GDUFA II – IID Commitments

April 1, 2021

aam Association for Accessible Medicines

PBOA PHARMA & BIOPHARMA OUTSOURCING ASSOCIATION

BPTF Bulk Pharmaceuticals Task Force

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GDUFA II IID Commitment

- **Section III(G) Inactive Ingredient Database Enhancements**
  - By October 1, 2020, FDA will ***complete*** enhancements to the Inactive Ingredient Database so users can perform electronic queries to obtain accurate ***Maximum Daily Intake and Maximum Daily Exposure*** information for each route of administration for which data is available.
  - FDA will update the Inactive Ingredient Database on an ongoing basis, and post quarterly notice of updates made. Such notices will include each change made and, for each change, the information replaced.

Accurate Maximum Daily Intake and Maximum Daily Exposure Information

Industry expectations:

- MDEs listed should represent the highest MDE for a specific grade of material/route of administration

Current issue:

- For specific grade & route of admin, MDEs missing for multiple listings resulting in an increase to Controlled Correspondence for industry and FDA.

Ingredient Name	Route	Dosage Form	UNII	Potency Amount	MDE
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	CAPSULE	Z78RG6M2N2	80.25 mg	
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	CAPSULE, DELAYED RELEASE	Z78RG6M2N2	74.51 mg	
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	CAPSULE, EXTENDED RELEASE	Z78RG6M2N2	336 mg	
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	TABLET	Z78RG6M2N2	300 mg	
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	TABLET, COATED	Z78RG6M2N2	33 mg	
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	TABLET, EXTENDED RELEASE	Z78RG6M2N2		**600 mg**
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	Z78RG6M2N2	300 mg	

Accurate Maximum Daily Intake and Maximum Daily Exposure Information

Industry expectations and as communicated by FDA:

- MDEs listed should be higher than Max Potency for specific grade of material/route of administration

Current issue:

- MDE values lower than Max Potency for same grade of material and same route of administration

Ingredient Name	Route	Dosage Form	UNII	Potency Amount	MDE
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, FILM COATED	288VBX44JC	214.5 mg	
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, EXTENDED RELEASE	288VBX44JC	250 mg	
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, COATED PARTICLES	288VBX44JC	445 mg	
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	FILM, SOLUBLE	288VBX44JC		18 mg
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, ORALLY DISINTEGRATING	288VBX44JC		25 mg
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	CAPSULE	288VBX44JC		45 mg
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	288VBX44JC		80 mg
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, MULTILAYER, EXTENDED RELEASE	288VBX44JC		84 mg

Post quarterly notice of updates made and changes

Changes made in nomenclature, UNIIs, loss of data and/or line-items where tracking information for the change is not always available or at best, very difficult to trace when multiple changes were made simultaneously.

Ingredient Name	Route	Dosage Form	UNII	Potency Amount	
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET	288VBX44JC	1943 mg	Q3, 2018
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET	288VBX44JC	1943 mg	Q4, 2018
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET	288VBX44JC	1943 mg	Q1, 2019
HYPROMELLOSE 2910 (15000 MPA.S)					Q2, 2019

- removed from IID Q2, 2019 without explanation
- still missing as of Q1, 2021

Ingredient Name	Route	Dosage Form	UNII	Potency Amount	
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, COATED PARTICLES	288VBX44JC	445 mg	Q1, 2021

Current Max Potency

Post quarterly notice of updates made and changes

INGREDIENT NAME	ROUTE	DOSAGE FORM	UNII	POTENCY AMOUNT	Record Updated	
POLYETHYLENE OXIDE 5000000	ORAL	TABLET, EXTENDED RELEASE	3IG9032SAH	142.09 mg	Y	15-Nov-16
	Same Potency listing from Nov 2016 through Dec 2018					
POLYETHYLENE OXIDE 5000000	ORAL	TABLET, EXTENDED RELEASE	3IG9032SAH	142.09 mg		7-Dec-18
POLYETHYLENE OXIDE 5000000	completely removed from IID without any notification or justification					15-Mar-19

FDA CC response to ANDA sponsor

If you are developing an ANDA and require evidence of previous use of an excipient and confirmation that a particular level will be accepted by OGD, we recommend that you submit your proposed formula to OGD through a controlled correspondence referencing the known marketed products to support use of the excipient in your proposed formula

According to Daily Med, this grade is used in at least 9 commercial drugs

Microcrystalline Cellulose Nomenclature & UNIIs

IID Database → All MICROCRYSTALLINE CELLULOSE listings have one UNII: **OP1R32D614**

SRS

Preferred Substance Name: MICROCRYSTALLINE CELLULOSE

UNII: OP1R32D61U

Synonyms and Mappings

- 9004-34-6
- 232-674-9
- AVICEL PH ← "all" grades
- CELLULOSE [MI]
- CELLULOSE GEL
- CELLULOSE GEL [FCC]
- CELLULOSE GEL [VANDF]
- CELLULOSE MICROCRYSTALLINE

Search *Substance Registration System* (automatic) (automatic) AVICEL

10 additional UNIIs based on grade

11 results for (automatic) starts with AVICEL

1. MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)
2. MICROCRYSTALLINE CELLULOSE 101 (UNII: 7T9FYH5QMK)
3. MICROCRYSTALLINE CELLULOSE 102 (UNII: PNR0YF693Y)
4. MICROCRYSTALLINE CELLULOSE 102 SCG (UNII: HHJ82DN6JJ)
5. MICROCRYSTALLINE CELLULOSE 103 (UNII: L5EC3P45R8)
6. MICROCRYSTALLINE CELLULOSE 105 (UNII: KO5GYV0DCB)
7. MICROCRYSTALLINE CELLULOSE 112 (UNII: X7XJ6RM9Q2)
8. MICROCRYSTALLINE CELLULOSE 200 (UNII: 5XDI2TS1EZ)
9. MICROCRYSTALLINE CELLULOSE 200 LM (UNII: VG6UJI79NF)
10. MICROCRYSTALLINE CELLULOSE 301 (UNII: W7YXH6D4BD)
11. MICROCRYSTALLINE CELLULOSE 302 (UNII: 91B875MM4H)

1 result for (automatic) equals MICROCRYSTALLINE CELLULOSE 103

Preferred Substance Name: MICROCRYSTALLINE CELLULOSE 103

UNII: L5EC3P45R8

Synonyms and Mappings

- 9004-34-6
- AVICEL PH 103
- AVICEL PH 113
- AVICEL PH-103
- AVICEL PH-113
- CELLULOSE, MICROCRYSTALLINE 103
- CELLULOSE, MICROCRYSTALLINE 113
- MICROCRYSTALLINE CELLULOSE 103
- MICROCRYSTALLINE CELLULOSE 113

AVICEL PH 103: UNII L5EC3P45R8
AVICEL PH 113: UNII L5EC3P45R8
AVICEL PH 102: UNII PNR0YF693Y
AVICEL PH 112: UNII X7XJ6RM9Q2

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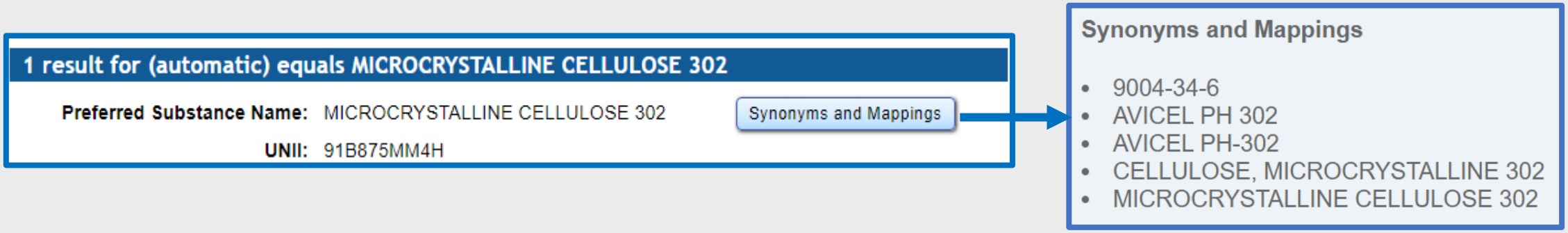
How do discrepancies between IID and SRS UNIIs impact pharma companies?

- Company wants to use AVICEL PH 302:
- MCC UNII OP1R32D614 listed in IID – does it cover all grades of MCC?
- Looks up MCC 302 in SRS – finds different UNII, no mapping to “microcrystalline cellulose” only to specific grade
- NO listing for any synonyms or UNII 91B875MM4H found in IID



RESULT: Since PH 302 is not mapped to UNII OP1R32D614 company decided they can not use it and stopped development of the drug

In Summary

- While industry appreciates the work that has been done, the approach used has created confusion resulting in additional workload for industry and FDA.
- This has increased the need to submit Controlled Correspondences.
- This has adversely impacted drug development and its timeline.
- Industry recommendations
  - Collapse IID dosage form listings for a given route of administration.
  - Only list one maximum potency or MDE for a particular grade of excipient.
  - MDE should represent the true maximum for the particular grade and route of administration.
  - Where Max Potency or MDE levels are reduced or line items eliminated, provide a detailed explanation as to what and why a change was made in the change log.
  - Harmonize nomenclature between IID and SRS.

Discussion