



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Telephone (973)526-6005

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

November 9, 2001

WARNING LETTER

**CERTIFIED MAIL-
RETURN RECEIPT REQUESTED**

Dr. Mortimer Sackler
Dr. Raymond Sackler
Co-CEO's
Purdue Pharma Inc.
One Stamford Forum
201 Tresser Blvd.
Stamford, CT 06901

File No.: 02-NWJ-05

Dear Dr. Mortimer Sackler and Dr. Raymond Sackler:

During two recent inspections of your manufacturing facility, from June 12, 2001 through July 6, 2001 and from July 30, 2001 through September 21, 2001, located at 700 Union Blvd., Totowa, NJ, investigators from this office documented serious deviations from current Good Manufacturing Practice regulations (cGMP) as delineated in Title 21, Code of Federal Regulations, Parts 210 and 211.

These inspections revealed that the manufacturing and quality controls and procedures used at this facility during the processing, packing or holding of prescription drug products, specifically Oxycontin controlled-release tablets, do not conform with cGMP's and, therefore, are adulterated within the meaning of Section 501(a)(2)(B) of the Federal, Food Drug and Cosmetic Act (the Act). The following are examples of deficiencies in your firm's Quality system that were cited by our investigators:

Your firm's Quality Unit failed to assure the identity, strength, quality and purity of Oxycontin controlled-release tablets. Specifically, it failed to prevent a contaminated inactive ingredient, stearyl alcohol, from being used in the manufacture of this product. The stearyl alcohol contained foreign black particulate matter that was not detected by your Quality Unit prior to manufacture.

Additionally, the Quality Unit failed to assure that your NDA-listed supplier of stearyl alcohol was providing your firm with unadulterated material. Specifically, your Quality Unit was unaware that stearyl alcohol was being provided to your NDA-listed supplier by more than one vendor. In fact, your firm's August 2, 2001 correspondence to this office states, "Purdue Quality assurance personnel conducted an investigation at the stearyl alcohol manufacturing site in [REDACTED] and identified the source of the particulate matter." It was only after our investigator requested interstate documentation for two lots of stearyl alcohol that your Quality Unit realized that you were receiving and using

material from unqualified vendors and thereby posing a risk to the identity, strength, quality and purity of your product.

Your firm was aware of the need to qualify vendors prior to using materials in finished product as evidenced by your response to the FDA-483 dated August 2, 2001. Your response explains that "...a site cGMP audit, sample evaluation for conformance to established specifications, sample inspection for particulate matter, physicochemical characterization, process validation and finished product accelerated stability studies..." would be included in any vendor qualification. However, you did not follow your vendor qualifying procedures for the stearyl alcohol used in your Oxycontin product line. This is especially critical since the stearyl alcohol is a critical component that helps control the release rate of the Oxycontin product.

The appearance of "black spots" in one of your products is not new at your firm. This issue was previously brought to your attention and our concerns were explained to you in Warning Letter #98-NWJ-18, dated March 23, 1998. Specifically at that time, there was no investigation by your Quality Unit after black spots were found during the manufacture of MS Contin 200 mg-tablet validation lot #3GM. Correspondence sent by your firm to our office dated March 3, 1998, stated that the investigation "could not be found" but a promise was made to "Reinforce our procedures to fully and completely document investigations into future incidents of this type." No further information regarding this incident was provided and your firm has now failed to "...fully and completely..." document the aforementioned investigation into the current black particulate matter.

We acknowledge your comment made in the August 2, 2001 correspondence to our office which states "...it is understood, and generally accepted by industry, that some baseline level of stainless steel may be present in food and pharmaceutical products, primarily due to equipment wear and that stainless steel is considered an appropriate and preferred material of construction for equipment in contact with pharmaceutical products..." We do not agree, however, with the concept that a randomly dispersed contaminant, such as the black particulate matter in your stearyl alcohol, can be effectively removed manually by visual examination to render an adulterated lot compliant. Your September 27, 2001 correspondence to our office confirms the fact that you are currently receiving adulterated stearyl alcohol that contains "hot spots" of contamination, which require removal prior to use. Your initiation of the visual examination and manual removal of the contaminant along with the setting of a specification for an acceptable amount of contamination in this raw material have not been made in order to comply with official compendium standards. Therefore, if your firm plans to add this new specification and test method in an effort to provide increased assurance that your drug product will have the characteristics of identity, strength, quality and purity which it purports or is represented to possess, then proper submission of a supplemental change to your approved drug application should be made. Please be reminded that it is your firm's responsibility to obtain components for your drug products that are manufactured under appropriate manufacturing practices and controls.

We acknowledge your intention to recall 388 lots of Oxycontin tablets from the market as part of your corrective action plan to address the above referenced deficiencies.

The following are other areas of concern in the manufacture of Oxycontin controlled-release tablets which may lead to inconsistencies and inaccuracies when reconciling the actual yield for each lot of this schedule 2 narcotic:

- Theoretical rather than actual values were used in batch record calculations for un-recovered material from fluid bed bags. Our investigators noted that development and validation studies regarding un-recovered fluid bed bag waste material ranged from 0.92kg to 3.9kg, but your firm consistently used a fixed theoretical value of [REDACTED] in batch record calculations. Additionally, a fixed value of [REDACTED] for granulation moisture content was used in batch records to determine granulation mass rather than actual values. Again, our investigators noted that moisture content ranged from 2.5% to 5% during development and validation studies conducted by your firm.
- Batch records lacked documentation to explain discrepancies observed between batches. For example, variable quantities of film coating solutions were discarded; pharmacy weighing sheets were modified or replaced and lot to lot inconsistencies were observed in the amount of waste generated and recorded during compression.

Additionally, written Annual Product reviews contained incorrect and/or incomplete information.

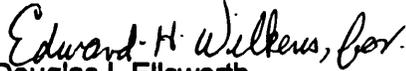
We acknowledge your planned corrective actions outlined in your September 27, 2001 response to the FDA-483, and these corrective actions will be verified during the next inspection of your firm.

The above issues are not intended to be all-inclusive of the deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of government contracts. You should take prompt action to correct deficiencies at your facility. Failure to implement corrective measures may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

You should notify this office in writing, within fifteen working days of receipt of this letter, of the additional steps you have taken to correct the noted deficiencies. If corrective actions can not be completed within fifteen working days, state the reason for the delay and the timeframe within which corrections will be implemented.

Your response should be sent to the Food and Drug Administration, New Jersey District Office, 10 Waterview Boulevard, Parsippany, NJ 07054, to the attention of Mr. Joseph F. McGinnis, R.Ph, Compliance Officer.

Sincerely,


Douglas I. Ellsworth
District Director
New Jersey District