## Development of appropriate metrics for the energy intensity in biopharmaceutical production

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The ability to optimise and evolve from a demand side perspective in terms of energy use is becoming increasingly important for manufacturing processes. This is be the focus of this research, which aligns with the European Commission's EU2020 strategy which calls for a highly competitive manufacturing industry in Europe as the basis of a knowledge and innovation-based economy, and with the Irish Government's Innovation 2020 strategy, which seeks to promote research and innovation and in energy, manufacturing and health.

A report by SEAI (Sustainable Energy Authority of Ireland) in 2007 indicated that HVAC (Heating Ventilation and Air Conditioning) can contribute to as much as 80% of the energy consumption on industrial sites. The sites with the largest proportion of energy going to HVAC are those facilities that require clean areas to produce their products. Such facilities are governed by strict (ISO) regulations regarding cleanliness, temperature and humidity control of so called 'cleanrooms'.

The biopharmaceutical industry relies heavily on such facilities, in particular in designated aseptic processing areas where active pharmaceutical ingredients (API) are compounded with excipients (e.g. Water For Injection (WFI)), sterilised and filled in sterile primary packaging (e.g. vials) with or without an accompanying lyophilisation (freeze drying) stage. Such facilities are required because the final product is typically injected (a parenteral) and thus requires to be sterile. Aseptic processing facilities rely heavily on high spec HVAC facilities (utilising High Efficiency Particulate Air (HEPA) filters) to help maintain exacting air quality standards aimed at facilitating the maintenance of sterility. These are thus extremely costly to design and operate (for example, the electricity costs for running a pilot facility at UCC is estimated to cost in the region of €80 per day).

Facilities such as these require meaningful metrics to develop an understanding about the levels of energy consumption associated with providing clean environments. Many sites have traditionally leaned on simplistic 'energy/kg product' metrics, in particular in the production of small molecule (chemically synthesized) pharmaceuticals. However, particularly in the case of large molecule biopharmaceutical production these metrics can be uninformative and of limited meaningful value and are therefore not conducive to securing targeted energy performance improvements. This is particularly true of sites with significant HVAC loads, such as aseptic processing areas of biopharmaceutical production facilities, whereby clean spaces need to be maintained, regardless of the quantity, if any, of product being produced.

This research will endeavour to understand the energy costs of maintaining clean environments and hence develop meaningful metrics to indicate performance in achieving the required standards. It will for example, compare the 'energy/kg product' metric with potentially more meaningful metrics such as 'energy/$m^2$ aseptic area floor space'. It will then consider the use of smart manufacturing approaches (improved measurement and control) to reduce the energy cost of maintaining environments and thereby developing quality and cost effective products.

**Fluidised Bed Granulation; Integrating Micro and Macro scale Analysis.**

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Granulation is an operation that is widely employed in the pharmaceutical sector. One method of achieving the target granule size is by using fluidized beds to agglomerate the fine powder constituents with a sprayed-in liquid binder. Fluidised bed technology offers great versatility but the many combination of operating conditions and configurations plus the large number of interacting sub-processes and material properties, makes understanding and control of the output complex. Control of final granule size, structure and drug uniformity is essential for downstream processing operations such as tableting and a prerequisite for this is a fundamental understanding of the process together with a validated modeling approach. The aim of this project is to carry out experimental trials in fluidized bed agglomeration using the extensive facilities at UCC. Comprehensive physicochemical analysis of input material properties and product (size, shape, porosity, composition, etc.) will be undertaken and related to process and operating conditions. Computer modeling of the process will be carried out to determine predictive strategies to control granule size and its dispersion.

Granulation can be examined at two distinct scales; the micro-scale and macro-scale. At the micro-scale the focus is on the behavior of individual granules in the system and whether a collision yields a coalescence event or not. This is usually analysed by a combination of detailed contact mechanics, liquid binder deposition behavior, binder liquid mass transfer analysis, etc. At the macro-scale the aim is to examine the size evolution (and the dynamic change of any other properties of interest) for the entire population of particles. This is conventionally achieved by Population Balance Modelling (PBM) to generate the output probability density functions for the quantities of interest. The PBM approach requires accurate expressions for the dependence of aggregation rate on time and granule size and the nature of the aggregation kernel.

This project will employ a novel technique to link the micro and macro scale methods. Specifically granulation is decomposed into its three sub-processes by considering that aggregation requires collision between wetted surface of particles having appropriate kinetic energy properties. Expressions for each of these processes can be found from analysis of the fundamental physics provided by micro-scale analysis and these expressions can be configured to provide aggregation rate and kernel for the PBM simulation. Much research has already been conducted in the general area of granulation which provides an ideal opportunity to utilize this critical process further to investigate a variety of novel processing concepts within the pharmaceutical and Biopharmaceutical continuous/modular processing, real time data analytics/pat granulation.

Both Dr. Kevin Cronin and Dr. Ring have long experience in modelling granulation processes and have supervised a variety of research projects in this field. These include work on aggregation of breakfast cereals to obtain improved textural properties, granulation of semolina to improve process efficiency, fundamental studies on granulation physics with model glass bead systems

## Pharma/ Biopharma 4.0 - Factory Of The Future

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The Pharmaceutical and biopharmaceutical industries are facing challenging times, ranging from the emergence of novel biopharmaceutical medicines to the concepts of specialised drugs for smaller patient groups and personalised medicine. The pharma/biopharma industry avails of unique opportunities in manufacturing diversified portfolios of individualised drugs on a smaller scale, but fulfilling these presents a range of ongoing challenges with respect to process robustness and to proving repeatable stability on batch level.

The fourth industrial revolution, namely Industry 4.0, is ongoing, with the characteristics of cyber physical systems (CPS) production, based on heterogeneous data and knowledge integration.(Lu, 2017)

Applying fundamental principles of Industry 4.0 to create a Pharma/Biopharma 4.0 model is a most topical issue as it will be a fundamental enabler to address the challenges of the "personalised medicine" of the future. Information processing needs are complex and require seamless integration with efficient production systems, which implies tackling issues from production agility, process efficiency to enhanced compliance.

The project combines the expertise of Dr Denis Ring, in the area of in pharmaceutical production optimisation and Dr Jorge Oliveira's, extensive experienced in data analysis and modelling. This work will perform an in-depth analysis of the current state of manufacturing technologies employed in the Irish pharma/biopharma sector. Examining the enabling technologies of Industry 4.0 and in what manner, they can be leveraged to provide a template for future manufacturing excellence against a range of metrics, manufacturing agility, continuous processing, real time monitoring, sustainability and factory of the future.

The work envisages a multidisciplinary approach combined with industry liaison for review and advice of the work progression to support the development of the case studies and the applicability of the results.

<u>The work programme outline envisaged is the following:</u>

1 - Assessment of the pharmaceutical manufacturing processes with emphasis on the challenges towards small batch and personalised medicine and use of bioinformatic data in batch production

2 - Assessment of state of the art Industry 4.0 concepts, with emphasis on case studies reviewing the integration of market (consumer) data with industrial assembling processes

3 - Mapping of opportunities by crossing the outcomes of the two assessments (with input from industry liaison)

4 - Review of (digital) enabling systems such as The Industrial Internet of Things (IIoT) and digitalisation applicable to the sector.

5 - Selection of a case studies to develop a prototype Industry 4.0 production platform integrating bioinformatic data with process operation

6 - Development of the prototype optimisation of production and productivity factors and assessment of the results

7 - Selection of opportunities for further work

Lu, Y., 2017. Industry 4.0: A survey on technologies, applications and open research issues. Journal of Industrial Information Integration 6, 1-10.

## Shelf life modelling of microbiome therapeutics

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Microbiome research is one of the most promising areas of research for human health, with many recent developments leading to substantial improvements in treatments available to address various diseases, from chronic conditions to serious illnesses. Greater understanding of the human gut and of its interaction with the immune system, nutrient digestion and various health conditions has led to exciting possibilities for new medicines. One of the earlier applications of "healthy-gut research" has been chronic gut diseases such as Inflammatory Bowel Disease and Inflammatory Bowel Syndrome. The Alimentary Pharmabiotics Centre at UCC was one of the world pioneers in this area, having, amongst other achievements, patented, licensed and commercialised novel medicines currently on the market in various countries, such as Alflorex.

These medicines are live cells that need to be produced and preserved until ingestion by the patients, so they can then modulate their microbiome towards a healthy balance. It is therefore critical that the bioactivity of the probiotic cells is maintained throughout the entire production process as well as storage. Cell viability may however decrease over storage time. Factors influencing their viability over time include processing factors and technologies, as well as intrinsic and extrinsic factors of the package format chosen for the product and storage conditions. Package and storage factors include compositional aspects, pH and water (content and/or activity), external factors (temperature, humidity) and, eventually, the mass transfer process of oxygen and water vapour across the package.

Being able to understand and quantify the loss of cell viability that occurs during storage is key to develop product/package systems that maximise shelf life. The supervisor of this proposal has worked with Alimentary Health for a couple of years, analysing data obtained over extended periods of time with a variety of package formats, applying kinetic models to quantify the loss of cell viability over time (shelf-life). A better understanding of the impact of the various relevant factors will enable much more effective tools for product development and validation, such as accelerated shelf-life testing (whereby the shelf-life of a product at normal storage conditions can be predicted faster by using abuse conditions in tests).

The objective of this project is to analyse existing shelf life data of selected probiotics, identify and then quantify the impact of the relevant factors on shelf life, and thus obtain and validate predictive shelf life models. As there is very limited information for this type of products, the outcome will be of general interest to bioactive modulators in general.

Work programme outline:

1. Review of the accumulated data set of shelf life of probiotics (provided by Alimentary Health), modelling approaches used, model predictors developed and the issues of data analytics involved in the work done to date with various batches and package formats

2. Selection of processing and package factors for further testing and in-depth study of their influence

3. Experimental design and data collection towards accelerated shelf life testing tools

4. Development of the shelf-life predictors as software tools

5. Validation of the software tools with challenge testing (simulated variable and abuse storage conditions)