CLEARSOL™
A Broad-Spectrum Drug Solubilizer

CLEARSOL™ TECHNOLOGY

Unlock Your Drug's Potential by Overcoming Its Solubility Limitation

LATITUDE
Pharmaceuticals Inc.

LATITUDE: A FORMULATION DEVELOPMENT SPECIALIST

- Founded: 2003
- Located in San Diego, CA
- Primary Business Areas
  - Formulations for insoluble & unstable drugs
  - Drug delivery systems (DDS)
  - IND development & submission services
  - Out-licensing of DDS and 505(b)2 drugs
- Experienced in multiple dosage forms with specialty in liquid formulations, e.g. solutions, gels, liposomes, emulsions, etc.
- > 800 CRO formulation projects completed
- 30 R&D staff

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INSOLUBILITY: A ROADBLOCK TO DRUG DEVELOPMENT

- 90% of new chemical entities (NCEs) are insoluble[1]
- Drawbacks of existing solubilizers:
  - Incapable of dissolving enough drug
  - Not generally useful (cyclodextrins)
  - Complex and unstable structures (liposome, emulsion)
  - Drug precipitates after dilution (solvent)
  - Poor safety (solvent, surfactant)
  - Difficult manufacturing process (nanoparticles)
- A safe, powerful and wide-spectrum drug solubilizer is needed

[1]Insoluble drug delivery strategies: review of recent advances and business prospects; Acta Pharmaceutica Sinica B, Acta Pharmaceutica Sinica B, Volume 5, Issue 5, September 2015, Pages 442-453

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CLEARSOL™ FORMULATION

- A clear aqueous solution
- Comprises three key excipients
- Key excipients are GRAS, FDA-approved (for injection and other routes of administration), cGMP and have DMFs
- Does not contain ANY synthetic surfactants (e.g. Cremophor®, polysorbates), cyclodextrins, organic solvents, or any chemical that is not FDA-approved
- Compatible with buffer, preservatives, and other excipients

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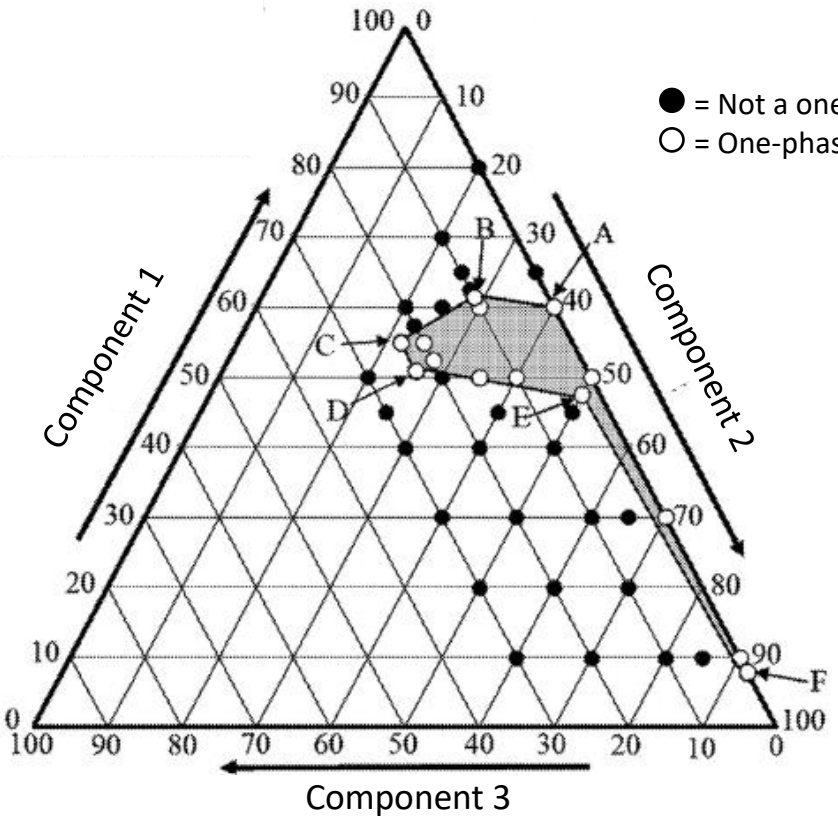
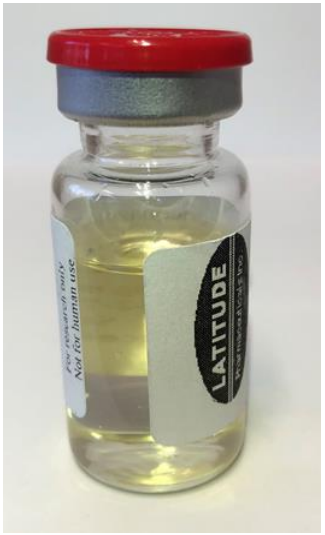
CLEARSOL™ COMPOSITION



A phase diagram depicting regions where mixing ratios of the three components result in a ClearSol™ solution

CLEARSOL™ PHARMACEUTICAL PROPERTIES

- Provided as a sterile solution in vials
- Ready-to-use (ready to inject or to admix with API)
- pH 7 (acceptable range of 3.5 – 10)
- Can be freely diluted in water or an infusion fluid
- Drug solubilization is insensitive to pH
- 0.2-micron filterable
- Can be terminally sterilized by autoclave
- Stable at all common storage conditions
- R&D, GLP or GMP grades available
- Available also in lyophilized powder or granule forms



ClearSol vehicle

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CLEARSOL™ UTILITY

- Increase drug solubility
- Enhance drug oral bioavailability
- Allow safe dosing by injections
- Replace other toxic or complex solubilizers
- De-aggregate proteins and peptides
- Cleanse skin and mucous membranes
- Dissolve undesirable body deposits, e.g. uric acid, cholesterol etc.

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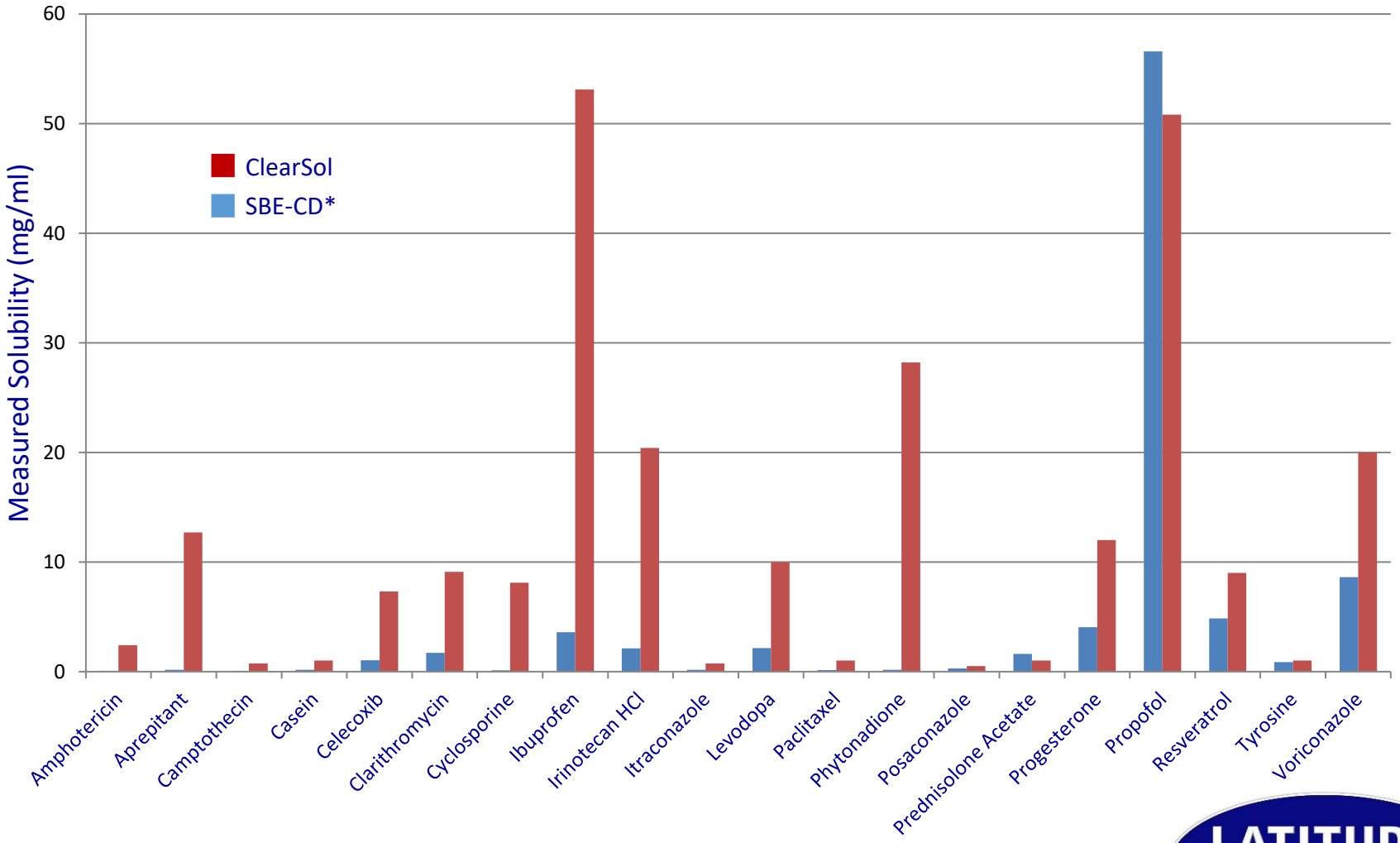
CLEARSOL™ ADVANTAGES

Solubilizer Class	Examples	Wide-spectrum[a]	Efficient[b]	Safe[c]	Easily Diluted[d]	Ease of Dissolution[e]	Ready-to-use[f]
CLEARSOL™		+	+	+	+	+	+
Organic solvents	Ethanol, propylene glycol, PEG	-	+	-	-	+	-
Surfactants	Polysorbates, Cremophors, Solutol	+	+	-	-	-	+
Hydrophilic polymers	PVP, PVA	-	-	-	-	-	-
Cyclodextrins (CD)	Hydroxypropyl-β-CD, Sulfobutylether-β-CD	-	+	+	+	-	-
Emulsions	Intralipid	-	-	+	+	-	+
Liposomes	SVL, MVL	-	-	+	+	-	-
Nanoparticles	Lipid particles, Albumin bound particles	-	+	-	+	-	-

[a]**Wide-spectrum**: solubilizes a wide range of drugs including elements, small molecules, peptides and proteins, regardless of drug MW, size or physical properties; [b]**Efficient**: solubilizes a drug to a high concentration with minimal amount of solubilizer; [c]**Safe:** free of vehicle-related systemic and local toxicity; [e]**Easily diluted:** can be diluted in water or a infusion fluid (e.g., 0.9% NaCl, 5% Dextrose) without precipitation; [f]**Ease of dissolution**: effort required to dissolve drug in solubilizer. CLEARSOL typically requires simple hand-shaking to dissolve a drug; [g]**Ready-to-use:** CLEARSOL formulations can be dosed directly without further preparative steps required.

CLEARSOL™ IS A BETTER SOLUBILIZER THAN CD



*SBE-CD (sodium salt) was used at a concentration of 15.8%, the same percentage used in VFEND® (voriconazole), IV injection

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CLEARSOL™ IS A "WIDE-SPECTRUM" SOLUBILIZER

Insoluble Drug Name	Concentration required for injection (mg/mL)*	Solubility achieved by CLEARSOL™ (mg/mL)	Solubility achieved by SBECD (mg/mL)
Amiodarone	50	118	9.25
Amphotericin	0.1-5	2.4	0.07
Aprepitant	7.2	12.7	0.15
Camptothecin	0.12-2.8	0.5 - 1	0.06
Clarithromycin	5	9.1	1.71
Cyclosporine (peptide)	0.5-2.5	8.1	0.11
Celecoxib	4-8	7.3	1.03
Ibuprofen	4-100	53.1	3.58
Itraconazole	3.3-10	0.5 - 1	0.17
Irinotecan HCl	20	20.4	2.12
Levodopa	1.5-15	10	2.13
Paclitaxel	1.2-6	1	0.13
Phytonadione	2-10	28.2	0.15
Posaconazole	1-18	0.5	0.27
Prednisolone acetate	1	1	1.61
Progesterone	50	12.0	4.06
Propofol	10	50.8	56.6
Voriconazole	10	20	8.60
Success Rate		**78%**	**22%**

SAFETY AND REGULATORY ACCEPTANCE

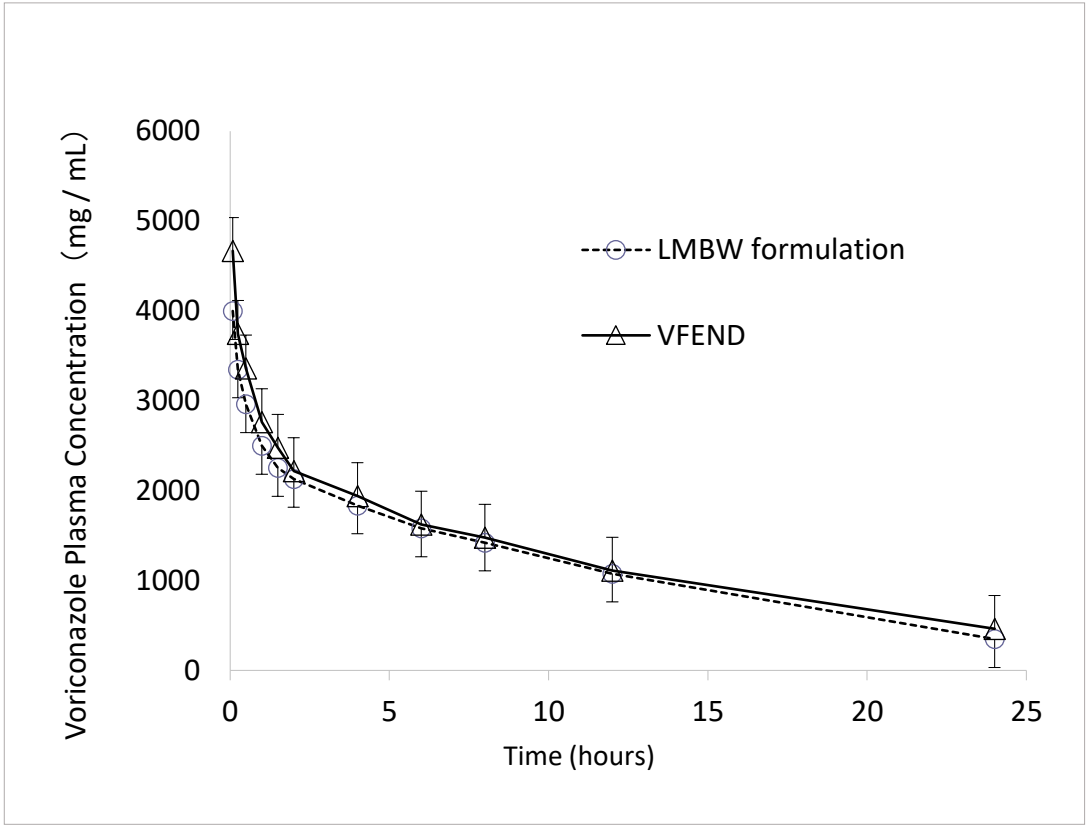
- Demonstrated in multiple preclinical models & in human
- One FDA-approved IND & one US Phase-1 trial completed

Study	Animal	Route of Administration	Maximum CLEARSOL™ Dose in Human Equivalent Dose (HED mg/kg/day)	Dosing regimen	Systemic toxicity	Injection site reaction	Note
1	Rats	Slow Intravenous injection (15 min infusion)	145 (MTD)	Single dose, rangefinder	Maximally Tolerated Dose (MTD) at 900 mg/kg rat = 145 mg/kg HED	No	
2	Rats	Slow Bolus Intravenous injection (5 min infusion)	121	Daily dosing, repeated for 28 days	No kidney toxicity, while an equivalent dose of SBECD caused renal tubular & cortex vacuolization at 750 mg/kg/day rat	Not up to 75 mg/kg HED	Head-to-head safety comparison with SBECD
3	Beagle dogs	Slow Intravenous injection (30 min infusion)	83.4	Daily dosing, repeated for 28 days	Well tolerated. No mortality or significant change in BW, vital signs, ophthalmologic exam, EKG, blood chemistry 1:4 animals showed mild hepatic microscopically at 1.5g/day dog	No	
4	Rats	Subcutaneous injection	136	Single dose	No mortality at 843 mg/kg rat	No	
5	Rats	Subcutaneous injection	169	Single dose	Well tolerated, no mortality or significant change in BW, vital signs, ophthalmologic exam, EKG, blood chemistry at 1048 mg/kg rat	minimal reversible injection site reactions	GLP
6	Human	Subcutaneous injection (abdomen or outer thigh)	3.6 (assuming 60 Kg person)	Single dose	No SAEs & no TEAEs were judged to be serious, and all resolved by the end of the study	Well tolerated	Phase-1 under a US IND, 35 subjects
7	Human	Oral & topical	All ingredients in CLEARSOL™ are GRAS and are assumed safe for oral and topical use				

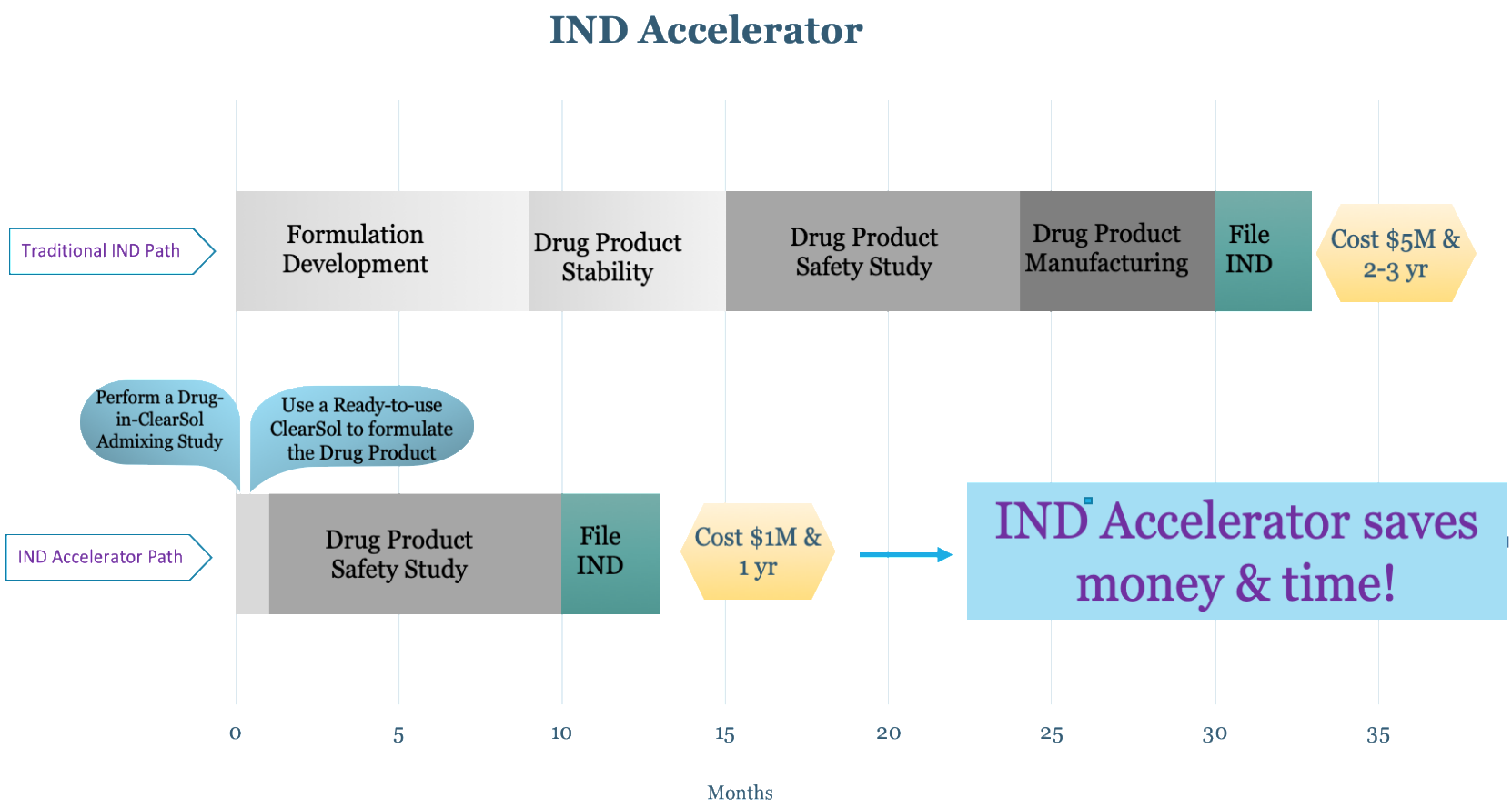
CLEARSOL™ PHARMACOKINETICS

Voriconazole in CLEARSOL™ & SBE-CD following IV

Drug Name	$T_{1/2\,(h)}$	AUC (hr*ng/mL)
ClearSol-V	7.9	29302.9
VFEND	8.9	30744.4



CLEARSOL™ ACCELERATES YOUR IND



TRY CLEARSOL™

- Sign MSA to use CLEARSOL™
- Send API to LATITUDE for a solubility evaluation free of charge or
- Obtain free sample of CLEARSOL™ for solubility test
- Purchase more CLEARSOL™ for IND development

LATITUDE Pharmaceuticals Inc.

9675 Businesspark Ave.
San Diego, CA 92131
Tel: 858-546-0924
Fax: 858-546-0958
www.latitudepharma.com