April 12, 2010

VIA FEDERAL EXPRESS

WARNING LETTER
(10-ATL-12)

Christopher B. Begley  
Chief Executive Officer  
Hospira, Inc.  
275 N. Field Drive  
Bldg. 2  
Lake Forest, Illinois 60045

Dear Mr. Begley:

During our January 12 - 19 and January 26 - February 23, 2010 inspection of your pharmaceutical and device manufacturing facilities located at 4285 North Wesleyan Boulevard, Rocky Mount, North Carolina, and at 8484 U.S. Highway 70 West, Clayton, North Carolina, respectively, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)], in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with, CGMP.

We reviewed your firm's responses of February 9 and March 16, 2010, and note that they lack sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

CGMP Violations
A. Clayton facility

1. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].

For example, your firm failed to assure adequate process design and control of Liposyn, Propofol, and Cleviprex emulsion products to prevent objectionable particulate contamination (primarily stainless steel). Such controls would include, but are not limited to, appropriate component controls, equipment suitability, equipment maintenance, and filtration.

This particulate contamination problem has been a persistent and serious issue at your firm for multiple years. For example, 16 lots of Propofol and Liposyn manufactured in 2007 contained visible particulate contamination. Your firm did not detect the particulate problem until November 2009 when you performed the second annual retain inspections, which were three to nine months overdue. By then, all 16 lots had expired. Further, substandard manufacturing practices led to three recent major recalls. These recalls were initiated due to excessive contamination with particulates (primarily stainless steel) and included 78 lots of Propofol, 121 lots of Liposyn, and 24 lots of Cleviprex. These lots were manufactured at your Clayton facility between January 2008 and February 2010.

Your failure to follow written procedures, assure prompt investigation, determine root cause, and implement appropriate corrective action resulted in exposure of patients to objectionably contaminated drugs.

Your March 26, 2010 response states that you will enhance your monitoring program for particulates and complete revalidation activities for all products manufactured at the Clayton facility. The manufacturing processes for Liposyn, Propofol, and Cleviprex will now include a (b)(4) prior to filling. Your response is inadequate because it is unclear if your firm has determined the root cause of the problem and resolved it. In addition, you have not provided an interim plan to ensure the quality of drug products that you continue to manufacture and distribute, prior to the completion of your corrective action and validation activities.

This is a repeat observation from the April 2009 inspection.

2. Your firm has failed to ensure the responsibilities and procedures applicable to your quality control unit are in writing and are followed [21 C.F.R. § 211.22(d)].

For example, your Quality Control Unit (QCD) failed to: (1) ensure that the manufacturing processes for your Liposyn, Propofol, and Cleviprex drug products are adequately designed, controlled, and monitored; (2) implement adequate corrective and preventive actions related to objectionable particulate contamination in Liposyn, Propofol, and Cleviprex drug products; and (3) complete and approve 178 manufacturing investigations within 30 days and issue NDA Field Alert Reports (FAR) in a timely manner.
Your March 16, 2010 response describes a number of improvements made to the QCU since the April 2009 inspection, including revising procedures and hiring personnel. However, the most recent inspection noted serious ongoing violations at this facility despite your efforts to address manufacturing inconsistencies, enhance the monitoring program for particulates, and improve your exception reporting practices.

This is a repeat observation from the April 2009 inspection.

3. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications, whether or not the batch has already been distributed, or extend investigations to other batches of drug product that may have been associated with the specific failure or discrepancy [21 C.F.R. § 211.192].

For example, you failed to conduct adequate investigations that result in your implementation of corrective actions to prevent recurrence of the problems and evaluate other potentially affected lots. Specifically, particulates were identified during an inspection of retain samples for two partially distributed lots of Liposyn on January 21, 2010. Subsequently, an exception Report (ER) 1685 was opened on January 25, 2010, due to the particulate contamination. Although your firm recently experienced multiple serious particulate issues leading to product recalls, you failed to: 1) conduct testing to identify the foreign particulates (which were primarily stainless steel) until February 4, 2010; 2) place the remaining product from the two affected Liposyn lots on distribution hold until February 5, 2010; and 3) inspect retain samples from associated lots until February 10, 2010.

Your March 16, 2010 response outlines new and revised procedures for investigations and corrective and preventive actions. However, your response is inadequate because you do not address the failure of the Clayton site to follow QAP-0012, "Exception Reports," or explain whether your review of the large number of open investigations indicates process related deficiencies.

We also find your response inadequate because you have not explained why Liposyn and Propofol retain samples were not inspected (from the October 2009 corrective action implementation) to verify adequacy until January 2010. This verification was conducted three months after production resumed following the first of three recalls. Timely assessment of quality indicators, such as out-of-specification findings and complaints, is essential to detecting and determining the scope of product or process deficiencies.

In addition, you have not provided the following revised procedures: QAP-0012; QCP.05.001, "Deviation and CAPA Management"; QAP-0037, "Complaint Handling Procedure"; QAI-0191, "Inspection Instructions Solutions/Emulsions"; QAI-0101, "Inspection Instructions for Packaged Product Retains"; and QCP.05.002, "Laboratory Investigations Procedure."

This is a repeat observation from the April 2009 inspection.
4. Your firm has not established acceptance criteria for the sampling and testing conducted by
the quality control unit to assure that the batches of drug products meet each appropriate
specification and appropriate statistical quality control criteria as a condition for their
approval and release [21 C.F.R. § 211.165(d)].

For example, your firm does not have acceptance criteria for the five day retain sample
inspection of emulsion products. In addition, QAI-0101 does not require the initiation of a
manufacturing investigation when any visible particulates are found during the five day retain
sample inspection.

Your March 16, 2010 response states a Particulate Analysis Protocol (GP-10-02) was
implemented in January 2010, which requires initiating an investigation when particulates are
observed during the five day retain sample inspection. However, your response is inadequate
because you have not provided the protocol, nor does your response include the acceptance
criteria.

5. Your firm has not established scientifically sound and appropriate sampling plans designed
to assure that drug products conform to appropriate standards of identity, strength, quality,
and purity [21 C.F.R. § 211.160(b)]. For example,

a. The sampling size used by the QC laboratory to determine sub-visible particulates via
microscopic methods in your small volume emulsion parenteral products is not
scientifically sound. For example, your release testing, procedures consists of selecting
(b)(4) samples (b)(4) bottles) from each lot (between (b)(4) and bottles for Propofol).

b. The sampling size used for the five day retain sample inspection is not scientifically
sound. For example, your procedures consist of selecting (b)(4) bottles from each Liposyn
lot (ranging from (b)(4) bottle), (b)(4) bottles from each Propofol lot (ranging from (b)(4)
- (b)(4) bottles), and (b)(4) bottles from each Cleviprex lot (ranging from (b)(4) bottles).

Your March 16, 2010 response states that you have implemented a. statistically sound
sampling plan for the five-day inspection and for the sub-visible microscopic analysis.
However, your response is insufficient because you have not provided the new sampling plans
or your justification for using such plans.

This is a repeat observation from the April 2009 inspection.

B. Rocky Mount facility

1. Your firm does not have adequate written procedures for production and process controls
designed to assure that the drug products you manufacture have the identity, strength, quality,
and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].

For example, the mixing processes for the (b)(4) products included in your mixing tank
validation matrix are not adequately validated. You conducted validation activities only for
Mannitol and Endrate, which you deemed to be the "worst case" products based on their
solubility indexes. However, other products in your validation matrix such as Amidate, Amikacin, and Droperidol have lower solubilities than Mannitol or Endrate. You have not provided a scientific rationale to justify that the mixing studies conducted for Mannitol and Endrate are adequate and fully representative of the mixing processes for the other (b)(4) products.

In addition, you have not identified the component attributes (e.g., solubility and viscosity) and process parameters (e.g., speed, temperature, and pH) that are important to produce a solution for all (b)(4) products.

Your February 9, 2010 response states that you will develop a protocol to assess the process parameters of each of the (b)(4) products and conduct product specific mixing validations for Amidate, Amikacin, and Droperidol (of which the adequacy would need to be verified). However, your response also states that you have validated the (b)(4) products. These two statements in your response appear contradictory.

We note that your response is also inadequate because you have not provided the "statistically and scientifically sound rationale for the application of the solution tank mixing validation matrix." If you are using a matrix approach to validate the mixing processes for multiple products, you must show that the mixing step is the same (e.g., component attributes, processing equipment, and manufacturing parameters) for all products covered under the matrix. Unless you are able to demonstrate that your matrix approach is scientifically sound, all products must be individually validated.

In addition, we are concerned about the length of time your firm has needed to develop and implement its Validation Prioritization Plan at the Rocky Mount facility. You have been aware of our concerns regarding process validations since 2005. While your response states that you conduct finished product release testing to ensure safety and efficacy, the quality of your drug products cannot be ensured by testing alone. Please provide an interim plan to ensure the quality of the drug products that you continue to manufacture and distribute, prior to the completion of your validation activities.

**Quality System and Medical Device Reporting Violations**

The inspection also revealed that your firm manufactures (b)(4) and heparin lock flush solutions. Under section 201(h) of the Act (21 U.S.C. § 321(h)), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body. The inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351 (h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with CGMP requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations, Part 820. These violations include, but are not limited to the following:

A. Clayton facility
1. Failure to adequately validate with a high degree of assurance, and approve according to established procedures, the results of a process that cannot be fully verified by subsequent inspection and test [21 C.F.R § 820.75(a)].

For example, the manufacturing process for (b)(4) has not been validated.

We reviewed your response dated February 9, 2010, and conclude that the adequacy of this response can not be determined. In your response, you indicate that you provided the (b)(4) manufacturing process validation documents to the inspector during the inspection; however, we did not receive any such documents at that time nor were they provided with your response.

B. Rocky Mount facility

1. Failure to adequately validate with a high degree of assurance, and approve according to established procedures, the results of a process that cannot be fully verified by subsequent inspection and test [21 C.F.R § 820.75(a)].

For example, the mixing processes for heparin lock flush solutions (list numbers 1151 and 1152) are not validated. The batch records of the three lots used for Validation Study RC02016 had reportedly been destroyed. A "worst case" validation approach was used to support the manufacturing process of these solutions in (b)(4) mixing tanks as discussed previously. The "worst case" process validation used to support the validation of heparin lock flush solution was performed heating the solution to (b)(4) Heparin is manufactured at (b)(4) temperature and requires a recirculation step. The mixing process validation conducted only evaluated the acceptability of mixing time after QS of the product. The validation did not consider mixing time prior to the final QS and did not include a recirculation step. Different heparin solutions contain different chemical ingredients, different excipients and potentially different critical process parameters. The potential critical process parameters like: pH, temperature, (b)(4) mixing time and mixing speed have not been identified and evaluated. The "worst case" validation approach utilized does not support the heparin solutions manufacturing processes performed at your facility.

We reviewed your response dated February 9, 2010, and have concluded that it is inadequate because, even though it indicates that the product will be placed on corporate quality hold pending a Product Assessment, no timeline was provided for the completion of the process validation. Your response indicates that manufacturing will resume upon approval of formulation specifications, batch record documentation, final product testing and product specification limits. The heparin lock flush solutions manufacturing processes must be validated prior to product distribution.

Our inspection also revealed that your heparin lock flush solutions devices are misbranded under section 502(t)(2) of the Act, 21 U.S.C. § 352(t)(2), in that your firm failed or refused to furnish material or information respecting the device that is required by or under section 519 of the Act, 21 U.S.C. § 360i, and 21 Code of Federal Regulations, Part 803 - Medical Device Reporting (MDR) regulation. Significant violations include, but are not limited to, the following:
2. Failure to submit adverse events reports [21 C.F.R. § 803.10(c)].

For example, during the inspection it was noted that adverse events were still being reported as MedWatch events to CDER instead of MDRs to CDRH. The investigator relayed concerns with your firm's appropriate transfer of the product to device regulations. He recommended your firm ensure that corporate quality is appropriately conducting any required risk management analysis and reporting events to CDRH.

We reviewed your response dated February 9, 2010, and conclude that it is inadequate because, even though you recognized that your firm has not completed the transition of the heparin lock flush products from pharmaceutical products to device products and you committed to update corporate policies and site SOPs to ensure completion of the transition and complete compliance with all FDA device requirements, you have not provided a timeline to complete the transition. The requirement to report adverse events related to heparin catheter lock flush Solutions to CDRH has been in effect since August 17, 2006, as published in Federal Register Vol. 71 No. 159, pages 47499 - 47500.

The violations cited in this letter are not intended to be an all inclusive list of violations that may exist at your facilities. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of new drug applications listing your facilities, until the above violations are corrected. Furthermore, premarket approval applications for Class III devices to which the Quality System regulation violations are reasonably related will not be approved until the violations in this letter have been corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations. Include an explanation of each step taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the drug products manufactured at these facilities, and provide the date(s) and reason(s) you ceased production.

We note that an initial NDA FAR was submitted to our Atlanta District Office on January 18, 2010, regarding particulates in 50 lots of Fosphenytoin Sodium Injection after receiving several complaints dating back to 2008. Your contract testing laboratory's analysis indicates the particulates consist of silicon, silver, carbon, sulfur, and calcium, all of which you claim are intrinsic to the product and process. Be advised it is your responsibility to fully investigate
complaints and other product quality indicators in a timely manner. The FAR indicates that you have (b)(4) Fosphenytoin and (b)(4) a root cause is identified and further analysis is conducted. Please provide your findings, the final impact on distributed lots as well as disposition of those lots on (b)(4) and address whether manufacturing (b)(4)

Finally, we note that the CGMP violations listed in this letter include a similar violation (failure to identify actions needed to correct and prevent the recurrence of defective product) to the violation cited in the August 12, 2009 Warning Letter to Hospira's Morgan Hill, California facility. It is apparent that Hospira's attempts to implement global corrective actions after past regulatory actions by the FDA have been inadequate. Be advised that corporate management has the responsibility to ensure the quality, safety, and integrity of its drug products and devices. FDA expects that your corporate management will immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP and QS regulations where applicable.

Your reply should be directed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead. If you have any questions regarding any issue in this letter, please contact Mr. Campbell at (404) 253-1280.

Sincerely,

/S/

John R. Gridley, Director
Atlanta District