U.S. FOOD & DRUG ADMINISTRATION

May 31, 2022

Ms. Jessica Simpson
Senior Manager, Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 05-22-008-Z

Dear Ms. Simpson:

This is regarding the official monograph for **Clonidine Transdermal System**. We have the following comments:

1. We recommend USP reevaluate the utility of the monographs for transdermal and topical delivery systems (TDS) and explore other means (e.g., general chapter) for establishing quality standards for these products instead.
2. In the **ASSAY** section, we recommend revising the sample preparation method to allow flexibility because different formulations may need different extraction procedures to achieve complete drug extraction from the TDS.
3. We recommend deleting the **IMPURITIES** section because of unique challenges of establishing compendial impurity specifications for TDS.

   a. The acceptance criteria for impurities in TDS are calculated using the total drug load (not strength) of the product. Since generic TDS are not required to have the same area and total drug load as the reference product, impurity acceptance limits on the basis of % drug load or TDS area are also product specific.

   b. The current acceptance limit with unit of $\mu g/cm^2$ is based on a particular product and may be particularly misleading to generic manufacturers.

   c. The challenges pertaining to the extraction procedures as described above for the assay are also applicable to sample preparation for impurity procedures. Formulation differences, including different adhesive polymers and different size and thickness of the product, may require different procedures for complete extraction of impurities from the polymer matrix.
4. We recommend considering changes outlined in #2 and #3 above for some other official USP monographs for TDS, such as Rotigotine Transdermal System monograph.

We hope these comments will be helpful to USP and the Monograph Development-Small Molecules 2 Expert Committee. Please feel free to contact Dr. Jin Zhang on my staff at

Jin.Zhang1@fda.hhs.gov if there are any questions. Please use the reference number provided above on any ensuing correspondence.

Sincerely yours,

Pallavi Nithyanandan -S

Digitally signed by Pallavi Nithyanandan -S
Date: 2022.06.03 11:18:52 -04'00'

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