Supporting Information

The Evolving State of Continuous Processing in Pharmaceutical Manufacturing: A Survey of Pharmaceutical Companies and Contract Manufacturing Organizations

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The survey was conducted using Survey Monkey (<u>www.surveymonkey.com</u>), a link to which was sen
to all participants. The following is a printout of the survey.
Section A: Dereannel Information
Section A: Personnel Information
3 / 11 27%
3 / 11 27%
3. Do you have a team of people (chemists/engineers) that dedicates greater than
50% of their time to pharmaceutical continuous manufacturing?
Yes
○ No
4. What is the total size of the group that <u>dedicates greater than 50% of their time</u>
to pharmaceutical continuous manufacturing?
1-5 people (chemists/engineers)
6-10 people (chemists/engineers)
>10 people (chemists/engineers)
5. If you don't have a dedicated team, what number of people
If you don't have a dedicated team, what number of people (chemists/engineers) at your organization have experience (greater than 2
projects) developing a continuous process?

1-5 people (che	emists/engineers)			
6-10 people (ch	nemists/engineers)			
11-20 people (d	chemists/engineers)		
>20 people (che	emists/engineers)			
Comment				
6. Please select	the percentage	of people which t	fall into the follow	ving categories.
	No Degree	Bachelors Degree	Masters Degree	PhD
People dedicated greater than 90%	_	onsisted of a drop- 5%, 26-50%, 51-75		owing options:
of their time to Continuous Process development				
People dedicated 50-89% of their time to Continuous Process development				
People dedicated 5-50% of their time to Continuous Process development				
	how many peop	tion of a typical to ole with each educ Bachelors Degree		
Process Chemists	Each entry con 1, 2, 3, 4, >=5	sisted of a drop-do	wn with the follow	ing options:

	No Degree	Bachelors	s Degree	Maste	rs Degree		PhD
Analytical Chemists							
Process Engineers							
Automation Engineers							
Project Managers							
Technicians							
8. Comments on S	ection A: Per	sonnel Inf	ormation	n/Staff	Resourc	ing A	pproach
		Prev	Next	t			

Section B: Equipment Experience - Continuous Reaction Infrastructure
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4 / 11			36%		
Do you have continuous processing car responding, use the following scale of 0 necessary.			•		en
0 = No capability 1 = Have capability 2 = Extensive Use (Used for at least 2 ր 3 = GMP Qualified	orojects in last 3 ye	ears)			
9. Please respond for <u>Plug Flow Rea</u>	ctor - Heated liqu	id only	<u>L</u> .		
	()	1	2	3
< 1 kg					
1 - 20 kg					
> 20 kg					

10. Please respond for <u>Plug Flow Reactor - Heated liquid only</u>.

< 1 kg				
Pressure range:				
< 1 kg				
<u>Temperature max</u> :				
1 - 20 kg				
Pressure range:				
1 - 20 kg				
Temperature max:				
> 20 kg				
Pressure range:				
> 20 kg				
Temperature max:				
44 Bloom was also Blooks Blooks On				
11. Please respond for Plug Flow Reactor - Cry	<u>ogenic iiqu</u>	<u>lia oniy</u> .		
	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				
12. Please respond for <u>Plug Flow Reactor - Cry</u>	ogenic liqu	<u>ıid only</u> .		
< 1 kg				
Temperature minimum:				

1 - 20 kg				
Temperature minimum:				
> 20 kg Temperature minimum:				
13. Please respond for Packed-Bed Rea	ctor (solid/liquid d	or solid/li	iquid/gas	<u>s).</u>
	0	1	2	3
< 1 kg				
1 - 20 kg				
1 - 20 kg				
> 20 kg				
14. Please respond for Packed-Bed Real < 1 kg Pressure range:	otor (oonamqara)	<u> </u>	gararga	21.
< 1 kg				
Temperature:				
< 1 kg				
Gases Used:				
1 - 20 kg				
<u>Pressure range</u> :				
1 - 20 kg				
1 - 20 kg				
Temperature:				

1 - 20 kg			
Gases Used:			
> 20 kg			
Pressure range:			
> 20 kg			
<u>Temperature</u> :			
> 20 kg			
Gases Used:			
15. Please respond for Plug Flow Reactor (gas/li	quid).		
• — -	0	1	2 3
< 1 kg			
1 - 20 kg			
> 20 kg			
16. Please respond for Plug Flow Reactor (gas/li	iquid).		
< 1 kg			
Pressure range:			
< 1 kg			
<u>Temperature</u> :			
< 1 kg			
Gases Used (List):			

1 - 20 kg Pressure range:				
riessule lange.				
1 - 20 kg				
Temperature:				
1 20 kg				
1 - 20 kg Gases Used (List):				
> 20 kg				
Pressure range:				
> 20 kg				
Temperature:				
> 20 kg				
Gases Used (List):				
17. Please respond for <u>CSTR - Low pressure</u> .				
	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				
18. Please respond for <u>CSTR - Low pressure</u> .				
< 1 kg				
Range:				

1 - 20 kg				
Range:				
> 20 kg				
Range:				
19. Please respond for <u>CSTR - High pressure</u> .				
	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				
20. Please respond for <u>CSTR - High pressure</u> .				
< 1 kg				
Range:				
1 - 20 kg				
Range:				
> 20 kg				
Range:				
21. Do you make, design and modify your own c	ontinuou	s reacto	r setups'	?
Yes				
○ No				
Please specify reactor types you modify (e.g., plug flow rea	ctor heated	, packed-b	ed reacto	r).

22. What leve customers?	el of detail do you provide about your reactor design to your
Full P&ID (Process and Instrumentation Diagram)
Simplified I	P&ID (Process and Instrumentation Diagram)
Basic react	tor dimensions and configuration
No informa	tion provided
of developme	equipment type (not to include makes and models) and at what scale ent they are used: < 1kg; 1 - 20 kg; > 20 kg
Type 1:	
Type 2:	
Type 3:	
Type 4:	
	es of pumps to you use? chods do you use to measure and control mass flow rates?

26. Do you have demons		•	•
compounds? If yes, ple number of runs, and thr			number of examples,
27. Comments on Section	on B: Equipment	Experience	- Continuous Reaction
Infrastructure			
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5 / 11	45%

28. Have you ever carried out any of the following reactions on a continuous basis? Please check as many boxes as needed.

	< 1 kg	1-100 kg	> 100 kg	GMP Experience
Photochemical Reactions				
Electrochemical Reactions				
Ozonolysis				
General oxidations				
Fluorination				
Diazomethane				
Azides				

	< 1 kg	1-100 kg	> 100 kg	GMP Experience
Hydrazine				
Nitration				
Organolithiation				
Nitroalkane reactions				
CN (Strecker/ Bucherer-Bergs)				
Phosgene				
Ammonia				
Hydroformylation				
Cabonylation				
Hydrogenation				
Aerobic oxidation				
Cyclopropanation				
Grignard/Barbier reaction				
< 1 kg1-100 kg> 100 kg	ntinuous chemis xperienc	tries you've work e	ed on and indi	cate as above:
Chemical transformation 1				
Chemical transformation 2				
Chemical transformation 3				

Chemical			
transformation 4			
30. Comments	on Section C: Supporte	d Chemistries	
	_		
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Do you have continuous post-reaction processing capabilities in any the following
area? When responding, use the following scale of 0-3 and select as many boxes per
row as necessary.

55%

0 = No capability

1 = Have capability

2 = Extensive Use (Used for at least 2 projects in last 3 years)

3 = GMP Qualified

31. Please respond for SMB Chromatography.

	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				

32. Please respond for <u>Continuous Separation and Extraction</u>.

	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				
33. Please respond for <u>Continuous Distillation</u>	<u>.</u>			
	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				
34. Please respond for Packed Column Scaver	nging.			
	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				
35. Please respond for Continuous Crystalliza	tions.			
	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				
36. Comments on Post Reaction Processing S	ection			

37. Please indicate the types of continuous filtration methods used.

1:				
Continuous filtration 2:				
Continuous filtration 3:				
38. Please respond for your <u>Continuous</u>	filtration method	<u>1</u> using	the 0-3 s	scale as
above.				
	0	1	2	3
< 1 kg				
1 - 20 kg				
> 20 kg				
39. Please respond for your <u>Continuous</u> above.	filtration method	<u>2</u> using	the 0-3	scale as
	0	1	2	3
< 1 kg	0	1	2	3
< 1 kg 1 - 20 kg	0	1	2	3
-			2	3
1 - 20 kg				
1 - 20 kg > 20 kg 40. Please respond for your <u>Continuous</u>				
1 - 20 kg > 20 kg 40. Please respond for your <u>Continuous</u>	filtration method		the 0-3 s	scale as
1 - 20 kg > 20 kg 40. Please respond for your Continuous above.	filtration method		the 0-3 s	scale as

41. Comments on Continuous filtration methods section.

42. Please indicate the types of co	ntinuous dryin	g metho	d used.		
Continuous drying method 1:					
Continuous drying method 2:					
Continuous drying method 3:					
43. Please respond for your <u>Contir</u> above.	nuous drying m	nethod 1	using th	e 0-3 sca	ale as
above.		0	1	2	3
< 1 kg					
1 - 20 kg					
> 20 kg					
44. Please respond for your <u>Contir</u> above.	nuous drying m	nethod 2	using th	e 0-3 sca	ale as
		0	1	2	3
< 1 kg					
1 - 20 kg					
> 20 kg					
45. Please respond for your <u>Contir</u> above.	nuous drying m	nethod 3	using th	e 0-3 sca	ale as
		0	1	2	3
< 1 kg					
1 - 20 kg					

	0	1	2	3
> 20 kg				
46. Comments on Continuous drying methods se	ction			
47. What is the largest number of unit operations as a continuous processing train?	that you	have ru	n sequen	tially
10 g - 1 kg				
Largest Number of Continuous Unit Operations (#)				
< 1 kg				
List example of sequential unit operation run in a processing	<u>train</u>			
1 - 20 kg				
Largest Number of Continuous Unit Operations (#)				
1 - 20 kg List example of sequential unit operation run in a processing	train			
List example of sequential unit operation full in a processing	<u>uani</u>			
> 20 kg <u>Largest Number of Continuous Unit Operations (#)</u>				
Largest Number of Continuous Offic Operations (#)				
> 20 kg List example of sequential unit operation run in a processing	ı train			
and operation for a processing	, <u>a a</u> 1			

48. What is your strategy on the use of surge tanks at the stable hold points? What is the desired surge tank capacity? 24 hours? 12 hours? Less? None?

49. Do you have any integrati	ion with dru	g product m	anufacturing operations?

Section E: Analytical Capabilities				
7 / 11		64%		
Please check if you have the following capabilities, u	sing the	following	scale of	0-3.
 0 = No capability 1 = Have capability 2 = Extensive Use (used for at least 2 projects in last 3 = GMP Qualified 	t 3 years)			
50.				
Off-line or At-line (not coupled to process - manu	ıal samp	le retriev	ral)	
Please check if you have the following capabilities using the above scale.				
	0	1	2	3
Chromatography - HPLC/uPLC				
Chromatography - GC				
Spectroscopy - IR				

	0	1	2	3
Spectroscopy - Raman				
Spectroscopy - NMR				
Spectroscopy - UV/Vis				
Other - Refractive Index				
Other - Camera				
Other - FBRM				
Other - Mass Spectrometry				
Other - pH				
Other (not listed)				
51.				
51. On-line/In-line (Coupled with process) Please check if you have the following capabilities				
On-line/In-line (Coupled with process) Please check if you have the following capabilities	es using	the abov	/e scale . 2	3
On-line/In-line (Coupled with process) Please check if you have the following capabilities Chromatography - HPLC/uPLC				
On-line/In-line (Coupled with process) Please check if you have the following capabilities Chromatography - HPLC/uPLC Chromatography - GC				
On-line/In-line (Coupled with process) Please check if you have the following capabilities Chromatography - HPLC/uPLC Chromatography - GC Spectroscopy - IR				
On-line/In-line (Coupled with process) Please check if you have the following capabilities Chromatography - HPLC/uPLC Chromatography - GC Spectroscopy - IR Spectroscopy - Raman				
On-line/In-line (Coupled with process) Please check if you have the following capabilities Chromatography - HPLC/uPLC Chromatography - GC Spectroscopy - IR Spectroscopy - Raman Spectroscopy - NMR				
On-line/In-line (Coupled with process) Please check if you have the following capabilities Chromatography - HPLC/uPLC Chromatography - GC Spectroscopy - IR Spectroscopy - Raman Spectroscopy - NMR Spectroscopy - UV/Vis				
On-line/In-line (Coupled with process) Please check if you have the following capabilities Chromatography - HPLC/uPLC Chromatography - GC Spectroscopy - IR Spectroscopy - Raman Spectroscopy - NMR Spectroscopy - UV/Vis Other - Refractive Index				
On-line/In-line (Coupled with process) Please check if you have the following capabilities Chromatography - HPLC/uPLC Chromatography - GC Spectroscopy - IR Spectroscopy - Raman Spectroscopy - NMR Spectroscopy - UV/Vis				

Other Mass Spectrometry			0	1	2	3
Other - Mass Spectrometry						
Other - pH						
Other - Process Temperature						
Other - Process Pressure						
Other (not listed)						
52. How are analytical metho	ods integrate	d into p	rocess	control?		
			< 1 kg	1 - 100 kg	> 100 kg	GMP
For Information Only						
Approval for Forward Process						
Feedback Control						
Real time Release Testing						
Other (please specify)						
53. Comments on Section E:	Analytical C	apabilit	ies			
	_					
	Prev	Ne	xt			

8 /	11	73%
_	contributed to a regulatory filir cess requiring the following?	ng on a continuous
NDs		
NDAs		
EOP2 Meeting		
ANDAs		
NDAs		
5. How do you def	ine batch identity for your cor	ntinous processes?

56. How do you define batch history we middle of a continuous "batch"?	when feed materials are changing in the
57. How do you handle diverting flow process parameters go outside of the	during temporary process excursions when range defined in the batch record?
58. Do you handle cleaning similar to process hoses? How do you verify th	existing cleaning procedures for pumps and ne system is clean?
	ng any continuous process technologies to ufacturing site? If so, please describe any nsfer.
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Section G: Issues Rela	ated to the Adoption of Co	ntinuous Manufacturing
9/11 (82%
60. Do you provide cus should be done continu	tomers with a recommendate	tion on whether a process
Yes		
No No		
61. What factors go into continuously?	o analyzing whether a proce	ss should be done
62. Over the past 5 year batch to continuous?	rs what percentage of your	business has shifted from

63. Over the next 15 years, what percentage of your business do you expect will shift from batch to continuous?
64. With regard to the previous question, are the barriers primarily technical or business challenges?
Business
Technical
Please provide any comment(s) you may have regarding the shift from batch to continuous and/or the primary barrier as indicated above.
65. What is your desired balance between developing processes for batch and then converting them over to continuous, versus designing for continuous processes from the beginning?
66. If the customer does not specify processing technology and you are a contract manufacturer, what circumstances prompt your consideration of continuous processing technologies?

67. Do you have any publications or publically disclosed presentations demonstrating your continuous processing and/or manufacturing experience? If so, please list.

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