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Defining the implementation of single-use technology: a comparative evaluation of a single-use bioreactor with a stainless-steel bioreactor

The exploitation of single-use systems (SUS) has become a major subject in the biopharmaceutical industry, covering the entire product life cycle, with applications in discovery, development and through to licensed product. The implementation of SUS is a complex subject and subject to differing interpretations. The experience of SUS implementation in Valneva (Nantes, France) is reported here, reviewed together with other references and our lessons learned to illustrate that implementation must be a structured process with clear aims. Some experience gained is illustrated with a practical example that illustrates the difference in exploitation between a single-use bioreactor and a classical stainless steel bioreactor, showing how using SUS can improve operating efficiency and time.

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A decade ago the exploitation of single-use systems (SUS) was an emerging trend in manufacturing sciences for the biopharmaceutical industry [1]. Since that time, the growing interest in the application of single-use technology within the industry has now developed into a major business, covering many different potential applications [2–4]. The biomanufacturing industry has now moved forward in a relatively short period of time. The major concerns or 'hot topics' have changed from considering potential SUS utilization to SUS exploitation and the associated business and regulatory issues. A number of examples exist [5–7]. The main application for single-use technology was thought to be in a product development role, mainly because of material constraints at larger volumes. However, the technology has been embraced by producers and contract manufacturing organizations alike in applications across this part of the product life cycle [7].

Many advantages have been cited for the implementation of SUS over classical stainless steel systems, also called multiple-use systems (MUS). For example, an efficiency gain with turnaround (campaign changeover) and the fact that steaming-in-place (SIP) and clean-in-place (CIP) processes and their validation are not required both provide an advantage for SUS [8]. However, there are very few publications that discuss these advantages in any depth [9–11]. Our general impression is that over the last 6–7 years of rising popularity for SUS, many end users have initially embraced the technology in order to obtain a better understanding of the capabilities, advantages and disadvantages that the technology can offer. The disadvantages can sometimes only become apparent at later stages in the product life cycle. Some examples for this would be technology overdosing and qualification costs. Technology overdosing can happen where multiple SUS suppliers are used or where similar equipments are purchased in parallel in different functional areas within the same organization without cooperation or coordination. Spiraling qualification costs

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Key Terms

Exploitation: Practical or productive use of a single- or multiple-use system.

Single-use system: System designed for a single utilization and largely based on disposable components. Frequently has the aim of replacing a multiple-use system. Examples would be manufacturing systems such as bioreactors, filtration or chromatography systems.

Single-use technology: Top-level term that refers to single-use systems in the broadest of sense.

Implementation: Defining, verifying, procuring, installing and qualifying a system ready for deployment and exploitation.

Systems: Integrated ensembles of components forming a piece of equipment designed for a specific purpose.

Multiple-use systems: Reusable systems often based on stainless steel components. Examples would be manufacturing systems such as bioreactors, filtration or chromatography systems.

Single-use bioreactors: Subset of single-use system.

Deployment: Setting up and preparing a single-use system or multiple-use system for exploitation.

can originate from such uncoordinated procurement later in the product life cycle. Both of these issues can be mitigated by a risk-based and structured approach to implementing the technology employing process validation principles and stakeholder management over the project life cycle [12,13].

At Valneva (Nantes, France), a small 1500 m^2 pilot facility is operated for investigational medicinal product manufacturing in support of business operations with the cell substrate, EB66®. This cell substrate is based on duck embryonic stem cells and can support the production of many different viral vaccines and therapeutic proteins [14]. In the context of these operations we have implemented several different SUS projects over the last 6 years, including single-use bioreactors (SUBs), filtration systems, chromatography systems and various types of manifolds [15]. The authors employed a flexible and simple project plan, appropriate to company needs.

At the end of the implementation processes a 'lessons learned' post-implementation review, in which the experience of the implementation process and efficiency gain observed for operations in the plant were analyzed. As mentioned earlier, one of the principle reasons for the selection of a SUS solution over a MUS solution is the reported gain in efficiency. Nevertheless, as already mentioned, we have not found clearly reported information on this claim. The aim of this special report is to define the term 'implementation' in the context of SUS and to document our experience of these implementation processes for the single-use technology exploited at Valneva. Clearly, while this example is based on the authors' specific experience, it is believed that it provides a comparison between the exploitation of MUS and SUBs from an operational perspective in a development scenario.

Defining implementation

The complex nature of single-use technology means that a SUS implementation process requires careful handling. It should not be confused with a simple, 'order, install and use' philosophy, an approach that can create both short-term problems where issues are overlooked or forgotten and, as already mentioned, can potentially create delays and cost over-runs later in the product development process. Here we define SUS implementation organized as a project plan, with structured content, having sequential or sometimes parallel life cycle driven workflows. While performed in the context of Valneva development operations it is, in principle, applicable to all stages in product development from discovery to commercial manufacture. This concept is illustrated in the following section.

Implementation of a SUB project

As with any new, innovative technology, the best practices for implementing and exploiting it can evolve over time. In the absence of a recommended scheme, for our single-use technology projects we adopted the project plan described in **Table 1**. At the time, the company was a small biotech with few resources. The aim, therefore, was the definition of a strategy that converts the business objectives into a practical framework in a simple but coherent manner [12,15].

The business objectives were very straightforward: increase business opportunities by expanding facility capacity in a cost-effective manner. The existing capacity installed in the facility consisted of two GMP-compliant stainless steel Applikon (Delft, The Netherlands) bioreactors of 30/25 l and 130/100 l total/working volumes; these two MUS are semi-automatic and steaming in place (SIP) and clean in place (CIP) capable [101]. For the CIP operations a mobile CIP skid is used. The two bioreactors have operated very well and continue to provide a quality solution for clinical manufacturing operations. However, in order to support additional operations with EB66, a capacity increase was performed with an additional production suite. After evaluation of the business case, it was decided to install two GMP SUBs; the Pierre Guerin (Mauze, France)/ATMI (CT, USA) Nucleo bioreactors of 25/20 l and 250/200 l total/working volumes [102] were chosen from three different designs by following the project plan and deliverables described in **Table 1**.

Lessons learned from the implementation of the single-use technology

The lessons learned post-implementation review is very important as part of the overall implementation process. For our single-use technology, the lessons learned review was composed of the following elements:

- Key points by type of single-use technology;
- Operational comparisons between MUS and SUS;
- Budgetary comparisons, including annual maintenance costs.

Table 1. Elements of the project plan for the implementation of single-use systems in the Valneva facility.

Subject	Tasking	Deliverables
Stakeholders	Internal and exterior stakeholders identified	All technical and commercial contacts identified and contacted
Strategy	Increase production capacity rapidly without major investment; perform a risk-based evaluation of operating scenarios	Two independent production processes can run in parallel with minimal additional utilities and the existing warehouse and intermediate storage areas are adequate
Feasibility	Availability of suitable technology	Largest SUB compatible with available space; ease of use and campaign changeover
Scoping	CSTR preferred (stirred vessels) over wave rocker mixing	Peer reviews of suppliers and preferred supplier identified
Technical requirements	Technical verification. Confirm that the equipment is suitable for the process and that it will fit with the facility; data mining; compatibility of the film with the cell line	Verification of SUS performance, compatibility with the product and facility and compliance with EU-GMP; collection of the appropriate technical data on the SUS product; appropriate testing of cell growth
Evaluation	Supplier agreeable to equipment evaluation	On-site test with chosen SUS candidate
Planning	Implementation within 12 months as part of a 24-month facility upgrade; supplier flexible and willing to adapt to company strategic priorities	Regular stakeholder review and reporting; compatibility with the budget and operational planning
Materials management	Procurement process and supplier management; SUS quality; waste management addressed	Procurement contracts for the equipment and SUS components; for the SUS supplier, supply chain and maintenance support, an acceptable geographical location of suppliers is essential; Supplier visits and supply and quality agreements to be set in place; compliance with local, national and EU requirements
Training	Deployment, execution and maintenance	On-site support
HSE	Personnel safety at all operational levels	Support for HSE plan
Qualification	Preparation of qualification protocols and manufacturing documentation	Equipment qualification is risk-based and straight forward and completed in a reasonable timeframe
Exploitation	Deployment and productive use	Facility, equipment and consumables ready for productive use in a reliable manner

CSTR: Continuous stirred-tank reactor; HSE: Health, safety and environment; SUB: Single-use bioreactor; SUS: Single-use system.

Here we report principally on the first two elements. The first part concerns key take home points that should be borne in mind for subsequent implementations and are shown in **Table 2** [16]. The contents of this table are not exhaustive but do provide an overview of key issues. The second part considers a comparison between the deployment and exploitation of MUS and SUS bioreactors from an operational perspective and this is shown in **Table 3**. For the budgetary component, it is not possible to disclose full operating costs, but this part has been illustrated with a comparison of maintenance costs.

The lessons learned table provides useful insight into our experiences with SUS implementation. After some problems early in the adoption of single-use technology at Valneva, many potential problems were avoided by an adaptation of the implementation process, particularly with regard to the evaluation of technical requirements and on-site testing whenever possible. These points require a good relationship between the end-user and supplier. Three points where the importance of this approach was beneficial concern the preparation of self-made assemblies, the utilization of single-use bags for indirect impact sampling activities and the communication of appropriate data to the supplier with regard to on-site handling of the SUS. Our experience with the first two points has already been described [12]. The last point concerned a problem of pH and dissolved oxygen probe polymer joints for fixing these probes

Table 2. Implementation of single-use technology: the lessons learned.

Type of SUS	Observation	Remarks
Manifolds, connectors and connection systems	The preference is for procurement of commercially made systems (from vendors or suppliers) rather than self-made systems (i.e., those made on site); training important for sterile connection devices	There can be a significant quality gap between these two alternatives and those who wish to economize by following the self-made route should be careful to address these issues; there is possibility for standardization here
Ready to use media and buffers supplied in SUS	Obtaining adequate technical data regarding the SUS components used for these products is sometimes difficult	This is implementation that has been inherited from someone else; care is required when specifying and agreeing container and connections design
SUBs	Supplier lock-in can be a significant disadvantage from a back-up or dual sourcing perspective	Attention to staff training because of complexity of deployment and the reliability of welds and bag fabric
Filtration systems	Vary from simple depth filtration rigs to more complex TFF systems	Filtration components are often more flexible than for the SUBs in terms of inter-operability; take care with customization which is frequently necessary
Chromatography systems	These are generally the most complex systems and require careful attention to detail during deployment	Make sure the SUS is compatible with the solvents and buffers used
Storage systems	Try to limit the number of different suppliers in order to reduce the supplier qualification burden; customization of SUS can be an arduous experience	Make sure the SUS is compatible with the products stored; attention to extractables and leachables impact when used for sampling; there is possibility for standardization here
All systems	Attention to potential impact of extractables and leachables on cell culture or other process issues; quality of secondary packaging is very variable; the supplier or vendor must have a Change Notification system in place; a SUS is not necessarily ready to use out of the box; avoiding bag ruptures – dialogue with the supplier and on-site training is essential for end users as a risk mitigation factor; attention to system 'integrity' verification	See reference [16]; many suppliers, including custom media, use poor quality or insubstantial final packaging; average procurement and qualification time in our hands is roughly 4 months (down from ~12 months or more for large MUS equipment); ready to use – some process conditioning or other quality-related attributes may be necessary prior to exploitation; availability of appropriate leak testing is important

MUS: Multiple-use system; SUB: Single-use bioreactor; SUS: Single-use system; TFF: Tangential flow filtration.

in a SUB bag. Inadequate exchange of information resulted in an autoclaving process at a temperature too high for the materials concerned. Early experience with the SUB resulted in some bag failures with the stirring mechanism; however, these issues were corrected by the supplier via constructive dialogue and on-site training. Further information about the potential problems with single-use bags and how these have been addressed have also been published [17,18].

Deployment & exploitation: a comparative evaluation of operating efficiencies with SUBs & stainless-steel bioreactors

The comparison between the exploitation of MUS and SUS from an operational perspective is shown in Table 3. A description is shown of the full operational cycle for the exploitation of SUS and MUS bioreactors in a pharmaceutical development setting as carried out at Valneva. The process is based on a simple batch monoclonal antibody upstream process cycle. Note that the times represented in Table 3 are shown with and without the bioprocess segments (seed train and/or the batch culture). A number of conclusions can be drawn and these are summarized in Figure 1.

Considerable productivity gains can be achieved by exploiting SUS over MUS, as illustrated in Figure 1. This enables a much more rapid batch-to-batch turn-around in situations where productivity is important. The data equally illustrate the potential feasibility for efficiency in, or a reduction of, staff overheads when using SUS. These data show the tendency and will assist process modeling to clearly demonstrate such advantages that will be dependent on individual circumstances and process knowledge. An example of such a utility is referenced in

[103]. While we are unable to share capital and most operating expenditures for the SUB project, Table 3 shows the annual maintenance costs for the SUB and MUS bioreactors and the CIP unit required for the MUS. The difference is striking, with the SUB only requiring approximately 25% of the combined annual maintenance costs for the stainless steel bioreactor and its CIP station.

Conclusion

At the time the implementation work was performed, Valneva was a small company. In order to match Valneva's resources with its ability to do the work, the overall philosophy was to maintain a simple and straightforward risk-based approach exploiting the principles in ICH Q9 [104]. In applying the elements in Table 1, the

Table 3. A comparison of process timing for stainless steel and single-use bioreactors.

Step number	Process description	Timing (h and days)		Comments
		MUS† 100/130 l‡	SUS§ 200/250 l‡	
1	Preparation precultures/ seed train	16 days	16 days	This timing excluded from the totals (shown at the end of the table)
2	Clean hold	0	0	MUS – clean and empty/SUS – no bag present
3	CIP flush	5 h	0	For MUS if validated clean hold time is expired
4	Preparation add-on equipment	2 h	1 h	Production support preparation
5	Preparation bioreactor	8 h	2 h	MUS – addition manifolds, valves/SUS – this is the bag deployment and preparation phase
6	Calibration pH probe	2 h	2 h	–
7	SIP	3 h	0	–
8	Medium addition	1 h	1 h	–
9	Hold for stabilization	12 h	12 h	–
10	Calibration DO probe	2 h	2 h	–
11	Preparation and inoculation	3 h	1.5 h	–
12	Cell proliferation and product accumulation	7 days	7 days	This timing excluded from the total (shown at the end of the table)
13	Harvest by TFF	8 h	8 h	This timing excluded from the total (shown at the end of the table)
14	Filter integrity testing	1 h	1 h	–
15	Inactivation (decontamination)	4 h	3 h	SIP for the MUS/SUS – bag removal and autoclaving
16	CIP	16 h	0	–
17	Remove add-on equipment	1 h	0.5 h	Valves, probes and so forth
18	Clean add-on equipment	8 h	0	–
19	Preventive maintenance	8 h	0	–
Total process	–	76 h	26 h	Excludes bioprocess times
Total process	–	10.5 days	8.4 days	Includes bioprocess times except preculture

The principle operations are shown whereby the same process has been operated in both types of vessel, the only difference being the vessels working volumes, which are shown as working/total volumes in litres. Process timings are for information only and are not counted in the comparisons discussed in the text. These bioprocesses are based on a simple batch process of EB66® cells producing a monoclonal antibody.
†Annual maintenance cost of MUS bioreactor: €12,500; annual maintenance cost of CIP: €10,500.
‡Working/total volumes in litres.
§Annual maintenance cost of SUS bioreactor: €6000; annual maintenance cost of CIP: €0.
CIP: Clean in place; DO: Dissolved oxygen; MUS: Multiple-use system; SIP: Steaming in place; SUS: Single-use system; TFF: Tangential flow filtration.

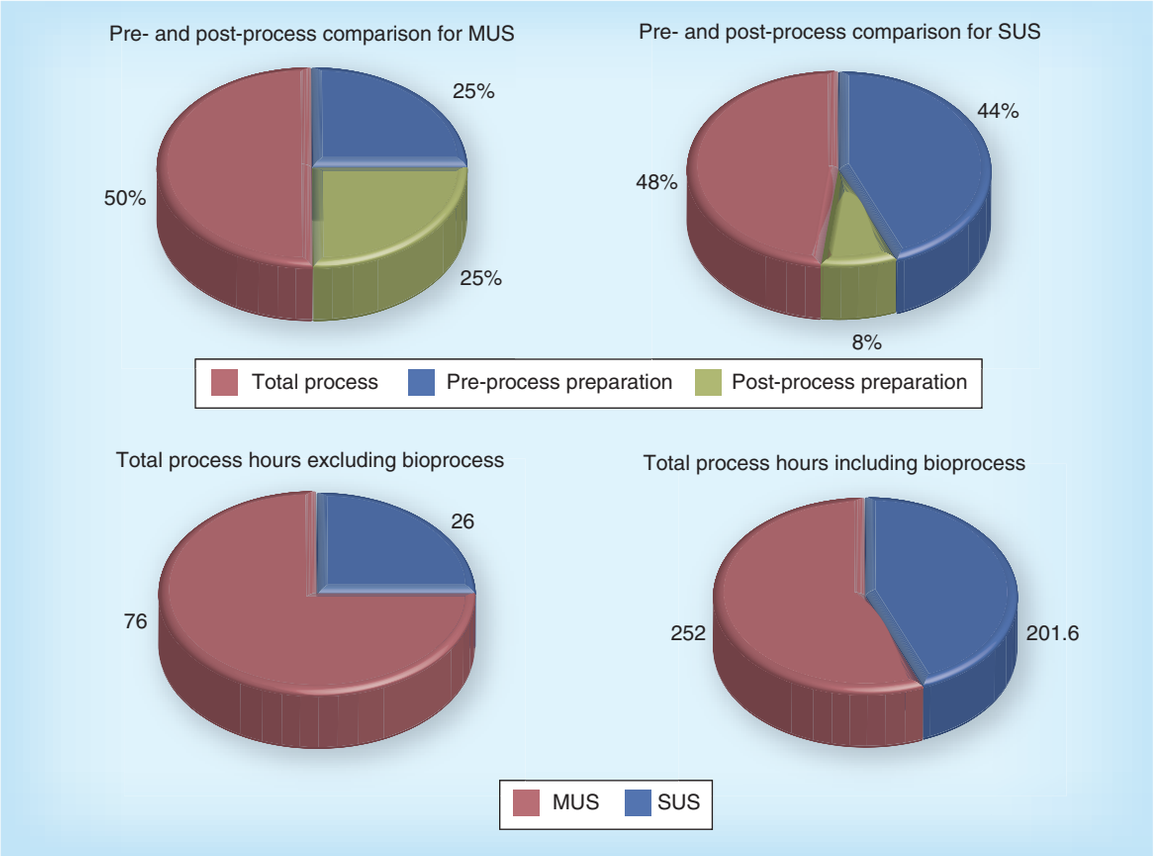

Figure 1. A comparison of single- and multi-use system processing times. Comparison of process times with and without the bioprocess component taken from data shown in **Table 3**. The main impact and benefit from exploiting a SUS is during the pre- and post-operational steps, in particular, the post-process operations are significantly reduced with SUS compared with MUS.
MUS: Multi-use system; SUS: Single-use system.

authors have also worked with industry colleagues, both suppliers and other end-users of SUS to maximize the chances of project success. Experience gained from the implementation of several different types of single-use technology and suppliers is that a structured approach has proved essential to timely and successful project completion; this has also been illustrated by other workers [19–23]. In carrying out many different SUS implementation projects the authors have gained an overall vision of this technology and its advantages and pitfalls as summarized in the lessons learned **Table 2**. It should be emphasized that these observations have been made in the context of a pharmaceutical development environment. Nevertheless, many of these comments will also apply to licensed product situations.

Several organizations are preparing technical guidance on the implementation and exploitation of SUS. More recently, the Parenteral Drug Association (PDA) has prepared a Technical Report on SUS. It is based on a Quality by Design philosophical basis of approach and it makes recommendations for technology choices, business models, qualification and implementation. At the time of writing, the PDA Technical Report is in the final stages of editing and it is highly likely that the recommendations and practices described in this document will significantly impact future industry best practices [24,25].

For some time, the main areas of interest surrounding the use of SUS or MUS have been their economic and technical feasibility and product compatibility, and there are several evaluations available on these topics [12,26–30]. As mentioned in the introduction, as the technology matures, industry focus has now turned towards the exploitation of SUS. The key issues or 'hot topics' have changed and at the time of publication can probably be summarized as follows:

- Extractable and leachables concerns;
- Standardization and adaptability;
- Supplier qualification and supply chain.

Many SUS users begin to understand the inherent complexity of this technology at an early stage. Much attention has been directed towards understanding extractables and leachables. This comes partly from a lack of applicable regulatory texts specifically designed for SUS and partly from the nature of the regulations that do apply. The industry has focused on the nearest equivalents. However, there are now several perfectly good technical guidances or organizations that can provide that help [31,105] and there are cross-industry initiatives ongoing that have a specific aim in bringing industry and regulatory consensus [32,106]. A number of approaches have been published regarding standardization [33] and supplier qualification [34]. Single-use technology cannot be treated and validated like classical MUS such as stainless steel bioreactors; one will never use the SUS that one has validated. This new technology can be exploited in direct-impact scenarios such as bioreactors and filtration systems, but equally in indirect-impact situations such as sampling and quality control operations. In either case, the nature of the materials implies that they should be treated as critical raw materials requiring extensive technical verification and supplier qualification [12,34,35]. The PDA SUS technical report addresses these issues from a Quality-by-Design approach and has named this technical verification process Technical Diligence, which will become an important tool, in parallel to and complementing a quality audit process [12,25,36].

The field of single-use technology still has many evolutionary cycles to come, but has in a very short time illustrated great promise as a technology platform for the 21st century.

Future perspective

Single-use technology now attracts very broad interest within the biopharmaceutical industry and can provide innovative solutions for product development and manufacturing sciences in all parts of the product life cycle. This Special Report has reviewed the importance of a structured implementation process for SUS and illustrated how one of the benefits of the technology can be levered to make a bioprocess more efficient. It is postulated that the utility of this technology will attract a significantly greater market share in the years to come. In particular, suppliers and end-users will have a better understanding of one another, the materials and its complex qualification through the technical diligence process for SUS

Executive summary

Background
- The uptake of single-use technology has become a major business in the biopharmaceutical industry.
- Industry has moved on from considering applications to the full exploitation of single-use systems (SUS).
- SUS have a number of advantages over classical technology, but there are pitfalls.
- Practical examples from the Valneva GMP clinical manufacturing facility.

Defining implementation
- SUS are complex and require careful handling.
- A structured approach can avoid errors and delays.
- Use a project plan and define workflows for development operations with SUS.

Implementation of a single-use bioreactor project
- Elements defining SUS implementation for the project plan.
- Comparison of Applikon stainless steel bioreactors and Pierre Guerin/ATMI single-use bioreactors.

Lessons learned from the implementation of a single-use technology
- A post implementation process review of the experience gained.
- Comparison of process timing between SUSs and multiple-use systems (MUSs).

Deployment & exploitation: a comparative evaluation of operating efficiencies with single-use bioreactors & MUS
- Review of the comparative data.
- Productivity gains by exploiting SUS over MUS.
- Maintenance costs are reduced.

Conclusion & future perspective
- Advantages of a structured approach to implementation for single-use technology.
- The upcoming PDA Technical Report on SUS employs a Quality-by-Design approach and will be an important reference document.
- Current hot topics in the single-use technology field.
- SUS should be treated as critical raw material.
- Appropiate guidance for extractables and leachables.
- Future developments, standardization and technical diligence.

supplier qualification. This will lead to technology that has greater flexibility, ease of use and capacity for standardization.

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References

1 Langer ES. Ten years later: innovation driving single-use technology advances. *BioPharm. Int. Suppl.* 26 (4), 4–8 (2013).

2 Repetto R. Single use systems evolution and innovation. Presented at: *PDA Single Use Systems Workshop*. Bethesda, MD, USA, 22–23 June 2011.

3 Martin J. A brief history of single-use manufacturing. *BioPharm. Int. Suppl.* 25 (11), 5–6 (2011).

4 Shukla AA, Gottschalk U. Single-use disposable technologies for biopharmaceutical manufacturing. *Trends Biotechnol.* 31(3), 147–154 (2013).

5 Mullen B. Late stage development and process validation for single-use systems in biopharmaceutical drug substance manufacturing. Presented at: *PDA Workshop on Single-Use Systems for Pharmaceutical Applications*. Uppsala, Sweden, 29–30 November 2011.

6 Vanersecke F. Single-use technology: an innovative concept of production for an innovative vaccine. Presented at: *The Challenges of Single-Use Technology, Biopractis Workshop.* Nantes, France, 21 April 2013.

7 Tapiwala D. Single-use platform: fujifilm diosynth downstream case study – implementation challenges in manufacturing for accelerated operational flexibility. Presented at: *IBC's 10th Annual Single-Use Applications for Biopharmaceutical Manufacturing.* Durham, NC, USA, 3–4 June 2013.

8 Munk M. Technical Report, section 3 overview. Presented at: *PDA Single Use Systems Workshop*. Bethesda, MD, USA, 22–23 June 2011.

9 Calvosa E. Large scale disposable bioreactor for vaccines manufacturing – applications to anchorage dependent cell line. Presented at: *IBC's 6th International Single-Use Applications for Biopharmaceutical Manufacturing.* CA, USA, 1–3 June 2009.

10 Long I. Facility design and resource optimization for multi-product vaccine manufacturing. Presented at: *PDA Workshop on Single-Use Systems for Pharmaceutical Applications*. Uppsala, Sweden, 29–30 November 2011.

11 Pietrzykowski M, Flanagan W, Pizzi V, Sinclair A, Monge M, Brown A. An environmental life cycle assessment comparison of single use and conventional process technology for the production of monoclonal antibodies. Presented at: *GEHC Disposables LCA Webinar.* Uppsala Sweden, 26 October 2011.

12 Brown S. The challenges of adopting single-use technology. *BioPharm Int. Suppl.* 25 (11) 4–8 (2012).

13 Pluta PL. FDA lifecycle approach to process validation – what, why and how? *J. Valid. Technol.* 17(2) 51–61 (2011).

14 Brown S W, Mehtali M. The Avian EB66(R) cell line, application to vaccines, and therapeutic protein production. *PDA J. Pharm. Sci. Tech.* 64(5), 419–425 (2010).

15 Brown S. A risk-based approach to single use systems selection and implementation for IMP manufacture. Presented at: *Informa Bioproduction, Disposables for Biopharmaceutical Manufacturing.* Barcelona, Spain, 27–28 October 2010.

16 Kline S. The impact of extractables and leachables on cell cultures. Presented at: *IBC's 10th Annual Single-Use Applications for Biopharmaceutical Manufacturing.* Durham, NC, USA, 3–4 June 2013.

17 Bei W. Operational considerations for single-use systems. Presented at: *IBC's 5th Annual Single-Use Applications for Biopharmaceutical Manufacturing.* CA, USA, 2 June 2008.

18 Wong R. Preventing product loss – beyond assembly design. Presented at: *IBC's 10th Annual Single-Use Applications for Biopharmaceutical Manufacturing.* Durham, NC, USA, 3–4 June 2013.

19 Olbrich C, Burkhard A. Selection and implementation of single-use systems (SUS) for clinical trial manufacture. Presented at: *PDA Workshop on Single-Use Systems for Pharmaceutical Applications.* Uppsala, Sweden, 29–30 November 2011.

20 Schreiber B. Hybrid SU facilities – optimizing existing SS facilities & applying SU to create value. Presented at: *IBC's 10th Annual Single-Use Applications for Biopharmaceutical Manufacturing.* Durham, NC, USA, 3–4 June 2013.

21 Restelli M. Single-use technology for a bacterial vaccine production. Presented at: *PDA Europe Workshop on Single-Use Systems for Pharmaceutical Applications.* Milan, Italy, 15–16 January 2013.

22 O'Connor K. Challenges of implementing single-use systems into existing commercial manufacturing facilities. Presented at: *IBC's 10th Annual Single-Use Applications for Biopharmaceutical Manufacturing.* Durham, NC, USA, 3–5 June 2013.

23 Shen K, Van Vu B, Nikunj D, Fluke B, Xue L, Clark DW. Implementing single-use technology in tangential flow filtration systems in clinical manufacturing. *BioPharm International*, 2 November (2010).

24 Repetto R. PDA task force for single use systems. Presented at: *PDA Single Use Systems Workshop*. Bethesda, MD, USA, 22–23 June 2011.

25 Brown S. Technical report section 7 implementation of single-use systems. Presented at: *Single Use Systems Workshop*. Bethesda, MD, USA, 22–23 June 2011.

26 Johnson K. Economic comparison between stainless steel and single-use systems. Presented at: *The World Vaccine Congress*. Washington, DC, USA, 10–13 April 2012.

27 Poles-Lahille A, Richard C, Fisch D *et al*. Comparing fed-batch cell culture performances of stainless steel and disposable bioreactors. *BioPharm International*, 1 January (2011).

28 Diekmann S, Dürr C, Herrmann A, Lindner I, Jozic D. Single use bioreactors for the clinical production of monoclonal antibodies – a study to analyze the performance of a CHO cell line and the quality of the produced monoclonal antibody. *BMC Proc.* 5(Suppl. 8), P103 (2011).

29 Dudziak G. Full Plastics – generic antibody manufacturing using total disposable technology. Presented at: *BioProcess International Conference*. RI, USA, 20–24 September 2010.

30 LaBreck M, Perreault M. An economic analysis of single-use tangential flow filtration for biopharmaceutical applications. *BioPharm International*, 2 November (2010).

31 Morren K. Extractables & leachables. Presented at: *The Challenges of Single-Use Technology, Biopractis Workshop*. Nantes, France, 21 April 2013.

32 Ball D. Establishing threshold levels of extractables & leachables parenteral and ophthalmic drug products – application to single-use manufacture discussion of proposed PQRI qualification plan. Presented at: *Pharma IQ Disposable Solutions for Manufacturing Conference*. Brussels, Belgium, 19–20 February 2013.

33 Kelleher C. Standardization in single use technologies – need for consistency in design. Presented at: *Pharma IQ Disposable Solutions for Manufacturing Conference*. Brussels, Belgium. 19–20 February 2013.

34 Low D. Supplier qualification. Presented at: *PDA Single Use Systems Workshop*. Bethesda, MD, USA, 22–23 June 2011.

35 Rathore AS, Low D. Managing raw materials in the QbD paradigm, Part 1: understanding risks. *BioPharm. Int*. 23 (11), 34–40 (2010).

36 Brown S. Implementation and technical diligence. Presented at: *IBC's 10th Annual Single-Use Applications for Biopharmaceutical Manufacturing*. Durham, NC, USA, 3–4 June 2013.

» Websites

101 Applikon multiple-use stainless steel bioreactor. www.applikon-bio.com/index.php?option=com_content&view=article&id=279:general&catid=65:pilot-plant-systems-steam-in-place&Itemid=299&Itemid=299

102 Pierre Guerin/ATMI nucleo single-use bioreactor. www.atmi.com/ls-assets/pdfs/bioreactors/nucleo/Nucleo%20Brochure_Single%20Pages.pdf

103 Biosolve platform. www.biopharmservices.com/biosolve

104 ICH: Q9 Quality Risk Management (2005). www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

105 Bio-process systems alliance, technical guides. www.bpsalliance.org/ guides.html

106 The extractables and leachables safety information exchange (ELSIE). www.elsiedata.org