Mid-term evaluation

Title of the programme: **New Generation of Biologics**
Acronym of the programme: **BioPharm.Si**
S4 priority area: **Health**

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1 Introduction: basic data on the project and mid-term evaluation

The BioPharm.si programme aims to develop a scale down model of a continuous and integrated biomanufacturing process for production of biologics.

Objectives: Biopharmaceuticals or biologics are among the most sophisticated achievements of life-science and medicine. They offer both high efficacy and reduced side effects. As the programme proposal states, their manufacture, however, is operationally and technologically challenging. Producing large molecules reproducible on an industrial scale requires manufacturing capabilities with a very high level of sophistication. Biologics are produced in genetically modified living cells, that must be carefully selected for productivity and safety, frozen for storage, thawed without damage, and grown to high density in a bioreactor. The biologics, the target molecules, must then be separated from the reproducing cells and the production media, that without changing their biological properties. Relying on such complex processes that would exhibit poor reproducibility is time consuming and expensive. The main objective of the programme is the design and development of continuous processes, affordable products and services that will be highly reproducible, will lower the costs and shorten the time for the development of the biologics.

This was to be achieved by connecting globally recognized companies and interdisciplinary research groups, coming both from the institutes and universities.

Duration of the programme: 2016-2020
Number of partners: 10 (coordinator CO BIK, centre of excellence, 4 industrial partners and two public research institutes and 3 faculties from University of Ljubljana.

The programme is organised in seven R&D projects, focused on (1) genetic markers; (2) process control methods; (3) novel sensors; (4) innovation in bioprocess data analytics; (5) data warehousing to support data-driven production; (6) new approaches in mechanistic modelling, and (7) intelligent bioprocess monitoring and control.

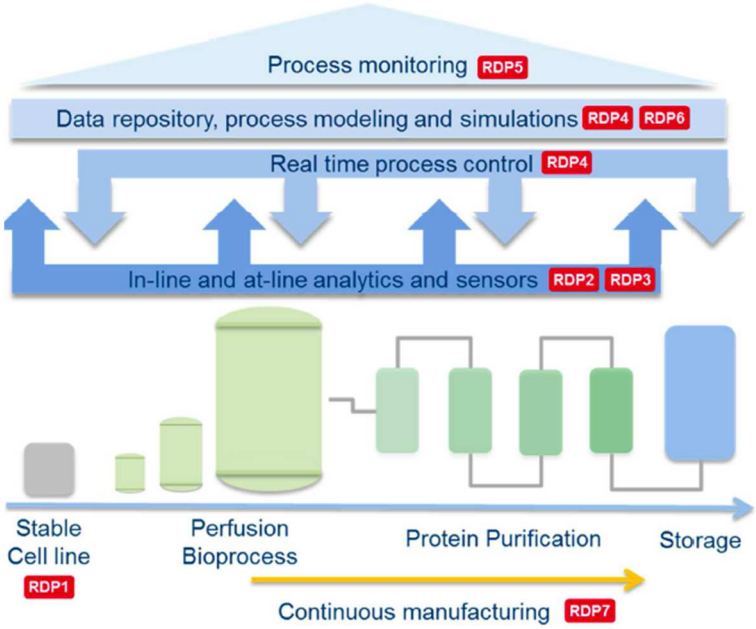
For the purpose of mid-term evaluation, the researchers provided a 23-page progress report. The report followed the organisation of the programme and was therefore structured into 7 RDP and within each of these by individual task. During the on-site evaluation on April 2nd (Ajdovščina, CO BIK premises) and April 3rd (Ljubljana, Faculty of Computer Sciences,

University of Ljubljana), the RDP were presented by the key researchers in power point presentations, which were made available to the evaluator. Also, some of the developed tools were demonstrated.

2 Assessment of the progress made with regard to the objectives outlined in the project proposal of the programme and its research and development projects

2.1 General observations with regard to mid-term report and visit

My comments below are structured according to the presentations given at the meeting.



BioPharm.si was innovative in conceptualizing the structure of a continuous process; in compartmentalizing this structure into the needed elements; in dividing and allocating the elements into RDPs; and in “inhibiting” the RDPs with highly skilled researchers from both academia and private industry.

BioPharm.si is organised into 7 RRPs, and the interplay between these RRPs was clearly outlined in the application, see below.

During the on-site evaluation, the leader of the programme Matjaž Peterka presented an overview of the programme, its aim and progress made till mid-term review.

In particular, he stressed that there are many new potentials for new developments of biologics, e.g. new vaccines. A limiting factor now is use of batch production. The idea in BioPharm.si is development of a continuous process. This will ensure higher productivity, flexibility, and product stability. On the downside has been lack of a regulatory framework and uncertainty about the market demand, but the industry now increasingly sees continuous process manufacturing as the future.

The purpose of BioPharm.si is stated as “development if continuous processes, affordable products and services that will be highly reproducible, will lower the costs and shorten the time for the development of biologics.” While not stated in the purpose it became clear during the meeting that the focus is on processes for production of biosimilars, where an important component is that the biosimilar should be as similar as possible to the original product.

At the meeting, some RDPs were grouped in the presentations in line with the role of the lead partner.

Kristina Gruden thus presented both the RRP 1: Genetic markers as well as RRP3: Cells in biologics manufacturing. Following were the main points of her presentation.

Globally, about 70% of biologics are produced in Chinese Hamster Ovary (CHO) cells. The purpose of these RRPs is therefore to improve procedures for this production. Four goals are addressed:

1) Improve productivity of cells; this involves e.g. better design of parental cell lines; optimizing of transgene insertion into genome.
2) Are the cells alone? Define the metagenome; this is an important topic because possible contamination has been one of the points making governmental agencies reluctant to approve marketing of biologics. It involves e.g. methods for identification of potentially harmful organisms.
3) Decrease the development time of production cell lines. This involves prediction of stability of cell lines.
4) Monitoring the well-being of cells within bioreactors. E.g. Identification of selected genes that can define high producing clones already at day one.

A number of results have been obtained already: Patent (in writing) of best insertion site for transgenes; pipelines for identification of cell culture metagenome and for statistical identification of markers of high productivity; methodology for genome editing of CHO cells; and some toll boxes in preparation.

PAT methods and sensors I (RRP2, RRP 3) were presented by Drago Kuzman:

The methods and sensors concept in the project is focused on process understanding; process monitoring and process control. Essential in these steps are higher throughput and cheaper and more detailed monitoring than used so far in production of biologics. The purpose here is to identify/develop sensors that are cheap, fast, and with high capacity. The purpose is development of biosimilars, and amongst other things the monitoring process therefore aims to ensure that the product is similar to the original, and that safety is preferably better. An innovative development here is a Raman spectrometer for monitoring of glycerol and glucose concentrations in the reaction tank. The future plans include development of novel sensors and methods concepts, and prototype evaluation in real industrial processes.

Additional information on PAT methods and sensors II (RRP2, RRP 3) was given by Matjaž Peterka.

He stressed that a key step here is development of a pressure sensor. The idea is that changes in pressure in a tube can be used to measure thickness of absorbed layer/particle binding in the tube, because the absorbed layers will stop the flow. This is a very innovative idea initiated by CO BIK Centre of Excellence.

Aleš Belič presented RRP5: Information support to new biologics development, which involves development of custom data warehouse to collect and align data from different data

sources, and develop control panels that will allow users to monitor processes to applying state-of-the-art data analytics methods. The data warehouse is built to serve different purposes: modular design; use of free and open software; support flexibility of development environment, allow request of arbitrary composition of data; and accessibility via state-of-the art analytical tools. At present, the researchers in the programme claim that no commercial tool is available to fulfil these requirements, and no suitable data warehouse architecture is available. The building of the data warehouse includes two main tasks; the set up of a data structure, and the entry of data into this structure. The collaboration with Lek is crucial here, because the company has all data sources need to “fill in” the data warehouse such as lab-logs; process read-outs; quality assurance measurements; etc.

The RRP4 consists of innovations in bioprocess data analytics, mainly focusing on development of the analytical tool for use of the data warehouse described above. This tool is called Orange. The data warehouse can be mined to, for instance, identify approaches for optimization of bioprocesses or for development of new biologics. This means that BioPharm.si programme is transforming Slovenian pharma industry into a data driven industry.

The presentations of part of the RR4 and RR5 took place next day in Ljubljana, Faculty of Information Science. Simon Štampar presented intelligent bioprocess monitoring and control, which include several steps in automated bioreactor feeding with adaptive predictive control with the main goal to cultivate CHO cells; to produce biological drugs; and to optimize the process. Another aspect of this is the practical monitoring tools, as user friendly dashboards, data charting facilities, and tools for generation of reports etc. “with just a few mouse clicks”.

The RRP6 consists of new approaches in mechanistic modelling and was presented by Blaž Likozar. The purpose here is to develop a model that can predict what will happen in a production process - so it is a mechanistic model describing the metabolism of the CHO cells. This model can be incorporated into the Orange tool.

Last RRP (7) Continuous manufacturing of Biologics addresses one of the key challenges in production of biologics, which is the limitation in use of batch processes only. It is the goal of BioPharm.si programme to develop a continuous process. This requires establishment of continuous cell cultivation and adjustment of the physiological state of the cells in the reactor. Aleš Podgornik, who presented this RRP, works also with development of continuous production of bacteriophages.

2.2 Key highlights: which achievements stand out

The progress report lists a number of achievements so far: 25 innovations registered; 3 patent applications in preparation; and 9 technology process and organisation solutions registered. It is difficult for an outsider to evaluate to what extent this list fulfils the foreseen plans. It was, however, a clear impression from the presentations that all the researchers have made real progress. An increase in FTEs is recorded.

What was stressed by the research team as a special achievement is the increased commitment of the business partners, who have invested additional funds (11% and 20%)

in the implementation of the programme. This suggests they see the importance of the research and believe in positive outcome.

In spite of the fact that there is still some time till the end of the programme, several new services have already been offered to the global market.

2.3 Changes to the programme

According to the mid-term report as well as deliberations by work package leaders, no significant changes have so far been made. Minor adjustments were made with regard to schedule (few tasks were completed before original schedule).

Additional investment in research equipment is reported in the amount of €1.2 million.

2.4 Work plan till the end of the programme

No changes in the workplan are foreseen, the programme is progressing according to the proposed time-line.

3 Role of the partners in the project

The on-site evaluation revealed smooth cooperation between the partners also because the roles are clearly assigned and well-coordinated.

4 Internal (between the project partners) and external communication

During the on-site evaluation it was mentioned that internal communication runs very smoothly, also because from the start, the RRP coordinators meet regularly every month to review the progress and plan further activities. Less was reported on external communication, except that plans are being made to establish a spin-off.

5 Assessment of dissemination and exploitation of the project results in the phase TRL7-

The research team mentioned that several of their findings are going to be developed further, especially solutions with regard to the already registered solutions and processes and the patents filed.

6 Cooperation between public and private partners (assessment of synergies)

BioPharm.si includes partners from private companies – big and small – from university and from non-university public research institutions.

The many and multifaceted partners seem to have a very nice and smooth collaboration. When asked how this important part of the project was achieved, the researchers answered that Slovenia is a small country where many know each other; and that they deliberately invest a lot of time in monthly status meetings. The aim being that they all knew both their

own and the other partners' work, and that everybody would be able to give an overview of the project. It is my impression also that Matjaž Peterka ensures a very good working atmosphere and coordination.

It is clear that Lek facility-wise is a prerequisite for the project. But given that Lek is also an internationally owned company, there is a risk that the continuous production process once developed is moved from Slovenia to another country. When asked about this, the researchers answered that in this case Slovenia would still have the know-how accumulated in the project and the well-educated people, and that the project would not have had the same development potential without the "real-life-lab" in Lek.

BioPharm.si combines Slovenian skills and opportunities in a very good way. Given that BioPharm.si is partly financed by public money, I could miss a "build in reflection" on the social benefit of the work in the form of one or two researchers from humanities/social sciences. But as this has not been a requirement from the Ministry, this should be taken as a constructive suggestion, and definitely not as a criticism of BioPharm.si.

7 Conclusion and recommendations

BioPharm.si represents an impressive collaboration between academia and private industry in Slovenia. The project is a good example of how progress can be made by an innovative and skilled combination of a small country's competences and resources. There is no doubt that BioPharm.si will bring Slovenia in the forefront of production of biologics.

The project aims for optimizing the process for production of biosimilars, but I imagine that the elements can be used also for development of new biologics. The data warehouse and the Orange-analytical tool must be key elements for design of and simulation of the production process for new biologics.

The BioPharm.si projects represents a good combination of highly creative minds. There seems to be a very friendly atmosphere in the group ensuring free flow of ideas and collaboration, a prerequisite for success in a project like this. I am confident that BioPharm.si will achieve its goals.