September 15, 2003

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

RE: Docket No. 2000N-1484: Comments on Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule – Published March 14, 2003

Teva Pharmaceutical Industries Ltd. and its subsidiaries appreciate the opportunity to comment on the proposed safety reporting regulations. We have assessed the potential impact of these new rules from the prospective of a large, global manufacturer of both Innovative and Generic drug products. As one of the largest global Generic companies, we would specifically like to express our pleasure that the current, unnecessary, duplicative ANDA Periodic Safety Reporting by the vast generic markets has been recognized and directly addressed for revision in accordance with the ICH Guidelines. We agree that our resources and efforts should be centered on more crucial areas of safety surveillance and signal detection. Our comments are offered in support of the primary goal of preserving patient safety, followed by a desire for harmonization and modernization.

FDA Form 3500A: Our initial comment concerns the MedWatch form that was not addressed in the proposed new rule. We strongly urge the FDA to fully update the MedWATCH Form 3500A to incorporate and accommodate previous and the current changes proposed in this new rule.

III.A.1 – Definitions - SADR: FDA states that many of the proposed amendments are intended to "harmonize" with international standards. In support of that effort, we request the FDA abandon its intent to adopt the proposed new definition and use of the term Suspected Adverse Drug Reaction (SADR), as this will only result in disharmony, not harmony of <u>global</u> pre- and postmarketing reporting requirements.

The greatest impact of this new terminology will be on IND clinical trial reporting. FDA's current premarketing reporting requirements under 21CFR 312 require that <u>all</u> Adverse Events/Experiences (AE) associated with the use of the drug, "whether or not considered drug related," must be documented and reported for IND clinical trials. There is some confusion because the discussion of the implementation of the proposed new definition of an "SADR" only specifically referenced expedited reporting under Section 312.32. This seemingly suggests intent

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to eliminate the current requirement to document all AEs during a clinical trial, (i.e., even those where drug relationship has been reasonably ruled out). AE reporting requirements in the Annual IND Safety Report were not addressed in the PSUR discussion (see additional comment under III.E).

If we are correct in our assumption, we believe this would result in the opposite intent of the FDA to more effectively capture vague, but potentially important safety signals prior to NDA approval. Occasionally, it is those least suspected, presumed "not related" clinical and laboratory events at isolated centers that ultimately provide a suggested signal when ultimately combined and analyzed across multiple clinical centers. The interpretation of the new definition, as is, suggests such documentation would no longer be required if an investigator believes he or she can rule out drug relationship. Although doubtful, is this an accurate interpretation of the FDA's proposal?

We also believe the FDA is inadvertently restricting investigators, who presumably know the patient best, the ability to use their professional medical judgment. We disagree that the literal translation of "reasonable" possibility that the product caused the response equates directly to "drug relationship can not be equivocally ruled out". The proposed translation of the phrase will essentially be an endeavor to turn a theoretical positive into an absolute negative. Frequently, the only way to attempt to truly rule out possible drug relationship with some certainty would be by instituting closely monitored drug dechallenge and rechallenge. That procedure is not always definitive or feasible, and is frequently risky to patients, impractical or unethical in many clinical instances.

If an event can not be attributed to a concurrent condition, medication or other treatments with 100% assurance, we believe the proposed new SADR definition would indeed result in a flood of irrelevant 15-Day IND Safety Reports. Disclaimers or not, in our current litigious environment physicians will continue their increasingly conservative use of causality assessments of unassessable, unlikely, and remote, as opposed to a more definitive yes or no assessment, thus making all unexpected/unlableled events imminently reportable as 15-Day Expedited Reports.

This new practice will certainly put a strain on FDA resources and dilute the time FDA Medical reviewers should be spending assessing more "meaningful", truly suspect reports. This new practice will also put an added strain on clinical investigators and members of IRBs and Ethics Committees who will be receiving a new flood of confusing IND Safety Reports. The non-medical IRB reviewers may have difficulty determining the true potential safety impact of all the generally meaningless remote and unlikely reports submitted for their review. Without a doubt, some studies of complicated, progressive disease states could require the submission of several IND Safety Reports per week. This will be a great expense across the industry in both the manpower and supplies necessary to complete the global notification process.

We fully agree with FDA's suggestion (and the ICH Guideline) that protocols clearly include a list and clear instructions for handling study "safety endpoints" that meet the definition of the protocol efficacy endpoints and/or known consequences of the disease under study that would not be reported as SADRs. As this is infrequently implemented by many, less experienced companies, we further suggest that FDA make this a much more prominent statement in the final rule.

Additionally, we urge the FDA to take this excellent opportunity to include expanded, updated explanations in the definition or discussion section of the new rule to address the true meaning of "outcome of hospitalization" in relationship to the intended regulatory reporting criteria definition of a Serious AE. A number of old and currently conflicting FDA Guidance documents remain in

circulation that have not been updated and consolidated. This would be an opportunity to restate the medically logical exceptions for hospitalizations that were preplanned for essentially unchanged, pre-existing conditions (e.g., knee replacement for long-standing, pre-existing, degenerative arthritis, battery replacements for functioning pacemakers, etc.), or for routine diagnostic testing, planned study procedures, or the expected periodic treatment of specified disease efficacy endpoints, etc. that do not at all meet the intended definition of an SAE. More importantly, these events do not even fulfill the actual definition of an "AE". However, it is an extremely common misconception by many global investigators and companies conducting clinical studies to just react to the term "hospitalization" while attempting to fulfill reporting requirements.

We agree that adverse events that may extend these types of hospitalizations would then meet the regulatory definition of an SAE. Under the new proposal, would this need to be an SADR that causes an extended hospitalization, or any adverse event?

III.A.6 - Active Query: We agree that early initiatives to attempt to obtain postmarketing clarifications through an active verbal query process is beneficial, but we acknowledge that experience has frequently shown us that the chances of making direct verbal contact with a busy pharmacist, office nurse or physician on the first few attempts are slim. Even when contact is made, the necessary patient information is not readily assessable to the healthcare professional at that time, or they quickly refuse to release any information without signed permission from the patient, based on their misinterpretation of the HIPPA confidentiality standards. Continued delay is generally encountered. We urge the FDA to proactively remind healthcare providers that HIPPA confidentiality rules do not apply to the mandatory regulatory reporting covered by these proposed regulations.

III.A.7 –
Solicited Reports: The era of ever-increasing "solicited" reports is here to stay with the growing influx of marketing initiated "Patient Support" programs. These growing marketing-supported programs and their potential 100s of 1000s of consumer AE reports per year are overwhelming to a Pharmacovigilance Department if reporting is not processed realistically. We request the FDA further clarify the definition of solicited and the expected reporting requirements to fully describe the following: 1) that inbound calls made directly to the program by a consumer currently enrolled in the applicant's-sponsored patient support program, pregnancy registry, etc. would also be classified as a solicited report (i.e. the consumer is enrolled in a program for that product and ***otherwise would never have made an inbound call to voice a complaint or mention an AE during an assistance inquiry conversation),*** 2) do **all** serious solicited reports need to be entered into the drug safety database, or only the expedited serious – unexpected, always expedited and medication error reports? (as previously defined for postmarketing studies), 3) likewise, would only "expedited" solicited reports need to be reported and tabulated by body system in an Annual Report, or are you stating all "serious", solicited reports must be tabulated? It is currently not clear, and 4) do any non-serious, "solicited" consumer reports need to be documented in the applicant's database and reported to the FDA in an annual report? (These would be the 100s of 1000s of reports noted in the 1st sentence.). Such reports are currently only omitted following requests for waivers.

- **Patient Pregnancy/Safety Registries** - We would like to take this opportunity to offer a suggestion for consideration regarding FDA-mandated registries (e.g. isotretinoin, clozapine, ribraviron, etc.). The need for such safety and outcome tracking registries is on the rise. It has generally been the responsibility of the innovator to establish and maintain the initial registry. As more generics arrive on the market, the FDA has

diligently requested the generic applicants to establish their own registries. This is a duplicative effort that establishes the clear risk of duplicate patient entries and loss to follow-up as patients are prescribed substitute generics after using the innovative product. We propose a possible proactive solution for this would be for one "product" registry to be used in all cases, preferably maintained by a third-party contractor. As new generics enter the market, the ensuing manufacturers would be obligated to share in the cost of maintaining the applicable "key ingredient" registry. This will not only avoid possible confusion and duplication of effort, but will also help reach the targeted statistical enrollments at a faster, combined rate. It also would provide one source of consistent data analysis for the applicants and FDA and other regulatory authorities to review over time.

- **Postmarketing Studies:** We request the FDA further clarify the new reporting requirements for "solicited" postmarketing study reports, both for those studies sponsored by the applicant itself, and for reports received from competitor-sponsored studies. We currently interpret this regulation to mean only the continued reporting of expedited events (as assessed by the "applicant") will be required by the FDA and other regulatory agencies for postmarketing study reports. We question if the receiving "applicant" is still permitted to assess the possible relationship to the study drug (as is currently contained in the ICH E2A Guideline on Expedited Reporting) when determining if expedited submission for such reports is required?

- **Lawsuits:** We appreciate FDA's acknowledgment that class action lawsuits serve little purpose in the drug surveillance arena. These inflated reports are generally duplicative in the least, and tend to be received by every known manufacturer and distributor of the drug product. We would request that FDA clearly indicate that "applicants" need not process and submit AE reports from legal summons in which the specific "applicant's" named product is not clearly identified as having been actually prescribed to the consumer. In prior years, we were obligated to process 1000s of Fen-Phen complaints in which our specific phentermine product was clearly not prescribed or consumed. It's overwhelming enough to be forced to hire additional employees to handle the influx of these "legal" complaints, but such manpower efforts should only be required for processing reports for which the "applicant's" approved product was actually consumed and suspect. We would suggest that such reports also be classified as "solicited" reports to provide clarification for the global reporting process. Does FDA plan to provide a universal definition of "class action" to assist our non-US colleagues?

III.A.8 – Medication Errors: We request the FDA further clarify this proposed rule and explain the rationale for requiring all domestic medication errors and "potential" errors to be submitted as 15-day expedited reports. We would suggest that a greater benefit from this new approach to reduce such errors based on label confusion and similar proprietary names would only be gained from tracking those errors performed in the prescribing and pharmacy dispensing functions. We fail to see the intended benefit to consumer safety by reporting actual and near miss hospital and nursing home incidents involving an overburdened nurse who had properly prepared a patient's medication, but in haste "almost" administered it to the wrong patient. This would be a process error better handled and addressed internally and by JCAH accreditation reviews. An additional question is the number of suspect drugs to be identified in actual and potential medication errors?

III.D – Postmarketing Expedited Reports - 30 & 45-Day Follow-up Periods: We suggest the submission timelines for reporting "follow-up" efforts for reports with incomplete datasets or unexpected SADRs with unknown outcomes be unified and consistent at 30 days. The addition of a mandated 45-day period will only add confusion to the global reporting process. It is doubtful that 45 days would provide anymore success than a 30-day inquiry period. Standardization of reporting timelines will encourage much more consistency and adherence across the industry.

III.D.4 – Always Expedited Reports: We question the value of expediting clearly "expected" events contained in the proposed "Always Expedited" list. We can understand and support the intent and potential patient safety value of the FDA reviewing such unexpected events in an expedited fashion, but fail to see the added value of dedicating valuable resources to processing and reviewing clearly labeled, unchanged expected events. In the clinical study setting, this will again infer unintended alarm and place an undue burden on the investigators and members of IRBs and Ethics Committees. We would propose the language be amended to only require expedited submission of "expected", always reported events when there is a suspicion that the incidence may have significantly, and unexplainably, increased over a more frequent, specified time period, (e.g. quarterly instead of annually in the premarketing and immediate postmarketing phases). This would mandate more intensive periodic review of critical clinical safety data and provide a more efficient, uniform mechanism for monitoring and promoting patient safety surveillance.

III.D.7 – Supporting Documentation: We express reservation over the proposed requirement to submit available death certificates, autopsy reports and hospital discharge summaries for all domestic and "foreign" expedited reports within 3 months. This not only goes against the intent of electronic submissions, but the time and cost of translation of foreign reports will also be extensive. Reporters will certainly charge for these potentially extensive activities, or local affiliates of the applicant will be forced to absorb the time and expense associated with internal translations. Also, in this instance, the agency has proposed yet another new time period for reporting requirements. We suggest this follow-up time period be unified with the 30 days proposed for submission of other missing data, and then within 15 days of actual data receipt.

III.D.8 – Scientific Literature: In the current era of increasing mergers and global marketing of multiple approved generic equivalents of an innovator's product, we request the FDA be clearer about literature reporting responsibilities. We believe expedited reports based on scientific literature reports should only be submitted by applicants for serious, unexpected events that are clearly identified as being associated with the use of the "applicant's" specific approved product, not just the similar, generic key ingredient potentially marketed globally and in the US by multiple global applicants. If this is not clarified, over reporting of the same events and confusion will certainly continue. This problem will only increase, and there is currently much confusion across the industry regarding actual reporting obligations and regulatory expectations, particularly by global generic manufacturers who may currently market over 500 registered products.

III.E – Postmarketing Periodic Safety Reporting:

- **Contact Person (Licensed Physician):** The proposal states applicants will be required to have a licensed MD ultimately responsible for the review and assessment of an applicant's safety data. Clarification is requested as to where and if all physicians need to be licensed. Is this licensed anywhere in the United States, the specific state in which they are assessing the safety data, any foreign country if currently working in the United

States, or just the specific country where the overall responsible Corporate Medical Director of Drug Safety is located?

- **Semiannual Submission of Individual Case Study Reports for TPSRs:** This proposed requirement contradicts FDAs introductory statement that it acknowledges that the safety profile of drug products approved in the USA prior to January 1, 1998, especially those marketed even longer globally, is well established and documented. If FDA's intent is to now receive and evaluate foreign reports of serious, "expected" events, why agree to harmonize with the ICH every 5 year reporting period, and then increase the reporting frequency from the current annual status to an increased semiannual time table for older products? We believe such listings should be included in the TPSRs. Why would the intent of coordinating with the ICH standard of reporting time tables and contents now be cumbersomed unnecessarily to an even more frequent reporting requirement than is currently in place in the USA? Additionally, the FDA has not indicated how long this new reporting requirement would be required – forever? We believe such submissions in the TPSRs, or on an annual basis at the most, would be more than sufficient and would certainly ease the multiple reporting time schedules being proposed, especially for generic companies with many 100s of products. . We urge the FDA to reconsider this periodic reporting proposal.

- **Annual IND Safety Reports:** The handling of this dual reporting requirement once an NDA has been approved and clinical studies continue under the IND is not clear with the adoption of the PSUR format. International PSURs require the inclusion of clinical study data. The anniversary approval dates of the IND and NDA in the USA are always different. Will safety sections in the Annual IND Update Report no longer be required as previously outlined, once an NDA has been granted? If clinical safety data reporting is switched to the PSUR format following NDA approval, what will be the data cutoff date – the IND effective date, or the anniversary of the NDA or IBD date? Additional clarification for IND reporting would be appreciated.

- **OTC Switch Products:** These increasing product lines were not addressed in the proposed regulations. Annual Safety Reports are currently not required for OTC products. If a formal prescription only product has been given approval to switch to OTC status, will continued submission of annual TPSRs or PSURs still be required? If so, will all AE reports for the OTC line now need to be documented and submitted to the FDA if they do not meet the currently required "15-Day expedited" reporting requirements for other OTCs? We suggest these switch products be addressed in the new regulations and PSUR and non-expedited reporting requirements be discontinued once a product has been granted OTC status.

Teva recognizes that some inadequate reporting practices of a minority of applicants and investigators in the past have placed patients in danger, thus fueling some alarm globally and within the agency. We suggest that rather than departing from ICH agreements and eliciting some over reporting from all applicants in an effort to prevent future peril, FDA might consider the following: 1) only requiring increased Periodic and expedited reporting of global serious events in those instances where a company has had a documented poor performance in the past,

2) mandating expanded reporting for clinical trials once a product or study design has been identified as posing a potential increased or unforeseen risk to participants, 3) concurrently amending the IND/IRB Regulations and Guidelines to incorporate a mandate of more frequent review of overall safety data, including a requirement for an "independent" Safety Monitoring Committee, under predefined circumstances, and 4) re-evaluating the impact of some of the overlapping safety reporting obligations being imposed on the globally expanding generic markets.

Thank you for considering our comments.

Sincerely,

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