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January 16, 2007

Food and Drug Administration
Division of Dockets Management
HFA-305
5630 Fishers Lane - Room 1061
Rockville, MD 20852

Re: Docket No. 2005N-0403 and RIN 0910-AA49

Dear Sir/Madame:

Hollister-Stier Laboratories is a manufacturer of Allergenic Extracts, as well as a contract manufacturer of parenteral drugs and biologics. By definition, we are a "small business entity". The comments provided in this letter are divided into "general comment, allergy specific, and contract manufacturing-specific sections. The allergy-specific points were previously submitted in a December 1, 2006 letter, but are repeated in this letter.

A. General Comment

Part 207.3 (a)(7): Proposed language of "same city" is too specific. Our manufacturing site is located in the City of Spokane, with a warehouse in the City of Spokane Valley, 15 miles from the main facility. The existing description is sufficient, avoiding need for a second Establishment Registration, considering only on the short distance between the two facilities.

B. Allergenic Products: PHS Act 351

For purposes of this letter, the Allergenic Product business can be divided up into 3 product groups:

i. Single Antigen and Stock Mixtures comprised of:

- *Diagnostics*
 - Scratch, Prick/Puncture
 - Intradermal
- *Therapeutic bulks*
 - Multiple finished good (F.G.) sizes
 - Typically consists of the strongest extract strength or strengths

ii. Custom Formulations (For the physician's practice)

- *Custom combinations of allergens*
- *Custom Strengths*
- *Choice of F.G. size*

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iii. Custom Patient Formulations (prescriptions) ordered by a physician and shipped directly to the physician for dispensing to patient

- *Sets of dilutions*
 - 2 or more vials
- *Custom Formulations*
 - Strengths are not standard from set to set
- *Maintenance (Refills)*
 - Custom Formulations
 - Strengths are not standard
 - Choice of vial size

Ninety-nine percent of all products (groups i, ii and iii) are shipped directly to physicians or clinics. Rarely are these products handled through distributor/pharmacy networks.

- 1. Proposed Rule - part 207.9 and 207.41** state that allergenic extracts must have NDC numbers. Hollister-Stier's BLA's contain some 650 unique allergens and an additional number of "stock mixtures". These allergens are currently represented through only 10 NDC numbers, each defined as "as ordered" (i.e. no specific finished good package configurations listed).

Applicable only to group "i" above, considering the number of allergens in our BLA's and the potential number of finished good package forms, the proposed NDC requirement would result in the necessity to create more than **3500** NDC numbers. In actual practice, we presently manufacture approximately **350** unique allergens. The proposed NDC requirement would mandate the creation of greater than **1000** NDC's.

Presently, we do not have the means or resources to create unique NDC's for infinite possibilities of products as defined in groups "ii" and "iii" above. Nor, do we have any idea on how to create sufficient NDC's to address the infinite potential for allergen combinations and product forms.

Pertinent to Group "iii" products, Hollister-Stier developed and submitted years ago, 3 unique NDC numbers to address custom formulations for patients. This was done to assist physicians and third party payers with the tracking of products and payments. This was well received in resolving the issue.

- 2. Part 207.2(a)** requires the NDC Number in human readable format to be printed on labels. Hollister-Stier acknowledges that this will involve the following steps:
1. Complete reformatting of at least 'X' vial label types.
 2. Submittal of formats to CBER for approval.
 3. Establishment of all required NDC No's.
 4. Acquisition of additional small font printers
 5. Extensive computer program development.

Hollister-Stier points out that the application on product labels of such a number of unique NDC's, can only increase the likelihood of misbranding.

3. Prescription Professional Labeling (PPL), in SPL format, is to be submitted electronically with each NDC. Hollister-Stier utilizes 8 PPL's to address allergen finished good formats. In certain situations, we will have 3 different PPL's to address different finished good forms of the same allergen.
 - One for diagnostic scratch test.
 - One for diagnostic intradermal test.
 - One for the therapeutic bulk.

Another way of looking at this subject is to say that we will link 350 unique allergens (NDC's) to one Patient Prescription Insert (PPI); the same 350 allergens to an intradermal PPI, and the diagnostic (same 350 allergens) to a therapeutic PPI.

In summary, Hollister-Stier concludes the following:

1. Based upon the content of the proposed rule, we believe the FDA needs a better understanding of the implications and impact to the Allergenic Extract industry, as well as FDA's own resources, both initially and on an ongoing maintenance.
2. 21 CFR Part 610.53 allows allergenic extracts to remaining in inventory at the manufacturing site for up to 3 years, with a 3-year finished good expiry applied at the time of distribution. For firms holding the finished good (F.G), the proposed 3-year NDC implementation period would require either relabeling of the product or discarding of the F.G. inventories. For this reason, allergenic extracts labeled with "No U.S. Standard of Potency" should be exempted from implementation for at least 4 years.
3. FDA must clearly establish resources upfront (meetings, representatives, etc.), to assist this company and the others in the allergenic product industry, so that there is a clear understanding of requirements as applicable to the products groups listed previously in this letter; thus mediating errors and costly false starts at the beginning of the program.
4. The resource and financial burden of this proposed rule will be great to both the Allergenic Extracts Industry and to the FDA in the implementation and maintenance of these records. For this reason, the current use of generic categories of NDC numbers (applicable to groups of allergens and not finished good form-specific) is the best approach.
5. Hollister-Stier is not convinced that the issuance of NDC numbers to each individual allergen and form will improve recall, adverse event knowledge, drug shortage, bio-terrorism, or other programs administered by the FDA. The FDA already has programs to effectively deal with these subjects.

6. The proposed regulation requests that each package size, from single vial shelf pack through wholesale package, be described under the individual NDC.

Hollister-Stier, pertinent to diluents produced, has interpreted package size to represent single vial of a specific fill volume. Practically speaking, one diluent may have 5 or more different, specific fill volumes. For years, this approach has been suitable for end users.

C. Contract Manufacturing Business

Pharmaceutical companies contract with Hollister-Stier to manufacture their NDA, ANDA or BLA products.

Hollister-Stier may perform any of the following depending on the contract:

1. Compound the API and fill into primary containers, then ship product to NDA, ANDA and BLA sponsor.
2. Same as above, but performing secondary “final” packaging.
3. Receive pre-formulated API (‘drug substance’) and fill into primary containers, then ship to NDA, ANDA and BLA sponsor.
4. Same as #3, but performing secondary “final” packaging.

Under the proposed Part 207.33(c), the NDA or BLA sponsor’s Drug Listing role is not defined. It is the sponsor that should file the Drug Listing and the prescription product labeling. This should not be performed by a contract manufacturer, as we have described above. Hollister-Stier requests that the sponsor’s Drug Listing responsibility be defined, so that this industry clearly understands the sponsor/contract manufacturer’s listing responsibilities.

In closing, Hollister-Stier is convinced that the authors of the proposed regulation as written, do not grasp the complexity of products manufactured in the Allergenic Product Industry, as well as the Contract Manufacturing Industry. We firmly believe that it will take face to face meetings to establish clear boundaries on what both parties can efficiently manage, and that will give the FDA the basic information needed to achieve its goals.

The proposed rules are too complex in their present form. Quite simply, they are attempting to change too many systems at the same time.

Within the current, approved rules, a concerted effort should be made to correct entry errors, while publishing clearer guidances on the application of NDC’s. Only after an effort is made to improve the present system, should the FDA consider small adjustments to the establishment registration and listing rules.

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HollisterStier
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Hollister-Stier appreciates the opportunity to present our concerns to the Agency.

Sincerely,

A handwritten signature in black ink, appearing to read "David Mirabell".

David Mirabell
Director, Regulatory Affairs

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