Memorandum

2007 '03 SEP 30 A9:21

To: Food and Drug Administration
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CC:

From: PPD Medical Communications
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Date: 9/29/03

Re: Commentary on Proposed Changes in the "Tome"

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We have had the opportunity to review the proposed rule changes dated March 14, 2003, and we attended the teleconference on April 30, 2003. During review, several questions arose concerning the recommended changes. This memo is submitted to identify specific concerns relevant to Post-Marketing Pharmacovigilance activities.

First, we agree with the recommended changes concerning identifiable SADRs. Some companies have been known to use a variety of tactics to limit their reporting responsibilities, e.g. excluding events compatible with the patient's past medical history; expanding labeled events by using a variety of sections in the package insert; making discretionary or arbitrary assessments of event severity or specificity; and aligning verbatim terms to "synonymous" labeled events. The list can go on describing the various methods of classification utilized throughout the industry. We commend FDA efforts to define reportability using a more conservative (i.e. inclusive) approach, a philosophy to which we ascribe here at PPD. To provide additional guidance to industry, we suggest the following:

1. Specify exact section(s) of the package insert that should be considered when classifying an event as 'labeled', in that considerable variation now exists throughout the industry. For example, some approach "causal relationship unknown" as labeled events or consider a variety of package insert sections as labeled (e.g. class warning statements appearing in the warnings and precautions sections). Without further definition, companies will likely continue to broadly employ the package insert to limit their reporting responsibilities.

2. Better define specificity and severity. For example, many companies may not consider a reported blood pressure of 220/110 to justify greater specificity or severity than the labeled event terms, "hypertension" or "increased blood pressure." These cases may continue to be underreported, as companies are frequently reluctant to report events that may negatively affect product labeling. Assessment of specificity is a problem throughout the industry in that considerable discretion is given to the safety officer. Please define with more examples. The current regulations do not offer sufficient guidance to address ambiguous cases in a consistent manner.

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3. Lack of effect (**LOE**) presents a particularly difficult challenge. Certain companies restrict LOE reports to only those instances that clearly involve a potency concern and/or a potential GMP issue; many events therefore go unreported. For example, a patient subpopulation with a particular characteristic or underlying disease process may demonstrate relative resistance to the effects of a product, but since potency *per se* is not a stated concern, a report is not generated. The relationship may thus never be recognized. To address this shortcoming, terminology must be added to MedDRA to capture suboptimal drug response. For example: A critical care patient is treated with a pressor to raise mean arterial pressure, but the response provides only a modest rise to 50 mm Hg. The product is discontinued, and another product is used that effects a rise to 75 mm Hg, thus enabling adequate tissue and organ perfusion. Is LOE narrowly defined only as potency-related issues? Would this be considered a LOE? Does a report need to specifically state "LOE" before being considered reportable? The FDA needs to define LOE more precisely so all companies will be uniform in their use of the term. Furthermore, FDA needs to better define situations where a medication may produce suboptimal results. For regulatory purposes, is LOE expected or unexpected? MedDRA already contains codes such as "drug ineffective," "inappropriate drug response," "therapeutic drug response unexpected," and "drug ineffective for unapproved indication." Many companies associate these codes with LOE. **A specific code needs to be incorporated for all drug responses that are not adequate** (e.g. to sustain life, to eradicate bacterial or fungal infection, or to elevate blood pressure sufficiently to ensure adequate tissue perfusion). Such events need to be captured for accuracy of surveillance; to do so requires that FDA make a specific determination on standardized codes to adequately capture such events and offer proper guidance to industry via examples.

4. Literature report guidance enables too much variability in what constitutes a reported SADR. Many companies utilize a procedure wherein the author of the literature report must show direct attribution to the suspect medication. For example, a statement such as "twenty patients experienced symptom X post-operatively following use of the product" may not necessarily constitute direct attribution. Additional attribution would include substantiating comments such as, "The post-operative incidence of symptom X in those patients who received the product were increased nearly twofold relative to the control group." We suggest that the standard set by FDA for post-marketing spontaneous reports should also apply to literature events. Furthermore, the guideline should give consideration to the age of the product. For example, for newly-approved products, all serious and nonserious unexpected literature events would be reported, regardless of whether the author directly attributes the event to use of the product. For any product greater than 5 years old, FDA might require that only *serious* SADRs to be reported, regardless of author attribution. In addition, the concept could be extended to periodic safety reports such that within the first 5 years of new product approval, all literature reports would be submitted. Clearly, FDA needs to further define expectations for literature reporting; current regulations give companies too much discretion in identifying SADRs, thereby significantly limiting reportable events.

5. Many times SADR literature reports identify an "estimated number" of reported patients that experienced a particular event, in addition to the patients presented for discussion. For example, "an estimated additional 260 patients with symptom X were also seen at these institutions." This statement reflects additional reports that should be submitted to FDA. The narrative should include the verbatim of the additional reports (e.g. estimated additional 260 patients). Many companies rule out estimated numbers as not reportable based upon internal procedures. It is requested that guidance be provided on the reporting of estimated numbers.

6. "Active query" needs to be operationally defined. Active query provides the optimal approach when gathering information for an expedited report. Unfortunately, healthcare professionals are either 1) too busy to take time away from their patients to provide additional information, or

2) reluctant to provide additional information due to privacy concerns and liability. Notwithstanding the fact that HIPAA permits the transfer of clinical information relevant to product safety reporting obligations, many physicians will likely continue to refuse release of information, in that most are not yet well versed in the new patient privacy regulations. A few points to consider concerning the documentation of "active query" follow-up: Is a written summary that describes attempted follow-up efforts sufficient documentation? Concerns may arise on the adequacy of follow-up attempts, particularly for older multi-source products licensed to smaller companies. No proof can be provided that a company has pursued active follow-up sufficient to meet FDA regulations (*i.e.,* "your word against mine.") We suggest that FDA consider development of a standard form that directs the release of medical information related to an SADR from a healthcare professional to a pharmaceutical manufacturer without fear of liability. This page could readily be faxed to the healthcare professional with a cover letter that describes the initial reports and defines the rationale for the "active query" request. Additionally, this form might be utilized to request medical records. In the past, a consumer would sign a release form, and a copy was then forwarded to the physician/hospital with a cover letter requesting additional information on a specific event. An FDA-sanctioned form would increase direct query dialogue and obviate the need for additional individual mailings. At this late stage, two direct mailings might be implemented, thus exhausting all reasonable efforts to obtain additional information.

7. Enhanced documentation of medication errors is another positive move toward protecting the safety of the consumer. FDA needs to provide specific guidance by example on reportable medication errors. For example, a drug dosage is indicated at .25 mg/kg, but the healthcare professional inadvertently injects 2.5 mg/kg. The chronological order of events, treatment, and outcomes are documented, but the reporter provides no acknowledgment of medication error. We expect that many medication errors will thus go unreported, as fear of potential litigation will negatively impact disclosure of such events. Allowing companies to use discretion will undoubtedly limit these reports in that many companies will fail to submit unless the phrase "medication error" is actually reported verbatim in the narrative. Companies need to be forced to report as medication errors *any* inadvertent events that occur outside the labeled dosing and administration information.

8. In reference to literature reports, FDA should consider making definitive recommendations on the frequency with which literature searches should be performed. Specific guidance on the choice of databases to be searched would also be extremely beneficial. Does FDA concur with the recommendations of the CIOMS V Working Group on these issues?

9. Off-label medication use is an additional source of SADRs. Many companies have internal guidance that may limit submission as an expedited report because an event is labeled -- even though the indication (or patient population) is not listed in the PI. Reportability for such events need to be qualified via definition and example. If a product is used off-label, should SADRs be classified as unexpected, even though the reported event appears in the PI as an adverse reaction?

Although the changes recommended by the FDA will clearly identify additional SADRs, the processing of these identified reports will significantly impact the economics of each product such that corporations may look to pass through the additional expense to the consumer. Thus, the end result will include an increased burdened to our healthcare system. A universal system must be incorporated that utilizes a single form to collect additional information.

Active query will assist in the processing of serious reports, but will not enable complete collection of information relative to a reported event. Most active queries will involve follow-up with the initial

reporter (e.g. pharmacist, physician, nurse, physician assistant). Most reporters are unfamiliar with information required by the regulatory agencies. Although the FDA has made the MedWatch 3500 readily available on the internet, most often reporters are uneducated as to what information needs to be submitted. Additionally, their time is limited, further compromising the possibility of acquiring initial or follow-up information. **A form should be developed and approved by FDA that will be distributed to all hospitals and pharmacies with their stock orders, and to physicians' offices with the distribution of samples**. All healthcare professionals will be asked to **complete the form prior to contacting the manufacturer. This will enable more information to be collected during the initial contact, either by phone or fax.** Also, this form can be readily available as a pdf on the FDA website. Many times in the past, I can recall talking to a healthcare professional in an effort to gain additional information concerning an event. Little information was obtained since the reporter was unaware of the information I wished to obtain or did not expect me to call. A simple form consisting of a front and back identifying the relevant information in an orderly fashion will allow greater collection while controlling the overall cost of completing an investigation. Additionally, **a form supplemented by a letter from FDA describing HIPAA and the process as mandatory would likely educate healthcare professionals and reduce misunderstandings surrounding the new guidelines and the release of medical information.** A copy of this letter will accompany each serious SADR form. Thus, not only will additional information be gathered on first contact, physicians will become more comfortable with the release of medical information through HIPAA knowledge. These events will clearly provide benefits to both FDA and the industry. The FDA will gain more information concerning serious SADRs, and industry can optimize this process to effectively utilize resources while maintaining a product cost relative to the present pricing. We have attached a sample form below that can be readily incorporated into the drug distribution network.

FDA SUSPECTED ADVERSE EVENT REPORT FORM (SADR)

Manufacturer Name:
Phone #(123) 456-7890 Fax: (123) 567-8901

Date of Report:_____ Product:_____ Variant(e.g. 10 mg):_____ Lot #:_____ Exp. Date:_____

Reporter Information:

Name of Reporter:_____ Telephone #:_____ Fax #:_____

Address (include City, state, & zip code)_____

Patient Information:

Patient Initials:_____ Address (city, state & zip cope)_____ Gender: [ ]male [ ] female

Date of birth:_____ Age:_____ Weight:_____(lbs) Height:____ (ft)_____(in) Ethnic Origin:_____

Patient involved in Clinical Trial: ☐No ☐Yes Subject #:_____ Study #:_____ Protocol #:_____

Concomitant Medical Products (include Rx, OTC, Dietary, Herbal and recreational drugs. Please note dose, frequency, duration and indication for use):

_____

_____

_____

_____

_____

_____

_____

Allergies (e.g. drug, food): (Note specific allergen and reaction): _____

_____

_____

Medical History:(historical and current; family history; include smoking, alcohol and caffeine description of use)

_____

_____

_____

_____

_____

_____

_____

_____

_____

Suspect Drug Information:

Indication for use:_____ **Previous Exposure:** [ ]Yes[ ]No [ ]Unk **Tolerance:** [ ]Yes[ ]No[ ] Unk

Date of first use:_____ **Date Discontinued:**_____ **Duration of use:**_____ **Dose:**_____ **Frequency:**_____

Hospital Admission: [ ] Yes [ ] No [ ] Unk Admit Date:_____ Discharge Date:_____

ED Visit: [ ] Yes [ ] No [ ] Unk Length of ED visit (hours): _____

Treatment by HCP and Drug information (product and dosage):_____

_____

_____

_____

_____

_____

_____

Outcome: (Comment on all reported events including diagnosis, signs and symptoms; discuss current symptoms and any changes)

_____

_____

_____

_____

_____

Suspected Adverse Drug Reaction (SADR) Details:

All information relevant to the event (e.g. blood tests, EKG, CT, MRI, X-ray, copy of discharge summary):
Date of Onset of Adverse Event: _____
Narrative of Adverse Event:

The sample report form, combined with a letter from FDA that mandates the collection of data, will undoubtedly lead to more efficient use of active query, while simultaneously providing potential to limit additional expense to industry that would most likely be passed to the consumer. Furthermore, a universal form would enable all pharmaceutical manufacturers to routinely gather comparable and relevant information.

FDA's discussion of PSURs in the Tome provides no acknowledgement of ICH E2C's concept of the international birthdate (IBD) as a means for harmonizing and synchronizing periodic reports to multiple regulatory agencies around the world. Instead, it appears that FDA continues to establish timelines for periodic reports based solely on U.S. approval dates. It would be extremely helpful to global companies if FDA could adopt a more inclusive and flexible approach to report scheduling based on the IBD.

Additional items need to be addressed to provide parallel guidelines with the EU and accepted PSUR conventions. Volume 9 of "*Rules Governing Medicinal Products in the European Union*" highlights specific reporting intervals and inclusions to these reports. Regarding PSUR submission, volume 9 states, "PSURs are normally required to be prepared at 6-month intervals for the first two years following the medicinal products authorization in the EU, annually for 2 years at the first renewal, and then 5-yearly at renewal thereafter." Furthermore, "Ordinarily, all dosage forms and formulations, as well as indications for a given pharmacologically active substance for medicinal products authorized to one MAH may be covered in one PSUR. Within the single PSUR, separate presentations of data for different dosage forms, indications or populations (e.g children vs adults) may be appropriate."

Relative to periodic reports, it is of utmost concern that FDA's proposed PSUR reporting schedule outlined in "the Tome" does not parallel EU guidance or recommendations of CIOMS V Working Group. Though pharmaceutical manufacturers will not likely admit to "passing through" the cost of production of frequent PSURs with customized appendices, the variability of national requirements will undoubtedly incur additional expenses that will likely be paid with pharmaceutical price increases.

A review of Periodic Safety Reports for products approved before January 1, 1998 would require a report to be submitted every 5 years after U.S. application approval. Periodic safety reports for products approved after January 1, 1998 would require report submission semi-annually for the first 2 years, annually for the next 3 years, and every 5 years thereafter. Additionally noted is the guidance to provide reports at 7.5 years and 12.5 years. In contrast to the recommended U.S. reporting schedule, Volume 9 of "*Rules Governing Medicinal Products in the European Union*" describe PSUR reporting as semi-annually for the first 2 years after medicinal product authorization in the EU, annually for 2 years at the first renewal, and every 5 years thereafter -- which coincide with CIOMS V guidance. The complexity arises with older products not approved through centralized or mutual recognition procedures. Without cooperation of the various regulatory bodies to enable alignment of the international birth date globally, companies will continue to be burdened by the inability to synchronize reporting schedules. Additionally, U.S. reports at 7.5 and 12.5 years are not aligned with the overall reporting schedule set forth by the EU, and their production will incur expenses that may not be justified. For example, a product that has been on the market prior to 1998 has undoubtedly demonstrated a safety profile that enabled its continued availability. Most, if not all, safety concerns would have presented themselves previously. Although medications approved before January 1, 1998 have proven their safety profile, companies continue their review of the safety reports as received. Excluding certain drug categories (e.g. antibiotics), minimal additional knowledge or safety signal information will be generated for such products by providing additional reports at 7.5 and 12.5 years. These reports represent an additional burden that cannot be justified; this burden will be expensed in some form related to the product. Hypothetically, additional expenses could influence a company to withdraw an NDA in instances where the burden for continued product availability exceeds the reduced margin provided by the older product. While it could be argued that new medications released in the past 5 years provide additional benefits not seen with older marketed products, removal of older products with proven safety profiles may lead to significant increases in health costs. A consumer forced to change his medication after 7 to 10 years due to discontinuation of the product may lead to noncompliance, higher prescription costs for newer alternative products, adverse events not previously experienced by the consumer, and even potential hospitalization. Are the additional reports generated at the 7.5 and 12.5 year intervals valuable enough

to warrant possible discontinuation of availability or increase in events related to medication changes? As we try to provide the most comprehensive compilation of safety information to protect the public, one must realize that such actions can ultimately lead to potential consumer harm.

A review of the expected content of the PSUR as outlined by the EU and CIOMS V include the following sections/discussions:

- Introduction
- World-wide marketing authorization (MA)
- Regulatory or MA actions for safety reasons
- Changes to reference safety information
- Patient exposure
- Presentation of individual case histories
- Cases presented as line listings
- Presentation of line listings
- Summary tabulations
- MA analysis of individual case histories
- Studies
- Newly analyzed studies
- Targeted new safety studies
- Published studies
- Efficacy related information
- Late-breaking information
- Overall safety evaluation
- Conclusion

The "Tome" provides guidance to U.S. manufacturers for additional information to be included in appendices to the PSUR, despite the fact that EU has no such requirement. Supplemental information requested by FDA includes:

- Summary tabulations to include reports from poison control centers and epidemiological data bases.
- Discussion (compared to a line listing) of nonclinical, clinical and epidemiological studies concerning important safety information.
- Company core data sheet based upon next reporting period (EU based upon start of reporting period)
- Consumer reports including serious SADRs, nonserious SADRs, cumulative non-healthcare professional data for serious unlisted and discussion of impact on overall safety Summary table of spontaneous listed and unlisted reports with unknown outcome and discussion
- Class action lawsuits summary table of serious and nonserious, and listed and unlisted cases with discussion
- Lack of efficacy reports with assessment as compared to clinical trials and addressed associated to ADRs
- Medication error reports with summary tabulation of all domestic reports including actual medication error for serious, nonserious, no ADRs and potential medication errors with discussion of overall safety impact.
- Resistance to antimicrobial drug products including in vitro susceptibility relationship of change to clinical outcome, therapeutic failure possibly due to resistance, and discussions upon revision to U.S. labeling.
- U.S. Patient exposure information to include estimate of patients, average dose, length of treatment, or bulk sales with an explanation/justification of patient days or prescriptions detailing the method used to estimate.
- Location of safety records including addresses.
- Contact physician including name, phone, fax number and email of licensed physician and medical interpretation.

As previously mentioned during the discussion of reporting schedules, these additional appendices may greatly influence a company's decision to continue manufacture of older products. To prevent overburden and ease of compliance, the FDA should work toward a guidance that better harmonizes with CIOMS V and the EU.

A review of the requested appendiceal information provides insight for discussion:

- Clinical studies as highlighted in the "Tome" could be *misinterpreted* during review as complete account of the information may not be readily available to provide an educated summary. Thus mistakes could jeopardize the consumer's safety. Information should initially be reported to FDA, and any follow-up by FDA should be reported back to the company.
- To align with CIOMS V and EU pharmaceutical companies should be directed to use the company core data sheet that was ***actively referenced at the beginning*** of the reporting period. Utilizing a core data sheet that has been updated during a reporting period will force review of all previous reports up to the date changes occurred in the core data sheet. This review will incur added burden not only with individual case review, but also in editorial review of the line listings.
- Although we agree with the reporting of non-healthcare, unconfirmed and unlisted reports, incomplete information will influence the accuracy of complete review and should be limited to:
    1. The frequency as related to potential safety signals.
    2. Reporting unconfirmed reports in the first 5 years of availability. Long-term collection of unconfirmed reports may not be warranted if the product has a proven safety profile. Certain exceptions may occur, e.g. a product with an associated serious event that warrants ongoing liver function tests or antibiotics that may develop a pattern of resistance should be guided to continue unconfirmed reports *as related to the specific safety profile in question*. For example, changes in liver function tests would continue to be monitored, but only reported as a frequency increase or expedited report. Similarly, antibiotic reporting would be based upon a documented increased resistance pattern.
- Inclusion of class action lawsuits as requested by FDA will provide little to no additional benefit. As we are all well aware, upon public broadcast of a potential safety issue by the news media, attorneys tend to take advantage of the situation to solicit reports of harm from clients willing to "sign on the dotted line." CIOMS V identifies these reports as "solicited," and under present FDA guidance, only *serious and unexpected* reports are to be submitted. Furthermore, many lawsuits identify events unrelated to the specific safety issue, but continue to be captured in a safety database only to be readily discounted upon receipt of medical records from the attorney, usually 6 to 12 months after initial awareness. In summary, this questionable information will increase 'noise' in the safety database and substantially confound the generation of potential signals. Companies should be expected only to comment on serious unexpected cases confirmed by medical records, and this commentary should be captured in the section of the PSUR relevant to that review.
- Lack of efficacy (LOE) reports originating from review of clinical trials provides little or no relevant safety information, as clinical trials occur in an artificial environment that controls every aspect of the patient/ subject interaction (e.g.medical history, concomitant medications including OTCs, dosing schedule, and at times, ethnicity. In the real world, additional uncontrolled variables greatly influence LOE reports. Discussions should thus be based solely upon reports obtained during post-market safety surveillance.
- While we agree with the surveillance and capture of medication error reports, the presentation should be part of the existing line listings with a discussion of the overall safety impact provided during the overall safety evaluation. Additionally, while the line listing should include all reports classified as serious, the commentary might indicate a numeric value for reports identified as nonserious. Furthermore, the commentary should discuss the significance of nonserious events, while presenting potential plans of action related to the total medication errors reported (e.g. label changes, HCP education, consumer education, or continued monthly review of data to determine further action).
- Resistance to antimicrobial drug products -- including *in vitro* susceptibility and therapeutic failure -- should be included in the overall line listings and not in separate appendices. This, too, should be addressed as described in the surveillance of Medication Errors.
- U.S. patient exposure information (including estimates of patient populations, average dose, duration of treatment, or bulk sales) should be part of the patient exposure section of the PSUR. Upon presentation the

global use should be provided first to enable comparison of these numbers to the values available in the U.S. It is here that SADRs may show greater relevancy to the U.S and require additional review to ascertain reasons for the observed increase (e.g. prescribing errors, lack of consumer/ HCP education).

- Location of safety records -- including addresses and physician contact information -- should parallel guidelines set forth by the European Medicines Evaluation Agency (EMEA) in volume 9 (page 58) of the rules governing medicinal products and CIOMS V. We see no advantage for reporting this information in a separate appendix when the information is identified on page 2 as name and contact details of the qualified person responsible for pharmacovigilance. This page may also include the data lock point of the next report, the marketing authorization holder's name and address, list of serial numbers, and distribution list.

In summary, PPD welcomes FDA proposed changes as presented in the 'Tome,' but requests additional constructive guidance in specific problematic areas that remain ambiguous. Once implemented, it is clear that the revised regulations will offer a substantial positive impact on public safety. Additionally, further aggressive actions to collect data (i.e. the previously-described universal SADR form) may reduce the financial impact of implementation while simultaneously promoting efficiency in the collection of data.