Regulatory Approval Process for Drug Products Containing New Excipients with Case Studies

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Disclaimer

The opinions expressed in this presentation are those of the speaker and do not reflect the opinion of the FDA, EMEA or any other regulatory agency nor do they provide specific regulatory guidance.

Pharmaceutical company: will not use an excipient in a product unless it's been "approved".

FDA: will not approve an excipient unless it is used in a product

Reasons for Selecting an Excipient in a Formulation:

1. **Global Regulatory Acceptance.**
2. Safety.
3. Function in the formulation.
4. Physical & chemical compatibility with the active and other excipients.
5. Cost.
6. Formulator preference.
7. Stability.
8. Compatibility with the package.

Types of New Excipients

- New grade of excipient
  - Change in *physical* form of the excipient (e.g. particle size, moisture content, density)
  - Ex.: Avicel PH101, 102, etc.; low-moist. Pregel. Starch
- Co-processed excipients
  - Two established excipients combined via a physical process (e.g. spray-drying) to produce an excipient with improved physicomechanical properties
  - Ex.: ProSolv (MCC/SiO_2); Advantose (Fructose/Starch)
- New excipient (novel)
  - New chemical entity (includes longer polymer chain length)
  - Ex.: Cyclodextrins; Solutol (Macrogol 15-Hydoxystearate)

Types of New Excipients

- New route of administration for an established excipient
  - Ex.: Inhalation grade Lactose
- Larger amount of excipient per day by a previously approved route of administration

Definitions

FDA: Inactive ingredient: “any component of a drug product other than the active ingredient”

In the past: excipients were “inactive ingredients” (sucrose, cornstarch)

We now know excipients may impact solubility, bioavailability, stability, etc.

FDA: “New Excipient” - ingredients intentionally added to therapeutic and diagnostic products, but that are

(I) not intended to exert any therapeutic effects at the intended dosage (although they may act to improve product delivery)

(ii) not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.

Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, FDA, May 2005

Acceptability of Excipients

FDA Inactive Ingredients Database (IID)

www.accessdata.fda.gov/scripts/cder/iig/

Ingredients in approved drug products

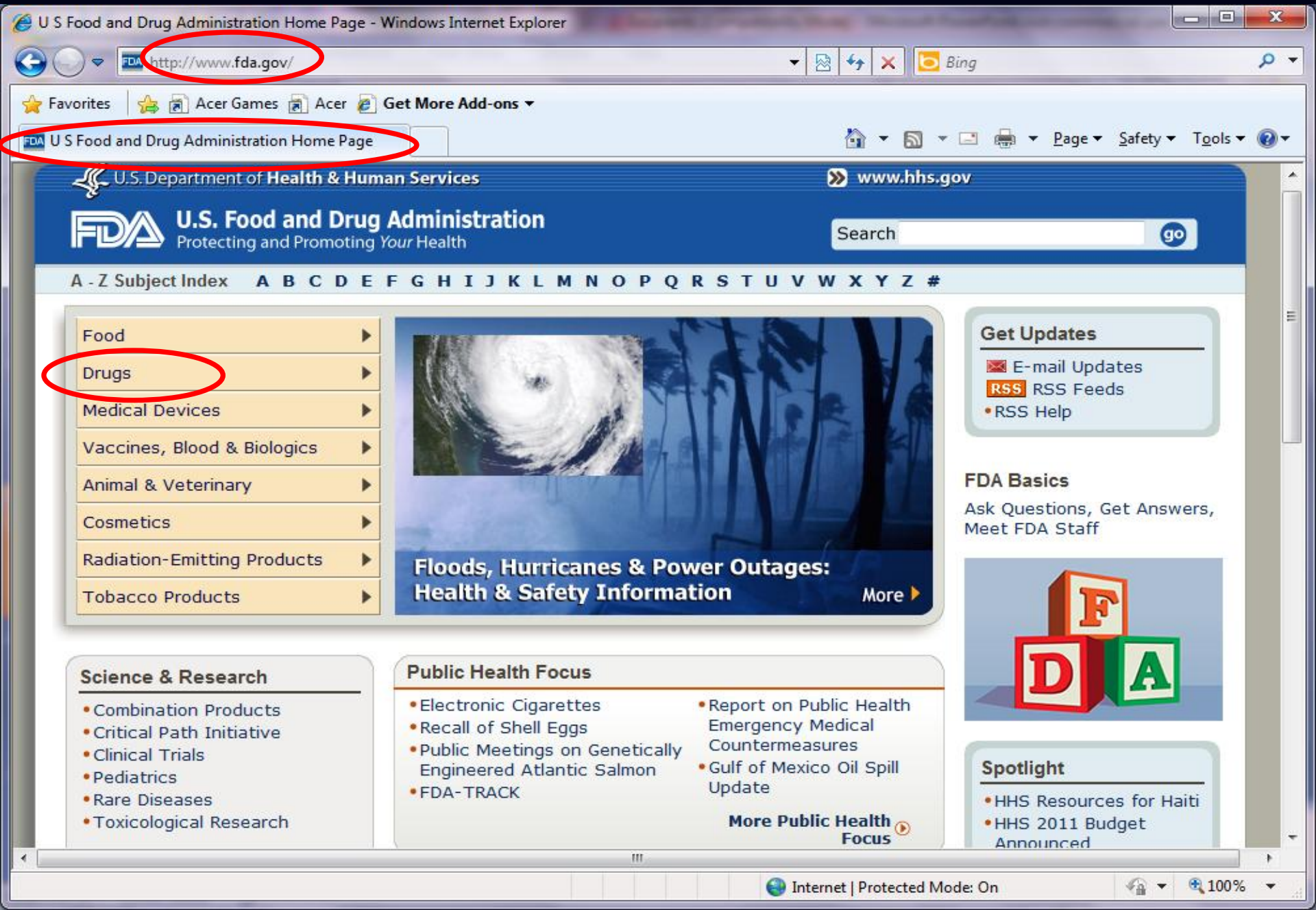
Difficult to search; synonyms

Amounts given in mg, %, mg/mL, etc.

By route of administration

Ingredient approved for parenteral administration may be considered “new” for oral use

www.fda.gov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Small Business Assistance
Small pharmaceutical business is integral in bringing innovative medical products to the U.S. marketplace.

The Past, Present, and Future of FDA Human Drug Regulation
A free Continuing Education activity.

Medication Health Fraud
Health scams can lead patients to delay proper treatment and cause injuries.

Spotlight

- Influenza (Flu) Antiviral Drugs and Related Information
- Access to Investigational Drugs
- Drugs@FDA
- Orange Book Search
- National Drug Code Directory

Recalls & Alerts

- MedWatch: The FDA Safety Information and Adverse Event Reporting Program
- Recalls, Market Withdrawals, & Safety Alerts

Emergency Preparedness
Bioterrorism, drug preparedness and natural disaster response

Drug Approvals and Databases
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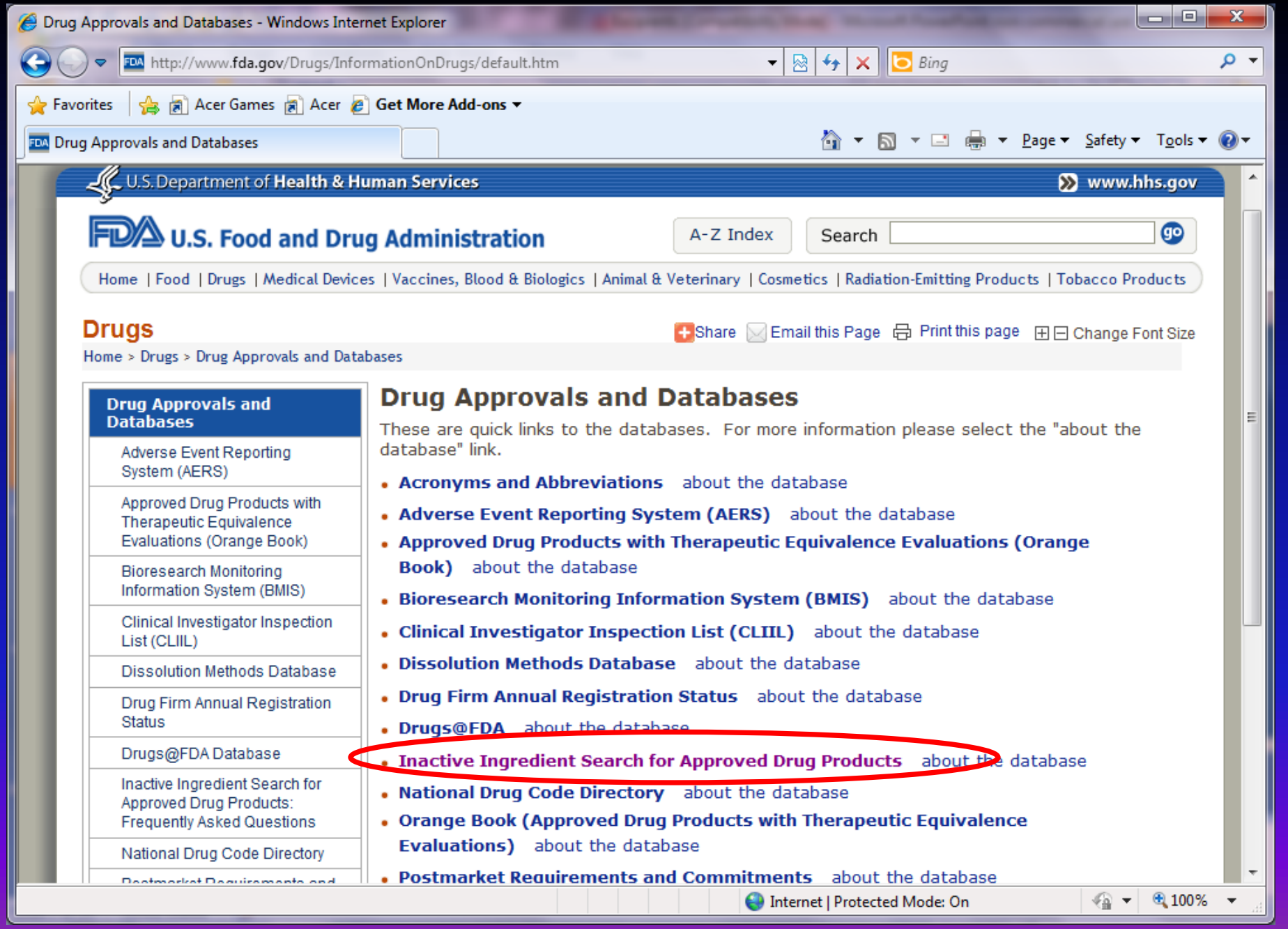
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Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)
Bioresearch Monitoring Information System (BMIS)
Clinical Investigator Inspection List (CLIIL)
Dissolution Methods Database
Drug Firm Annual Registration Status
Drugs@FDA Database
Inactive Ingredient Search for Approved Drug Products: Frequently Asked Questions
National Drug Code Directory
Drug Approvals and Databases
These are quick links to the databases. For more information please select the "about the database" link.
Acronyms and Abbreviations about the database
Adverse Event Reporting System (AERS) about the database
Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) about the database
Bioresearch Monitoring Information System (BMIS) about the database
Clinical Investigator Inspection List (CLIIL) about the database
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Inactive Ingredient Search for Approved Drug Products about the database
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Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) about the database
Postmarket Requirements and Commitments about the database
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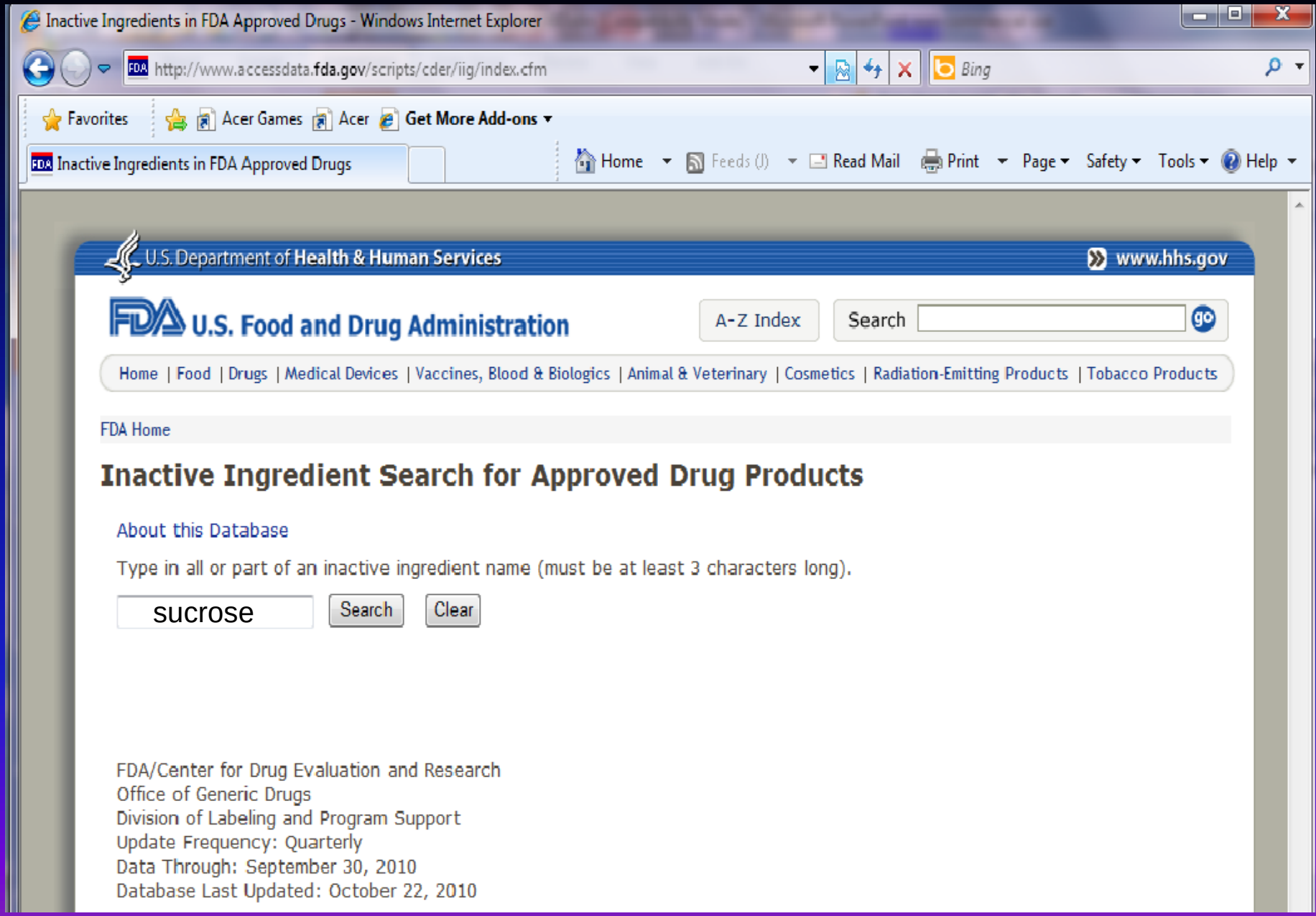
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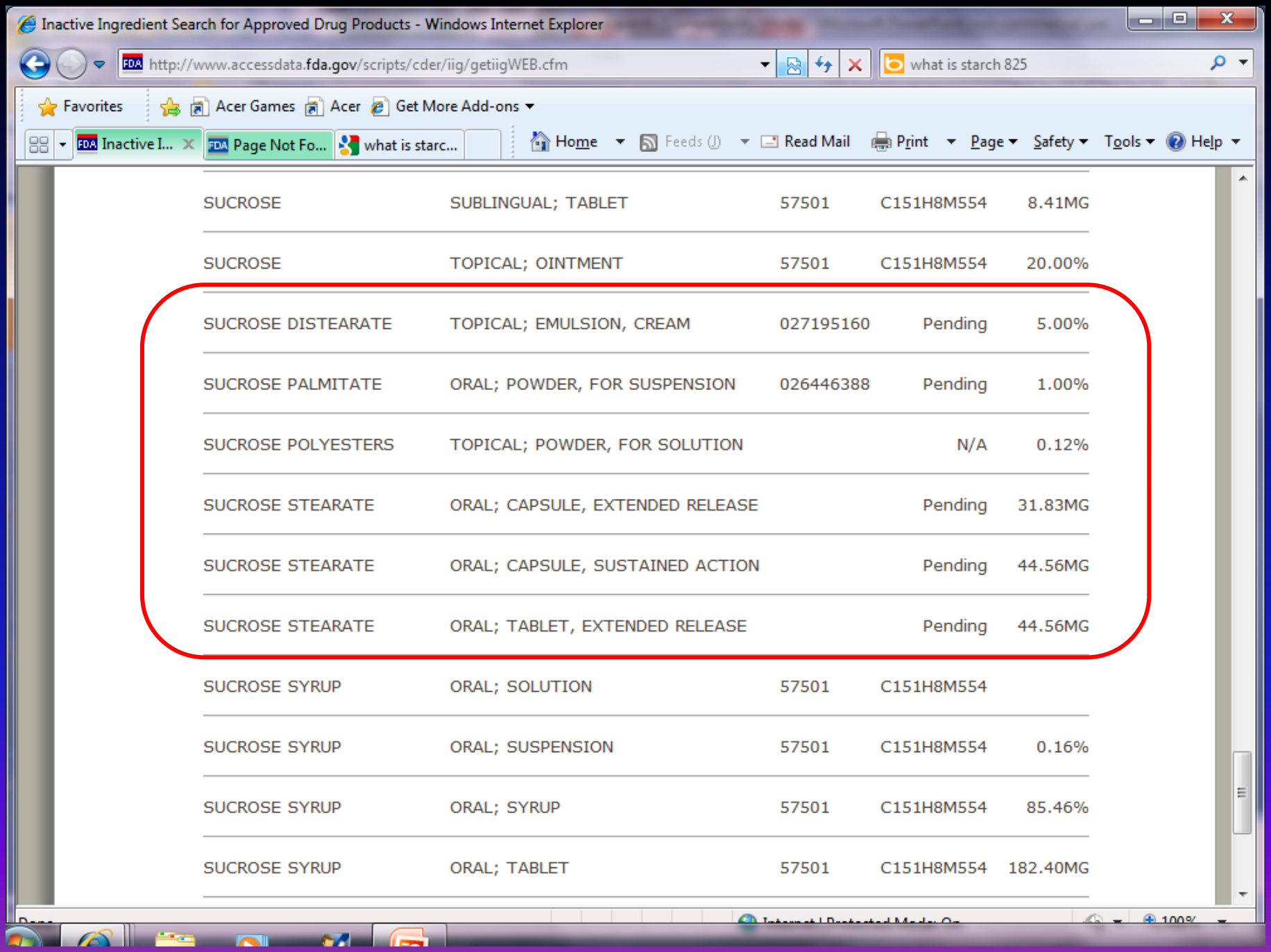
FDA Home
Inactive Ingredient Search for Approved Drug Products
About this Database
Type in all or part of an inactive ingredient name (must be at least 3 characters long).
sucrose
Search
Clear
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency: Quarterly
Data Through: September 30, 2010
Database Last Updated: October 22, 2010

Inactive Ingredient Search for Approved Drug Products

About this Database Back to Search Page

Search Results for: "sucrose"

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
ALUMINUM HYDROXIDE - SUCROSE, HYDRATED	TOPICAL; EMULSION, CREAM		N/A	
CALCIUM PHOSPHATE DIBASIC DIHYDRATE-SUCROSE AGGLOMERATE	ORAL; TABLET, COATED		N/A	
DC ANTIFOAM AF TRITURATION 1% ON SUCROSE	ORAL; POWDER, FOR SOLUTION		N/A	0.26%
DC ANTIFOAM AF TRITURATION 1% ON SUCROSE	ORAL; POWDER, FOR SUSPENSION		N/A	
SUCROSE	BUCCAL/SUBLINGUAL; TABLET	57501	C151H8M554	91.00MG
SUCROSE	BUCCAL; TABLET	57501	C151H8M554	16.60MG
SUCROSE	INTRAMUSCULAR; POWDER, FOR	57501	C151H8M554	6.24%



SUCROSE	SUBLINGUAL; TABLET	57501	C151H8M554	8.41MG
SUCROSE	TOPICAL; OINTMENT	57501	C151H8M554	20.00%
SUCROSE DISTEARATE	TOPICAL; EMULSION, CREAM	027195160	Pending	5.00%
SUCROSE PALMITATE	ORAL; POWDER, FOR SUSPENSION	026446388	Pending	1.00%
SUCROSE POLYESTERS	TOPICAL; POWDER, FOR SOLUTION		N/A	0.12%
SUCROSE STEARATE	ORAL; CAPSULE, EXTENDED RELEASE		Pending	31.83MG
SUCROSE STEARATE	ORAL; CAPSULE, SUSTAINED ACTION		Pending	44.56MG
SUCROSE STEARATE	ORAL; TABLET, EXTENDED RELEASE		Pending	44.56MG
SUCROSE SYRUP	ORAL; SOLUTION	57501	C151H8M554	
SUCROSE SYRUP	ORAL; SUSPENSION	57501	C151H8M554	0.16%
SUCROSE SYRUP	ORAL; SYRUP	57501	C151H8M554	85.46%
SUCROSE SYRUP	ORAL; TABLET	57501	C151H8M554	182.40MG

New Excipient Approval

Data package depends on what type of “new”

“As another example, 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 and the previously studied excipient are sufficiently similar…We will consider such excipients on a case-by-case basis.”

Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, FDA, May 2005

New Excipient Approval

FDA Guidance, May 2005, *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*

ICH Guidance: S7A *Safety Pharmacology Studies for Human Pharmaceuticals*

S1A, S2B, S3A, S3B, S4A, S5A, S5B, M3

Preclinical testing based on expected duration of exposure

- Short-term exposure (≤ 2 weeks)
- Intermediate exposure (2 weeks to 3 months)
- Long-term exposure (> 3 months)

New Excipient Approval

Will the new excipient be co-developed with a new drug substance?

If yes – “sponsors can develop new excipients concurrently with safety evaluation of new drug…by adding groups of animals that receive the excipient to studies that would have been conducted anyway to develop a drug substance”

If no – more resources for independent development of an excipient

New Excipient Approval

Has the new excipient been used in humans?

Yes – food additive

"The Centers recognize that existing human data for some excipients can substitute for certain nonclinical safety data, and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies…"

Short-term Use (≤ 2 weeks)

Short-term and *infrequent* use.
By the intended clinical route

1. Acute tox - rodent & mammal
   not necessary to determine LD_{50}
   may be omitted if high dose is used in repeat-dose studies
2. ADME
3. Standard battery of genotoxicity studies
4. One-month repeat-dose tox studies – rodent & mammal
5. Repro tox

Short-term Use (≤ 2 weeks)

Intermediate Use (2W – 3M)

Short-term and *infrequent* use.
By the intended clinical route

1. Acute tox - rodent & mammal
   not necessary to determine LD_{50}
   may be omitted if high dose is used in repeat-dose studies
2. ADME
3. Standard battery of genotoxicity studies
4. One-month repeat-dose tox studies – rodent & mammal → **3 months**
5. Repro tox

Short-term Use (≤ 2 weeks)

Intermediate Use (2W – 3M)

Long-term Use (>3M)

Short-term and *infrequent* use.
By the intended clinical route

1. Acute tox - rodent & mammal
   not necessary to determine LD_{50}
   may be omitted if high dose is used in repeat-dose studies
2. ADME
3. Standard battery of genotoxicity studies
4. One-month repeat-dose tox studies – rodent & mammal → **3 months** → **6 months**
5. Repro tox

Long-term Use (>3 months)

Carcinogenicity testing

ref. ICH S1A *The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals*

- 2-year carcinogenicity bioassays in two appropriate species **OR**
- 2-year carcinogenicity study in one rodent species plus an *alternative* in-vivo model **OR**
- Documentation providing scientific justification that carcinogenicity data are not necessary

New Excipient Approval

- Photosafety
- Sponsor is encouraged to contact the appropriate division for specific questions
- FDA may ask for additional studies
- Pulmonary, Injectable and Topical products have additional guidance

New Excipient Approval

- Previous slides describe *nonclinical* studies for safety evaluation of excipients
- Additionally need clinical studies, usually a placebo in clinical trials for a new drug product

DMFs

Drug Master Files - enable manufacturers of components used in a drug product to submit information to the FDA for review and the information remains confidential

Applicant – gets a *letter of authorization* from the manufacturer for their DMF – included in filing

DMFs are not approved

Excipients are a **Type IV** DMF

Guideline for Drug Master Files, FDA, Sep 1989

Development of a USP/NF Monograph

Proposed monograph data package for a new excipient goes to USP expert committee on excipients for review

If accepted → PF for public comment

If no comment → committee may allow it to become official monograph in 60 to 90 days

Comments → back to committee → revise or leave as is → publish revised monograph in PF

Normally takes 6 to 15 months for monograph to be published

**NEW* - PENDING MONOGRAPHS*

authorized but not official, cannot use USP or NF

USP/NF Monographs

Once published – recognized as official and gov't agencies are authorized to enforce them to assure that products in the US are in total compliance

Also, future filings may simply state that the excipient will comply with the USP/NF monograph without supplying the tests, methods or safety data.

"Inclusion of an excipient in a USP/NF monograph or other non-FDA document is not an indication that the substance has been reviewed by the FDA and found safe for use" *(May 2005 Guidance)*

Food Additives

Food Additive Petition

"Listing of Food Additive Status"

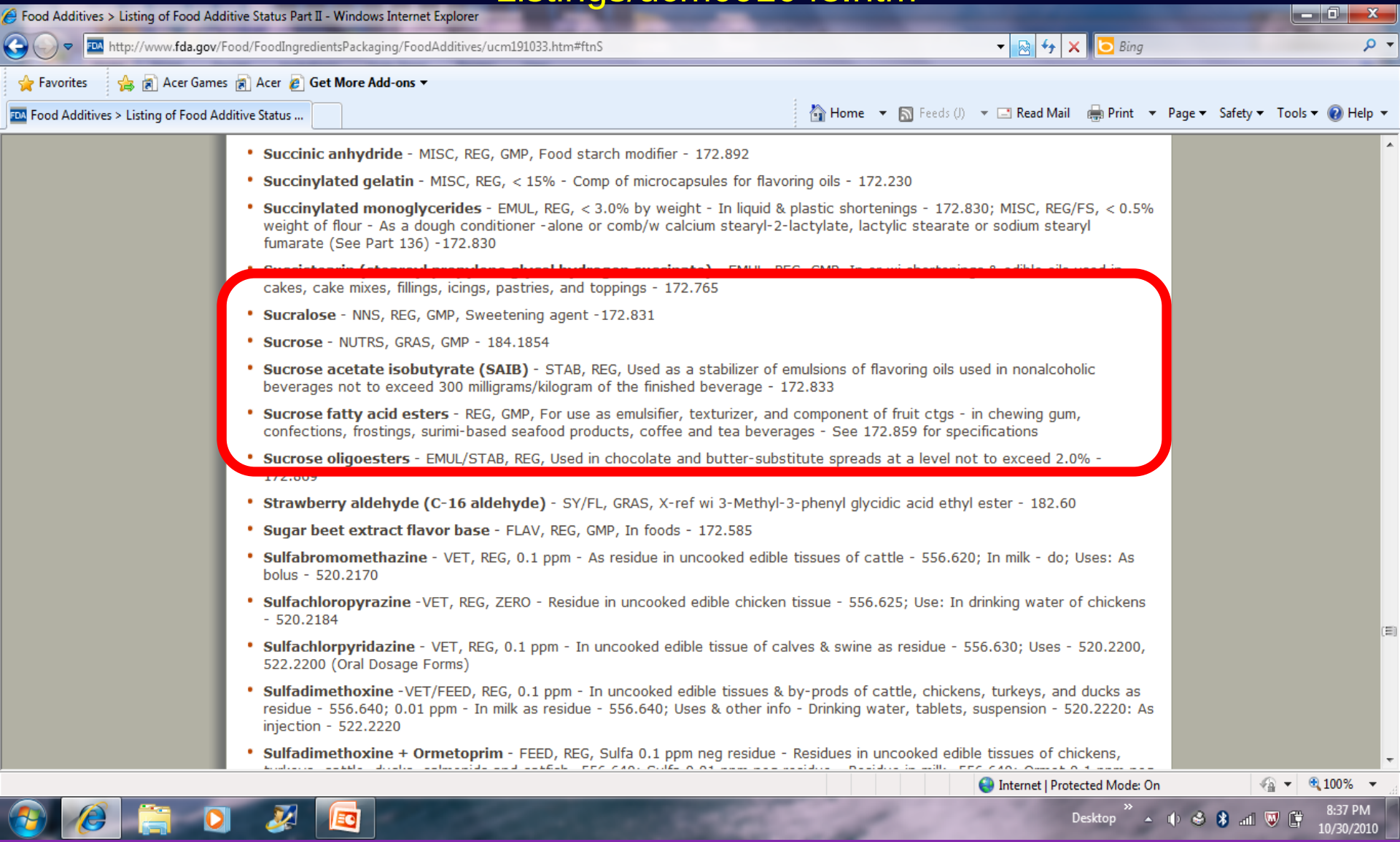
GRAS (Generally Recognized as Safe)

JECFA (Joint Food & Agriculture and World Health Organization Expert Committee)

Japan – food additives are considered as new excipients when used in a drug formulation

Listing of Food Additive Status (FDA)

www.fda.gov/Food/FoodIngredientsPackaging/FoodAdditives/FoodAdditiveListings/ucm091048.htm



- **Succinic anhydride** - MISC, REG, GMP, Food starch modifier - 172.892
- **Succinylated gelatin** - MISC, REG, < 15% - Comp of microcapsules for flavoring oils - 172.230
- **Succinylated monoglycerides** - EMUL, REG, < 3.0% by weight - In liquid & plastic shortenings - 172.830; MISC, REG/FS, < 0.5% weight of flour - As a dough conditioner -alone or comb/w calcium stearyl-2-lactylate, lactylic stearate or sodium stearyl fumarate (See Part 136) -172.830
- cakes, cake mixes, fillings, icings, pastries, and toppings - 172.765
- **Sucralose** - NNS, REG, GMP, Sweetening agent -172.831
- **Sucrose** - NUTRS, GRAS, GMP - 184.1854
- **Sucrose acetate isobutyrate (SAIB)** - STAB, REG, Used as a stabilizer of emulsions of flavoring oils used in nonalcoholic beverages not to exceed 300 milligrams/kilogram of the finished beverage - 172.833
- **Sucrose fatty acid esters** - REG, GMP, For use as emulsifier, texturizer, and component of fruit ctgs - in chewing gum, confections, frostings, surimi-based seafood products, coffee and tea beverages - See 172.859 for specifications
- **Sucrose oligoesters** - EMUL/STAB, REG, Used in chocolate and butter-substitute spreads at a level not to exceed 2.0% -
- **Strawberry aldehyde (C-16 aldehyde)** - SY/FL, GRAS, X-ref wi 3-Methyl-3-phenyl glycidic acid ethyl ester - 182.60
- **Sugar beet extract flavor base** - FLAV, REG, GMP, In foods - 172.585
- **Sulfabromomethazine** - VET, REG, 0.1 ppm - As residue in uncooked edible tissues of cattle - 556.620; In milk - do; Uses: As bolus - 520.2170
- **Sulfachloropyrazine** -VET, REG, ZERO - Residue in uncooked edible chicken tissue - 556.625; Use: In drinking water of chickens - 520.2184
- **Sulfachlorpyridazine** - VET, REG, 0.1 ppm - In uncooked edible tissue of calves & swine as residue - 556.630; Uses - 520.2200, 522.2200 (Oral Dosage Forms)
- **Sulfadimethoxine** -VET/FEED, REG, 0.1 ppm - In uncooked edible tissues & by-prods of cattle, chickens, turkeys, and ducks as residue - 556.640; 0.01 ppm - In milk as residue - 556.640; Uses & other info - Drinking water, tablets, suspension - 520.2220: As injection - 522.2220
- **Sulfadimethoxine + Ormetoprim** - FEED, REG, Sulfa 0.1 ppm neg residue - Residues in uncooked edible tissues of chickens,

cakes, cake mixes, fillings, icings, pastries, and toppings - 172.765

- **Sucralose** - NNS, REG, GMP, Sweetening agent -172.831
- **Sucrose** - NUTRS, GRAS, GMP - 184.1854
- **Sucrose acetate isobutyrate (SAIB)** - STAB, REG, Used as a stabilizer of emu
  beverages not to exceed 300 milligrams/kilogram of the finished beverage - 172.
- **Sucrose fatty acid esters** - REG, GMP, For use as emulsifier, texturizer, and co
  confections, frostings, surimi-based seafood products, coffee and tea beverage

"…in an amount not to exceed that reasonably required to accomplish the intended effect"

For JECFA:
www.inchem.org/pages/jecfa

GRAS

GRAS distinguished from food additive in the common knowledge about the safety of the substance

GRAS notification → 90 days, FDA responds:

(1) agency does not question the determination

(2) notice does not provide sufficient basis for GRAS determination

Case Study: IPEC New Excipient Safety Evaluation Procedure

Minimize risk

NEEC – New Excipient Evaluation Committee, independent expert review

Minimize need for new studies to support safe use of an excipient

Wyeth's approach to First-in-Human Formulation Development

- Bonafide formulations with Right-First-Time approach to avoid PK bridging between clinical trial phases
- One formulation from FIH to Proof-of-Concept 90%
- POC to commercial 80%
- Trend to APIs with low water solubility
- Across 55 FIH oral products from 2003 to 2009, 18.2% were solution or semisolid in capsule
- Goal: To have the best formulation in terms of delivering the drug, room temperature stability, global acceptability and reasonable cost

Cremophor vs Solutol

Cremophor® EL (Polyoxyl 35 Castor Oil, NF)

Cremophor® RH40 (Polyoxyl 40 Hydrogenated Castor Oil, NF)

Two solubilizing excipients developed by BASF prior to the development of Solutol® HS-15

Polyoxyl 35 Castor Oil is in 8 FDA-approved drug products

Polyoxyl 40 Hydrogenated Castor Oil is in 7 FDA-approved drug products

In contrast to Cremophor®, Solutol® HS-15 is known to have less significant histamine release in animal toxicity studies. It is a non-ionic solubilizer and emulsifying agent composed of polyglycol mono- and di- esters of 12-hydroxystearic acid (lipophilic part) and about 30% of free polyethylene glycol (hydrophilic part). Polyoxyl Stearates are used in about 35 FDA-approved drugs as seen from the FDA inactive ingredient database.

Solutol® HS-15 - used in an injectable human drug, Oxidize® (Diclofenac sodium) manufactured by Beta S.A., Buenos Aires, Argentina. Solutol HS-15 has been used in Canada since 1989 in multivitamin injections in two injectable formulations, a 2 mg/mL formulation containing 7% Solutol HS-15, and a 10 mg/mL formulation containing 10% Solutol HS-15.

Why Does a Pharmaceutical Company Take the Risk to Use a Novel Excipient?

- Solutol HS-15 is classified as “new” excipient since it hasn’t been used in the U.S. in any marketed product
- JECFA established an Acceptable Daily Intake (ADI) for similar excipients, PEG-8-Stearate and PEG-40-Stearate. Solutol HS-15 is a PEG-15-HydroxyStearate and should have a very similar safety profile as the other PEG-Stearates.
- While Solutol HS-15 does cause the release of histamine from mast cells, it is less allergenic than the closely related structure Cremophor approved by FDA.

Collaboration Between Wyeth, BASF and IPEC

In 2007, Jay Goldring (Wyeth Consumer) and the Chair of IPEC Safety Committee started a job rotation program in Wyeth Early Pharmaceutical Development.

Dr. Sherry Ku approached several excipient suppliers for possible collaboration in the IPEC new excipient review process

BASF took the challenge and agreed to collaborate and pay the Tox consultant fee.

As the first excipient through the system, FDA agreed to review the package and reply with assessment.

Dr. Goldring coordinated the information input, expert review, and review by FDA.

IPEC New Excipient Safety Evaluation Procedure - Solutol HS-15

- Aclairo - independent toxicology consulting firm working under an IPEC agreement for novel excipient evaluation.
- BASF prepared a comprehensive preclinical package for Aclairo on Solutol® HS-15 that included:
  - Summary of CMC information
  - Toxicology reports – oral and I.V.
    - Acute, subchronic, reproductive and genotoxicity
  - BASF's internal safety expert report
  - Safety evaluation assessment by EMEA
  - Information on Cremophor and other related excipients

Contributed Human Experience – Clinical Studies with Formulation containing Solutol HS-15

- Two (2) phase 1 studies were clinically completed in the United States
  - A single ascending dose (SAD) study conducted in healthy subjects and a multiple ascending dose (MAD) study conducted in healthy subjects.
- In a Phase 2 POC study (6 weeks dosing), an endoscopic examination (7 days GI safety study) was performed at up to 5 capsules of the placebo.
  - No Adverse Events (AE) in 12 patients dosed.
- Overall the AE profile from this study showed that a single oral dose of up to 10 capsules of the Wyeth formulation (containing 150 mg Solutol/capsule) are generally safe and well tolerated

IPEC Novel Excipient Safety Review- Review by Aclairo and FDA

- Aclairo provided an independent safety evaluation report for Solutol HS-15.
- IPEC Safety Committee Chair submitted Aclairo's report and all other documents submitted to Aclairo to the FDA for review for consistency with FDA's own review process.
- After receiving FDA feedback, BASF requested USP to consider a Solutol HS-15 monograph. USP consulted with FDA's Compendial group and published monograph in Jan/Feb 2009 issue of PF

New Technologies Can Drive the Introduction of *New* Excipients

Hot Melt Extrusion (HME)

Microprilled Poloxamer – BASF/Roche

Spray-Dried Solid Dispersions

HPMCAS – Shin-Etsu/Bend/Pfizer

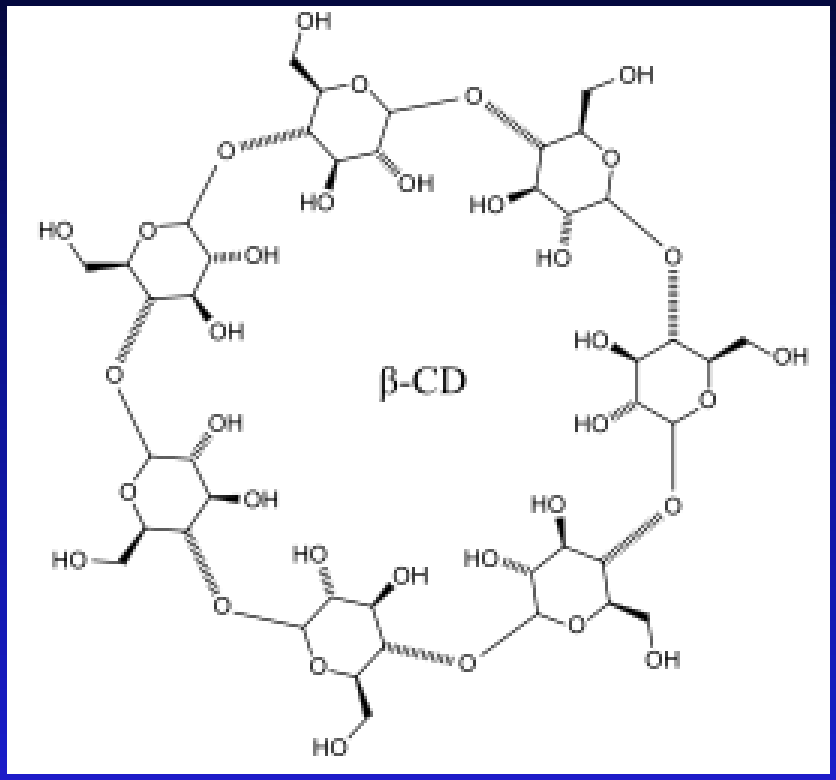
Need polymer levels higher than previous approved uses

Excipient and pharma manufacturer work in partnership to put together the tox data package

Case Study: Cyclodextrins

Solubilization of poorly soluble actives
Taste-masking
Stabilization

Natural parent Cyclodextrins:
Alpha, beta, gamma:
6, 7, 8 glucose units



Parent CDs Approval

First approved in Japan in 1983 as a food additive, and then as a pharmaceutical excipient

Notification of GRAS status accepted by FDA

JECFA ADI – alpha & gamma: “not specified”

beta: 0 – 5 mg/kg bw (300 mg/60kg)

not specified: refers to a food substance of very low toxicity, which, based on the available data and the total dietary intake of the substance arising from its intended condition of use does not represent a hazard to health.

Alpha and Beta – USP/NF, Ph.Eur., JPE

Gamma – USP/NF, Ph.Eur in process, not in JPE

Need for a Safe Parenteral CD

Safer CD sought through chemical modification

HP-β-CD – partially substituted poly(hydroxy-propyl) ether of beta cyclodextrin

improved solubility

improved renal safety

developed by Janssen as Encapsin®

Sporanox® - oral solution and I.V.

unexpected finding – pancreatic neoplasms

limited use

Sulfobutylether-β-Cyclodextrin

- Systematic approach to introduce anionic substituents onto β-CD to design renal safety into the molecule
- Developed by CyDex as Captisol®
- SBE – sodium sulfonate salt separated from the lipohilic cavity by a butyl spacer group
- Degree of substitution : 7 (no unreacted β-CD)
- Enhanced water solubility
- CyDex worked with Pfizer to develop two products: Vfend® (voriconazole) I.V. and Geodon® (ziprasidone) I.M.

Sulfobutylether-β-Cyclodextrin

Extensive saftey studies

- Especially renal function

Captisol® DMF – tox package for parenteral, ophthalmic, oral, nasal and inhalation administration

Listed in FDA IID:

- I.M. 44.14%
- I.V. 67.50%

Stella & He Toxicologic Pathology, 2008, 36:30-42.

Case Study: Calcium Phosphates

$CaHPO_4 \cdot H_2O$

$Ca_9(PO_4)_5(HPO_4)OH$

$CaHPO_4 \cdot 2H_2O$

$CaHPO_4$

$Ca_{10}(PO_4)_6(OH)_2$

$Ca_8H_2(PO4)_6(OH)_2$

$Ca_3(PO_4)_2$

$Ca(H_2PO_4)_2 \cdot H_2O$

$Ca_4(PO_4)_2O$

Dicalcium Phosphate

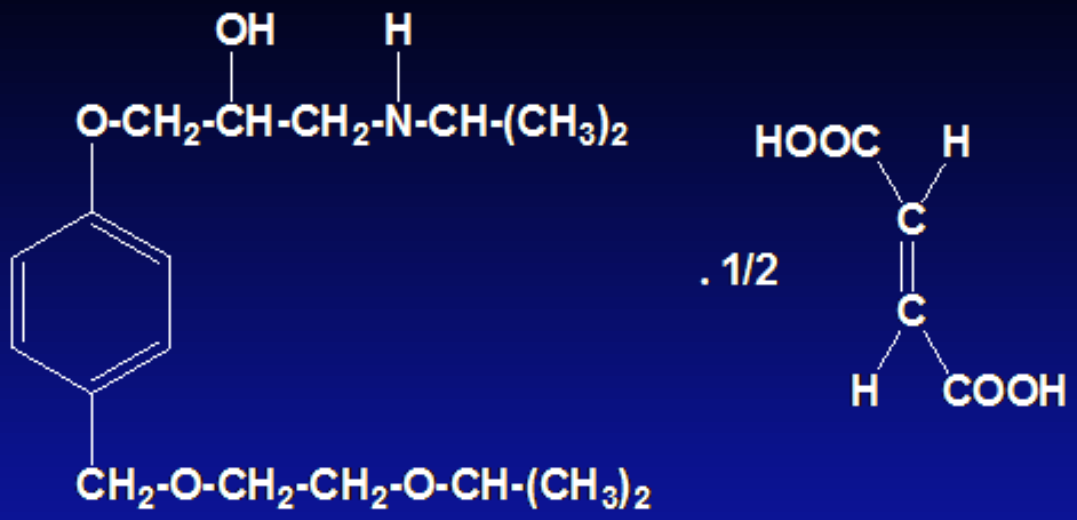
Three types typically used in solid dosage forms:

- Dibasic Calcium Phosphate Anhydrous
- Dibasic Calcium Phosphate Dihydrate
- Tribasic Calcium Phosphate

Available in powdered and granular form

Dibasic Calcium Phosphate Dihydrate irreversibly gives off water above 40-45°C, and gives misleading stability predictions

Formulators use Anhydrous to avoid potential or real instability.



Bisoprolol Fumarate

Tablet Formulation

Anhydrous Dicalcium Phosphate USP → Anhydrous Dicalcium Phosphate USP

Powdered
stable

"NEW" Granular
unstable

Non-USP Properties

	Powdered DCPA	Granular DCPA
Particle size	Powder	Granular
Density (tapped)	~83 lb/ft^3	~50 lb/ft^3
pH 20% slurry	6.6 - 7.4	5.0 – 5.6
Surface area	0.5 – 2 m^2/g	20 – 30 m^2/g

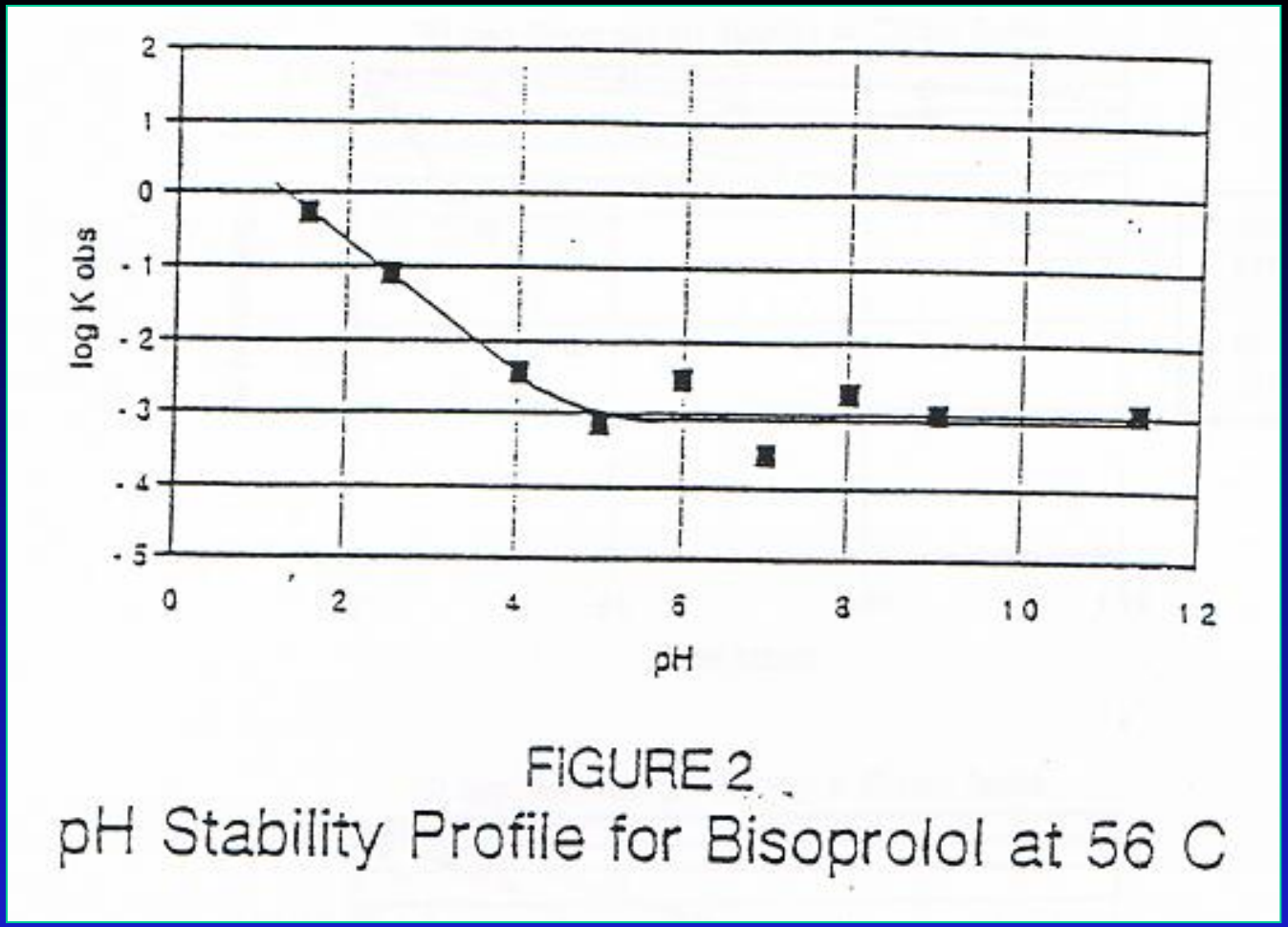


FIGURE 2
pH Stability Profile for Bisoprolol at 56 C

Pretreating the Granular Dicalcium Phosphate to remove surface acidity → product once again is stable

Dulin, W. Drug Dev Ind Pharm, 1995, 21(4), 393-409.

Calcium Phosphates and Bone

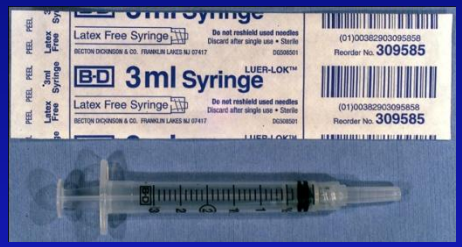
Calcium Phosphate matrices have been tested for facilitating bone repair since 1920. In 1970s hydroxyapatites were used. In 1980s, calcium phosphates were introduced into the clinic.

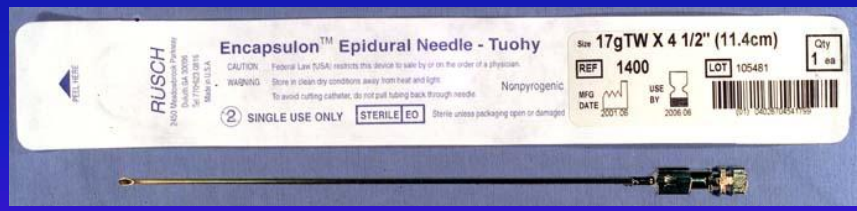
Chemistry, process and many functional properties (structure, crystal and particle size, specific surface area, and porosity) affect the ability of a calcium phosphate to perform as a bone cement.

Calcium Phosphate Matrix (CPM) (Etex Corp)

Forms a paste easily injected by hand. Inject within 15 minutes from time of mix.

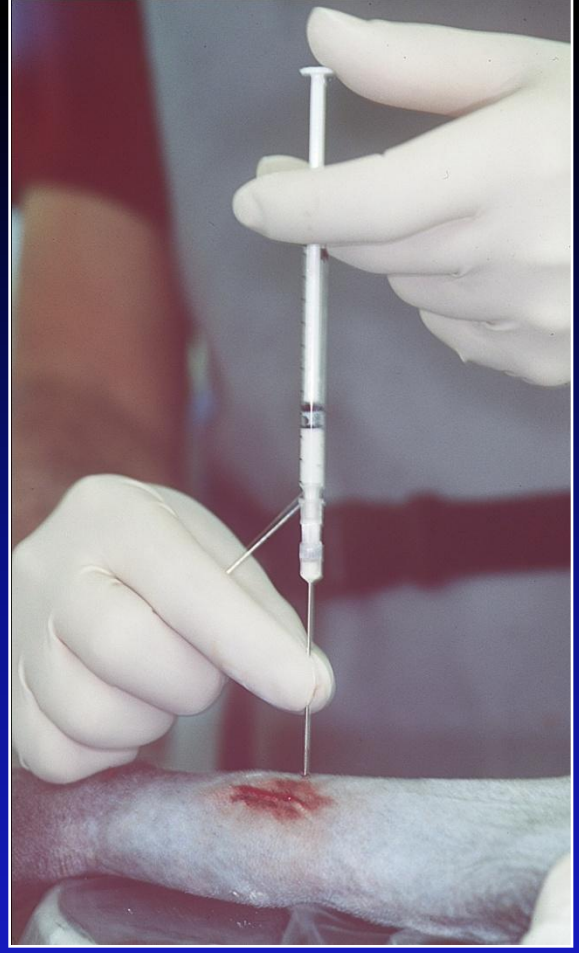
Recombinant Humanized Bone Morphogenic Protein-2 (rhBMP-2) (Wyeth Biopharma)





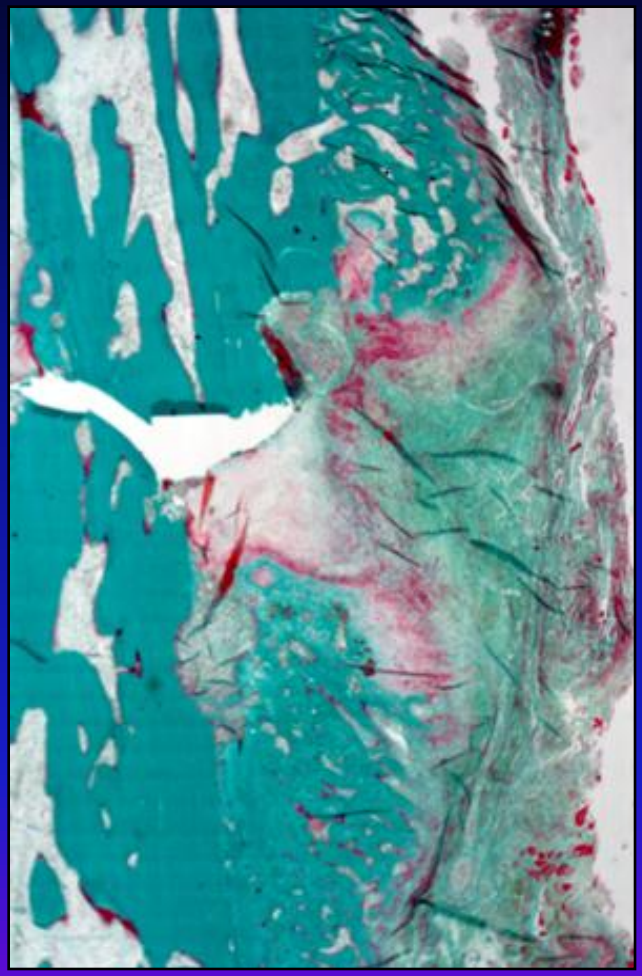
CPM

- Endothermically-setting calcium phosphate paste with unique rhBMP-2 retention
- Formulated as an injectable biodegradable paste
- Specifically designed to particulate following administration

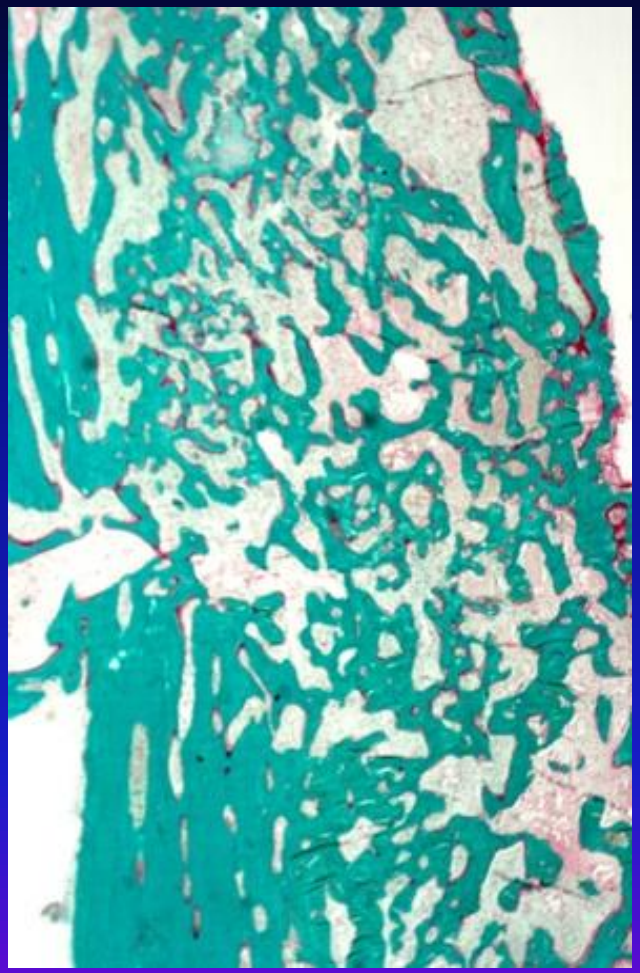


Amorphous Calcium Phosphate
+
Dicalcium Phosphate Dihydrate
+
Sodium Bicarbonate

Histology: NHP fibula osteotomy (8 wks)



Surgical Control



rhBMP-2/CPM

CASE STUDY

Partnering With Big-Pharma:
Pfizer & CyDex's Positive Experience: A Case Study

By: Contributor Guy Furness

Drug Delivery Technology, Jan 2006