BioPhorum

USER REQUIREMENT SPECIFICATION FOR SMALL FLEXIBLE FILLERS

CONNECT
COLLABORATE
ACCELERATE™

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About BioPhorum

BioPhorum's mission is to create environments where the global biopharmaceutical industry can collaborate and accelerate their rate of progress, for the benefit of all. Since its inception in 2004, BioPhorum has become the trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum now comprises more than 53 manufacturers and suppliers. These are deploying their top 2,000 leaders and subject-matter experts to work in six focused phorums, articulating the industry's technology roadmap, defining the supply partner practices of the future, developing and adopting best practices in drug substance, fill finish, process development and manufacturing IT.

In each of these phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities available, create partnerships that enable change and provide the quickest route to implementation. This means the industry shares, learns and builds the best solutions together.

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1.0 Introduction

Flexibility and agility of future drug product-filling facilities within the biopharmaceutical industry are becoming increasingly important. Traditional manufacturing has relied on technology, which can produce large quantities of product rapidly and efficiently, but this is only suited to handling large quantities of product in a single presentation due to utilization and/or when considering economies of scale. This is particularly the case when equipment is dedicated to specialized medicines, with capacity being lost due to product change-overs. Such products are becoming increasingly rare.

The products of the future are more likely to be targeted at smaller patient populations, i.e. specialized medicines and are likely to be more complex to manufacture and have higher unit values. The shift to specialized medicines increases the need for flexibility (including rapid change-overs and different presentations, e.g. syringes to vials) and changes the focus from complex, high-speed lines with extended product, to product change-over times and large footprints. As specialized medicines are produced in lower quantities, the proportion of plant capacity consumed by change-overs increases and that utilized for manufacture diminishes.

Custom-built fill-finish lines work well for high quantity products; however, they do not meet the needs of a varied product portfolio. In conjunction with the emergence of targeted products, the time taken to bring new drug products to market is a critical challenge for the future. Using standard technology rather than that which is highly customized will facilitate bringing these products to market faster. Small flexible fillers provide the ability to develop a product on the same platform and scale that will be used in a commercial production set-up. This supports faster product introduction and reduced technology transfer times and costs by allowing standardization and using similar technologies and batch sizes as those used in the development process.

The use of flexible technologies allows manufacturers to match their output more closely with patients' needs, thus reducing inventory levels and increasing their ability to respond to changes in demand from specific markets.

As product sales increase, then higher demand can be accommodated by adding more small-scale/flexible fillers. This scale-out versus scale-up concept provides:

- a standardized filling technology
- a more timely implementation route (reduced installation, training, etc.)
- the location of appropriate capacity near the point of use.

Increasing regulatory expectations are driving the need for higher quality systems. This is driving organizations to automate operations to reduce human interaction, which is the primary source of contamination in aseptic drug product manufacturing. Automation in conjunction with standardization provides significant benefits, including reductions in contamination. The industry is looking for automated operations without human intervention which will

- load materials and components
- fill containers with product
- close the filled container
- provide 100% monitoring of fill
- faster product change-overs for vials, syringes and cartridges.

The purpose of this document is to provide an overview of the current needs of the industry regarding small flexible fillers. It intends to inform and assist equipment manufacturers in the development of appropriate technology and reduce the need for customization.

2.0 Assumptions

The following assumptions have been made in the development of this User Requirement Specification (URS):

1. normally the maximum batch size 6k units – minimum uptime is 70% (as the aim is to fill one batch per shift)
2. for productivity purposes, manufacture will be of individual batches (there will not be a campaign run of batches)
3. there may be three batches of different products filled in 24 hours or two batches in a 16-hour day
4. the change-over time from the last good vial to first good vial – 30 mins for non-Antibody-drug Conjugate (ADC) products
5. lypholization cycles are not included in the assumptions for productivity
6. the types of products being filled will be monoclonal antibodies and ADCs
7. products are oxygen and light sensitive
8. the timeframe for operation is the next three years
9. there is a standard and off-the-shelf approach with limited customization, including incoming materials and components
10. simple to approve through the regulatory authorities
11. it will operate in a GMP environment, meeting the requirements of the territories in which it will be used
12. it will meet all the health, safety and environmental requirements of the territories in which it will be used
13. the volume filling range in a unit is 0.1ml to 20ml. There will be different filling solutions in the same filler for different volume ranges.

Area	Combined need/requirement
De-nester	System should provide the capability to use either a nested configuration or bulk materials. (I.e. an individual unit does not need the capability to handle both). Bulk materials are assumed to be sterilized and pyrogen-free
Aseptic filler and capper	Capacity: up to 1,000 units/hr at maximum specified fill
	Grade A/ISO 5 or better
	No human intervention is needed inside the sterile area after decontamination
	Integrated and automated 100% in process control (IPC) for fill weight required, with feedback control
	The Change -over time between the last good unit to first good unit is no more than 30 minutes, including the removal of residual sterilant. The residual level must be to 1 PPM, or less.
	Able to cap and stopper in one step for liquid products. Need an option for the complete/partial stoppering for lyophilization products
	Closed container integrity needs to be tested in real-time to facilitate real-time release. This may be a separate 'plug-and-play' module
	Include an option to include gas overlay and detection in the headspace of a vial
	Zero particles introduced to the product during the operation
	Minimal product loss during filling operation – the reject rate target is 0.05%
	Intervention losses shall not to exceed one tub or tray, or one vial in the case of bulk
	Capability exists for temperature control of the product (range 2–30o C ± 1o C) and control the humidity of the environment to prevent condensation
	Capability exists for variable dosages within the same fill lot (in conjunction with in-line formulation)
	All materials inside the filler need to be compatible with decontamination materials
Packaging components	Capable of filling multiple formats (vials 2R to 50R, syringes 0.5 to 10ml, cartridges and carpules up to 10ml) with quick or no changeover time
	Components will be supplied ready to use
	Capability exists for unit serialization
General	Users must be able to operate the isolator/filler without the need to use gloves; i.e. the filler / isolator should be gloveless.
	There are non-supplier-dependent, single-use/disposable product contact parts
	The technology must be capable of handling toxic and non-toxic materials
	Modular (plug-and-play) and mobile capability
	Automated environmental control and monitoring exists (both viable and non-viable)
	Capability exists for remote operation/self-diagnostic check and control as much as possible
	Calibration and maintenance times are minimized
	There is a sanitary design