Family Approach to Excipient Safety Review

David Schoneker
Vice Chair for Science and Regulatory Policy – IPEC-Americas
Director of Global Regulatory Affairs – Colorcon

dschoneker@colorcon.com

Multiple stakeholders; **one objective.**

International Pharmaceutical Excipients Council

Collaborative solutions for excipient industry stakeholders

IPEC-Americas Discussions with FDA on IID Issues – Including the Family Approach

December, **2011**

May, **2016**

Facilitating the Review of Excipients in ANDA Submissions

IPEC-Americas recognizes and applauds the FDA for their recent work at updating and improving information listed in the inactive ingredients database (IID); however,

The ANDA process should be more efficient to help the Agency and industry meet GDUFA goals, reduce confusion and minimize redundant reviews

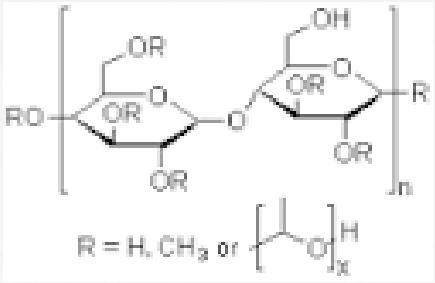
IPEC-AMERICAS HAS REQUESTED FDA TO:

- Use the excipient family approach to facilitate **common pharm-tox evaluations for related excipients,** especially at the time of filing
- Prioritize the one time review of **excipient families**, including hypromellose, polyethylene oxides, silicone, and carbomers
- Implement a **standardized approach** for supplying inactive ingredients information to streamline the submission and review processes
- **Revise FDA guidance documents** by correcting contradictory and inconsistent information

IID Team - Project status through May 2016

Project	Status (minutes posted at website below)
Pharm tox information to support prioritized families of excipients (hypromellose, polyethylene oxide, silicone, carbomers)	Data and references compiled and submitted in 2012, **awaiting final review and posting**
Interim process for providing family justification – especially at time of filing	**Proposed and awaiting FDA internal agreement and support** ***NOTE**: The ANDA RTR guidance needs updating to be consistent with the interim process*
Pharm Tox table/template	Developed, awaiting final FDA approval (**Model product data submitted in 2012**)
Phase I IID FAQ	Finalized in mid 2014, awaiting FDA guidance
Phase II IID FAQ	Drafted but on hold until interim process for providing family justification is vetted within the FDA.

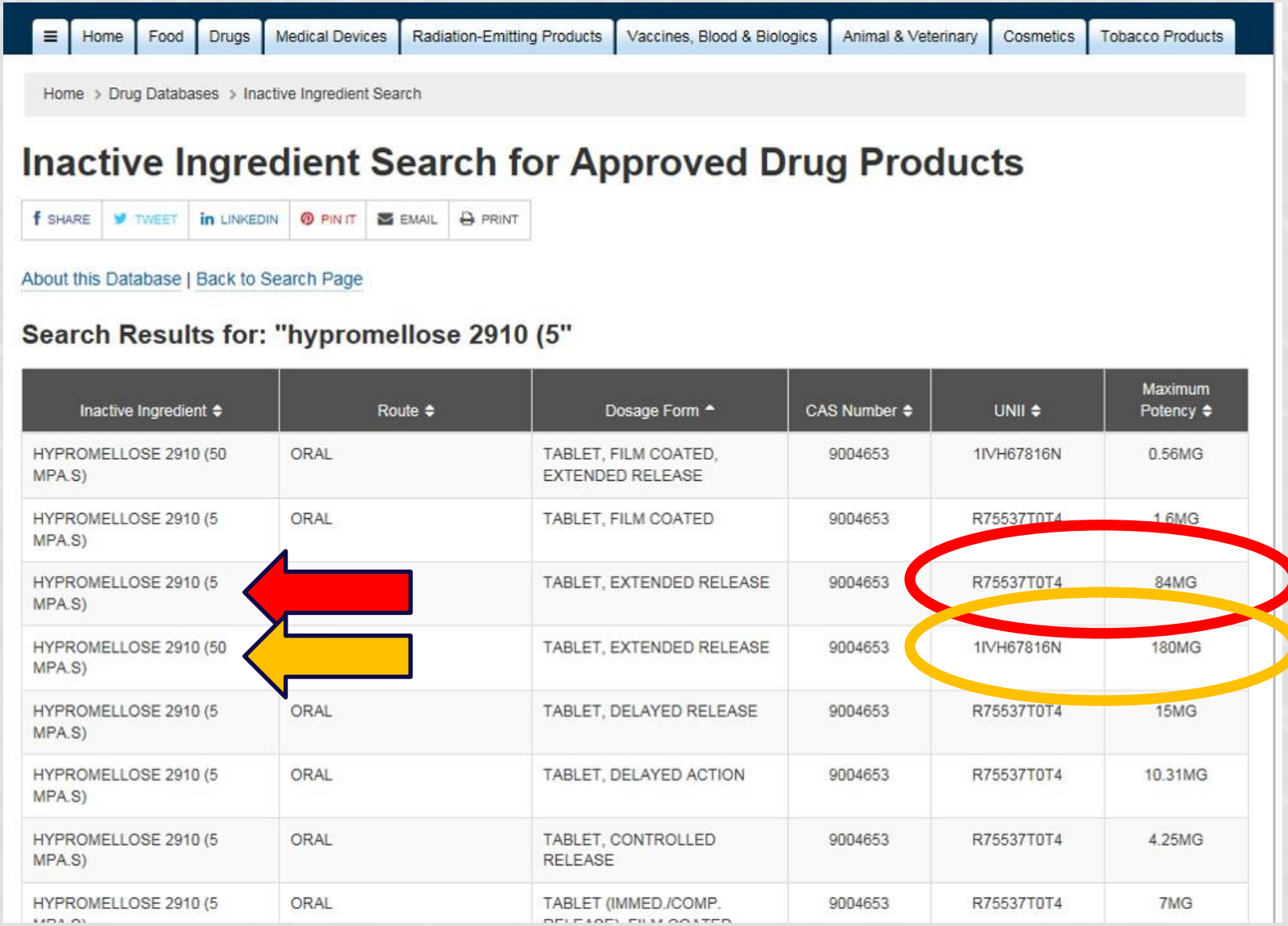
http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm380688.htm



What is the Family Approach?

Many Excipients (such as polymers) are chemically similar but may have various grades in the family that all are the same from a toxicological standpoint

IID Listings for Hypromellose 2910



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Inactive Ingredient Search for Approved Drug Products

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Search Results for: "hypromellose 2910 (5"

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency
HYPROMELLOSE 2910 (50 MPA.S)	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	9004653	1IVH67816N	0.56MG
HYPROMELLOSE 2910 (5 MPA.S)	ORAL	TABLET, FILM COATED	9004653	R75537T0T4	1.6MG
HYPROMELLOSE 2910 (5 MPA.S)	ORAL	TABLET, EXTENDED RELEASE	9004653	R75537T0T4	84MG
HYPROMELLOSE 2910 (50 MPA.S)	ORAL	TABLET, EXTENDED RELEASE	9004653	1IVH67816N	180MG
HYPROMELLOSE 2910 (5 MPA.S)	ORAL	TABLET, DELAYED RELEASE	9004653	R75537T0T4	15MG
HYPROMELLOSE 2910 (5 MPA.S)	ORAL	TABLET, DELAYED ACTION	9004653	R75537T0T4	10.31MG
HYPROMELLOSE 2910 (5 MPA.S)	ORAL	TABLET, CONTROLLED RELEASE	9004653	R75537T0T4	4.25MG
HYPROMELLOSE 2910 (5	ORAL	TABLET (IMMED./COMP.	9004653	R75537T0T4	7MG

IID Listings for Hypromelloses

Inactive Ingredient Search for Approved Drug Products

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Search Results for: "HYPROMELLOSES"

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency
HYPROMELLOSES	ORAL	CAPSULE	9004653	3NXW29V3WO	150MG
HYPROMELLOSES	ORAL	CAPSULE, COATED PELLETS	9004653	3NXW29V3WO	3.32MG
HYPROMELLOSES	ORAL	CAPSULE, DELAYED ACTION	9004653	3NXW29V3WO	67.87MG
HYPROMELLOSES	ORAL	CAPSULE, DELAYED ACTION, COATED, HARD GELATIN	9004653	3NXW29V3WO	20MG
HYPROMELLOSES	ORAL	CAPSULE, DELAYED ACTION, ENTERIC COATED	9004653	3NXW29V3WO	NA
HYPROMELLOSES	ORAL	CAPSULE, DELAYED ACTION, ENTERIC COATED, HARD GELATIN	9004653	3NXW29V3WO	96MG
HYPROMELLOSES	ORAL	CAPSULE, ENTERIC COATED PELLETS	9004653	3NXW29V3WO	64.43MG
HYPROMELLOSES	ORAL	CAPSULE, EXTENDED RELEASE	9004653	3NXW29V3WO	117MG
HYPROMELLOSES	ORAL	CAPSULE, HARD GELATIN	9004653	3NXW29V3WO	73.9MG
HYPROMELLOSES	ORAL	CAPSULE, SOFT GELATIN LIQUID-FILLED	9004653	3NXW29V3WO	118MG
HYPROMELLOSES	ORAL	CAPSULE, SUSTAINED ACTION	9004653	3NXW29V3WO	670.04MG

IPEC-Americas Position on Family Approach

- **Polymer excipients should be treated as a "family of substances" when considering safety/toxicity**
- Update and streamline the IID, short-term-use spreadsheet approach
- Individual UNII numbers identify different grades within a family

HPMC

UNII Codes ≠ Safety Assessment

SRS UNII code	• **Unique identification code for a defined substance in a drug product**	**One-to-ONE**

Safety assessment info and max use level	• **All UNII codes for family of similar products**
	  • UNII #1
	  • UNII #2
	  • UNII #3
		One – to- MANY

Family Approach for Excipient Safety Assessment

- **The current IID and current FDA policies related to handling grades of polymers is insufficient to support efficient drug development and approval**
- Requiring toxicology data for **every grade** of an excipient is **not substantiated by scientific rationale and is not aligned with a risk-based approach.**

Synonyms	Solvent	UNII	Preferred Substance Name
Carbopol® 71G NF polymer	ethyl acetate	F68VH75CJC	Carbomer homopolymer Type A (allyl pentaerthriitol crosslinked)
Carbopol® 971P NF polymer	ethyl acetate	F68VH75CJC	Carbomer homopolymer Type A (allyl pentaerthriitol crosslinked)
Carbopol® 981 NF polymer	cosolvent	F68VH75CJC	Carbomer homopolymer Type A (allyl pentaerthriitol crosslinked)
Carbopol® 941 NF polymer	benzene	F68VH75CJC	Carbomer homopolymer Type A (allyl pentaerthriitol crosslinked)
Carbopol® 980 NF polymer	cosolvent	4Q93RCW2E	Carbomer homopolymer Type C (allyl pentaerthriitol crosslinked)
Carbopol® 940 NF polymer	benzene	4Q93RCW2E	Carbomer homopolymer Type C (allyl pentaerthriitol crosslinked)

- Different solvent grades have same UNII code
- All listings have the same chemistry and toxicology
- FDA has approved drugs with all 3 solvent grades

- **Utilizing a family approach during a safety review of related grades of excipients** used in a generic drug could lead to **a more efficient review and reduction of need for FDA resources** without compromising patient safety.

Family Approach for Excipient Safety Assessment

- **IPEC-Americas has supplied significant information to FDA to justify the use of a Family approach** to excipient safety assessment for related excipient grades
- Currently, FDA reviewers are "*re-reviewing*" the **same excipient toxicology data over and over for each grade of excipient in a family** – since new data does not exist for each grade - *redundant work*!
- Applying the family approach **will reduce the amount of redundant, non-value-added resources** needed to evaluate excipients under GDUFA, while maintaining the necessary safety to patients.

NEED FOR FAMILY APPROACH

Benefits of the Family Approach

- **Transparency** to drug formulators on maximum excipient use levels by route as supported by toxicity data.
- **Minimizes** need for **multiple FDA reviews** of the same excipient toxicology data once a maximum use level has been accepted.
- **Expedites FDA review** of NDA's/ ANDA's.
- **Minimizes errors and resources** to maintain IID
- **Reduces the complexity** of the IID
- **Supports** continued use of unique **UNIIs to identify individual polymers** by MW and degree of substitution.

Risk Based Considerations

- **High molecular weight polymers are not readily absorbed and would be nontoxic**
- Prior human use of an excipient in food (direct food additives) and cosmetics should have sufficient safety data to qualify a new excipient for oral or topical applications
  - **HPMC uses in food products: beverages, pie fillings, ice cream, bread, pasta, breaded coatings, breakfast cereals, tortillas, cakes, cookies, biscuits, granola bars, fruit juices, fish sticks, meat substitutes, peanut butter, sugar substitutes, candy bars, fruit roll-up type snacks, etc..**
  - **Most of these food substances are among the top 25 sources of calories among American children ages 2 years and older according to the NHANES 2005-2006 survey**
- High MW polymer families have a demonstrated history of safety, e.g. hypromelloses, PEGs, dimethicones and carbomers.

SCIENCE BEHIND THE FAMILY DISCUSSION

Using Appropriate Risk Management Concepts

- **Focus should be on high risk "safety" issues**
- **Many common excipients are NOT high risk (e.g. hypromelloses, polyethylene oxide, dimethicones and carbomers)**
  - Data has been available for years for families of these products. Submitting the same data for each grade of material, multiple times to different reviewers does not make sense!
  - These excipients have been used for **DECADES** without adverse "safety" events
  - Risk of adverse event due to "safety" issues/concerns are relatively low
  - **Bracketing of grades of polymers for safety assessment has been standard toxicology practice by experts for years**
  - **FDA CURRENTLY uses this approach for food additives and cosmetic ingredients and in the past has used it for pharmaceutical excipients**

Key Principles

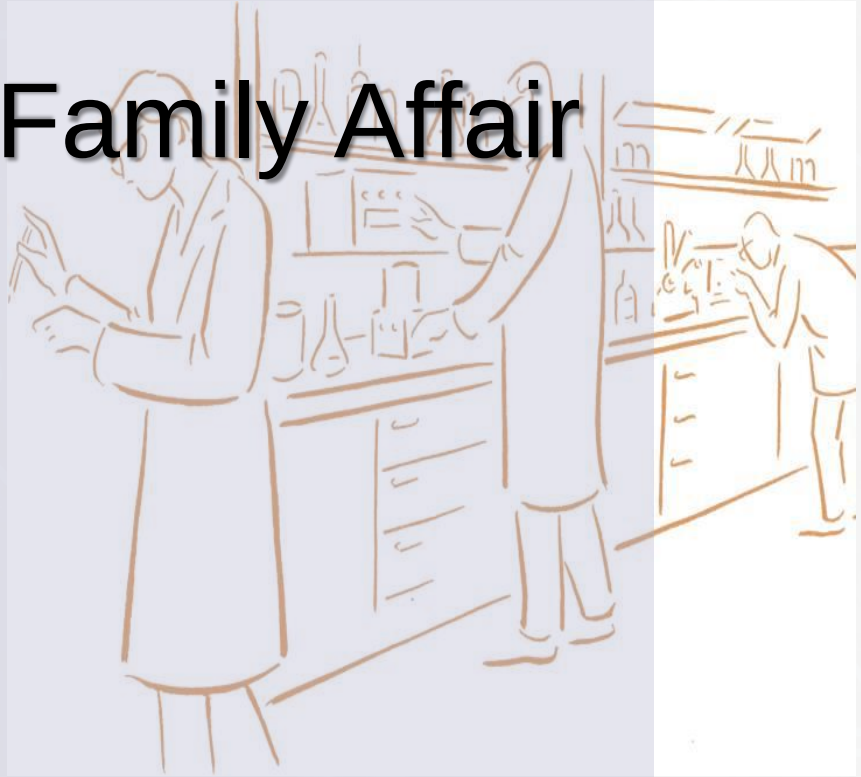
- High molecular weight polymers are **not readily absorbed** (oral >1,000 Daltons, topical >400 Daltons) and are **nontoxic**, (EPA 49 CFR No. 226, Nov, 21, 1984) i.e., PEGs, carbomers, hypromellose.
- CDER Guidance for Industry - Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients - Sect. 3 E:

> *"excipients that are **large polymers** that differ from previously characterized excipients only in molecular weight (chain length) can be **adequately characterized** in an abbreviated manner **using less safety data**, provided that the new excipient is **sufficiently similar** to the others with regard **to physical state, PK, levels of unreacted monomers and other impurities**"*

- ICH Principles:
  - Reduce animal testing (duplication)
  - Streamline regulatory assessment (save time)
  - Maximize resources
  - All without compromising safety

Excipients – A Family Affair

Polymers

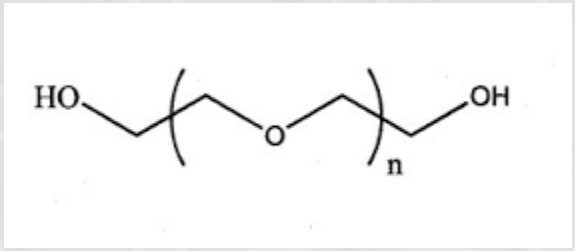


How is a Polymer Defined?

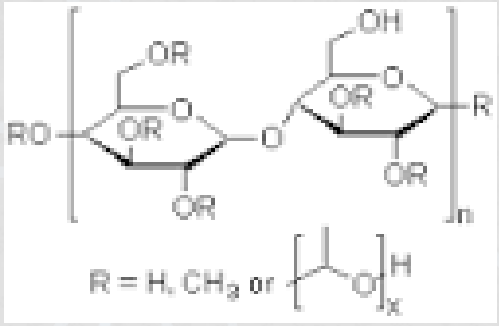
- **US FDA** (Callahan et al.,)
  - Structural repeating units, type, geometry, type of copolymer (block or random), ratio of monomers, modifications, molecular weight or properties related to molecular weight, biological source for many biopolymers

Presentation "Defining Excipients in the Substance Registration System" – Slide #10
http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm380688.htm

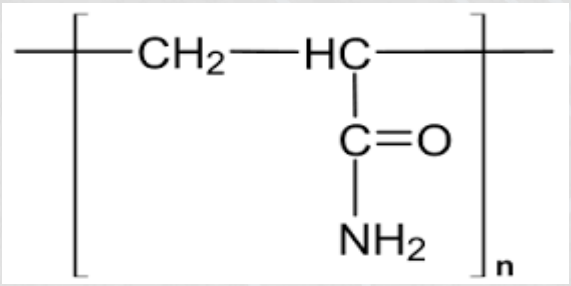
Typical Polymers



PEG



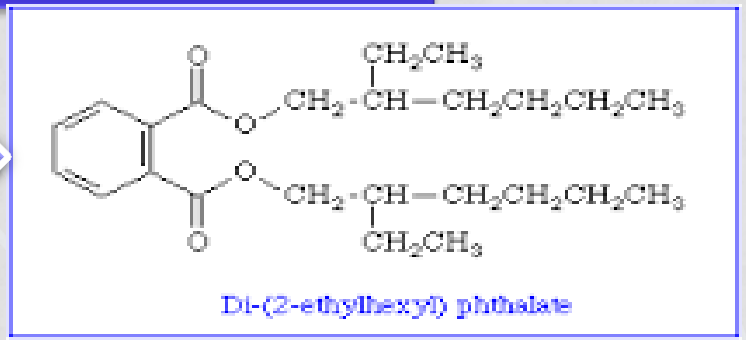
Hypromellose

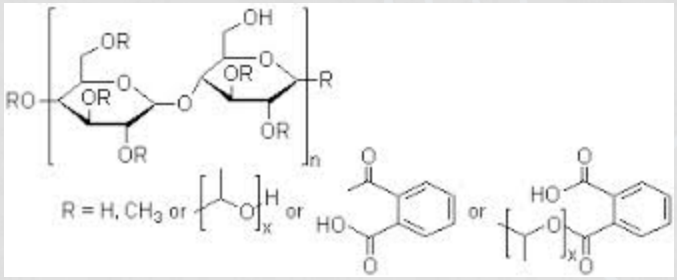


Polyacrylamide

Key is ≥3 Repeating Monomer Units

Di(2-ethylhexyl) phthalate *is not a polymer*





Hypromellose phthalate *is a polymer*

CDER Regards Polymers as Individual Substances

HPMC example

IID Listing	UNII
HYPROMELLOSE 2910 (3 MPA.S)	0VUT3PMY82
HYPROMELLOSE 2910 (5 MPA.S)	R75537T0T4
HYPROMELLOSE 2910 (6 MPA.S)	0WZ8WG20P6
HYPROMELLOSE 2910 (15 MPA.S)	36SFW2JZ0W
HYPROMELLOSE 2910 (50 MPA.S)	1IVH67816N
HYPROMELLOSE 2910 (4000 MPA.S)	RN3152OP35
HYPROMELLOSE 2910 (15000 MPA.S)	288VBX44JC
HYPROMELLOSE 2906 (50 MPA.S)	612E703ZUQ
HYPROMELLOSE 2906 (4000 MPA.S)	5EYA69XGAT
HYPROMELLOSE 2208 (3 MPA.S)	9H4L916OBU
HYPROMELLOSE 2208 (100 MPA.S)	B1QE5P712K
HYPROMELLOSE 2208 (4000 MPA.S)	39J80LT57T
HYPROMELLOSE 2208 (15000 MPA.S)	Z78RG6M2N2
HYPROMELLOSE 2208 (100000 MPA.S)	VM7F0B23ZI

Substitution Type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

IID Listing	UNII
HYPROMELLOSES	3NXW29V3WO

EPA/ECHA: all HPMC (hypromellose) grades are the same

Generally Polymers Are/Have

- **High molecular weight**
  - Carbohydrate: rye pentosans 225,000 to 700,000 Da
  - Hypromellose 4000 to 1,900,000 Da
  - PEO 200,000 – 8,000,000 Da
  - PEG 400 – 100,000 Da
- **Not absorbed (exception water soluble fiber)**
- **Chemically inert**
- **Similar toxicity across MW**
  - PEG 400 to PEO 8,000,000

Family Approach (Read-Across)

- **What is a Family/Group (ECHA)**
  - structurally similar with physicochemical, toxicological, ecotoxicological and/or environmental fate properties that are likely to be similar or to follow a regular pattern may be considered as a ***group*** of substances.
    - Common functional group (*i.e.* chemical similarity within the group) C14-16 (even numbered) and C16 (branched) saturated and unsaturated aliphatic hydrocarbons
    - Common precursors and/or likely common breakdown products *via* physical and/or biological processes which result in structurally-similar degrading chemicals
    - A constant pattern in the properties across the group (*i.e.* of physico-chemical and/or biological properties)

Family Approach (Read-Across)

- **Read-Across (ECHA)**
  - Technique for predicting endpoint information for one substance, by using data from the same endpoint from (an)other substance(s). The read-across approach must be considered on an endpoint-by-endpoint basis due to the different complexities (*e.g.* key parameters, biological targets) of each endpoint.

- **EPA**
  - Chemical Assessment Clustering Engine designed to help facilitate read across to fill data gaps for untested substances

Excipient Polymers

- **Model Excipient Polymers**
  - Meet EPA's definition of Polymers of Low concern*
    - Includes functional groups carboxylic acids, aliphatic hydroxyl, unconjugated olefinic groups, etc (i.e. no reactive groups)
    - Stable non-reactive backbones of high molecular weight.
  - Polyethylene Oxide and Hypromellose (HPMC)
    - Peered reviewed in JEFCA and/or CIR documents
    - HPMC – GRAS status for food additives
  - Pharmacokinetic and Oral Repeat Dose Studies in Animals and Humans

*EPA (1997) Polymer Exemption Guidance Manuel, Office of Pollution and Prevention and Toxics, EPA 744-B-97-001

What Has Been Submitted to FDA & Other Agencies

- **Hypromellose (HPMC)**
  - GRAS: 20 g/day limit via food
  - JECFA: reviewed multiple cellulosics (HPMC, ethyl, carboxymethyl, etc.); did not limit consumption via food, i.e., ADI "not specified" = does not represent a hazard to health.
  - CIR: toxicology data from 26 cellulosics show the family to be non-toxic.
  - Standardized tox templates have been provided for all 4 priority excipients by IPEC-Americas

Microsoft Word Document

Conclusions

- **The family approach and read across are appropriate for polymers**
  - Non-toxic
  - Limited or no absorption (large inert molecules)
- **Where dietary approvals exist, there is minimal concern for pharmaceutical use**
  - HPMC GRAS ≤20 g/day indicate a lack of toxicity for entire family
  - JECFA ADI "not specified"

Summary - Top Priorities and Current Focus Areas

- Refining the excipient family approach to facilitate **common pharm-tox evaluations**
- Review of **priority excipient families**, including hypromellose, polyethylene oxides, silicone, and carbomers
- A **standardized approach** for supplying excipient information to streamline the submission and review processes
- **Revise FDA guidance documents** by correcting contradictory and inconsistent information

We MUST Streamline this process and use good science to assess the REAL Risk!

IPEC-Americas Expectations

- **Formalized acceptance by FDA for use of the Family Approach**
  - Use of the Family Approach for
    - Hypromellose
    - Polyethylene oxide
    - Carbomers
    - Dimethicone
  - Post "reviewed" Family Approach spreadsheets on FDA website
  - Process for submitting pharm/tox templates for other "priority" excipient families

Current Situation

- FDA is **still** reviewing all the information submitted by IPEC-Americas in 2012-13 and is **still** discussing the acceptability of the family approach internally

- **FDA - no set timeline for decision at this point**

- IPEC-Americas is hopeful that a decision will be made soon to help clarify the use of many polymers in generic drug development

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Questions?