# ReadyToProcess increases facility capacity and shortens change-over time

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# ReadyToProcess increases facility capacity and shortens change-over time

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## Introduction

Contract manufacturers work to tight schedules, producing multi-products on several production lines. Cleaning is a critical element that impinges on valuable production time. CMC Biologics in Denmark has evaluated ReadyToProcess™ as a means of increasing uptime through eliminating some cleaning steps.

The cleaning evaluation study considered the man-hours needed to clean equipment in a production campaign, comparing conventional chromatography systems and columns with products from the ReadyToProcess platform. The evaluation is based on modelling and data from normal routines within the CMC facility. Columns and systems were of comparable dimensions.

## Initial preparation and cleaning procedures using conventional chromatography solutions

When using conventional chromatography solutions, a campaign equipment rationale must be written for all equipment before production can begin. This document provides an evaluation of the predefined acceptance limits to determine whether they are adequate with respect to the total equipment surface area in the campaign, the estimated number of doses to be produced, and the daily dose size for both previous batches and for the planned batch. The risk of product carry-over is calculated, evaluated and also documented in the campaign equipment rationale.

Cleaning processes are implemented as part of the initial preparations for a campaign when equipment is set-up, system inlets and outlets installed, column tube cleaned and packed with media, and HETP testing carried out. It is also included during a campaign, between batches. Cleaning and cleaning validation follow approved protocols and provide proof that equipment is properly clean.

At the end of a campaign a cleaning verification is performed. This involves following a prescribed cleaning protocol that defines the parameters used to verify cleaning. At CMC, these parameters are:

*Rinse samples*
- TOC (Total Organic Carbon)
- Endotoxin
- Bioburden

*Swab samples*
- TOC

*Visual inspection*

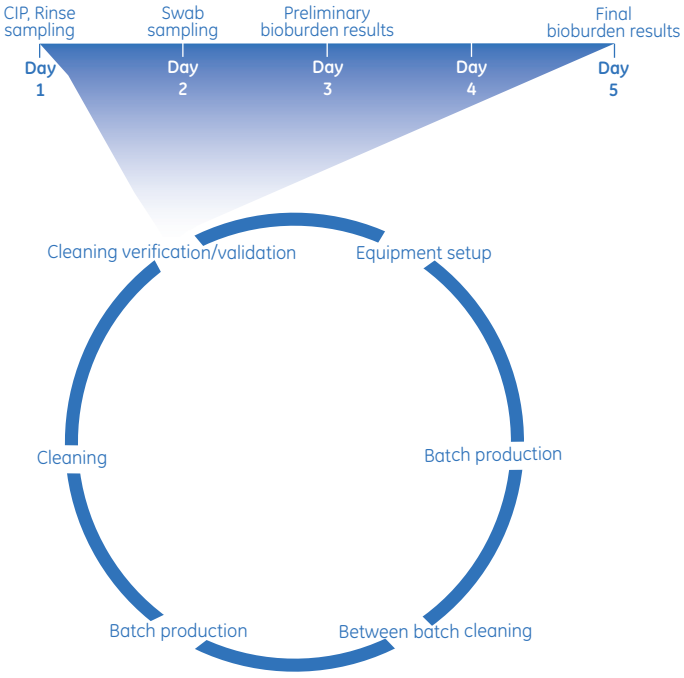


**Figure 1.** Overview of sampling and response times for cleaning results at CMC.

**Table 1.** Steps and time allocated to preparing and cleaning a chromatography system. Note that in this study specific time and costs for preparation of CIP solutions are considered negligible in relation to facility costs.

| Timing | Activity | Estimated time needed | Comment | Step eliminated in a single use process |
|---|---|---|---|---|
| Before use of new equipment | Produce cleaning protocol | 1 day | | ✓ |
| Before start of a campaign | Campagne equipment rationale | 0.5 day | Includes QA review | ✗ |
| Before start of a campaign | Equipment set up | 0.5 day | | ✗ |
| Before start of a campaign | Cleaning before use | 0.5 day | Includes preparation of CIP solutions | ✓ |
| During a campaign | Cleaning in between lots | 1 day | | ✗ |
| After a campaign | Preparation of sampling | 1–2 hours | Training in protocol, wash of sampling glasses | ✓ |
| After a campaign | Cleaning after use | 0.5 day | | ✓ |
| After a campaign | Rinse sampling, drain of system and swab sampling | 1 day | Includes preparation of CIP solutions | ✓ |
| After a campaign | QC assays | 0.5–1 day | Two persons half a day | ✓ |
| After a campaign | Cleaning report | 1 hour | Includes review | ✓ |

The procedure also includes the analytical assays, reviewing results and approving each assay. The bottleneck in the cleaning verification process is the time taken for assay results to be ready. Preliminary bioburden results can be read 3 days after sampling, but a final result is not available until after 5 days (Fig 1).

## Conventional vs single-use

For a production campaign using conventional chromatography equipment, the total time needed to clean a system is 6–7 man days (Table 1) and for a column 5–6 man days (Table 2). However, the equipment is not

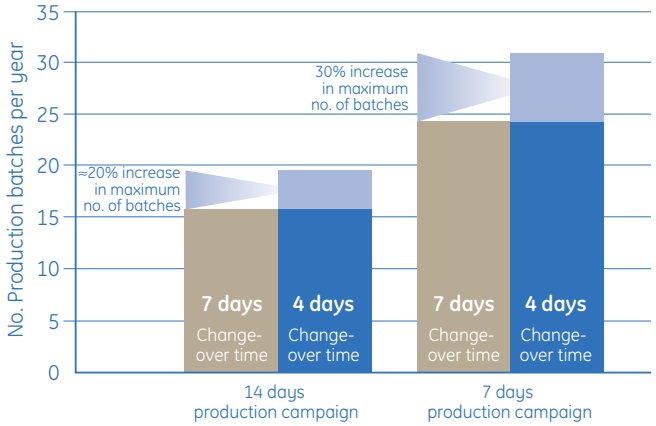


**Figure 2.** Estimated increase in the number of batches in a 14-day and 7-day production campaign schedule with single-use products.

**Table 2.** Steps and time allocated to preparing and cleaning a chromatography column. Note that in this study specific time and costs for preparation of CIP solutions are considered negligible in relation to facility costs.

| Timing | Activity | Estimated time needed | Comment | Step eliminated in a single use process |
|---|---|---|---|---|
| Before use of new equipment | Produce cleaning protocol | 1 day | Only for new equipment The cleaning protocol is reused | ✓ |
| Before start of a campaign | Campagne equipment rationale | 0.5 day | Includes QA review | ✗ |
| Before start of a campaign | Equipment set up | 0.5 day | | ✓ |
| Before start of a campaign | Cleaning before use | 0.5 day | Includes preparation of CIP solutions | ✓ |
| Before start of a campaign | Column packing and HETP test | 1 day | Includes preparation of packing and HETP solutions | ✓ |
| During a campaign | Cleaning in between lots | 0.5 day | | ✗ |
| After a campaign | Preparation of sampling | 1–2 hours | | ✓ |
| After a campaign | Column unpacking, exchange of spare parts etc. | 1 day | Two persons half a day | ✓ |
| After a campaign | Cleaning after use and sampling after use | 1 day | Two persons half a day, includes preparation of CIP solutions | ✗ (Column can be cleaned and stored until batch release) |
| After a campaign | QC assays | 0.5–1 day | Actual depends on if assays for several instuments are run at the same time | ✓ |
| After a campaign | Cleaning report | 1 hour | Includes review | ✓ |

ready for use in another production campaign until the results from the post-campaign cleaning are approved, which is at least 5 facility days after CIP and sampling was done (Fig 1).

The tables do not take into consideration time for handling failed cleanings and deviations. The consequence of a failed cleaning is that time has to be spent on evaluation and follow up of errors. In a worst case scenario, part of the cleaning or QC work may have to be repeated. Extra time for failure is not included in production schedules and can thus affect production capacity. Within the industry, the average failure rate for cleaning is about 10%.

Employing single-use columns and systems offers a number of distinct advantages that save time within a facility. ReadyToProcess columns are pre-packed and pre-sanitized, so there is no need for column packing or cleaning procedures pre- and post-campaign. As a consequence, the risk of a cleaning failure and any subsequent rescheduling of production are avoided, and the amount of documentation and analysis in the cleaning process is reduced. By their nature, single-use products also remove the risk of product cross-contamination.

## Increases capacity by 30%

Removing time-consuming steps with single-use products provides an opportunity to increase production capacity Tables 1&2. For a facility with a 49-week production schedule (3 weeks allocated to maintenance and calibration) and production campaigns of 14 days, eliminating cleaning steps can mean a reduction in change-over from 7 to 4 days, which would give an increase in the number of batches produced per year from 16 to 19. For 7-day production campaigns, the same reduction in change-over time would increase the maximum number of batches per year from 24 to 31, or by 30% (Fig 2).

Single-use products will also benefit multi-product facilities that demand a fast change-over between production campaigns. This is particularly important for facilities where the upstream capacity is larger than the downstream capacity, for example where both microbial fermentation and mammalian cell culture bioreactors deliver harvest to the same downstream production line.

## Faster route to clinic

By eliminating some of the time-consuming steps from a campaign – within initial set-up, cleaning, analysis and documentation – downtime can be turned into uptime and production capacity within a facility increased. In cases where rapid facility change-over is demanded, single-use products will be especially useful. The ReadyToProcess platform will be a good choice for early clinical phases or for potent products. A standard design with fixed column sizes makes the concept valuable for many applications and for a faster route to market.

## ReadyToProcess

The ReadyToProcess platform simplifies and accelerates bioprocessing, reducing upfront investment and shortening development time. The platform has features that effectively eliminate the need to clean, sterilize, or validate multiple-use systems in the manufacturing process. Products are designed to enable lean and responsive biopharmaceutical development and production with assured safety and cost-efficiency, from cell culture and fermentation to purification. The ReadyToProcess platform comprises fluid handling, filtration and chromatography solutions, as well as the WAVE Bioreactor™ and WAVE Mixer™.

## CMC Biologics

CMC is a contract manufacturing organization, with manufacturing facilities in Europe (CMC Biologics A/S) and the USA (CMC ICOS Biologics Inc) offering a wide range of integrated cGMP manufacturing services using microbial fermentation and mammalian cell culture processes. CMC's headquarters are located in Copenhagen, Denmark, part of the Medicon Valley region and its US facility is based in Seattle, WA.
The range of services offered for both mammalian cell culture and microbial fermentation include the following:

- Process development and scale-up of protein processes
- Production of biopharmaceuticals for: pre-clinical, clinical trial phase I, II, III, and market supply
- Consultancy in facility design, quality and regulatory issues
- New technology evaluation
- Analytical Development & Quality Control

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