U.S. FOOD & DRUG ADMINISTRATION

Excipients@FDA

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FDA MISSION

The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

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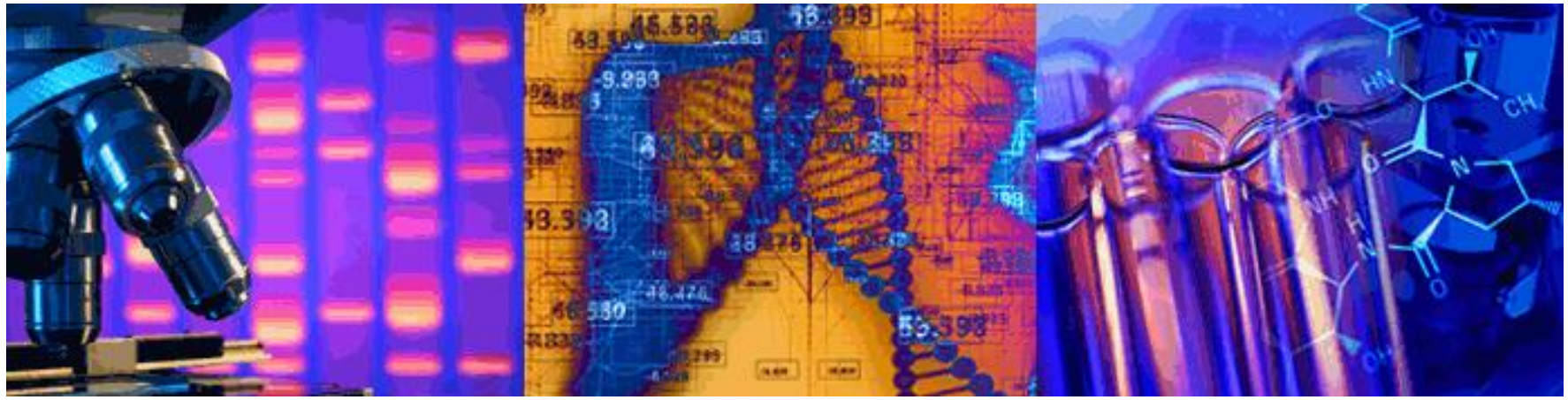
FDA U.S. FOOD & DRUG ADMINISTRATION

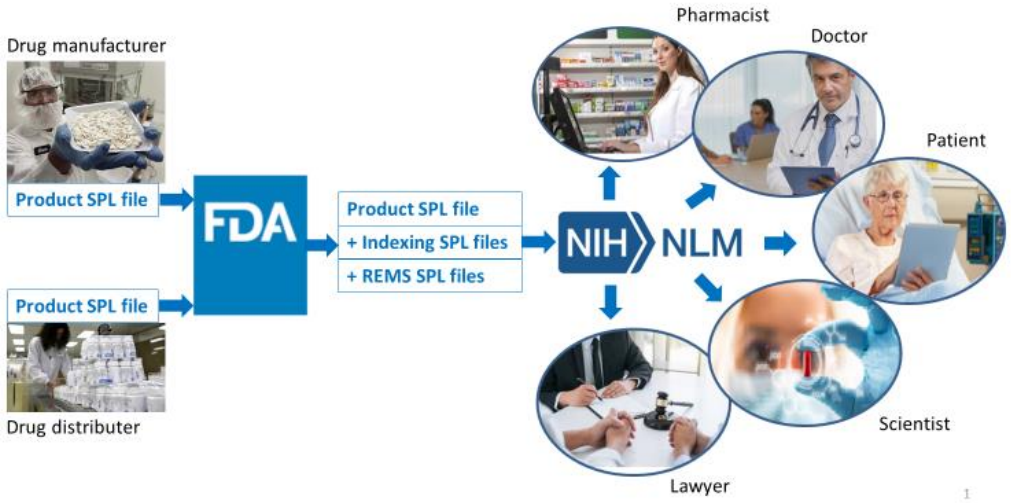


Office of the Chief Scientist/Office of Health Informatics

Frank Switzer, PhD

STRUCTURED PRODUCT LABELING (SPL)

SPL Product Data Exchange

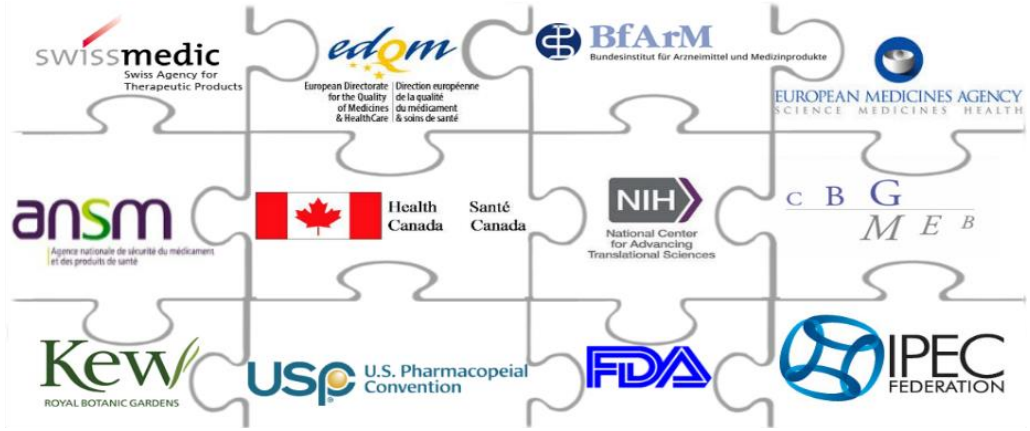


Structured Product Labeling (SPL) is a Health Level Seven (HL7) standard based on the Clinical Document Architecture and HL7 Reference Information Model (RIM) accredited by the American National Standards Institute (ANSI) for the exchange of product and facility information

FDA uses SPL documents

Global Substance Registration System (GSRS)

Collaborating Internationally to define (to the molecular level) substances that are used in commercial products



G-SRS

Government off-the-shelf software developed in collaboration with NIH NCATS which provides highly curated substance Information globally

Stats
Over 180,000 substances included
Six types of substances including chemical, protein, nucleic acid, polymer, structurally diverse, and mixture.
Features
Provides a unique identifier for each substance
Supports multiple languages
Compliant with ISO 11238 standard

FDA U.S. FOOD & DRUG ADMINISTRATION

Global Access | Information Sharing | Regulatory Applications | Open Source

GSRS

FDA Global Substance Registration System

Global access to **library of unique substances**

Freely distributable and predominantly **open source**

Implements the **ISO 11238 standard** (Identification of Medicinal Products)

Links substance to regulatory applications, clinical trials and adverse events

Curates substances and creates scientific relationships between substances

What is GSRS?

- ISO 11238 compliant registration module for substances providing global access to information
- Library of substance identities with their generated Unique Ingredient Identifiers (UNIIs)
- Knowledgebase of substance information that helps consumers, clinicians, and researchers know what substances are in commercial products

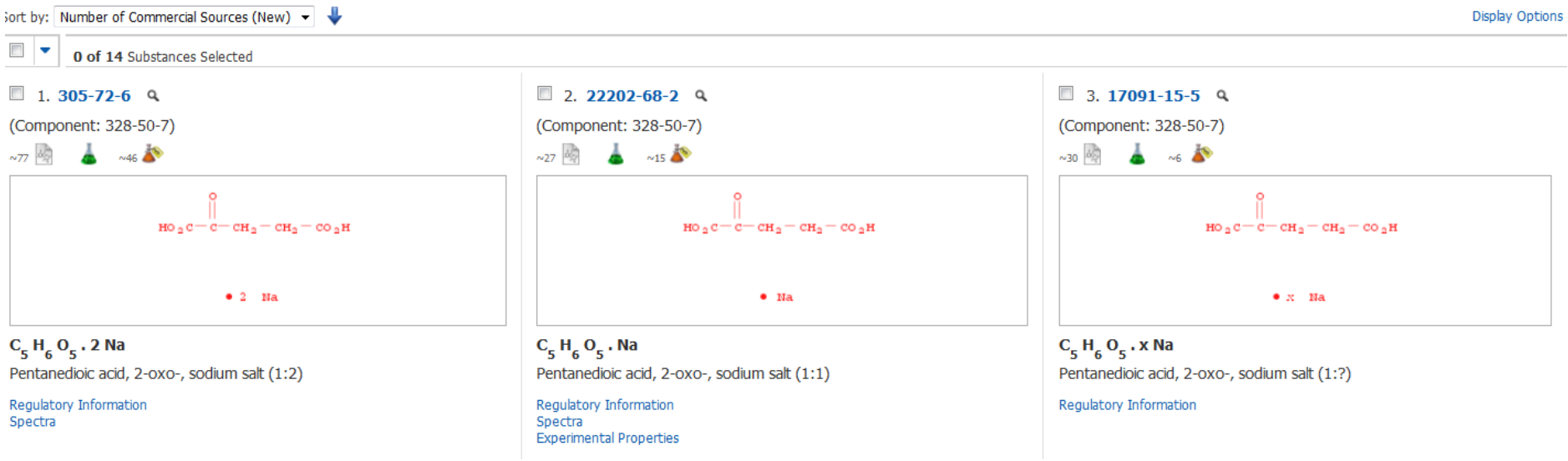
What does GSRS provide?

- Reduces burden on industry, ensures ingredients in products are accurately represented
- Defines ingredients independent of language
- Forms a knowledge base of ingredients and their associated relationships
- Integrates information across domains (applications, clinical trials, pharmacology, products)

Unique Ingredient Identifier

- The UNII consists of ten alphanumeric characters.
- Non-semantic non-chronological identifier
- The first nine alphanumeric characters are randomly generated.
- The tenth alphanumeric character is determined through a mathematical algorithm, and is appended to the first nine.
- $36^9 = 10^{13}$ potential identifiers

What About CAS RNs?



DISODIUM OXOGLURATE
FLP7P4RM46

MONOSODIUM OXOGLURATE
8GFV60F71R

Ambiguous
NO UNII

What About CAS RNs?

- 0 to many RNs for substances –**not an identity standard**
- CAS has no consistent way to capture polydispersity
- CAS RNs are copyrighted

UNII Guiding Principles

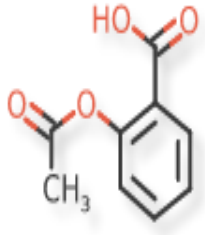
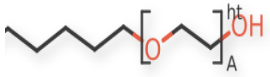
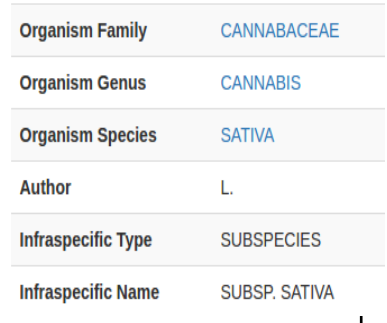
- **Limited Ambiguity**
  - Uniqueness
  - Identity
  - Internal Consistency
  - Completeness
- **Confidentiality**
  - Single code to track ingredient throughout product lifecycle

Why Aggregate/Curate?

- Data sources can be incomplete/ambiguous/contradictory
- To provide a set of substance master data
- To facilitate interoperability
  - Richer data facilitates communication
  - Data must be useful both to humans and systems

What is a substance?

A substance is a conceptual physical entity, which is capable of separate existence, and is defined uniquely based on its immutable chemical, physical and/or taxonomic properties.

Substance Type	Chemical	Polymer	Protein	Nucleic Acid	Structurally Diverse
Defined By	Chemical Structure	Structural Repeat Unit(s)	Amino Acid Sequence(s)	Nucleobase Sequence	Taxonomic Information + Part
Example			>A35X00TA2K RCPGCGQGVQAGC PGGCVEEEDGGSP AEGCAEAEGCLRR EGQECGVYTPNCA PGLQCHPP...	>303159CVH9 TAAACGTTATAACGTTA TGACGTCAT	

Organism Family	CANNABACEAE
Organism Genus	CANNABIS
Organism Species	SATIVA
Author	L.
Infraspecific Type	SUBSPECIES
Infraspecific Name	SUBSP. SATIVA

Polymer Excipient Examples

- HPMC (Hypromellose)
- HPC (Hydroxypropyl Cellulose)

Hypromellose (HPMC)

Table II. Typical viscosity values for 2% (w/v) aqueous solutions of *Methocel* (Dow Wolff Cellulosics) and *Metolose* (Shin-Etsu Chemical Co. Ltd.). Viscosities measured at 20°C.

***Methocel* and *Metolose* products**	**JP/PhEur/USP designation**	**Nominal viscosity (mPa s)**
Methocel K3 Premium LV	2208	3
Methocel K100 Premium LV	2208	100
Methocel K4M Premium	2208	3 550
Methocel K15M Premium	2208	17 700
Methocel K100M Premium	2208	100 000
Methocel E3 Premium LV	2910	3
Methocel E5 Premium LV	2910	5
Methocel E6 Premium LV	2910	6
Methocel E15 Premium LV	2910	15
Methocel E50 Premium LV	2910	50
Methocel E4M Premium	2910	3 550
Methocel E10M Premium CR	2910	12 700
Methocel F50 Premium LV	2906	50
Methocel F4M Premium	2906	3 550

Hypromellose (HPMC)

Trade Name	UNII	Display Name
METHOCEL K3	9H4L916OBU	HYPROMELLOSE 2208 (3 MPA.S)
METHOCEL K100	B1QE5P712K	HYPROMELLOSE 2208 (100 MPA.S)
METHOCEL K4M	39J80LT57T	HYPROMELLOSE 2208 (4000 MPA.S)
METHOCEL K15M	Z78RG6M2N2	HYPROMELLOSE 2208 (15000 MPA.S)
METHOCEL K100M	VM7F0B23ZI	HYPROMELLOSE 2208 (100000 MPA.S)
METHOCEL E3	0VUT3PMY82	HYPROMELLOSE 2910 (3 MPA.S)
METHOCEL E5	R75537T0T4	HYPROMELLOSE 2910 (5 MPA.S)
METHOCEL E6	0WZ8WG20P6	HYPROMELLOSE 2910 (6 MPA.S)
METHOCEL E15	36SFW2JZ0W	HYPROMELLOSE 2910 (15 MPA.S)
METHOCEL E50	1IVH67816N	HYPROMELLOSE 2910 (50 MPA.S)
METHOCEL E4M	RN3152OP35	HYPROMELLOSE 2910 (4000 MPA.S)
METHOCEL E10M	0HO1H52958	HYPROMELLOSE 2910 (10000 MPA.S)
METHOCEL F50	612E703ZUQ	HYPROMELLOSE 2906 (50 MPA.S)
METHOCEL F4M	5EYA69XGAT	HYPROMELLOSE 2906 (4000 MPA.S)

Hydroxpropyl Cellulose (HPC)

Table III. Moisture content of *Klucel* (Ashland Specialty Ingredients).

Grade	Molecular weight[a]	Moisture (%)
Klucel EF	≈80 000	0.59
Klucel LF	≈95 000	2.21
Klucel JF	≈140 000	1.44
Klucel GF	≈370 000	1.67
Klucel MF	≈850 000	1.52
Klucel HF	≈1 150 000	4.27

a. Weight average molecular weight determined by size exclusion chromatography.

HPC Types

Table V. Viscosity of aqueous solutions of *Klucel* (Ashland Specialty Ingredients) at 25°C.

Grade	Molecular weight	Viscosity (mPa s) of various aqueous solutions of stated concentration			
		1%	2%	5%	10%
Klucel HF	1 150 000	1500–3000	—	—	—
Klucel MF	850 000	—	4000–6500	—	—
Klucel GF	370 000	—	150–400	—	—
Klucel JF	140 000	—	—	150–400	—
Klucel LF	95 000	—	—	75–150	—
Klucel EF	80 000	—	—	—	300–600
Klucel ELF	80 000	—	—	—	150-300

HPC Types

Table VI. Viscosity of 2% aqueous solutions of *Nisso HPC* (Nippon Soda Co. Ltd.) at 20°C.

Grades[a]	Molecular weight	Viscosity (mPa s) of 2% aqueous solution
SSL	40 000	2.0–2.9
SL	100 000	3.0–5.9
L	140 000	6.0–10.0
M	620 000	150–400
H	910 000	1000–4000

HPC Types/UNIIs

Trade Name	Exp WAMW (GPC)	Pub WAMW (GPC)	UNII	Display Name
Klucel HF	1,570,000	1,150,000	RFW2ET671P	HYDROXYPROPYL CELLULOSE (1600000 WAMW)
Klucel MF	1,210,000	850,000	U3JF91U133	HYDROXYPROPYL CELLULOSE (1200000 WAMW)
Klucel GF	459,000	370,000	VQ8ZWO78F6	HYDROXYPROPYL CELLULOSE (430000 WAMW)
Klucel JF	157,000	140,000	0A7M0N7SPE	HYDROXYPROPYL CELLULOSE (160000 WAMW)
Klucel LF	108,000	95,000	5Y0974F5PW	HYDROXYPROPYL CELLULOSE (110000 WAMW)
Klucel EF	97,500	80,000	UKE75GEA7F	HYDROXYPROPYL CELLULOSE (90000 WAMW)
Klucel ELF	70,000		66O7AQV0RT	HYDROXYPROPYL CELLULOSE (70000 WAMW)
NISSO HPC VH			U3JF91U133	HYDROXYPROPYL CELLULOSE (1200000 WAMW)
NISSO HPC H	652,000		1L0RPI3ASP	HYDROXYPROPYL CELLULOSE (650000 WAMW)
NISSO HPC M	398,000		VQ8ZWO78F6	HYDROXYPROPYL CELLULOSE (430000 WAMW)
NISSO HPC LM			YJL324Y3EQ	HYDROXYPROPYL CELLULOSE (130000 WAMW)
NISSO HPC L	75,500		UKE75GEA7F	HYDROXYPROPYL CELLULOSE (90000 WAMW)
NISSO HPC SL	45,500		8VAB711C5E	HYDROXYPROPYL CELLULOSE (45000 WAMW)
NISSO HPC SSL	20,400		KZQ570MOA5	HYDROXYPROPYL CELLULOSE (20000 WAMW)

L-HPC Types

Table II. Typical properties of hydroxypropyl cellulose, low-substituted, for selected grades.

Grade	Hydroxypropoxy content (%)	Angle of repose (°)	Average particle size[a] (μm)	Density (bulk) (g/cm³)	Density (tapped) (g/cm³)
LH-11	11	48	50	0.33	0.56
LH-21	11	45	45	0.38	0.63
LH-B1	11	40	55	0.48	0.70
LH-31	11	49	20	0.28	0.59
LH-22	8	46	45	0.37	0.63
LH-32	8	50	20	0.21	0.55
NBD-020	14	43	45	0.32	0.52
NBD-021	11	43	45	0.32	0.52
NBD-022	8	43	45	0.32	0.52

Group 1 Specified Substances

- Currently being implemented in the GSRS
  - Single Substance
    - Physical Property Data
      - Data related due to intermolecular interactions
        - » Polymorphs
        - » Particle Size
        - » Particle Shape
        - » Density
    - Biological Property
      - Sterility
      - Viral Testing (country of Origin)
      - source
      - Microhettorogeniety
        - » Glycosylation (Quantitive)

Group 1 Specified Substances

- Currently Being Implemented in the GSRS
  - Multiple Substance Ingredients
    - Composition (Quantitative)
      - » Colorants
      - » Flavors
  - Herbal Extracts
    - Extraction solvents
    - Solvent-Plant ratio
    - Physical Form
    - Composition (Quantative)

Use of Specified Substance Group 1

- IID
  - Limits of Amounts
  - Levels may be grouped by family
  - Need to educate industry
- Listing
  - May be needed for colorants and flavors
- PQ/CMC
  - Need for SSG1
  - Changing can have a major effect on stability and function
  - Excipients frequently control bioavailability and have a major effect on stability
  - Formulations should be entered by industry and validated by review (GSRS)

Formulations

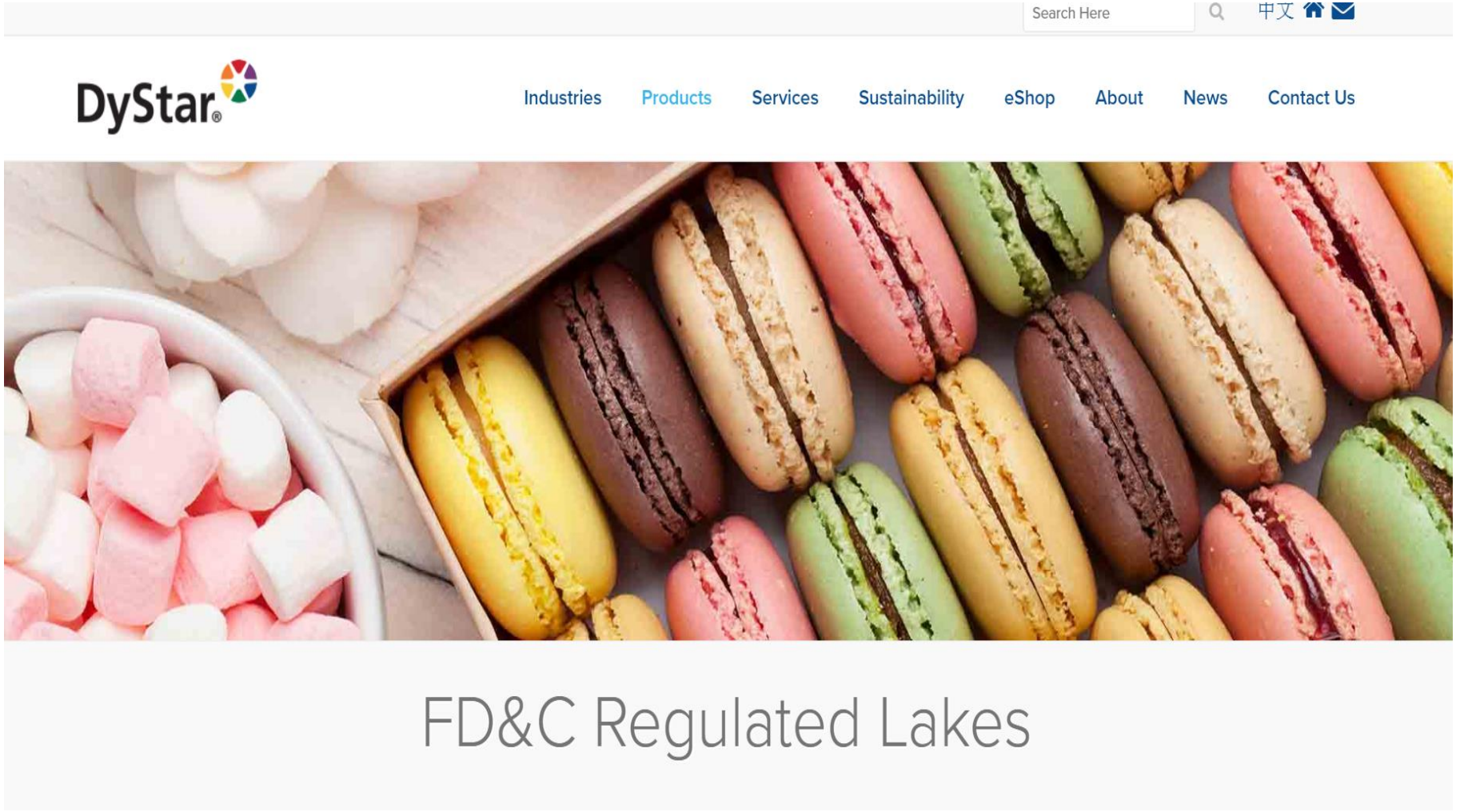
- Quantitative Formulations
- Change during development
- When to capture
  - NDA, ANDA, BLA
  - Supplements
- How
  - Currently contractors enter
  - Industry could enter the data
  - Reviewer could validate
  - EMA distinguishes coatings and core in capturing tablet, capsule formulations

Microcrystalline Cellulose

Product Name	Product Grades	Nominal Particle Size, µm	Moisture, %	Bulk Density, g/cc
Roller Compaction	Avicel DG	45	NMT 5.0	0.25 - 0.40
Wet Granulation	Avicel PH-101	50	3.0 to 5.0	0.26 - 0.31
Direct Compression	Avicel PH-102	100	3.0 to 5.0	0.28 - 0.33
Direct Compression	Avicel HFE*-102	100	NMT*** 5.0	0.28 - 0.33
Superior Compactibility	Avicel PH-105	20	NMT 5.0	0.20 - 0.30
Superior Flow	Avicel PH-102 SCG**	150	3.0 to 5.0	0.28 - 0.34
Superior Flow	Avicel PH-200	180	2.0 to 5.0	0.29 - 0.36
High Density	Avicel PH-301	50	3.0 to 5.0	0.34 - 0.45
High Density	Avicel PH-302	100	3.0 to 5.0	0.34 - 0.46
Low Moisture	Avicel PH-103	50	NMT 3	0.26 - 0.31
Low Moisture	Avicel PH-113	50	NMT 2	0.27 - 0.34
Low Moisture	Avicel PH-112	100	NMT 1.5	0.28 - 0.34
Low Moisture	Avicel PH-200 LM	180	NMT 1.5	0.30 - 0.38
Mouthfeel Improvement	Avicel CE-15	75	NMT 8	N/A

http://www.dpharmaceutical-products/anisco.com/pharmaceuticals/avicelr-for-solid-dose-forms/

Aluminum Lake Pigments



https://www.dystar.com/fdc-regulated-lakes/fdc-blue-no-2-

Aluminum Lake Pigments

DyStar

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FD&C Blue No. 1 Aluminum Lake (11-13%)	Brilliant Blue Lake	11-13%	
FD&C Blue No. 1 Aluminum Lake (28-31%)	Brilliant Blue Lake	28-31%	
FD&C Blue No. 2 Aluminum Lake (11-14%)	Indigotine Lake	11-14%	
FD&C Blue No. 2 Aluminum Lake (30-36%)	Indigotine Lake	30-36%	
FD&C Red No. 40 Aluminum Lake (14-17%)	Allura Red Lake	14-17%	
FD&C Red No. 40 Aluminum Lake (36-42%)	Allura Red Lake	36-42%	
FD&C Yellow No. 5 Aluminum Lake (15-18%)	Tartrazine Lake	15-18%	
FD&C Yellow No. 5 Aluminum Lake (25-28%)	Tartrazine Lake	25-28%	
FD&C Yellow No. 5 Aluminum Lake (36-42%)	Tartrazine Lake	36-42%	
FD&C Yellow No. 6 Aluminum Lake (15-18%)	Sunset Yellow Lake	15-18%	
FD&C Yellow No. 6 Aluminum Lake (36-42%)	Sunset Yellow Lake	36-42%	

Acknowledgements

FDA

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Thank You

Empowering a healthy tomorrow