3-23-2022

Addressing the pain-points of single-use intensified multi-product downstream and liquid processing in a dancefloor production room layout

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Simplifying Progress

Defining a Sustainable Technology Roadmap in Response to Real-Life Customer Experiences for Intensified Downstream Processes

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Introduction

The sales of biologics reached over 505 billion in 2020 and the market continues to have accelerated double-digit growth under the COVID-19 burden, thus biopharmaceutical companies continue to pipeline biologics for a mounting global patient base. Nevertheless, biologics are changing, and the needs of their manufacturing are changing with them. Emerging biologics (e.g., antibody–drug conjugates, viral vectors, mRNA, bi/multi-specifics) are coming with complex or lean manufacturing requirements. Additionally, the global market is searching for more affordable &sustainable biologics and biosimilars, creating an increasingly competitive space within the emerging countries who seek to manufacture locally.

The BioPhorum Operations Group (BPOG), a cross-industry organization of biopharmaceutical end users and suppliers, collected biopharmaceutical industry drivers stating:

- 90% reduction in capital expenditure (CAPEX) and manufacturing costs in the next decade.
- reduce product changeover times by 90% to improve responses to variability in demand
- drive down new facility build times by 70%

The question is, how does this translate to actionable and prioritized points of improvement for a biological implementer & supplier to work on?

With this general need in mind, combining Design Thinking methodology and insights from single-use biological manufacturing users were gathered through an extended survey with key biopharma industry companies and institutes representing the various user groups. All interviewee responses were populated, to enable the categorization and sorting of distinct user perceptions of likes, pain-points, and benefits. The outcome of the activity was the starting point to define what are the critical components for a sustainable technology roadmap to address the needs for the rapidly intensifying biologics manufacturing market.

Design Thinking Methods:

The objective is useability.
To ask & listen, to watch & learn, to handover and let the user use their intuition & interaction. Reflecting on the gathered information, grouping & filtering, prioritizing & sorting. With this, the beginning of the ideation starts with the key question “how might I help this user”. Switching between focus mind states and creative flow, iterate the ideas, test how they work and ask the user for feedback. Only within this modus can we assured to emergence of customer validated solutions.

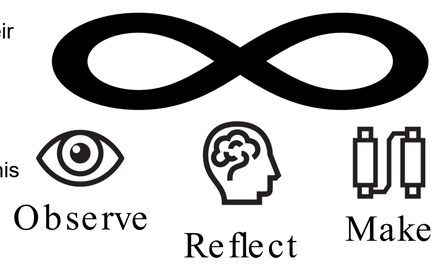


Figure 1: infinite cyclic process of design thinking method

The first step is to get to know your user(s)….

Persona &As-Is-Scenario approach

A persona is a fictional character that represents a certain group of people. The persona comprises the characteristic, behaviors, wishes, fears, habits &cultural backgrounds of this particular user type. Thus, to gain a deeper insight of the user and identify the relevant problems and needs we created 4 personas for SU downstream processing.

Operators & operator managers	Technical Single-use / process managers engineers	Commercial supply base, site or project leads	Quality Assurance & Management

Table 1: list the 4 key personas created to reflect on the pain points in SU downstream production

We created these 4 key personas (table 4) within our user base. We gave them names and personalities then journeyed them through a day or for the duration of a SU facility project. We took their perceptions, benefit and concerns into empathy mapping, and drafted the first pain points into an initial map .

We listened to real operators in batch downstream processing in their 8 hour shift to know what needs to be done for the subsequent shift and we heard from their managers and their concerns & challenges of 24 hour batch processing. In addition, we considered:

- Product Journey of a SU instrument or a SU consumable from user request – our production/assembly to user arrival to in-process usage and end of product life
- Information flow – Engineering technical document package for the Common technical documentation submission / Business rational to conceptual process modelling / facility layout & capacity planning

Empathy Mapping

Put on the user’s shoes and imagine yourself in the context of that journey. A simple but very effective tool to perceive what the users is feeling and perhaps thinking. Map out what the user says, does, feels or things while journeying along the scenario map. Eventually the map will sharpen the awareness of user’s view, (concerns &benefits) and help align the business and development activities.

Observed – Pain point mapping

Pain points were clustered &detailed out from a panel of initial user interviews (n =28) utilizing as-is- scenario technique. Frequent why, who what, when &where questions enabled categorization within certain pain-points but 17 made it to the final map (table 2), analysis (Figure 2) and contributed to the problem statement

	Difficult to Handle	Fear of Leakages & failures	Lack of Automation	Lack of easy IT & leak test capability	Poor Sensoring / Sensor Performance
Supply Chain Complexity	Too big / Cleanroom Demand	Lack of detail and consistency in Qualification / Documentation	Challenging Scalability / Volume / Processes Transfer	High CAPEX, OPEX&GoGs	Over Dependency on One Supplier (AOS)
Lack of Harmonized Industrial Standard Connection	Difficult to Connect to higher Automation structures	Poor chemical compatibility or material stability	Long Response- / Lead Times	Lack of Standardization that can reduce # of SU Items	Low Sustainability / Waste Management

Table 2: break down of segments &persona pains

Reflect – Pain point analysis

Looking at the whole dataset (figure X) tells a single story of the perceived pain across the 47 interviewed users' personas from around the world. From the highest felt pain “lack of standardization of single use technology” to the technologies being “too big or not suitable for the cleanroom” all have an impact to the different user groups. When using category filters or linking principal components analysis (PCA) we can dig into the statistics and see further trends and groupings. Not all pain is felt to the same intensity by each persona, region or segment.

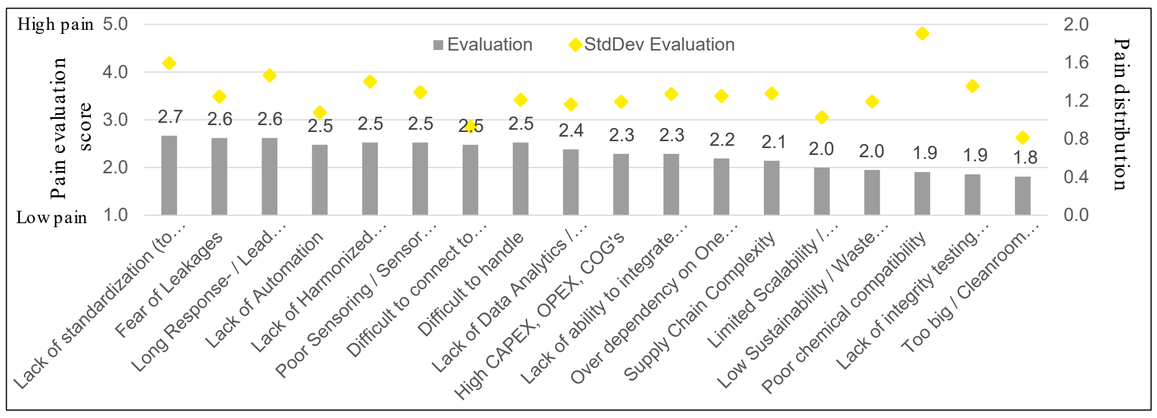


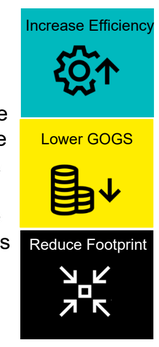
Figure 2: Quantitative Pain point intensity mapping of perceived challenges of SU downstream processing. All regions, all personas &all segment groups n=47 – 5 was the most intensely felt pain, 0 was no pain.

Customer hills (intensification)

Going by the thought process of ‘get more out of what I have–or build something where I can get more in less time or in less space’ from a customer standpoint, the following represent the hills/ obstacles which a customer must consider when intensifying upstream:

- Upstream PI [table 3; Scenario 2 & 3] means higher bioreactor output and drives the need for more efficient DSP. DSP steps need to go faster, more forceful or bigger to process the material in same time to retain the facility working shift structure an minimize the impact of the existing equipment & infrastructure.
- Upstream PI [table 3 scenario 4] feeds the need for continuous downstream manufacturing as the outward flow rate needs to match the downstream processing rate. This is likely to extend to weeks or possible months of constant processing time.

Ultimately the future facility aims to increase the space time yield of its product(s) while reducing cost of good and decreasing the facility footprint.



Downstream process intensification levels

level 1 — Intensified, standalone unit operation increases the individual step productivity or efficiency.

level 2 — Connected process: subsequent process steps start before first step is finished; software orchestration is beneficial, min. 2 steps; fits for batch &perfusion USP; could be staggered batch; may have pooling tanks; might be called clustered or linked process

level 3 — Continuous process: special, more integrated case of a connected process with steady state flow; software orchestration is a must have; predominantly for perfusion USP; only small intermediate (surge) tanks; might be named semi-continuous or pseudo-continuous

level 3.1 — Flow-through continuous process: further integrated case with complete steady state flow. All bind and elute steps are replaced with flow through mode. Molecule does not stop – impurities are removed from stream

Make - Bioprocess intensification scenario mapping

Upstream scenario	Scenario 1	Scenario 2	Scenario 3	Scenarios 4
USP type	2 kL Standard Fed batch	2 kL High Inoculation Fed Batch	2 kL Concentrated Fed Batch	500 L Perfusion
Titer (nominal), duration Productivity	5 g/L, 12 d 0.4 g/L/d	8 g/L, 12 d 0.7 g/L/d	15 g/L, 14 d 1.1 g/L/d	2.2 g/L @ 1vvd – 12 d (max. 60 d), 2.2 g/L/d
Midstream				
Cell removal & Clarification output	2,000 L 10,000 g @ 5 g/L	2,000 L 16,000 g @ 8 g/L	2,000 L 30,000 g @ 15 g/L	6,000 L @ 1vvd 13,200 g @ 2.2 g/L
DSP Intensification level	**None or level 1**	**Level 2**	**Level 2**	**Level 3**
Step duration	~1-2 shift	~1-2 shifts	~2 shifts	12 days
Capture & Polishing 1+2 type	Batch, single device FT + B&E	Dual device w/o overloading FT + B&E	Multi device with overloading 2x FT	Multi device, with overloading / parallel batch 2x FT
Viral inactivation	Batch, mixing tanks	Dual mixing tanks	Low pH Photonic	Inline (inflow), continuous VI
Virus removal, concentration, & buffer exchange	Batch, Low bioburden	Batch, Low bioburden	Batch, Low bioburden	Conti, closed processing (zero bioburden)
DSP Line Output	200 kg/a	300 kg/a	500 kg/a	160 kg/a (650 kg/a @ 2kL)

Table 3: outlines the intensification scenarios of both upstream and downstream. Additional, how a batch or continuous upstream flow feeds into a batch, connect or continuous downstream . Scenario 1/2/3 are not mutually exclusive to the downstream intensification levels which aim to debottleneck the relevant purification steps to increase efficiency, reduce footprint or lower the cost contribution.

Discussion and Future Outlook

Key concern or pain points to come out of the study; efficiency, simplicity &sustainability (economic &ecological)

- How can I go faster but not risk my process? Higher levels of orchestration, reduce both the downtime &frequency of turnarounds , increase consumable compatibility to more SU system, safe robust n/outlets connections, sustainability of consumables, non-product contact materials, primary and secondary packaging
- What happens if one SU component is broken? – detection and risk to the integrity of the process , balance the costs of product with what will I get out of my use.

Conclusion Problem Statement

Following these Bioprocessing trends, growth and commercial business drivers the rise of intensified downstream processing amplify the demands on single-use technology. hills like;

- reducing the risk of leakage, contamination &failure where there are higher driving forces, longer process duration & more connections points
- decreasing # and/or volume of static points (surge bags) and connecting steps in-line for a continuous process flow
- easing operator handling, while minimizing user error risk as complexity increases over multiple connected process steps and higher degrees of process control &automation orchestration
- growing material / design complexity/flexibility and more comprehensive variant management
- ratifying the reduction of economic and ecological impact of single-use processes

Innovation single use flow kit, sensor, actuator &connectivity technologies to enable a new generation of consumable & single use systems