Activity of inactive ingredients:
Foundations for innovation in drug excipients

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FDA U.S. FOOD & DRUG ADMINISTRATION

Agenda

1. Inactive ingredients: A brief overview

1. Making inactive ingredients an active area of research

1. Identifying unknown activities of inactive ingredients

2. Ensuring dynamic research into inactive ingredients

The Word “Excipients”

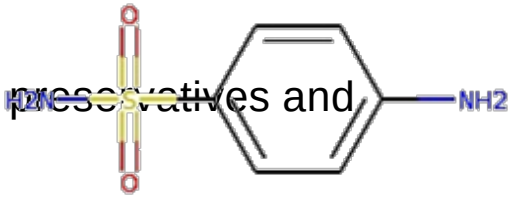
- The legal/medical definition is:
  - “A **usually** inert substance (as gum arabic, syrup, lanolin, or starch) that forms a vehicle (as for a drug or antigen); especially: one that in the presence of sufficient liquid gives a medicated mixture the adhesive quality needed for the preparation of pills or tablets.”

Google Books

Excipients, Toxicology, and Regulation

- 1902 – Congress authorizes Harvey Wiley to study the effect of preservatives and coloring agents on digestion/health
  - Treats streptococcus
- 1907 – 7 colors listed as suitable for foods
- 1938 – FD&C Act
- 1958 – List of 200 substances published as “generally regarded as safe” (GRAS)
  - Initial list
- 1958/1960 – Amendments requiring manufacturers to demonstrate safety of food/color additives
- 1966 – FDA/NAS/NRC collaborate to evaluate safety of 4,000 drugs used between 1938 and 1962
- 1969 – President Nixon orders review of GRAS list due to cyclamate toxicity study – banned in the US today
- 1982 – Red book published (toxicological principles)
  - Last time additive is banned, a history of food/drug law

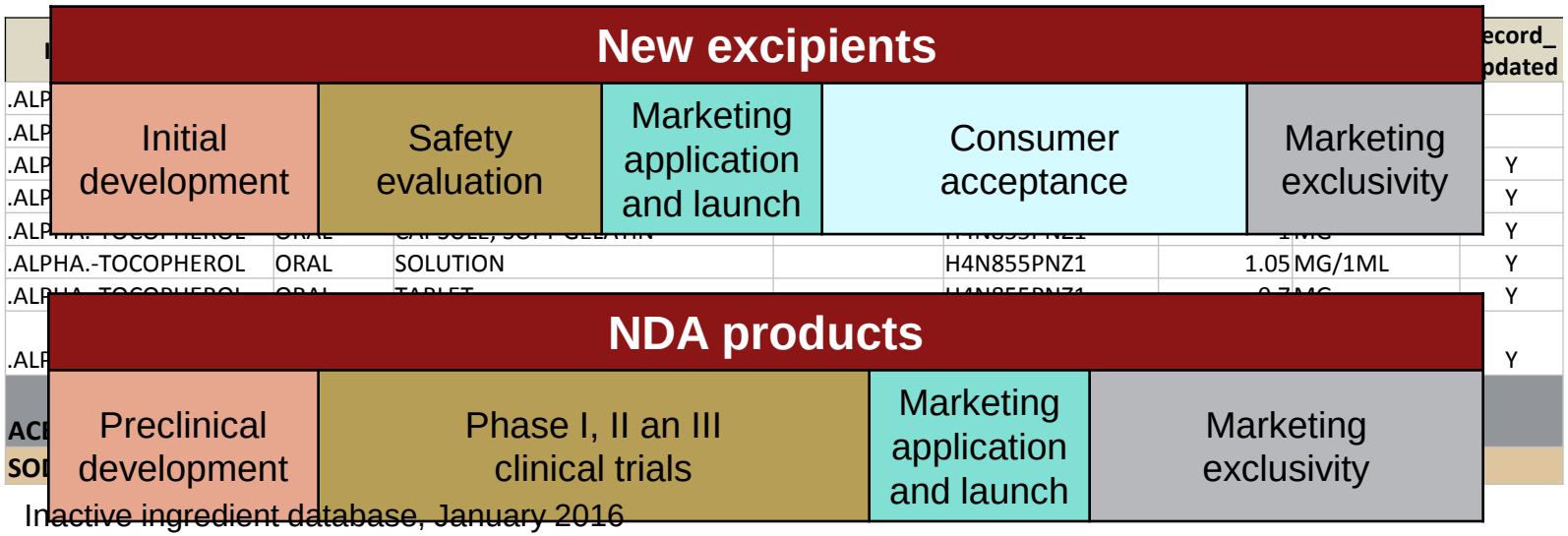
- 1902-1937 Elixir Sulfanilamide Incident
  - Killed more than 100 people across 15 states (October, 1937) after request for liquid delivery rather than tablet/powder formulation (June, 1937)
  - The liquid was diethylene glycol
    - Commonly found in anti-freeze and incredibly toxic
  - The owner, S.E. Massengill, claimed no responsibility; the chemist, Harold Watkins, killed himself
    - Charged for mislabeling as “elixir” rather than “solution”
    - Featured in the US today
  - Led to the 1938 Food, Drug, and Cosmetic Act
    - No safety checks prior – poison was only bad for business



http://www.fda.gov/

Little Return for Excipient Development

- New excipient applications treated like new drug applications
- New excipient → higher costs, more development time → less market time → lower profits → NO DEVELOPMENT INTEREST
- FDA only known source of published inactive ingredient database



Koo, O. M. Y. *American Pharmaceutical Review* **2011**, *7*.

FDA CERSI Project

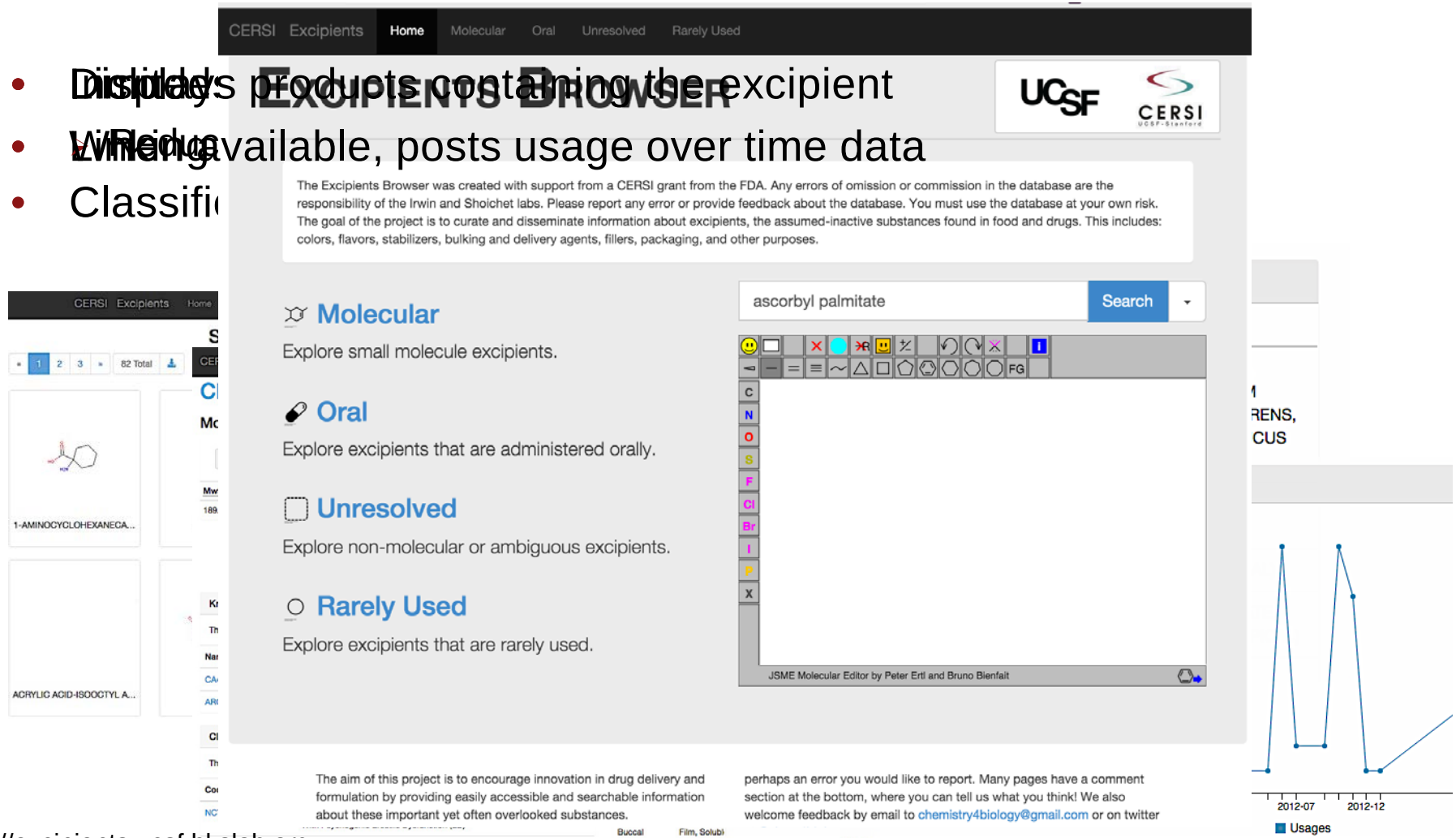
- Project title: Chemoinformatic Tools to Predict the Effects of Excipients in Generic Drugs

- **Goal 1: A community database of FDA excipients**

Irwin, J., Pottel, J., Zou, L., Wen, H., Zuk, S., Zhang, X., Sterling, T., Shoichet, B., Lionberger, R. and Giacomini, K. *Clinicial Pharmacology and Therapeutics*, **2016**, DOI: 10.1002/cpt.458

Simplifying Available Information

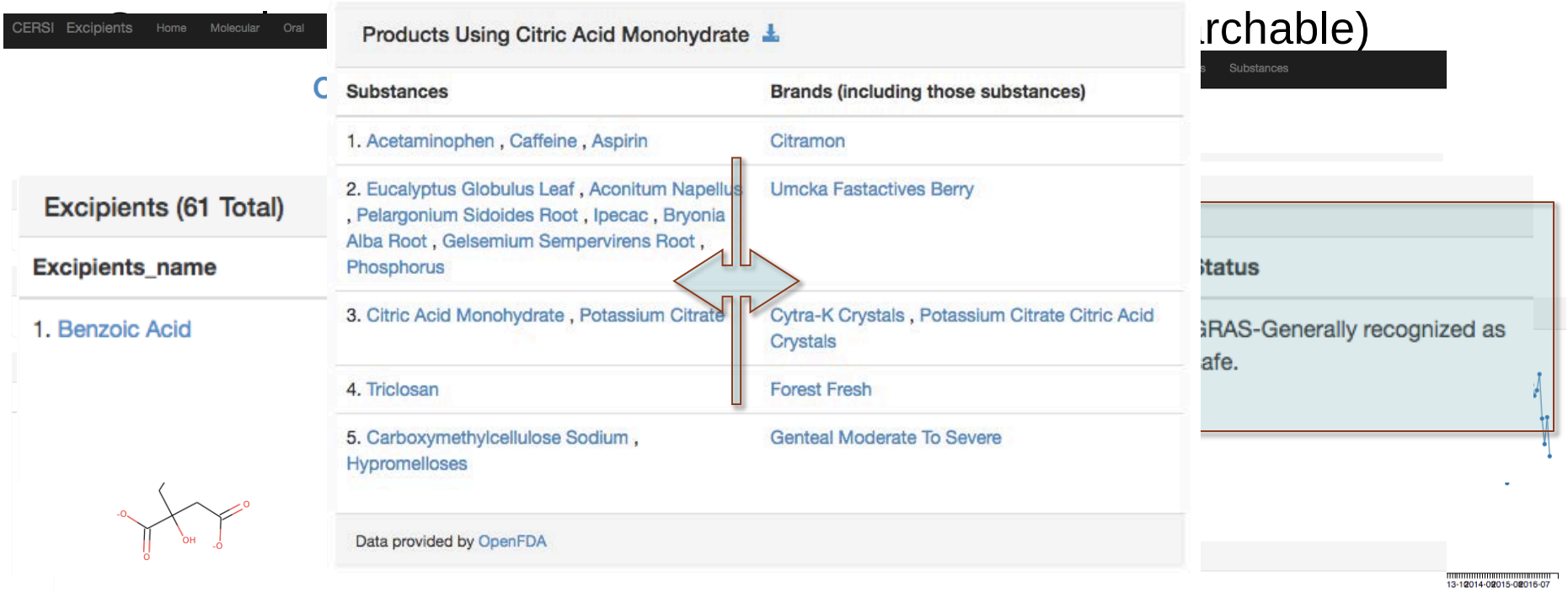
- Displays products containing the excipient
- Where available, posts usage over time data
- Classifi



http://excipients.ucsf.bkslab.org

Further Utilities Added to Excipients Browser

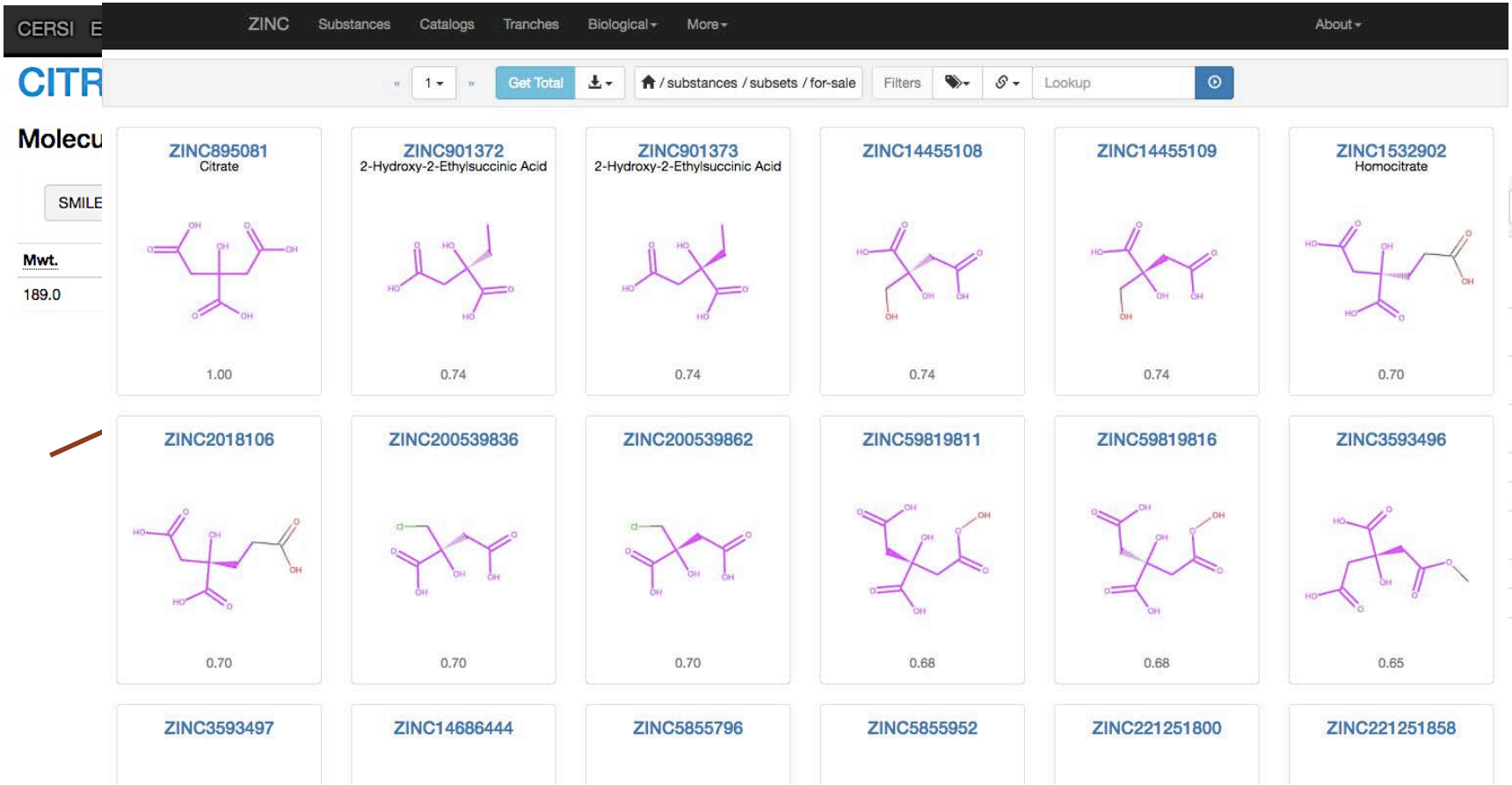
- Cleanup of the molecular page, more data included
- Reorganization by active substance rather than brand
- **Active substance** and **brand** pages for formulation differences



http://excipients.ucsf.bkslab.org

Creating Opportunities for Innovation

- Linking to available resources (purchasing, analoging,…)



FDA CERSI Project

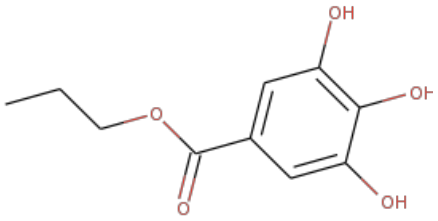
- Project title: Chemoinformatic Tools to Predict the Effects of Excipients in Generic Drugs

- Goal 1: A community database of FDA excipients
- **Goal 2: To investigate the pharmacology of molecular excipients**

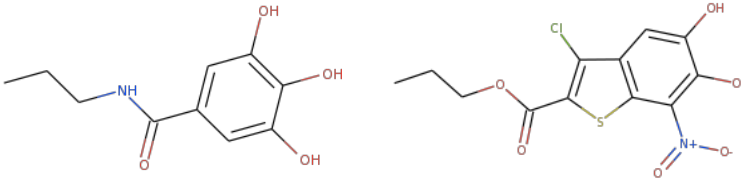
Irwin, J., Pottel, J., Zou, L., Wen, H., Zuk, S., Zhang, X., Sterling, T., Shoichet, B., Lionberger, R. and Giacomini, K. *Clinicial Pharmacology and Therapeutics*, **2016**, DOI: 10.1002/cpt.458

Similarity Ensemble Approach (SEA)

Propyl Gallate (antioxidant)

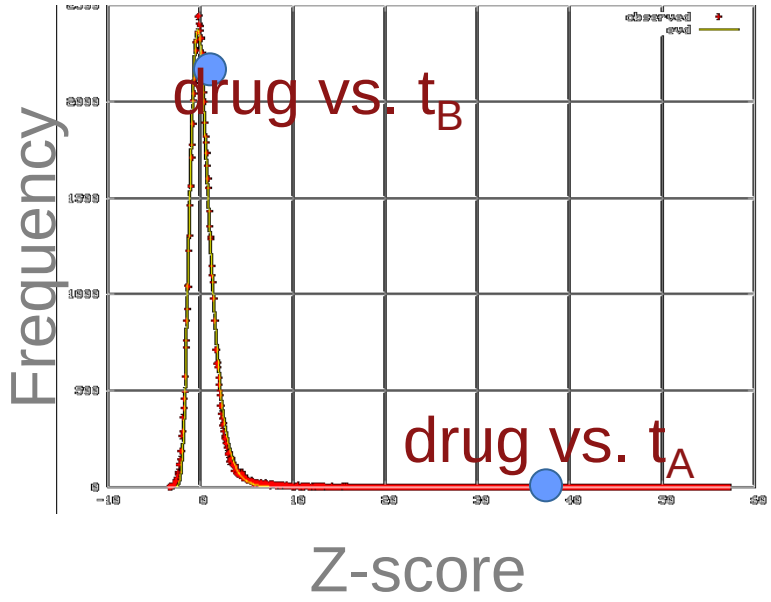


Prediction: COMT
Catechol O-Methyltransferase
Known binders (IC_{50} < 10uM):



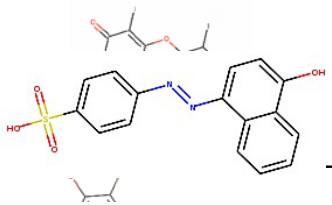
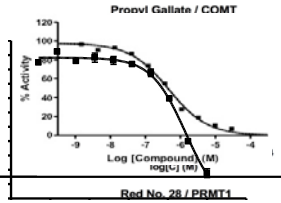
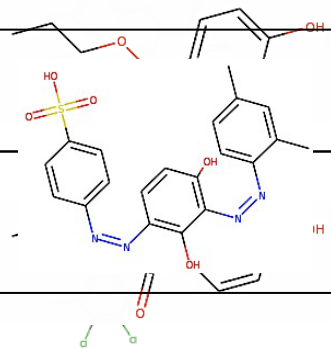
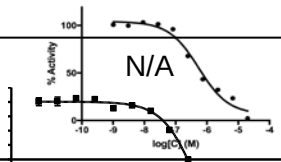
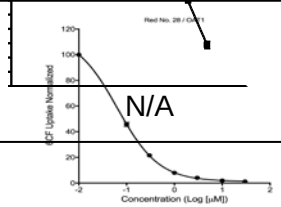
SEA scores: 10^{-10} to 10^{-23}

Statistical model



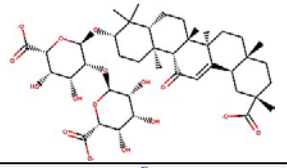
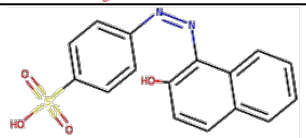
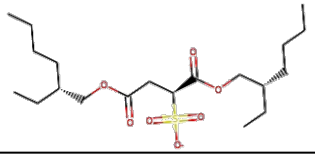
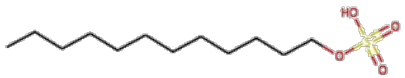
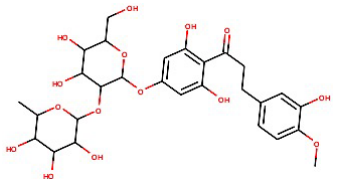
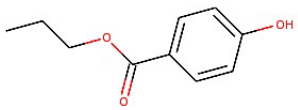
Confirmed Activity of Excipients

Excipients	Predictions	Tested	Confirmed	False Positive - Aggregators	Solubility issues
445	21565	108	48	2	8

Excipient	Structure	Target	SEA Score	IC50	D/R Curve
Propyl Gallate Acid Orange 20		COMT (Catechol O-methyltransferase) PRMT1 (Protein arginine N-methyltransferase 1)	3.56E-27 1.41E-25	402 nM 25 uM	
D&C Red No. 28 Propylparaben (Phloxine B)		PRMT1 (Protein arginine N-methyltransferase 1) BRD4 (Bromodomain-containing protein 4) SLC22A6 (Solute carrier family 22 member 6/OAT1)	1.64E-14 1.11E-27 2.73E-16	66% @ 699 nM 46 uM 58% @ 64 nM	 
D&C Red No. 28 Propylparaben (Phloxine B)		ESR2 (Estrogen receptor beta)	2.73E-16	10uM	N/A

Specific Targets: Transporters (OATP2B1)

Excipients	445
Predictions	47
Tested	18
Confirmed	9
Total OATP2B1 Inhibitors	24 identified
New OATP2B1 predictions after recycling data	1/4 hits
OATP1B1 predictions/testing	7/13 hits

Excipient	Structure	Ki (uM)
Glycyrrhizin		165.3
D&C Orange No. 4		1.9
Docusate Sodium		2.3
Lauryl Sulfate		2.8
Neohesperidin Dihydrochalone		17.9
Propylparaben		198.2

Revitalizing Excipients

- Resurgence in interest regarding excipients and development
  - Enhanced excipients database
  - Potential for “analoging”
- Identified several biological targets for several excipients
  - Enzymes found in the gut
  - Transporters found in the gut

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Questions?

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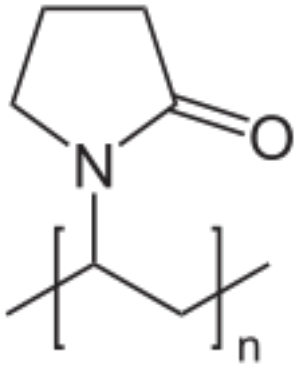
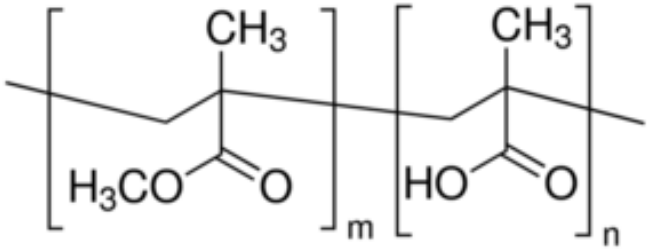
Extra slides

Polymers – described by monomer(s)?

- Povidones
- http://excipients.ucsf.bkslab.org/excipients/povidones/
- https://en.wikipedia.org/wiki/Polyvinylpyrrolidone

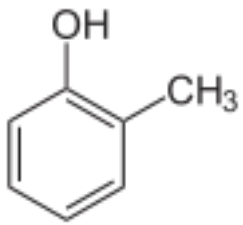


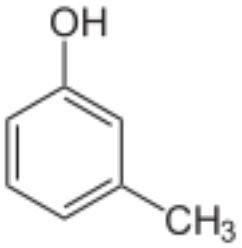
- Methacrylic acid – methyl methacrylate
- http://excipients.ucsf.bkslab.org/excipients/methacrylic_acid_-_methyl_methacrylate_copolymer_11/
- http://www.sigmaaldrich.com/catalog/product/usp/1396604?lang=en&region=US

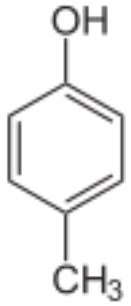


Mixtures – described by each component?

- Cresol
- http://excipients.ucsf.bkslab.org/excipients/cresol/
- https://en.wikipedia.org/wiki/Cresol

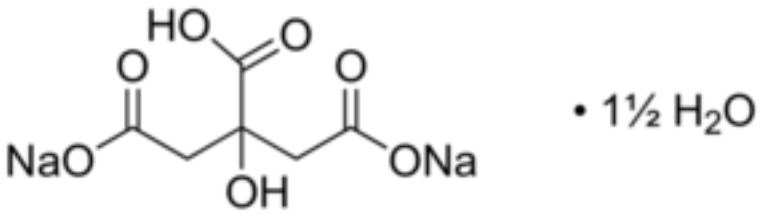






Salts – described by neutral form?

- Citrate (Disodium citrate sesquihydrate)
- http://excipients.ucsf.bkslab.org/excipients/disodium_citrate_sesquihydrate/
- http://www.sigmaaldrich.com/catalog/product/aldrich/359084?lang=en&region=US



Some will remain non-molecular

- Air
- Flavor banana 8763
- Ink thinner
- Oatmeal
- Soap