CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

CHEMISTRY REVIEW(S)

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 18-FEB-2010

TO: N 22272 File for OxyContin® (oxycodone hydrochloride controlled-release) Tablets

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THROUGH: Prasad Peri, Ph.D.
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SUBJECT: Review of CMC-related labeling in the 04-FEB-2010, amendment of N22272

BACKGROUND: The DAARP sent a complete response letter to the applicant of N22272 dated 30-DEC-2009. There were no remaining CMC-related issues that were to be addressed by the applicant and the CMC team had recommended in the fourth CMC review dated 23-JUL-2009, that the application be approved. The latest resubmission contains labeling and labels that are revised from those last reviewed by the CMC team in the third CMC review dated 28-APR-2009. The revisions to the labeling and labels is the subject of this fifth CMC review.

EVALUATION: The package insert (PI) that was included in the 04-FEB-2010, amendment includes some revisions relative to the labeling in the 27-MAR-2009, amendment, which was the subject of the third CMC review. Specifically, in all places in the new PI, with the exception of the Structured Product Labeling data table and the header on the first page, the dosage form descriptor is "controlled-release tablets." In the exceptions, it is listed as an "extended-release tablet." Recall that ONDQA recommended to the clinical division that the applicant be asked to change the dosage form descriptor to "extended-release tablets" to be consistent with current policy. The DAARP decided that this would not be requested of Purdue as it may lead to confusion when the product was approved as a replacement for the older approved OxyContin, which currently is described as a "controlled-release tablet."

In the current USP there is a monograph entitled "Oxycodone Extended-Release Tablets." Because of differences in the acceptance criteria for dissolution for Purdue's current reformulated OxyContin, this product would not be able to meet the acceptance criteria in the USP monograph. Specifically, the new formulations of OxyContin will meet the following dissolution acceptance criteria:

Drug released (%)

Time/strength (mg)	**10**	15	**20**	30	**40**	60	**80**
1 hour	(b) (4)						
4 hours							
12 hours							

These acceptance criteria are different from what is in the USP for the 10, 20, 40, and 80 mg strength of oxycodone extended-release tablets, i.e.,

FOR TABLETS LABELED TO CONTAIN 10 MG:

Time (hours)	Amount dissolved
1	between (b) (4)
4	between (b) (4)
12	not less than (b) (4)

FOR TABLETS LABELED TO CONTAIN 20 MG:

Time (hours)	Amount dissolved
1	between (b) (4)
4	between (b) (4)
12	not less than (b) (4)

FOR TABLETS LABELED TO CONTAIN 40 MG:

Time (hours)	Amount dissolved
1	between (b) (4)
4	between (b) (4)
12	not less than (b) (4)

FOR TABLETS LABELED TO CONTAIN 80 MG:

Time (hours)	Amount dissolved
1	between (b) (4)
4	between (b) (4)
12	not less than (b) (4)

In general, it is seen that at both 1 and 4 hours, the target *in vitro* release for the Purdue 10, 20, 40, and 80 mg reformulated product is less than the target represented by the USP monograph. However, at 12 hours, all acceptance criteria require not less than (b) (4) release.

Since the applicant is not using the monograph name for their reformulated product, and the clinical division finds this to be acceptable, there is no requirement that the applicant state in the labels and labeling that the drug product does not meet the USP monograph for Oxycodone

Extended-Release Tablets. Nevertheless, they have added the following statement to the DESCRIPTION section:

(b) (4)

To be more precise, this statement should be revised to the following:

> 'OxyContin 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets, as described in this section are not tested according to and do not meet the "Oxycodone Hydrochloride Extended-Release Tablets" monograph in the USP.'

Alternatively, the applicant could just remove reference to the USP monograph for Oxycodone Hydrochloride Extended-Release Tablets altogether in the PI as the USP specifically states:

> "The identity of an official article, as expressed by its name, is established if it conforms in all respects to the requirements of its monograph and other relevant portions of the compendia. The FD&C Act stipulates that an article may differ in strength, quality, or purity and still have the same name if the difference is stated on the article's label. FDA requires that names for articles that are not official must be clearly distinguishing and differentiating from any name recognized in an official compendium. Official preparations (a drug product, a dietary supplement including nutritional supplements, or a finished device) may contain additional suitable ingredients. (See General Notices.)"

Comment: *Revise the DESCRIPTION section of the labeling to state that the new OxyContin formulations 'do not meet the "Oxycodone Hydrochloride Extended-Release Tablets" monograph in the USP."' Alternately, remove the statement completely as you are not using the name from the official monograph.*

Other changes to the PI include the description of the dosage form in the DOSAGE FORMS AND STRENGTHS section of the HIGHLIGHTS portion. In the previous version the tablets were described as (b) (4) whereas in the new version, the tablets are described as "controlled-release." This change is acceptable and complies with the regulation 21 CFR 201.57(a)(8). Likewise, in the full DOSAGE FORMS AND STRENGTHS section, the tablets are no longer described as (b) (4) but are characterized as "film-coated." This section is compliant with 21 CFR 201.57(c)(4).

The only significant non-editorial change made to the DESCRIPTION section is the removal of the following statement:

(b) (4)

In addition, as already mentioned, the section now includes a statement indicating that the drug product does not comply with the USP monograph (see comment to be forwarded to the applicant above). Overall, this section is compliant with the information required by 21 CFR 201.57(c)(12).

The only change that has been made to the HOW SUPPLIED/STORAGE AND HANDLING section is that the tablets are no longer described as (b) (4) The section still complies with 21 CFR 201.57(c)(17).

The amendment also provides updated mock-up bottle labels for each of the strengths. Relative to the last set of labels that were reviewed by the CMC team from the 27-MAR-2009, amendment, the new versions include the following message:

The last reviewed version of the bottle labels included a clear indication of where the product lot number and expiration date would appear. That is no longer clear on the current revised versions, as can be seen in the example of the 10 mg strength label reproduced below:

Comment: *For each strength of the drug product, revise and resubmit the mock-ups of the bottle labels such that it is clear where the lot number and expiration date will be located.* (b) (4)

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