Bioproduction's transfer and uspscale evaluation on HCPs content

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INTRODUCTION

Many therapeutics are nowadays produced in cellular systems. When biopharma develops these new Biologics, they go through different steps including Bioprocess optimization, with ultimate goal to increase production yield and sometimes they change the production site. However, transferring a bioproduction requires upstream/downstream processes modifications, potentially modifying product purity or efficiency and the Host Cell Proteins (HCPs) content. In this poster, we deployed a MS-based analytical strategy called HCP-PROFILER to characterize HCPs through an upscale bioproduction on a new site and a comparison with a previous GMP batches.

PROBLEMATIC & STRATEGY

Upscaling a bioproduction from Demo to GMP run involved the use of different systems in the USP and in the DSP, especially when the production site was transferred. These modifications can induce a complex phyico-chemical mechanism bias that can have an impact on the final HCPs contained into a drug substance. Here, we deployed a MS-based assay called HCP-PROFILER (Fig. 1), to individually identify and quantify each HCP in a upscaling process.

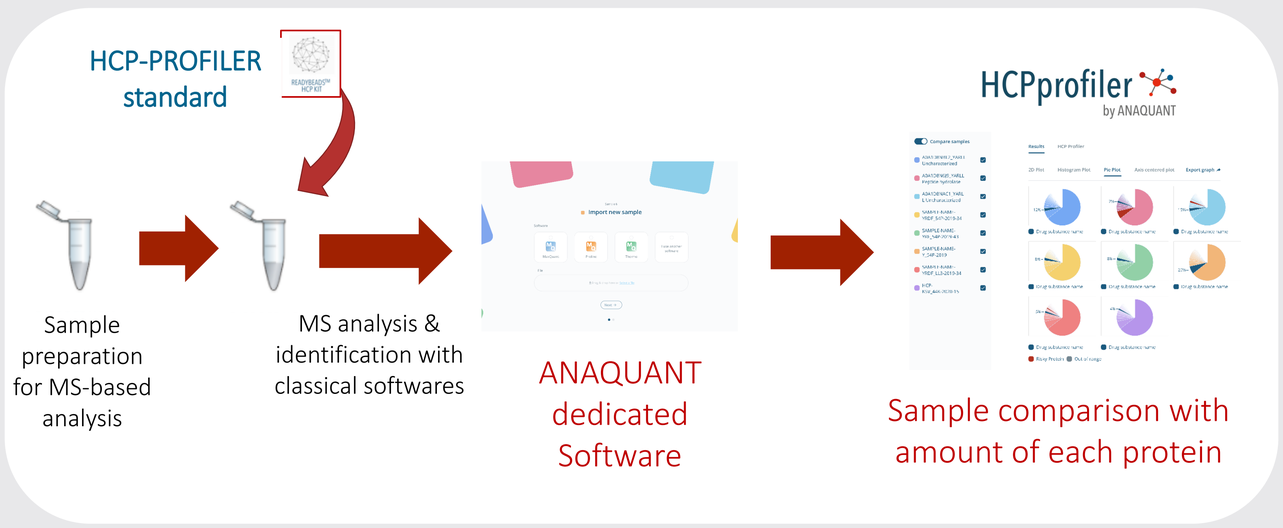

Figure 1: HCP-PROFILER integrated workflow.

This solution is based on an innovative standard relying on a hydro-soluble bead owning an internal calibration curve including several peptides at well-defined concentration levels; and an integrated software for user-friendly data management and viewing. The standard is added into the sample before MS analysis, and calibration curve allows overpassing instrumental variations, to compare batches produced over months.

HCP COMPARISON AT QUALITATIVE LEVEL

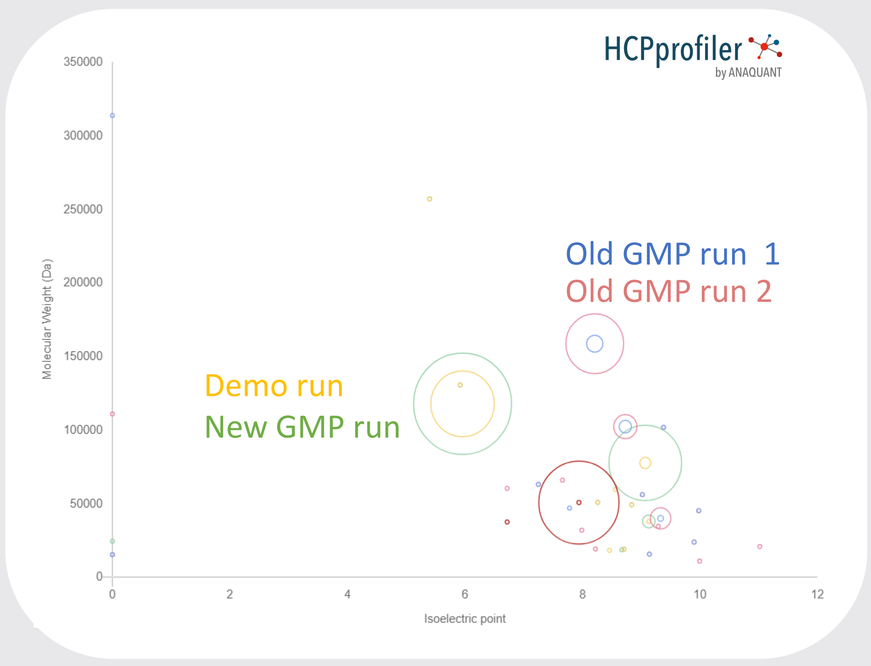

Figure 2: 2D-plot obtained from comparison of identified HCPs in 4 different drug substance batches.

Two sets of data were generated: HCPs from the previous GMP runs and HCPs from the new Demo and GMP runs (Fig. 2). This showed a complete modification of the HCPs with potential impact on the quality, efficiency and safety of the drug substance.

COMPARISON AT QUANTITATIVE LEVEL

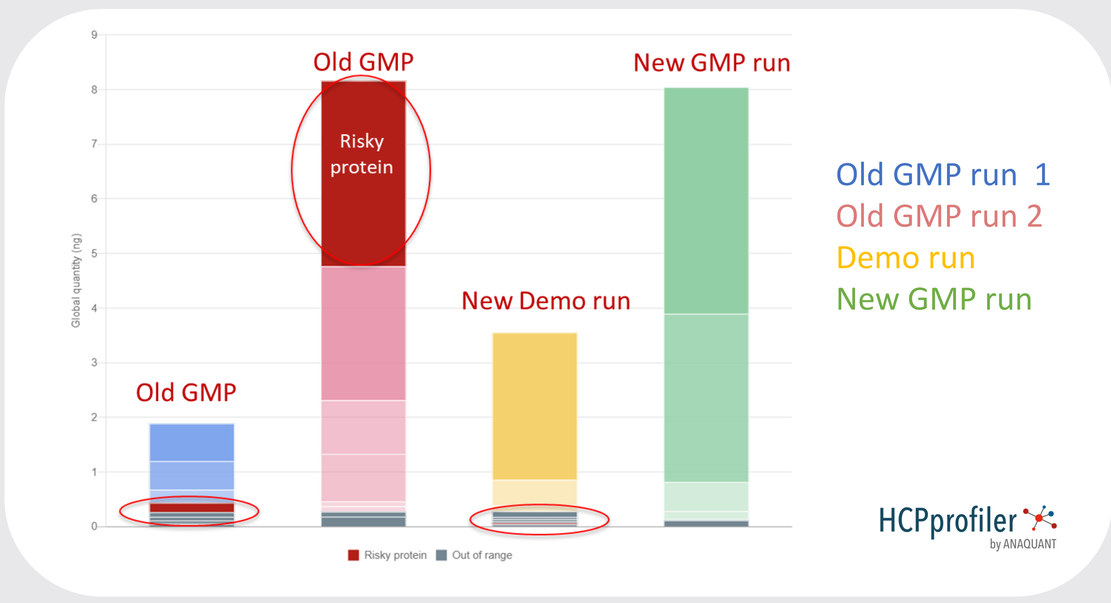

Figure 3: Representative HCP quantities into 4 different DS batches.

At equal drug's quantities injected, it was evaluate that GMP batches from the previous production site contained risky HCPs with endopeptidase activity that could impact the drug efficiency and stability (Fig. 3, Tab.1). Regarding the new production site, only risky ones were detected into the Demo run and none of them in the GMP run despite the fact that there was twice more quantity of HCPs. Then, the new production site would have improved the drug substance efficiency compared to the previous site and also by upscaling the process and an ELISA test could not have highlighted the DSP improvement.

RISKY PROTEIN QUANTIFICATION

Table 1: Quantification of the risky proteins potentially involved in the drug integrity

	Expressed in ppm			
Description	Old GMP run 1	Old GMP run 2	Demo run	New GMP run
endopeptidase	85.0	1699		
Chitinase	6.7			
Peptidyl-prolyl cis-trans isomerase	2.8	18.2	18.9	
sialate O-acetylesterase			8.0	
serine-type endopeptidase			20.6	9.5
Cathepsin L1			10.6	

CONCLUSIONS

HCP-PROFILER integrated workflow allowed both HCPs identification and accurate individual quantities assessment in a bioproduction transferred with an upscaling step evaluation. It demonstrates the heterogeneity of the HCPs according to the site but also according to the production systems. This difference could not have been identified by using standard ELISA kit for the batch comparison.

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REFERENCES:
Silva and al., Mol Cell Prot, 2006 | Trauchessec and al., Proteomics, 2021