USP Perspective on Atypical Actives
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USP Excipients Stakeholder Forum
USP Perspective on Atypical Actives

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Outline

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Atypical Actives – USP Compendial Perspective

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- *NF* PEG to *USP* PEG 3350
- *NF* Desoxycholic Acid to *USP* Deoxycholic Acid

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Role of USP Quality Standards in Law

- In the United States under the Federal Food, Drug, and Cosmetic Act (FD&C Act), both *United States Pharmacopeia* (*USP*) and the *National Formulary* (*NF*) are recognized as official compendia for drugs marketed in the United States.
- **Section 501 - Adulterated Drugs and Devices**
  - A drug with a name recognized in *USP-NF* must comply with compendial identity or be deemed adulterated, misbranded , or both (501(b) & 502(e)(3)(b)). …..***Cannot label away from identity*!**
  - Must also comply with compendial standards for strength, quality, and purity, unless labeled to show all differences (501(b) & 21 CFR 299.5).
  - Removing the *USP-NF* designation from labeling does not obviate the requirement to conform to compendial requirements.

Role of USP Quality Standards in Law

FD&C Act [21 U.S.C. 321] Section 201(g)(1)

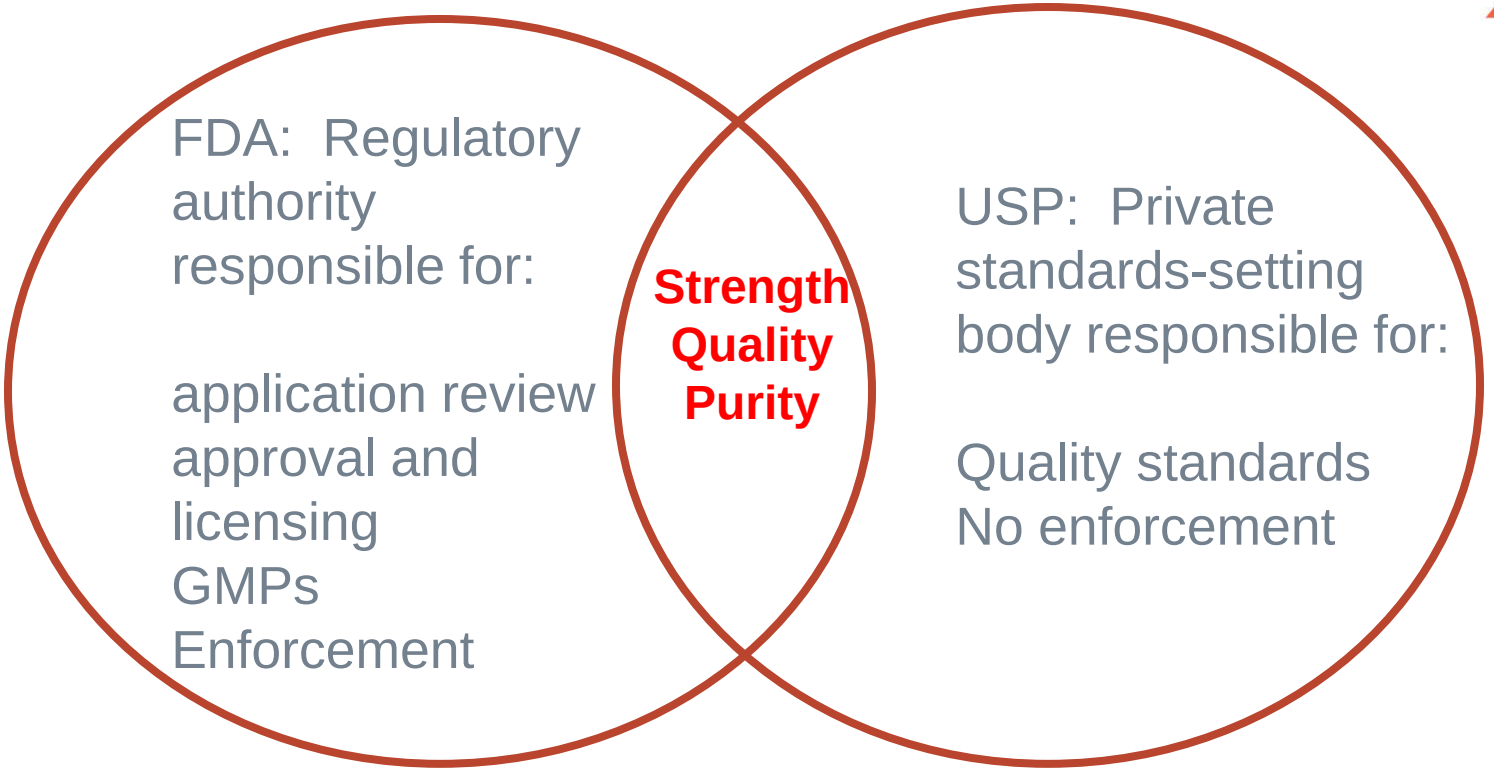
The term “drug” means:

- recognized in an official US compendium: United States Pharmacopeia, Homoeopathic Pharmacopoeia, or National Formulary
- intended to provide diagnosis, cure, mitigation, treatment, or prevention of disease
- intended to affect the structure or any function of the body
- **intended for use as a COMPONENT of any article meeting the above criteria**

According to USP General Notices

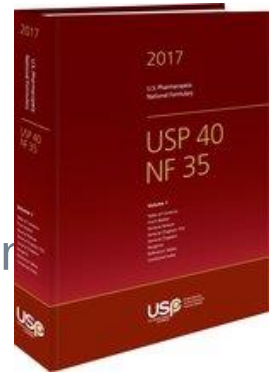
- Section 2.20. Official Articles
  - An official article is an article that is recognized in *USP* or *NF*
  - Official articles include both official substances and official products.
  - Both a drug substance (API) and an excipient are considered an official substance
- Section 3.10. Applicability of Standards
  - “Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs”.
- Section 3.20 Conformance to Standards
  - The designation “*USP–NF*” may be used on the label of an article provided that the label also bears a statement such as “Meets NF standards as published by USP,” indicating the particular compendium to which the article purports to apply.

FDA vs. USP


FDA: Regulatory authority responsible for:
application review
approval and licensing
GMPs
Enforcement
Strength
Quality
Purity
USP: Private standards-setting body responsible for:
Quality standards
No enforcement

Atypical Actives - *NF* – Historic Overview

The *National Formulary (NF)* was first published in 1888 by the American Pharmaceutical Association



- 1975: USP Convention purchases the *NF*
- 1977: *USP* and *NF* scope redefined:
  - *USP* standards for drug substances, dosage forms and compound preparations;
  - *NF* standards for excipients.
- 1980: Published *USP20-NF15* combining the two publications under one cover to create the *United States Pharmacopeia – National Formulary (USP–NF)* but remain **separate compendia**
  - Monographs for excipients used as actives are **typically** published in the USP section of the compendium.

Atypical Actives – Compendial Point of View

No definitions exist within USP-NF for "Atypical Active" or "Dual Active"

- Current understanding is:
  - Atypical Actives are substances which have been registered as the active ingredient in a medicine but whose primary industrial use is not as a pharmaceutical active substance.
  - Dual Actives are substances that can play the role of either active or inactive ingredients (excipients) in drug dosage forms.
- USP needs help with identifying atypical actives and dual actives and understanding their differences

USP Work Relating to Atypical Actives

USP Excipients Group:

- Created list of USP official substances registered as APIs and appearing on the FDA IID (Inactive ingredient Database) list for excipient use. Current list contains 94 APIs.
- Reviewed the Excipient Expert Committee list of excipients- 38 excipients are in the *USP* section of the compendium. Some used in OTCs

DEHYDRATED ALCOHOL	JUNIPER TAR	SACCHARIN SODIUM
TOLU BALSAM	MANNITOL	SAFFLOWER OIL
ALCOHOL	METHYLCELLULOSE	SODIUM CHLORIDE
ANHYDROUS CITRIC ACID	MINERAL OIL	SORBITOL SOLUTION
CALCIUM SACCHARATE	MINERAL OIL, RECTAL	SOYBEAN OIL
CARBOXYMETHYLCELLULOSE SODIUM	NONOXYNOL 9	TALC
CARBOXYMETHYLCELLULOSE SODIUM PASTE	PECTIN	TITANIUM DIOXIDE
CASTOR OIL	PETROLATUM	TOPICAL LIGHT MINERAL OIL
CITRIC ACID MONOHYDRATE	PHENYLETHYL ALCOHOL	TOPICAL STARCH
DEXTROSE	POLYVINYL ALCOHOL	TYLOXAPOL
GLYCERIN	POVIDONE	WHITE PETROLATUM
HYPROMELLOSE	PROPYLENE GLYCOL	XYLOSE
ISOPROPYL ALCOHOL	SACCHARIN CALCIUM	

Case Studies: Polyethylene Glycol (PEG) 3350

PEG 3350 originally included in the PEG *NF* family monograph as one of several grades of the excipient

- The Excipient EC working with stakeholders:
  - Developed a separate PEG 3350 *USP* monograph
  - Proposed appropriate test procedures and methodologies in Pharmacopeial Forum (PF) 39(6) and PF41(4) to **uniquely identify** PEG 3350 and to properly determine the **strength** (content) to reflect its use as an **API**
- *USP* monograph for Polyethylene Glycol 3350 now covers uses **both** as an **active** and **inactive ingredient**

Case Study: Polyethylene Glycol 3350 (New)

Successfully collaborated with multiple manufacturers (raw materials and drug formulations), trade organizations, and FDA

Polyethylene Glycol 3350 [officially adopted into *USP 39-NF 34 2S* (2016)] [via PF 39(6) (2013) and PF 41(4) (2015)]

- Definition
  - Polyethylene Glycol is an addition polymer of ethylene oxide and water, represented by the formula H(OCH2CH2)nOH, in which n represents the average number of oxyethylene groups. The apparent weight-average molecular weight is 3015–3685 g/mol (Da). It contains NLT 97.0% and NMT 103.0% of polyethylene glycol 3350, calculated on the anhydrous basis. It may contain a suitable antioxidant.
- Identification
  - A. Infrared Absorption <197F> or <197A>
  - B. Chromatographic Identity

Case Study: Polyethylene Glycol 3350, 2

- Assay
  - HPLC (Size-exclusion) with a refractive index detector
- Method and validation reports received from the sponsor
- Impurities
  - Residue on Ignition
    - Follows the USP general chapter <281> Residue On Ignition
  - Control of inorganic impurities or salts
    - Limit of Ethylene Oxide and Dioxane
      - Proceed as directed in Ethylene Oxide and Dioxane <228>, Method II
      - Method II in the chapter <228> is a GC procedure
    - Limit of Ethylene Glycol and Diethylene Glycol
      - HPLC with a refractive index detector
      - Method and validation reports received from the sponsor

Case Study: Polyethylene Glycol 3350, 3

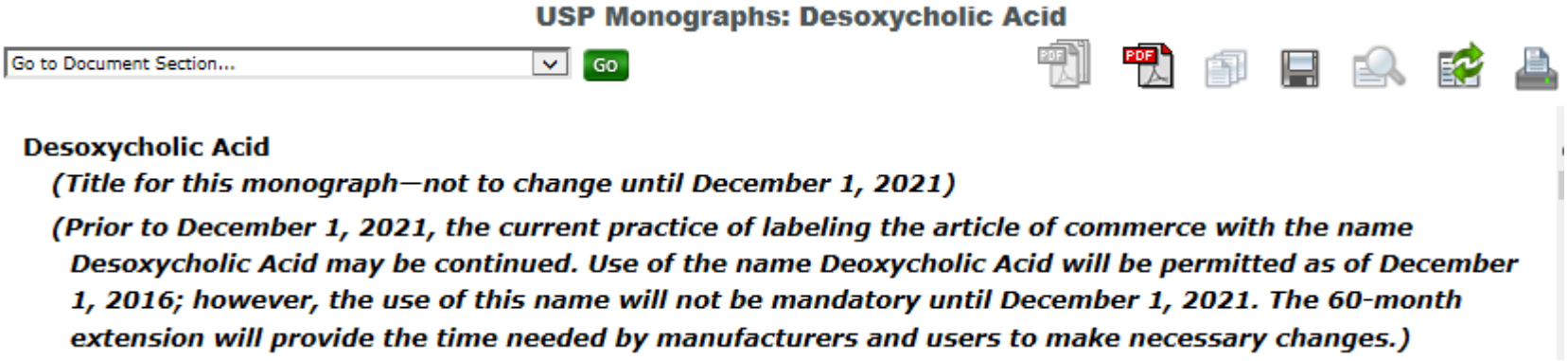
- Impurities
  - Limit of Formaldehyde and Acetaldehyde
    - HPLC with a UV detector
    - Method and validation reports received from the sponsor
- Specific Tests
  - Apparent Weight-Average Molecular Weight and Polydispersity
    - HPLC (Size-exclusion) with a refractive index detector
    - Method and data received from the commenting company
  - Confirmation studies conducted in USP laboratory
    - Hydroxyl Value
    - Acidity and Alkalinity
    - Water Determination <921>, Method I

Case Studies: Desoxycholic Acid, *NF* 33

Because of the use of desoxycholic acid as an API in an FDA-approved drug, it is proposed to change the monograph designation from *NF* to *USP* and to update the monograph tests to reflect the use of desoxycholic acid as an API.

This updated monograph is listed in the *NF* section as a cross-reference to the *USP* general monographs section to reflect its use as both an active and inactive ingredient.

The title “Desoxycholic Acid” is proposed to be changed to “Deoxycholic Acid” to reflect the nomenclature used in the USAN and in the FDA Inactive Ingredient Database



Case Studies: New Deoxycholic acid *USP 40 1S*

USP Monographs: Deoxycholic Acid

Go to Document Section... Go

Change to read:

Deoxycholic 1S (*USP40*) **Acid**

(Title for this monograph—to become official December 1, 2021)

(Prior to December 1, 2021, the current practice of labeling the article of commerce with the name Desoxycholic Acid may be continued. Use of the name Deoxycholic Acid will be permitted as of December 1, 2016; however, the use of this name will not be mandatory until December 1, 2021. The 60-month extension will provide the time needed by manufacturers and users to make necessary changes.)

DEFINITION

Change to read:

Deoxycholic 1S (*USP40*) Acid contains NLT 97.0% and NMT 103.0% 1S (*USP40*) of deoxycholic 1S (*USP40*) acid ($C_{24}H_{40}O_4$), calculated on the anhydrous 1S (*USP40*) basis. Deoxycholic Acid can be of animal or synthetic origin. FDA has not approved the use of animal-derived Deoxycholic Acid as a drug substance. 1S (*USP40*)

Add the following:

- **LABELING:** Label it to indicate whether Deoxycholic Acid is derived from an animal or synthetic source. Deoxycholic Acid intended for use in preparing parenteral dosage forms is so labeled. 1S (*USP40*)

Atypical Actives – Compendial Point of View

Confusion appears to exist due to the following:

- Lack of clarity in US statutes, regulations and *USP-NF* compendial specifications that leaves stakeholders unsure of which requirements apply to Atypical Actives
- Some Atypical Actives may be manufactured in registered API facilities to ICH Q7 standards; however, for most no information is available
- Many monograph standards existed prior to ICH Q7 development

Challenges and Opportunities

- Identifying excipients used as APIs and move to *USP* compendium
- Identifying excipients that are no longer used as APIs and move to the *NF*
- Identifying appropriate GMPs that can be applied for each case

- Why?
  - Address *General Notices Section 2.20 Official Articles* (*USP* or *NF*) and Section 3.10. Applicability of Standards (which GMPs?)
  - GMP requirements apply differently when labeled as *USP* or *NF*.
  - Use of *USP* General Information Chapter <1078> Good Manufacturing Practices For Bulk Pharmaceutical Excipients as a guideline -
    - "This general information chapter provides guidelines for methods, facilities, and manufacturing controls to be used in the production of pharmaceutical excipients in order to ensure that excipients possess the quality, purity, safety, and suitability for use that they purport to possess."

Next Steps

USP needs help from its stakeholders in identifying atypical actives and updating the standard if necessary

Possibly, form a USP Expert Panel on Atypical Actives to engage stakeholders?

USP Expert Panel to include experts in both excipients and APIs used as atypical actives as well as regulatory representatives

USP also appreciates the opportunity to work with FDA and other stakeholders to update *USP-NF* monographs for Atypical Actives

Opportunities for Stakeholder Participation

Submit your comments and/or Request for Revision to USP

(https://www.usp.org/get-involved/partner/submission-monograph-modernization

https://www.usp.org/get-involved/partner/modernization-priority-new-monograph-lists)

Comment on revision proposals in *Pharmacopeial Forum*

(http://www.usppf.com/pf/pub/index.html)

Attend Excipient round-table meetings, stakeholder forums, and workshops

Visit USP Excipient Web site (https://www.usp.org/excipients)

Thank You

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