Digital Twins for Drug Product Design and Manufacture

Creating virtual medicines and medicines manufacturing systems to ensure they are effective and efficient before creating them in the real world

The ADDoPT project has developed and implemented advanced digital design techniques that streamline drug design, development and manufacturing processes

The ADDoPT Vision

The ADDoPT vision is the creation of virtual medicines and medicines manufacturing systems - products and processes - to make sure that they are effective and efficient before creating them in the real world. The key element in the digital design workflow is the creation of a virtual representation or "Digital Twin" of a product or process based upon a mathematical model that predicts its performance. This allows a vastly more efficient and effective design process.

Traditional practice involves an iterative design cycle consisting of building a physical prototype and its real-world testing. Through repetition of the cycle, a workable solution is reached and the product is developed, without knowing whether more robust and/or more efficient solutions exist. In ADDoPT, Digital Twins have been developed on the basis of predictive science (mechanistic models) with data analytics used to address gaps in the mechanistic understanding. Once calibrated, using greatly reduced physical experimentation, these Digital Twins can predict the performance of products or processes across a far greater design space than was used in calibration and with respect to a much wider range of material attributes and process parameters to identify those which are truly critical. Consequently, performance of the Digital Twin can be evaluated without the continual need for the production and testing of a physical prototype (efficiency gains) and robustness can be more comprehensively evaluated and optimised with respect to raw material and physiological variability. Rapid iteration of the digital design test cycle then leads to an optimum virtual product that can be replicated with confidence in the real world. Eliminating the physical make-test cycle is inherently much more efficient in material, time and cost. Our ability to model physical and biophysical properties of tablets such as hardness or bioavailability without making prototype formulations demonstrates the potential of digital approaches to vastly improve the efficiency of drug development.

Benefits to Patients and Industry

Digital design has the potential to significantly improve the speed and efficiency of Pharmaceutical product and process development. This is important given current industry trends.

ADDoPT

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Until now clinical trials have typically been lengthy and are often unsuccessful. The advent of more targeted precision medicines allows for smaller trials and improved chances of success. Whilst in the past clinical development was almost always on the critical path to launch and commercialisation, we are now seeing more examples where development of the commercial product and its manufacturing process are the rate limiting steps on the path to market. The efficiency of Digital Design offers pharmaceutical product and process development groups a way of addressing this emerging challenge.

An implication of Precision Medicines is that more products will need to be developed: better targeted medicines will improve efficacy for specific patient populations but will reduce the size of population that each medicine will serve. In order to meet the needs of the overall population more products will have to be developed overall, and the demands on product and process development groups will increase in an already resource and cost constrained environment. Digital Design offers these groups the opportunity to achieve a step change increase in productivity in order to address this challenge.

The primary benefits of Digital Design are increased speed and efficiency of development however other benefits are apparent over traditional heuristic and purely data driven techniques currently widely used in development to underpin Quality by Design. Digital Design techniques generally need fewer experiments as the scientific knowledge captured in mechanistic models acts as *a priori* information. This leads to experimental and material efficiencies. Additionally, mechanistic modelling techniques allow for a more rigorous assessment of robustness and key sources of quality variability, enabling a more holistic approach to addressing raw material variability. Typically process optimisation work is done with input materials of fixed quality or limited material variability. The use of Digital Design and process modelling allows for an evaluation of the impacts of input product variability on product performance as part of the modelling process.

The benefits of Digital Design to industry flow through to patients in the form of faster access to and enhanced availability of new medicines and better assured supply

From Digital Design to Digital Operations

The fruits of Digital Design will be most fully reaped through an integrated Digital Operations approach to manufacture. Having a calibrated digital twin of the manufacturing system and equipment that identifies and predicts the key relationships between material characteristics, process parameters and product performance allows medicines manufacturers to identify readily the manufacturing and control systems that are needed to assure product quality. Subsequently, the digital twin can streamline process optimisation, accelerate technology transfer and underpin both advanced process monitoring (inferred measurements for quality attributes that cannot be reliably measured in-line or at-line) and model predictive control to ensure the robustness of ongoing manufacture.

The following case studies demonstrate that a shared ambition to achieve step-change improvement in pharmaceutical product and process development has led to examples of improvement that are already bringing real benefits to industry and patients today