

HOW CAN SINGLE-USE BIOPROCESSING TECHNOLOGIES TACKLE CURRENT BOTTLENECKS?

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Traditional systemic administration of chemotherapeutic agents does not differentiate between healthy and diseased tissue. **Antibody-drug conjugates** (ADCs) are highly efficacious drugs with lower side effects than traditional chemotherapies and are produced by linking monoclonal antibodies (mAbs) with cytotoxic, highly-potent, small drug molecules. [1] The cytotoxic payloads of the ADCs are 100 to 1000 times more potent than classical chemotherapy drugs, and thanks to the affinity of the mAbs for antigens, can be delivered with high specificity to targets such as receptors on the surface of tumor cells. [2]

There are approximately 300 ADC candidates between the discovery phase and phase III clinical development. Around 75 of these are being used in approximately 100 clinical trials. The growing importance of this class of drug is illustrated by the fact that between 2014 and 2015 the number of ADC candidates in the drug development pipeline increased 3-fold. [3][4]

The economic significance of ADC drugs is shown by the annual revenues of the two regulatory approved ADC products, *ado-trastuzumab emtansine* (Kadcyla®; Genentech/Roche/Immunogen) and *brentuximab vedotin* (Adcetris®; Seattle Genetics/ Millenium). These generated sales in 2014 of \$540M and \$178M respectively. By 2024 the market for ADC therapies is expected to reach \$10B. [5]. For this revenue projection to be realized consideration must be given to the development, scale-up and validation of suitable ADC manufacturing strategies.

Emerging manufacturing strategies for ADCs

Firstly, conjugation technology is a rapidly evolving field and a variety of conjugation platforms are available. Non-site specific chemical conjugations use the thiols of Cysteine residues and the amines of Lysine residues.

Two commonly used conjugation methods are the *Maytansinoids* and the *Auristatins* platforms. The *Maytansinoids* platform is based on the conjugation of a DM1 or DM4 cytotoxin to the antibody on a Lysine residue while that of *Auristatins* platform is based on the conjugation of a **Monomethyl Auristatin E (MMAE)** cytotoxin on a Cysteine amino acid residue. These non-site specific methods give a relatively heterogenous mixture of *drug-antibody ratios* (DARs), which can lead to variations in potency, toxicity and efficacy.

In order to reduce variations in DAR, developers of ADCs are increasingly interested in site-specific conjugation methods such as *Genentech's Thiomab-drug conjugate* (TDC) platform, which was designed to allow for a more controlled way of ADC construction through genetic engineering and chemistry, or *Innate Pharma's Bacterial Transglutaminase* (BTG) platform, which address the heterogeneity of the coupling between the antibody and the drug of interest, amongst many others. [6]

The conjugation step is a chemical reaction between solutions and can be performed in glass or stainless steel mixing tanks. These vessels allow various parameters such as temperature, agitation and pH to be readily controlled. Once the targeted yield and DAR have been obtained the goal is to purify the ADC drug. Large-scale ultrafiltration systems are often used to perform the concentration and diafiltration of the ADC drug

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About Hélène Panier

Hélène Panier, MSc, is since 10 years involved in biomanufacturing - focusing on the development of innovative processes and businesses. As a result of her close cooperation with market players, she acquired a wide experience in Bioproduction and Implementation of various Business Strategies (Vaccines, mAbs, Biosimilars, CMOs, etc). She joined Sartorius in 2006 as an Application Specialist for PT division in Europe, focusing on DSP process development for various applications, and moved later to Key Account Management where she managed projects in Europe, US and Asia. Hélène is also having a CRO/CMO business development background. Before joining Sartorius she worked for a French CMO, developing their Biopharmaceutical market in Europe. As a Platform Marketing Manager for Antibody-drug conjugates (ADCs) she is in charge of Sartorius' technical and strategic development of the ADC platform. Her aim is to position current technologies and also initiate, follow up and drive R&D projects and collaborations in order to develop innovations that would fulfill ADCs developer and producer needs. Her focus is on single-use technologies, as this is a core competence of Sartorius. Hélène is having a Master in Biochemistry from the University of Nantes (France) and a Master (Ingenieur Dpl) in Biotechnology for ENSTBB, Bordeaux (France)



and remove solvents and unconjugated cytotoxins.

Chromatographic steps based upon the principles of ion-exchange, mixed-mode or hydrophobic interaction can be used to increase the purity of the monomeric isoform and remove high molecular weight species such as antibody aggregates. Further ultrafiltration steps can be required to concentrate the ADC and perform buffer exchanges to ensure it is solubilized within the appropriate solution for storage of the drug substance. Mixing steps ensure the final solution is homogeneous prior to filling into bottle or bag containers that are used for storage of the bulk drug substance. ADC solutions can be stored either in liquid form or frozen, depending on the molecule stability and shipping strategy. Intermediate filtration steps are performed during the purification of ADCs to control levels of bioburden within the drug substance. [7]

Key challenges during the processing of cytotoxic compounds include compliance with Health and Safety regulations, containment to prevent environmental contamination and the validation of the methods used to clean equipment and ensure cross-contamination events do not occur. On the other hand, working with biologics and injectable drugs requires the protection of the product from environmental contaminations and the control of bioburden that could generate endotoxins which can be pyrogenic. To comply with cGMP guidelines processes must be operated under positive pressure in order to protect the product yet **consideration must be given to how operators will be protected** from the product under positive pressure. [8]

Organizations with both the suitable production capacity and the appropriate expertise to be able to process biologics and highly potent APIs are relatively uncommon. Pharmaceutical companies frequently outsource to *Contract Manufacturing Organizations* (CMOs) the production of ADCs for clinical trials.

We estimate that **approximately 70% of batches produced under cGMP are outsourced** to CMOs.

Single-Use Technologies for ADC Manufacturing

Single-use production technologies are commonly used during the manufacturing of biopharmaceuticals. Single-use process platforms have been developed comprising of standardized equipment configurations suitable for entire classes of biologic drugs. [9]

The benefits of single-use technologies include the reduction in upfront capital costs of establishing manufacturing processes and the reduced requirement for utilities such as clean-in-place reagents, water for injections and clean steam for equipment sterilization. They allow greater design flexibility than stainless steel equipment enabling changes to be made in order to select optimum processing configurations during development and scale-up. [10]

The application of single-use technologies to specific ADC processing steps has been described previously. [11] We believe that single-use technology can be applied to all ADC processing steps from conjugation through to final formulation and filling. By doing so, ADC manufacturers can derive all of the benefits generally associated with the technology but can also address the more specific concerns relating to containment and product cross contamination.

Advances in single-use automation limit the number of manual actions operators must perform. Pre-assembled transfer sets minimize connection and disconnection steps thereby limiting the risk of operator exposure to high potency molecules. A characteristic of the technology which makes it especially attractive is that product contact parts are provided pre-sterilized used once and then disposed of. This significantly reduces the risk of cross contamination between either batches of the same product or batches of different products. CMOs often operate multi-product facilities and technology that helps avoid the contamination of one product with another has high utility. A question remaining, however, is how best to dispose of contaminated waste?

Crucially, using single-use technology avoids the difficulties of executing intensive cleaning validation protocols, which are needed to demonstrate the removal of highly potent and hazardous molecules, from product contact surfaces. [12].

The future of ADC production with single-use technologies

Further development work is ongoing to address some of the remaining challenges associated with ADC manufacturing using single-use platforms. The compatibility of plastic components with solvents must be carefully reviewed to ensure complete robustness of the processing solution. Similarly, appropriate analyses of compounds that may leach out of product contact materials must be performed, under the relatively aggressive processing conditions encountered during ADC manufacture.

This work will only enhance the supporting data packages associated with single-use processing technology further facilitating the introduction of completely disposable ADC manufacturing platforms. With these solutions available, producers will benefit from greater flexibility, lower risk of cross contamination and reduction in the time and resources required to complete cleaning validation protocols.

In this way, the speed with which ADCs will be brought to market can be significantly increased and will



About Nick Hutchinson

After completing his Engineering Doctorate in Biochemical Engineering at UCL, Nick Hutchinson performed process development and technology transfer roles at Lonza Biologics in the UK. He has since held positions in product management, strategic marketing and general marketing management. He now works for Sartorius Stedim Biotech where he supports the production of articles and management of technical content.

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support the revenue projections for this important new class of pharmaceuticals.

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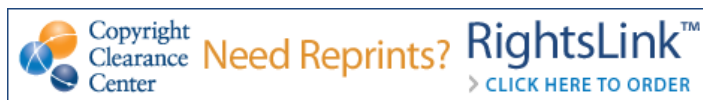
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Disclosures: Hélène Panier, MSc is a Platform Marketing Manager at Sartorius Stedim Biotech.



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