.

The requirement to obtain these records for all deaths and hospitalizations, and to translate and submit the translations to FDA places an unreasonable burden on applicants. While we do make every effort to obtain these documents when relevant to the report, the information contained in the documents is summarized in the narrative and other appropriate fields in the individual case report. This should be sufficient for evaluation of the significance of the report, and the Agency can always request copies of any documents held by the applicant when necessary.

We also request that FDA clarify how this requirement can be met when expedited reports are submitted to the Agency electronically.

We do not think it is appropriate to include a list of all other relevant documents maintained by the applicant in the narrative. Case narratives are used internationally for multiple purposes in addition to completing FDA 3500A forms, and this sort of information may not be appropriate for those other uses. Including this information in the narrative is not in accord with ICH E2B, which states that the narrative should be a "case narrative including clinical course, therapeutic measures, outcome and additional relevant information". In addition, the instructions for completing the FDA 3500A form state that this section should contain a description of the event or problem. As noted above, the Agency can always request copies of these documents from the applicant when necessary.

314.80(c)(2)(x) Postmarketing "expedited reports" – Submission of safety reports by contractors (also 310.305(c)(2)(xi) and 600.80(c)(2)(x))

This section requires contractors to submit all SADRs and medication errors to the applicant within 5 days of receipt; requires all contracts to specify the contractor's postmarketing safety reporting responsibilities; and requires the contractor to maintain certain records regarding the information transmitted to the applicant.

Comment: Although these requirements appear in the section of the regulations dealing with expedited reports, they appear to apply to all SADRs and medication error reports received by contractors. In one sense, these are expedited reports, as the proposal requires submission by the contractor to the applicant within 5 days of receipt. However, as the other paragraphs in this section of the proposed regulations deal with submission of expedited reports to FDA, it might be more appropriate to move this paragraph to a separate section.

We think section (A) of this proposed rule is unnecessary and should be deleted. Depending on the relationship between the contractor and the applicant, it may not be necessary or appropriate for all SADRs and medication errors to be submitted to the applicant within 5 days. For example, if the contractor has responsibility for performing follow-up (including active query), there is no need for the applicant to receive partial information on day 5. In addition, meeting this timeframe may be impossible with international licensing partners who must first translate the information into English.

As indicated in section (B), all contracts between an applicant and a contractor must specify the postmarketing reporting responsibilities of the contractor. The contract should also delineate the timeframes for submitting information to the applicant. It appears that this proposed rule mandates that all follow-up activities and submissions to FDA must be carried out by the applicant. While this may occur in the majority of cases, in others, it may be more appropriate for the contractor to carry out some or all of these responsibilities. This is particularly true with international licensing agreements, where it is very likely that the contractor will carry out all local activities, due to differences in language, culture, time zones, etc., that make it impossible for these activities to be carried out by US-based personnel. We request that FDA provide clarification that this flexibility is allowed, provided the responsibilities of both the contractor and applicant are clearly delineated in the contract.

314.80(c)(2)(xi) Postmarketing "expedited reports" – Report identification (also 310.305(c)(2)(xii) and 600.80(c)(2)(xi))

This section requires each type of expedited report to be identified as to its type (e.g., expedited report – serious and unexpected; expedited report – always expedited, etc.), and for each type of report to be submitted to FDA under separate cover.

Comment: We question the usefulness of this information, and request that FDA provide some guidance regarding where on the FDA 3500A form this information should be located. In addition, we would like some rationale from FDA regarding the need to submit each type of report under separate cover. This could require up to ten different submissions to FDA each day, and it is difficult to see how this could possibly comply with the requirements of the Paperwork Reduction Act. Since GSK submits expedited reports to FDA electronically, we also request guidance regarding how the identification and separate submission requirements can be met with electronic reporting, as this is not part of ICH E2B.

314.80(c)(3) Postmarketing periodic safety reports (also 600.80(c)(3))

This section notes that for products approved prior to January 1, 1998, applicants have the option to submit either TPSRs or PSURs, but for products approved after January 1, 1998, PSURs must be submitted.

Comment: We request that the Agency clarify which provisions apply if there are several approved NDAs for the same active moiety, some approved prior to January 1, 1998, and some approved after that date.

314.80(c)(3)(i) Postmarketing periodic safety reports – Traditional Periodic Safety Reports (TPSRs) (also 600.80(c)(3)(i))

Paragraph (A)(3) in this section requires a discussion of any increased frequency of serious expected SADRs, and an assessment of whether the frequency of lack of efficacy reports is greater than that predicted by clinical trials.

Comment: For some older products, clinical trial data regarding efficacy might not be available. We request guidance from the Agency regarding how this situation should be handled. We also request clarification regarding FDA's expectations for increased frequency analysis, since the Agency previously revoked similar regulations. Does FDA intend to provide guidance regarding methods of analysis and the quality of information necessary to determine whether there is a "meaningful change" in the data?

Paragraph (B)(1) in this section requires summary tabulations for all domestic reports of serious expected SADRs, nonserious unexpected SADRs, nonserious expected SADRs, and expected SADRs with unknown seriousness (outcome).

Comment: As noted above, we disagree with FDA's contention that manufacturers will have difficulty determining whether an SADR is serious or not, regardless of whether the outcome is known. Most manufacturers previously determined the events that are considered serious when the concept of "important medical events" was added to the definition of serious in 1997. Therefore, we question the need for a separate tabulation for expected SADRs with unknown seriousness (outcome). A similar comment applies to paragraph (B)(2).

Paragraph (B)(3) describes summary tabulations of SADRs not previously submitted to FDA, including reports from class action lawsuits.

Comment: As noted in our comments on the definition of Spontaneous report above, we agree with FDA's proposals to exclude information derived from class action lawsuits from consideration as spontaneous reports. However, we believe that the proposed rule does not go far enough, and that the same considerations should be given to all information compiled or received in support of litigation actions, regardless of whether they are asserted in a class action, mass tort cases, or an individual lawsuit. This would extend to inclusion of all SADRs received through litigation in the summary tabulations described in paragraph (B)(3).

Paragraph (B)(4) requires tabulations of actual and potential medication errors by various categories. For potential medication errors, the proposed rule requires the tabulation to provide the number of reports for specific errors.

Comment: As noted in our comments on the definition of potential medication errors above, we do not believe that potential medication errors are within the scope of this proposed rule, as they involve neither an adverse experience (SADR) nor a patient. However, if the Agency persists in including this type of report in the final rule, we request that the following comment be considered. It is not clear what "specific errors" the Agency has in mind, as by definition, no error actually occurs with a potential medication error, and there are no specific MedDRA terms to describe medication errors with this level of specificity. In fact, there is currently no MedDRA term to distinguish potential medication errors from actual medication errors. We request that the Agency provide clarification on these points.

Paragraph (D) of this section requires a list of the current address(es) where all safety reports and other safety-related records for the drug product are maintained.

Comment: Multinational pharmaceutical companies such as GSK maintain local Operating Companies (OCs) in most countries in the world. All of these OCs have responsibility for receiving local adverse event reports, following up on them, forwarding the information to the

central safety department within specified timeframes, and maintaining records of these activities. As such, they all maintain "safety reports and other safety-related records". Surely FDA does not want the addresses of each of our OCs. We request that FDA clarify this requirement to specify the address(es) of the US site(s) where adverse event data are maintained and entered into the company's adverse event database.

Paragraph (E) requires the name, telephone number, fax number and e-mail address of the licensed physician responsible for the content and medical interpretation of the information contained in the TPSR.

Comment: We request that FDA clarify what is meant by "licensed" physician, and the rationale for requiring that a licensed physician review the report. It is entirely possible that an "unlicensed" physician or other health care professional with extensive pharmacovigilance experience is eminently more qualified to review and interpret the medical information contained in the report than a newly licensed physician with little pharmacovigilance experience. For multinational companies, it is possible that the "responsible physician" is not located in the US. In these circumstances, it is more useful for the company to provide the name of a contact person in the US who can ensure that FDA has access to appropriate personnel or records in a timely manner. In addition, we would like to suggest that this information could be provided in the cover letter, rather than in a separate section of the report, as the responsible physician/company contact is usually the individual who signs the cover letter.

314.80(c)(3)(ii) Postmarketing periodic safety reports – Periodic Safety Update Reports (PSURs) (also 600.80(c)(3)(ii))

This section specifies the periodicity for submitting PSURs, based on the US approval date of the application.

Comment: PSURs often cover more than one application. We request that FDA clarify that periodicity of PSURs is based on the US approval date for the first application covered by the PSUR. In addition, due to the significant additional work that will be required to produce the US-only appendices if FDA retains these requirements in the final rule, we request that the timeframe for submission be changed from 60 days to 90 days after the data lock point.

Paragraph (A)(2) of this section describes the Introduction section of the PSUR, and indicates that any data duplication with other PSURs be identified in this section.

Comment: We request that FDA clarify whether this section should include information on co-suspect products that are included in other PSURs/TPSRs.

314.80(c)(3)(ii)(C) Actions taken for safety reasons (also 600.80(c)(3)(ii)(C))

Paragraph (3) of this section requires submission of copies of any communication with health care professionals, such as "Dear Health Care Professional" letters.

Comment: We question the need for submitting copies of these letters. The actions taken for safety reasons are described in the PSUR, and in most cases FDA would have received a copy of the correspondence at the time it was issued. In fact, FDA is often involved in drafting and approving such letters before they are issued by the company.

314.80(c)(3)(ii)(E) Worldwide patient exposure (also 600.80(c)(3)(ii)(E))

Paragraph (2) of this section indicates that data should be broken down by age and gender; and that pediatric use be further broken down by age group.

Comment: These data are rarely, if ever, reliably available on a country basis, much less on a worldwide basis. We request that the Agency provide clarification regarding the lengths to which they expect applicants to go to obtain this information. It should be noted that ICH guidelines state that age and gender breakdowns should be provided when possible **and relevant** (as opposed to the proposed rule, which states this **must** be provided if possible).

314.80(c)(3)(ii)(F) Individual case safety reports (also 600.80(c)(3)(ii)(F))

This section requires that cumulative data must be reported for serious and unlisted SADRs.

Comment: This proposed requirement represents an onerous burden for applicants. It is unlikely that cumulative reviews of serious and unlisted SADRs for all PSURs will provide useful information regarding patient safety. Cumulative data are not required by ICH guidelines, and we request that FDA delete this requirement.

314.80(c)(3)(ii)(G) Safety studies (also 600.80(c)(3)(ii)(G))

This section requires a discussion of all applicant-sponsored nonclincal, clinical and epidemiologic studies that were newly analyzed during the report period that contain important safety information.

Comment: The proposed regulation states that copies of full study reports should be appended to the PSUR if new safety issues are raised or confirmed by the study. This seems a bit excessive, and is not fully consistent with ICH guidelines, which require submission of full study reports only if deemed appropriate. An alternate suggestion would be to summarize those studies that identify new safety issues, and provide full study reports to the Agency on request.

314.80(c)(3)(ii)(I) Overall safety evaluation (also 600.80(c)(3)(ii)(I))

Paragraph (1)(ii) in this section requires that the applicant highlight any new information on increased reporting frequencies of listed SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence.

Comment: We request clarification regarding FDA's expectations for increased frequency analysis, since the Agency previously revoked similar regulations. Does FDA intend to provide guidance regarding methods of analysis and the quality of information necessary to determine whether there is a "meaningful change" in the data?

314.80(c)(3)(ii)(K) Appendices (also 600.80(c)(3)(ii)(K))

Comment: In general, these US-specific Appendices will require almost as much effort to produce as the PSUR itself; from a patient safety perspective, the value of this extra effort is minimal at best. We would urge FDA to adhere more closely to the internationally agreed ICH PSUR guidelines.

Paragraph (1) in this section requires copies of the Core Company Data Sheet (CCDS) in effect at the beginning of the report period, and that in effect at the end of the period.

Comment: This requirement is not consistent with ICH guidelines, which require appending only the CCDS in effect at the beginning of the report period for PSURs covering one year or less; or only the CCDS in effect at the end of the report period for 5-year PSURs. We request that FDA revise this paragraph to be consistent with ICH requirements.

Paragraph (3) in this section concerns summary tabulations of non-HCP reports, and requires that cumulative data be reported for serious and unlisted SADRs.

Comment: ICH guidelines do not require cumulative data to be included in summary tabulations; we request that FDA delete this requirement.

Paragraph (4) in this section requires summary tabulations for all spontaneous reports of listed and unlisted SADRs with unknown seriousness (outcome).

Comment: As noted above, we disagree with FDA's contention that manufacturers will have difficulty determining whether an SADR is serious or not, regardless of whether the outcome is known. Most manufacturers previously determined the events that are considered serious when the concept of "important medical events" was added to the definition of serious in 1997. Therefore, we question the need for a separate tabulation for SADRs with unknown seriousness (outcome).

Paragraph (5) describes summary tabulations of SADRs received by the applicant from class action lawsuits.

Comment: As noted in our comments on the definition of Spontaneous report above, we agree with FDA's proposals to exclude information derived from class action lawsuits from consideration as spontaneous reports. However, we think that the proposed rule is still too restrictive, and that the same considerations should be given to all information compiled or received in support of litigation actions, regardless of whether they are asserted in a class action, mass tort litigation, or an individual lawsuit. This would extend to inclusion of all SADRs received through litigation in the summary tabulations described in this paragraph.

Paragraph (6) requires an assessment of whether the frequency of lack of efficacy reports is greater than would be predicted by the premarketing clinical trials for the product

Comment: As noted in our comment above on 314.80(c)(3)(ii)(I)(1)(ii) regarding increased frequency analysis for expected events, we request clarification regarding FDA's expectations for increased frequency analysis, since the Agency previously revoked similar regulations. Does FDA intend to provide guidance regarding methods of analysis and the quality of information necessary to determine whether the frequency of reports of lack of efficacy is greater than expected from clinical trials data?

Paragraph (8) requires summary tabulations of actual and potential medication errors by various categories. For potential medication errors, the proposed rule requires the tabulation to provide the number of reports for specific errors.

Comment: It is not clear what "specific errors" the Agency has in mind, as by definition, no error actually occurs with a potential medication error, and there are no specific MedDRA terms to describe medication errors with this level of specificity. In fact, there is currently no MedDRA term to distinguish potential medication errors from actual medication errors. We request that the Agency provide clarification on these points.

Paragraph (10) of this section requires a list of the current address(es) where all safety reports and other safety-related records for the drug product are maintained.

Comment: Multinational pharmaceutical companies such as GSK maintain local Operating Companies (OCs) in most countries in the world. All of these OCs have responsibility for receiving local adverse event reports, following up on them, forwarding the information to the central safety department within specified timeframes, and maintaining records of these activities. As such, they all maintain "safety reports and other safety-related records". Surely FDA does not want the addresses of each of our OCs. We request that FDA clarify this requirement to specify the address(es) of the US site(s) where adverse event data are maintained and entered into the company's adverse event database.

Paragraph (11) requires the name, telephone number, fax number and e-mail address of the licensed physician responsible for the content and medical interpretation of the information contained in the PSUR.

Comment: We request that FDA clarify what is meant by "licensed" physician, and the rationale for requiring that a licensed physician review the report. It is entirely possible that an "unlicensed" physician or other health care professional with extensive pharmacovigilance experience is eminently more qualified to review and interpret the medical information contained in the report than a newly licensed physician with little pharmacovigilance experience. As noted above, for multinational companies, it is possible that the "responsible physician" is not located in the US. In these circumstances, it is more useful for the company to provide the name of a contact person in the US who can ensure that FDA has access to appropriate personnel or records in a timely manner. In addition, we would like to suggest that this information could be provided in the cover letter, rather than in a separate section of the report, as the responsible physician/company contact is usually the individual who signs the cover letter.

314.80(c)(3)(iii) Postmarketing periodic safety reports – Interim Periodic Safety Update Reports (IPSRs) (also 600.80(c)(3)(iii))

This section requires interim periodic reports to be submitted 7.5 and 12.5 years after US approval. The data lock point should be the month and day of the international birth date, and the report should cover the period between the last PSUR and the data lock point for the IPSR.

Comment: We question the need for an interim periodic report, the timing of which does not comply with internationally agreed standards. In addition, we have some difficulty reconciling the dates and report periods given in the proposed rule, and request clarification from FDA. For example, the proposed rule states that the data lock point (DLP) is the month and day of the international birth date (IBD), but then states that the DLP is 7.5 years after US approval. It can't be both. See the example below.

US approval date: September 10, 1998
International birth date: December 16, 1997
Data lock point(s): June 16 (for 6-month reports with a report period of December 17 to June 16); December 16 (for annual reports and 6-month reports with a report period of June 17 to December 16)

Year	reporting period	submission date
1	6/17/98 – 12/16/98	2/16/99
	12/17/98 – 6/16/99	8/16/99
2	6/17/99 – 12/16/99	2/16/00
	12/17/99 – 6/16/00	8/16/00
3	6/17/00 – 12/16/00*	2/16/01
	12/17/00 – 12/16/01	2/16/02
4	12/17/01 – 12/16/02	2/16/03
5	12/17/02 – 12/16/03	2/16/04
7.5	12/17/03 – 12/16/05?? Or 3/10/06?	2/16/06 or 5/10/06**
10	12/17/03 – 12/16/08***	2/16/09
12.5	12/17/08 – 12/16/10?? Or 3/10/11?	2/16/11 or 5/10/11**
15	12/17/08 – 12/16/13***	2/16/14

* Technically, this report should cover 1 year, but is only 6 months, to bring the annual report schedule in line with the IBD.
** 7.5 years after US approval would be March 10, 2006; report would be due May 10 (60 days later). Or would report be due on February 16, which is 60 days after the IBD-based DLP? Similar questions apply to the 12.5 year report.
*** Or should the 10 year PSUR cover only the period since the 7.5 year IPSR? Similar questions apply to the 15 year report.

314.80(c)(3)(iii)(C) Actions taken for safety reasons (also 600.80(c)(3)(iii)(C))

Paragraph (3) of this section requires submission of copies of any communication with health care professionals, such as "Dear Health Care Professional" letters.

Comment: We question the need for submitting copies of these letters. The actions taken for safety reasons are described in the IPSR, and in most cases FDA would have received a copy of the correspondence at the time it was issued. In fact, FDA is often involved in drafting and approving such letters before they are issued by the company.

314.80(c)(3)(iii)(E) Worldwide patient exposure (also 600.80(c)(3)(iii)(E))

Paragraph (2) of this section indicates that data should be broken down by age and gender; and that pediatric use be further broken down by age group.

Comment: These data are rarely, if ever, reliably available on a country basis, much less on a worldwide basis. We request that the Agency provide clarification regarding the lengths to which they expect applicants to go to obtain this information. It should be noted that ICH guidelines state that age and gender breakdowns should be provided when possible **and relevant** (as opposed to the proposed rule, which states this **must** be provided if possible).

314.80(c)(3)(iii)(F) Safety studies (also 600.80(c)(3)(iii)(F))

This section requires a discussion of all applicant-sponsored nonclincal, clinical and epidemiologic studies that were newly analyzed during the report period that contain important safety information.

Comment: The proposed regulation states that copies of full study reports should be appended to the PSUR if new safety issues are raised or confirmed by the study. This seems a bit excessive, and not fully consistent with ICH guidelines, which require submission of full study reports only if deemed appropriate. An alternate suggestion would be to summarize those studies that identify new safety issues, and provide full study reports to the Agency on request.

314.80(c)(3)(iii)(H) Overall safety evaluation (also 600.80(c)(3)(iii)(H))

Paragraph (1)(ii) in this section requires that the applicant highlight any new information on increased reporting frequencies of listed SADRs, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence.

Comment: As noted in previous comments on this subject, we request clarification regarding FDA's expectations for increased frequency analysis, since the Agency previously revoked similar regulations. Does FDA intend to provide guidance regarding methods of analysis and the quality of information necessary to determine whether there is a "meaningful change" in the data?

314.80(c)(3)(iii)(J) Appendices (also 600.80(c)(3)(iii)(J))

Comment: In general, these US-specific Appendices will require almost as much effort to produce as the IPSR itself; the value of this extra effort is minimal at best. We would urge FDA to adhere more closely to the internationally agreed ICH PSUR guidelines.

Paragraph (4) in this section requires a brief discussion of all spontaneous reports of listed and unlisted SADRs with unknown seriousness (outcome).

Comment: As noted above, we disagree with FDA's contention that manufacturers will have difficulty determining whether an SADR is serious or not, regardless of whether the outcome is known. Most manufacturers previously determined the events that are considered serious when the concept of "important medical events" was added to the definition of serious in 1997. Therefore, we question the need for a separate discussion of SADRs with unknown seriousness (outcome).

Paragraph (5) requires a brief discussion of SADRs received by the applicant from class action lawsuits.

Comment: As noted in our comments on the definition of Spontaneous report above, we agree with FDA's proposals to exclude information derived from class action lawsuits from consideration as spontaneous reports. However, we think that the proposed rule is still too restrictive, and that the same considerations should be given to all information compiled or received in support of litigation actions, regardless of whether they are asserted in a class action, mass tort litigation, or an individual lawsuit. This would extend to inclusion of all SADRs received through litigation in the summary described in this paragraph.

Paragraph (6) requires an assessment of whether the frequency of lack of efficacy reports is greater than would be predicted by the premarketing clinical trials for the product

Comment: As noted in our comment on 314.80(c)(3)(iii)(H)(1)(ii) regarding increased frequency analysis for expected events above, we request clarification regarding FDA's expectations for increased frequency analysis, since the Agency previously revoked similar regulations. Does FDA intend to provide guidance regarding methods of analysis and the quality of information necessary to determine whether the frequency of reports of lack of efficacy is greater than expected from clinical trials data?

Paragraph (10) of this section requires a list of the current address(es) where all safety reports and other safety-related records for the drug product are maintained.

Comment: Multinational pharmaceutical companies such as GSK maintain local Operating Companies (OCs) in most countries in the world. All of these OCs have responsibility for receiving local adverse event reports, following up on them, forwarding the information to the central safety department within specified timeframes, and maintaining records of these activities. As such, they all maintain "safety reports and other safety-related records". Surely FDA does not want the addresses of each of our OCs. We request that FDA clarify this requirement to specify the address(es) of the US site(s) where adverse event data are maintained and entered into the company's adverse event database.

Paragraph (11) requires the name, telephone number, fax number and e-mail address of the licensed physician responsible for the content and medical interpretation of the information contained in the TPSR.

Comment: We request that FDA clarify what is meant by "licensed" physician, and the rationale for requiring that a licensed physician review the report. It is entirely possible that an "unlicensed" physician or other health care professional with extensive pharmacovigilance experience is eminently more qualified to review and interpret the medical information contained in the report than a newly licensed physician with little pharmacovigilance experience. As previously noted, for multinational companies, it is possible that the "responsible physician" is not located in the US. In these circumstances, it is more useful for the company to provide the name of a contact person in the US who can ensure that FDA has access to appropriate personnel or records in a timely manner. In addition, we would like to suggest that this information could be provided in the cover letter, rather than in a separate section of the report, as the responsible physician/company contact is usually the individual who signs the cover letter.

314.80(c)(3)(iv) Postmarketing periodic safety reports – Pediatric use supplements (also 600.80(c)(3)(iv))

Comment: Although we assume that the schedule for submission of PSURs and IPSRs outlined in this section would supercede the usual schedule (e.g., an application that was on an annual reporting schedule would revert to 6-monthly reports when a pediatric use supplement was approved), we request that the Agency explicitly state these requirements in the final rule.

314.80(c)(3)(v) Postmarketing periodic safety reports – Semiannual submission of individual case safety reports (also 600.80(c)(3)(v))

Comment: We question the need for submission of these reports to FDA at all, since the information contained in them is tabulated, summarized and evaluated in the various periodic submissions. FDA proposes to eliminate submission of line listings in PSURs, since they plan on receiving the information in these semiannual submissions of individual case safety reports. However, since the line listings are an integral part of the standard ICH PSUR document, it is inevitable that FDA will receive the line listings anyway. Therefore, there is no reason for the Agency to also receive individual case safety reports. No other regulatory agency finds this necessary, and we question FDA's need for this level of information. Furthermore, this

duplicative process requires additional resource that could be better utilized on proactive pharmacovigilance activities.

However, if FDA will not reconsider the need for this information, we request that the final rules provide for electronic submission of the semiannual reports in ICH E2B format.

314.80(c)(4) Reporting format (also 600.80(c)(4))

Comment: As GSK is already submitting the vast majority of our expedited reports electronically, we are disappointed that the proposed rules focus entirely on paper submissions, and we request that FDA allow for electronic submission in ICH E2B format in the final rules.

We do strongly support the use of MedDRA as the standard, internationally recognized terminology for adverse event reporting. Although the proposed rule does not include a request for comments regarding the recent HHS announcement regarding use of SNOMED as the accepted terminology in the US, FDA has raised this issue and requested comments via a "Q and A" document posted on its web site. We are not familiar with SNOMED, and have not had the opportunity to review the latest version of this terminology, or to evaluate the ability to map it to MedDRA. However, we strongly urge FDA to resist any efforts to shift from MedDRA to SNOMED, particularly with regard to SADR reporting (both pre- and post-marketing). For all of the reasons cited by FDA in the proposed rule, it is critical that a single medical terminology be used internationally for coding safety reports. Many pharmaceutical companies, including GSK, have invested considerable financial, time, and personnel resources to understand, implement, and maintain MedDRA. Unilateral adoption of a different terminology in the US would create major issues and problems for both industry and the Agency, particularly with regard to the lack of harmonization with international regulatory requirements concerning terminology.

We question the requirement for a licensed physician to review all reports prior to submission to FDA. While we agree that expedited reports should not be prepared and submitted solely by clerical personnel or others with no health care training or experience, we believe that adequately trained and experienced scientists can adequately review and evaluate the content of such reports. We recommend that applicants provide the name, address, and other details for a US-based company contact who can ensure that FDA has access to the appropriate personnel and records, rather than information for a responsible physician. In addition, we question how the requested information (name, telephone number, fax and e-mail address) would be included in electronically submitted expedited reports.

314.80(e) Patient privacy (also 310.305(e) and 600.80(e))

Comment: We agree with the proposal that the names and addresses of individual patients should not be included in reports submitted to FDA. However, we disagree with including the name and address of the reporter if the reporter is also the patient (or a family member of the patient). This would compromise the privacy of the patient, even if FDA does not disclose he information. If we were unable to assure patients that we would not release their personal information, it is unlikely that they would be willing to provide any information regarding their adverse events, or provide permission to contact their HCP to us.

314.80(i) Disclaimer (also 310.305(h) and 600.80(j))

The current disclaimer could be strengthened to address the issues related to the limitations of spontaneous reports with regard to causality assessment, with the addition of the following wording after the existing statement: "Moreover, due to the inherent limitations in the data

provided in reports submitted under this section, they shall not be construed as reliable scientific evidence for purposes of assessing causation".

314.81 Other postmarketing reports

Comment: We support FDA's proposed revisions to the NDA Annual Report requirements to eliminate safety information that is included in TPSRs, PSURs, and IPSRs.

600.80 – Biological Products – Postmarketing reporting of suspected adverse reactions
Any comments specific to biologicals, not previously covered in the comments on part 314.80

Comment: It is our experience that CBER staff frequently requests additional information on vaccines reports that we received from other regulatory authorities. We have never, to our knowledge, succeeded in obtaining additional information from these agencies, and we suggest that FDA make an exception for these reports, and recognize that no additional information is available.

Comments on FDA's analysis of benefits and costs

A. Benefits

The benefits outlined in the proposed rule are benefits of an efficient, fully-realized pharmacovigilance/risk management program, but not necessarily the benefits of this proposed rule. As mentioned in our comments to specific items in the proposed rule, we do not agree that these proposed rules will result in "the more efficient use of industry and regulatory resources" (section V.C.) in many respects.

We question several assumptions made by the Agency regarding the benefits of the proposed rule. For example, section V.C.2. of the proposed rule states that "...despite the growing evidence that avoidable SADRs and serious SADRs are important public health problems, and widespread acknowledgment that monitoring SADRs provides public health benefits, FDA continues to receive reports of only a small percentage of the serious and avoidable SADRs that occur in health care facilities." However, the proposed rule fails to mention that the Agency does currently receive **all** domestic reports of SADRs received by sponsors/applicants, either as expedited or periodic reports. The problem of underreporting does not lie with drug and biologic manufacturers, but with health care providers. The proposed rule goes on to state that by improving safety reporting by drug and biologic manufacturers, the proposed regulations "...may serve to provide a national framework for improved data collection and analysis of safety reports from a variety of sources". This seems like a rather large leap of faith, since, as outlined in our comments on specific items of the proposed rule, several of the proposals (e.g., active query, considering all reported events as causally related unless they can be definitively ruled out, etc.) are likely to result in less reporting by health care providers, due to the "hassle factor" and liability concerns. We request that the Agency provide the rationale for this assumption.

It is also unclear how FDA came to the conclusion that increased regulation of SADR reporting by drug and biologic manufacturers will result in a 2% reduction in hospitalizations due to SADRs. It appears that FDA expects that "improved timeliness and analysis of SADR data would lead to a better understanding and a more rapid communication of the risks of SADRs", which in turn, would reduce the incidence of SADRs and resulting hospitalizations. However, as discussed in our comments to specific proposals, increasing industry's compliance burden without improving

safety surveillance, and increasing the number of expedited reports submitted to FDA, will more likely detract both industry and Agency resources away from early detection of SADRs.

We agree with the Agency's statement that international harmonization of safety reporting requirements will lead to greater efficiency and cost savings. However, as outlined in our comments to specific proposals, many of the proposed regulations are not harmonized with international initiatives, and therefore, will not lead to the cost savings or the public health benefit postulated by the Agency. For example, the proposed 30/45-day follow-up reports are not required by any other regulatory authority, and increase the compliance burden without providing any additional safety information. Similarly, although allowing submission of PSURs is intended as a cost-saving initiative, the addition of extensive US-only appendices to the PSUR creates significant additional workload and eliminates most of the efficiency and cost savings envisioned by the proposed rule.

B. Costs

We believe that FDA has significantly underestimated the additional costs of compliance with many aspects of the proposed rules, both in the number of hours required to carry out the activities, and in the number of additional reports that will be required. In addition, FDA has completely overlooked the costs to the health care system as a whole. For example, while FDA estimates that the active query requirement will add two hours per report to industry costs, it does not account for the time spent by the reporter answering the questions and providing copies of hospital discharge summaries, autopsy reports, etc. Given that FDA expects to receive several hundred thousand expedited SADR and medication error reports, all of which require active query, this is a significant burden to the health care system, and one that may actually result in fewer, poorer quality reports in the future.

With regard to estimates of industry time, we disagree with FDA's determination that PSURs take 40 hours to prepare. Current average time to prepare a PSUR is approximately two to four times this estimate, without taking into account time required to prepare the additional US-only appendices. This includes the time required to gather and analyze the information, write the report, generate and assemble the supporting materials, and review and approve the report internally.

Other requirements that appear to have been significantly underestimated include:

- The 8 hours to analyze and prepare a report concerning information sufficient to consider product administration changes.
- The one hour each for contractors and applicants to exchange safety data, which does not appear to take into account current practices among licensing partners, where most data are exchanged promptly (often electronically) following processing by the original recipient, not as raw data faxed between partners.
- The one hour/year to maintain records of written procedures for the surveillance, receipt, evaluation, and reporting of safety information to FDA. With regard to this item, it appears that FDA has assumed that each company will have only one procedure covering all aspects of pre- and post-marketing safety surveillance. This is not realistic, when one considers that the procedures need to cover every aspect of receipt, review, evaluation, follow-up, and reporting worldwide, not to mention the associated database conventions to assure consistent data entry worldwide. GSK has over 100 SOPs, working practices, and database conventions covering these activities and processes, and spends considerably more than an hour/year assuring that they continue to meet international regulatory and internal requirements.

We also believe that FDA has considerably underestimated the number of reports that will be generated under the new expedited reporting requirements proposed in these rules. Examples of these underestimates include the following:

- IND Safety Reports: In the period from July 1, 2002 through June 30, 2003, GSK submitted 143 IND Safety Reports under 21 CFR 312.32, considerably greater that the average of 10.6/respondent cited in the proposal. As described in our specific comments, with the proposed definition of "reasonable possibility" to mean a relationship cannot be ruled out, we anticipate a significant increase in the number of IND Safety Reports that will require submission (estimated at least 3-fold in one clinical program).
- The number of expedited (serious and unexpected) reports submitted under 21CFR 314.80 and 21CFR 600.80 are also significantly higher than the estimates given in the proposals. In the period cited above, GSK submitted 7262 spontaneous expedited reports under 314.80, and 752 expedited VAERS reports, compared to the estimates of 177.3 and 43.5, respectively, cited in the proposed rule. We acknowledge that as a large multinational company, GSK would be expected to submit more than the average number of expedited reports. However, the total numbers of such reports cited in Table 21 also seems low, when compared with the figures cited in CDER's 2002 "Report to the Nation" (128,869 expedited reports submitted by manufacturers).
- FDA estimates that the "always expedited" provisions outlined in 21 CFR 314.80 of the proposed rule would result in an annual increase of 15 reports per respondent (Table 21). Application of the proposed rule to just one GSK drug/expected event combination (seizures and bupropion) would result in an annual increase of approximately 200 expedited reports. This same provision would result in an annual increase of approximately 75 expedited reports for what is essentially lack of effect with another of our products (seizures in association with lamotrigine, an anti-epileptic product). Extrapolation of these data to the other 17 events proposed for "always expedited" status and across all drugs for which these events are expected will inevitably lead to significantly more than 15 expedited reports per respondent, with little, if any, increase in benefit to the public health.