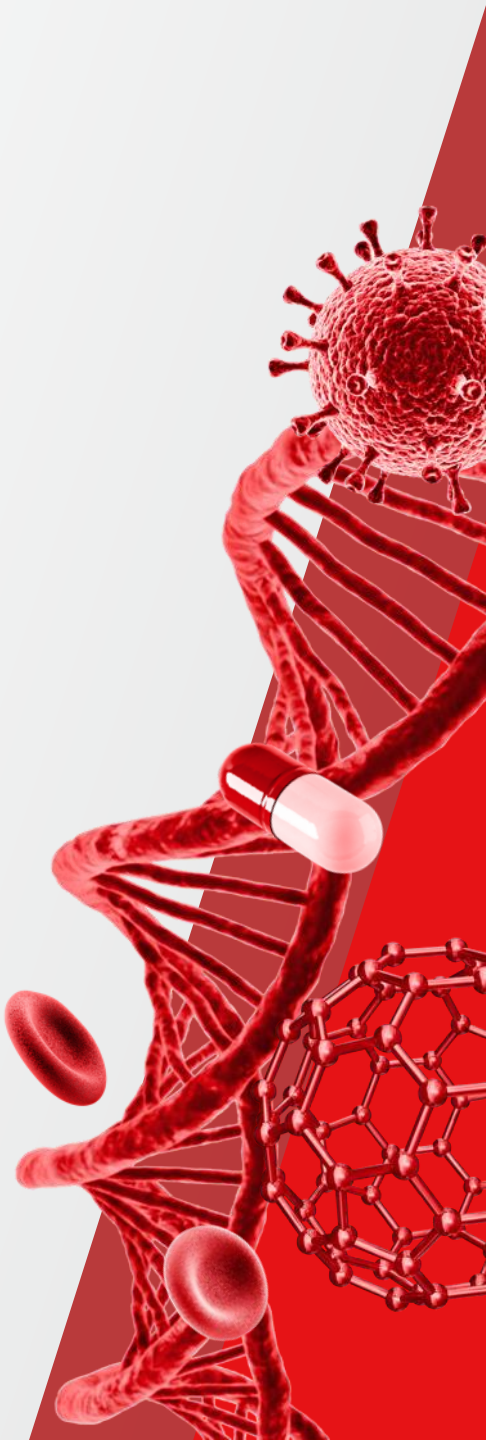
Adopting ASAP into a CDMO

Case studies and leveraging *in silico* modeling

Sanjay Konagurthu, PhD
Senior Director, Science and Innovation
Pharma Services Group



The world leader in serving science

 sanjay.konagurthu@thermofisher.com

Thermo Fisher Scientific

Life Sciences Solutions Group & Laboratory Products (LSG)

- BioProduction Division
- Biosciences Division
- Clinical Next-Generation Sequencing Division
- Genetic Sciences Division
- Laboratory Chemicals Division
- Laboratory Products Division

Specialty Diagnostics Group (SDG)

- Immunodiagnostics Division
- Healthcare Market Division
- Microbiology Division
- Anatomical Pathology Division
- Clinical Diagnostics Division
- Transplant Diagnostics

Analytical Instruments Group (AIG)

- Chromatography and Mass Spectrometry Division
- Chemical Analysis Division
- Materials and Structural Analysis Division
- Unity Lab Services

Customer Channels Group (CCG)

- Research and Safety Market Division

Clinical Research Group (CRG)

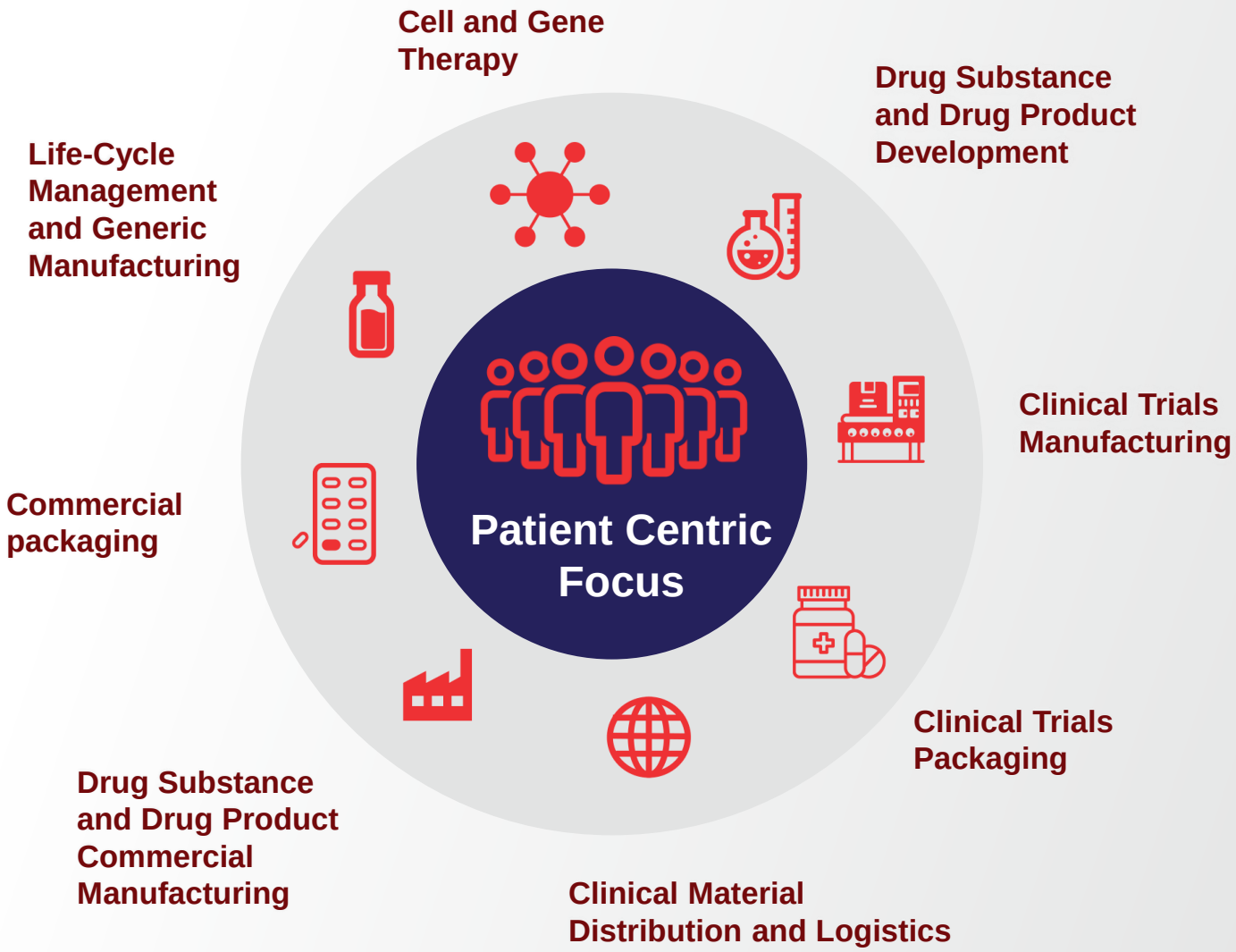
- Pharmaceutical Product Development Laboratories (PPD)

Pharma Services Group (PSG)

- Drug Product Division – North America
- Drug Product Division – Europe
- Biologics Active Pharmaceutical Ingredients
- Small Molecule Active Pharmaceutical Ingredients
- Softgel Products
- Viral Vector Services
- Clinical Pkg & Distribution

Industry leading end-to-end pharma services capabilities to simplify the supply chain for customers

- Expertise in drug development, clinical trial logistics and commercial manufacturing
- Flexible business models customized to meet your needs
- A partner from development through commercial supply
- Achieved through a global network of 55+ sites globally

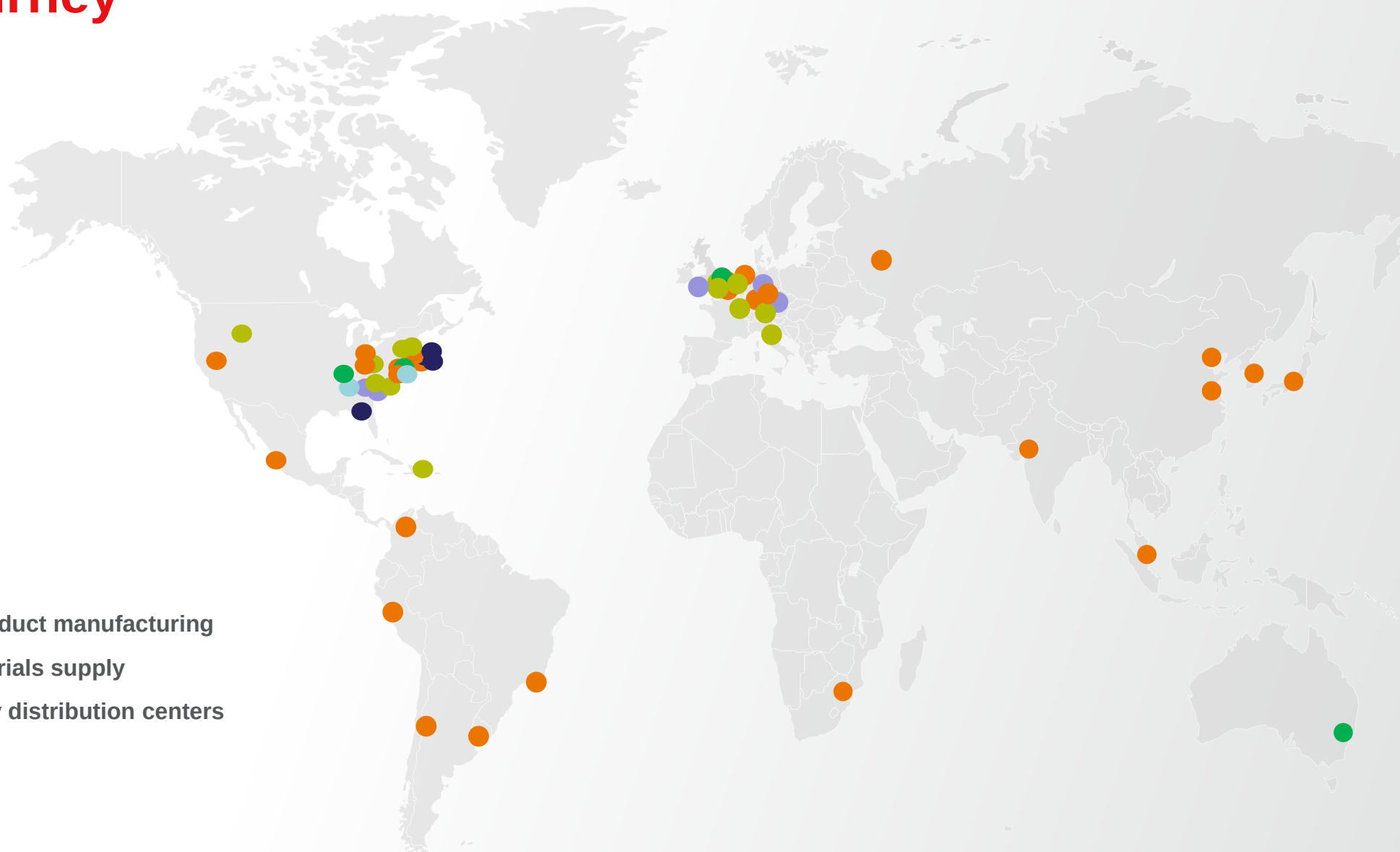


Integrated global network of technical, quality and customer engagement teams to support the drug development journey

~17,000
colleagues in 55+ sites

~3,500
scientists, technicians and engineers with deep technical expertise

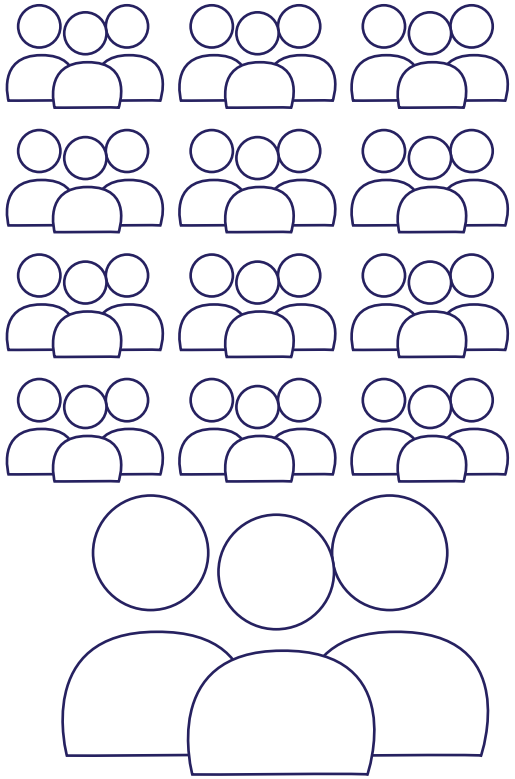
~3,000
quality specialists



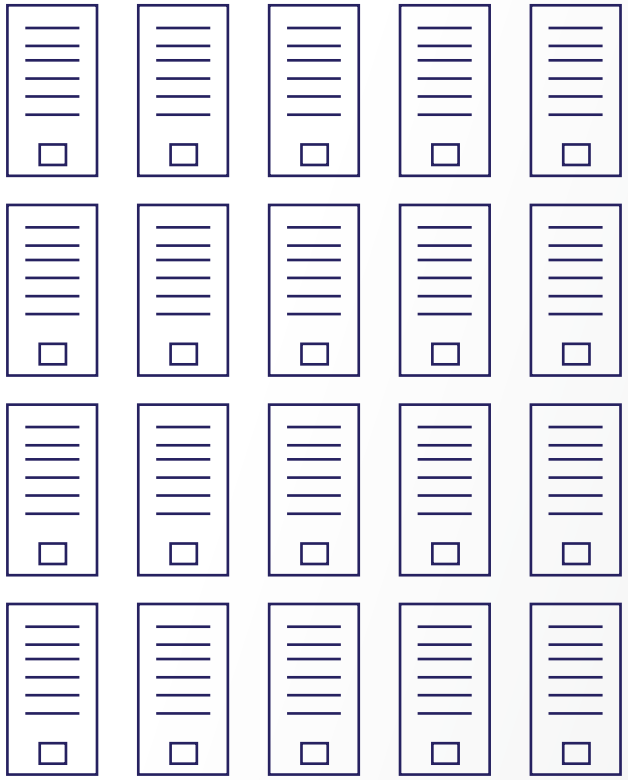
- API
- Biologics
- Viral vector
- Drug product manufacturing
- Clinical trials supply
- Specialty distribution centers

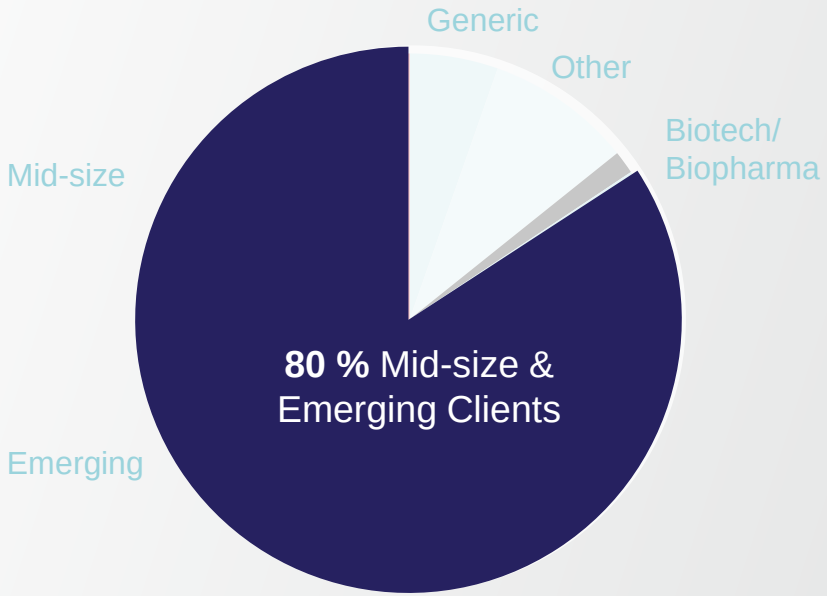
Customer Base

Over **250**
emerging clients



Top 20 Pharma
Companies





Wide variety of molecules, chemistries and therapeutic areas

A Broad Selection of Dosage Forms – Dev, Clinical & Commercial

- Immediate-Release Tablets (Coated and Uncoated)
- Powder-Filled Capsules
- Fast Dispersible Tablets
- Liquid-Filled Capsules
- Sublingual Tablets

- Controlled-Release Tablets (Coated and Uncoated)
- Polymer Matrix
- Pulsatile Release
- Beads in Capsules

- Hydrophilic Gel Matrix
- Polymer Coating
- Wax Matrix
- Powders / Granules / Coated Beads
- Multiparticulates
- Bilayer Tablets
- Laser-Drilled Tablets
- Trilayer Tablets
- Coated Beads
- Tablets in Capsules
- Microtablets

Softgels

- Softgel Capsules
- Twist-Off Softgels
- EnteriCare® Enteric Softgels
- Versatrol™ Controlled-Release Softgels

- Chewels® Chewable Gels
- LiquiSoft™ Chewable Liquid-Filled Softgels

- Soflet® Gelcaps
- Solvatrol™ Enhanced Solubility Softgels

Sterile Products

- Liquid Vials
- Lyophilized Vials
- Prefilled Syringes
- Cartridges

- Liquid Small Volume Parenteral
- Liquid Large Volume Parenteral

Highly Regulated Products

- Controlled Substance
- High-Potency Products

Regulatory

Excellent Global Track Record

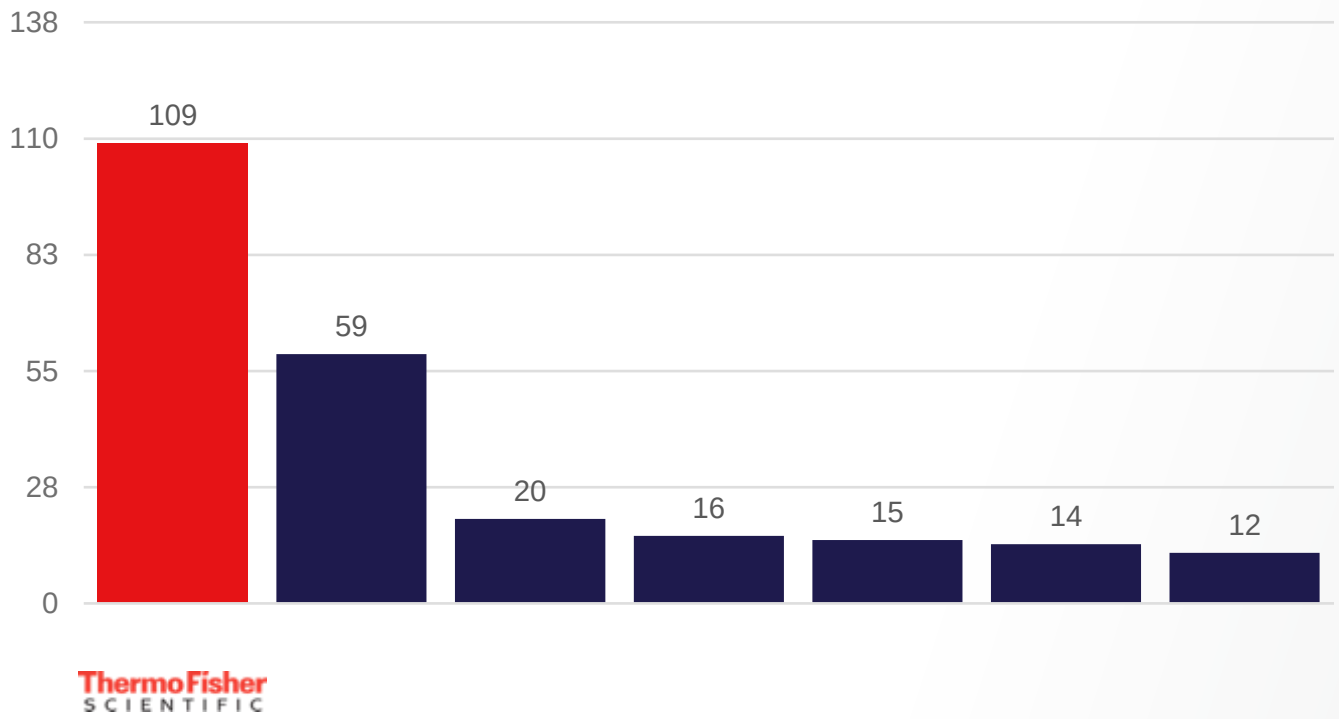
- US FDA
- PMDA
- EMA
- ANVISA
- Health Canada

20+ Inspected and approved by 20+ different regulatory authorities

30 **Waived** pre-approval inspections

20% Inspections with **zero** observations

NDA Approvals



- **109** NDA approvals for therapeutic drugs from **2010-2019***
- **More than the next 3 CMOs combined**
- Both **small** and **large** molecules
- **Early development and clinical trial material**

Outsourced NDA-approved products 2010-2019*

*Data does not include NDA approvals for non-therapeutic drugs.

Source: PharmSource, A GlobalData Product, Trend Report – CMO Scorecard: Outsourcing of NDA Approvals and CMO Performance – 2020 Edition

Global Drug Product Sites Leveraging ASAP across Network

High Point, USA
Center of Excellence for Softgels

Cincinnati, USA
Center of Excellence for Controlled Release &
Controlled Substances

Toronto, Canada
Center of Excellence for Highly Potent Products

Whitby, Canada
Center of Excellence for Scale Up

Milton Park, UK
Center of Excellence for Early Development and Solubility Enhancement

Tilburg, Netherlands
Center of Excellence for Softgels & Solubility Enhancement

Bend, USA
Center of Excellence for Solubility Enhancement

Greenville, USA
Center of Excellence for Sterile and Oral Solid Dose Develop ment

Bourgoin, France
Center of Excellence for Mid & Late stage OSD Development

Ferentino, Monza Italy
Center of Excellence for Sterile liquid and lyophilized product development

Case Studies

Chemical Stability 30:70 X:HPMCAS ASD Tablets – 28d Study

Sample No.	Sample Condition			Saturated Salt Solution
	time (day)	°C	%RH	
1	0	5	0	NA
2	28	40	71	sodium nitrate
3	28	50	29	sodium iodide
4	28	50	51	sodium bromide
5	28	50	64	potassium iodide
6	28	60	0	calcium sulfate
7	28	60	11	lithium chloride
8	28	60	26	sodium iodide
9	27	70	0	calcium sulfate
10	26	60	42	potassium carbonate
11	24	40	71	sodium nitrate
12	23	50	29	sodium iodide
13	21	40	71	sodium nitrate
14	19	50	29	sodium iodide
15	18	40	71	sodium nitrate
16	17	60	0	calcium sulfate
17	16	50	29	sodium iodide
18	15	50	51	sodium bromide
19	14	60	11	lithium chloride
20	12	50	64	potassium iodide
21	11	60	26	sodium iodide
22	10	60	0	calcium sulfate
23	9	60	42	potassium carbonate
24	9	70	0	calcium sulfate
25	8	50	51	sodium bromide
26	7	60	11	lithium chloride
27	5	50	64	potassium iodide
28	5	60	26	sodium iodide
29	3	60	42	potassium carbonate
30	3	70	0	calcium sulfate

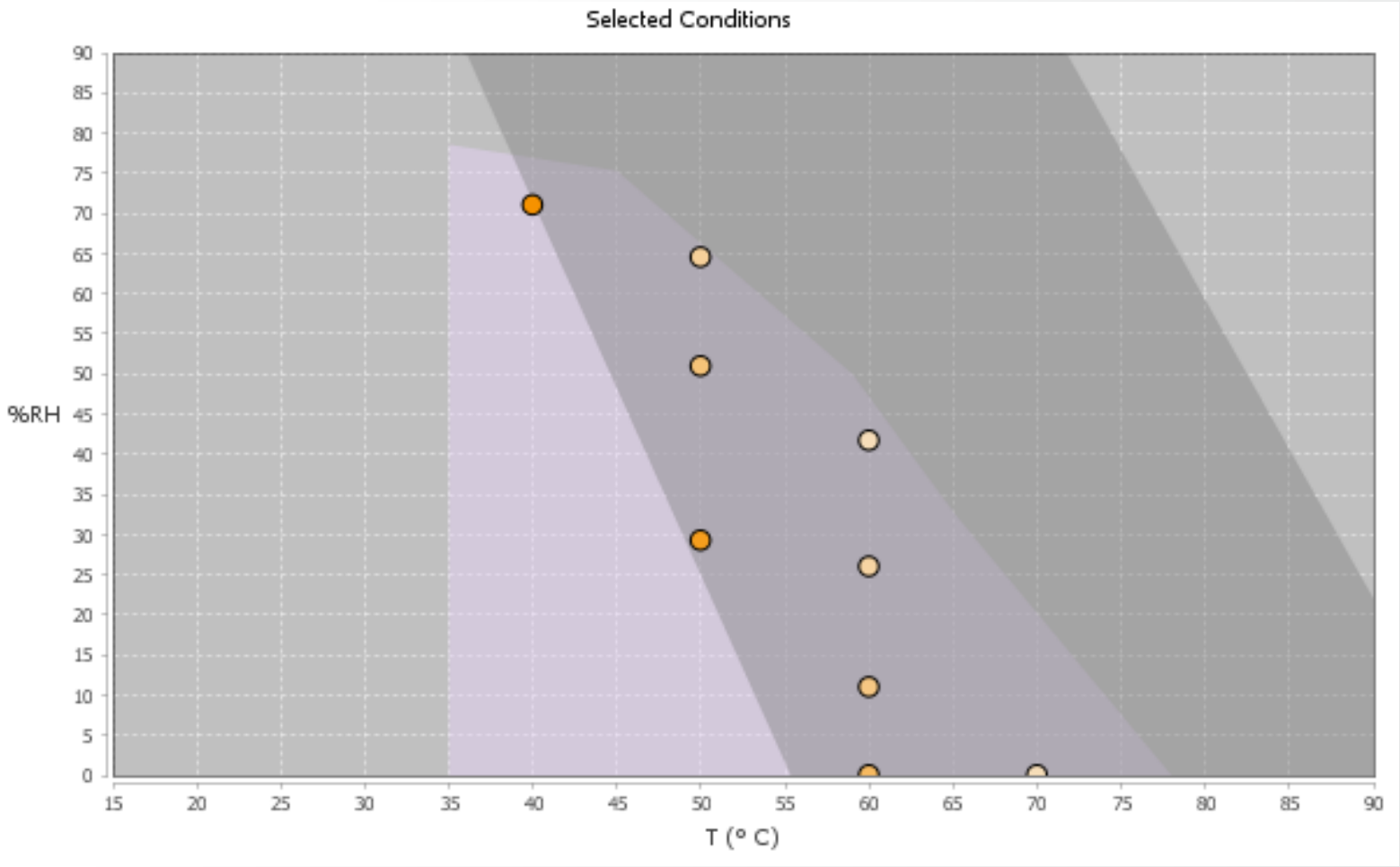


Fig. Graphical representation of ASAP study design for tablets. The dark grey shaded region represents the temperature/RH space where it is predicted to be possible to reach the specification limit (isoconversion point) during the ASAP study. The circles illustrate the selected conditions; the darker the circle the longer it will take to reach isoconversion.

ASAP Samples Impurities Summary

- All degradant species that grew consistently and had data at most timepoints were modeled (red)

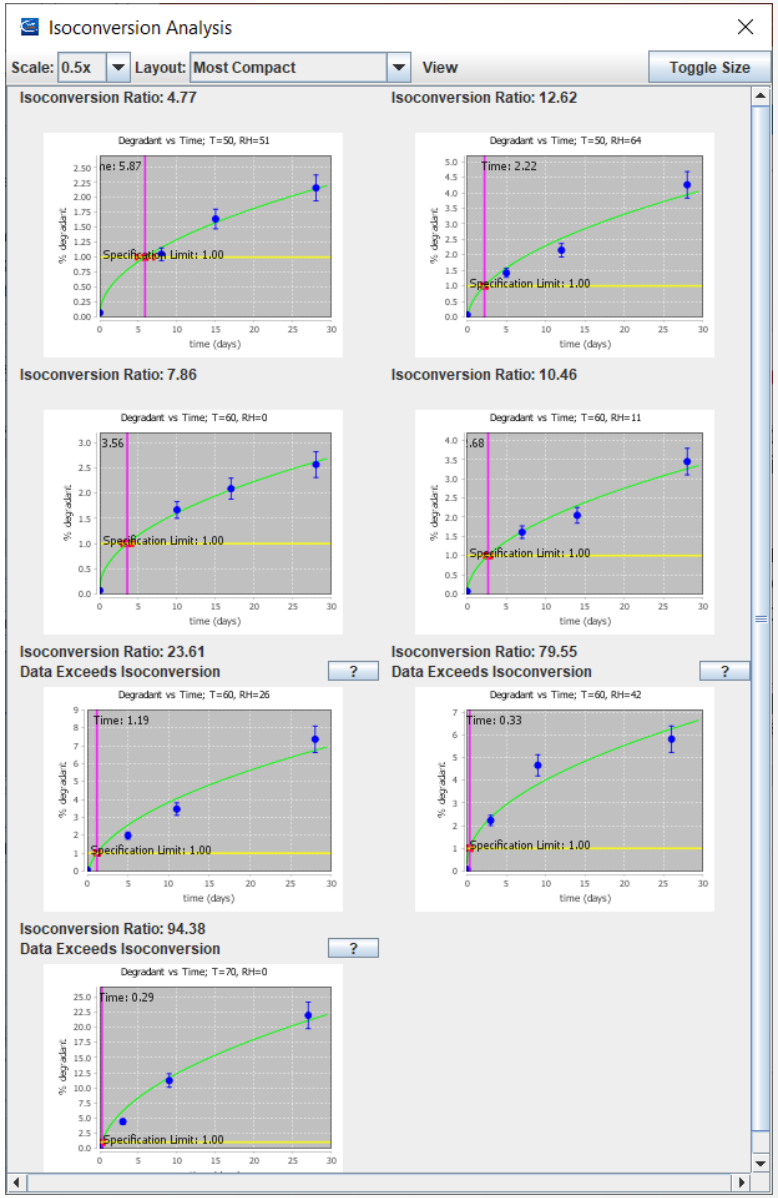
Time (days)	Temperature (°C)	Humidity (% RH)	0.142	0.146	0.157	0.171	0.177	0.191	0.199	0.204	0.219	0.231	0.247	0.258	0.272	0.282	0.295	0.303	0.306	0.316	0.323	0.34	0.388	0.394	0.519	0.527	0.538	0.542	0.557	0.582	0.637	0.664	0.683	0.700	0.703	0.726	0.749	0.763	0.790	0.803	0.805	0.816	0.833	0.835	0.854
28	60	26	0.02		0.03					0.03	7.36						0.21	0.25	0.08			0.12				0.04									0.43					0.1		0.05	0.14		0.34	0.15
28	60	11									3.45						0.19	0.29				0.07				0.03									0.22					0.06			0.04			
28	60	0									2.57						0.15	0.23				0.06				0.03									0.12					0.04			0.03			
28	50	64									4.26						0.15	0.21								0.03									0.25					0.03			0.04			
28	50	51									2.16						0.13	0.18																	0.07	0.02				0.03						
28	50	29									0.48						0.06	0.09																	0.14											
28	40	71									0.86						0.08	0.1																	0.22											
27	70	0	0.13	0.07	0.16	0.07	0.05	0.1	0.15	0.42	22	0.03	0.15	0.18	0.05	0.04	0.29	0.33	0.38	0.02	0.02	0.91	0.03	0.03	0.14	0.41	0.05	0.14	0.11	0.03	0.03	0.06	0.27	1.95		0.09	0.23	0.05	0.26	0.16		0.42		0.87	0.54
26	60	42	0.03							0.03	5.81						0.19	0.28				0.10				0.04		0.03						0.43					0.09	0.02		0.09	0.19		0.07
24	40	71									0.9						0.08	0.11																0.18											
23	50	29									0.69						0.08	0.11																0.17											
21	40	71									0.65						0.07	0.09																0.18											
19	50	29									0.57						0.07	0.09																0.16											
18	40	71									0.66						0.06	0.08																0.17											
17	60	0									2.09						0.12	0.15	0.03			0.03												0.13					0.03						
16	50	29									0.49						0.07	0.08																0.13											
15	50	51									1.64						0.11	0.14																0.14					0.03						
14	60	11									2.05						0.12	0.14	0.03			0.02												0.14					0.03						
12	50	64									2.15						0.11	0.14																0.15					0.03						
11	60	26									3.46						0.17	0.22				0.04				0.03		0.03						0.31					0.05			0.03			
10	60	0									1.67						0.11	0.14																0.11											
9	70	0	0.04		0.04					0.07	11.2						0.38	0.4	0.15			0.29			0.03	0.11		0.05			0.02			0.98			0.04		0.07			0.13		0.22	0.17
9	60	4									4.66						0.38	0.47				0.03				0.04								0.42					0.04			0.05			
8	50	51									1.05						0.08	0.09																0.12					0.02						
7	60	11									1.61						0.11	0.14																0.15											
5	60	26									1.98						0.12	0.14																0.24					0.03						
5	50	64									1.42						0.09	0.1																0.26											
3	70	0									4.39						0.19	0.23				0.04				0.04		0.03						0.65					0.05			0.06			
3	60	42									2.23						0.12	0.13																0.41					0.03			0.02			
0	5	0									0.07																																		

Time (days)	Temperature (°C)	Humidity (% RH)	0.881	0.886	0.894	0.906	0.915	0.918	0.932	0.938	0.955	0.957	0.96	0.966	0.976	0.992	1	1.011	1.024	1.029	1.041	1.044	1.054	1.058	1.064	1.07	1.074	1.079	1.085	1.089	1.09	1.093	1.099	1.105	1.108	1.109	1.112	1.114	1.121	1.14	1.146	1.161	1.168	1.176	1.18
28	60	26			0.07		0.17				0.05			0.15	0.04	0.05	88.69				0.03		0.34					0.05	0.04	0.03		0.02	0.03		0.15		0.09						0.26		0.12
28	60	11			0.04		0.15				0.05			0.15			94.53				0.03		0.23					0.03	0.03						0.07		0.08						0.07		0.03
28	60	0			0.03		0.15				0.05			0.15			95.8				0.04		0.21					0.03	0.02						0.04		0.08						0.04		0.02
28	50	64					0.13				0.04			0.15			94.1				0.03		0.14												0.06		0.07						0.13		0.06
28	50	51					0.12				0.04			0.15			96.75				0.03		0.1													0.05	0.07						0.03		
28	50	29					0.12				0.04			0.15			98.74				0.04		0.05															0.07								
28	40	71					0.12				0.04			0.15			98.24				0.04		0.05															0.07								
27	70	0	0.04	0.03	0.24	0.03	0.19	0.11	0.1	0.05	0.13	0.09	0.04	0.18	0.12	0.15	57.75		0.03	0.09	0.04	0.05	2.71	0.05	0.02	0.13	0.06	0.22	0.21		0.11	0.34	0.22	0.03		0.11	0.09	0.08	0.06	0.03	0.06	0.03	2.12	0.02	0.68
26	60	42			0.05		0.17				0.05			0.15	0.03	0.02	90.91				0.03		0.29					0.04	0.04	0.02					0.11		0.09			0.02			0.22		0.07
24	40	71					0.11				0.04			0.15			98.24				0.04		0.05														0.07								
23	50	29					0.13				0.04			0.15			98.44				0.03		0.06														0.07								
21	40	71					0.12				0.04			0.15			98.52				0.04		0.05														0.07								
19	50	29					0.12				0.04			0.15			98.61				0.03		0.05														0.07								
18	40	71					0.12				0.04			0.15			98.54				0.03		0.05														0.07								
17	60	0					0.14				0.04			0.15			96.63				0.03		0.15					0.02							0.03		0.08						0.03		
16	50	29					0.12				0.03			0.15			98.75	0.02			0.03		0.05														0.07								
15	50	51					0.13				0.03			0.15			97.3	0.02			0.03		0.08												0.04		0.08						0.03		
14	60	11					0.15				0.04			0.15			96.68				0.03		0.15					0.02							0.04		0.08						0.03		
12	50	64					0.13				0.04			0.15			96.75				0.03		0.09												0.05		0.07						0.05		
11	60	26			0.02		0.15				0.04			0.15			94.6	0.02			0.03		0.17					0.03	0.02						0.09		0.08						0.1		0.03
10	60	0					0.14				0.03			0.15			97.25	0.02			0.03		0.12					0.02							0.02		0.08						0.02		
9	70	0			0.07		0.18		0.02		0.09			0.15	0.03	0.07	81.51	0.02		0.03	0.03		0.59			0.04		0.12	0.08				0.09	0.08		0.04	0.11					0.91		0.42
9	60	4			0.02		0.15				0.05			0.15		0.02	92.39				0.03		0.18					0.05	0.03						0.1		0.08						0.23		0.09
8	50	51					0.13				0.03			0.15			98.1				0.03		0.06												0.02		0.08								
7	60	11					0.15				0.03			0.15			97.31	0.02			0.03		0.11												0.03		0.08						0.02		
5	60	26					0.15				0.03			0.15			96.74	0.02			0.03		0.11					0.02							0.05		0.08						0.04		
5	50	64					0.14				0.03			0.15			97.55				0.03		0.06												0.03		0.07						0.03		
3	70	0			0.02		0.17				0.04			0.15		0.02	92.88	0.03			0.03		0.2					0.04	0.04						0.11	0.02	0.09						0.26		0.06
3	60	42					0.15				0.03			0.15			96.29	0.02			0.03		0.1					0.02							0.05		0.08						0.08		
0	5	0					0.09				0.03			0.15			99.53				0.04		0.02														0.07								

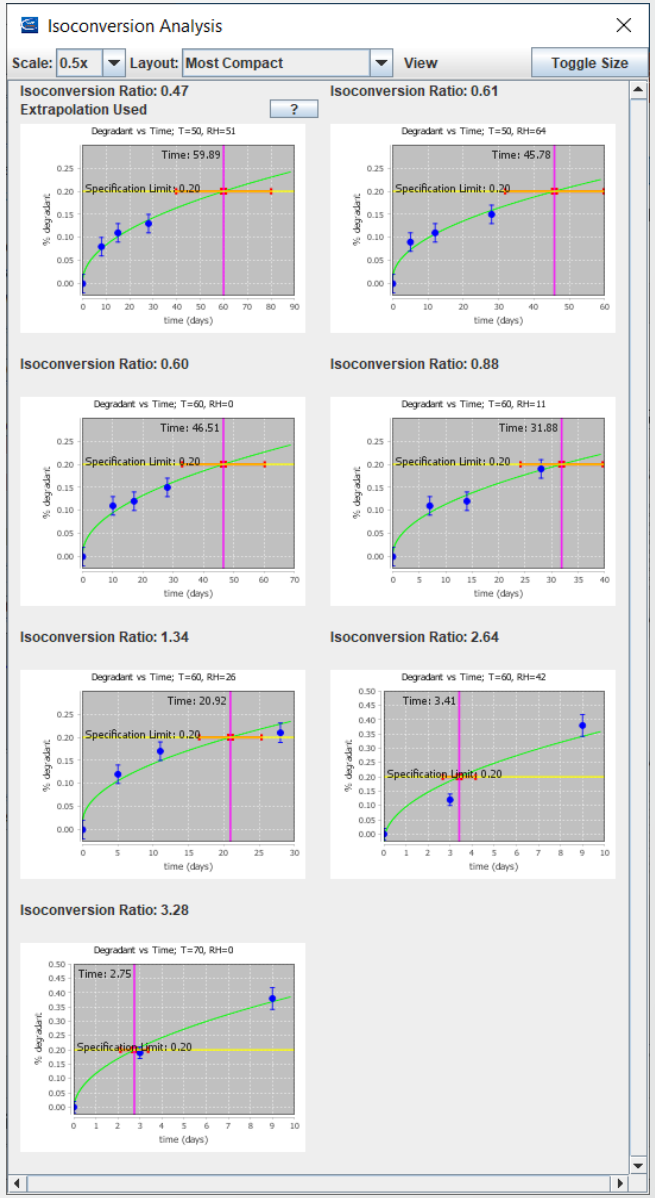
Isoconversion Fit Method Selection

- Diffusion fit method used: appropriate when the rate-limiting step for degradation is diffusion.
- This is common in amorphous solid dispersions.

RRT 0.219



RRT 0.295



ASAPprime® Calculated Model Parameters

- **E_a term**, average is 27.3 ± 9.6 kcal/mol for a variety of products (ref: FreeThink Technologies)
  - All species had higher than average E_a indicating high temperature dependence of the reaction.
  - High activation energy also means that although there is high reactivity at high temperature, the tablet is expected to be very stable at ambient conditions.

- **B term**, average is 0.044 ± 0.026 for a variety of products (ref: FreeThink Technologies)
  - The species at RRT 0.219, RRT 0.295, RRT 0.303 and, RRT 0.7 had higher than average B terms indicating high moisture sensitivity and these degradant levels can be more easily controlled via packaging protection.

Table. ASAPprime® modeled parameters for degradant growth of degradants in amorphous dispersion tablet..

Formulation	RRT	Spec. limit (%)	ln A	E_a (kcal/mol)	B	R^2	Q^2
30:70 X:HPMCAS ASD Tablet	0.219	1.0	96.41 ± 15.24	64.83 ± 10.17	0.057 ± 0.01	0.978	0.914
	0.295	0.2	97.68 ± 16.25	68.35 ± 10.92	0.057 ± 0.014	0.943	0.850
	0.303	0.2	82.33 ± 12.36	57.73 ± 8.28	0.047 ± 0.011	0.955	0.901
	0.700	0.2	157.32 ± 23.68	107.78 ± 15.9	0.100 ± 0.019	0.964	0.802
	1.054	0.2	91.36 ± 13.29	63.78 ± 8.93	0.028 ± 0.011	0.979	0.922

Degradant Plots

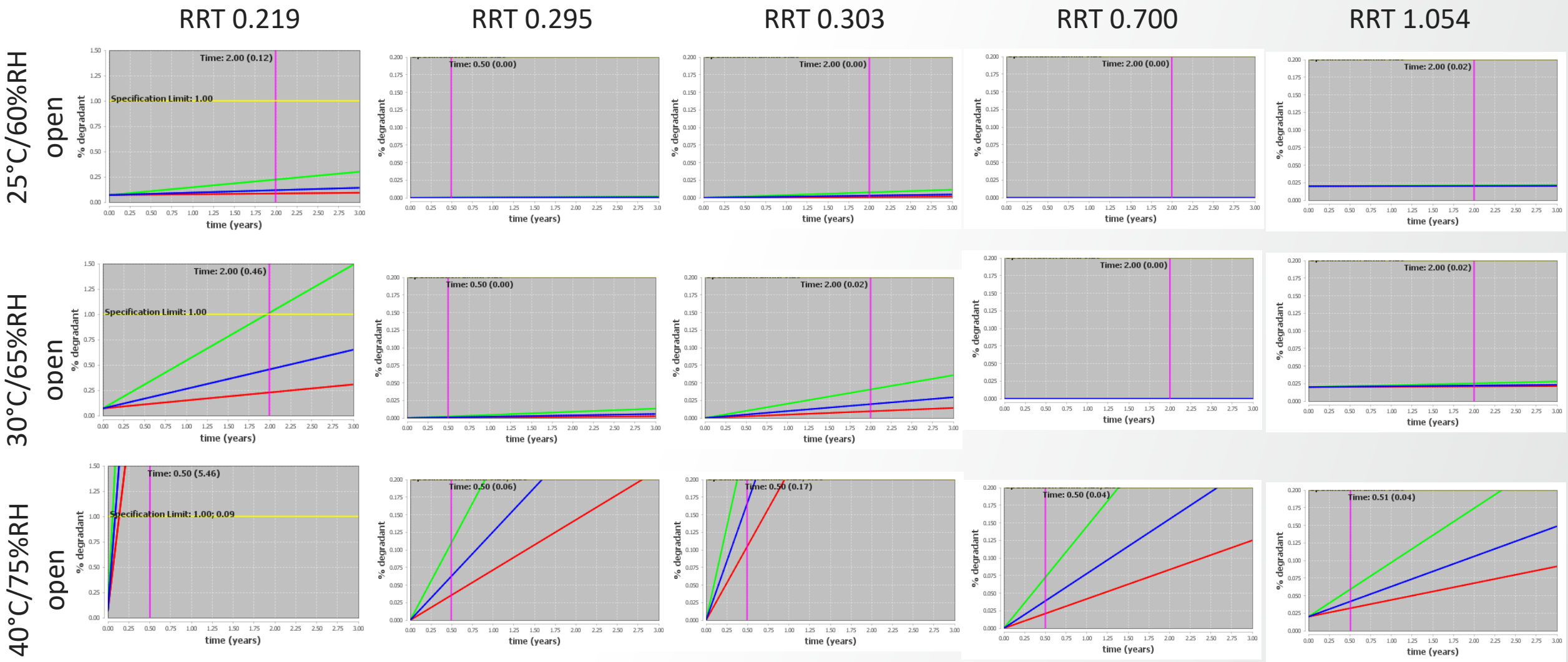


Fig. Predicted growth in 30:70 X:HPMCAS ASD Tablet at open conditions, Blue: predicted mean, Green: mean plus two standard deviations, Red: mean minus two standard deviations.

ASAPprime® Shelf-Life Predictions

- Shelf-life limiting species is at RRT 0.219 due to lowest probability of passing the specification after 6M closed 40°C/75%RH

- Addition of 2.0g desiccant increases probability of passing specification limit to greater than 98% for all degradant species.

Table. ASAPprime® shelf-life predictions for amorphous dispersion tablet in various packaging configurations.

Formulation	RRT	Spec. limit (wt%)	%Probability of Passing Spec after						
			open			closed[a]			closed[b]
			2Y @ 25°C/60%RH	2Y @ 30°C/65%RH	6M @ 40°C/75%RH	2Y @ 25°C/60%RH	2Y @ 30°C/65%RH	6M @ 40°C/75%RH	6M @ 40°C/75%RH
30:70 X:HPMCAS ASD Tablet	0.219	1.0	99.5	83.7	0.00	99.9	99.3	91.4	98.7
	0.295	0.2	100.0	100.0	98.1	100.0	100.0	100.0	100.0
	0.303	0.2	100.0	99.9	65.9	100.0	100.0	99.9	100.0
	0.700	0.2	100.0	100.0	99.6	100.0	100.0	100.0	100.0
	1.054	0.2	100.0	100.0	99.9	100.0	100.0	100.0	100.0

[a] 30 cc HDPE/HIS bottles, 30 count 0.5g silica desiccant
[b] 30 cc HDPE/HIS bottles, 30 count 2.0g silica desiccant

Compound Y Softgels (200 and 400mg) : 21-day ASAP Study

Sample No.	Condition	
	time (day)	°C
1	0	5
2	21	50
3	21	60
4	15	50
5	11	60
6	11	70
7	10	50
8	7	50
9	6	60
10	5	70
11	5	80
12	3	60
13	3	70
14	2	80
15	1	70
16	1	80

- Temperature only conditions selected for softgel study because API (in liquids and suspensions) insensitive to moisture.
- Softgels were emptied and the fill was stressed separately from the whole capsule, and a few cross-over samples were analyzed to confirm no change to degradation.

ASAP Samples Impurities Summary – 200 mg Softgel

- All degradant species that grew consistently and had data at most timepoints were modeled (red)

Sample Description	Condition	Sample Mass (mg)	0.153	0.171	0.188	0.207 sorbitol ester 1	0.231	0.254	0.284	0.31	0.322	0.34 sorbitol ester 2	0.379	0.39	0.643 PEG-esters	0.957	1.26	1.323	1.387	1.46	1.58	Total Impurities (w/w%) All	Esters Only	Excluding Esters
200mg Compound Y Softgel Fill	0 days@5°C	468.75	ND	<0.02	<0.02	0.04	ND	<0.02	<0.02	ND	<0.02	0.03	<0.02	<0.02	0.40	0.02	ND	ND	<0.02	ND	ND	0.49	0.44	0.05
	0 days@5°C	520.8	ND	<0.02	<0.02	0.04	<0.02	<0.02	<0.02	ND	<0.02	0.03	<0.02	<0.02	0.42	0.03	ND	ND	<0.02	ND	ND	0.51	0.46	0.05
	21 days@50°C	477.16	ND	0.03	<0.02	0.24	0.03	<0.02	0.05	<0.02	<0.02	0.16	<0.02	<0.02	2.06	0.03	ND	ND	<0.02	<0.02	ND	2.59	2.29	0.30
	21 days@60°C	491.12	ND	0.06	0.03	0.35	0.14	<0.02	0.05	<0.02	0.04	0.25	0.03	0.03	3.61	0.04	ND	<0.02	0.02	ND	ND	4.64	3.99	0.66
	15 days@50°C	489.81	ND	<0.02	<0.02	0.12	0.03	<0.02	0.07	ND	<0.02	0.08	<0.02	<0.02	1.17	0.03	ND	ND	<0.02	ND	ND	1.48	1.28	0.20
	11 days@60°C	484.76	ND	0.03	<0.02	0.23	0.08	<0.02	0.06	ND	0.03	0.16	<0.02	<0.02	2.28	0.03	ND	ND	<0.02	ND	ND	2.90	2.50	0.39
	11 days@70°C	499.52	ND	0.07	0.03	0.45	0.12	0.02	0.04	<0.02	0.04	0.32	0.04	0.04	4.68	0.04	ND	ND	0.02	ND	ND	5.91	5.17	0.74
	10 days@50°C	468.65	ND	<0.02	<0.02	0.12	<0.02	<0.02	0.03	ND	<0.02	0.08	<0.02	<0.02	1.10	0.03	ND	ND	<0.02	ND	ND	1.37	1.23	0.14
	7 days@50°C	504.1	<0.02	<0.02	<0.02	0.08	<0.02	<0.02	0.04	ND	<0.02	0.05	<0.02	<0.02	0.79	0.03	ND	ND	<0.02	ND	ND	0.99	0.87	0.12
	6 days@60°C	488.04	ND	<0.02	<0.02	0.14	0.04	<0.02	0.05	ND	<0.02	0.10	<0.02	<0.02	1.43	0.03	<0.02	ND	<0.02	<0.02	ND	1.79	1.57	0.22
	5 days@70°C	488.96	ND	0.04	<0.02	0.25	0.07	<0.02	0.04	ND	0.03	0.18	0.02	0.02	2.40	0.03	ND	ND	<0.02	<0.02	ND	3.08	2.67	0.40
	5 days@80°C	489.09	ND	0.07	0.04	0.54	0.08	0.02	0.03	<0.02	0.04	0.39	0.05	0.05	5.17	0.04	<0.02	ND	0.02	<0.02	<0.02	6.55	5.76	0.79
	3 days@60°C	493.02	ND	<0.02	<0.02	0.10	<0.02	<0.02	0.04	ND	<0.02	0.07	<0.02	<0.02	0.99	0.03	<0.02	ND	<0.02	ND	ND	1.22	1.09	0.13
	3 days@70°C	485.96	ND	0.03	<0.02	0.21	0.04	<0.02	0.03	ND	0.02	0.15	<0.02	<0.02	1.90	0.03	<0.02	ND	<0.02	<0.02	ND	2.41	2.11	0.30
	2 days@80°C	488.55	ND	0.03	<0.02	0.19	0.05	<0.02	0.03	ND	0.03	0.14	<0.02	<0.02	1.94	0.03	<0.02	ND	<0.02	ND	ND	2.44	2.14	0.30
	1 day@70°C	491.97	ND	<0.02	<0.02	0.08	<0.02	<0.02	0.03	ND	<0.02	0.05	<0.02	<0.02	0.78	0.03	<0.02	ND	<0.02	ND	<0.02	0.96	0.86	0.10
	1 day@80°C	487.63	ND	0.02	<0.02	0.16	<0.02	<0.02	0.02	ND	0.02	0.11	<0.02	<0.02	1.48	0.03	<0.02	ND	<0.02	ND	<0.02	1.86	1.65	0.21

ASAP Samples Impurities Summary – 400 mg Softgel

- All degradant species that grew consistently and had data at most timepoints were modeled (red)

Sample Description	Condition	Sample Mass (mg)	0.153	0.171	0.188	0.207 sorbitol ester 1	0.231	0.254	0.266	0.284	0.31	0.322	0.34 sorbitol ester 2	0.379	0.39	0.643 PEG-esters	0.68	0.957	1.26	1.323	1.387	1.46	1.74	Total Impurities (w/w%) All	Esters Only	Excluding Esters
400mg Compound Y Softgel Fill	0 days@5°C	867.38	ND	<0.02	<0.02	0.05	<0.02	<0.02	<0.02	<0.02	ND	<0.02	0.04	<0.02	<0.02	ND	0.49	0.03	<0.02	ND	ND	ND	ND	0.61	0.05	0.56
	0 days@5°C	847.63	ND	<0.02	<0.02	0.05	<0.02	<0.02	ND	<0.02	ND	<0.02	0.04	<0.02	<0.02	ND	0.50	0.03	ND	ND	<0.02	ND	ND	0.61	0.05	0.56
	21 days@50°C	865.17	ND	0.04	0.02	0.35	0.03	<0.02	ND	0.05	<0.02	0.03	0.26	0.02	0.02	2.62	ND	0.03	ND	ND	<0.02	<0.02	ND	3.48	3.00	0.48
	21 days@60°C	847.47	ND	0.07	0.04	0.52	0.08	0.02	ND	0.05	<0.02	0.04	0.39	0.04	0.04	4.63	ND	0.04	ND	ND	<0.02	ND	ND	5.96	5.19	0.77
	15 days@50°C	864.94	ND	0.02	<0.02	0.19	0.02	<0.02	ND	0.05	<0.02	<0.02	0.13	<0.02	<0.02	1.56	ND	0.03	ND	ND	<0.02	ND	ND	2.00	1.75	0.25
	11 days@60°C	860	ND	0.04	0.03	0.35	0.05	<0.02	ND	0.05	<0.02	0.03	0.26	0.03	0.03	2.94	ND	0.03	ND	ND	<0.02	ND	<0.02	3.82	3.31	0.51
	11 days@70°C	856.48	ND	0.08	0.05	0.62	0.06	0.03	ND	0.04	0.02	0.05	0.47	0.06	0.06	5.69	ND	0.04	<0.02	ND	<0.02	ND	ND	7.25	6.37	0.89
	10 days@50°C	857.45	ND	<0.02	<0.02	0.18	<0.02	<0.02	ND	0.04	ND	<0.02	0.07	<0.02	<0.02	0.76	ND	0.03	ND	ND	<0.02	ND	ND	1.07	0.94	0.13
	7 days@50°C	860.9	ND	<0.02	<0.02	0.12	<0.02	<0.02	ND	0.03	ND	<0.02	0.09	<0.02	<0.02	1.03	ND	0.03	ND	ND	<0.02	ND	ND	1.30	1.15	0.14
	6 days@60°C	860.5	ND	0.03	<0.02	0.22	0.02	<0.02	ND	0.04	<0.02	<0.02	0.17	<0.02	<0.02	1.84	ND	0.03	<0.02	ND	<0.02	ND	ND	2.34	2.06	0.28
	5 days@70°C	844.3	ND	0.04	0.02	0.32	0.04	<0.02	ND	0.03	<0.02	0.03	0.23	0.03	0.03	3.00	ND	0.03	<0.02	ND	<0.02	ND	ND	3.79	3.34	0.45
	5 days@80°C	860	ND	0.08	0.05	0.69	0.04	0.03	ND	0.03	0.03	0.05	0.52	0.06	0.06	6.06	ND	0.04	<0.02	ND	<0.02	<0.02	ND	7.74	6.81	0.93
	3 days@60°C	865.65	ND	<0.02	<0.02	0.15	<0.02	<0.02	ND	0.03	ND	<0.02	0.11	<0.02	<0.02	1.23	ND	0.03	<0.02	ND	<0.02	ND	ND	1.54	1.38	0.16
	3 days@70°C	859.19	ND	0.04	0.02	0.29	0.02	<0.02	ND	0.03	<0.02	0.02	0.21	0.02	0.02	2.29	ND	0.03	<0.02	ND	<0.02	ND	ND	3.00	2.60	0.40
	2 days@80°C	855.51	ND	0.04	0.02	0.28	0.03	<0.02	ND	0.03	<0.02	0.03	0.21	0.02	0.02	2.49	ND	0.03	<0.02	ND	<0.02	ND	ND	3.19	2.79	0.40
	1 day@70°C	878.36	ND	<0.02	<0.02	0.12	<0.02	<0.02	ND	<0.02	ND	<0.02	0.08	<0.02	<0.02	1.03	ND	0.03	<0.02	ND	<0.02	ND	ND	1.25	1.14	0.11
	1 day@80°C	864.1	ND	0.03	<0.02	0.22	<0.02	<0.02	ND	<0.02	ND	0.03	0.16	<0.02	<0.02	1.82	ND	0.03	<0.02	ND	<0.02	ND	ND	2.28	2.04	0.24

Compound Y Softgel ASAPprime® Calculated Model Parameters

- **E_a term**, average is 27.3 ± 9.6 kcal/mol for a variety of products (ref: FreeThink Technologies)
  - All species had lower than average E_a indicating low energetic barrier for degradation.

Table. ASAPprime® modeled parameters for degradant growth of degradants in softgel capsules..

Formulation	RRT	Spec. limit (%)	ln A	E_a (kcal/mol)	R^2	Q^2
200 mg Compound Y Softgel	0.21	1.5	27.495 ± 5.031	20.910 ± 3.428	0.988	0.956
	0.34	1.5	27.493 ± 5.757	21.127 ± 3.925	0.987	0.952
	0.64	15.0	26.779 ± 2.394	18.840 ± 1.611	0.995	0.984
400 mg Compound Y Softgel	0.21	1.5	22.309 ± 3.340	17.179 ± 2.246	0.981	0.877
	0.34	1.5	26.311 ± 3.721	20.121 ± 2.539	0.999	0.998
	0.64	15.0	25.215 ± 2.511	17.616 ± 1.685	0.990	0.936

Compound Y Softgel ASAPprime® Shelf-Life Predictions

- 200 mg softgels have higher probabilities of passing the specification than the 400 mg softgels.
- Shelf-life limiting species is at RRT 0.21 for both strengths of softgels due to having the lowest probability of passing the specification after 2Y open 25°C/60%RH

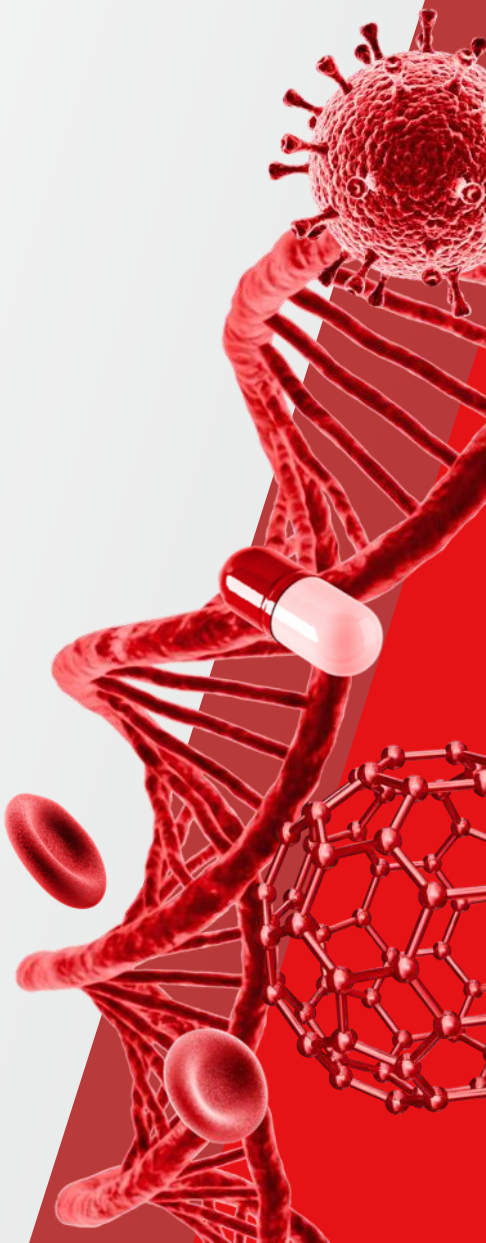
Table. ASAPprime® shelf-life predictions for softgel in various packaging configurations.

Formulation	RRT	Spec. limit (wt%)	%Probability of Passing Spec after open		
			2Y @ 25°C/60%RH	2Y @ 30°C/65%RH	6M @ 40°C/75%RH
200 mg Compound Y Softgel	0.21	1.5	98.8	94.7	99.7
	0.34	1.5	99.2	97.2	99.9
	0.64	15.0	100.0	99.1	100.0
400 mg Compound Y Softgel	0.21	1.5	91.0	49.9	96.5
	0.34	1.5	99.5	96.3	99.9
	0.64	15.0	99.3	75.3	99.9

ThermoFisher SCIENTIFIC

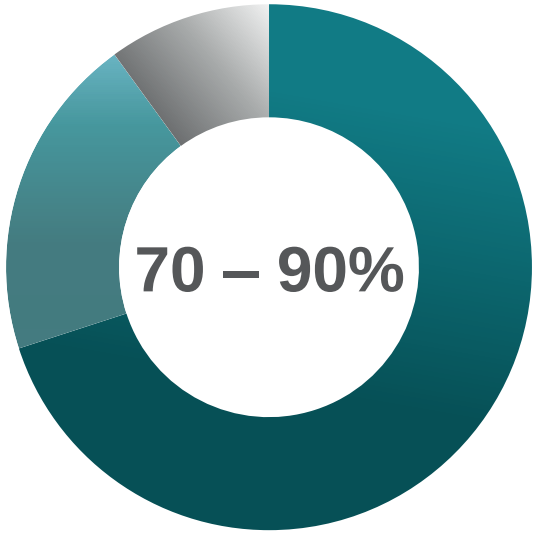
Quadrant 2®

In Silico Modeling Platform for Solubility and Bioavailability Enhancement

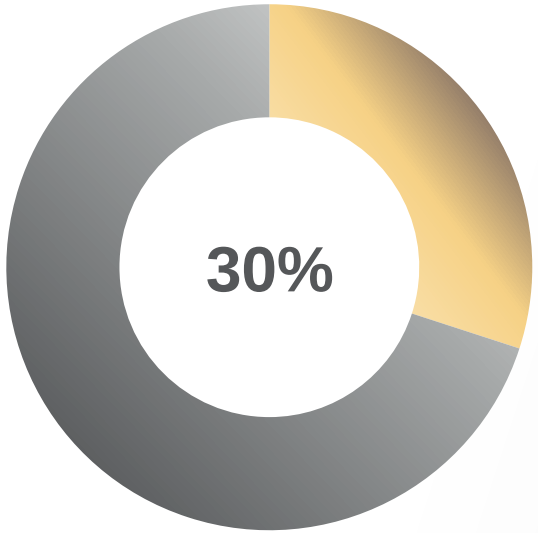


The world leader in serving science

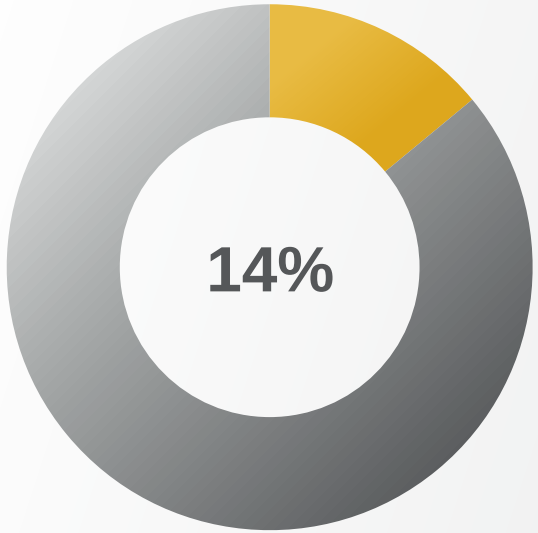
Today's Environment: Increasing Complexity, Increasing Risks



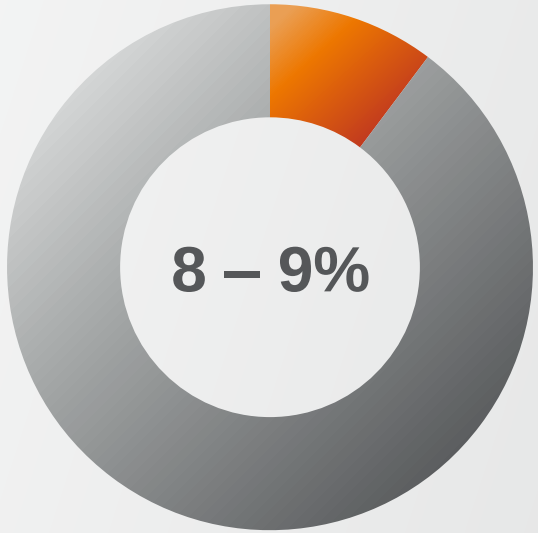
Solubility and **bioavailability** challenges



Phase I



Phase II

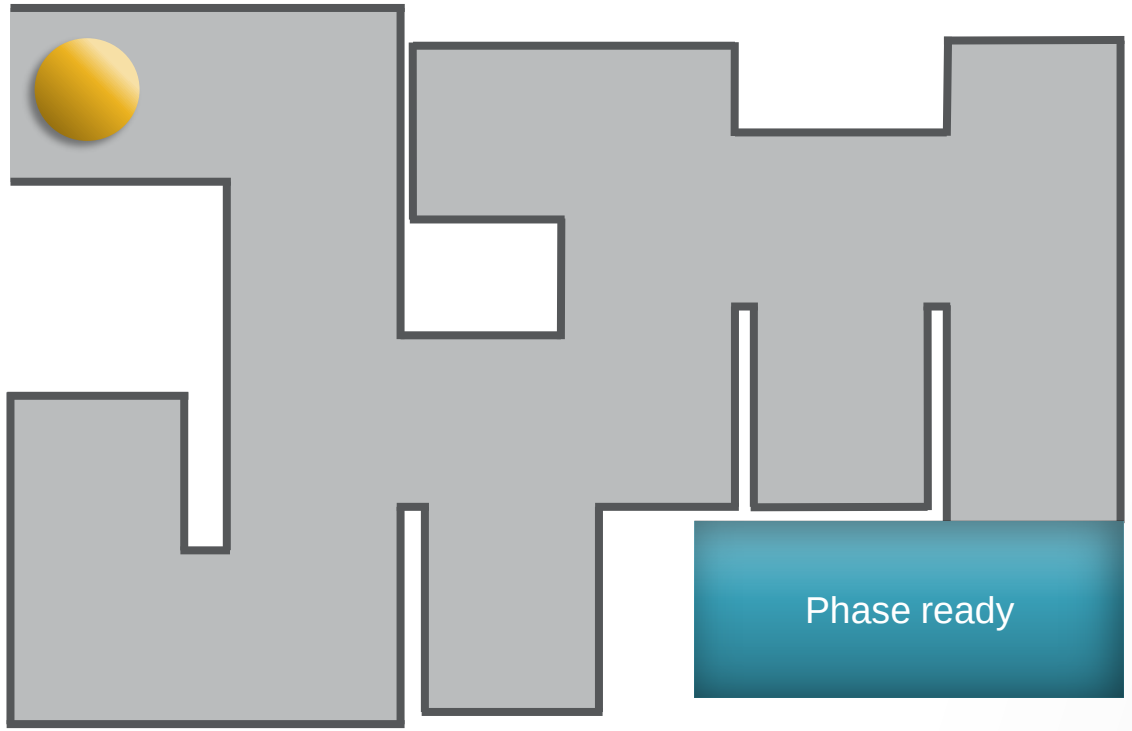


Phase III / NDA

Source: http://www.fdareview.org/03_drug_development.php

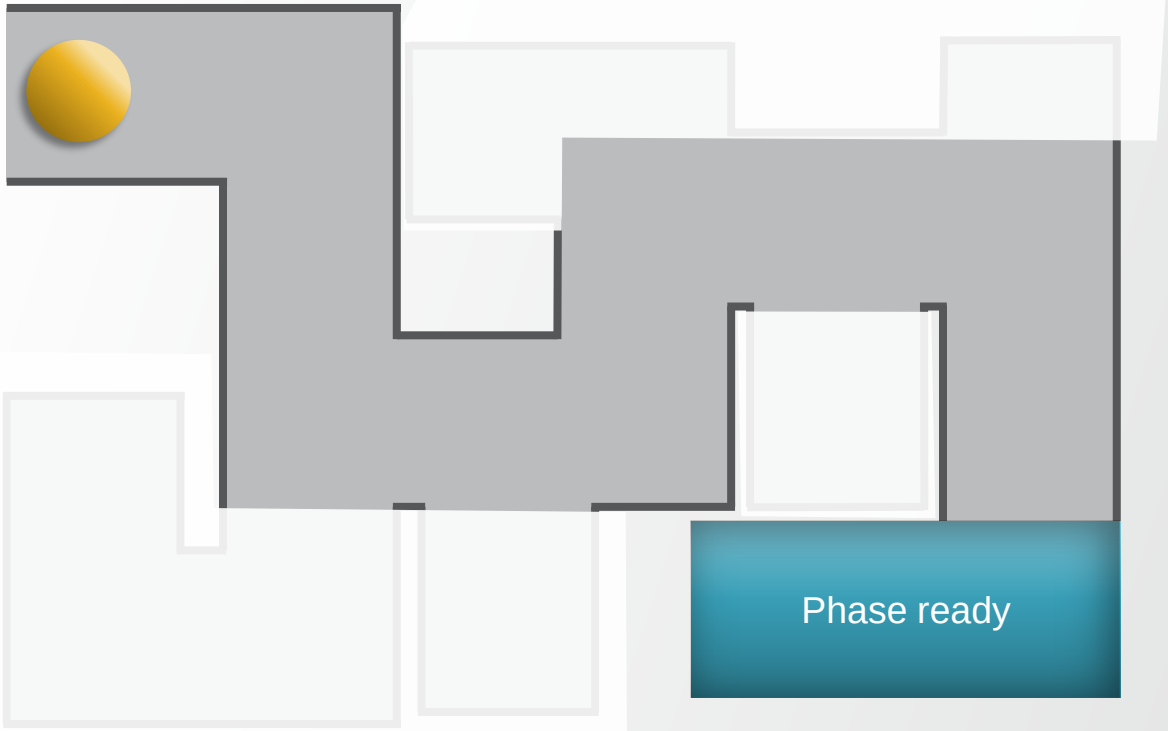
A Better Approach Exists to Being ‘Phase Ready’

Traditional Approach



Duration to get to Phase 1 CTM (14 to 19 months)

Quadrant 2®



Duration to get to Phase 1 CTM (8 to 9 months)

Quadrant 2® *in silico* Platform

- API chemical structure
- Physicochemical properties
- Business and clinical objectives

quadrant 2

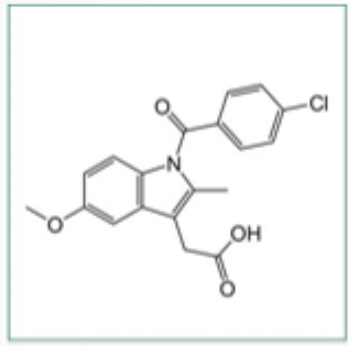
Thermo Fisher's exclusive computational modeling

- Technology selection
- Excipient selection

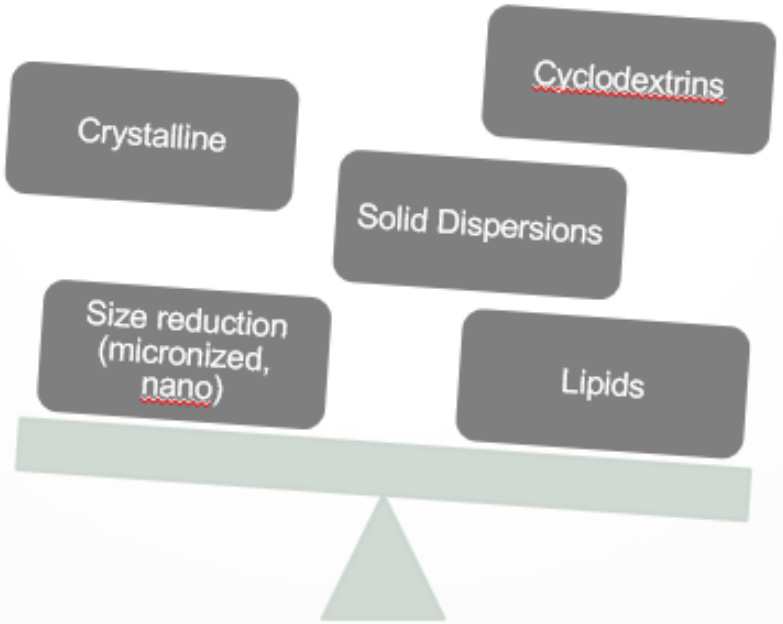
Quadrant 2® Technology Selection Process

- Green → "High likelihood of success"
- Yellow → "Needs to be evaluated"
- Red → "Not likely to succeed."

Drug Structure



Selection Algorithm

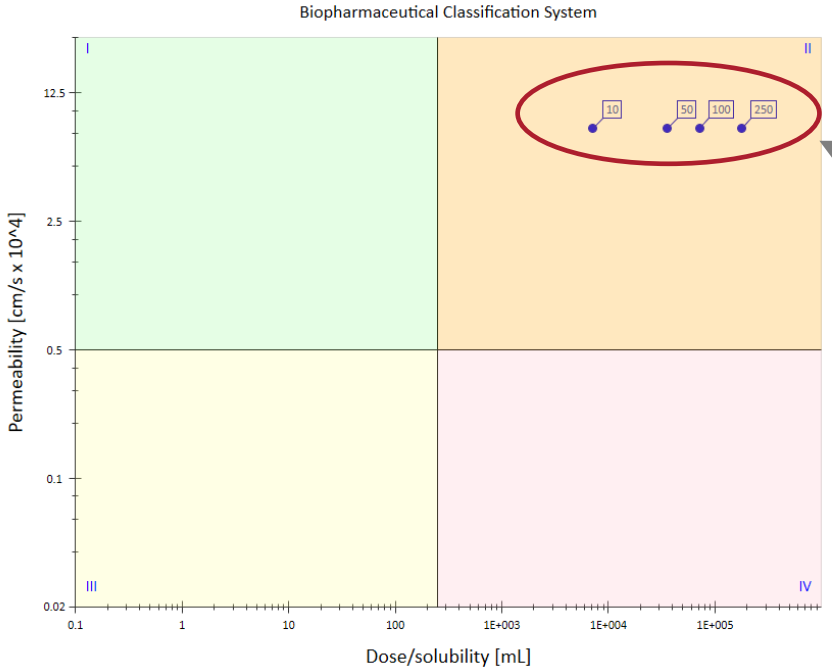


Technology Options

- Dispersions – spray dry
- Dispersions - HME
- Dispersions – coated beads
- Lipids
- Size reduction
- Amorphous
- Complexes

Quadrant 2® Technology Selection – Compound X

Compound Properties	
Melting Point °C	130
Molecular Weight	450
Solubility (mg/mL)	0.002
pKa(s) - calc	7.3
logP -AlogP	6.5
pH	**logD (calc)**
1.5	3.0
5.0	4.2
6.5	5.6
7.4	6.2



Technology Selector Output

Low Dose (<50 mg)	Medium Dose (50-200 mg)	High Dose (> 200 mg)
Lipids	Lipids	Lipids
Micronization	Micronization	Micronization
Nano-Milling	Nano-Milling	Nano-Milling
Dispersions - HME	Dispersions - HME	Dispersions - HME
Dispersions - Spray Dry	Dispersions - Spray Dry	Dispersions - Spray Dry
Dispersions - Coated Beads	Dispersions - Coated Beads	Dispersions - Coated Beads
Complexes	Complexes	Complexes
Amorphous	Amorphous	Amorphous

* *Spray Drying and Coated Beads requires that a suitable organic solvent can be identified for adequate process throughput* (typically a drug/polymer solubility >10mg/mL in a solvent system with a b.p. < 100°C)

* *Hot Melt Extrusion requires that the drug is thermally stable at processing conditions*

BCS Class II/DCS IIb Compound
(Representative human dose amounts highlighted in blue boxes)

Quadrant 2® Formulation Screening Process

API chemical structure

Physicochemical properties

Business and clinical objectives

quadrant 2

Thermo Fisher's exclusive computational modeling

Technology selection

Excipient selection

Quadrant 2® Excipient Selection Process: Amorphous Dispersion Example

API chemical structure

Physicochemical properties

Business and clinical objectives

quadrant 2®

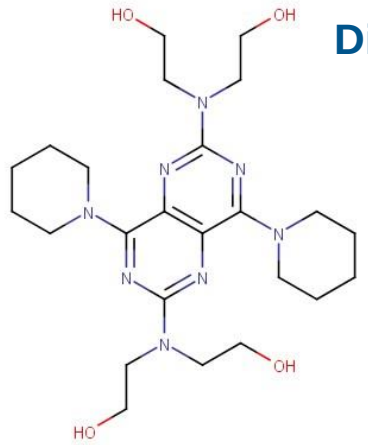
Thermo Fisher's exclusive computational modeling

Technology selection

Excipient selection

Formulation: Polymer Selection for Amorphous Dispersions

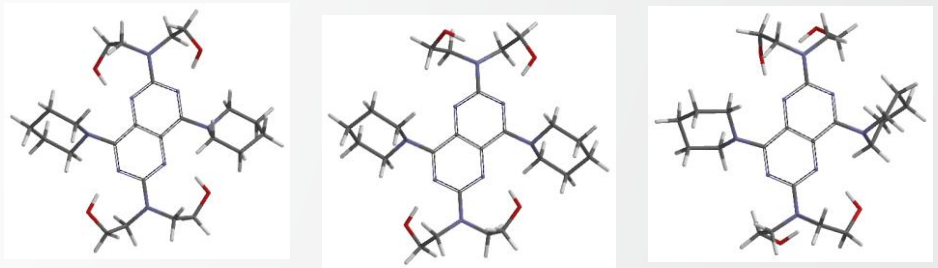
2-D



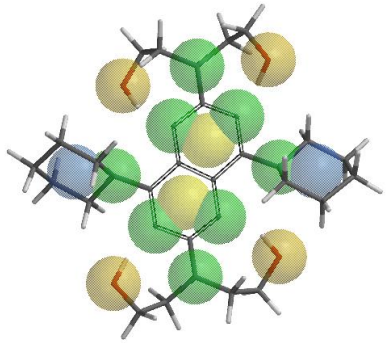
Dipyridamole

3-D Quantum Calculations

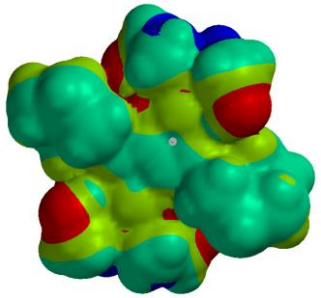
Conformers



Descriptors



- Hydrogen Bond Acceptor (8)
- Hydrogen Bond Donor/Acceptor (4)
- Aromatic/Hydrophobic (4)



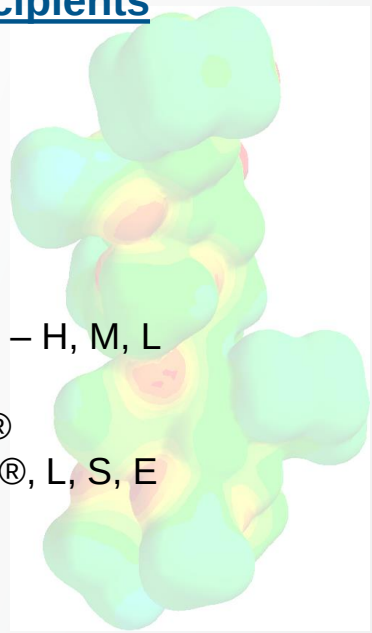
Negative

Neutral

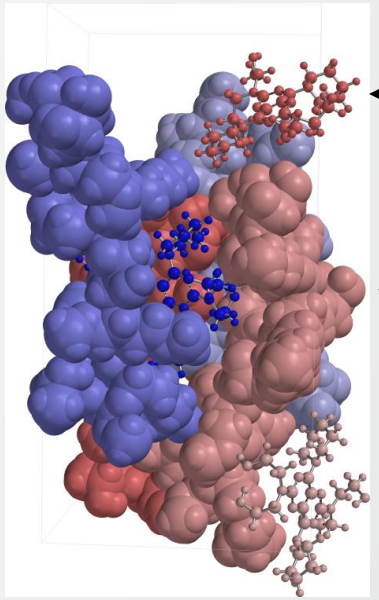
Positive

Excipients

HPMC
PVP
PVP-VA
CMEC
CAP
HPMCP
HPMCAS – H, M, L
PVAP
Soluplus®
Eudragits®, L, S, E
PEG's
Others….



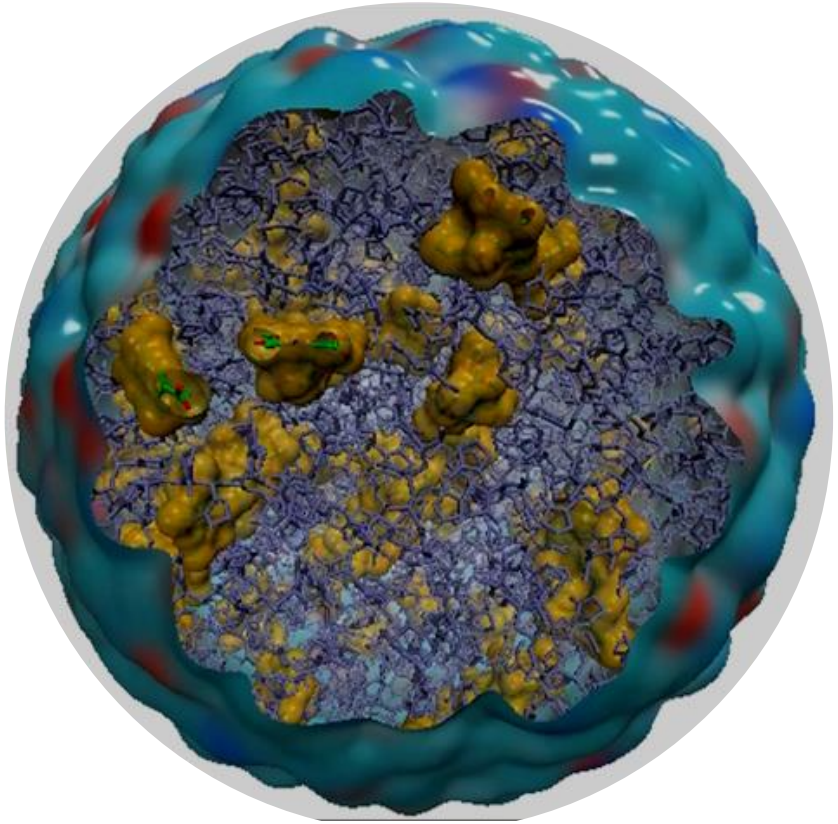
Drug-Polymer Interaction



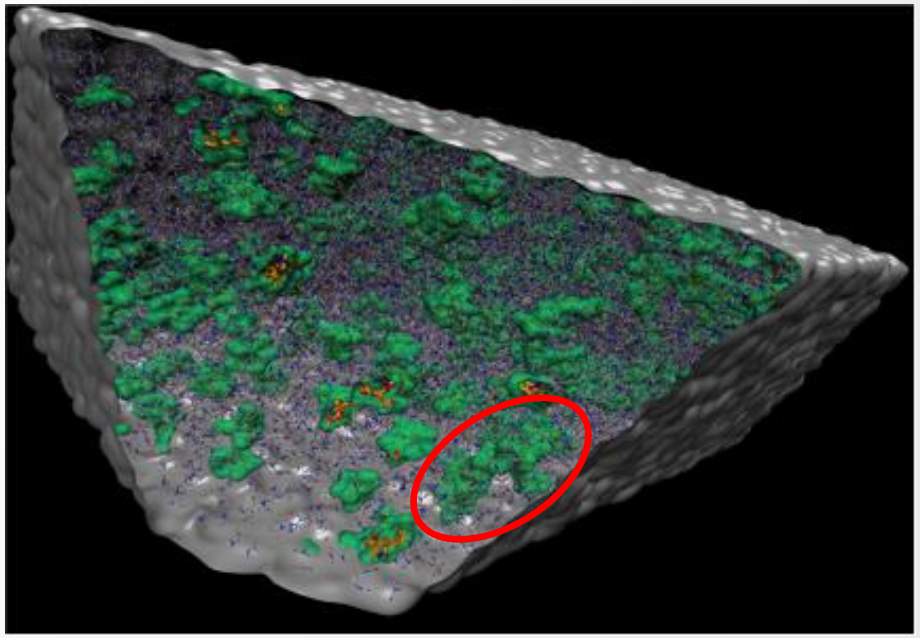
Dipyridamole
(Ball and Stick)

HPMC
(Space Filling)

Molecular Dynamics (MD) Simulations - Prediction of Drug Loading and Physical Stability

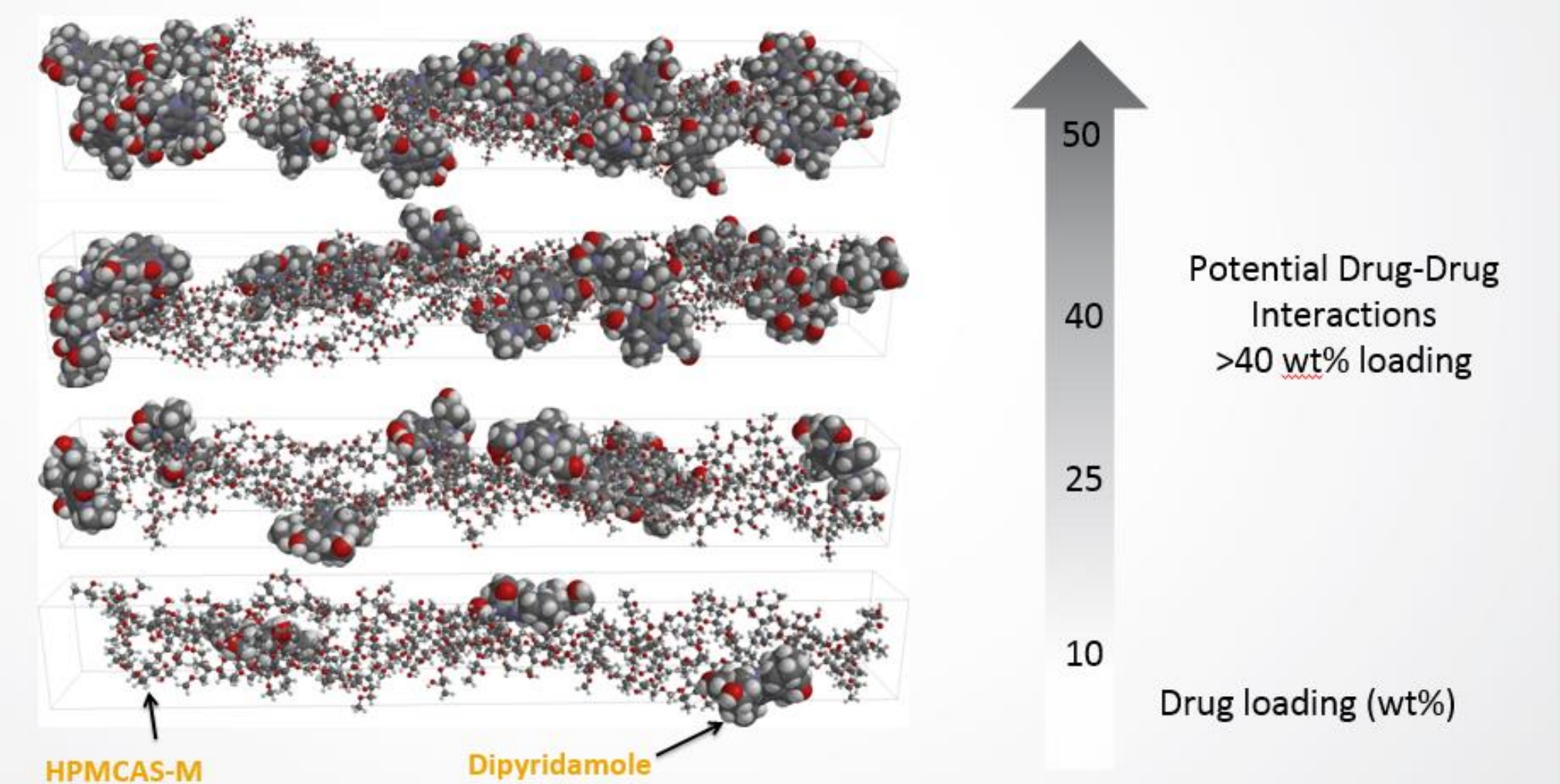


Molecular Dynamics Simulations of 10/90 API (Yellow) /PVP VA64 (Blue) Solid Dispersion.



Molecular Dynamics Simulations of a 20/80 NIF (Green)/PVP (Grey) Solid Dispersion showing clusters due to drug-drug interactions.

Predicting Drug Loading and Physical Stability

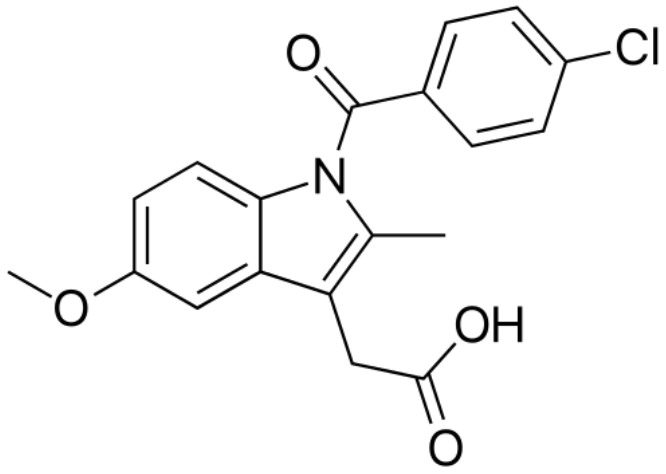


Predicted Maximum Drug Loading for Dipyridamole Amorphous Dispersions

Polymer	Calculated Maximum Drug Loading (wt%)
HPMC	38
PVP VA64	43
Soluplus	52
HPMCAS-M	42
HPMCP HP-55	42
Eudragit L100	43

Selection of Excipients for Lipid-based Formulations - Example

Indomethacin



Predicted Excipient Solubility Table (Lipidic Vehicles)

Excipient	~ Predicted Solubility (mg/g)
Capmul MCM EP	29
Captex355	5
Carbitol	187
Cremophor EL	72
Maisine 35 1	13
PEG400	135
Soybean Oil	2

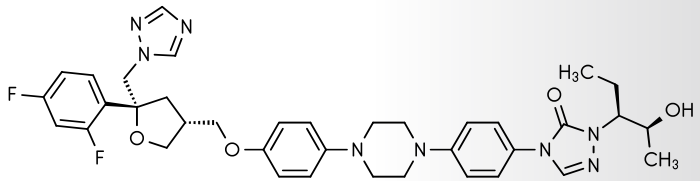
- Predicted lipid-excipient solubility provides a guideline for the feasibility of a lipid-based formulation (e.g., soft-gel, LFHS).

Quadrant 2® Technology And Excipient Selection: Proven Accuracy

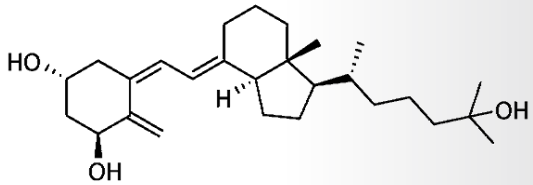
quadrant 2

Validated with ~ **350** drug molecules

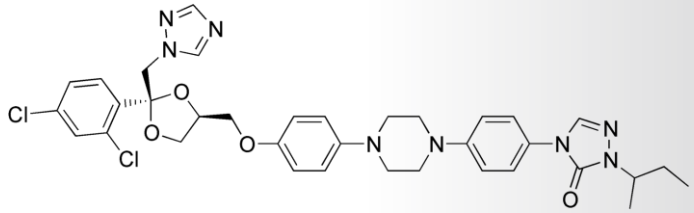
Posaconazole (Noxafil) – HME



Calcitriol (Rocaltrol) – Lipids



Itraconazole (Sporanox) – Coated Beads and (Onmel) - HME



Accuracy

Technology Selection	90%
Excipient Selection	80%

Leveraging Data Science for ASAP

Table. ASAPprime® model parameters

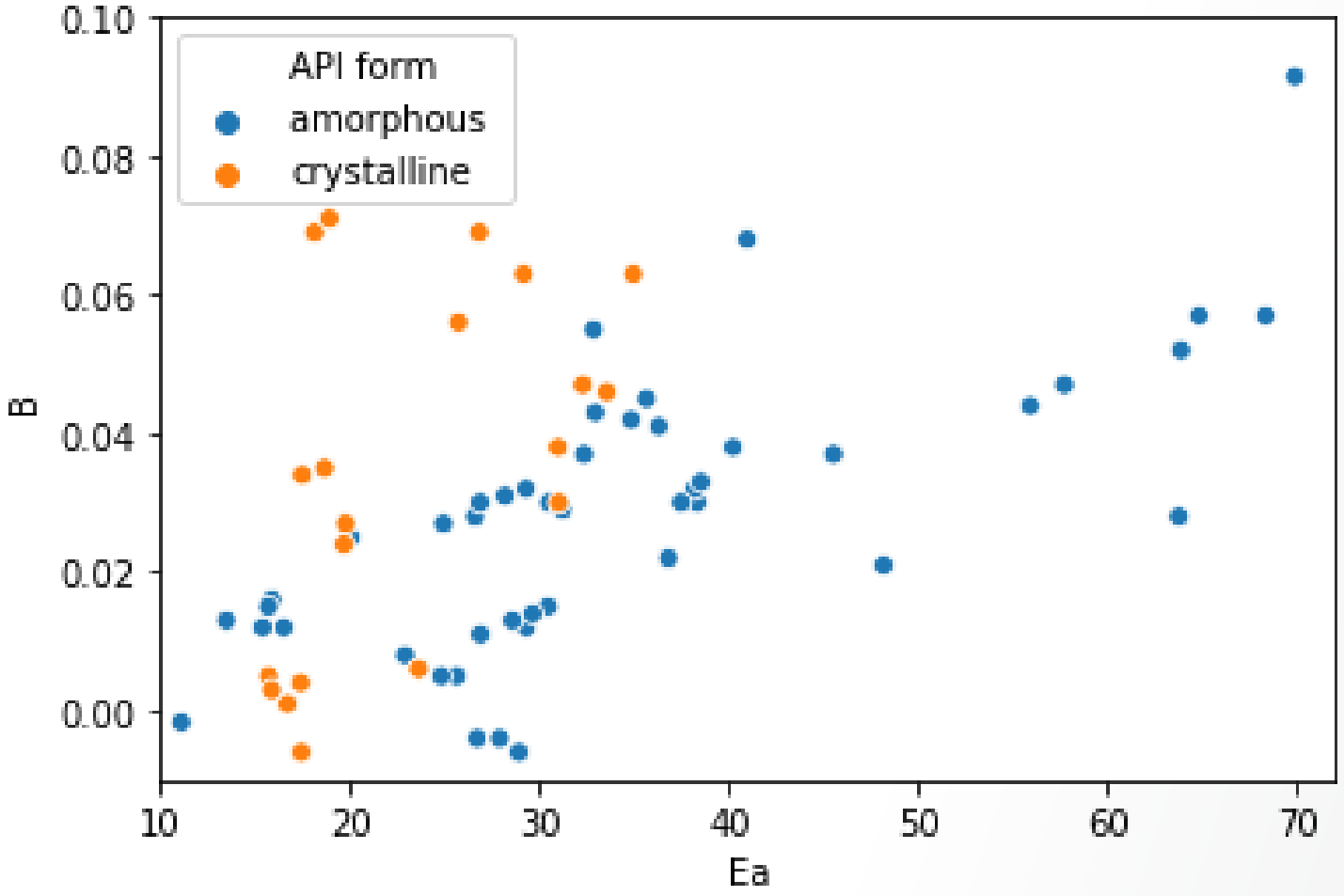
	lnA	Ea	B
min	14.490	11.100	-0.006
mean	46.596	35.022	0.033
max	197.420	136.020	0.125

Database ~70 models across ~ 40 programs

Enables efficient querying of data for use in **machine learning** algorithms, and data visualizations to **identify trends**

ASAP Model Parameters Comparison

Physical state of drug substance



Drug Products formulated with **amorphous** API tend to have Ea terms correlated with B terms, i.e. high Ea and B terms or low Ea and B terms

Drug Products containing **crystalline** API tend to have low Ea terms and a range of B terms.

Thank you