BIOTECH

Technical Regulatory Topic

USTR 3490

Batch Definition and Traceability in Continuous Bioprocessing

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1 Introduction

A continuous manufacture platform operates with interconnected unit operations over an extended amount of time compared to the step-by-step operating approach of a batch process. Defining a batch or lot may therefore not come as naturally and is one of the most frequently asked questions when dealing with continuous processing.

A lot in batch manufacture is typically associated to the upstream bioreactor. The integrated platform however can easily see continuous or continual introduction of raw material from multiple bioreactors, purified seamlessly in the same downstream platform. Additionally, material is not typically held in surge containers between unit operations to the same extent as in batch operation. Material cascades to the following unit operation before all quality attributes have been assessed. A deviation or non-conformity occurring in one step may therefore propagate to the following unit operations before actions can be taken. As such it is essential to understand the rate at which material flows through the cascade of unit operations. To identify and trace material at all times in the dynamic process, establishing the connection between material and batch is a necessity [1].

2 Batch and Lot Definition

Batch definitions given by regulatory authorities do not reference the manufacturing principle and are applicable to both standard batch and continuous processes [2]. The batch definitions as given by the Federal Drug Administration (FDA) and the European Medicines Agency (EMA) are as follows:

FDA: Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture [3].

EMA: A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval [4].

The regulatory framework allows the manufacturer to define a batch using different rationales:

- The batch can be based on a fixed time or set amount of product irrespective of the raw material lots used in the manufacture of the product;
- The batch can be based on time constants of the process, such as the cyclic behavior of multicolumn chromatography or low-pH virus inactivation steps.

When working with time constants it can be meaningful to harmonize the cycle time of several unit operations [1]. It must be considered that the cycle time can vary throughout the process in certain settings, for example in dynamic column loading during chromatography steps. While column loading is generally based on a fixed volume with fixed time, dynamic column loading describes a chromatography column being loaded based on the protein concentration of the upstream feed, or break-through of the column during the load step. With varying product titers from upstream operations and reduced binding capacity of the chromatography adsorbent over time, the load time and hence the cycle time of the chromatography process changes.

With the boundary conditions given by the regulators, it is the responsibility of manufacturers to provide a risk-based rationale for batch and lot definition. A failure mode and effects analysis (FMEA) considers the process risks depending on the chosen batch definition. The smaller the chosen batch size, the lower the impact of a possible batch rejection but the larger the analytical and quality control efforts. An analysis can also determine what part of the product to include in the batch during start up and shutdown of the continuous platform [1].

3 Lot Traceability and Deviation Management

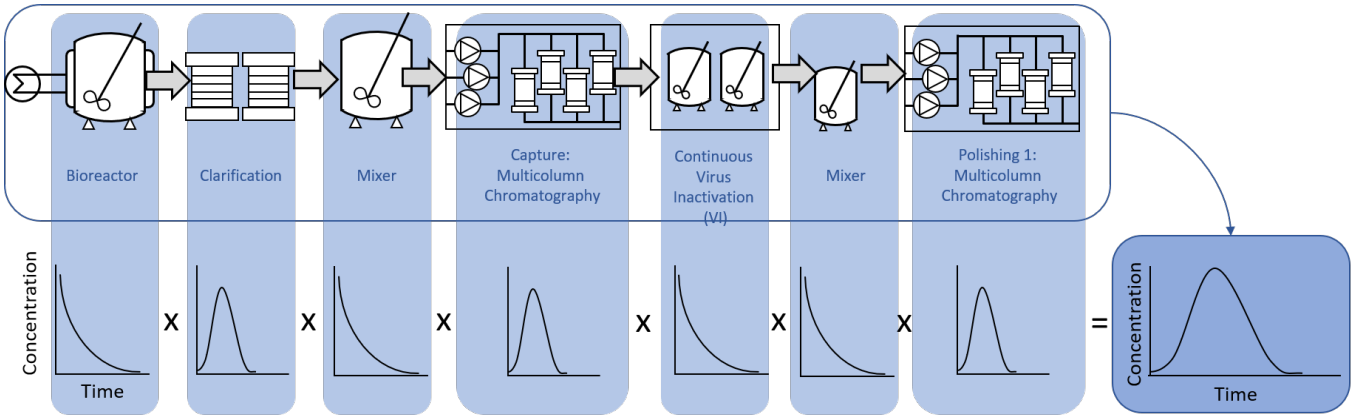
In integrated processing it is essential to understand how fast material propagates through the cascade of unit operations, to allow tracking batches and potential process upsets as they move through the platform. The FDA has asked for a scientific approach to characterize material flow, for example by characterizing the *residence time distribution* (RTD) [2]. The RTD is a probability distribution that allows evaluating propagation velocity and residence time of product or impurities. By characterizing the RTD of each unit operation as well as the combination thereof in the integrated cascade, it is possible to identify product at any stage of the process train. This allows retrospective determination of batches or lots that have been affected by a process deviation or even indicate at what stage of the cascade to isolate or divert product.

An RTD can be determined a) experimentally through tracer experiments where a representative non-reactive tracer is introduced into the system and concentration changes are measured over time, b) through online process monitoring of specific products and their attributes or c) by modeling of process steps [2, 5]. Pulse-response measurements or step changes are visible in characteristic peak shapes which determine back mixing in the unit operation as well as axial dispersion. While RTD has been implemented successfully in continuous manufacture for powder or granulation steps of small-molecule drugs [6], the more complex liquid handling steps in biotechnological processes and the higher susceptibility of substances to changing physical properties, constitutes additional challenges. It is important that the RTD experimental settings represent the full range of planned operating conditions and that it takes variables such as material attributes, flow rates, or equipment operation into consideration [2]. Experimental proof of concept of the RTD approach has been provided by Merck• (US) and Sencar *et al* who demonstrated how material can be virtually tracked in a continuous bioprocess using a model-based RTD approach [7].

A traceability evaluation is conceptually shown in Figure 1. An RTD can be performed on every step of the process as shown in the Figure, it can however also be considered to implement a risk-based approach to reduce the extent of the RTD study. The risk is based on the probability of a process upset and the detection time of a resulting deviation. If performed for single or grouped unit operations, high-risk segments are identified for RTD experiments. Such high-risk areas can include post-use filter integrity test failure e.g. viral or sterile filtration steps, or column fouling and peak-cutting failure in multicolumn chromatography.

Figure 1

Conceptual design of a residence time distribution for part of a continuous processing platform for biologics.



4 References

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