

1-14-12 notes



DID YOU KNOW?

Valentino J. Stella PhD,
KS State Commerce Committee,
January 19, 2012



The GB Stella Legacy (genes)



The Higuchi Legacy
see "My Mentors"
J. Pharm. Sci. 90,
969-978 (2001)

Josiah P. Cooke
(1827-1894)
Harvard

↓

Theodore W. Richards
(1868-1928)
Harvard
Nobel prize -1914

↓

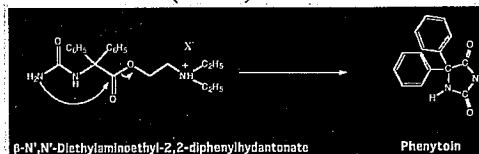
Farrington Daniels
(1889-1972)
Harvard

↓

John Willard
(1908-1996)
Harvard/Wisconsin

↓

Takeru Higuchi
(1918-87)
Berkeley/Wisconsin

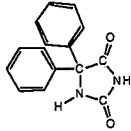


Senate Commerce Committee
Date: January 19, 2012

Attachment 1

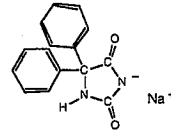


Cerebyx®



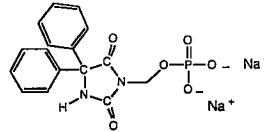
Phenytoin

m.p. 293°C
Water solubility, 20-25µg/mL
pKa, 8.3
Low lipid solubility
(erratic oral and parenteral bioavailability)



Sodium Phenytoin

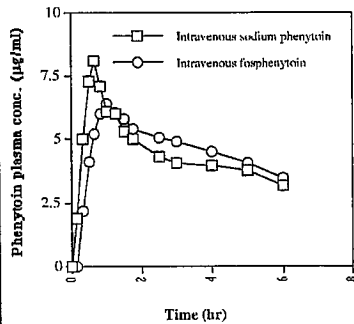
Good water solubility
Injectable dosage form
contains 40% PG
10% ethanol
50% water
pH ≈ 12



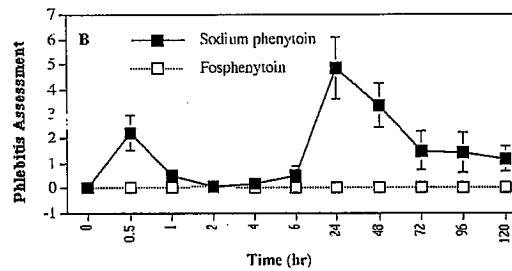
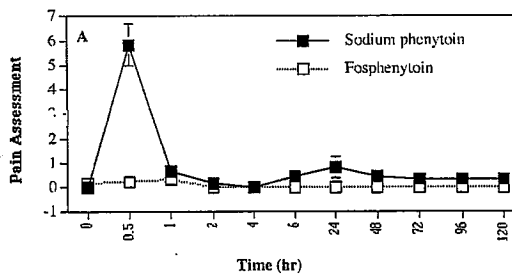
Fosphenytoin

Water soluble
Chemically stable at neutral pH values
Rapidly bioreversible, $t_{1/2} \approx 1$ min in rats
 $\approx 8-17$ min in humans
Non-irritating and quantitatively releases
phenytoin after IM and IV administration

Fosphenytoin – great product
with many licensing
challenges. A lot was
learned from this



Phenytoin plasma concentration (mean, 12 subjects) versus time (first 6 h.) curves after IV infusion over 30 min. of equimolar doses (250 mg phenytoin) of sodium phenytoin, open squares, and fosphenytoin, open circles. Jamerson et al., *Epilepsia* 31, 592-597 (1990).





And then there are moments like this!

Hi,

Thought you may think this is interesting...

Last week my youngest, Jessie, took a fall and knocked herself unconscious (severe concussion). The ER doctor was instructed to give her an anti-seizure drug - just in case. That drug? Fosphenytoin. It was kind of neat to have participated in the development of a drug that was being administered to my daughter, albeit ~25 years later. I feel that it is difficult for us in the drug development arena to know the full impact of what we do. This experience brought it close to home.

Jessie is home now and doing well. She has had a miraculous recovery and so far we haven't seen any lasting effects of her injury.

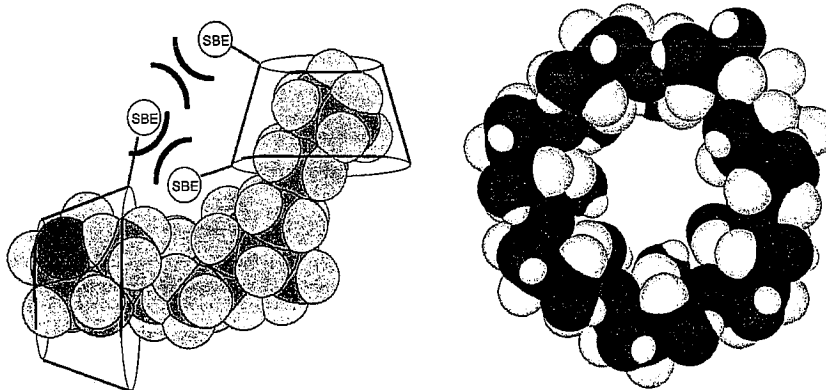
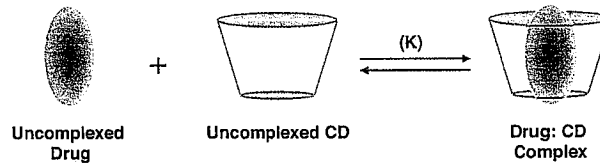
Hope you are doing well.

Take care, Rob

Robert A. Myers, PhD
RAM Pharma Consulting, LLC
2713 Martin Ct.
Idaho Falls, ID

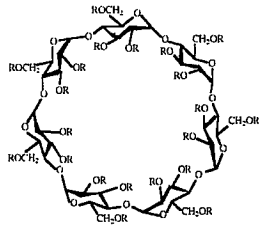
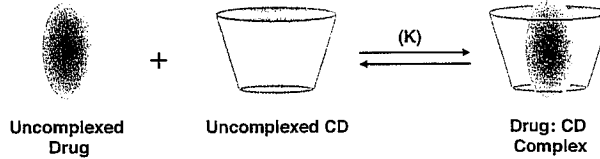


WHY CYCLODEXTRINS?

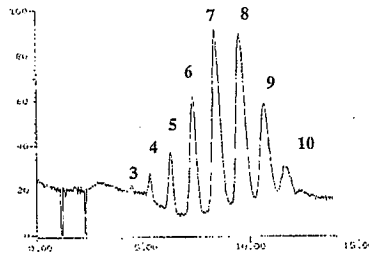




(SBE)_{7M}-β-CD (Captisol®)



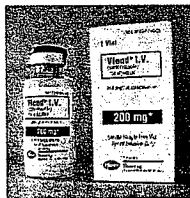
R = -CH₂CH₂CH₂CH₂SO₃Na or -H
 (SBE)_{7M}-β-CD (Captisol®)
 (average degree of sulfobutyl substitution is 7)



Tait, Skanchy, Thompson, Chetwyn, Dunshee, Rajewski, Stella, Stobaugh
J. Pharm. Biomed. Anal., 10 (9), 615-622 (1992)



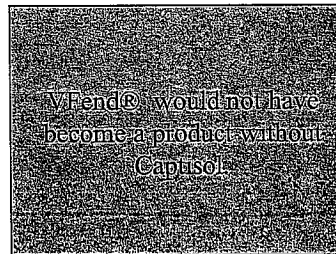
Pfizer Vfend IV Captisol-Enabled Voriconazole Anti-fungal



Formulation Objective: 10 mg/ml

Standard Formulation Approaches
 Failed to give Appropriate Dose
 In Reasonable Delivery Volume

16% Captisol (pH 6-7) Achieved Target

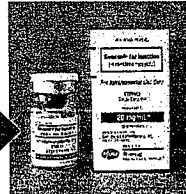


Vfend IV 200 mg drug in 16% Captisol



Pfizer Geodon IM Captisol-Enabled Ziprasidone Mesylate Anti-psychotic-Schizophrenia

The Technology was also found to be excellent for Geodon IM, an injectable for an anti-schizophrenic Agent. Both products helped get Captisol accepted.



1st Target IM Dose ~ 40 mg/ml

	Solubility (mg free base/ml)	
	Water	40% Captisol
Free Base	0.0003	
Mesylate Salt	0.9	44.0

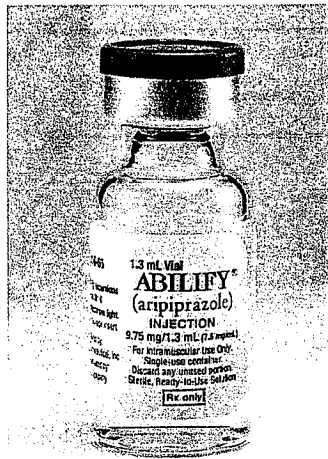
40% Captisol – Improved Solubility
 150,000 X Free Base
 50 X Mesylate Salt

Geodon IM 20 mg drug in 30% Captisol



Some Newly Approved Products

Cerenia™ (maropitant citrate) Injectable Solution



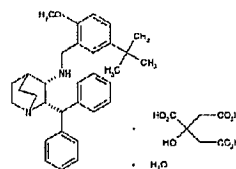
Antiemetic

For subcutaneous injection in dogs only

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description: Maropitant is a neurokinin (NK₁) receptor antagonist that blocks the pharmacological action of substance P in the central nervous system (CNS). Maropitant is the non-proprietary designation for a substituted quinuclidine. The empirical formula is C₂₃H₂₆N₂O₂·C₆H₆O₂·H₂O and the molecular weight 678.81. The chemical name is (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine citrate monohydrate. Each mL of CERENIA Injectable Solution contains 10 mg maropitant, 63 mg sulfobutylmethacrylate-cyclodextrin, 3.3 mg meta-cresol and water for injection.

The chemical structure of maropitant citrate is:

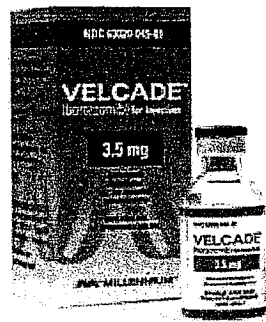


Indications: CERENIA (maropitant citrate) Injectable Solution is indicated for the prevention and treatment of acute vomiting in dogs.

• Amiodorone IV (nexterone)

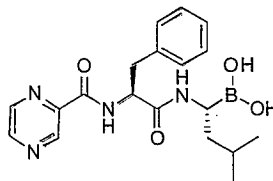


Velcade® (bortezomib)



<http://www.communiquative.com/siteimages/page441.jpg>

- Approved by FDA May 2003
- Multiple myeloma
- 2004 sales \$143 million¹
- 2006 projected \$225-250²

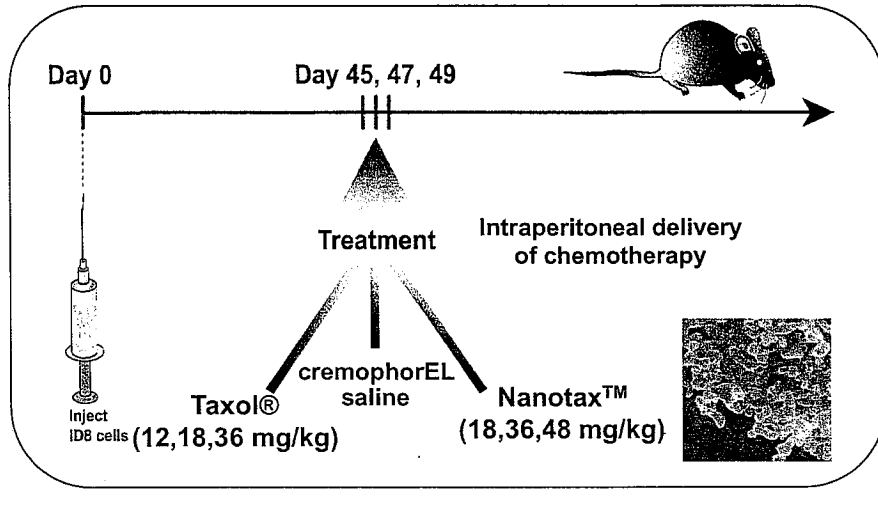


1. Sanchez-Serrano, I., Success in translational research: lessons from the development of bortezomib. *Nat Rev Drug Discov* 2006, 5, (2), 107-14
2. http://investor.millennium.com/phoenix.zhtml?c=80159&p=irol-newsArticle_Print&ID=801177&highlight=



Nanotax®

Does Nanotax alter the progression of ovarian cancer in the mouse model — when delivered intraperitoneally?



Control



Nanotax



"Nanotax treated mice had no ascites and very limited tumor seeds."



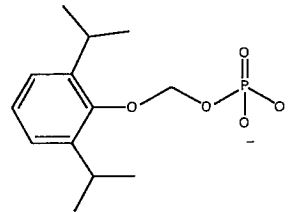
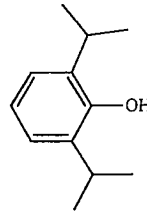
Propofol

Propofol (Diprivan™ - Zeneca)

- Oil/water emulsion
- World-wide sales \$800 MM
- Generic products approved
- Pain upon injection
- Decreased mean arterial pressure

Propofol POM Prodrug (PQ1002)

- Clear aqueous formulation
- Potential pain reduction
- Rapid conversion to propofol *in vivo*

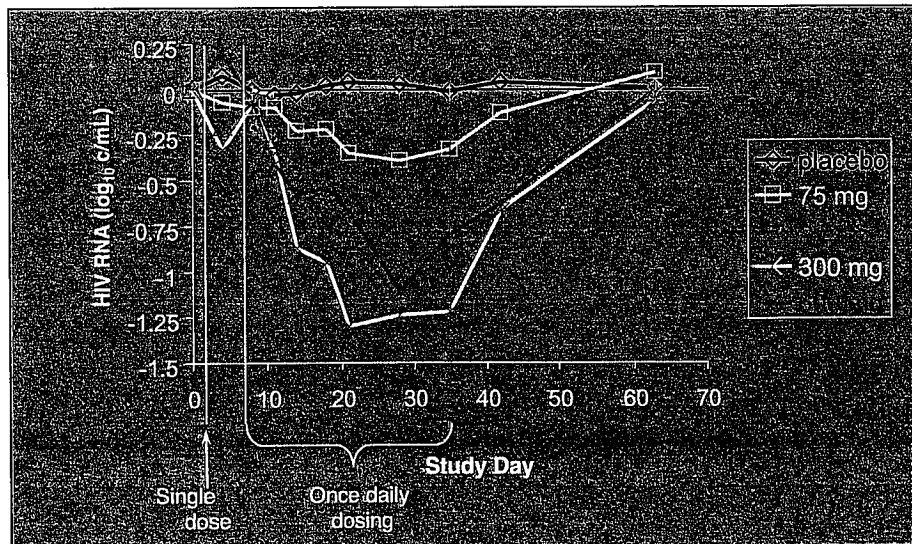


Lusedra

- Ready-to-use solution
- Excellent substrate for enzymatic cleavage
- $t_{1/2}$ in vivo 1.5 minutes
- Excellent yields
- Patentable (patent approved in USA)



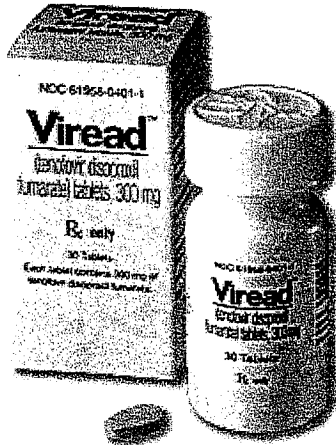
Change from Baseline in HIV RNA



(Slides on Tenofovir supplied by Reza Oliyai (Gilead))



(tenofovir disoproxil fumarate)



First nucleotide RTI

One tablet, once daily

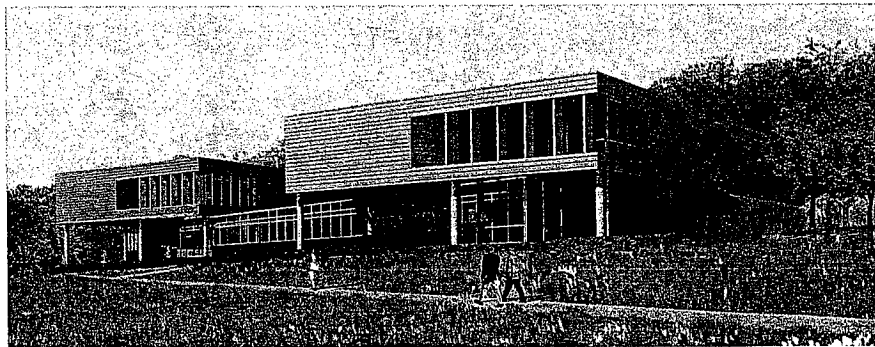
Significant HIV RNA reductions

Durable activity against nucleoside resistant HIV

Favorable safety profile



BTBC, Lawrence





The Big Boss
in his younger
days

Pharmaceutical R&D Execs

Now a
Transplant
Specialist

Pharmacist

Missionary
in
China



First Lab of Graduate Students and Technicians circ 1976