

Water Insoluble Drug Development: Strategies, Technologies, Case Studies

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Water Insoluble Drug Development

- Case Studies
 - TriCor/Fenofibrate
 - Kaletra
 - The Inevitable Generic Competition
 - The Emergence of Specialty Pharma
 - Approved Water Insoluble Drugs 2000-2010
- Technology Selection Strategies
 - The Impact of Drug Delivery
 - Life Cycle Management
 - How do you study the space and your competition?
- Marketed Product Attributes
 - Color, shape, size, form...


Case Studies

The TriCor* Story

Date	Action
1960's	Fenofibrate discovered by Fournier
1975	Lipidil Capsule approved in Europe.
1993	FDA approved as Lipidil 100 mg capsule but Fournier did not market
1997	Fournier granted Abbott an exclusive license including US4895726 (fenofibrate co-micronized with a solid surfactant)
1998	Tricor-A (Lipidil Micro) 67 mg capsule approved in US (Abbott)
1999	Tricor-A 134 mg and 200 mg approved in US
1999	Novopharma (Teva) filed PIV on '726 patent
2000	Impax files PIV on '726 patent

*TriCor is a registered trademark of Abbott laboratories.

The TriCor Story

2001	Tricor-B tablet 54 mg and 160 mg approved. Abbott pulls capsule from market. TRICOR B had an additional indication for HDL effect.
2001	TRICOR-A listed as obsolete in the National Drug Data File causing Teva's generic TRICOR-A to be identified as a brand drug resulting in a higher co-payment.
2002	Teva files PIV for Tricor-B 54 mg and 160 mg tablets (US6074670, US6277405, US6589552, US6652881)
2004	Teva and Impax receive tentative approval for generic Tricor-B
2004	<p>Abbott's Tricor-C approved as 48 mg and 145 mg tablets using Elan's NanoCrystal technology as a new NDA. TRICOR-C precluded generic substitution of those approved for TRICOR-B (food effect). TRICOR C has patent protection until 2018.</p> 

The TriCor Story

2008	Abbott pays Teva/Impax \$184M in Tricor anti-trust settlement. Agree to launch date of generic 145 mg.
2008	Abbott's Trilipix (choline fenofibrate) approved. US7259186 patent on fenofibric acid salts valid until 1/07/2025. Exclusivity Expiration 12/15/2011. (Source Orange Book)
2009	Trilipix Delayed Release Capsules launched in US in January
2010	Trilipix PIVs already filed by Watson and Impax. Litigation initiated by Abbott.
2011/2012	Market of generic 145 mg TriCor no sooner than March 28, 2011. Launch expected some time in 2012

Meanwhile.....

The TriCor Story: Specialty Pharma Makes Its Mark

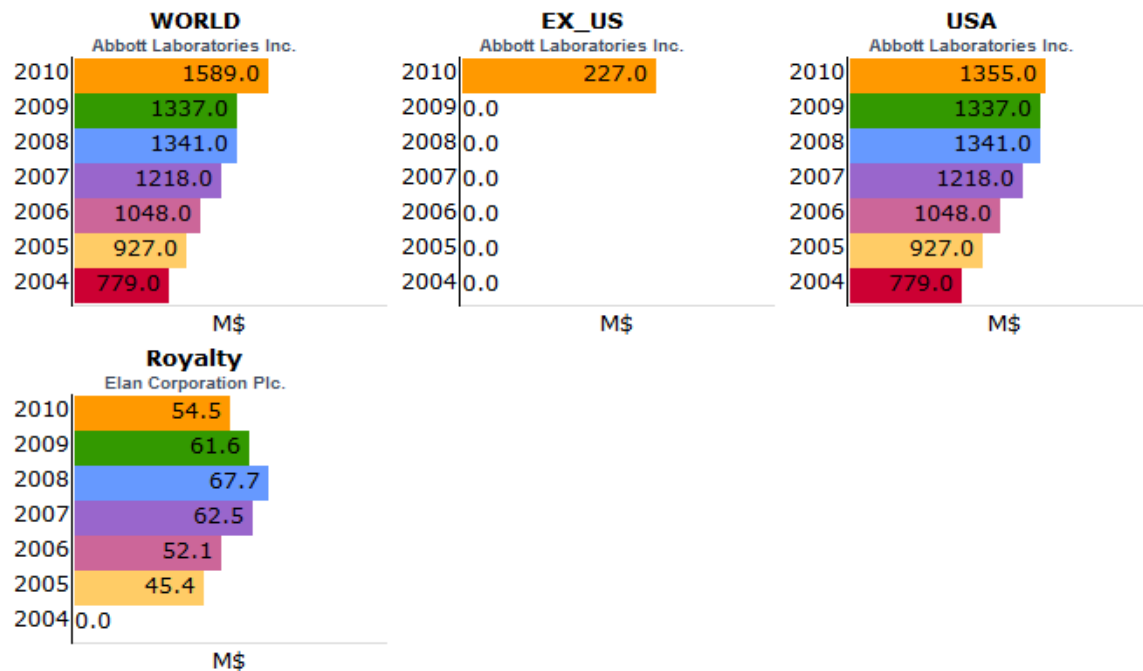
New Formulations (NDA's) of Fenofibrate Developed and Marketed

2004*	Ethypharm's Antara 43 mg, 87 mg, 130 mg capsules approved in US. 2008 sales of \$70 million. Marketed in US by Lupin.
2005	SkyePharma's Triglide 50 mg and 160 mg approved in US. Marketed in US by Shionogi (First Horizon/S
2006	Galephar/Cipher Lipofen 50 mg, 100 mg 150 mg capsules approved in US. Marketed by Kyowa in US.
2007*	LifeCycle Pharma's Fenoglide 40 mg and 120 mg tablets approved with MeltDose technology in US. Marketed in US by Shionogi (Sciele).
2009	URL's Fibracor 35 mg and 105 mg tablets (fenofibric acid) approved.

* Paragraph IV's filed


What Is At Stake?

Tricor NanoCrystal Tablets • TriLipix Delayed Release Capsules Sales



Source: PharmaCircle, LLC

Case Study: Kaletra

Date	Action
2000 	Soft gel capsule 133.3 mg Lopinavir/33.3 Ritanovir Approved in US as HIV protease inhibitor. Formulation: FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide and water. Also approved as an Oral Solution
2001	Soft gel capsule/Oral Solution approved in Europe.

Recommended storage: Store KALETRA soft gelatin capsules at 36°F - 46°F (2°C - 8°C) until dispensed. **Avoid exposure to excessive heat.** For patient use, refrigerated KALETRA capsules remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), capsules should be used within 2 months.

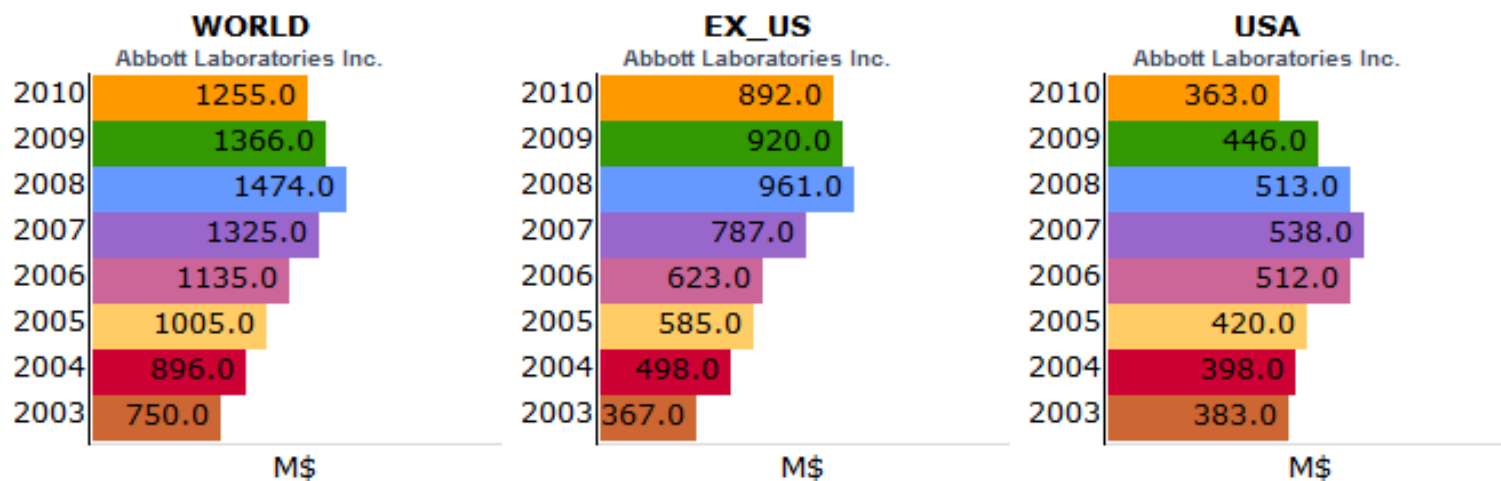
*Kaletra is a registered trademark of Abbott laboratories

Case Study: Kaletra

2005	US approval of Kaletra Tablet 200 mg/ 50 mg and 100 mg/25 mg Lopinavir/Ritanovir using Soliq's Meltrex technology. Reduced pill burden from 3 capsules 2X daily to 2 tablet/2X daily.
2009	Tentative approval of generics from Mylan/Matrix, Cipla, and Aurobindo.
2009	The United States non-composition of matter patent covering lopinavir/ritonavir will expire in 2016. Abbott filed suit in March 2009 alleging Mylan's proposed generic products infringe Abbott's patents. Upon Matrix's motion, the court granted a five-year stay of the litigation unless good cause to lift the stay is shown.

Case Study: Kaletra

Kaletra Soft Gel Capsules • Kaletra Tablets • Kaletra Oral Solution Sales

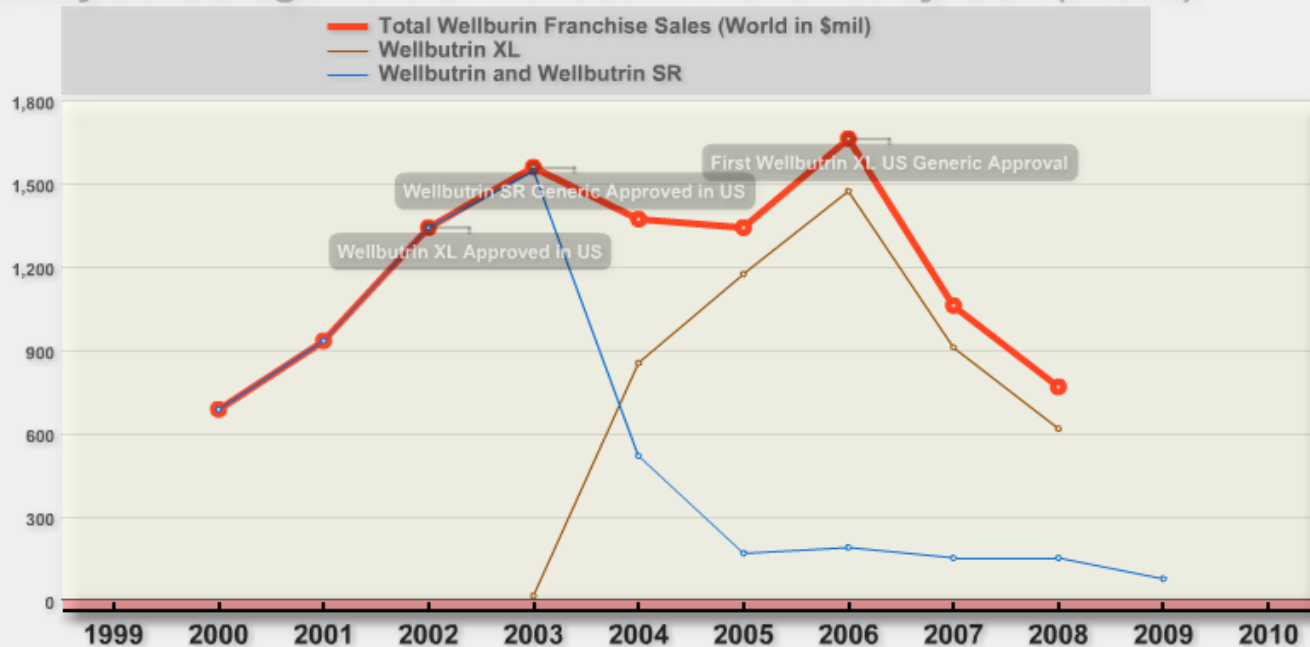


Source: PharmaCircle, LLC

Generic Competition

The Generic Effect

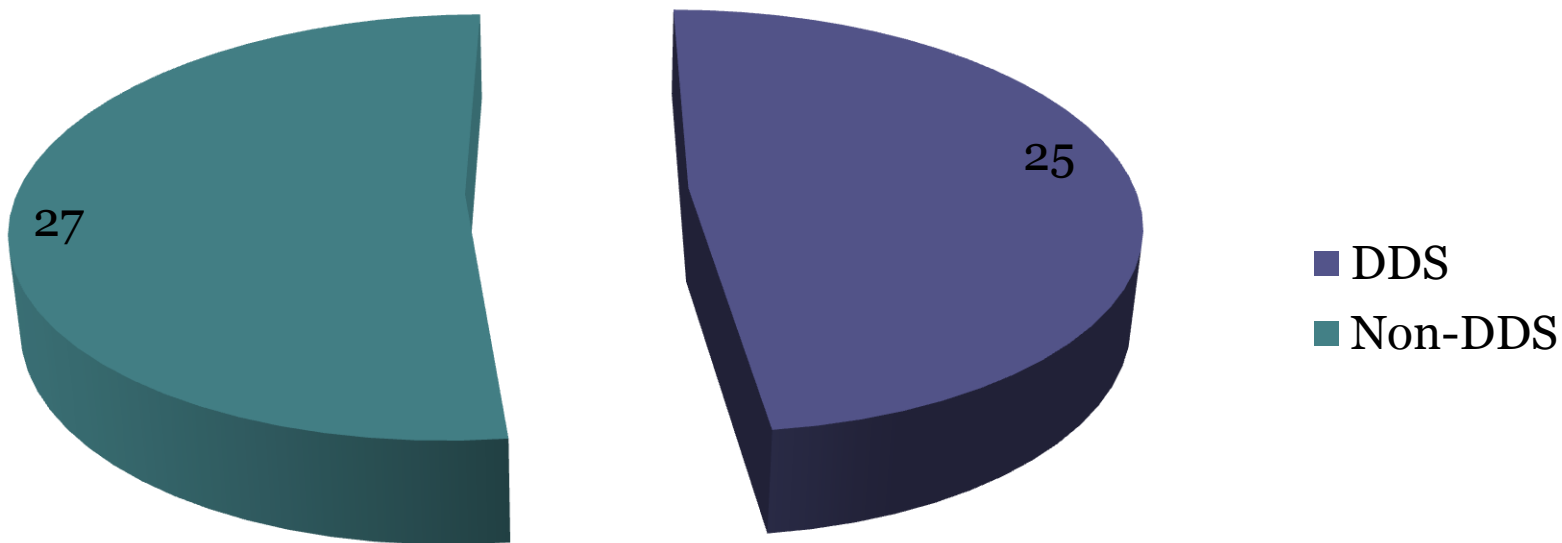
Lifecycle Management of Wellbutrin Franchise by GSK (World)



Oral-Once-daily Dosage Form Strategy

Products with Generic Patent Challenges

2010 PIV Filings



Source: US FDA

2010: PIV Drug Delivery Filings

Solubilization	Fenoglide	Jalyn/Duodart	Rapamune (0.5 mg)
Oral MR	Dexilant	Exalgo/Jurnista	Oxycontin OTR
	Biaxin XL	Ranexa	Focalin XR (30 mg)
	Simcor (750 mg/20 mg, 500 mg/20 mg)	Mirapex ER	Oleptro
IntraOral	Metozolv ODT	Orapred ODT	Aricept ODT
	Edluar		
Other	Vivelle Dot	Taclonex Ointment	Locoid Lipocream
	Latisse	Zymaxid	Olux-E Foam
	Pulmicort Respules (1mg/2mL)	Protopic	Retin-A Micro

Generic Competition

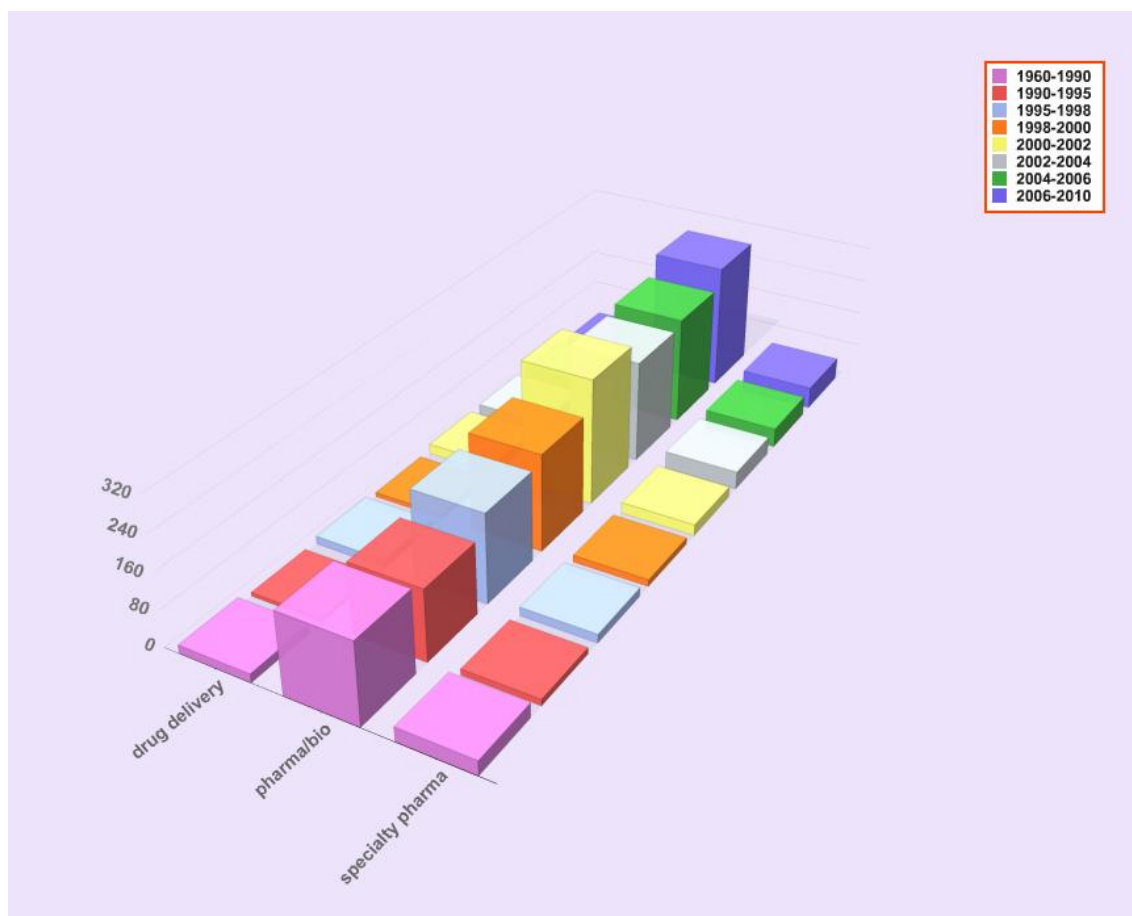
- Increase in PIV patent challenges earlier in patent life
- Increased sophistication in DD technologies
 - Water insoluble techs (nanoparticles, amorphous, etc.)
 - Drug/Device combinations
 - Injectable Depot
 - Transdermal
- Several large, well funded, skilled, generic firms with global presence
 - Teva
 - Watson
 - Sandoz
 - Mylan
 - Actavis
 - Ranbaxy

The Emergence of Specialty Pharma

Specialty Pharma

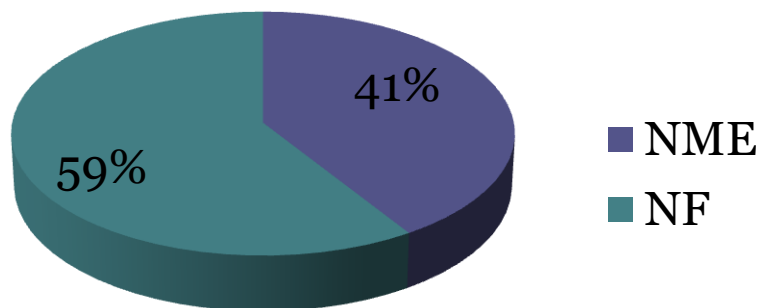
- Specialty Pharma company formations are on the rise
- Success Rates for New Formulations (NF) are higher than NCE's.
- Companies are developing complex technologies
 - Not just Oral CR dosage forms
 - Amorphous, nanoparticles, injectable depot, transdermal, Polymer prodrugs/PEGylation.

Year Founded vs. Business Models

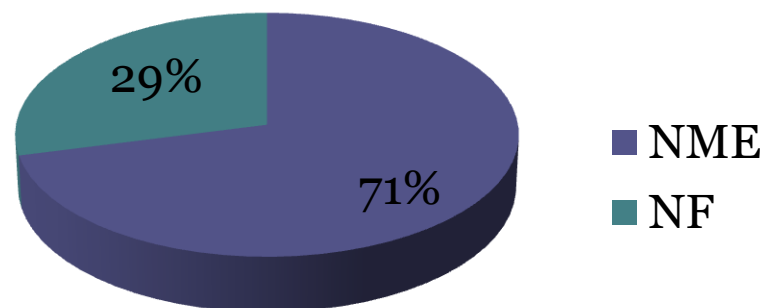


NME vs. NF Products and Pipeline

US Marketed NDA Products



Current NDA Pipeline



US Marketed Products: NDA's

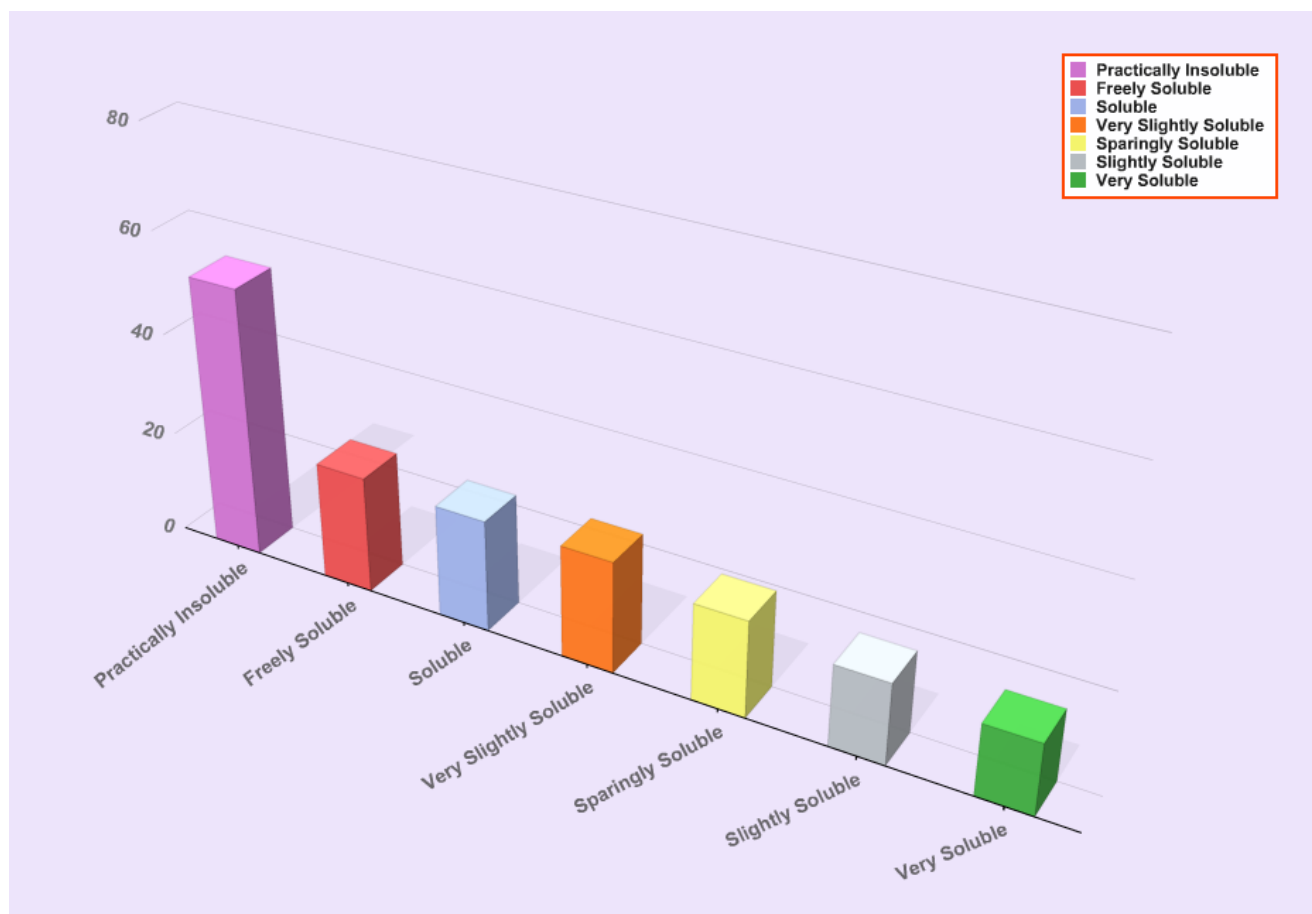
Molecule Type	Total	NME	NF	DDS
Small Molecule	4987	1479	2316	2513
Peptide	164	71	68	93
Protein	511	212	260	204
Antibody	128	107	0	21
siRNA	0	0	0	0

Global NDA Pipeline

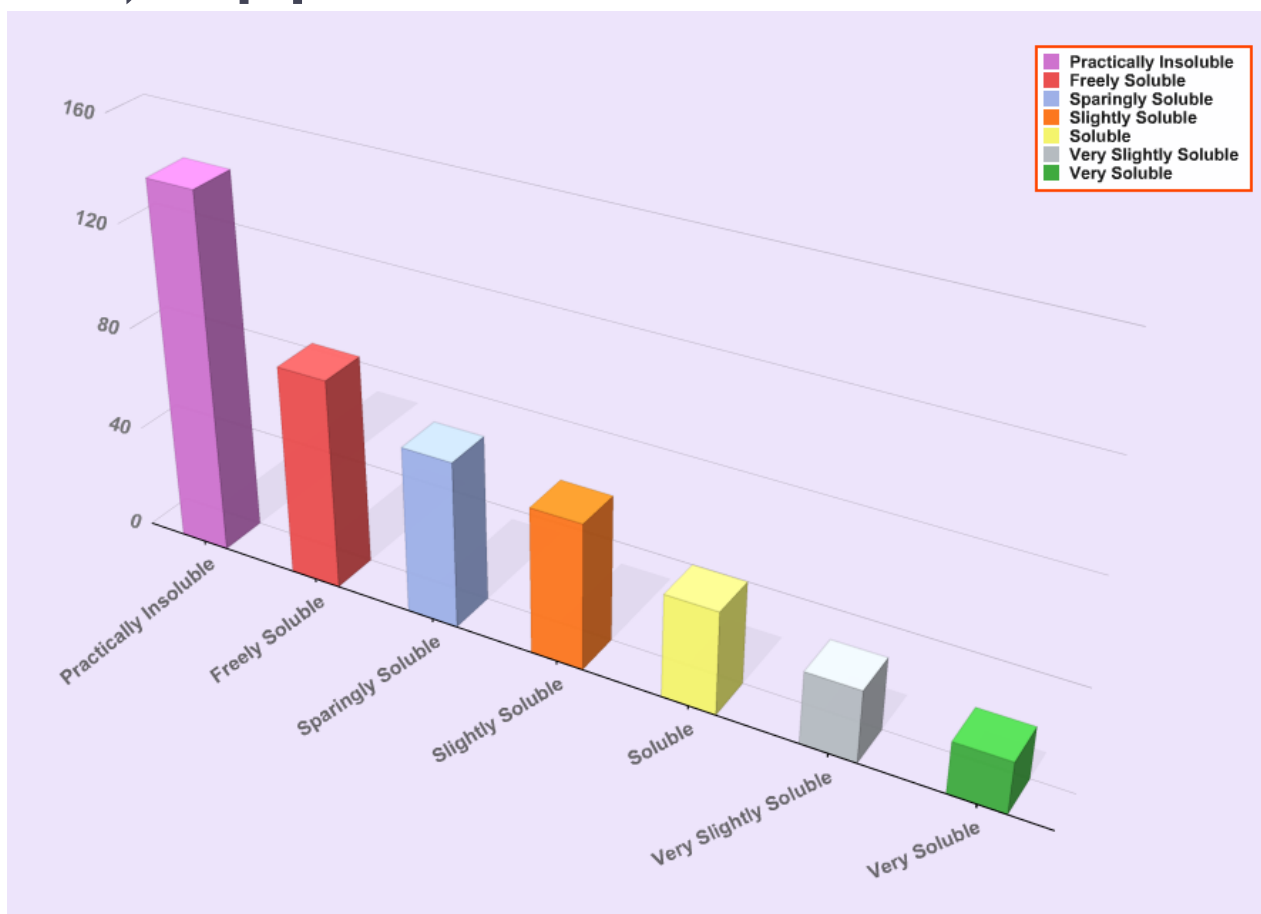
Molecule Type	Total	NME	NF	DDS
Small Molecule	5997	3619	1981	2597
Peptide	782	576	150	317
Protein	1185	806	279	485
Antibody	1314	1123	168	91
siRNA	186	186	0	121

Water Insoluble Drugs

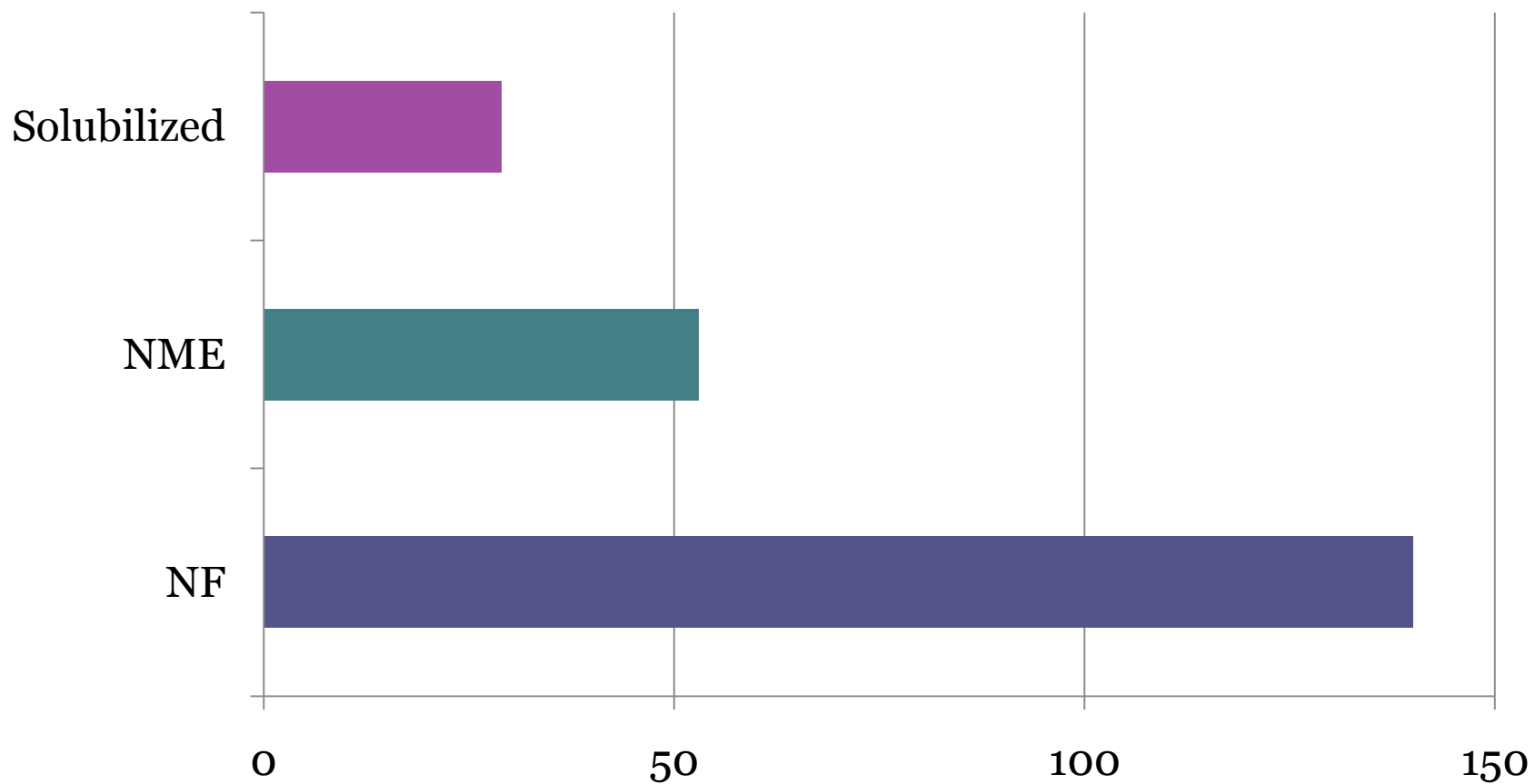
Water Solubility of NME's Approved in US Since 2000



Water Solubility of New Formulations (NF) Approved in US Since 2000



Practically Insoluble Drug Products Approved in US Since 2000



What Do We Mean By Solubilization Technology?

Solubilized	Not Solubilized
Nanoparticles	Micronization
Lipid SEDDS	“Standard” wetting agents
Amorphous, Solid Solution/Dispersion	Standard tablet, capsule, solution, powder processing
Cyclodextrins	Somewhat subjective
Dendrimers	
Micelles/Emulsions	

Solubilization Technology Utilization

- Only 15% of practically insoluble drugs (NME or New Formulation) utilized solubilization technologies.
- Water Insoluble Technologies Really Needed?

OR

- Opportunity for improved therapies?

Approved Drugs: 2000-2010

Solubilization Technology

Brandname	Approved	Dosage Form	Company	Type	Technology
ITRACONAZOLE (Hyphanox)	2010	Tablet	STIEFFEL/GSK	NF	Solid Disperion
NORVIR TABLET	2010	Tablet	ABBOTT	NF	Meltrex
JALYN (DUODART)	2010	Capsule	GSK	NF	Softgel/SEDSS
INVEGA SUSTENNA	2009	Suspension; Injectable (Ext. Release, IM)	J&J	NF	NanoCrystal
ZIPSOR	2009	Capsule	XANODYNE	NF	Softgel/SEDSS
FIBRICOR	2009	Tablet	URL	NF	Nanoburst
ALOXI	2008	Capsule	HELSINN	NF	Softgel/SEDSS
NEXTERONE	2008	Injectable	PRISM	NF	Captisol
CLEVIPREX	2008	Emulsion; IV	MEDICINES CO	NF	Emulsion
INTELENCE	2008	Tablet	J&J	NME	Amorphous

Approved Drugs: 2000-2010

Solubilization Technology

Brandname	Approved	Dosage Form	Company	Type	Technology
HYCAMTIN	2007	Capsule	GSK	NF	Softgel/SEDDS
FENOGLIDE	2007	Tablet	SHIONOGI/ LIFECYCLE	NF	Softgel/SEDDS
ABILIFY INJECTION	2006	Injectable	OTSUKA	NF	Captisol
TIROSINT	2006	Capsule	INSTITUT BIOCHIMIQUE	NF	Softgel/SEDDS
AMITIZA	2006	Capsule	SUCAMPO	NME	Softgel/SEDDS
LIPOFEN	2006	Capsule	CIPHER	NF	Softgel/SEDDS
KALETRA TABLETS	2005	Tablet	ABBOTT	NF	Meltrex
MEGACE ES	2005	Suspension; Oral	PAR	NF	NanoCrystal
TRIGLIDE	2005	Tablet	SKYEPHARMA	NF	IDD-P Microparticle
ABRAXANE	2005	Suspension, Injectable	ABRAXIS	NF	Nab Nanoparticle

Approved Drugs: 2000-2010

Solubilization Technology

Brandname	Approved	Dosage Form	Company	Type	Technology
APTIVUS	2005	Capsule	BOEHRINGER	NME	Softgel/SEDSS
TRICOR C	2004	Tablet	ABBOTT	NF	NanoCrystal
ANTARA	2004	Capsule	ETHYPHARM	NF	Other
EMEND	2003	Capsule	MERCK	NME	NanoCrystal
VFEND INJECTION	2002	Injectable; IV (Infusion)	PFIZER	NF	Captisol
GEODON	2002	Injectable; IM	PFIZER	NF	Captisol
MITOZYTREX	2002	Injectable	SUPERGEN	NF	Cyclodextrin
AVODART	2001	Capsule	GSK	NME	Softgel/SEDSS
RAPAMUNE	2000	Tablet	WYETH	NF	NanoCrystal
KALETRA CAPSULE	2000	Capsule	ABBOTT	NME/NC	Softgel/SEDSS

Impact of Drug Delivery

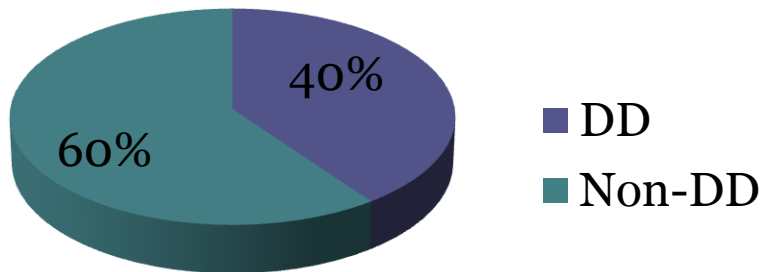
Top 20 Product Sales Worldwide-2010

Product	Sales (M\$)	Molecule Type	Route	DDS
Lipitor	10733	Small Molecule	Oral	No
Plavix	9483	Small Molecule	Oral	No
Advair	7988	Small Molecule	Inhalation	Yes
Enbrel	7216	Protein	Injection	Yes*
Humira	6548	Antibody	Injection	Yes
Remicade	6445	Antibody	Injection	No
Avastin	6100	Antibody	Injection	No
Diovan	6053	Small Molecule	Oral	No
Rituxan	6001	Antibody	Injection	No
Crestor	5691	Small Molecule	Oral	No
Seroquel	5302	Small Molecule	Oral	Yes*
Herceptin	5126	Antibody	Injection	No
Zyprexa	5026	Small Molecule	Oral, Injection	Yes*
Singulair	4987	Small Molecule	Oral	Yes*
Nexium	4969	Small Molecule	Oral, Injection	Yes*
Lantus	4828	Protein	Injection	Yes*
Gleevec	4265	Small Molecule	Oral	No
Actos	4200	Small Molecule	Oral	No
Lovenox	3643	Carbohydrate	Injection	No
Aricept	3643	Small Molecule	Oral	Yes*

*Sales reported for franchise which includes multiple formulations

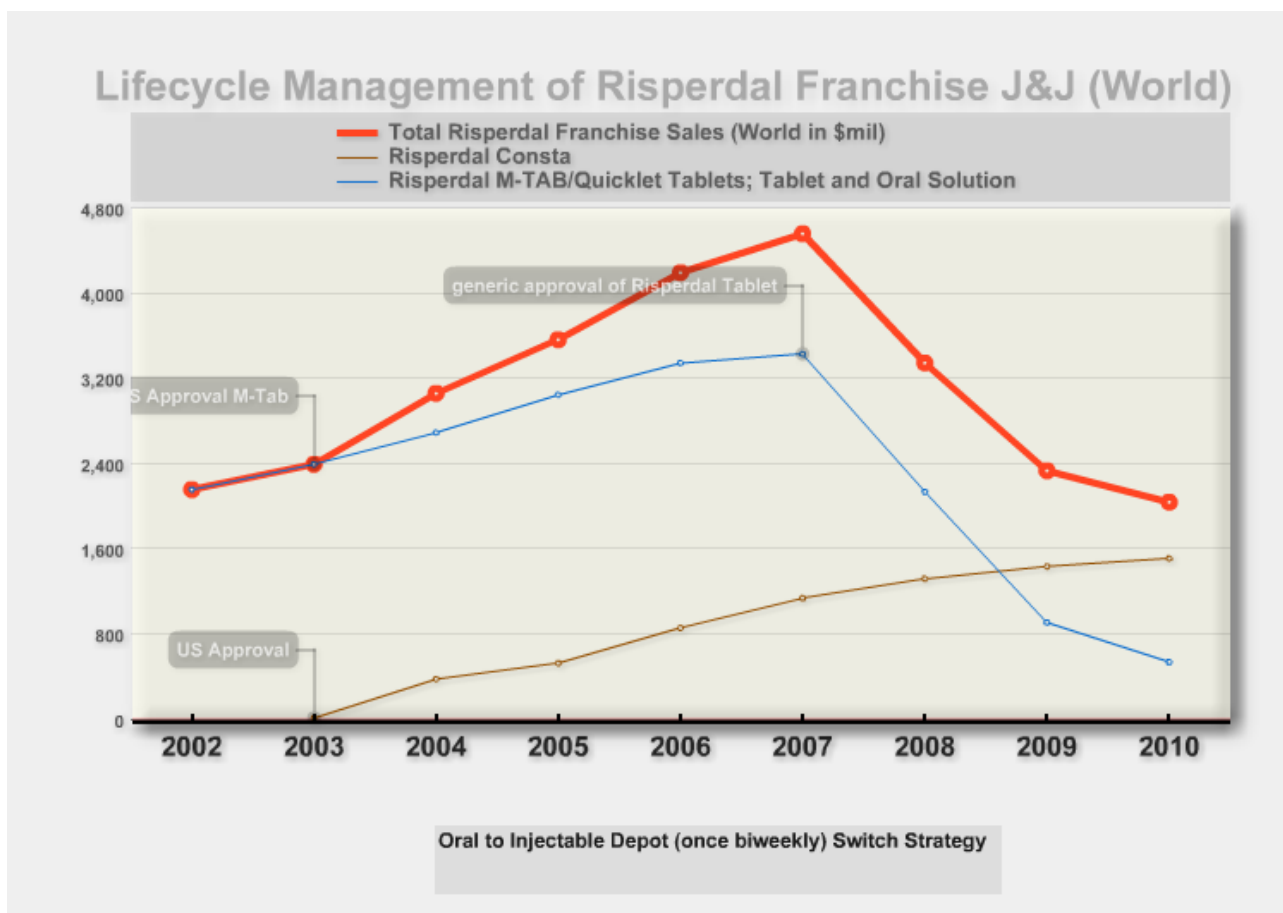
Drug Delivery in Top 20 Products

Top 20 Product Sales



- 40% of Top 20 products have an element of Drug Delivery
- DD contributes to \$51 Billion USD in sales for Top 20 products
- DD is applied to small molecules and biologics

Drug Delivery and LCM: Risperdal



Impact of DD Technology on Products

- **Emend**
 - Solubilization technology enabled product to reach market. Sales of \$380 million USD in 2010.
- **Megace ES**
 - Eliminated food effect and reduced dose size. Important for patient population that has difficulties eating/swallowing. Sales of approx. \$70 million USD.
- **Intence**
 - Solubilization technology enabled product to reach market
- **Invega**
 - OROS and Nanocrystal technologies created products with good safety/efficacy profiles. May be difficult for Generics to copy. Sales of \$424 million USD in 2010.
- **TriCor**
 - Reduced dose, eliminate food effect, LCM delayed Generic introduction. Sales of \$1.6 billion USD in 2010.
- **Geoden**
 - Allowed for an injectable form to reach market. Franchise sales of over \$1 billion USD in 2010

Impact of Drug Delivery: Summary

- Drug delivery provides measurable value
 - Utilized in some capacity in 40% of Top 20 pharmaceutical products with sales of 51 billion USD worldwide.
- Drug delivery increases revenues via patent protection and life cycle products
 - Delays generic introduction in some cases and provides additional franchise revenues.
- Drug delivery has to make sense
 - Does not provide inherent value to all programs. Must be product/market driven.

Information and Business Intelligence

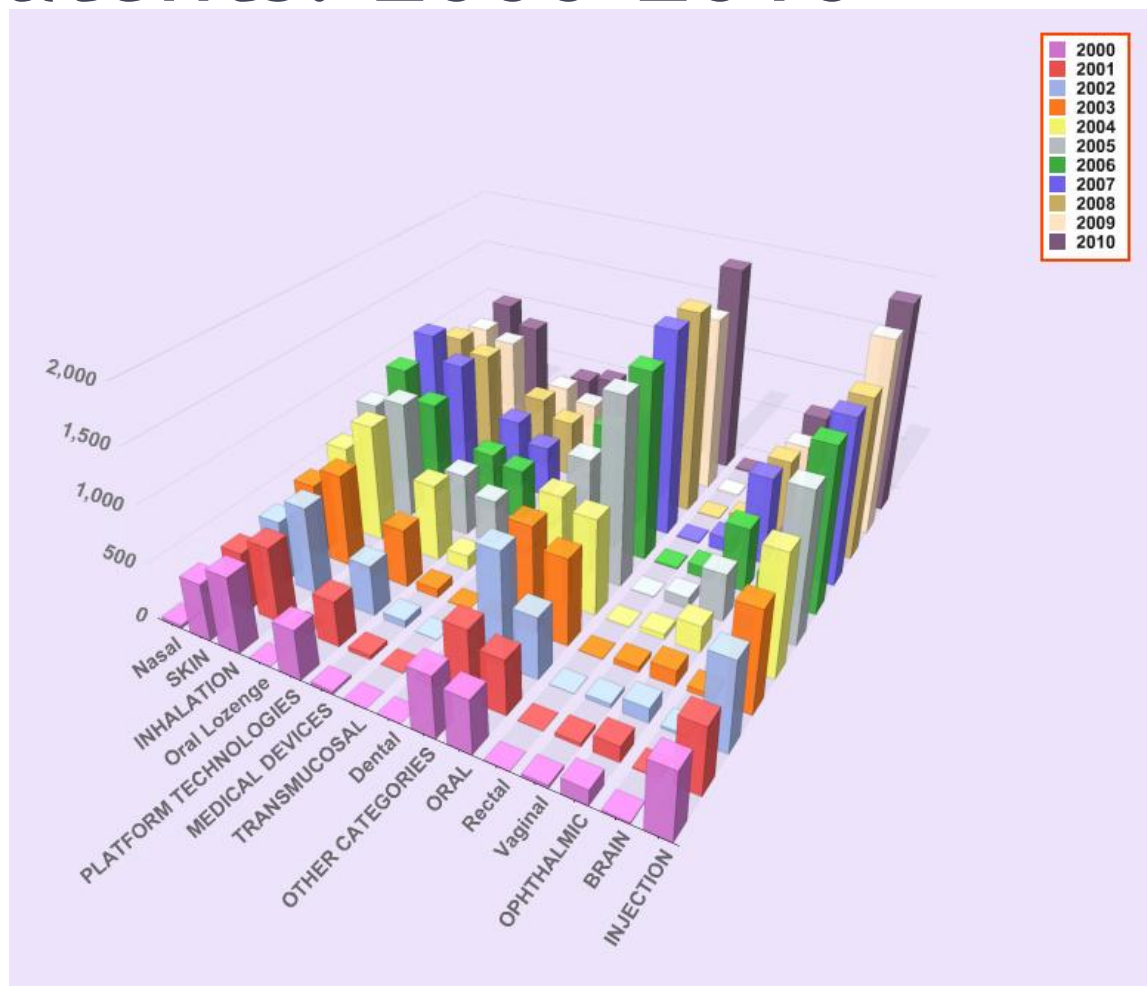
Due Diligence and Competitive Intelligence

- Need to know “Who is in the space?” “What are they doing?”, “Where are they going?”, “When do they expect to get there?”, and “How?”
- Need detailed analyses of all players to assess your competitiveness.
- Analyses can come from internal resources, external sources(i.e. consultants) or a mixture of both.

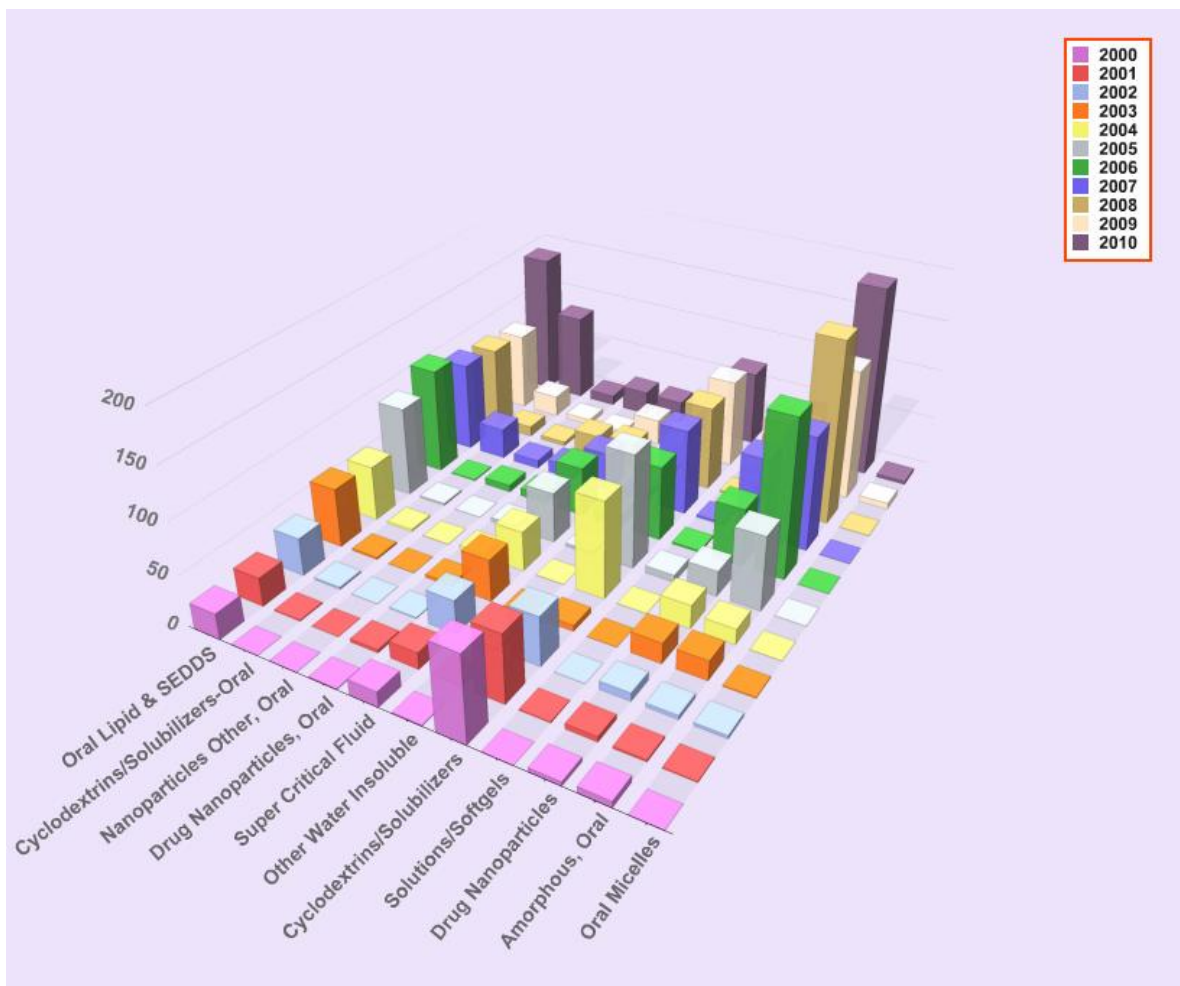
Keeping Up with Technology

- According PharmaCircle:
 - Over 60,000 patents published/issued in DD 2000-2010
 - Approximately 4,000 distinct DD technologies identified
 - Approximately 1,600 companies have patented DD technology
 - Large Pharma
 - Specialty Pharma
 - Generics
 - Drug Delivery (are there really any of these left?)

DD Patents: 2000-2010



Oral Water Insoluble Patents: 2000-2010



DD Technology Assessment

- Do you need it?
- How do you compare technologies?
- What is your strategy?
 - Look at multiple technologies
 - Internal vs. external technology
 - Who do partner with?
 - What are key decision points?
 - How do you move quickly and efficiently?

DD Technology Assessment: Nanoparticles

Technology*	NanoCrystal	Solumatrix	NanoActive
Phase	Marketed	Phase 2	Preclinical (recently validated GMP equipment 1/2011)
GMP	Yes	Yes	Yes
Process	Wet milling	Dry milling	Precipitation
Solvents	Aqueous based	Aqueous wash after dry milling	Various aqueous/organic
Additives/ Stabilizers	PVA, PVP, docusate sodium, SLS, and others.	Sodium chloride, sodium hydrogen sulfate, sodium carbonate, sodium bicarbonate, or ammonium chloride, CTB	Dextran, PVP, Carbopol
Particle Size	<400 nm	100-500 nm	<500 nm

*Trademarks of Elan, iCeutica and NanGenex respectively

DD Technology Assessment: Nanoparticles

Technology*	NanoCrystal	Solumatrix	NanoActive
Special Equipment	Yes	No (ball mill)	Yes
Batch Sizes	10 mg – Commercial	Lab to Phase II	500 mg to 2-4 kg/8 hr
Routes	Oral, injectable, topical, inhalation and nasal	Oral, injectable, topical, inhalation and nasal	Oral, injectable, topical, inhalation and nasal
Example IP	Multiple issued and published US/World patents.	US2009028948, EP1830824, WO2008000042	WO2009133418, WO2010146408, WO2010146407, WO2010146406
Partners	Multiple including Merck, Janssen, AZ, Pfizer, BMS...	Iroko Pharmaceuticals, Undisclosed large pharma company	NanoForm Therapeutics Ltd.

*Trademarks of Elan, iCeutica and NanGenex respectively

Product and Technology Deals

- Need to understand past and current deal terms
 - Upfront Payments
 - Royalties
 - Milestones
 - Development Fees
 - Phase Deal Signed
 - Therapeutic Category
 - Route
 - Technologies licensed (DD, Discovery)

Product and Technology Deals

Header	Date	Deal Type	Owner/Lic	Licensee	Phase	Therapeut Category	Technolog	Product/P	Deal Territory	Total Deal Value	Upfront Payment
AltheRx Completes Acquisition of First Product Solabegron from GlaxoSmithK	2011-03-24	Product Acquisitions	AltheRx Pharmaceuticals Inc.	• GlaxoSmithKline	Phase 2	• Overactive Bladder • IBS		Solabegron Solabegron 2			
Champions Biotechnology Inc. Announces Potential \$27 Million Technology Collaboration with Cephalon, Inc.	2011-03-24	Pharma Services Deals	Champions Biotechnology Inc.	• Cephalon Inc.	Pre Clinical	• Cancer		CEP-32496 CEP-37440		\$28.39M	1.39 M\$
R-Tech Ueno: Announcement of the Execution of a	2011-03-23	Product Deals	R-Tech Ueno Ltd.	• Sucampo Pharmaceuticals Inc.	Marketed	• Glaucoma		Rescula Ophthalmic Solution 6 2	• ex-Japan (Sucampo Pharmaceuticals Inc.)	\$3M	3 M\$

Products/Pipeline Assessment

- Molecule Type (small molecule, biologic, siRNA)
- Mechanism
- Delivery Route (injectable, oral, transdermal)
- Phase
- NME, New Formulation, New Combination..
- Dose (25 mg or 1000 mg)
- Dose Frequency (QD, BID)
- Dosage Form (shape, size, color....)
- Technology and IP

Current Pipeline Summary

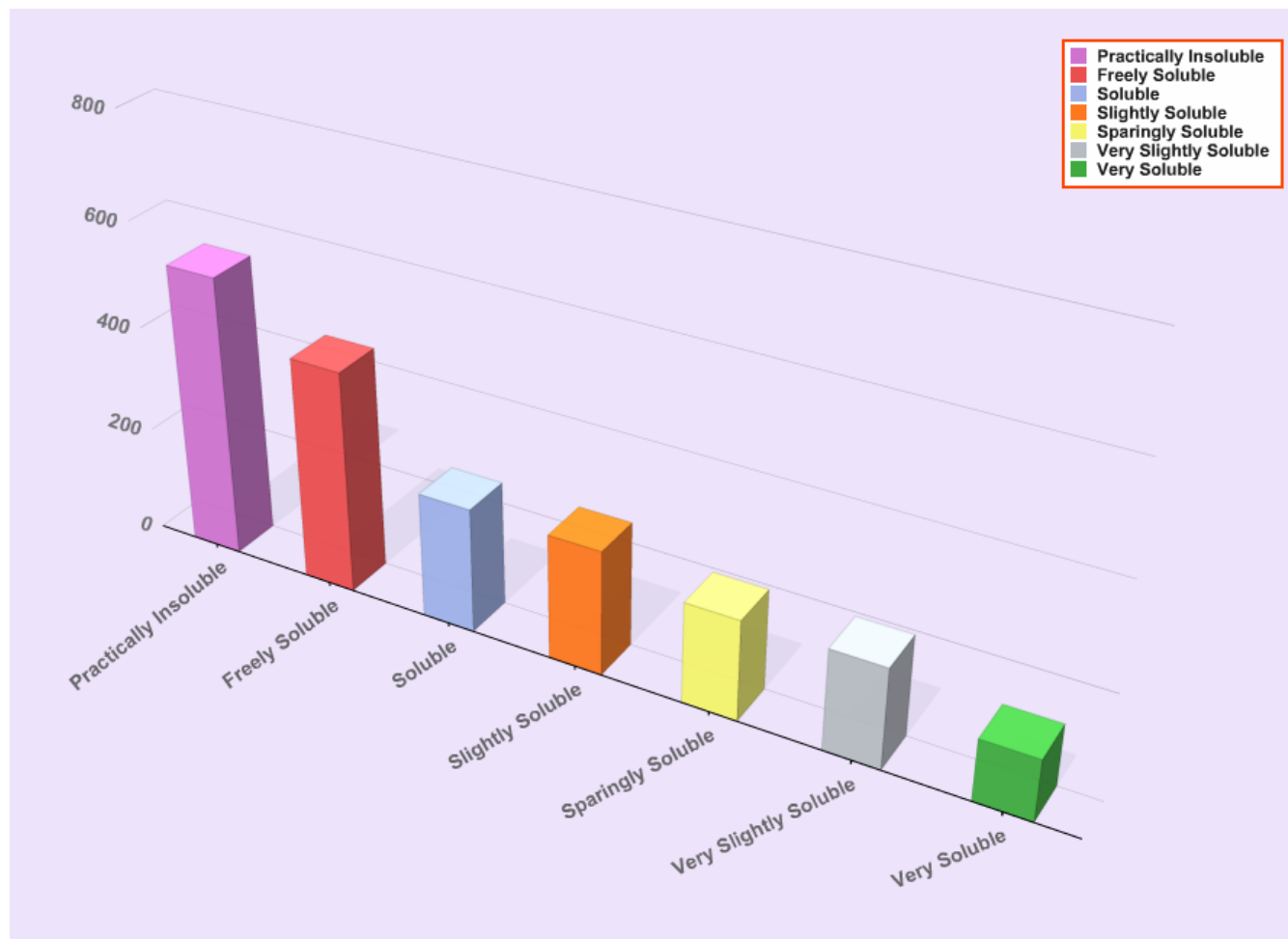
<i>Molecule Type</i>	<i>Total</i>	<i>NME*</i>	<i>New Formulation*</i>	<i>DDS</i>
Small Molecule	5997	3619	1981	2597
Peptide	782	576	150	317
Protein	1185	806	279	485
Antibody	1314	1123	168	91
siRNA	186	186	0	121

Water Insoluble Drugs Pipeline

- Do we really know????
- Water solubility of NME pipeline programs usually not publicly available.
- Technology approaches also not usually available until later phases or until registration/approval.

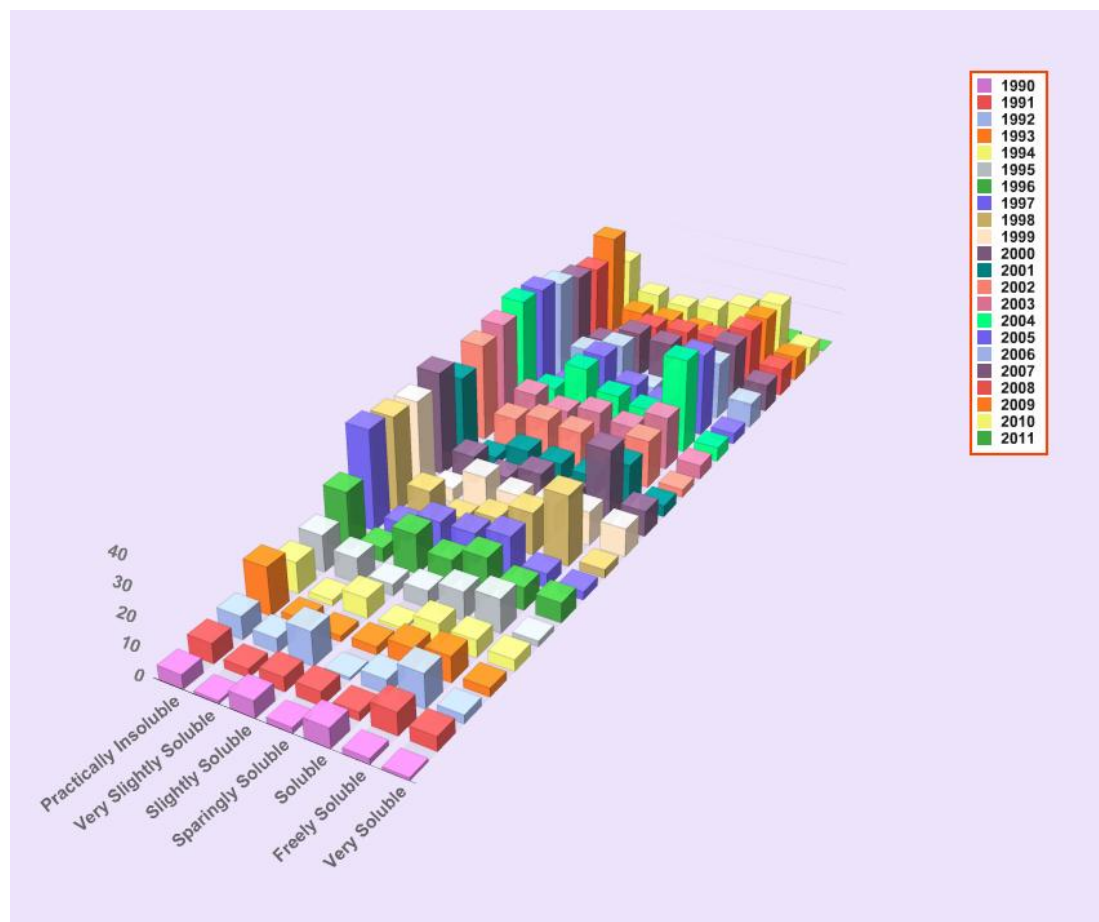
Oral Marketed Product Attributes

Water Solubility: Oral Products US



Water Solubility: Oral Products US

1990-2011



Top 10 Oral Products: Attributes**

Product	DDS	Ther. Category	Form	Dose (mg)	Colors	Shapes
Lipitor	No	Cardiovascular	Tablet	10, 20, 40, 80	White	Elliptical
Plavix	No	Cardiovascular	Tablet	75, 300	Pink	Round
Diovan***	No	Cardiovascular	Tablet	40, 80, 160, 320	Yellow Red Grey-Orange Dark Grey-Violet	Oval Almond Almond Almond
Crestor	No	Cardiovascular	Tablet	5, 10, 20, 40	Yellow Pink Pink	Round Round Oval
Seroquel XR	Yes*	CNS	Tablet	25, 50, 150, 200, 300, 400	Peach White Yellow	Capsule Capsule Capsule
Seroquel	No*	CNS	Tablet	25, 50, 100, 200, 300, 400	Peach White Yellow White Yellow	Round Round Round Capsule Capsule

*Sales reported for franchise which includes multiple formulations.

** For US market

***Capsule form discontinued

Top 10 Oral Products: Attributes**

Product	DDS	Ther. Category	Form	Dose (mg)	Colors**	Shapes**
Zyprexa	No*	CNS	Tablet	2.5, 5, 7.5, 10, 15, 20	White Blue Pink	Round Elliptical Elliptical
Zyprexa Zydis	Yes*	CNS	ODT	5, 10, 15, 20	Yellow	Round
Singulair	No*	Respiratory	Tablet	10	Beige	Rounded square
Singulair Chewable	Yes*	Respiratory	Tablet	4, 5	Pink Pink	Oval Round
Singular Granules	No*	Respiratory	Powder	4	White	NA
Nexium Delayed Release Capsule	Yes*	GI	Capsule	20, 40	Amethyst	Capsule
Gleevec***	No	Oncology	Tablet	100, 400	Yellow/Orange Yellow/Orange	Round Oval
Actos	No	Diabetes	Tablet	15, 30, 45	White	Round

*Sales reported for franchise which includes multiple formulations.

** Colors/Shapes for US

***Capsule form discontinued

Oral Marketed Products Attributes

- Of the Top 10 Oral Products
 - Cardiovascular and CNS are top therapeutic categories
 - Tablets dominate oral forms
 - In US, many oral dosage forms are colored. Not as many “little white pills”

Concluding Remarks

Summary

- Need to understand the market and competition
 - Need Data AND Analyses
- Generic companies are more aggressive and more sophisticated
- Specialty Pharma is a growing sector
- Drug Delivery has a large, measurable role in successful products and franchises
- A successful development strategy integrates ALL areas: R&D, Marketing, IP, Information Services, Licensing, Executive Management,...

Thank You!