

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200533Orig1s000**

**CHEMISTRY REVIEW(S)**

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

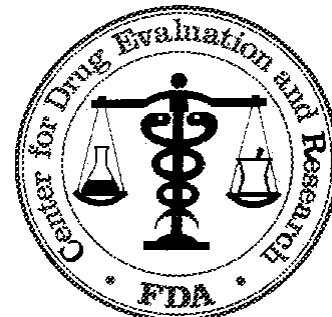
**DATE:** 25-OCT-2010

**TO:** N200533 File

**FROM:** Craig M. Bertha, Ph.D.  
Chemistry Reviewer  
ONDQA, Division III, Branch VIII

**THROUGH:** Prasad Peri, Ph.D.  
Acting Branch Chief  
ONDQA, Division III, Branch VIII

**SUBJECT:** Updated dissolution acceptance criteria proposed in the 18-OCT-2010, meeting briefing document



**SUMMARY:** The DAAP sent the applicant a complete response letter dated 01-OCT-2010, for the application. As a result of an evaluation of the IVIVC models and dissolution data, the biopharmaceutics team in ONDQA requested that the applicant revise the dissolution acceptance criteria for the drug product. The purpose of this memorandum is to outline the changes proposed for the drug product dissolution acceptance criteria and how these relate to the dissolution data that have been provided in the application for all strengths of the drug product.

The dissolution specification acceptance criteria that had been proposed in the original application and the newly proposed limits, to be applied to all strengths, are outlined in the table below.

| <b>Dissolution Acceptance Criteria (Original) (% release)</b> |               |                |                |                |
|---|---------------|----------------|----------------|----------------|
| <b>strength/time</b>  | <b>30 min</b> | <b>180 min</b> | <b>360 min</b> | <b>600 min</b> |
| <b>50 mg</b>  | (b) (4)       |                |                |                |
| <b>100 mg</b>   |               |                |                |                |
| <b>150 mg</b>   |               |                |                |                |
| <b>200 mg</b>   |               |                |                |                |
| <b>250 mg</b>   |               |                |                |                |
| <b>Newly proposed limits (all strengths)</b>                  |               |                |                |                |

Based on the 18 months of 25°C/60%RH stability data that have been provided thus far in the application for the drug product packaged in both the bottles and blisters, it is likely that the dissolution testing will routinely comply with the new acceptance criteria. The following table provides the minimum and maximum individual dissolution results that were observed for the 25°C/60%RH stored drug product in both packaging types.

**imum and maximum dissolution for bottled and blister packaged drug product on stability over 18 months at 25°C/60%RH**

| Batch/strength/DissTime |             |             |              |              |              |              |              |              |              |              |              |
|-------------------------|-------------|-------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 08G01/50/30             | 08G07/50/30 | 08G24/50/30 | 08G01/50/180 | 08G07/50/180 | 08G24/50/180 | 08G01/50/360 | 08G07/50/360 | 08G24/50/360 | 08G01/50/600 | 08G07/50/600 | 08G24/50/600 |

(b) (4)

|            |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|
| [Redacted] |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|

|              |              |              |               |               |               |               |               |               |               |               |               |
|--------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| 08G23/100/30 | 08G25/100/30 | 08G29/100/30 | 08G23/100/180 | 08G25/100/180 | 08G29/100/180 | 08G23/100/360 | 08G25/100/360 | 08G29/100/360 | 08G23/100/600 | 08G25/100/600 | 08G29/100/600 |
|--------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|

(b) (4)

|            |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|
| [Redacted] |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|

|              |              |             |               |               |              |               |               |              |               |               |              |
|--------------|--------------|-------------|---------------|---------------|--------------|---------------|---------------|--------------|---------------|---------------|--------------|
| 08G31/150/30 | 08H04/150/30 | 08H06150/30 | 08G31/150/180 | 08H04/150/180 | 08H06150/180 | 08G31/150/360 | 08H04/150/360 | 08H06150/360 | 08G31/150/600 | 08H04/150/600 | 08H06150/600 |
|--------------|--------------|-------------|---------------|---------------|--------------|---------------|---------------|--------------|---------------|---------------|--------------|

(b) (4)

|            |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|
| [Redacted] |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|

|              |              |              |               |               |               |               |               |               |               |               |               |
|--------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| 08H20/200/30 | 08H22/200/30 | 08H26/200/30 | 08H20/200/180 | 08H22/200/180 | 08H26/200/180 | 08H20/200/360 | 08H22/200/360 | 08H26/200/360 | 08H20/200/600 | 08H22/200/600 | 08H26/200/600 |
|--------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|

(b) (4)

|            |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|
| [Redacted] |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|

|              |              |              |               |               |               |               |               |               |               |               |               |
|--------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| 08G09/250/30 | 08G17/250/30 | 08G15/250/30 | 08G09/250/180 | 08G17/250/180 | 08G15/250/180 | 08G09/250/360 | 08G17/250/360 | 08G15/250/360 | 08G09/250/600 | 08G17/250/600 | 08G15/250/600 |
|--------------|--------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|

(b) (4)

|            |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|
| [Redacted] |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|

| 30 min     |  |  | 180 min |  |  | 360 min |  |  | 600 min |  |  |
|------------|--|--|---------|--|--|---------|--|--|---------|--|--|
| [Redacted] |  |  |         |  |  |         |  |  |         |  |  |

(b) (4)

|            |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|
| [Redacted] |  |  |  |  |  |  |  |  |  |  |  |
|------------|--|--|--|--|--|--|--|--|--|--|--|

It is also noted that the revised acceptance criteria for the 180 and 360 minute dissolution time-points are no longer (b) (4) i.e., the limit at which point the ICH Q6A guidance would recommend that appropriate bioavailability data be provided to validate the acceptance ranges.

**RECOMMENDATION:** From a quality control CMC perspective, there is no objection to the changes that have been made to the dissolution acceptance criteria. Ultimately, the final acceptance of the revised acceptance criteria will be dependent upon the evaluation of the biopharmaceutics team.

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Craig M. Bertha, Ph.D.  
CMC Reviewer, ONDQA

cc:

OND/DAAP/DChiapperino  
ONDQA/DIV 3/CBertha/25-OCT-2010  
ONDQA/DIV 3/PPeri  
ONDQA/DIV3/DChristodoulou  
ONDQA/SSuarez Sharp

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CRAIG M BERTHA  
10/25/2010

PRASAD PERI  
10/26/2010  
I concur

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