Making Industry Data Available in GInAS

An IPEC-Americas Perspective

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Agenda Items

- IPEC-Americas Perspective - Industry involvement
- Possible use of GInAS for safety references, spectral identification, & elemental impurity information
- Industry assessment of GInAS data for accuracy
- Information/data handling sourced from multiple excipient manufacturers
- Possible misuse of the GInAS data
- Specified substances – confidentiality requirements
- Changes needed in SRS/UNII nomenclature Rules
- Process for updating GInAS data/information found to be incorrect

IPEC-Americas Perspectiveon GInAS

- IPEC-Americas supports the development of the GInAS database
- A global ingredient database such as GInAS would be helpful to compile and standardize substance information that can be available to global regulators and the industry
- HOWEVER, it will be critical to have each manufacturer for a substance entered into GInAS involved in reviewing and ensuring that the data/information loaded into GInAS is correct

IPEC-Americas Perspective on GInAS

- Types of industry data and information to consider adding to the GInAS database early on might include:
  - **Safety data and toxicology summary information related to the safety of the excipient and excipient families**
  - **Spectral library identification information**
  - **Elemental impurity concentrations, where available**
- Some defining properties and/or product specifications may be difficult to acquire due to various issues, including confidentiality

UNII Codes ≠ Safety Assessment

Need to differentiate between Substance ID (particular material / substance) versus safety coverage (may have been designed to cover a family of materials).

UNII code	• **Identification of a specific substance which exists in a previously approved 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

IID Listings for Hypromellose

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, SUSTAINED ACTION		3NXW29V3WO	670.04MG
HYPROMELLOSES	ORAL; TABLET, COATED		3NXW29V3WO	245.00MG
HYPROMELLOSES	ORAL; TABLET, CONTROLLED RELEASE		3NXW29V3WO	65.70MG
HYPROMELLOSES	ORAL; TABLET, DELAYED ACTION, ENTERIC COATED		3NXW29V3WO	127.29MG
HYPROMELLOSES	ORAL; TABLET, EXTENDED RELEASE		3NXW29V3WO	400.00MG
HYPROMELLOSES	ORAL; TABLET, FILM COATED		3NXW29V3WO	536.80MG
HYPROMELLOSES	ORAL; TABLET, MULTILAYER, EXTENDED RELEASE		3NXW29V3WO	8.40MG
HYPROMELLOSES	ORAL; TABLET, ORALLY DISINTEGRATING		3NXW29V3WO	6.11MG

Inactive Ingredient Search for Approved Drug Products

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Search Results for: "hypromellose 2910

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL; TABLET, SUSTAINED ACTION, COATED			6.00MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL; TABLET, SUSTAINED ACTION, FILM COATED			54.00MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL-21; TABLET			0.75MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL-28; TABLET			0.75MG
HYPROMELLOSE 2910 (5 MPA.S)	ORAL; TABLET			2.02MG
HYPROMELLOSE 2910 (6 MPA.S)				1.76MG
HYPROMELLOSE 2910 (6 MPA.S)				6.43MG

If the new SRS/UNII nomenclature is used to determine the acceptable level of Hypromellose 2910 (5 MPA s), this would result in saying that levels over 2.02 mg/dose might require full safety data which doesn't make any sense!

Inactive Ingredient Search for Appro... Drug Products

About this Database Back to Search Page

Search Results for: Hydroxypropyl Methylcellulose E5

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
HYDROXYPROPYL METHYLCELLULOSE E5	ORAL; CAPSULE			9.00MG
HYDROXYPROPYL METHYLCELLULOSE E5	ORAL; TABLET		Pending	1.50MG

Safety of Hypromellose, HPMC

- There are many grades (industrial, cosmetic, food and excipient) and viscosities (5 mPa.s, 50 mPa.s, 5000 mPa.s etc) for HPMC as well as all other cellulose ethers. Numerous toxicology studies have been performed on all of these with consistent results, regardless of the grade tested. Further, the toxicology of the different types of HPMC is not dependent on the methoxy and hydroxpropoxy content.

- Viscosity is not specified by JECFA as a factor related to the safety of these additives.
  Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Hydroxypropyl Cellulose Toxicology Monograph 687, FAS 26–JECFA 35/85, 1989; *http://apps.who.int/ipsc/database/evaluations/search.aspx*.

- CFSAN concluded that for cellulose and cellulose derivatives there is no safety effect arising from a change in viscosity.
  http://www.gpo.gov/fdsys/pkg/FR-2011-07-15/pdf/2011-17928.pdf

Different viscosity "family" of polymers with same toxicology profile

Inactive Ingredient	Route;	dosage form	CAS#	UNII	Max Potency
HPMC –Hypromellose/hydroxypropyl methylcellulose chemical composition differences are distinguished only by type, which is defined in compendia monographs, and are based on methoxy and hydropropoxy content. Viscosity is a physical parameter used to differentiate grades within a type.					
Hypromellose 2208 (15000 mPa.s)	ORAL	Capsule, sustained action, hard gelatin		Z78RG6M2N2	2.771 mg
Hypromellose 2208 (15000 mPa.s)	ORAL	Tablet, sustained action		Z78RG6M2N2	480 mg
Hypromellose 2208 (60000 mPa.s)	ORAL	Tablet, extended release		2F7T07H9ZD	175 mg
Hypromellose 2208 (80000 – 120000 mPa.s)	ORAL	Tablet, extended release	9004653	VM7F0B23ZI	54 mg
Hypromellose 2910 (15000 mPa.s)	ORAL-21	Tablet		288VBX44JC	0.75 mg
Hypromellose 2910 (15000 mPa.s)	ORAL	Tablet, enteric coated particles		288VBX44JC	445 mg
Hydroxypropyl methylcellulose 2906	ORAL	Tablet, film coated	9004653	Pending	[none]
Hydroxypropyl methylcellulose 2906	ORAL	Tablet	9004653	Pending	50 mg

Different viscosity "family" of polymers with same toxicology profile

Inactive Ingredient	Route;	dosage form	CAS#	UNII	Max Potency
Ethylcellullose – some listings have viscosity grade, others do not					
Ethylcellulose 20 mPa.s	ORAL	Tablet, extended release	9004573	BJG0S321QY	28.3048 mg
Ethylcellulose 50 mPa.s	ORAL	Tablet, extended release		6I475159RA	5.8728 mg
Ethylcelluloses	ORAL-28	Tablet		7Z8S9VYZ4B	1.05 mg
Ethylcelluloses	ORAL	Tablet, sustained action		7Z8S9VYZ4B	308.80 mg
Carboxymethylcellulose Sodium					
CMC Sodium	ORAL	Capsule, sustained action	9004324	K679OBS311	0.469 mg
CMC Sodium	ORAL	Capsule	9004324	K679OBS311	160 mg
CMC Sodium	ORAL	Tablet, coated	9004324	K679OBS311	2.2 mg
CMC Sodium	ORAL	Tablet	9004324	K679OBS311	48 mg
CMC Sodium	ORAL	Tablet, sustained action	9004324	K679OBS311	155 mg
Methylcellulose					
Methylcellulose	ORAL	Capsule, extended release	9004675	N/A	2.67 mg
Methylcellulose	ORAL	Tablet	9004675	N/A	183.6 mg

Safety Data for GInAS

- Industry would probably be willing to supply safety data on excipient families which could be included in GInAS **where that data is published**
  - **IPEC-Americas could help develop a template and process for how this data might be collected and provided**
- Non-published safety data is typically considered to be confidential and probably would **NOT** be supplied without some type of Intelectual Property (IP) protection mechanism similar to what exists for a Drug Master File (DMF)
  - **Must guarantee the information is not available under FOI**

Spectral Library Information

- Excipients from various manufacturers may have different spectral profiles due to compositional differences from different raw materials sources and manufacturing processes
- IPEC-Americas has worked with the US FDA to help establish a “spectral library” for common excipients from various manufacturers
- IPEC-Americas would be interested in working with the GInAS group to define how this library of information could best be incorporated into the GInAS database

Elemental Impurity Data

- IPEC-Americas members have collaborated with personnel from the FDA Research laboratories in St. Louis and have provided them with blinded samples of various excipients that they analyzed for extensive (ICH Q3D) elemental impurity profiles
  - **Samples were blinded for supplier information by IPEC-Americas to ensure supplier anonymity**
- FDA laboratory personnel have completed their analysis and plan to publish their data soon.
  - **FDA has indicated an interest in finding an appropriate mechanism for making this data broadly available for use during *assessing the risk* of elemental impurity concentrations for drug products.**

Elemental Impurity Data

- Various industry groups have begun to compile "typical" elemental impurity data for some excipients and APIs
- A template is being developed to standardize how information related to sample preparations, analytical methods and data should be compiled and shared
- Elemental impurity data uploaded into GInAS must be clearly defined as "typical" since it is expected that the data will be based on a limited number of samples from only a few suppliers.
- Data should:
  - **NOT be used to represent any type of specification or established range**
  - **ONLY represent "likely concentrations" based on currently available data**

Elemental Impurity Data

- Traceability to, and confidentiality of the supplier of the data for each substance is CRITICAL
  - **Without appropriate confidentiality protection, manufacturers may not share their data**
- IPEC-Americas is considering the design and implementation of a mechanism where suppliers could submit their data for vetting, blinding and subsequent uploading into GInAS
  - **Source of funding for administration of the process / database is required for this to proceed**

Correctness Assessment of Data

- Substance data/information uploaded into GInAS should be assessed for accuracy, by substance manufacturers, prior to publicizing it in the GInAS database.
- The data/information assessment should take place, *through a standardized process*, well **BEFORE** publicizing it in the GInAS database
- Information found to be incorrect (by manufactures) should be corrected (via a a simple mechanism) **PRIOR** to publicizing it in the GInAS database

Handling Information/Data from Multiple Manufacturers

- Need to define a mechanism to address excipient formulation and/or processing differences (which can be significant) between manufactures of the same substance
  - **the type and level of additives or residual processing aids can vary between manufacturers**
- Need to ensure STRICT CONFIDENTIALITY adherence for competitively sensitive formulation and manufacturing information.

Possible Misuse of GInAS Information/Data

- Publicizing compositional/impurity profile information for a manufacturer could lead to misuse by other manufacturers who could use and/or misrepresent the data/information as their own.
  - **This information could sometimes be used by competitors to identify confidential aspects of a manufacturer's process or simply say that their product also meets this criteria when this may not be true**
  - **Manufacturers typically will only provide detailed compositional / impurity profile information when an appropriate mechanism exists to ensure that the information is held confidential by the party (regulatory authorities) authorized to view it.**
    - **This may be difficult in some countries where these assurances may not be adequately controlled**

Specified Substances L1

- Information to be included in Specified Substances appears to include specific quantitative formulation (%s) for excipient mixtures
  - **This can only be provided by the specific excipient manufacturers or with their permission regardless of what FDA may have on file due to IP concerns**
- Can certain information such as this be made only visible to regulators?
- **KEY ISSUE** - Confidentiality of trade secret information such as manufacturing process and quantitative formulation information of excipient mixtures

Slide 18

L1 do you mean substance identifiers? No where in my search of the US FDA CDER website or the SRS/UNII webpages do I find reference to a specified substance
ULMAN, KATHERINE L., 6/4/2014

Specified Substances – Confidentiality

- IP Protection **MUST** exist in the same manner as is done with DMFs – this information can only be visible to regulators and cannot be available through FOI

- **Bottom Line** – if appropriate IP Protection cannot be guaranteed, industry will probably not be willing to assist in providing specified substance information for inclusion in GInAS

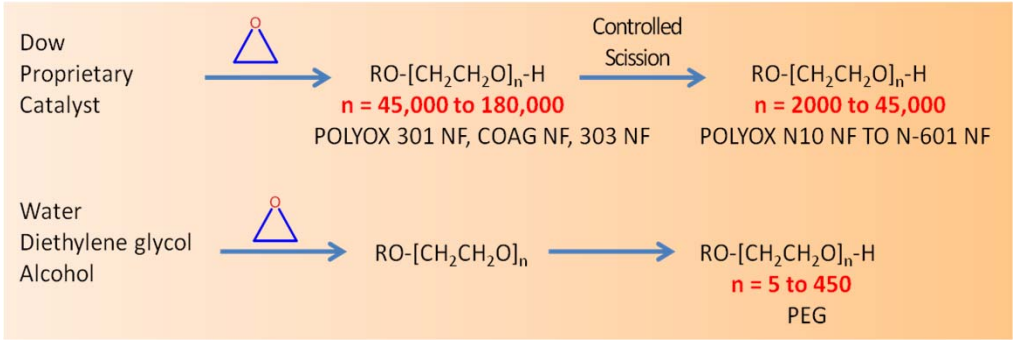
SRS/UNII Nomenclature Rules – Changes Needed

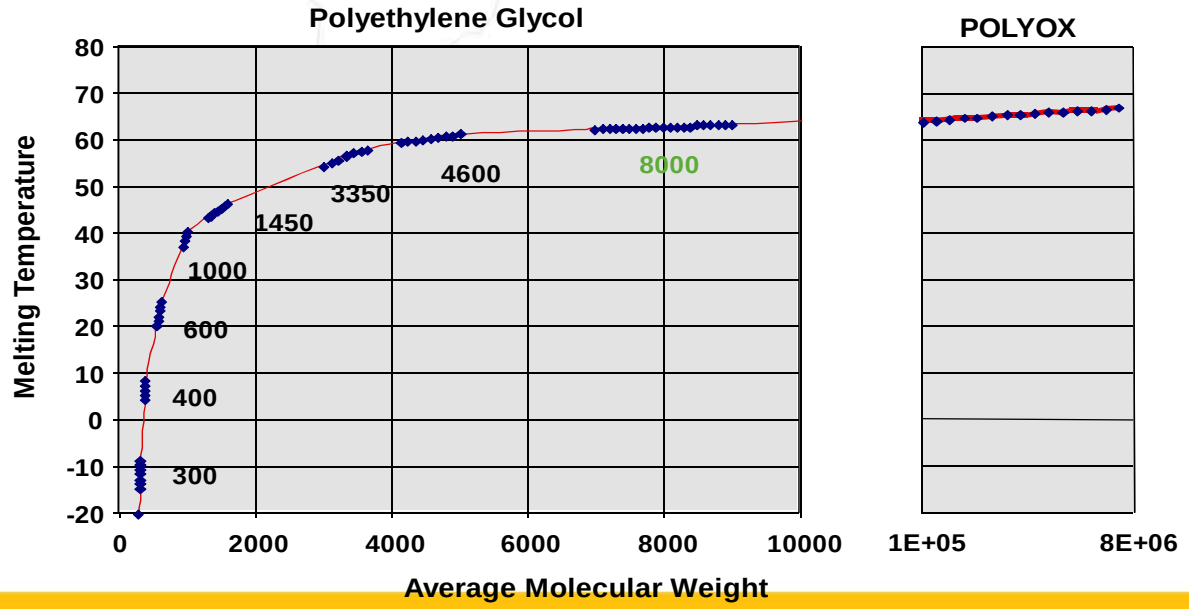
- Nomenclature issues with some currently registered substances have created significant concerns and confusion throughout industry
- Prior to deployment of GInAS, it critical to assess and correct, where needed, SRS/UNII nomenclature rules
- Two examples:
  - **Polyethylene oxide changed to polyethylene glycol**
  - **Aluminum lakes changed to aluminum oxide and the associated dye**

Polyethylene oxide(POLYOX) versus Polyethylene glycol (PEG)

Polyethylene oxide vs Polyethylene glycol

1) Different physical states
2) Different molecular weights
3) Different manufacturing process
4) Different impurity profiles





Organism	Test Type	Route	Reported Dose (Normalized Dose)
Polyethylene Oxide WSR N-10 (100,000 daltons)			
Rat	LD50	Oral	>4000 mg/kg* (148,000 mg/m²)
Rabbit	LC50	Dermal	>2000 mg/kg* (74,000 mg/m²)
Polyethylene Oxide WSR 301 (4,000,000 daltons)			
rat	LD50	Oral	>2000 mg/kg* (74,000 mg/m²)
Rabbit	LD50	Dermal	>400 mg/kg* (14,800 mg/m²)

Aluminum Lakes

- FD&C and D&C Aluminum Lakes are unique substances defined in 21 CFR
- 21 CFR requires that these lakes be labeled as “FD&C or D&C <Dye Name> Aluminum Lake”
- Grades are identified by dye strength (ie; 15-17% or 38-42%)
- The SRS/UNII nomenclature creates significant confusion throughout industry and can’t be used in regulatory documentation or labels due to conflicting regulations
- Current SRS/UNII rules have defined these Lakes as:
  - **aluminum oxide and**
  - **individual dye used in manufacturing**
- Aluminum Lakes are **NOT** mixtures of these materials!

Simple Mechanism for Corrections

- When data/information uploaded into GInAS is found to be incorrect, **a process for industry to make corrections is needed**.
- The process should be:
  - **simple**
  - **standardized.**
  - **allow for quick changes**

IPEC-Americas Involvement

- IPEC-Americas members would like to be actively involved in further development of the GInAS database.
- IPEC-Americas members would welcome discussions with the GInAS implementation team as they work to develop acceptable resolutions for the concerns identified in this presentation
- IPEC-Americas members appreciates the opportunity to participate in this meeting and in the future development of GInAS

THANKS FOR YOUR TIME & ATTENTION