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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®

October 14, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Safety Reporting Requirements for Human Drug
and Biological Products

Dear Sir or Madam:

The Food and Drug Administration (FDA) proposed rule on Safety Reporting Requirements for Human Drug and Biological Products, which was published in the *Federal Register* on March 14, 2003, has been reviewed in the context of safety reporting of medicines available directly to the consumer. The Consumer Healthcare Products Association (CHPA)¹ submits these comments on certain provisions of the proposed rule as they would affect over-the-counter (OTC) drug products approved under New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs).

Executive Summary

CHPA welcomes the underlying rationale for the proposed rule, including the move by the FDA towards global harmonization of safety reporting requirements in alignment with the European Union and Japan. This alignment process will save considerable valuable resources for both industry and the governmental agencies in the processing of safety reports and allow more effective pharmacovigilance and continued protection of public health.

CHPA member companies have reviewed the provisions in the proposed rule primarily in terms of the postmarketing safety reporting requirements for consumer healthcare products. OTC drugs have long marketing histories and are known to have favorable safety profiles, and so unexpected serious adverse events are unlikely with their use. While clinical trials are undertaken for OTC drug products, this activity is considerably less than that required for initial approval of a prescription medicine and would result in a relatively lower frequency of serious adverse events.

In this context, the content of the proposed rule, specifically Sections II through III.I, was reviewed with focus on the implications for post-marketing safety reporting for OTC drug products subject to NDA or ANDA requirements, and comments are given below.

¹ CHPA, founded in 1881, is the national association representing manufacturers and distributors of over-the-counter (OTC) drug products and dietary supplements. CHPA members account for over 90 percent of OTC drugs marketed in the United States.

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While the rationale behind FDA's proposals is clear, the practical implications may be problematic and in some cases extraordinarily resource-intensive; their contribution to continued public health in the context of OTC drug pharmacovigilance is debatable. To balance the real need for harmonized safety reporting and pro-active pharmacovigilance with not unlimited resource, one option is to adopt a targeted risk management approach to consumer healthcare products with perceived safety issues. This would, however, require further dialogue between the industry and the agency. It would incorporate elements of FDA's proposals but on a selective, mutually-agreed product-specific basis.

Introduction

On March 14th, 2003, the FDA published proposals to amend the safety reporting requirements for human drug and biological products (21 CFR Parts 310, 312 et al.: Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule).

These proposals have been reviewed by CHPA member companies from the consumer healthcare viewpoint. Because products marketed under the OTC drug monographs are not subject to reporting of post-marketing adverse events, these comments on post-marketing surveillance will be confined to OTC products approved under an NDA or ANDA and for which adverse event reporting is mandatory. Comments pertaining to clinical studies for OTC drug products will be confined to those circumstances for which they are subject to an IND.

Background

CHPA member companies market a diverse range of products for consumer use, including cosmetics and dietary supplements, as well as monograph and NDA OTC drug products. Some of the same companies also market prescription drugs. Safety reporting for this diverse range of products is covered by different regulations specific to the class of product. Reporting requirements for an OTC product approved under an NDA or ANDA are identical to those for a prescription product similarly approved.

Adverse event reporting is not required for OTC drug products subject to monographs. FDA has determined these products have well established active ingredients that are "generally recognized as safe." Similarly, dietary supplements are also not the subject of required safety reporting procedures. Some healthcare companies (including many CHPA member companies) do, however, voluntarily submit expedited reports to the FDA for serious adverse events on products in these classifications, although they are not required.

In addition to being marketed in the United States, this diverse range of consumer products is also available in many other countries where they are subject to regulations that may require expedited and/or periodic safety reporting.

Comments on FDA Proposals

These comments address the FDA proposals as they would apply to reporting requirements for OTC drug products, which do not appear to have been taken into account by the agency. CHPA supports the underlying rationale for harmonization of safety reporting requirements among the United States, Europe, and Japan. With a common reporting process, including global acceptability of periodic safety update reports (PSURs) and adoption of MedDRA common terminology, duplication of effort is minimized for both industry and agencies. This increased efficiency, with individual agencies having common datasets available for review, should further allow resources to be increasingly focused on proactive pharmacovigilance and the continued protection of public health.

These comments are made in response to the description and discussion of the proposed ruling as detailed under "Supplementary Information: Table of Contents" of the proposal.

Comment on III.A.1. Suspected Adverse Drug Reaction (SADR)

- The proposed definition of a suspected adverse drug reaction (SADR) is too board and not consistent with ICH E2A Guideline or EU Clinical Trials Directive on ADR reporting. These documents include the concept that there are facts, evidence, or arguments to support a causal relationship (e.g., a temporal relationship, a pharmacologically predictable event, de-challenge and re-challenge data). The proposed rule defines "reasonable possibility" as synonymous with "the relationship cannot be ruled out." If this is incorporated into the final rule, investigators participating in premarketing and postmarketing clinical trials who perform causality assessments for all serious adverse events, as well as the sponsors of those trials, will have no choice but to interpret "the relationship cannot be ruled out" as synonymous with "nothing can ever be completely ruled out." This would eliminate clinical judgment in assessment of causality by both investigator and sponsor, resulting in a substantial increase in the volume of expedited reports and increased workload for both the agency and the sponsor. The definition needs to allow investigators and sponsors to consider events to be possibly related to concurrent illnesses or concomitant use of other medication.
- The proposed definition of SADR will compromise the integrity of clinical studies without a corresponding improvement in reducing subject risk. The proposed definition of a SADR will create a significant negative impact on the integrity of studies, given the need to break the blind on an increased number of serious, unexpected, related events. The impact of breaking the blind for all medications would have a negative impact on the efficiency of clinical trials (a larger sample size would be needed to produce the required statistical power) without a corresponding improvement in reducing risk to study subjects. Indeed, it would be difficult to estimate an appropriate sample size at the outset of a Phase III clinical trial, when the "losses" due to breaking the randomization code would be unknown. Many studies have independent data-review boards to monitor the safety of the study as it progresses; this approach allows an informed, independent and additional safety assessment without comprising study integrity.

- The proposed definition of SADR will create spurious adverse events not related to the drug. Pre-study definition of events of interest, agreement of disease- or treatment-related events and aggregate analysis of safety data on study completion are considered effective safety management approaches. Under the definitions in the proposed regulation, many spurious events would be considered at least possibly related to drug therapy. CHPA recommends that any amendments in the reporting regulations support and encourage professional judgment to ensure reporting of the most important events related to a drug's safety.

For these reasons, it is recommended that the FDA-revised definition for SADR not be incorporated into the final rule and that the current ICH E2A Guideline definition, supported by CIOMS and present in the European Clinical Trial directive, be adopted.

Comment on III.A.6. Active Query

- FDA should adopt a targeted risk management approach rather than an active query approach to adverse event reporting consistent with the ICH stature that "emphasis should be placed on the quality of the reports and not on its source." The approach would be to focus on the process of information gathering in those areas of particular interest for specific products.

Individual companies have dissimilar structures and processes for receiving and handling interactions with consumers. Consumers are nearly always the initial reporter of an SADR, and they may or may not have consulted their healthcare provider (HCP), and also may not consent to the company contacting their HCP to obtain confirmation and follow-up information of the report. When the consumer's HCP is contacted, he or she may not recall the particular event in question because a consumer healthcare product rather than a prescription drug being suspect. Furthermore, a substantial proportion of SADR reports from consumer products are received by letter or e-mail from consumers, adding complexity to the use of active query as defined by "direct verbal contact."

It is the practice in many companies with NDA products for a customer response group to receive all calls from consumers (including those contacts which are potential SADRs). Call centers are staffed by HCPs and/or trained technical staff who determine whether a SADR is being reported and whether the report is serious or not. If nonserious, a minimum data set for the SADR is obtained and no active follow-up initiated. These nonserious reports are entered onto a specific database and used for trending analysis on a periodic basis. For the majority of these nonserious SADRs the consumers did not consult their HCP; hence active follow-up with the HCP would be inappropriate.

If a consumer reports a SADR that is serious, or potentially serious in nature, permission to contact the consumer's HCP is requested. Some of the CHPA member companies conduct active query or dialogue by an HCP that is focused on obtaining as much information as possible from the consumer on the adverse event(s) reported, with a detailed history taken. Consumers' medical knowledge is, however, variable, and that can limit the "active query" approach, specifically findings from physical examination and diagnostic and laboratory results.

The types of procedures for following up serious SADR on consumer products involves sending one or two letters to the identified HCP requesting further information, subject to the consumer's consent. Active follow-up, which potentially offers further, if not complete information from the consumer's HCP, is considered impractical in terms of the majority of consumer adverse event reports. For successful active query, the consumer's HCP may have to retrieve and review medical records, then spend time in discussion with the company's safety staff.

Active query, by an HCP of the company (not necessarily a physician), for follow-up information for serious SADR may be appropriate for consumer healthcare products if the patient/consumer's HCP is fully aware of the purpose behind the inquiry and there are specific areas of interest regarding adverse events reported. However, to impose this approach over all SADR (serious or nonserious) for all consumer healthcare products is of questionable value. In this context, ICH E2D ver 3.8 notes that "emphasis should be placed on the quality of the report and not on its source." Finally, when active query is deemed necessary by the company, the company should be allowed to determine the type of active query based on the reporter and type of adverse event and determine the appropriately trained healthcare professionals to contact the reporters. As previously indicated, written follow-up can in many situations, provide more detailed and accurate information.

We recommend following up via return letter as a viable and reasonable alternative to active query for SADR received from consumers. This form of follow-up allows consumers to identify the most accurate information and, combined with the consumer returning the product to request a refund of the purchase price, provides a reliable method of obtaining follow-up information. Another alternative to active query that should be considered in specific situations is the use of targeted questions for specific SADR reported. If a potential safety signal is identified, then pre-defined targeted questions can be used by both the customer call center and the safety staff when in contact with either the consumer or the HCP. This approach allows focused information gathering on areas of particular safety interest for specific products.

Comment on II.B.3.b. Unexpected SADR with unknown outcome (i.e., serious or nonserious).

- The term "SADR with unknown outcome" is ambiguous and needs to be clarified. In section II.B.3.b, FDA uses "unknown outcome" to mean a determination cannot be made whether a SADR is serious or nonserious, but "outcome" is usually interpreted as the outcome for the event, i.e., whether the event resolved, resolved with sequelae, or remains ongoing. The term "serious" or "nonserious" further defines the event itself (e.g., myocardial infarction is serious as it is medically significant, fatal/life-threatening, and/or involves hospitalization) rather than the outcome (e.g., recovered). The term "unknown outcome" could be amended to "unknown seriousness" to clarify this ambiguity.

Comment on II.B.3.c. Always expedited reports

- MedDRA terms need to be reviewed for their applicability to medical conditions listed as “always expedited reports.”

It is common safety reporting practice to tick the term “other” in the MedWatch form and a statement “medically significant” entered if the event is of serious medical concern. In the context of NDA products available to consumers without a prescription, the safety threshold is of necessity more sensitive than that for a medicine prescribed by a physician. The medical gravity of example SADR listed in this section would invariably result in an expedited report being submitted due to its seriousness and association with a nonprescription product.

FDA is proposing to require expedited reports for certain SADR although they do not meet the criteria for a serious or unexpected SADR or do not lead to a serious outcome. FDA should have the MedDRA terms clarified for each of the medical conditions listed as requiring an “always expedited report.” Because of the complexity of MedDRA, an international consensus process (such as CIOMS or ICH, in conjunction with MSSO should develop and maintain the MedDRA groupings that describe these conditions. Use of included MedDRA term groupings will be especially important for those medical conditions that are often reported in vague terms or are otherwise poorly described in spontaneous reports. These groupings of included MedDRA terms must be reviewed by FDA (preferably in cooperation with an international consensus body) with each new release of MedDRA and updated, as appropriate, to maintain the intended relevance. The list of conditions that trigger “always expedited reports” should be negotiated on a product-by-product basis as part of an overall approach to risk management.

Comment on III.A.8 and III.D.5. Medication Error

- Only those medication errors with a “serious” adverse event should be submitted in expedited reports for OTC NDA and ANDA products.

FDA proposes the submission of domestic reports of actual and potential medication errors to the agency within 15 calendar days. Expedited reporting of any “potential” medication error in the absence of a SADR is of limited value for gaining information on a product’s safety. Medication errors might be more appropriately classified into different subcategories, which might include such potentially relevant medical issues as name confusion, dose-formulation dispensing errors, and lack of product-label clarity.

Consumer healthcare products generally have a low adverse event risk, leading to a high benefit-to-risk ratio. The consumer product may have a “switch” heritage and/or many years of exposure and the importance and consequences of medication error are usually less than that for a recently introduced prescription product. The proposed rule makes a distinction between medication error and deliberate overdose of a drug, with the agency stating that it does not believe the latter is “preventable.” While this approach is logical, consumer reports

of medication error and deliberate overdose may, in practice, be unclear as to how the specific event should be classified. Reporting requirements regarding both potential and actual medication errors would require a 15-day expedited report for all cases of medication errors under the proposed rule. In the consumer healthcare arena, many reported cases of medication errors either result in no adverse events or events that are nonserious and self-limiting. Most events that are classified as medication errors involve accidental ingestion of a product resulting in no adverse event.

The increase in expedited reports of this nature would inundate FDA. A better alternative would be submission of only those medication errors that result in an adverse event meeting the criteria for "serious" or resulting in the consumer/patient seeking medical attention.

Comment on III.A.9. Company Core Data Sheet, Company Core Safety Information (CCSI), Listed SADR, Unlisted SADR, and Unexpected SADR

- CHPA supports the adoption of company core data sheets and company core safety information (CCSI). Their relationship with country labeling and the determination of expected/labeled are accepted.

Comment on III.A.10. Data Lock Point and International Birth Date

- Adoption of U.S. approval of application dates will increase duplicative efforts.

Adoption of the International Birth Date is accepted, but the date of U.S. approval of the application determining the frequency and time of submission to the FDA is questioned, as having an international and a U.S. birth date would give duplication and not synchronisation of periodic reporting. Such duplication diverts safety resource from proactive safety activities.

Comment on III.C.5. Determination of Outcome, Minimum Data Set, and Full Data Set

- The FDA use of the term "outcome" is confusing and needs clarification.

FDA uses "outcome" to mean whether a SADR is serious or nonserious is confusing and needs to be better defined. "Outcome" is usually interpreted as the outcome for the event, i.e., whether the event resolved, resolved with sequelae, or remains ongoing. (See comment above on II.B.3.b.)

The term "outcome" should be clarified to reflect that, if a determination of seriousness cannot be made for an unexpected SADR, then a report is submitted within 45 calendar days (see Table 6 of proposals).

- Additional expedited 45-day reports should only be required if additional information is obtained.

As previously commented (Section III.A.6), there's low likelihood of gaining additional information in follow-up on a consumer-reported SADR. The minimal gains of information about drug safety that could be expected from the requirements in the proposed rule for active query and follow-up would not justify the needed resources to conform. We therefore urge FDA to require additional expedited reports only if additional information is obtained.

Comments on III.D.1.; III.D.4.; and III.D.6. Serious and Unexpected SADRs; Always Expedited Reports; and Follow-up Reports

- There should be no requirement for follow-up reports unless additional information has been received.

Comment on III.D.8. Scientific Literature

- Clarification is needed about reporting information from *in vitro* and animal studies.

Current regulations require expedited reporting of information found in scientific literature from case reports or as a result of a formal clinical trial. FDA has proposed to also include epidemiologic studies, *in vitro* studies, and animal studies. Clarification is requested as how to report information from the latter two sources, as one of the four data elements for an adverse event report, i.e., an identifiable patient, would not be present.

Comment on III.E. Postmarketing Periodic Safety Reporting

- FDA should adopt the ICH format for periodic reporting and not request additional or dissimilar data, as this will only create additional work for the Agency and industry, with no public health benefit.

The proposed rule as it relates to PSURs does not allow for true international harmonization (for example, nonserious listed SADRs are proposed to be included in this Rule while they are not specified in ICH E2C). Additionally, the appendices are extensive and would contain a subset of the information already included in the core document.

The proposed rule indicates that the PSUR would allow applicants to submit a single core document for products that have an approved application (i.e., NDA, ANDA, BLA). Clarification is requested on how to handle products with multiple formulations or multiple active ingredient combinations, some of which are only approved outside the United States.

The proposed IPSR reporting cycle of 7.5 and 12.5 years (III.E.3), which is not in accordance with ICH E2C, should not be required; the ICH-specified 5- and 10-year post-approval reports should provide an adequate safety profile. If the 7.5- and 12.5-year cycle reports are retained, these reports should be required only if there has been: a new indication/dosage form approved; use of the product in a new population, or a prescription status change where the safety profile of the drug is expected to be significantly different.

Comment on III.E.1.h. and III.F.4. Contact Person

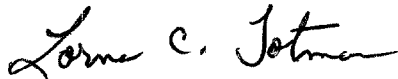
- FDA should not require a licensed physician to be responsible for the content of post-marketing safety (PMS) reports and PSURs/TPSRs for OTC drugs.

The agency should allow manufacturers to have HCPs in addition to or instead of licensed physicians reviewing such reports. Manufacturers should be responsible for the medical content and be able to determine the appropriate healthcare professional qualifications for preparing the reports. Highly trained HCPs with pharmacovigilance experience are better able to assess PMS reports than physicians with no experience.

CHPA welcomes the underlying rationale for the proposed rule, including the move by the FDA towards global harmonization of safety reporting requirements in alignment with the European Union and Japan. This alignment process will save considerable valuable resources for both industry and the governmental agencies in the processing of safety reports and allow more effective pharmacovigilance, e.g., individual agencies having common datasets available for review, should further all resources to be increasingly focused on proactive pharmacovigilance and the continued protection of public health.

CHPA supports many aspects of the proposed rule but recommends that FDA consider the impact of many of the proposed rule's specific provisions on all products marketed under an NDA or ANDA, including nonprescription OTC drugs. These comments are directed toward specific parts of the proposed rule that should be reconsidered in light of their implications for safety reporting for OTC drugs, which have long marketing histories and are known to have favorable safety profiles.

Respectfully submitted,



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Advancing Quality Healthcare
Through Over-the-Counter Medicines
and Nutritional Supplements

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5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Safety Reporting Requirements for Human Drug and Biological Products

Dear Sir or Madam:

Enclosed are three copies (plus one original) of comments submitted by the Consumer Healthcare Products Association in response to Docket No. 00N-1484, Safety Reporting Requirements for Human Drug and Biological Products. This notice was published in the *Federal Register* on March 14, 2003.

To confirm receipt, please date stamp the enclosed receipt and return it to my office in the self-addressed, stamped envelope I have included.

Thank you for your assistance.

Lorna C. Totman, Ph.D.
Senior Director of Scientific Affairs & Toxicology