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Polymeric Pharmaceutical Excipients in NF June 11, 2014

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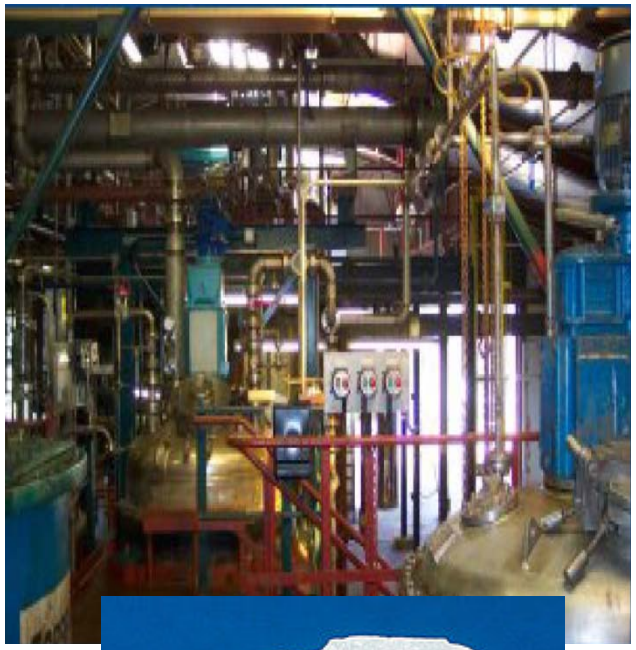
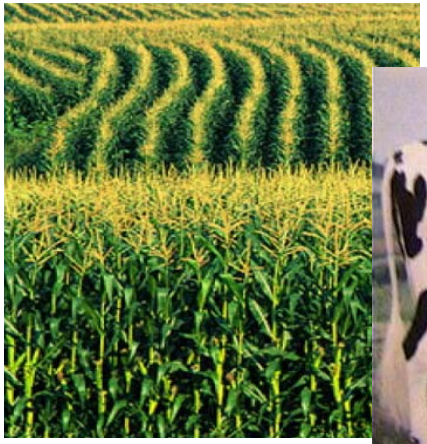
Pharmaceutical Excipients - Challenges

- No such thing as an “excipient” industry
- Manufacture for multiple industries
  - food, cosmetic, personal care, industrial, pharmaceutical
- Manufacturers are multinational in scope
- Large manufacturing facilities
- Complex supply chain comprising suppliers, brokers, repackagers, etc.,





Pharmaceutical Excipients-Challenges

- Excipients developed and manufactured *specifically* for *pharma use* sometimes have
  - Special grade or grades available (e.g., MCC, Mag. stearate)
- Multisource suppliers of the same grade
  - lot-to-lot/batch-to-batch/supplier inequivalence or variability
- Unlike API's, a vast diversity of excipient applications exist in product development.

Pharmaceutical Excipients – DEFINITION*

- Pharmaceutical Excipients—Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients can do the following:
  - aid in the processing of the drug delivery system during its manufacture,
  - protect, support, or enhance stability, bioavailability, or patient acceptability,
  - assist in product identification, and
  - enhance any attribute of the overall safety
  - assist in the effectiveness and/or delivery of the drug in use
  - assist in maintaining the integrity of the drug product during storage

* Modified from USP General Information Chapter, <1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients

USP-NF Excipient Monograph layout

- Title
- Definition
  - Contains a chemical definition with content limits, or describes the substance and the source(s) from which it is obtained. It may also refer to the method of manufacture.
  - Any permitted additives will also be indicated.
- Identification
- Assay
- Other Components
- Impurities
- Specific Tests
- Additional Requirements
  - Packaging and Storage
  - Labeling
  - USP Reference Standards
- Note: Not every excipient monograph will contain every section

Examples of Definitions for Excipients from USP-NF

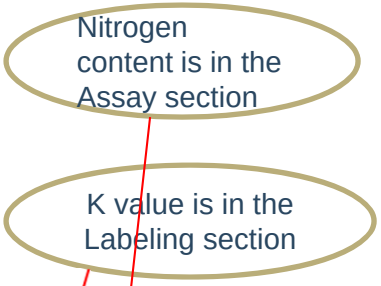
- Dibasic Calcium Phosphate Dihydrate USP
  - Dibasic Calcium Phosphate Dihydrate contains two molecules of water of hydration. It contains NLT 98.0% and NMT 105.0% of dibasic calcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$)
- Olive Oil NF
  - Olive Oil is the refined fixed oil obtained from the ripe fruit of Olea europaea Linné (Fam. Oleaceae). It may contain suitable antioxidants
- Microcrystalline Cellulose NF
  - Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Identification Tests in the USP-NF

- Traditionally these have been ‘wet’ chemistry tests relating to color changes, solubility, or precipitation.
- Not all ID tests are specific for the particular molecule
- We also have instrumental methods such as:
  - Infra Red spectroscopy
  - Chromatographic peak retention time
- We can have physical tests
  - Degree of substitution (based on intrinsic viscosity)
- Where possible, we are moving to more reliable instrumental methods.
- Where necessary we will be including compound-specific tests in monograph (to help combat adulteration).

Assays in USP-NF Excipient monographs

- Not all Excipient monographs have assays.
  - e.g. Microcrystalline Cellulose, Polyethylene Oxide.
- Not all assays are specific for the nominal component.
  - e.g. Povidone - Assay is by Kjeldahl Nitrogen Determination <461>



- DEFINITION : *Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. The different types of Povidone are characterized by their viscosity in aqueous solution, relative to that of water, expressed as a K-value (see Specific Tests, K-value). The K-value of Povidone having a stated (nominal) K-value of 15 or less is NLT 85.0% and NMT 115.0% of the stated values. The K-value of Povidone having a stated K-value or a stated K-value range with an average of more than 15 is NLT 90.0% and NMT 108.0% of the stated value or of the average of the stated range. It contains NLT 11.5% and NMT 12.8% of nitrogen (N: 14.01), calculated on the anhydrous basis. It has a nominal K-value of NLT 10 and NMT 120. The nominal K-value is shown on the label.*
- We are looking to develop/obtain more specific assays for those excipients that do not have them.

Other Components/Impurities

- In general, most excipients are not ‘pure’ due to presence of “other components” (sometimes referred to as Concomitant Components) that can be classified as:
  - Desirable (Functional)
    - They contribute to excipient performance and do not present a safety concern (e.g. additives/processing aids with a limit (*Gen. Notices* 5.20. Added Substances)
  - Acceptable
    - They do not present a safety concern.

- However, both the *USP-NF* and FDA categorize Impurities as
  - Inorganic (<281> Residue on Ignition)
  - Organic (<466> Ordinary Impurities)
  - Residual solvents (<467> Residual Solvents)

Additional Requirements

- Packaging and Storage
  - More specific instructions will be introduced for some excipients.
- Labeling
  - Specific details required to be included on the label or labeling.
- USP Reference Standards
  - A list of USP Reference Standards required to complete all the tests included in the monograph.

What a USP-NF Excipient Monograph does not contain

- Appearance
- Solubility
- Performance tests, except where they are required for e.g. grade differentiation
  - However, the intent is to differentiate between different grades of the same excipients, not to assess performance per se.
  - Performance requirements are application-specific, and there is no way a pharmacopeia monograph can cover all applications.
  - Performance assessment is for the excipient user, and perhaps the excipient manufacturer.

Monograph Modernization

- Primary driver is maintaining up-to-date quality standards to support USP's commitment to public health
- Need for modernization
  - Monographs have been official for several years, decades in some cases
  - Content does not reflect current expectations for procedures and acceptance criteria
  - General lack of specificity
- Modernization is a subset of USP's ongoing revision work, started using the term "modernization" in 2009
- FDA Modernization Task Group (Nov. 2010)
  - Letters for modernization of 17 excipients
  - ORA list 4
  - http://www.usp.org/usp-nf/development-process/monograph-modernization

USP Monograph Modernization

Benefits

- Strengthens the public standards
- Moves from non-specific to specific procedures
- Considers practical factors
  - removes unnecessary tests
  - safety/environmental issues such as eliminating use of chlorinated solvents
  - hard to find equipment
- Increases consistency across monographs
- Helps address public health risks that maybe increased by a complex global supply chain

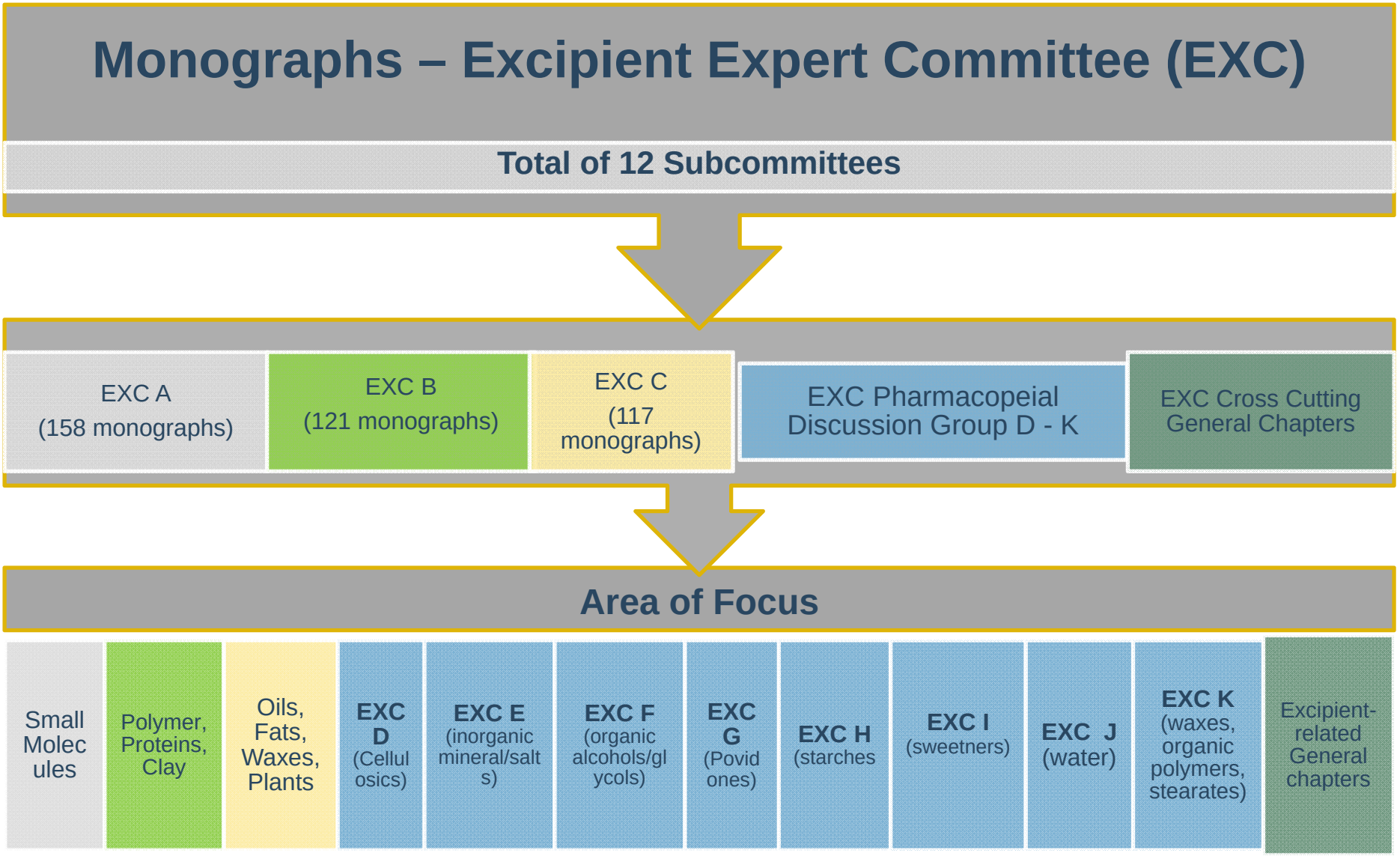
Excipient Monograph Modernization: Prioritization of Categories

- No Identification or non-specific Identification procedures
- No Assay or non-specific Assay procedures
- Stainless steel/packed column GC procedures
- Titration to GC/HPLC where appropriate
- No impurity test, (e.g., Povidones and peroxides/aldehydes)
- Safety-related concerns (e.g., chlorinated solvents).
- Labeling deficiencies , e.g., when used in parenteral/injectable applications
- Missing specific tests to control quality (e.g., Microbial/BE)
- Nomenclature and Definition issues reported to USP mainly by manufacturers (e.g., Glyceryl behenate - Glyceryl dibehenate) .

Polymeric Pharmaceutical Excipient Sources

- Animal
  - Shellac
- Vegetable
  - Microcrystalline Cellulose, Powdered Cellulose
  - Guar Gum
  - Zein
- Synthetic
  - Povidone
  - Poloxamer
  - Polyethylene Glycol, Polyethylene Oxide
- Semi-synthetic (chemical modifications)
  - Cellulose acetate, Hydroxypropyl cellulose
  - Polysorbate 20, 40, 60, and 80
- Biotechnology derived
  - rAlbumin Human

Monographs – Excipient Expert Committee (EXC EC) 2010-2015 Cycle



Polymeric Excipient Structures

- NF excipient polymers are defined in many ways -
- Example 1 : Polymer is defined by its monomeric repeating unit(s) with a molecular weight range
  - NF Polyethylene Oxide (PEO) monograph definition

    "Polyethylene Oxide is a nonionic homopolymer of ethylene oxide, represented: $H(OCH_2CH_2)_nOH$ in which n represents the average number of oxyethylene groups. The number n varies from about 2000 to 200,000. … ……."

    This represents the family monograph of PEO

    The PEO monograph represents polymers with average molecular weights from 88,000 – 8,800,000 g/mol

Polymeric Excipient Structures (Cont.)

- Example 2:
  - Polymeric excipients differentiated by different degree of polymerization
    - Microcrystalline Cellulose

      Defintion: "….Degree of Polymerization is NMT 350…"
    - Powdered Cellulose

      Defintion "..Degree of Polymerization is NLT 440.."
- Example 3:
  - A copolymeric excipient characterized by different ratio of monomers
    - Ethylene Glycol and Vinyl Alcohol Graft Copolymer

      Defintion: "Ethylene Glycol and Vinyl Alcohol Graft Copolymer is a graft copolymer of ethylene glycol and vinyl alcohol. It consists of about 75% of vinyl alcohol (– CH2CH(OH)–) units and 25% of ethylene glycol (– CH2CH2O –) units. … … "

Polymeric Excipient Recently Developed

- Development of Monographs with a focus on *Specific Nomenclature* and *Definition*
- *Nomenclature (official title is approved by the USP Nomenclature, Safety and Labeling (NSL) Expert Committee)*
- Example:
  - Polydextrose NF

    Definition "*Polydextrose is a randomly branched polymer prepared by melting and subsequent condensation of the ingredients, which consist of approximately 90 parts dextrose, 10 parts sorbitol, and up to 1 part citric acid or 0.1 part phosphoric acid. The 1,6-glycosidic linkage predominates in the polymer but other linkages are present. It contains NLT 90.0% of dextrose polymer units, calculated on the anhydrous and ash-free basis. … …*"
  - Hydrogenated Polydextrose NF

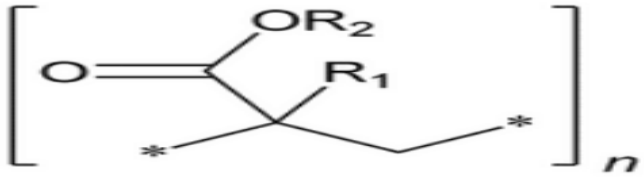
    Definition: "*Hydrogenated Polydextrose is obtained by transition metal catalytic hydrogenation of Polydextrose in aqueous solution. It contains NLT 90.0% of dextrose polymer units, calculated on the anhydrous and ash-free basis. The polymer chain end groups are mainly sorbitol-terminated.*"

Polymeric Excipient for Modernization

- Official, original monograph with nonspecific nomenclature was replaced by two updated modernized monographs each with *Specific Nomenclature* and *Definition*
  - Official / Original monograph
  - Methacrylic Acid Copolymer
  - "*Methacrylic Acid Copolymer is a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. "*
  - Replaced by two separate monographs
    - Methacrylic Acid and Methyl Methacrylate Copolymer
      "*Methacrylic Acid and Methyl Methacrylate Copolymer consists of methacrylic acid and methyl methacrylate monomers arranged in a random distribution. … …"*
    - Methacrylic Acid and Ethyl Acrylate Copolymer
      "*Methacrylic Acid and Ethyl Acrylate Copolymer consists of methacrylic acid and ethyl acrylate monomers arranged in a random distribution. … … "*

Polymeric Excipient Modernization (Cont.)

- During the modernization of Methacrylic Acid Copolymer , a new monograph was developed with a Specific Nomenclature and *Definition* to cover
  - Partially-Neutralized Methacrylic Acid and Ethyl Acrylate Copolymer
  - Definition: "*Partially-Neutralized Methacrylic Acid and Ethyl Acrylate Copolymer consists of methacrylic acid and ethyl acrylate monomers arranged in a random distribution, some units of methacrylic acid in the copolymer are neutralized by sodium hydroxide. … …*"



$R_1 = CH_3$; R_2 = H or
$R_1 = CH_3$; R_2 = Na or
R_1 = H; $R_2 = C_2H_5$

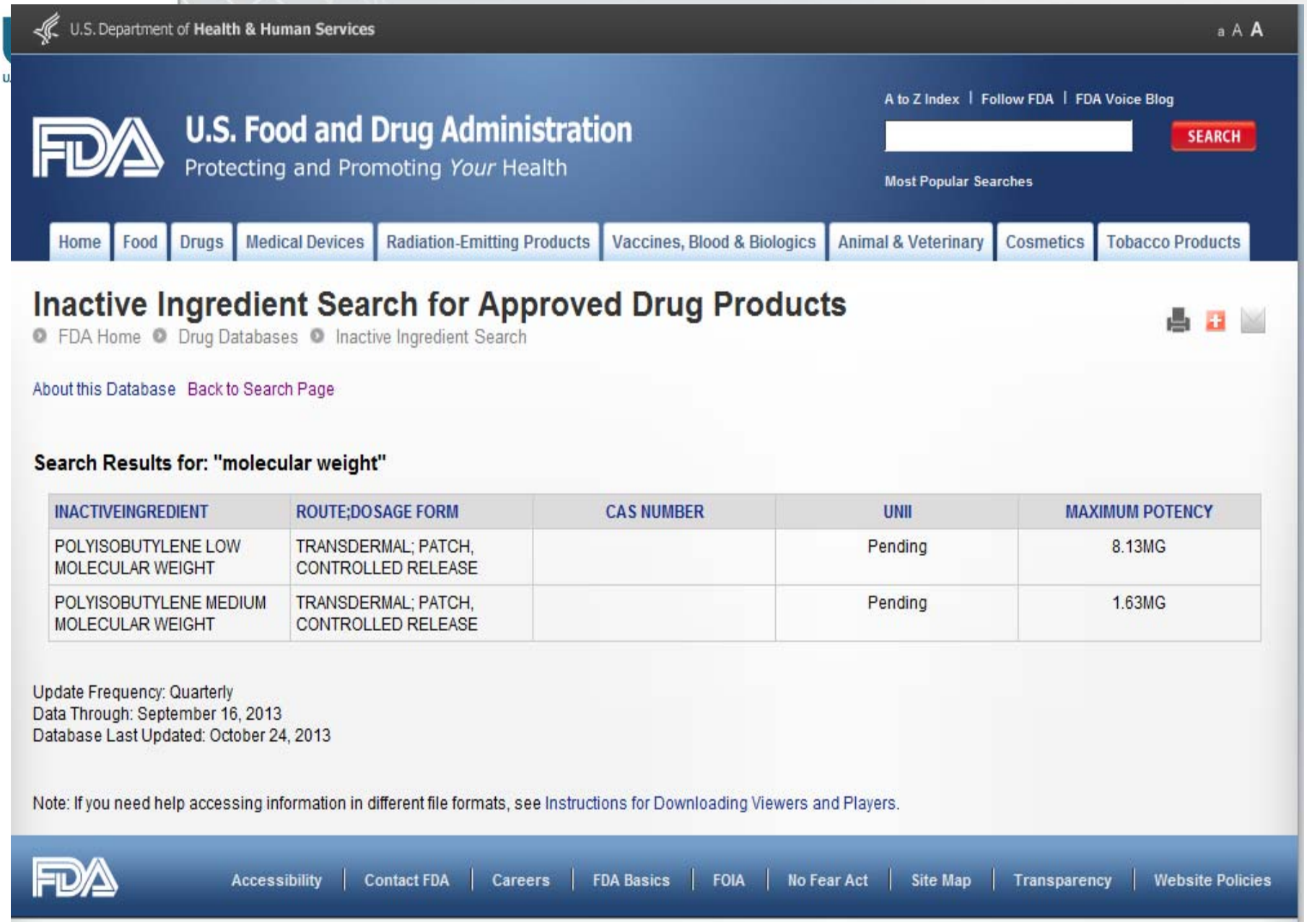
INACTIVEINGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
ETHYL ACRYLATE - METHACRYLIC ACID COPOLYMER	ORAL; CAPSULE, DELAYED ACTION, COATED, HARD GELATIN		N/A	100.687MG
METHACRYLIC ACID	ORAL; CAPSULE	79414	1CS02G8656	19.07MG
METHACRYLIC ACID	ORAL; CAPSULE, DELAYED ACTION	79414	1CS02G8656	20.401MG
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A	ORAL; CAPSULE	25212888	NX76LV5T8J	75.18MG
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A	ORAL; CAPSULE, ENTERIC COATED PELLETS	25212888	NX76LV5T8J	80.36MG
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A	ORAL; CAPSULE, EXTENDED RELEASE	25212888	NX76LV5T8J	56.76MG
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A	ORAL; CAPSULE, SUSTAINED ACTION	25212888	NX76LV5T8J	48.1MG
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A	ORAL; CAPSULE, SUSTAINED ACTION, HARD GELATIN	25212888	NX76LV5T8J	10.9MG
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A	ORAL; SOLUTION	25212888	NX76LV5T8J	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A	ORAL; TABLET	25212888	NX76LV5T8J	91MG
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A	ORAL; TABLET, DELAYED ACTION, ENTERIC COATED	25212888	NX76LV5T8J	140MG

Future modernizations for Polymeric Excipients

- Collaborate with stakeholders (agency and monograph sponsor) to update NF Carbomer monographs
  - Carbomer Homopolymer
  - Carbomer Copolymer
  - Carbomer Interpolymer

FDA IID

CARBOMER 980	TOPICAL; EMULSION, CREAM	139637857	4Q93RCW27E	1.2%
CARBOMER 980	TOPICAL; GEL	139637857	4Q93RCW27E	0.85%
CARBOMER 980	TRANSDERMAL; GEL	139637857	4Q93RCW27E	1.5%
CARBOMER 981	TOPICAL; GEL	138757683	F68VH75CJC	0.85%
CARBOMER 981	TOPICAL; LOTION	138757683	F68VH75CJC	0.2%
CARBOMER HOMOPOLYMER TYPE A (ALLYL PENTAERYTHRITOL CROSSLINKED)	ORAL; TABLET, EXTENDED RELEASE	138757683	F68VH75CJC	17.5MG
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	OPHTHALMIC; SUSPENSION	151687966	HHT01ZNK31	0.5%
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	OPHTHALMIC; SUSPENSION, DROPS	151687966	HHT01ZNK31	0.45%
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	ORAL; SUSPENSION	151687966	HHT01ZNK31	0.16%
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	ORAL; TABLET, CONTROLLED RELEASE	151687966	HHT01ZNK31	6.25MG
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	ORAL; TABLET, SUSTAINED ACTION	151687966	HHT01ZNK31	6.25MG
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL; GEL	151687966	HHT01ZNK31	0.8%
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL; SUSPENSION	151687966	HHT01ZNK31	0.4%
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL; GEL		4Q93RCW27E	1.6%



Acknowledgements

Hong Wang, PhD., Senior Scientific Liaison Excipients

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Questions

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Thank You