The Office of Pharmaceutical Science is advancing manufacturing and regulatory science through research acquisitions. To enhance the Agency's transparency initiative, OPS has developed the below list of all recent acquisitions related to manufacturing and/or regulatory science.

Contract Number: HHSF223200810029C
Development of QbD guidance elements on process design space, scale-up, and process validation

Regulatory Contribution: By utilizing proven scientific principles, this project will facilitate understanding between the FDA and industrial sponsors on the regulatory aspects of process scale-up, design space and validation of three most commonly used unit operations.

Research Approach: Processes that are designed and investigated at a developmental scale must ultimately be translated to a manufacturing scale. However, manufacturing processes are often designed without adequate consideration of scale-up. Scale-up of key operations is accomplished by reliance on extensive experience, experimentation and pilot plant studies due to a lack of fundamental understanding and limited availability of reliable models and scale-up procedures. The goal of this project is to implement and/or refine existing models of three commonly used critical unit operations (fluid bed granulation, fluid bed drying, and high shear granulation) to create design spaces and develop process control based models to predict and facilitate scale-up of pharmaceutical processes directly from the laboratory or pilot plant to the desired scale of manufacturing.

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Contract Number: HHSF223200910416P
Development of QbD guidance elements on process design space, scale-up, and process validation: Influence of the physics of tablet compression

Regulatory Contribution: The research will allow for completing the original project to include tablet compression and stability testing of the compressed tablets under long-term and accelerated conditions to identify influence of various critical variables.

Research Approach: The research will allow verification of all critical variables identified as part of the initial project using a design set of experiments in the DPQR labs and allow for determination of design space across the three unit operations (i.e., mixing, granulation and drying) outlined in the original proposal. The granules obtained at the end of drying phase will be compressed into tablets to evaluate the physics of tablet compression. Stability testing will be performed on these compressed tablets to understand the influence of the critical processing variables and formulation ingredients, on the stability of the finished dosage form.

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Contract Number: HHSF223200930382P
Study on the development of QbD for lyophilized protein parenteral manufacturing processes

Regulatory Contribution: The goal of this project is to develop an understanding of Quality by Design (QbD) approach as applied to the protein parenteral manufacturing processes. In the current proposal, scientists will work collaboratively with the FDA to develop a case study for protein parenteral dosage forms which can form the basis for constructing some of the guidance elements on this subject.

Research Approach: A typical protein API (e.g. glucagon) that is widely available and is representative of many, it not all, of the special issues associated with protein pharmaceuticals will be chosen for this study.

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Contract Number: HHSF223200910289P
In Vivo-in Vitro Correlation (IVIVC): Development of dissolution method strategies with an IVIVC for formulation of poorly soluble compounds

Regulatory Contribution: One of the most difficult aspects of drug development of poorly soluble compounds is the development of appropriate dissolution methods for these systems. In many cases, the parent molecule crystallizes during the dissolution test making the rate of dissolution abnormally slow. Thus, for poorly soluble compounds, dissolution tests are often empirically derived and may have no relationship to product quality. Because of this empiricism, the meaning and significance of dissolution failures is not clear. In such cases achieving quality by design is not possible. Without dissolution methods, formulation design and development is also not possible. Additionally, specifications may not be reflective of product quality or manufacturing reproducibility. For a commercial product, dissolution testing is used primarily to confirm manufacturing and product consistency, to evaluate the quality of the product during its shelf life, and to assess post-approval changes and the need for bio-equivalency studies.

Research Approach: The research will focus on the poorly soluble drug itraconazole. Although there are 4 common approaches to preparing a formulation of poorly soluble drugs with enhanced bioavailability: (1) cocrystals, (2) amorphous forms, (3) salts, and (4) nanocrystals, this project will focus on amorphous forms. This study is aimed at determining the feasibility of an in vitro dissolution method that is reflective of in-vivo performance of amorphous dispersions of itraconazole. The contractor will carry out a model dissolution test development project on itraconazole dispersions. This amorphous dispersion will be scaled-up and then this dispersion will be subjected to a surfactant screen and a solvent screen. The preference is to use a surfactant in water system. The appropriate solvents and surfactants will then be screened for crystallization potential. In this study the solutions produced during the dissolution test will be stirred for 8 hours and

the extent of crystallization measured visually. Amorphous itraconazole without polymers will be used as the control. Various polymers (at least 2) will be screened for their ability to prevent crystallization in an 8 hour test. In this test the solutions after dissolution will be stirred for 8 hours and observed/analyzed for crystallization. The timeframe may be adjusted if needed. The ability of this inhibitor to prevent crystallization at a given concentration (e.g. 10%) will be determined, initially in a simple yes-no test. Amorphous itraconazole will be used as the control.

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Contract Number : HHSF223200910010I
Mammalian cell culture: Application of concepts of PAT and QbD for mammalian cell culture production bioreactor operation utilized for production of human therapeutics

Regulatory Contribution: Quality by Design. As per the ICH Q10 guideline, "Quality by design means designing and developing manufacturing processes during the product development stage to consistently ensure a predefined quality at the end of the manufacturing process". The QbD approach involves identification of the product attributes that are of significant importance to product's safety and/or efficacy (TPP and CQA), design of the process to deliver these attributes; a robust control strategy to ensure consistent process performance; validation and filing of the process demonstrating the effectiveness of the control strategy; and finally, ongoing monitoring to ensure robust process performance over lifecycle of the product. Further, risk assessment and management, raw material management, and use of statistical approaches provide a foundation to these activities. The concept of "design space" is gaining popularity as a tool for implementation of QbD for pharmaceutical products.

Research Approach:
- Pick a biotech molecule, a cell line and a manufacturing process such that there is no intellectual property (IP) concerns in publishing the process and the data. The choice will need to adequately reflect the complexities associated with commercial mammalian cell culture processes.
- Identify the critical quality attributes (CQA) for the product. Utilize literature and industrial experience in doing this. Appropriate risk analysis methodologies will be utilized to perform this step.
- Once the CQAs have been identified, risk analysis tools will be utilized to identify the critical process parameters (CPP). Literature and prior experience with the mammalian cell culture processes will be utilized.
- Perform mechanistic modeling based on the fundamental mass and momentum transfer principles and our knowledge of cell metabolism. Experiments will be performed to provide key input to the model and the revised model will be validated by experiments performed under defined conditions (such as worst case conditions).
- Utilize process understanding gained from the modeling and experimental studies to create adaptive process control strategies and test them via experiments.
- Perform data analysis to propose a design space for the step, process model and optimal adaptive control strategy for the production bioreactor unit operation.

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Contract Number : HHSF223200910010I
Scale-up of lyophilization using dimensionless prediction

Regulatory Contribution: The research will provide a report that evaluates the influence of natural variations in the manufacturing environment on the critical quality attributes of freeze dried products at a laboratory scale. This shall include reference to literature articles that are pivotal to understanding this process.

Research Approach: The contractor shall develop a design of experiment (DOE) to quantify the frequency distribution of product temperatures and primary drying time due to vial heat transfer coefficient, edge vial heat transfer; fill volume and product heat resistance on a laboratory scale. This will include cake thickness variation and nucleation temperature control using modern technique. This DOE will include laboratory and manufacturing scale processes. The contractor shall focus this DOE on the evaluation of temperature variations during processing and the effects on the product's critical quality attributes. This should measure variation within batches and between multiple batches of the model drug. These attributes will include variation in appearance, stability and crystal morphology.

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Funding Opportunity Announcement (FOA) Number : RFA-FD-11-014
Critical Path Manufacturing Sector Research Initiative U01

Federal Register / Vol. 76, No 134/ Wednesday, July 13, 2011 / Notices
[Docket No. FDA-2011-N-0012]

Funding Opportunity Description: The Office of Pharmaceutical Science has conducted research within the academic community through contracts in order to improve the overall manufacturing and quality knowledge base. This research is important to the public sector, because research conducted in pharmaceutical sciences related to product quality is typically kept proprietary.

Development of the Critical Path Manufacturing Sector Initiative has focused attention on the continuing need for this kind of research in a way that can improve reliability of pharmaceutical product manufacturing and quality across the entire industry. This shared knowledge will increase the likelihood of successful manufacturing.

The grant will support programs and research as described below, related to the manufacturing of drugs, biological products and medical devices:

Education and training in the field of manufacturing and scale up, for product development partnerships, academic scientists, other product developers and product application reviewers.

Development of platform strategies and standardized approaches for medical product manufacturing to shorten timelines for manufacturers to produce quality medical products at commercial scale. This will provide publicly available models for manufacturing and scale up that will help enable small firms to expeditiously market important treatments.

Development of analytical methodologies and advanced computational methodologies to better characterize complex molecules and complex mixtures of molecules is needed to better understand and control manufacturing processes and product quality. Specific analytical techniques will better enable standardized approaches to manufacturing control and advance computational technologies will help to identify atypical samples of complex molecules. These advances will help assure pharmaceutical quality for the American public.

Research into improved techniques for collection and analysis of process data to control processes and to ensure that they are in statistical control will be done. This includes science-based flexible and adaptive approaches to manufacturing utilizing feed forward and feed backward information flow. Standardized approaches to assuring product quality using manufacturing and analytical data will support continued product quality and lessen manufacturing failures thus decreasing shortages of medically necessary products.

Development of techniques for assuring product quality using surrogates for desired clinical results will improve understanding of quality target product profile (QTPP). This approach takes advantage of the potential to use existing clinical data to determine clinically relevant specifications including unit to unit variability, drug dissolution and other material or product attributes and to support future manufacturing improvements while maintaining product quality.

Creating simulation models for manufacturing techniques including (but not limited to): biotech fermentation and cell culture, small molecule crystallization, freeze drying techniques, precision tablet coating will enhance industry knowledge. These models will enable a more predictable approach to manufacturing development and design of control systems. This predictability will shorten the critical path pipeline from laboratory to clinic and support continual improvement to achieve product quality of the drug's lifecycle.

Creating simulation models for complex drug delivery devices such as dry product inhalers, transdermal patches and liposomal products to better understand the product design and performance and to control the critical manufacturing parameters. These models will aid to speed the development of novel dosage forms and decrease the failure rates of these products.

Research into product formulation for special patient populations or product formulation to ensure chemical stability of active ingredients will shorten formulation development and thus, the critical path pipeline. This research does not require clinical nor animal

studies. Instead, it will lead to the creation of materials with physical properties in materials that have been previously identified as being desirable.

Physical characteristics of active ingredients and excipients in drug products, such as crystal morphology, co-crystal technology, dispersions and particle sizing including nano-technology are not fully developed in the public sector. This work will develop technology enabling control of these attributes. This will provide another dimension of control to the predictability of pharmaceutical products. This added control will enable new approaches to manufacturing novel dosage forms and shorten the time it takes to develop manufacturing processes and controls.

Development of specialized manufacturing techniques suitable for products administered in low dosages and for products with high toxicity or narrow therapeutic ranges. This will enable more rapid development of manufacturing techniques for these products.

Development of models for manufacturing and engineering of device products such as infusion pumps, prosthetic organs, defibrillators, tissue engineering devices, and combination products will help standardize the approach for bringing these medical products to market. This includes development of components for more reliable delivery of pharmaceuticals to the most desirable site of action, for example, controlling the air plume of inhaled products. This will shorten the time required to move such products from concept to patient and thereby shorten the Industrialization sector of the Critical Path.

Research into methods for laboratory synthesis of molecules that have been designed by computer simulation will shorten medical product development time. These methods will make the creation of these molecules more predictable. These technologies will also enable new drug discoveries to be brought to market faster with less variability, higher predictability of performance.

Approaches to improve facilities where this research will be conducted. Advanced technology development can be accelerated by better design of the facilities where this research is conducted. Creating and making these designs public will have the effect of accelerating technology across the industry. This will shorten the time it takes to bring these advanced technologies into the product manufacturing sector.