aegis
AEGIS PHARMACEUTICALS INC.
96 Route 23 | Little Falls, NJ 07424 | Phone: 973-256-4545 | Fax: 973-256-6526

June 12, 2003

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

Re: Docket No. 02D-0526 – Comments of Aegis Pharmaceuticals Inc.

Gentleperson:

Aegis Pharmaceuticals Inc. submits these comments on the Draft Guidance for Industry on Drug Product: Chemistry, Manufacturing and Controls Information; Availability in response to the Federal Register notice of January 28, 2003. This Draft Guidance addresses the information to be submitted in ANDAs and NDAs for drug products to ensure continued product quality. Recommendations are provided on the information that should be included for (1) description and composition, (2) manufacture, (3) control of excipients, (4) control of the drug product, (5) reference standard materials, (6) container closure systems, and (7) stability. Information is also provided on the type of pharmaceutical development information that should be included in an application submitted in the Common Technical Document (CTD) format.

Aegis finds this draft guidance an unnecessary escalation of requirements for the submission of ANDAs and NDAs. This escalation is most obvious in the requirements for the Pharmaceutical Development Report (PDR). Currently, the information described in the PDR is reviewed with a FDA investigator during an FDA audit. A drug developer collects this information as the process is being developed and it content and format is specific to the SOPs of the developer. This new requirement for inclusion in the ANDA and NDA and the prescriptive guidelines presented, will burden the Agency and restrict the development activities of the firm.

Aegis recommends that sections of this Draft Guidance where the requirements are escalated be eliminated or changed. These sections are detailed below. In addition, Aegis recommends that the 8 pages of the PDR be replaced with a list of topics that the ANDA and NDA applicant should consider in the process development of a drug product.

Discussion:

Aegis finds this draft guidance an escalation of requirements for the submission of ANDAs and NDAs. This escalation occurs in the Pharmaceutical Development Report (PDR) section and other sections of the draft guidance.

Presently, the information requested for inclusion in the PDR is reviewed with a FDA investigator during a FDA audit. The information is collected as the process is being developed and it is specific to the SOPs of the developer. This new requirement for inclusion in the ANDA and NDA and the prescriptive guidelines, will burden the Agency and restrict the development activities of the firm.

The burden to the Agency will be in slowing the review and approval of ANDAs and NDA. The PDR will be a large and concentrated report addressing chemistry, formulation and analytical information. The typical review chemist does not have the skills necessary to assess the quality of the development activities. This will lead to slower reviews, additional resources and inconsistent implementation of the guidance.

02D-0526 [redacted] C3 [redacted]

(Continued)

The restriction in the development process at the firm will come from the developer's tendency to satisfy the prescriptive requirements of the PDR and not fully explore the process parameters. This will result in a less comprehensive characterization of the process.

Aegis recommends that the 8 pages of the PDR be replaced with a list of topics that the ANDA and NDA applicant should consider in the process development of a drug product.

Additional examples of requirements escalation are listed below:

A. Lines 681 – 970 V. Manufacture (P.3)
This section states that a flow diagram should be included for the manufacturing process. Previously, many, but not all submissions included flow diagrams. To require such a diagram is requiring more information in the application.

   a. The flow diagram is discussed in lines 782-796 describes in detail the information that should be included. These include weights, critical process controls, and the equipment used. We believe that this is not necessary information for a flowchart and the information already exists in other sections of the application.
   b. Lines 816-822 discuss the description of the manufacturing process and the difference that exists between requirements for an ANDA and NDA. Both of these applications should have the same reporting requirements for the manufacturing process.

B. Lines 975 – 1126 VI. Control of Excipients (P.4)

   a. Lines 1084 – 1087 list the criteria needed to justify proposed excipients specification for non-compendial excipients. The criteria include relevant development data, batch analyses, data from drug product stability studies and information that is presented in other parts of the application. The statement that this justification should be as recommended for a drug substance (which will be given in a forthcoming guidance) is a substantial escalation of current requirements where, per current practice, it is up to the firm to justify the chosen specifications for non-compendial excipients according to their own SOPs.

   b. Lines 1121 – 1126 for novel excipients indicate that full details of manufacture, characterization, and controls with cross-references to safety data should be provided. The disclosure of a novel excipient's manufacturing process to a drug product developer is rare. This information is most likely to be in the DMF. To require the applicant to include this in application is unreasonable and an escalation of requirements.

C. Lines 1129 – 1509 VII. Control of Drug Product (P.5)
Items a, b, and c represent an escalation of requirements.

   a. Lines 1153 – 1155 requires that certain in-process tests be performed in lieu of finished product tests (such as hardness and tablet weight) and should be included on the COA. This not a standard practice and it does not appear in the GMP regulations. This is not consistent with current requirements and should be changed.

   b. Lines 1286 – 1305 require that batch analysis be provided for ALL batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies. To include ALL batches used for clinical efficacy and safety, bioavailability, bioequivalence, and primary stability studies will involve a huge amount of data of the type described in lines 1297 – 1305. This requirement should be changed to pivotal studies only.

(Continued)

c. Lines 1330 – 1334 presentation of assay, impurity results, degradation products and residual solvents results from ALL batches will involve a huge amount of data. This requirement should be changed to include pivotal batches only.

These examples of requirements escalation are the strongest cases where the draft guidance has increased the requirements as compared with the current guidance and practice. The above references illustrate how and where escalations of requirements occur and should serve as examples to change the draft guidance to better reflect current requirements.

Recommendations:

Aegis Pharmaceuticals recommends that the 8 pages of the PDR be replaced with a list of topics that the ANDA and NDA applicant should consider in the process development of a drug product.

We also recommend that the examples of escalation of requirements listed above be changed to reflect current approved guidance and practice. In addition, the draft guidance should be reviewed for additional examples of escalating requirements and they should also be revised to reflect current approved guidance and practice.

Aegis believes that following the recommendations made in our comments will reduce and potentially eliminate the increasing requirements reflected in the draft guidance.

Cordially yours,
Aegis Pharmaceuticals Inc.

Agnes Varis
President

AV:pa