IPEC Americas –GPhA-FDA-OPQ Face-to-Face Meeting, Inactive Ingredient Database (IID)
September 18, 2015

Attendees

FDA STAFF	ORGANIZATION: DHHS/FDA/	JOB POSITION	e-Mail
Susan Zuk	CDER/OPQ/OPPQ	Lead Chemist	Susan.Zuk@fda.hhs.gov
Rogelio Ruvalcaba, MS, RD	CDER/OPQ/OPPQ	Project Manager	rogelio.ruvalcaba@fda.hhs.gov
Lawrence Callahan	OC/OO/OIMT/OITI/ISS/DS	Chemist	callahanl@cder.fda.gov
Kristin Davis	CDER/OGD/OGDP/DLRS	Policy Advisor	davisk@cder.fda.gov
Mohamed Ghorab	CDER/OPQ/OPPQ/DRGS/PD	Lead Chemist	Mohamed.Ghorab@fda.hhs.gov
Huong Huynh	CDER/OGD/OB/DBIII	Pharmacologist, Division of Bioequivalence	Huong.Huynh@fda.hhs.gov
Michael Jones	CDER/OGD/OGDP	Regulatory Director	jonesm@cder.fda.gov
Julia Lee	CDER/OGD/ORO/DFR	Pharmacist	Julia.Lee@fda.hhs.gov
Jennifer Liang	CDER/OPQ/OLDP/DMRP/MR	Lead Chemist	Jennifer.Liang@fda.hhs.gov
Iain Margand	CDER/OGD/OGDP/DLRS	Regulatory Director, Division of Filing Review	iain.margand@fda.hhs.gov
Melanie Mueller	CDER/OGD/OB/DCR	Staff Fellow	Melanie.Mueller@fda.hhs.gov
Shahnaz Read	CDER/OPQ/OPPQ/DIPAP/P	Chemist	reads@cder.fda.gov
Arthur Shaw	CDER/OPQ/ONDP/DNDPII/	Chemist	shawa@cder.fda.gov
Frank Switzer	OC/OO/OIMT/OITI/ISS/DS	Chemist	Frank.Switzer@fda.hhs.gov
Nilufer Tampal	CDER/OGD/OB/DBIII	Pharmacologist	nilufer.tampal@fda.hhs.gov
Naiqi Ya	CDER/OPQ/OPF/DPAII	Supervisory Chemist	naiqi.ya@fda.hhs.gov
Johnny Young	CDER/OGD/ORO/DFR	Pharmacologist	johnny.young@fda.hhs.gov
PHONE			
Jasmeet Kalsi	CDER/OGD/ORO/DPM	Pharmacist	jasmeet.kalsi@fda.hhs.gov
Jason Woo	CDER/OGD/IO	Senior Medical Officer	Jason.Woo@fda.hhs.gov

IPEC MEMBERS	MEMBER COMPANY	Title	e-Mail
Katherine Ulman	Dow Corning Healthcare	Global Reg. Compliance Manager	Katherine.l.ulman@dowcorning.com
David Schoneker	Colorcon	Director, Global Reg. Affairs	DSchoneker@colorcon.com
Priscilla Zawislak	Ashland Inc.	Global Regulatory Affairs Manager	pszawislak@ashland.com
Meera Raghuram	The Lubrizol Corporation	Manager, Global Reg. Affairs & Strategies	Meera.Raghuram@lubrizol.com
Raphael Nudelman	Teva Pharmaceutical Industries Ltd.	Associate Director, Head of Chemical & Computational Toxicology	Raphael.Nudelman@teva.co.il
Kim Beals	IPEC-Americas Staff	Executive Director	Kim.beals@ipecamericas.org
GPhA		**Title**	**e-Mail**
Lisa Tan	Generic Pharmaceutical Association	Associate Vice President, Sciences and Regulatory Affairs	ltan@gphaonline.org

Meeting Summary

1. Meeting purpose

IPEC – Americas and GPhA to review historical IID issues/status with current FDA OPQ IID Excipient Working Group and to have FDA provide a status of its IID clean-up initiatives.

2. Meeting Agenda

Proposed:

Introductions	
Joint review of historical IID issues/status and future plans/timelines	refer to table of historical issues below
Joint review of URGENT IID issues	Based on most recent posting – see summary attached PER FDA REQUEST, FDA to address offline.
FDA overview of current IID activities and plans	FDA to share any activities not discussed as part of the historical overview
Miscellaneous topics if time available - **Implant product listings and interpretation** - **Clarity on FDA Policy for Type IV eDMFs**	*Lack of a consistent approach in IID potency values for implant products makes it difficult to interpret data* *Seeking clarity to what FDA's expectations are for putting historical Type IV DMFs in eCDT format.*
Collaborative agreement on next steps	
Wrap-up	

a. Introductions

Susan Zuk called the meeting to order. Introductions were provided from the FDA and from the industry.

b. Historical Overview (Dec 2011 – July 2015) of IID Issues identified/addressed by IPEC-Americas/GPhA and FDA OGD/OPQ IID EWG

To bring the new FDA attendees up to speed, an overview summary of IID EWG discussions topics between Dec 2011 and July 2015 was provided to attendees ahead of the meeting.

	Issue	Responsibility	Status	IPEC Comments	September 18 Meeting comments
1	Post IID Files by quarter for past few years	FDA	Complete	Began posting after first meeting in Dec 2011 and have posted all subsequent meeting minutes.	No comments during meeting
2	Post proposed IID changes a quarter prior to them being made to allow for public comments	FDA	Pending	FDA should provide a list of all changes under review for change prior to implementation. This process needs to be implemented to ensure that changes are reviewed prior to implementation and we can provide input in those areas were we have concern. The issues from recent IID update (August 12 IID version) are summarized separately.	No comments during meeting
3	Highlight changes to subsequent IID postings	FDA	Pending	FDA needs to implement a change controls procedure to indicate what changes have been made and when.	No comments during meeting
4	Define preferred IID nomenclature	FDA	Ongoing	Nomenclature of select excipients has been revised to include preferred names. However, the SRS database needs to be thoroughly reviewed and updated to capture all synonyms.	In-progress…. Need to continue to work with Larry and Frank to ensure historical nomenclature and all relevant synonyms are captured in the SRS database
5	Mechanism for communication of missing records	FDA	Pending	No pathway for communication of missing records as controlled correspondence is no longer an avenue for excipients manufacturers	For now continue to send questions to the mailbox previously provided by Susan….FDA currently in-process of creating a new mailbox for these questions.
6	Inclusion of missing records in IID	FDA	Ongoing	FDA should provide a completion date for entry of the backlog of NDAs and ANDAs into the IID.	Susan to share in her presentation following this review.
7	Develop list of priority excipients	IPEC	Complete	IPEC provided information on 4 priority excipients for review of issues related to potency, family approach and toxicology studies supporting ADIs. The priority excipients include: Hypromellose, Polyoxyethylene oxide, Silicones and Carbomers.	This item was considered CLOSED because the initial list of 4 + 10 priority excipients was provided by IPEC-Americas in 2012; however, IPEC-Americas agreed to work with the FDA on a new list once the review process has been finalized for the initial 4 examples.
8	Apply maximum potency currently in IID to related excipients in the same family	FDA	Ongoing	Family approach being discussed. There are many sub items related to the family approach which is summarized separately.	The IPEC-Americas/GPhA recommendations from the July 30, 2015 meeting are currently being discussed by the Agency and they will formalize and present their response sometime in October 2015.

9	Update IID database to capture ADI as current potency value does not provide dosage information	FDA	No progress		FDA currently discussing this and will share their thinking at a later date. IPEC clarified that includes the following: 1. Maximum daily intake from drug applications 2. ADI calculated based on the toxicology data available for excipients
10	Develop IID Q&A document to assist potential sponsors	IPEC/FDA	Pending	IPEC worked with the agency in developing a phase I IID FAQ. It was communicated that the FAQ would be included in an agency guidance document currently being developed. No FAQ has been posted to date.	Due to resolution for several of the items on the original Q&A as well as plans to resolve/communicate others, the need for this Q&A is being placed on-hold for now. The FDA has opened a public docket asking for industry to communicate current issues/concerns specific to the IID and its use.
11	Develop IID training for OGD reviewers	IPEC/FDA	Pending		IPEC-Americas clarified that this was an OFFER from industry to help provide an INDUSTRY PERSPECTIVE of the IID for FDA reviewer training. FDA to consider.
12	Revise FDA guidance documents (RTR and CC to correct contradictory and inconsistent information)	FDA	Pending		No comment during meeting.
13	Allowance for read across IID listings between routes of administration which are relatively similar such as buccal vs. sublingual or oral .	FDA	Pending	The scientific merits of the justification provided should be reviewed by a subject matter expert during the technical review process.	No comment during meeting.

c. Joint review of URGENT IID issues

Per comments from FDA this list is being reviewed and will be internally addressed. A couple of general comments included:

- During the last update the maximum potency and/or units for several listings were made due to a review/correction from the original application.
- Several of the items were related to SRS "synonym" references or other UNII related issues and these should be directed to fda-srs@fda.hhs.gov in the future.
- With regards to communication of changes to the IID, it was indicated that only significant changes can be captured and communicated. Due to complexity the databases and interrelationships, it is not feasible for the agency to identify all changes.

d. FDA overview of current IID activities and plans

Susan Zuk presented an overview of current FDA activities underway and planned. The topics covered are shown below.

1. Backlog progress

NDAs and ANDAs entered into the master database

- 100% NDAs approved 2008-2015
- 100% ANDAs approved 2013-2015
- 24% ANDAs approved 2008 – 2012

2. Communication of IID errors

- An IID mailbox, to inform the FDA of the need for IID corrections and to ask questions about the IID, will be available soon.

3. Update on IID clean-up and activities

- Projected clean-up completion April 2016
- Next IID publication projected for Oct 31, 2015
- Elimination of incorrect extreme values continues
- Topical potency units are being converted and correction to %w/w, %w/v, %v/v
- Next dosage form to fix is oral liquids
- Process of data entry verification continues to eliminate incorrect values from the IID. New and revised entries are reviewed by OPQ and corrected, if necessary. The corrections are confirmed prior to publication.

4. Soliciting Input

- A Federal Register Notice was published to solicit input from industry on how we can make the IID more useful. See FR Notice [FR Doc. 2015-20556]. We welcome feedback and will be reviewing the comments to the docket once it closes.

The FR Notice questions for industry are as follows:

1. How can we improve nomenclature in the IID (*e.g.,* use of preferred ingredient names and synonyms in the database)?
2. How should we identify excipient amounts listed in the IID?
3. How should we reflect updates to the current IID to ensure completeness and accuracy?
4. Should we restructure the IID, and if so, how?
5. Are there additional suggestions or comments for IID improvement?

- **Internal User Survey (being sent to FDA staff)**

  We are also conducting an internal survey for CDER staff. There are many questions about the IID. In general, the following three topics are covered:

  1. Should the IID have less granularity?
  2. What is the best way to represent excipient potency for different dosage forms?
  3. Can we collapse dosage forms to simplify the IID?

  Comments should be sent to http://www.regulations.gov

5. Proposal to collapse dosage forms

The EWG is exploring the feasibility of consolidating certain dosage forms. This was a topic at the last CDER EWG meeting. Such a change would require advanced notice to both industry and FDA users of the IID. Below are some examples of collapsed dosage forms that were shared for discussion at the EWG meeting.

- Oral solids (consolidate: tablets, coated tablets, capsules, powders)
- Topical (consolidate: ointment, gels, creams, emulsions, ophthalmic, rectal, vaginal, powders)
- Oral liquids (consolidate: solutions, suspensions, syrups, tinctures, elixirs)

Exceptions: Certain dosage forms were deemed to be non-collapsible because the levels of excipients should be specifically linked to these products.

- Inhalers
- TDDS
- Nasal spray
- Injection

6. Use of historical IID for justification of use

Discussion NOTES:

- *Johnny Young, OGD indicated that the Standard in effect at the time of filing will be referenced. If historical information is being used, justification must be provided. Would be nice to have some capture in change control for updated correction on the IID*
- *Need to figure out how we can make some of these corrections*
- *Lisa noted that some of the sponsors have been working on their filings for more than 2 years based on historical IID listings and now with changes there needs to be a better way to capture.*

Review determination
Technical determination.

e. Miscellaneous topics if time available

We did not have time to discuss the miscellaneous items on the agenda during the meeting.

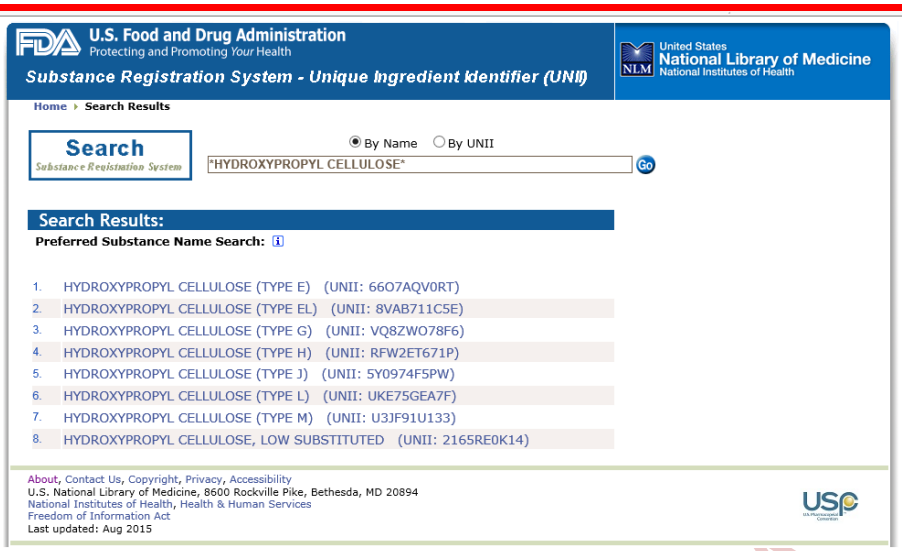
f. Collaborative agreement on next steps

Susan agreed to try and schedule longer future meetings. IPEC-Americas/GPhA team requested that the next meeting be held in December (December 11) at the time of the IPEC-Americas face-to-face committee meetings. Kathy to follow-up with Susan on this.

Appendix A
Urgent Issues

IPEC-Americas <u>urgent issues</u> with current upgrade (August 2015) of the IID database listings
In comparing listed ingredient information from the April 2015 US FDA IID database with listed ingredient information from the August 2015 US FDA IID database, several areas of concern were noted, examples of which have been summarized below. We believe that this is only a sampling of changes and issues that the industry will find confusing and difficult to understand.

1	**<u>Many decreased levels of use in the August 12th update</u>** **Some examples of where the max potency levels for oral applications decreased significantly are as follows:** • **Polyethylene Glycol 400 from 984.9 to 960.78mg** • **Simethicone from 36 to 7.5mg** • **Magnesium Stearate from 400.748 to 256.4mg** • **Corn Starch from 1135 to 600mg** • **Gelatin from 1000 to 733mg** • **FD&C Yellow No. 6 from 555 to 60.02mg** What should a generic drug manufacturer do if they formulated their ANDA product based on the earlier higher listings and now they find out that the level which was well under the old maximum level of use per dose is now higher than the new maximum level of use per dose? What guidance can be provided to the industry about what information may now be needed in their ANDA to show that the level they used is aligned with the previous versions of the IID? These are just a few examples of where the level decreased significantly. This will impact many ANDA's that are under development and the ones still at FDA under review. Clear guidance to industry on how to handle this situation is needed and this should be listed formally on the FDA website and not just be informal verbal guidance.
2	What does NA mean? It was added for some of the topical listings where before there were blanks in the maximum potency and in other cases the value from before was replaced with NA.
3	**Copovidone** was changed (in all instances) to copovidone K25-31. K25-31 is incorrect, if a K number is listed for copovidone it would be K28, but that is not the nomenclature used. The preferred substance name should be copovidone.
4	**Crospovidone** - the highest oral max potency, 792 mg is no longer listed. The highest oral listing now is 340 mg.
5	**Crospovidone** is now listed with 15 mPa.s @ 5%. This is not nomenclature used. Crospovidone per compendial designations is either Type A or Type B.
6	**Hydroxypropylcellulose** now has types listed as either H or L. The old version had a few L listings, but no H types. Most were listed as just hydroxypropylcellulose. It is unclear whether H or L refers to a viscosity type or substitution, though we believe it may be viscosity since there is a separate listing for low substituted hydroxypropylcellulose, which is often referred to as HPC-L. There are also hydroxypropylcellulose types E, G, J and M, but with the change to listing just H and L types, this is not reflected in the current IID. Drugs have been approved using these types, especially type E which is one of the most common types of hydroxypropylcellulose used. Further, the SRS still lists these types, but they are missing from the IID.



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Carbomer homopolymers (carbomers)

Deletion of records and addition of other records have created confusion. Clarification is needed for the following:

a. Records for **Carbomer 934** (Carbomer homopolymer Type B) for topical exposure with a potency of 1.498% has been deleted. A new record for carbomer homopolymer type C for topical route with a potency value of 1.75% has been added to IID. Clarification is needed on the deletion.

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Potency Unit	Current Record Status
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	57916924	4Q93RCW27E	1.75	%	Added Aug 2015
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	151687966	4Q93RCW27E	1.6	%	Deleted Aug 2015
CARBOMER 934	TOPICAL	GEL	9007163	Z135WT9208	1.498	%	Deleted Aug 2015

b. There are many records especially for the topical exposure route where potency value is provided both as % and wt. % and we need clarification on the difference between the records. An example is provided below.

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Potency Unit
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	57916924	4Q93RCW27E	1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	EMULSION, CREAM	57916924	4Q93RCW27E	1.2	%
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	EMULSION, CREAM	57916924	4Q93RCW27E	1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	CREAM	57916924	4Q93RCW27E	1.2	%W/W
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	CREAM, EMULSION, SUSTAINED RELEASE	57916924	4Q93RCW27E	1.2	%

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Carbomer homopolymers (carbomers)

Since carbomers are interchangeable whether they are crosslinked with allyl sucrose or ally pentaerythritol, the synonyms in the SRS database for carbomer homopolymer should be updated to include both cross linked materials. This is important so that both users and the agency drug reviewers are able to correlate generic and trade name nomenclature with preferred names in the IID. Two key points related to Carbopol polymers are following:

a) To allow customers to move from benzene grade to other preferred solvent grades of Carbopol, the UNII

Z135WT9208 synonyms in the SRS database for Carbomer 974 (ethyl acetate version) should be updated to include Carbomer 934. This will facilitate review and approval of Drug applications substituting benzene grade of Carbopol with more preferable solvent grades.

b) Carbopol grades 934P, 974P, 971P and 71G (carbomer homopolymers), carboxypolymethylene (Merck index nomenclature) should all be added synonyms for carboxypolymethylene in the SRS database.

The suggested synonyms are captured below:

Ingredient Name from IID PRIOR to 31July15 update)	UNII	Preferred Name (Currently in IID)	Add the following additional synonyms to the SRS database
CARBOMER 934	Z135WT9208	CARBOMER HOMOPOLYMER TYPE B (ALLYL SUCROSE CROSSLINKED)	Carbomer homopolymer Type B, Carbomer 974, Carbopol 974P
CARBOMER 934P	Z135WT9208	CARBOMER HOMOPOLYMER TYPE B (ALLYL SUCROSE CROSSLINKED)	Carbomer homopolymer Type B, Carbomer 974, Carbopol 974P
CARBOXYPOLYMETHYLENE	N/A	CARBOXYPOLYMETHYLENE	Carbopol 71G, Carbopol 971P, Carbopol 974P, Carbopol 934P

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Carbomer homopolymers

Update SRS database to include all synonyms. For carbomer homopolymers, carboxypolymethylene is a key reference and a valid synonym and should be added to the SRS database.

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Simethicone

In April the maximum potency listing for **Simethicone i**n an effervescent granule was 36 mg.

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Potency Unit	Date
SIMETHICONE	ORAL	GRANULE, EFFERVESCENT	8050815	Multiple	36	MG	April 2015 Listing
SIMETHICONE	ORAL	GRANULE, EFFERVESCENT	8050815	Multiple			August 2015 Listing

In August, the Maximum potency value was completely removed.

This is a concern for two reasons, one…there is no maximum potency listed simethicone in granule, effervescent and two this listing of 36 mg was the highest IID listing for any ORAL dose simethicone and

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Potency Unit	Date
SIMETHICONE	ORAL	TABLET, SUSTAINED ACTION	8050815	Multiple	7.5	MG	April 2015 Listing
SIMETHICONE	ORAL	TABLET, SUSTAINED ACTION	8050815	Multiple	7.5	MG	August 2015 Listing

the next highest listing is only for 7.5 mg

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Silicone Adhesive BIO-PSA (trimethylsilyl treated dimethiconol/trimethylsiloxysilicate crosspolymers)

In the April listing the **BIO-PSA Q7-4201** was assigned a UNII of 9N5G1G3D3H (which was the correct UNII); however, both the UNII and preferred names were changed in the August update. Both are now incorrect.

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Potency Unit	Date
SILICONE ADHESIVE BIO-PSA Q7-4201	TRANSDERMAL	FILM, CONTROLLED RELEASE		9N5G1G3D3H	228.23	MG	April 2015 Listing
TRIMETHYLSILYL TREATED DIMETHICONOL/TRIMETHYLSILOXYSILICATE CROSSPOLYMER (45/55 W/W; 100000 PA.S)	TRANSDERMAL	FILM, CONTROLLED RELEASE		5VBE2X0WG0	228.23	MG	August 2015 Listing
SILICONE ADHESIVE BIO-PSA Q7-4301	TRANSDERMAL	PATCH		5VBE2X0WG0	470	MG	April 2015 Listing
TRIMETHYLSILYL TREATED DIMETHICONOL/TRIMETHYLSILOXYSILICATE CROSSPOLYMER (40/60 W/W; 5000000 PA.S)	TRANSDERMAL	PATCH		9N5G1G3D3H	470	MG	August 2015 Listing

Similarly, in the April listing BIO-PSA Q7-4301 was assigned a UNII of 5VBE2X0WG0 (correct UNII assignment); however, both the UNII and preferred names were changed in the August update. Both are now incorrect.

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Microcrystalline cellulose

For **microcrystalline cellulose**, whereas the April 2015 database there were four different listings for cellulose, microcrystalline tablets for oral, (PH101, aqueous, 101, 102), the grade differentiations have now disappeared from the IID and all listings appear simply under the generic name Cellulose, Microcrystalline. Given the drive to utilize grade listings, it seems strange that the grade part of the nomenclature was removed. Are you treating MCC with a family approach already? If so, we are not against this change. We simply need to know what happened and why.

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Pot. Unit	Date	comments
CELLULOSE, MICROCRYSTALLINE PH101	ORAL	TABLET	9004346	OP1R32D61U	203.7	MG	15-Apr	
CELLULOSE MICROCRYSTALLINE, AQUEOUS	ORAL	TABLET		OP1R32D61U	240	MG	15-Apr	
CELLULOSE, MICROCRYSTALLINE 101	ORAL	TABLET	9004346	OP1R32D61U	232.74	MG	15-Apr	
CELLULOSE, MICROCRYSTALLINE 102	ORAL	TABLET	9004346	OP1R32D61U	900	MG	15-Apr	
CELLULOSE, MICROCRYSTALLINE	ORAL	TABLET	9004346	OP1R32D61U	1385.3	MG	15-Apr	
CELLULOSE, MICROCRYSTALLINE	ORAL	TABLET	9004346	OP1R32D61U	10	MG	15-Aug	new listing
CELLULOSE, MICROCRYSTALLINE	ORAL	TABLET	9004346	OP1R32D61U	203.7	MG	15-Aug	removed PH101
CELLULOSE, MICROCRYSTALLINE	ORAL	TABLET	9004346	OP1R32D61U	240	MG	15-Aug	removed aqueous
CELLULOSE, MICROCRYSTALLINE	ORAL	TABLET	9004346	OP1R32D61U	310.5	MG	15-Aug	removed 101?
CELLULOSE, MICROCRYSTALLINE	ORAL	TABLET	9004346	OP1R32D61U	641.5	MG	15-Aug	new
CELLULOSE, MICROCRYSTALLINE	ORAL	TABLET	9004346	OP1R32D61U	1553	MG	15-Aug	higher level

In the August upload there are 6 identical “ingredient names” with 6 different listings for maximum potency. Historically, it is our understanding that the intent was to only list the highest level of use for a particular route and dosage form once in the database. Why then are there so many multiple listings for the same exact route of administration and dosage form listed for MCC as shown above in GREEN? As shown in comparing the BLUE (April) and GREEN (Aug) listings, this resulted from removal of the grade designation; however, it will need to be corrected or it will create confusion by users (both industry and regulators).

Although shown above for ORAL, TABLET, there are multiple other examples of this for other microcrystalline cellulose TABLET listings (e.g. COATED; EXTENDED RELEASE; FILM COATED, etc.).

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Methacrylic Acid

IID continues to list entries of pure "methacrylic acid" for delayed release action. We cannot believe this but assume a mistake was made in the nomenclature relevant filing dossiers. Methacrylic acid as a pure acid is not able to support a delayed release function based on the opinion of a major manufacturer or methacrylic acid.

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Potency Unit
METHACRYLIC ACID	ORAL	CAPSULE, DELAYED ACTION	79414	1CS02G8656	20.4	MG
METHACRYLIC ACID	ORAL	CAPSULE, DELAYED ACTION	79414	1CS02G8656	20.401	MG
METHACRYLIC ACID	ORAL	CAPSULE, DELAYED RELEASE	79414	1CS02G8656	27.93	MG
METHACRYLIC ACID	ORAL	CAPSULE, DELAYED RELEASE	79414	1CS02G8656	27.93	MG
METHACRYLIC ACID	ORAL	CAPSULE, EXTENDED RELEASE	79414	1CS02G8656	55.58	MG
METHACRYLIC ACID	ORAL	CAPSULE, EXTENDED RELEASE	79414	1CS02G8656	55.58	MG
METHACRYLIC ACID	ORAL	TABLET, DELAYED ACTION	79414	1CS02G8656	16.29	MG
METHACRYLIC ACID	ORAL	TABLET, DELAYED RELEASE	79414	1CS02G8656	10.3	MG
METHACRYLIC ACID	ORAL	TABLET, EXTENDED RELEASE	79414	1CS02G8656	12	MG

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Silicon Dioxide, Colloidal

There are more than 50 examples were **Silicon Dioxide, Colloidal** has been replaced with Silicon Dioxide and both have been assigned the same UNII code;

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Pot. Unit	Date	comments
SILICON DIOXIDE, COLLOIDAL	ORAL	GRANULE	7631869	ETJ7Z6XBU4	100	MG	15-Apr	Colloidal
SILICON DIOXIDE	ORAL	GRANULE	7631869	ETJ7Z6XBU4	100	MG	15-Aug	
SILICON DIOXIDE, COLLOIDAL	ORAL	TABLET	7631869	ETJ7Z6XBU4	99	MG	15-Apr	Colloida
SILICON DIOXIDE	ORAL	TABLET	7631869	ETJ7Z6XBU4	99	MG	15-Aug	
SILICON DIOXIDE, COLLOIDAL	ORAL	TABLET, EXTENDED RELEASE	7631869	ETJ7Z6XBU4	70	MG	15-Apr	colloidal
SILICON DIOXIDE	ORAL	TABLET, EXTENDED RELEASE	7631869	ETJ7Z6XBU4	70	MG	15-Aug	

however, the various types of silica (e.g. colloidal silica, fumed silica and precipitated silica) which have all been assigned the same UNII code/preferred substance name, can be VERY DIFFERENT and have significantly different "safety" profiles.

Fused silica is glass consisting of silica in amorphous (non-crystalline) form

Fumed silica (SiO_2) is produced in a flame resulting powder has an extremely low bulk density and high surface area. Primary particle size is 5–50 nm. The particles are non-porous and have a surface area of 50–600 m^2/g. The density is 160–190 kg/m^3

Ground silica is a crystaline form of silica (SiO_2), also known as ground quartz or silica flour. It is produced by grinding high-purity quartz to finer than 200 mesh. It has a typical specific gravity of 2.65 g/cm^3.

Precipitated (amorphous) silica is a silica (SiO_2) produced by precipitation from a solution containing silicate salts. The particles are porous. Primary particles with a diameter of 5 - 100 nm, and specific surface area 5-100 m^2/g. Agglomerate size is 1 - 40 µm with average pore size is > 30 nm. Density: 1.9 – 2.1 g/cm^3.

Colloidal silicas are suspensions of fine amorphous, nonporous, and typically spherical silica particles in a liquid phase. Colloidal silicas exhibit particle densities in the range of 2.1 to 2.3 g/cm^3.

Aerogel is a synthetic porous ultralight form of silica derived from a gel, in which the liquid component of the gel has been replaced with a gas,

In April 2015, Silicone dioxide, colloidal was listed at a max oral use of 100 mg, now it is has been merged with other forms of silica and listed as silicone dioxide which has a max oral use of 170 mg. Why is Colloidal Silicon Dioxide no longer listed? As shown above, this material is different than regular silicon dioxide and needs to have a separate listing. This material is used in many, many approved drug applications so it needs to be listed to minimize confusion on what should be used.

15

Starch, Pregelatinized Corn

The April 2015 listing for **Starch, Pregelatinized Corn** appears to have been changed, based on the UNII number, to Starch, Corn which is incorrect. Starch, Pregelatinized Corn is not the same as Starch, Corn and they should NOT have the same UNII number. It appears that they had the same UNII number in the April 2015 listing (which was incorrect) but at that time they still had different names. Now the name seems to be merged and this will cause much confusion since Starch, Pregelatinized can be found in both the April 2015 and August 2015 listings. In both versions Starch, Pregelatinized does not have a UNII code. Someone who uses Starch, Pregelatinized Corn will be very confused by this and will not probably realize that the previous listings are now listed as regular Starch, Corn. This should be corrected to continue the Starch, Pregelatinized Corn listings but they should be assigned a separate UNII code from Starch, Corn. Also, a UNII code should be assigned to Starch, Pregelatinized if this is to cover other grades of Starch, Pregelatinized from Wheat, Rice, etc. Probably each source type of Starch, Pregelatinized should have a separate UNII number since they all are quite different in properties.

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Potency Unit	Date
STARCH, PREGELATINIZED CORN	BUCCAL	TABLET		O8232NY3SJ	16.6	MG	15-Apr

STARCH, CORN	BUCCAL	TABLET	9005258	O8232NY3SJ	16.6	MG	15-Aug
STARCH, PREGELATINIZED CORN	ORAL	CAPSULE	9005258	O8232NY3SJ	195.9	MG	REMOVED
STARCH, PREGELATINIZED CORN	ORAL	CAPSULE (IMMED./COMP. RELEASE)		O8232NY3SJ	110	MG	15-Apr
STARCH, CORN	ORAL	CAPSULE (IMMED./COMP. RELEASE)	9005258	O8232NY3SJ	110	MG	15-Aug
STARCH, PREGELATINIZED CORN	ORAL	CAPSULE, HARD GELATIN		O8232NY3SJ	289.2	MG	15-Apr
STARCH, CORN	ORAL	CAPSULE, HARD GELATIN	9005258	O8232NY3SJ	289.2	MG	15-Aug
STARCH, PREGELATINIZED CORN	ORAL	TABLET	9005258	O8232NY3SJ	482	MG	15-Apr
STARCH, CORN	ORAL	TABLET	9005258	O8232NY3SJ	482	MG	15-Aug
STARCH, PREGELATINIZED CORN	ORAL	TABLET (IMMED./COMP. RELEASE), FILM COATED		O8232NY3SJ	40	MG	REMOVED
STARCH, PREGELATINIZED CORN	ORAL	TABLET, COATED	9005258	O8232NY3SJ	285	MG	15-Apr
STARCH, CORN	ORAL	TABLET, COATED	9005258	O8232NY3SJ	285	MG	15-Aug
STARCH, PREGELATINIZED CORN	ORAL	TABLET, EXTENDED RELEASE		O8232NY3SJ	250	MG	15-Apr
STARCH, CORN	ORAL	TABLET, EXTENDED RELEASE	9005258	O8232NY3SJ	250	MG	15-Aug
STARCH, PREGELATINIZED CORN	ORAL	TABLET, FILM COATED	9005258	O8232NY3SJ	**15760**	MG	REMOVED

Also, The max potency level dropped from 15760 to 482mg for this material. Why was the corn differentiator taken out? Clearly there are differences between the grades of pregelatinized starch from corn, rice, etc. Should all grades of pregelatinized starch from any source use the same IID listing and level to justify a particular level of use in an ANDA?

16

Ethylene vinyl acetate copolymers

The April 2015 listing for **ethylene vinyl acetate copolymers** contained a maximum potency listing for Periodontal, Film, Controlled Release of 51 mg; however in the August 2015 update the maximum potency value is missing.

Ingredient Name	Route	Dosage Form	CAS Number	UNII	Potency Amount	Potency Unit	Date
ETHYLENE-VINYL ACETATE COPOLYMERS	PERIODONTAL	FILM, CONTROLLED RELEASE	24937788	NA	51	MG	15-Apr
ETHYLENE-VINYL ACETATE COPOLYMERS	PERIODONTAL	FILM, CONTROLLED RELEASE	24937788	NA		MG	15-Aug