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Review

Single-use in the biopharmaceutical industry: A review of current technology impact, challenges and limitations

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ABSTRACT

As the biopharmaceutical industry matures, the trend towards increased flexibility and productivity, faster time to market and greater profitability are driving the replacement of traditional stainless steel equipment by single-use technology (SUT). The use of SUT in the biopharmaceutical industry can significantly impact the manufacturing process efficiency by reducing capital costs, improving plant flexibility, reducing start-up times and costs, and eliminating both non-value added process steps and the risk of cross-contamination. In addition it significantly reduces process liquid waste, labour costs and on-site quality and validation requirements. This paper reviews the current status of the technology and the impact of SUT in the biopharmaceutical industry, with the aim of identifying the challenges and limitations that still need to be addressed for further adoption of these technologies. Even tough SUT has a multitude of systems available, its components and assemblies have little standardisation as well as a lack of harmonised tests and procedures among suppliers, with an array of guidelines from a variety of sources and no critical limits have been established. In addition, the use of SUT has new validation requirements such as leachables and extractables, suppliers' qualification and SUT lot-to-lot variability. The lack of expertise in these areas and the new training requirements when using SUT also need to be addressed. To date the majority of the available literature regarding SUT is found in trade journals where typically suppliers are the main contributors. There is still a lack of engagement of the academic community, which contributes to very limited scientific proof from independent peer-reviewed research to support performance of SUT. This is particularly the case during operation and integrity testing of SUT, during for example on-site testing, transport and disposal. Another area where no work has been undertaken concerns conceptual approaches for facility clean-room requirement and appropriate layout design using SUT. Investment in novel technologies, research, standardisation and training is paramount for further development and implementation of SUTs across all sectors of the biopharmaceutical industry.

Keywords: Single-use technology (SUT); Disposables; Biopharmaceuticals; Review; Costs; Regulation

Abbreviations: SUT, single-use technology; CMOs, contract manufacturing organisation(s); mAb, monoclonal antibody; BSL, biosafety level; CIP, cleaning-in-place; SIP, sterilisation-in-place; WFI, water for injection; DSP, downstream processing; CHO, Chinese hamster ovary; TFF, tangential-flow filtration; DFF, direct flow-filtration; SUB, single-use bioreactor; SMB, simulated moving bed; DO, dissolved oxygen; COGs, cost of goods sold; UF, ultrafiltration; HVAC, heating ventilation air conditioning; IQ, installation qualification; OQ, operational qualification; PQ, performance qualification; USP, United States Pharmacopoeia; BPSA, Bio-Process System Alliance; EP, European Pharmacopoeia; ISO, International Organisation for Standardisation; CRF, Code of Federal Regulations; ASTM, American Society for Testing and Materials; EN, European standard; FDA, Food and Drug Administration; HPLC, high-performance liquid chromatography; GC, gas chromatography; MS, mass spectrometry; PDA, Parental Drug Association; FTIR, Fourier-transform infrared spectroscopy; ICP, inductively coupled plasma; NVR, non-volatile residue; TOC, total organic carbon; UV, ultraviolet; EMEA, European Medicines Agency; PVC, polyvinyl chloride; PVA, polyvinyl acetate; LDPE, low-density polyethylene.

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1. Single-use technology (SUT)

As the biopharmaceutical industry matures the trend is towards higher flexibility and responsiveness of production facilities, the reduction of both manufacturing costs and timelines, in a background of increasingly strict regulatory and capacity demands.

Single-use technology (SUT) responds to a number of the critical future needs mentioned for the production of biopharmaceuticals by providing:

(1) *Flexibility* – by decoupling the process train from the facility infrastructure and transforming the facility into separate individual workstations, it is easier to reconfigure the facility. This results in greater process and product flexibility as well as portability, scalability and facility operations management. SUT also results in faster batch turn-around and product changes, improving process flexibility and speed to market (Kapp et al., 2010). If product demand increases, a rapid expansion of capacity can be achieved (Valle, 2009).
(2) *Reduced capital investment* – the cost structure is shifted to variable operating costs with a potential reduction in capital investment costs of >70% (Robinson, 2008) in equipment and facility infrastructures.
(3) *Increased speed* – faster construction, commissioning and launch of facilities using SUT, as well as easier handling and quick turnaround times (no change-over cleaning and reduced validation between different strains/products).
(4) *Safety* – fewer regulatory concerns and time, cost and labour reductions in validation requirements by >50% (Robinson, 2008) for cleaning systems, as well as decreased risk of cross-contamination and increased assurance of sterility (Kapp et al., 2010).

Table 1 presents future trends for different sectors of the biopharmaceutical industry such as new innovator companies and start-ups; contract manufacturing organisations (CMOs); monoclonal antibodies (mAbs), vaccine and smaller niche product categories manufacturers; and the impact of the use of SUT. Today, most single-use equipment is used for process development and clinical-scale manufacturing. Due to the nature of these processes, namely smaller batch volume requirements and shorter campaigns, a more adaptable and flexible manufacturing platform is required. SUT have answered these requirements in a cost effective manner, while reducing time to delivery of clinical material (ISPE, 2013). An example of the integration of a hybrid facility of fixed and single-use equipment is Biogen Idec's (NC, USA) clinical manufacturing facility that produces treatments for neurodegenerative diseases, haemophilia and autoimmune disorders.

The major exception to the use of SUT in process development and clinical-scale manufacturing is vaccines, where pressure for lower costs and new technology drives greater use of single-use components (Langer and Price, 2007). This is the case of Novavax (Rockville, MD), which produces flu vaccine using GE's ReadyToProcess™ single-use systems, and Merck & Co. (NC, USA) production facility for varicella vaccine in modular systems using SUT (Fig. 1).

At commercial scale SUT such as bags for material hold and transfer, preparation and storage of buffers and solutions, and

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