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March 12, 2007

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

**RE: Docket 2006N-0525
Supplements and Other Changes to an Approved Application**

Dear Sir or Madam:

On December 26, 2006, The United States Food and Drug Administration (USFDA) announced a public meeting [FR 72(3):574-576] to solicit comments regarding revisions to its regulations governing chemistry, manufacturing, and controls (CMC) supplements and other changes to approved marketing applications for human drugs. FDA's evaluation includes incorporation into the revised rule of risk-based approaches that rely on available knowledge, manufacturing process understanding and quality system to provide an enhanced risk-based approach to the CMC regulatory process.

At the outset, we would like to express our continued support for the 21 century quality initiative and the leadership provided by the Center for Drug evaluation and research. As The Food and Drug Administration's Strategic Action Plan "Protecting and Advancing America's Health: Responding to new challenges and opportunities" issued in August of 2003 states: "Efficient risk management requires using the best scientific data, developing quality standards, and using efficient systems and practices that provide clear and consistent decisions and communications for the American public and regulated industry....."

The plan further identifies FDA's enforcement strategy focusing on the most efficient way to get the most compliance with the law. The principles in the agency's science-based enforcement strategy include

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1. **Clarity:** The FDA must develop and use clear and consistent guidance and communication with regulated firms to promote voluntary compliance with the law. Many businesses are willing to comply with science-based regulations, but in areas as complex as food and medical product manufacturing with technologies that are constantly changing, the FDA has found that assuring a company's understanding of regulatory requirements can substantially improve compliance.
2. **Science:** The FDA must remain vigilant to ensure that its practices reflect and allow for the latest innovations in production, inspection, and enforcement techniques. The FDA's regulations should be no more burdensome than necessary, and should encourage valuable innovation in foods and medical products.
3. **Leveraging:** As the FDA's mission has become broader and more complex, it is increasingly beneficial to work with partners, including other federal and state agencies as well as private oversight organizations, to bring more resources and a more coordinated, powerful approach to enforcement.
4. **Deterrence:** In conjunction with the use of clear, science-based regulatory approaches, the FDA must also take effective action against those who deliberately engage in criminal activities or disregard the FDA's important regulations to promote public safety, including the use of punishments based on the most effective tools available, including enforcement actions and criminal prosecutions that will stand up in court.

CHPA is supportive of FDA's activities to attain these objectives.

As the viewpoints expressed at the February 7th public meeting confirmed, this is an important undertaking, because of the scope and potential impact on the regulated community. Achieving this objective will serve as a milestone for the 21st century quality initiative. To ensure the success of this effort, maintaining proper communication would be helpful. We appreciate the leading remarks of the offices of compliance and Pharmaceutical science at the meeting as well as remarks by CDER deputy director Douglas C. Throckmorton, MD on the need to reexamine the regulatory approach to drug product quality:

1. "Need to ensure that pharmaceutical quality is sustained as technology evolves

2. Need to ensure regulation does not impede new developments while still assuring product quality
3. Need for greater efficiency given workload and available FDA/industry resources”

These statements provide clarity, and focus our efforts in dedicating available resources to find innovative and effective ways to meet the set objectives.

Our written comments will focus on three areas. First, summary comments on the questions for discussion, raised in the December 26th Federal Register notice (sec. A). Second, general feedback on changes to approved applications (sec. B). Third, specific suggestions for revisions to 21 CFR 314.70 and/or associated FDA guidance documents under the current approach (sec. C).

To implement these points, we would request that a phased and gradual approach which enhances the integrity of the current system while concurrently developing the new quality by design approach be considered as the most appropriate means of achieving the goals of FDA and the regulated community. We look forward to working with FDA on this important matter.

A. Response to FDA Questions

1. *Is it valuable for the agency to move toward a more risk-based and quality systems oriented strategy for regulating post-approval CMC changes outside of the formal application review process? What are the advantages and/or disadvantages?*

Yes, CHPA supports the agency’s move toward a risk-based and quality systems oriented strategy for regulating post-approval CMC changes outside of the formal application review process. Advantages are reduced burden for both industry and FDA. No apparent disadvantages are foreseen, although an increased resource investment may be required up-front in order to achieve long-term benefits.

Quality system provides the organizational frame work to manage change. A suitable and effective quality system allows organizations to realistically deal with external factors and variable inputs. This is an efficient, agile and Flexible customer and product focused approach. It is compatible with a life cycle approach to assuring the quality of medicines.

While risk management is applied within the quality system, it can support fact and data based decisions by helping to assess the effects of the

A. Response to FDA Questions (continued)

change on the identity, strength, quality, purity, and potency of medicines as well as the categories of change.

2. *Would revising § 314.70 as described in this notice provide the same level of protection to the public as the current regulatory scheme with respect to ensuring the safety and efficacy of human drugs? What inspectional approaches might the agency consider to evaluate manufacturing changes while ensuring public safety?*

We contemplate the revisions to this rule to facilitate industry's approach to continual improvement.

Revisions may provide sufficient detail to describe public health protection goals and not impede implementation by being overly detailed. Revising § 314.70 as described in this notice would provide the same level of protection to the public as the current regulatory scheme with respect to ensuring the safety and efficacy of human drugs, since any reduced oversight would apply to situations where there is a high assurance of quality subject to risk assessment in addition to providing the incentive to bring enhancements that could result in improvements to quality. Regarding FDA's need to evaluate manufacturing changes while ensuring public safety, we would encourage the Agency to apply risk-based principles to systems-oriented inspections.

We'd like to reserve further comment on the issue of inspectional approaches to subsequent opportunities.

3. *Would revising § 314.70 as described in this notice change the regulatory burden on the pharmaceutical industry? If so, how would the burden change?*

The notice outlines the possibility of revising § 314.70 to reflect downgraded reporting categories (e.g. CBE instead of prior approval, annual report instead of CBE, etc.). If the downgraded reporting category still requires a filing, then this action would only allow changes to be implemented more quickly, without significantly reducing the overall regulatory submission burden.

The possibility of revising § 314.70 to add a new reporting category of manufacturing changes is mentioned that would not require notification to FDA. This action would offer great potential for industry to be relieved of

A. Response to FDA Questions (continued)

regulatory filing burden--but only if changes currently considered "reportable" are reclassified as "non-reportable". In other words, regulatory relief will not be realized if the Agency simply revised § 314.70 to list changes that the industry already understands to be "non-reportable" (e.g. the Agency's January 2001 Questions and Answers document for FDA's NDA/ANDA Changes Guidance indicates that CDER need not be notified about relocation of site for GMP support paperwork operations and/or excipient manufacturing, FR 69(68):18731 reflects that notification is not required for movement of production operations between buildings at the same manufacturing site, etc.).

Finally, CHPA requests that FDA considers "non-reportable" changes in the context of § 314.70(a)(1), which currently states that an applicant is expected to "...notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application...". Clarification is requested on whether removing inconsequential specificity from an application might be an acceptable approach that can be employed to reduce reporting burden.

4. *Would reducing the prescriptiveness of § 314.70 provide manufacturers with greater regulatory flexibility? Would it encourage manufacturers to adopt CMC-related risk management strategies? Would there be disadvantages?*

CHPA does not support generalizing § 314.70 since varying interpretations can contribute to inconsistency and perhaps departure from the intent of the rule. Criteria can be specific to avoid such problems. Therefore, FDA may aim to define change reporting requirements as clearly as feasible. The revision may also provide clarity and consistency of concepts by the application of risk assessment (e.g. under Paragraph 314.70 (b) the term "...Substantial potential....." may best be clarified by the "probability of accordance", a measure already well established in risk management.) Reduction of complexity and clear interpretation of the FD&C act along with a process and defined expectations in line with the act represent a less prescriptive approach.

B. General Feedback

CHPA suggests that the primary considerations in a risk-based regulatory scheme may be *indication* and *dosage form*. In general, OTC drug products have a lower level of risk as compared to prescription (Rx) drug products due to the nature of OTC indications and the relative simplicity of most OTC dosage forms. This contrast is demonstrated by the differences in the route of administration for example, between an injectable chemotherapeutic agent and a dandruff shampoo. However, CHPA recognizes that risk assessment may also be performed, and Rx or OTC status alone may be insufficient to determine risk classifications.

1. Secondary considerations in a risk-based regulatory scheme may also include:
 - Prior use profile (length of time in the market, extent of patient exposure, etc.)
 - Safety profile (frequency/severity of adverse events, etc.)
 - Company compliance profile (cGMP status, etc.)
 - Product quality profile (history of meeting in-process, release & stability criteria, etc.)
2. CHPA notes that for OTC drug products, the existing monograph system provides a framework for the regulation of certain drugs outside of a formal application review process. In cases where our collective experience has consistently shown overall risk to be low, CHPA suggests a new system may be warranted that would allow an OTC drug to transition from an (A) NDA to OTC monograph status through a more streamlined application process vs. the current process.
3. CHPA believes that approaches to reducing burden are consistent with Quality by Design in product and process development which may be based on scientific and risk management principles, affording organizations the ability to manage changes that impact product quality through change control systems.
4. CHPA suggests that additional opportunities might exist to provide regulatory relief to firms on a case-by-case basis. For example, upon meeting a set of pre-defined criteria (e.g. low-risk indication and dosage form, extensive prior use of product, cGMP compliance history, quality profile), firms could be approved to manage most changes through quality system change control and documentation systems.

B. General Feedback (continued)

5. Currently, reporting categories (prior approval, CBE, Annual Report) are based on the potential (substantial, moderate, or minimal) for a change to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness. CHPA agrees that it is appropriate to classify major changes in a prior approval category based on their **potential** adverse impact. However, CHPA invites the Agency to consider whether potential moderate changes (requiring CBE filings) can be classified as minimal changes (Annual Reportable) or non-reportable, if data exist to support there is no **actual** adverse impact on the product. A shared understanding of risk management can contribute significantly and move us beyond the current elementary considerations.
6. CHPA supports Agency efforts to downgrade changes from prior-approval or CBE **to annual reportable**. However, efforts to reduce regulatory burden should not focus solely on making more changes annual reportable. An equal emphasis may be placed on downgrading changes **from annual reportable** to non-reportable.
7. CHPA understands that changes to § 314.70 may be a time-consuming and long-term effort. As an interim step, we encourage the Agency to consider providing regulatory relief in the short term by revising associated guidance documents (SUPAC Guidance documents, NDA/ANDA Changes Guidance and the associated January 2001 Questions and Answers document, November 2004 Guidance on the Use of Enforcement Discretion for Compendia Changes, etc.).

C. Specific Suggestions for Revisions to 314.70 and/or Associated Guidance

1. Section VI.C.1.c. of FDA's NDA/ANDA Changes Guidance currently specifies a CBE30 requirement for all primary packaging site changes. CHPA agrees that the current CBE30 requirement may be appropriate in some cases (e.g. changing the primary packaging site for a sterile parenteral product). However, for certain types of low risk dosage forms (e.g. solid oral dosage forms, non-sterile solutions, etc.), industry experience has shown that primary packaging site changes are unlikely to adversely affect product quality, when appropriate qualification is performed (e.g. packaging line trials, confirmation of satisfactory cGMP status, etc.). Therefore, it is our opinion that FDA allows a reduced reporting category for "low-risk" primary packaging site changes, and considers a CBE30 level of regulatory control only for

C. Specific Suggestions for Revisions to 314.70 and/or Associated Guidance (continued)

primary packaging site changes that are scientifically and technically determined to be higher risk.

Similarly, Section VI.C.1.d. of FDA's April 2004 "Changes Guidance" currently specifies a CBE30 requirement for testing site changes. For any type of drug product, a testing site change is not expected to have a direct adverse impact, provided companion requirements are satisfactory (e.g. method transfer, confirmation of satisfactory cGMP status, etc.). Therefore, we suggest that the category for testing site changes be downgraded.

2. Section VI of FDA's NDA/ANDA Changes Guidance indicates that a prior approval supplement may or may not be required for a manufacturing site change, depending on whether the new site has a satisfactory cGMP inspection for the type of operation being moved. Attachment B to FDA's NDA/ANDA Changes Guidance explains how "type of operation" is represented by a "profile class code" that is specific to a dosage form, a type of drug substance, or a function performed by the site.

CHPA notes that the profile class code system described in the NDA/ANDA Changes Guidance appears to be inconsistent with FDA initiatives to regulate products using systems-based inspection and a science-based management approach. For example, if one follows the principles in Attachment B, a prior approval supplement would be needed to move primary packaging of immediate release tablets (TCM) to a site that only has a satisfactory cGMP inspection for extended-release tablets (TTR). This requirement does not seem logical since one can expect a site that is capable of packaging extended release tablets (TTR) to be equally capable of packaging immediate release tablets (TCM). CHPA would suggest the Agency to review and possibly update the profile class code system to facilitate more meaningful risk assessments for site changes.

3. Currently 314.70(c)(6) and Section VI.C.1.c. of FDA's NDA/ANDA Changes Guidance reflect that a CBE0 is required for "...changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity,

C. Specific Suggestions for Revisions to 314.70 and/or Associated Guidance (continued)

strength, quality, purity, or potency it purports or is represented to possess". Although it is explained in FR 69(68):18745 that the phrase "methods and controls" is applicable to the manufacturing process (and that the phrase does not relate to specifications which are by definition tests, analytical procedures, and acceptance criteria), confusion still tends to occur. For clarity and consistency with the intent stated in FR 68(69):18745, we suggest that the wording of 314.70(c)(6) be clarified to reflect "...manufacturing methods or in-process controls".

Additionally, please note that increased quality assurance is only one of many reasons why a manufacturing method may be changed. For example, a production process may be revised or optimized for environmental reasons (to reduce emissions) or for business reasons (to reduce cost of goods through efficiency gains). Regardless of the reason for a manufacturing method change, it is necessary to confirm lack of adverse impact on the product. However, it is not always possible to justify that the change provides *increased* quality assurance. Nevertheless, CHPA proposes that a CBE0 filing be allowed for changes in manufacturing method not only when such changes provide increased quality assurance, but also when such changes provide equivalent quality assurance (i.e. no adverse impact on product quality).

4. Currently, per Section IX.C.1.c. of FDA's April 2004 "Changes Guidance", a CBE30 is specified for a change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a **non-sterile** drug product in a **unit-of-use container**. Also, per Section IX.C.2.b. of FDA's April 2004 "Changes Guidance", a CBE0 is specified for a change in the labeled amount (e.g., grams, milliliters) of a **non-sterile/non-solid** drug product in a **multiple-unit container**. Lastly, per Section IX.D.3. of FDA's April 2004 "Changes Guidance", an Annual Report is specified for a change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams) of a **non-sterile/solid** drug product in a **multiple-unit container**.

C. Specific Suggestions for Revisions to 314.70 and/or Associated Guidance (continued)

As explained in FR 69(68):18745-6 and 18750-1, the above CBE30 requirement was not mandated due to stability or quality assurance reasons but rather due to agency concern that unit-of-use containers (which are dispensed to the patient “as is” without further modification except for the addition of appropriate labeling) may invite misuse (i.e. under use or overuse) depending on the quantity of drug product in the package. It is further explained in FR 69(68):18745-6 that FDA has less of an issue with changing the number of units and/or labeled amount of a drug product in multiple-unit containers (because they are not distributed directly to patients “as is” but are rather used by health care practitioners to dispense product in smaller amounts in accordance with a physician’s instructions).

CHPA suggests that, as prescriptive as they are, these requirements do not apply to OTC drug products and perhaps are more suited to prescription products as it delineated the aforementioned regulatory filing requirements for changing the number of units and/or the labeled amount of a drug product in a container. These distinctions are not relevant from an OTC standpoint, since OTC drug packages are neither unit-of-use containers nor multiple-use containers as defined by FDA’s Changes Guidance (because OTC products are not dispensed to the patient but rather purchased by the consumer). CHPA would like to remind the Agency that OTC products are appropriately labeled to indicate proper dosing instructions to prevent accidental misuse as we continue to campaign to educate the public on the safe use of these drugs. Furthermore, experience has shown that consumers of OTC drugs understand that the quantity of product purchased may be either insufficient, adequate, or more than is needed to complete a course of treatment. We hope the Agency would agree that consumers have demonstrated the ability to purchase appropriate and/or desired quantities of various OTC drug products such as pain relievers, cough drops, sunscreens, etc. for immediate and/or future use as needed. Given that OTC drugs are not prone to misuse based on the quantity of product in the package, we suggest that changes in the quantity of an OTC drug

C. Specific Suggestions for Revisions to 314.70 and/or Associated Guidance (continued)

product in a package may be assessed on a scientific/technical basis as we affirm our commitment to continually improve.

5. It was explained in FR 69(68):18739 that “FDA has particular concerns about changes in the type...or composition...of packaging components because these changes may affect the impurity profile of the drug product”. As a result, 314.70(b)(2)(vi) currently states that prior approval is required for “...changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product.” However, the wording of 314.70(b)(2)(vi) can be misunderstood to mean that prior approval is required for changes in packaging type or composition **if** there is potential to affect the impurity profile of the drug product. For clarity and consistency with the intent stated in FR 68(69):18739, we suggest revising the wording of 314.70(b)(2) to convey that prior approval is required for changes in packaging type or composition **since** such changes may affect the impurity profile of the drug product inline with risk and scientific assessments.
6. Section III.B.1.a. of FDA’s SUPAC-IR Guidance indicates that a change in the technical grade of an excipient (Avicel PH102 vs. Avicel PH200) warrants a prior approval supplement. It is unclear if this requirement would apply to an application where no particular technical grade is defined in the application because it is not a critical product quality parameter. For example, different grades of sucrose may have different particle sizes, but this parameter may be considered inconsequential for a solution product where the sucrose is dissolved during the production process.
7. Currently 314.70(e) states that an applicant may be able to justify a reduced reporting category for a **particular change** upon submission and approval of a protocol that describes the specific tests and acceptance criteria that would be used to demonstrate lack of adverse effect on the product. CHPA wishes to collaborate with the Agency to explore how the

C. Specific Suggestions for Revisions to 314.70 and/or Associated Guidance (continued)

use of protocols might be expanded further, as a way to provide regulatory relief for **general types of changes** (e.g. any type of packaging change) or **all non-major changes**, based on a firm's demonstrated ability to achieve and sustain a low level of risk through quality systems and cGMP compliance programs.

8. It was recommended in FR 69(68):18735 that firms should send field copies of appropriate submissions to the home FDA district office where the applicant's headquarters is located. This does not seem to be common practice. We would appreciate the opportunity to review this topic with FDA and seek FDA comment on whether 314.70(a)(5) and/or 314.440(a)(4) should be reworded to reflect actual practice or other alternatives.

Summary

It is CHPA's opinion that regulatory relief can be provided rather easily with simple and reasonable revisions to 314.70 and/or associated guidance documents. In addition, we suggest that regulatory burden may be further reduced by establishing risk-based mechanisms that would allow A(NDA) applicants to manage moderate and minimal changes through quality system change control, with reporting requirements limited to major changes only. CHPA would also note that, for OTC drug products, opportunities may exist to transition products from (A)NDA to monograph status based on quality history, safety record and risk assessments.

CHPA is encouraged by the opportunities afforded by our collective search for ways to improve the current approach to quality regulation under the 21 century quality initiative. FDA's review and consideration of the comments in this document are sincerely appreciated, and we thank the agency for the chance to contribute to the process.

Respectfully submitted,

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