Strategic Considerations in Co-Processing Scale-up

San Kiang

Drug Product Development,
J-Star/Porton, Cranbury, NJ

Email: san.kiang@jstar-research.com

07/13/22

Outline

- Background
- Manufacturing considerations
  - ❖ Methods
  - ❖ Facility
  - ❖ Solvent safety
- Quality & Testing considerations
- Regulatory considerations

Background

My Co – processing journey started at BMS

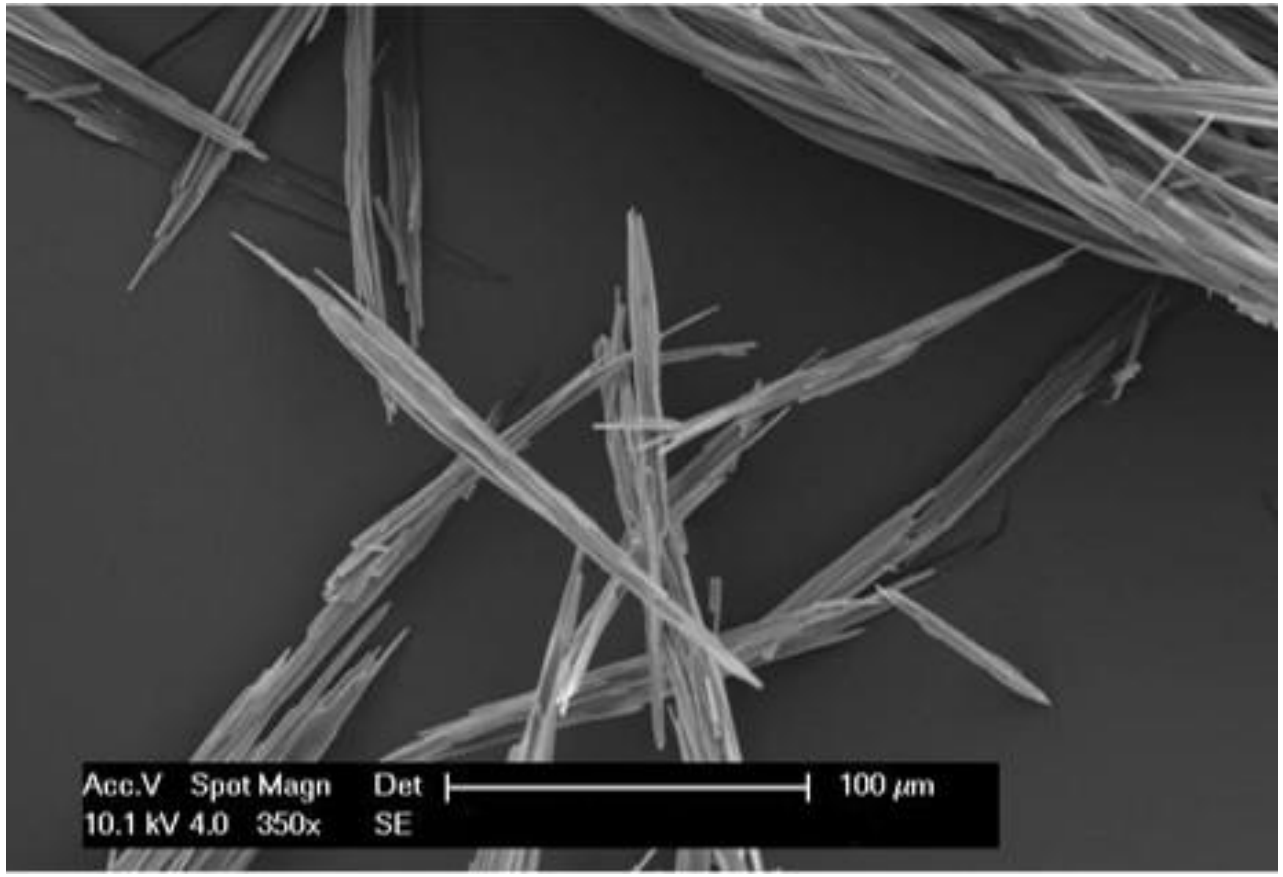
Particle engineering using excipient(s)

- Before
- During, or
- After Crystallization

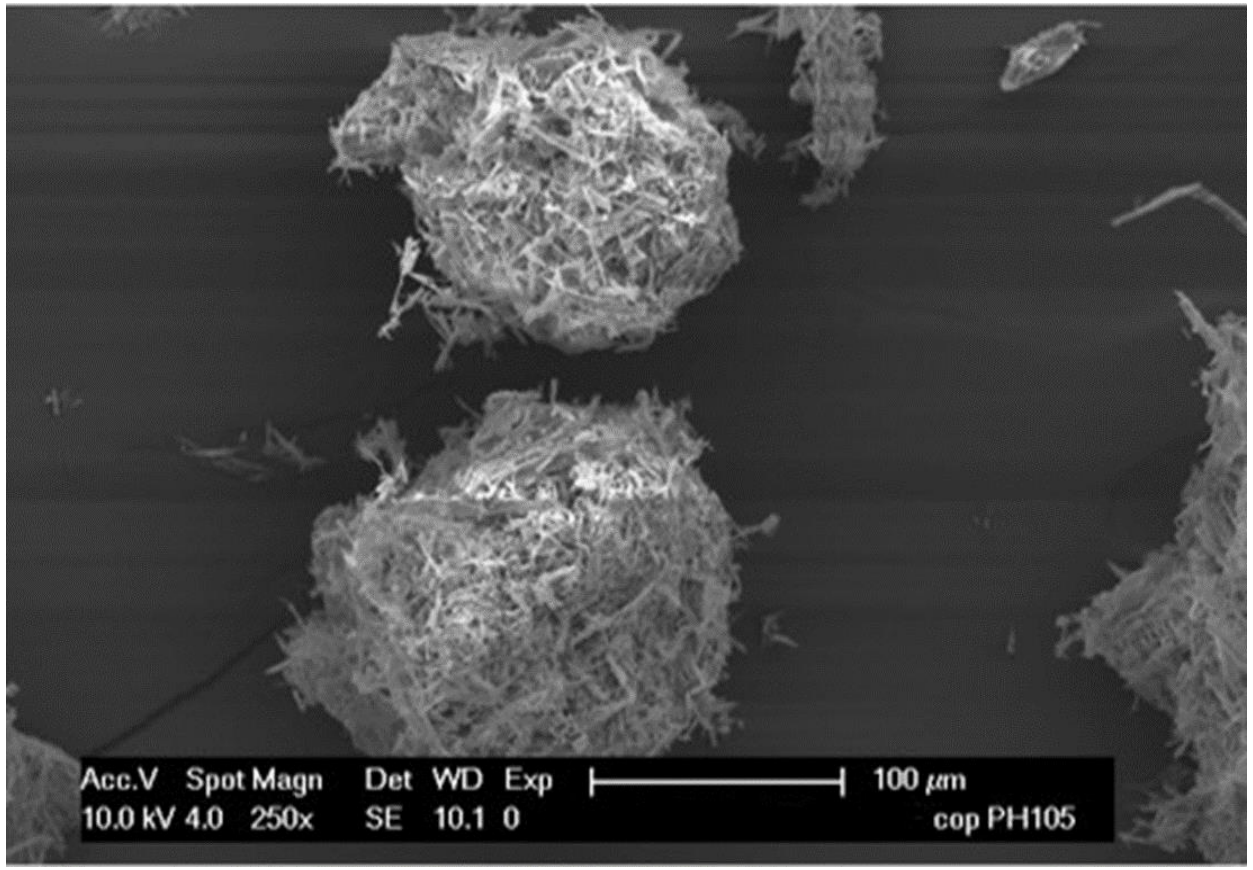
J-STAR RESEARCH, Inc.
A Porton Company

20 years ago

API as a solvate



Co-processed API with MCC, SiO_2



J★STAR RESEARCH, Inc.
A Porton Company

Manufacturing considerations

Coprocessing approach considerations

Process	Description	Process equipment	Analytical
API precipitation	by anti-solvent addition	• Crystallizers • Filter dryers • Microfluidizers • Wet mill • Jet mill • Cone/Co-mill	• Flowability – Flodex, FT4 Rheometer, Erweka GT • PSD – Mastersizer • Morphology – SEM • BD – Copley density tester • HPLC – API quantification • Powder segregation – Jenike fluidization segregation tester, Raman Microscope • PAT – Raman (solvent), FBRM (size), Blaze (image)
	with polymers – agglomeration due to polymer swelling		
	API precipitation in polymer matrix – Filtration - Drying		
	High pressure homogenization of D/E emulsion in aqueous media		
Heterogenous nucleation	Crystallization on excipient surface		
Inert carriers	API adsorption in mesoporous carriers		
Dry powder coating (non-solvent)	API coated with submicron excipients by high energy devices		

Manufacturing considerations

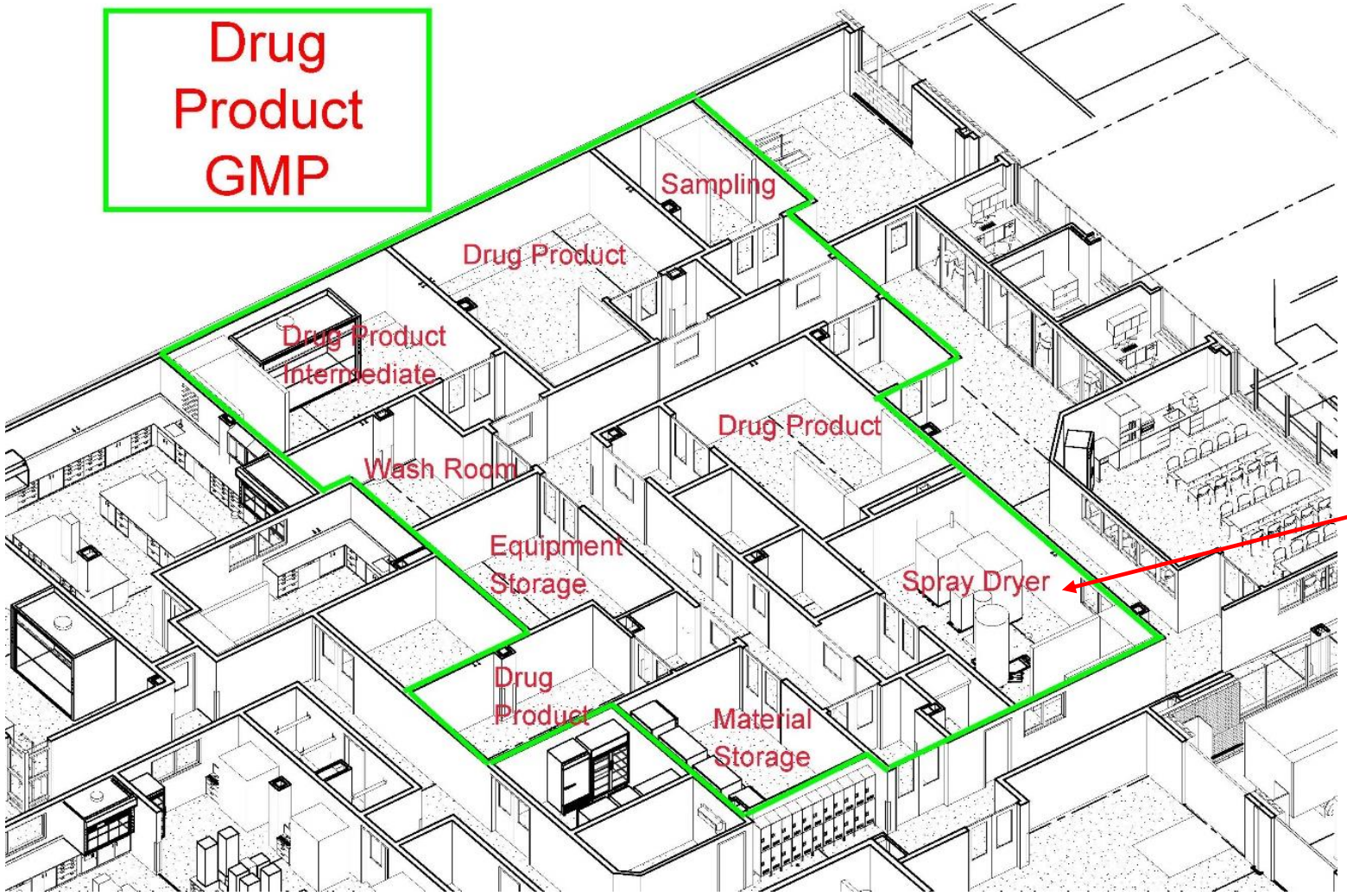
Facility considerations

	DS Mfg. site	DP Mfg. site
Solvent based co-processing mostly done	✓ Need DP license?	A few
Solvent handling capabilities • Safety measures • Controls • Process Equipment • Testing equipment	✓	Can use engineering controls. Continuous Processing (CP) can be good solution
Economical	✓	Can be with CP
CDMOs capable of coprocessing	↑	Very Limited
Non solvent based co processing		
Dry coating, adsorption	✓	✓

Manufacturing considerations

Solvent safety in a non-explosion proof area

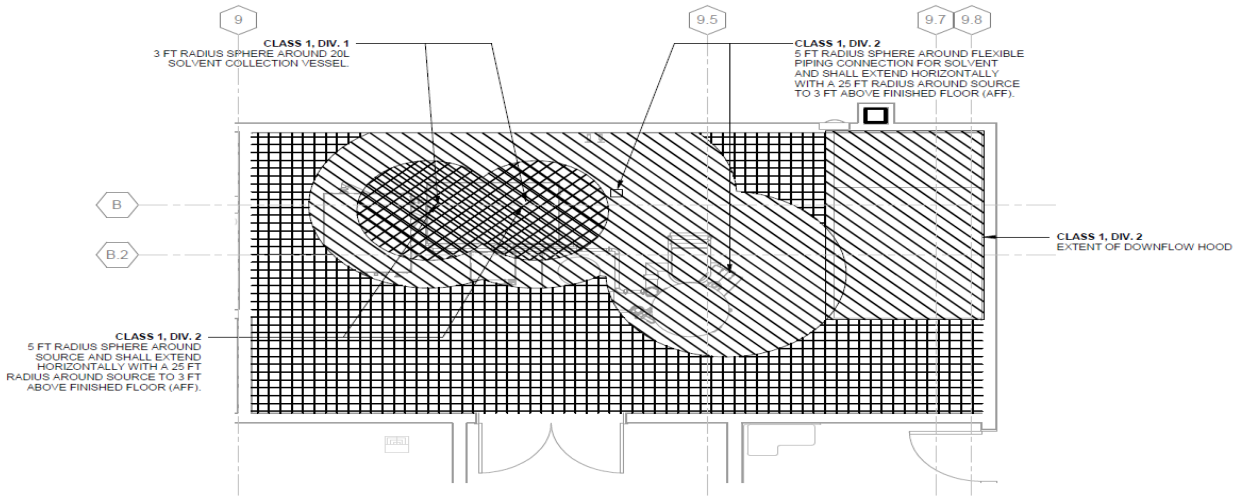
2 Clarke Dr
DP GMP/GLP Labs



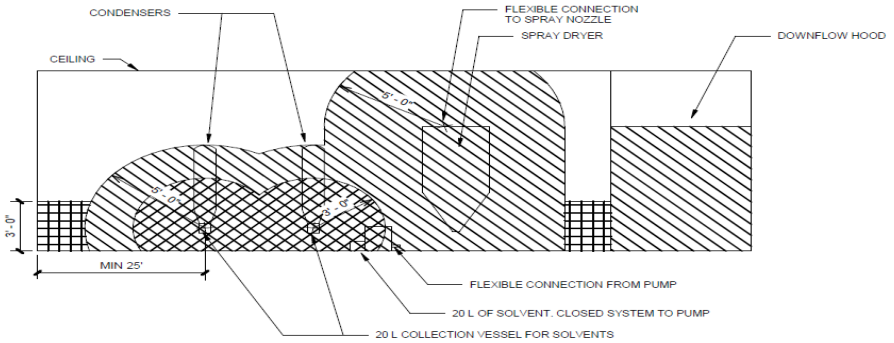
GEA Niro Spray Dryer
MOBILE MINOR- CC

J★STAR RESEARCH, Inc.
A Porton Company

Electrical Hazardous Location Classification Plan – E501



1 ENLARGED SPRAY DRYER LAB - CLASSIFICATION
SCALE :1/4" = 1'-0"



2 SPRAY DRYER LAB ELEVATION - NORTH VIEW - CLASSIFICATION
SCALE N.T.S

CLASSIFICATION LEGEND:

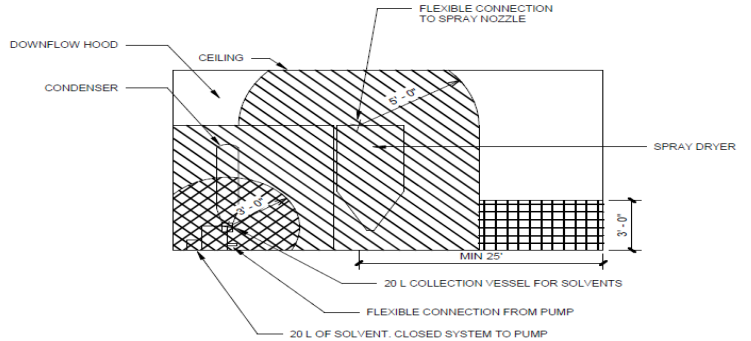
CLASS 1, DIVISION 1, GROUP B - 3' RADIUS SPHERE AROUND COLLECTION VESSEL

CLASS 1, DIVISION 2, GROUP B - 5' RADIUS SPHERE AROUND FLEXIBLE CONNECTIONS, COLLECTION VESSEL; FLOOR TO CEILING INSIDE DOWNFLOW HOOD

CLASS 1, DIVISION 2, GROUP B UP TO 36" A.F.F.

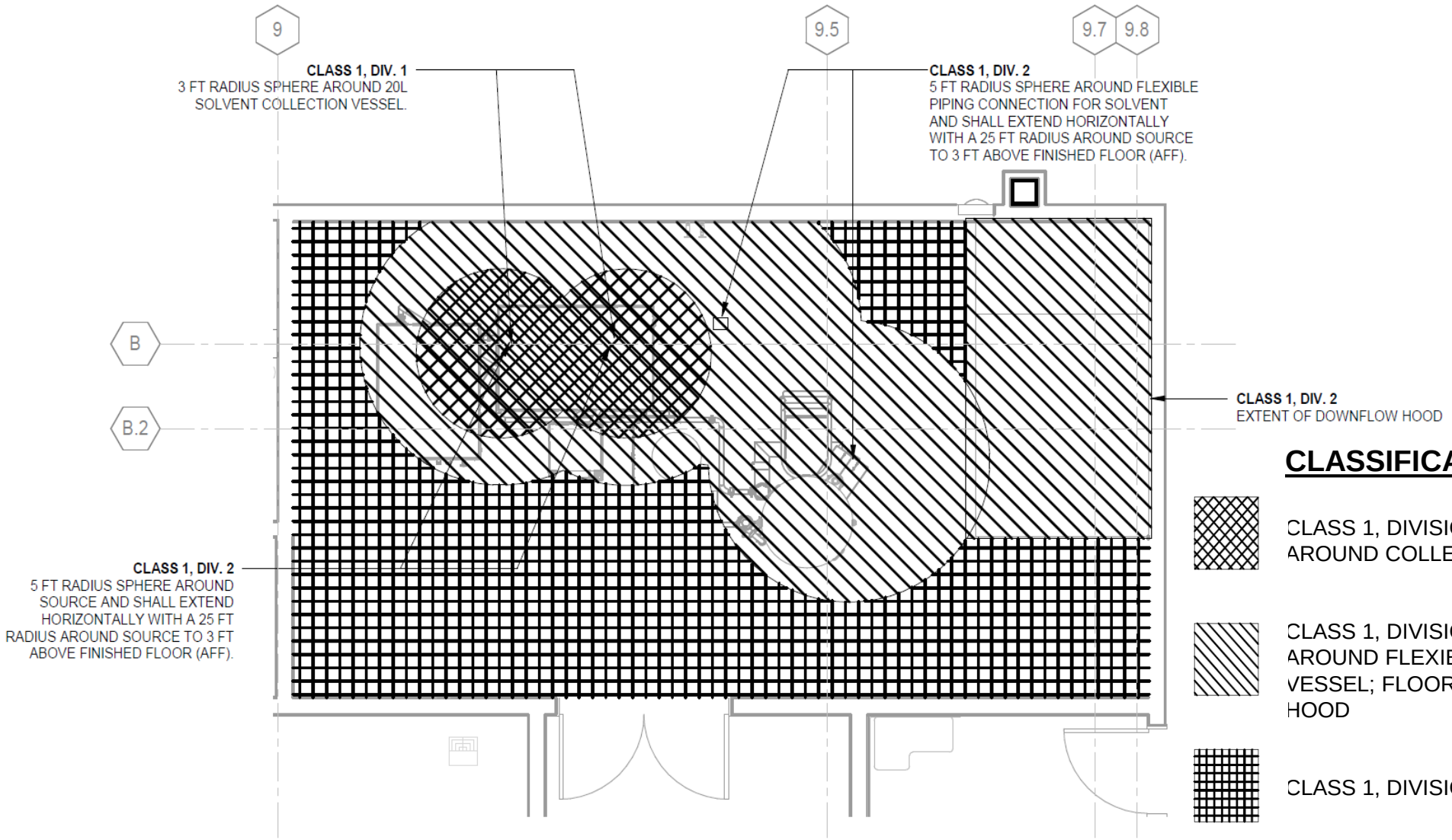
GENERAL NOTES:

1. REFER TO SHEETS E-101, E-201, E-301, AND E503 FOR POWER, LIGHTING, AND TELE/DATA DEVICES.
2. ALL CONNECTIONS AND PENETRATIONS INTO THE SPRAY DRYER ROOM SHALL CONFORM TO THE REQUIREMENTS OF NEC ARTICLE 500 APPLICABLE SECTIONS



3 SPRAY DRYER LAB ELEVATION - EAST VIEW - CLASSIFICATION
SCALE N.T.S

Spray Dryer Lab – Plan View – Classification



CLASSIFICATION LEGEND:

- CLASS 1, DIVISION 1, GROUP B - 3' RADIUS SPHERE AROUND COLLECTION VESSEL
- CLASS 1, DIVISION 2, GROUP B - 5' RADIUS SPHERE AROUND FLEXIBLE CONNECTIONS, COLLECTION VESSEL; FLOOR TO CEILING INSIDE DOWNFLOW HOOD
- CLASS 1, DIVISION 2, GROUP B UP TO 36" A.F.F.

J-STAR RESEARCH, Inc.
A Porton Company

Hazardous Areas Classification - NA

Class	Nature of Hazardous Material
Class I	Hazardous because flammable gases or vapors are present (or may be present) in quantities sufficient to produce explosive or ignitable mixtures.
Class II	Hazardous because combustible or conductive dusts are present (or may be present) in quantities sufficient to produce explosive or ignitable mixtures.
Class III	Hazardous because ignitable fibers or flyings are present (or may be present) in quantities sufficient to produce explosive or ignitable mixtures.

J★STAR RESEARCH, Inc.
A Porton Company

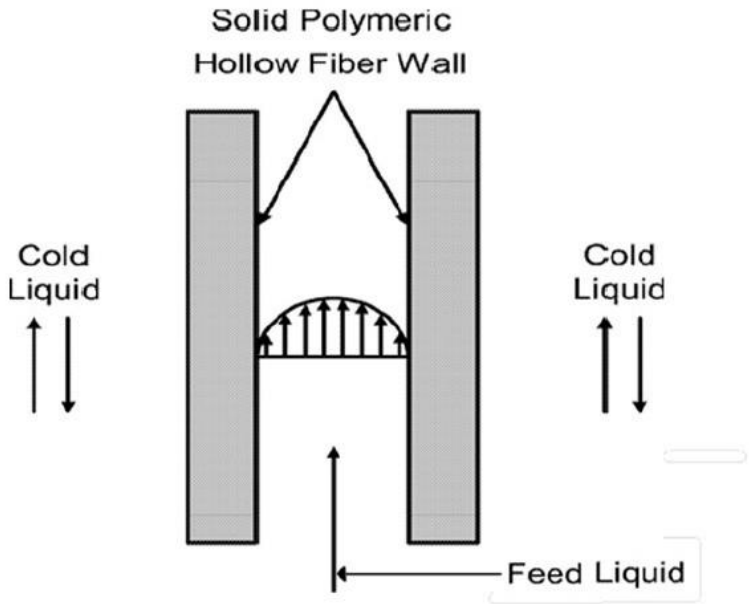
Usage & Storage Limits - Flammables

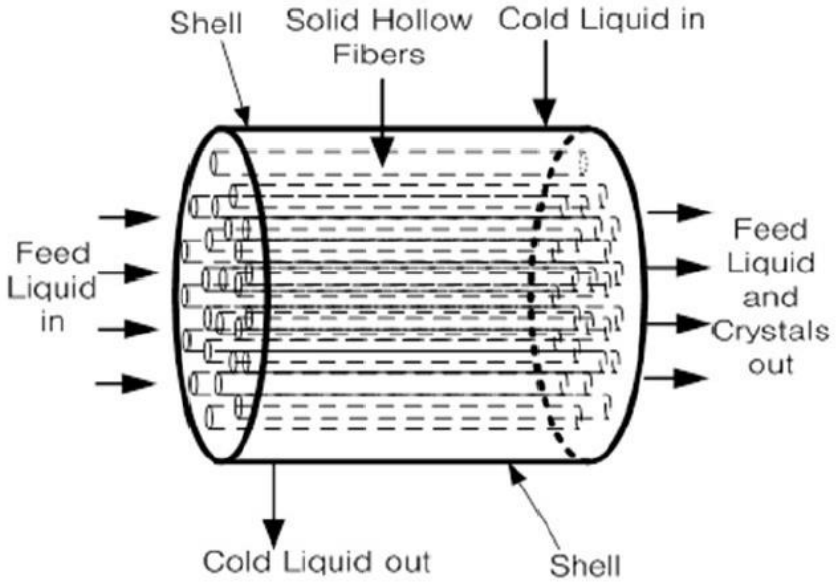
MAXIMUM ALLOWABLE QUANTITY PER CONTROL AREA OF HAZARDOUS MATERIALS POSING A PHYSICAL HAZARD[a, j, m, n, p]

MATERIAL	CLASS	GROUP WHEN THE MAXIMUM ALLOWABLE QUANTITY IS EXCEEDED	STORAGE[b]			USE-CLOSED SYSTEMS[b]			USE-OPEN SYSTEMS[b]	
			Solid pounds (cubic feet)	Liquid gallons (pounds)	Gas cubic feet at NTP	Solid pounds (cubic feet)	Liquid gallons (pounds)	Gas cubic feet at NTP	Solid pounds (cubic feet)	Liquid gallons (pounds)
Flammable gas	Gaseous Liquefied	H-2	NA	NA (150)[d,e]	1,000[d,e] NA	NA	NA (150)[d,e]	1,000[d,e] NA	NA	NA
Flammable liquid[c]	IA IB and IC	H-2 or H-3	NA	30[d, e] 120[d, e]	NA	NA	30[d] 120[d]	NA	NA	10[d] 30[d]
Flammable liquid, combination (IA, IB, IC)	NA	H-2 or H-3	NA	120[d, e, h]	NA	NA	120[d, h]	NA	NA	30[d, h]

J★STAR RESEARCH, Inc.
A Porton Company

Solid Hollow Fiber Cooling Crystallizer



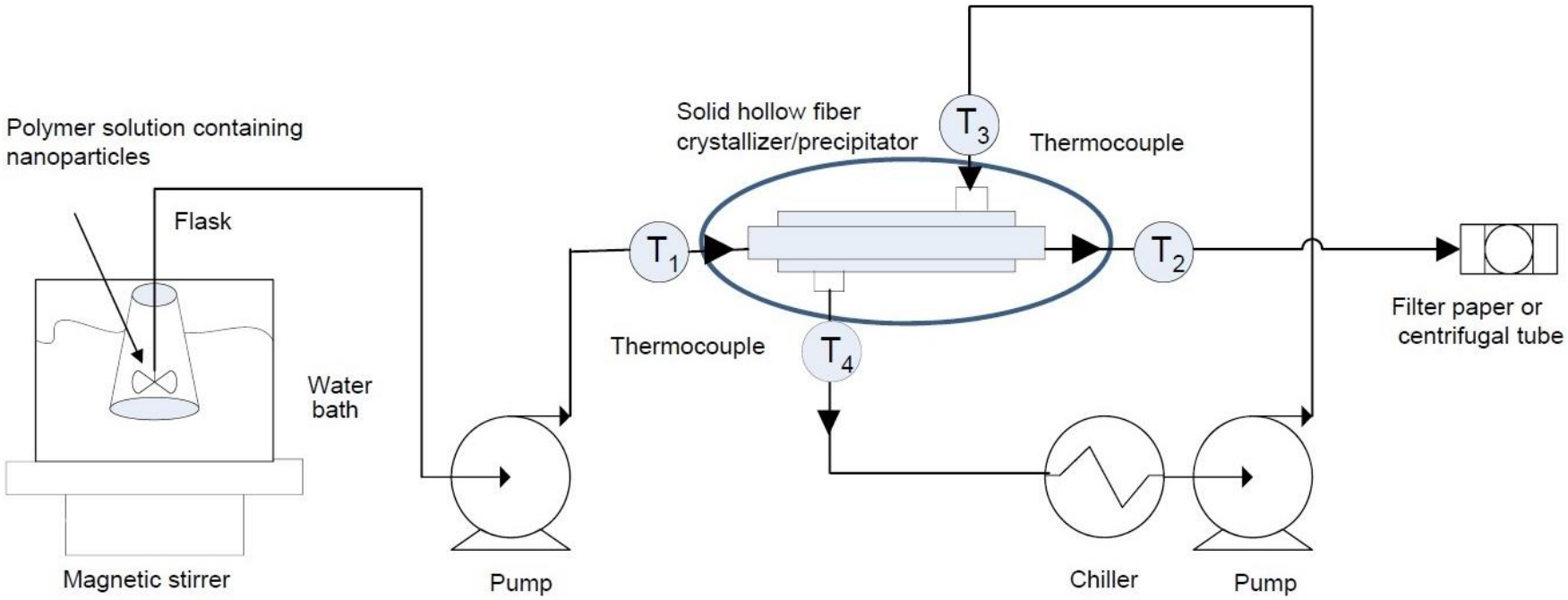


	Hollow Fiber I. D.	Hollow Fiber O.D.	Material	Numbers of fibers	Length	Shell diameter
Small module	420 µm	575 µm	Polypropylene (PP)	23	47 cm	8 cm
Large module	420 µm	575 µm	Polypropylene (PP)	46	47 cm	8 cm

*D.M. Zarkadas and K.K. Sirkar, " Solid Hollow Fiber Cooling Crystallization", Ind. Eng. Chem. Res., ***43***,7163 (2004).

J★STAR RESEARCH, Inc.
A Porton Company

Continuous co processing by CPT



Schematic diagram of solid hollow fiber cooling crystallization setup for continuous polymer coating of submicron and nanoparticles

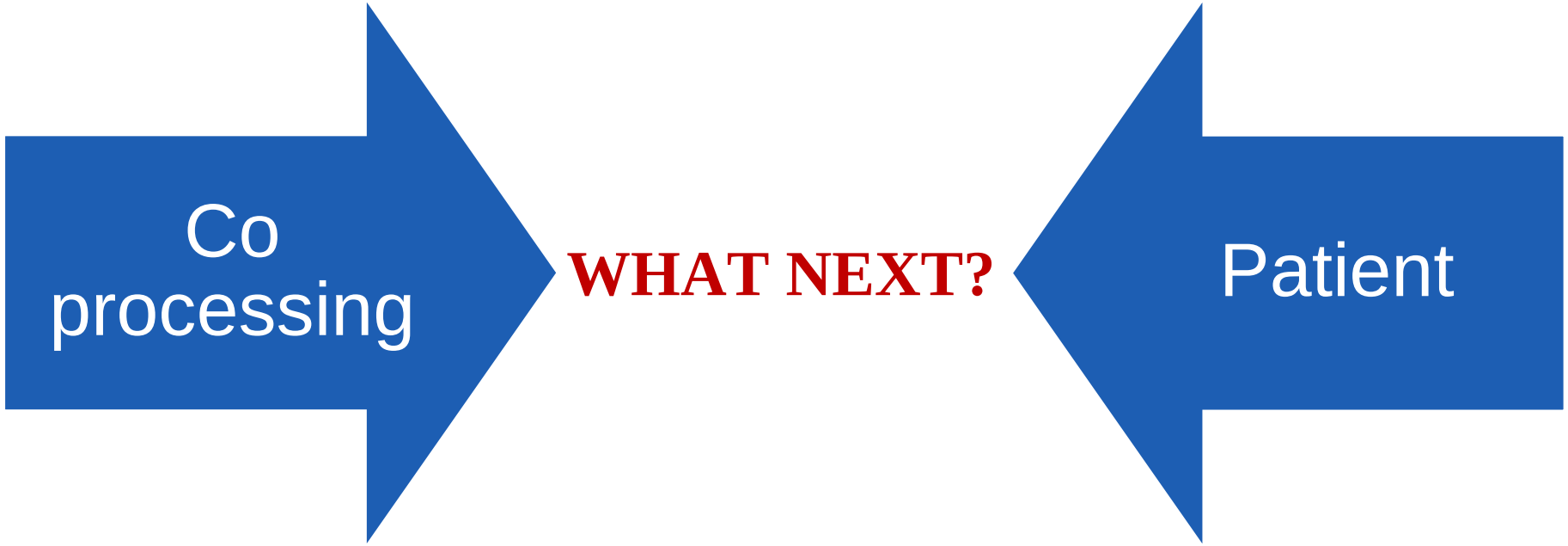
J★STAR RESEARCH, Inc.
A Porton Company

Quality & testing considerations

- Define CQAs based on CMAs & CPPs
- Assess impact of co processing on
  - Chemical stability of API
  - Residual solvent
  - Polymorphic changes
- In process tests & use of PAT
- Ratio of API & excipient
- Analyze co processed API stability based on historical data from
  - forced degradation studies,
  - D/E compatibility studies,
  - prototype, scale up & clinical batches
- Bulk hold stability studies before & after addition of excipient till DP mfg.
- Clinical performance of DP with co processed API & pure API
- Control strategies to achieve consistent quality

Regulatory considerations

- Co processed API is DS, API mix, intermediate or other?
- Perform QRA - robustness of formulation process vs. API properties
- Acceptance criteria for co processed API as DS –
  - Improved physical properties (shape, PSD, etc)
  - Specific mfg. conditions
- Release testing of co processed API
- Acceptance criteria/justification of physical properties up on storage
- Shelf-life assignment
- Specifications for co processed API (Q6A)
- Which sections of 3.2.S and/or 3.2.P need to be updated?


Co processing
WHAT NEXT?
Patient

Acknowledgements

Don Kientzler
Veeran Kadajji
Kaushalendra Chaturvedi

Q&A

THANK YOU

J★STAR RESEARCH, Inc.
A Porton Company