Communication of Extra-Compendial Content

Ed Gump and Kristi Muldoon Jacobs
Communication of Extra-Compendial Information

Sartans Monographs
Tailored Response to an Emerging Issue

- USP recognized nitrosamines/ARB as an emerging issue posing critical public health concerns
- USP received questions and communications from multiple stakeholders, asking for additional information and guidance
- Evolving issue → compendial solution not the appropriate response
- USP evaluated communication options that would be timely and responsive to stakeholder needs and concerns
- Compendial Notice with pop-up alert selected to provide a public service to compendial users
Dear Sir or Madam:

This letter is to inform applicants with an approved or pending application for an angiotensin II receptor blockers (ARB) drug product (DP), as well as holders of related drug master files (DMFs), of FDA concerns related to the presence of one or more toxic impurities in some ARB drugs. This general advice letter summarizes FDA findings to date and provides recommended actions to take to ensure that your drug product, drug substance/active pharmaceutical ingredient (API), and raw materials are absent of these impurities or below our recommended limit.

Background
In June 2018, FDA was informed of the presence of an impurity, identified as N-Nitrosodimethylamine (NDMA), from one valsartan API producer. Since then, FDA has
USP Monographs for ARBs

- Valsartan
  - Valsartan Tablets, Valsartan and Hydrochlorothiazide Tablets, Amlodipine and Valsartan Tablets.
- Losartan potassium
  - Losartan Potassium Tablets, Losartan Potassium and Hydrochlorothiazide Tablets.
- Irbesartan
  - Irbesartan Tablets, Irbesartan and Hydrochlorothiazide Tablets.
- Olmesartan medoximil
  - Olmesartan medoximil tablets.
- Eprosartan mesylate
- Candesartan cilexetil
  - Candesartan Cilexetil tablets, Candesartan Cilexetil and hydrochlorothiazide tablets
- Telmisartan
  - Telmisartan tablets, Telmisartan and Hydrochlorothiazide Tablets, Telmisartan and Amlodipine Tablets
USP created a Compendial Notice to summarize and link to FDA’s additional testing requirements for ARBs in which genotoxic impurities have been detected/suspected.

Pop-ups appear on monographs in the following families: valsartan, losartan, irbesartan.

[[Image of notice from USP]]

**FDA Resources for Angiotensin II Receptor Blockers Voluntary Recalls**

Type of Posting: General Announcement
Posting Date: 09-Aug-2019

Several medicines containing Angiotensin II Receptor Blockers (ARB) have been the subject of voluntary recalls due to the presence of potentially genotoxic impurities. See Table 1.

USP is adding a pop-up text to USP-NF Online to call the user's attention to FDA resources about the ARB recall, which will be displayed on 31-Aug-2019 when users access the drug substance and drug product monographs listed in Table 1.

Table 1: ARB monographs that will contain the pop-up text.*

*Pop-up text will be displayed on 31-Aug-2019.

- Although all text of the USP–NF that has reached its official date is “official text,” not all official text states requirements with which compendial users must comply. Some official text is intended to assist or guide compendial users or to serve informational purposes.

- The following sections of the USP–NF contain informational official text intended to aid compendial users, but do not state requirements with which users must comply:

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Any pop-up text displayed in the USP–NF Online, which serves to call the user’s attention to specific circumstances related to the use of a particular standard or standards

- Clarifies the compendial status of pop-ups
  - Pop-ups will not be used to state compendial requirements
USP may consider the use of pop-ups directing compendial users to extra-compendial content where the following factors exist:

- **Specificity**: clearly defined, specific issue identified by the regulator (e.g., known impurity in known product(s))

- **Actionability**: regulator has provided concrete, actionable path forward to resolve the issue (e.g., action levels, enforcement criteria, additional test methods)

- **Public health risk**: significant public health risk if additional information not provided (e.g., rising to the level of a class 1 FDA recall)

USP would limit scope to information made available by FDA (not ex-US regulators), consistent with the fact that *USP-NF* monographs are tailored to U.S. drug approvals and specifications

USP open to feedback on this approach.
Thank You

Empowering a healthy tomorrow