4th FDA/PQRI Conference on Advancing Product Quality Breakout Summaries

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PQRI
Product Quality Research Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

TRACK 3: NOVEL MANUFACTURING TECHNOLOGIES AND CHALLENGES FOR THE PRODUCTION OF PATIENT-CENTRIC DRUG PRODUCTS

Session 1: Novel Manufacturing Technologies and Challenges for Cell and Gene Therapies

Moderator: Michael Skidmore, Pharmaceutical Quality Consulting, Inc.

Speakers: Ramjay Vatsan, FDA

Palani Palaniappan, Sarepta Therapeutics

Michael Havert, bluebird bio

Presentations

1. Regulatory Expectations for Cell and Gene Therapies

   Ramjay Vatsan, FDA

2. Manufacturing and Validation Challenges

   Palani Palaniappan, Sarepta Therapeutics

3. Testing Strategies for Ex-vivo Gene Therapies

   Michael Havert, bluebird bio

Track 3 Session 1
Background/Premise/Challenges

- In the last six years, there has been an exponential increase in the number of cell and gene therapies developed and submitted to FDA for IND. Most significant growth in AAV and Lentiviral-based products.
- Cell and Gene Therapies pose unique challenges from a regulatory, development, and manufacturing perspective.
- Unlike more traditional formulations (small molecules and large peptides), there is frequently very little distinction between drug product and drug substance.
- CMC is often rate limiting step in bringing therapy to market.
- Other challenges include industrializing CGT, which are often developed in academic laboratories that use techniques that aren't scalable and adapting manufacturing processes to meet demand.
    - i.e. Multiple T-250 flasks to produce AAV or IV bags from apheresis then used to culture T cells and wash to produce a CAR-T

Key Points from Talk #1 Ramjay Vatson (FDA)

Regulatory Expectations for Cell and Gene Therapies

- In progressing from early to late phase in IND application process, Cell and Gene Therapy (CGT) sponsors must demonstrate sufficient control in manufacturing processes and take into account testing requirements unique to product, vector, and cell substrate.
- Early Stage Expectations - focuses on safety
  - Specification strategy should be broad and multi-parameter. Develop assays for product safety, identify, purity, and potency (quantitative) and qualify (sensitivity and specificity). Set acceptance criteria.
- Late Stage Expectations - focuses on advanced product characterization
  - By Phase II, should have robust product characterization and be cGMP compliant.
  - By Phase III should have sufficient experience to ensure tight control of product quality and consistency:
    - Narrow acceptance limits, Establish quality criteria, Define CPPs, Develop a validated and *biologically relevant* potency assay that quantifies the product's biological activity

Key Points from Talk #1 Ramjay Vatson (FDA)

Regulatory Expectations for Cell and Gene Therapies

- Several Gene Therapy (GT)-specific draft guidances released in last 9 months, the following are key highlights:
  - CMC Information for Human GT INDs
    - Viral vectors for GT categorized as Critical Manufacturing Components – subject to GMPs, process and method validation, and inspection during BLA review
    - Revised recommendations for cell bank selection, impurity testing, residual DNA testing, qualification of dose-determining assays, plasmids etc.
  - Testing for replication competent retrovirus-based GT
    - Revised recommendations for testing working cell banks for retroviral producer cells (should demonstrate <1 RCR per dose)
  - Long Term Follow-Up (LTFU) with Patients
    - How do you follow-up with patient after product has been approved
    - Updated preclinical evaluations for assessing risk of GT
  - Additionally: Guidances (3) on gene therapy products intended for treatment of Hemophilia, Retinal Disorders, and Rare Diseases
  - Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Feb 2019

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Key Points from Talk #2 Palani Palaniappan (Sarepta)

Setting the Standard in Gene Therapy Manufacturing

- Safety and efficacy of GT depends on each step in the production process and its effectiveness in preventing introduction or removing impurities
- AAV Production – Key Considerations & Major Challenges at Each Phase : Potency / Biological Activity is often impacted by scaling
  - Upstream Process
    - Must convert to scalable process and establish comparability before proceed to Phase I studies
    - Scaling up from 2D processes requires extensive optimization (e.g. hyperstack to iCellis 500 or cell suspension) For commercial production 2000L batches needed
  - Downstream Process
    - Current state is a sequential series of chromatography columns and TFF
    - Separation of incomplete viral particles is a significant challenge for AAV producers..
    - With current capabilities, impurity removal depletes product yield.

Key Points from Talk #3 Michael Havert (Bluebird Bio)

Testing Strategies for Ex-vivo Gene Therapies

Co-authored 2018 OTAT Guidances and dove deeper into details as well as providing a assay development timeline to support regulatory strategy and sponsor/ agency meetings

- **Safety tests** (compendial or platforms specific tests) and dose assays need to be established and qualified before for first-in-human studies
- Include sterility (bioburden), purity (mycoplasma), vector copy number, and PCR-based methods for detection of replication competent retroviruses. These tests are **often commercially available**
- **Product specific tests** (potency , impurity profiles, dose (number of genetically modified cells)). Can be developed during later clinical studies and will likely have to be **developed in-house for each product**, optimized, and qualified before BLA
- Use Established Reference Standards Materials to control for assay variability between labs and qualify in-house reference standards
  - Two available from AATC - one for retrovirus and one for lentivirus- Valuable for establishing reference standards for quantifying virus particles, genomic copies, and infectious titer (IU). Copy number in development.

Panel Discussion and Q&As

- Consideration for optimization and qualification of product specific characterization tests, such as potency, using patient materials.
  - Q: What approaches have you seen sponsors use for validating an assay using patient material, particularly when there are concerns with variability and limited samples?
  - A: Source material with a high likelihood of variability should not be used in assay qualification.
  - Q: What would be the appropriate cells to qualify the manufacturing process with? What is the comparability between Phase I and Phase III material and test results?
  - A: Recommended taking source material from registered sites and setting acceptance limits for the use of cells for further manufacture. Also recommended to evaluate at least one of two patient samples in addition to materials from healthy donors to demonstrate that the manufacturing process is capable of delivering desired product.
- It must be challenging to control for microbial contamination particularly when using patient cells, viruses, etc.
  - This isn't a concern unique to GT and not the first time drug developers as well as regulators have dealt with this issue – biologics are also at risk of the same kinds of contamination. Methods such as sterile filtration are not possible or amenable with GT. For some GT products it is not possible to completely sterilize the product, particularly since they contain living cells. FDA/CBER recommends taking a QbD approach and using rapid microbial assays as well as PCR-based assays at multiple points in production. Sponsors are however having to design best approaches to Aseptic Process Simulation for CAR-T and large production issues
- Q: Has Sarepta started to explore how they are going to move away from hyperstacks into a process design more robust / seamless aseptic process simulation?
  - A: Yes, starting to look at iCellis but validation is an ongoing process and there are other challenges in ensuring sterility of a large scale facility.

Overall Conclusions

- The recent guidances provide a strong platform for Cellular and Gene Therapy products and clarify how to file a CGT product in eCTD format.
- There are now 6 approaches for Accelerated Approval addressing patient demands for rapid access to new treatments and FDA mission to simplify approval process by providing transparency and additional rolling feedback
- Sponsors are co-developing processes with equipment manufacturers to address CGT unique needs with an eye to QbD
- Cell and Gene Therapy Guidance documents: https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/default.htm
- OTAT Learn Webinar Series: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

Session 2: Implementation and Regulatory Impact of Continuous Manufacturing, Part I

Moderator: Bob Meyer, Merck

Speakers: Cenk Undey, Amgen

Celia Cruz on behalf of Thomas O'Connor, FDA

Thomas De Beer, Ghent University, Belgium

Presentations

1. In Silico Modeling Approaches Towards Robust Design, Specification Setting and Establishing Control Strategies - Bio/Pharma Industry Perspective

   Cenk Undey, Amgen

2. Use of Computational Modeling in Specification Setting and Establishing Control Strategy – Regulatory Perspective

   Celia Cruz on behalf of Thomas O'Connor, FDA

3. PAT for Model Based Design, Optimization, Monitoring and Control of Continuous Manufacturing

   Thomas De Beer, Ghent University, Belgium

Session Background

Definitions & Reasons for Application Aren't Uniformly Understood

- Batch processing follows the path *load, transform, unload* → materials changed over time
- Continuous manufacturing (CM) is defined by *simultaneous flow into and out of a system* → materials changed over space dimension
- Many hybrid systems exist that blur the lines, e.g. fed-batch bioreactors

CM is touching on all aspects of pharmaceutical & biopharmaceutical manufacturing, e.g.

- Small molecule API synthesis and drug product manufacturing
- Large molecule bioreactors, separations and fill/finish operations

Landscape is maturing

- Academics developing new technologies and licensing to industry
- Established and new vendors expanding the available options
- Five approvals within US for drug products produced by CM, many with approvals in multiple international markets

Health Authority *draft* guidance documents are shaping adoption

- May 2018: PMDA's Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry
- Feb 2019: FDA's Quality Considerations for Continuous Manufacturing, Guidance for Industry
- Nov 2021: ICH Q13 Continuous Manufacturing for Drug Substances and Drug Products
- Seek to strike balance of supporting adoption through guidance, without hindering innovation

Key Points from Talk #1 - Cenk Undey (Amgen)

In Silico Modeling Approaches Towards Robust Design, Specification Setting and Establishing Control Strategies - Bio/Pharma Industry Perspective

- *In silico* modeling has significant potential to increase speed and efficiencies of process and product development, as well as later in the product life cycle
  - Calibration and validation via small number of targeted experiments
  - Obtain a richer characterization of the robust design space
  - Enable next-generation process monitoring and control applications
- Advances in computational power and scientific understanding are enabling more modeling
- PAT complements model development through data for validation and control strategy application
- Many types of models are being applied, e.g.
  - First principles based models are often preferred
  - Statistical / regression models widely applied
  - Artificial Intelligence and Machine Learning-based *in silico* models are emerging
- Application areas span a wide spectrum of products and processes, from ultrafiltration and vial filling to predictive control of bioreactors

Key Points from Talk #2 – Celia Cruz (FDA)

Perspective on the Validation of Computational Models for Establishing Control Strategies

- In QbD framework, mathematical models can be utilized at every stage of product development and manufacturing
- Predictive models have been implemented for developing and controlling processes
- In the future, computer-generated data may reach the same level as animal and human-based data.
- The regulatory framework for validation of computational models (i.e. control strategy) comes predominantly from CDRH
- FDA Modeling and Simulation Working group has over 200 members across all Centers whose focus is to apply modeling and simulation to support decision making
- The aim is to create guidance that will apply to various models, not just one analytical tool, and FDA is moving away from that approach, when possible
  - Generally, ICH Points to Consider document on low, medium and high impact models has some limitations
  - NIR guidance is an example of regulatory guidance on a very specific model
  - Ten "Not So Simple" Rules for Credible Application of Modeling & Simulation in Healthcare provided as a informative guide
- An excellent reference is ASME's Verification & Validation Standard #40 *Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices*
  - The concepts of this framework could be more broadly applicable including process models even thought it is for devices
  - ASME V&V40 guide outlines a process for making risk-informed determinations as to whether M&S is credible for decision-making for a specified context of use

Key Points from Talk #3 Thomas De Beer (Ghent University)

PAT for Model Based Design, Optimization, Monitoring and Control of Continuous Manufacturing

- Manufacturing innovation is crucial for the future of the industry, which can be realized with **model-based design** of **flexible manufacturing equipment**
- Described three case studies of this model-based design approach:
  1. Continuous Tablet manufacturing via Twin Screw Wet Granulation (TSWG)
     - Used population balance modelling to develop mechanistic understanding of functional role of individual screw elements during TSWG
     - Application of signal processing tools to develop models and apply control strategy
  2. Pharmaceutical Suspension Manufacturing
     - Used CFD model to optimize NIR spectroscopy implementation for in-line assay monitoring of a pharmaceutical suspension
  3. Continuous Freeze Drying
     - Re-designed pharmaceutical batch freeze drying tool, which was previously costly, time consuming, uncontrolled, and inflexible.
     - Used thermal imaging as PAT to develop and validate drying process
     - Working with partners to scale up process

Panel Discussion and Q&As

Q: For Dr. Cruz, how is it possible that we could accept equally as much modeling data as animal and human data?

A: You always need the data to validate the model however the purpose of the model is to test more conditions than you can feasible test in the lab.

Q: For all panelists, could you each speak to the academic and industry perspectives on moving these technologies into contract manufacturing organizations and other industries?

A: (De Beer) From the academic standpoint, we need to train the next generation of scientists in a interdisciplinary fashion (pharmacy and engineering) so they can appreciate the connections and contribute to the field.

A: (Undey) From pharma perspective, the agreements with CROs is a key point to introduce these terms and specify use of computational models however, you need to overcome the IP concerns.

A: (Cruz) From FDA's perspective, CDRH may have more to say on this matter since they have historically more advances in this field and have already started to apply AI, including one approved marketing application for diabetic retinopathy.

Overall Conclusions

- Patient-centric manufacturing requires novel manufacturing technologies, and novel tools to more rapidly develop those technologies
- Continuous manufacturing has taken hold as a potent complement to traditional batch manufacturing
  - CM broadens the array of available process options, but is not expected to fully replace batch manufacturing
- Digitalization, next-gen PAT and modeling are becoming easier to apply with advances in software, hardware and networks
  - Modeling of products and processes is emerging as a necessary and powerful tool for advancing novel manufacturing technologies
  - Integration of data across different data sources amplifies benefits
  - Guidance for verification and validation of models is most advanced in the medical device arena, e.g. ASME V&V 40 standard

SESSION 3: IMPLEMENTATION AND REGULATORY IMPACT OF CONTINUOUS MANUFACTURING (PART II)

Moderator: Pramod Kotwal, Merck

Speakers: Art Hewig, Amgen

Paul Collins, Eli Lilly and Company

Sharmista Chatterjee, FDA

Presentations

1. Transforming Biopharmaceutical Production Through the Deployment of Next Generation Manufacturing:

   Opportunities and Challenges

   Arthur Hewig, Ph.D., Amgen

2. Continuous Manufacturing- Framing a Future for Patients

   Paul Collins, Ph.D., Eli Lilly and Company

3. Novel Technologies to Support Patient Centric Drug Product Development: FDA Perspectives

   Sharmista Chatterjee, Ph.D., FDA

Session Background/Premise/Challenges

Focus: Patient Centricity and Biopharma Manufacturing Transformation

- Meet today's challenges/business needs with a focus on Continuous Manufacturing
- Change in paradigm from high volume blockbusters to low volume products in the pipeline
- Variety of specialty drugs (diverse portfolio) and personalized medicine
- Biopharma manufacturing needs to be nimble to meet fluctuating demand, requires easier customization and support speed to market
- High degree of automation with PAT to assure continued supply of high quality drugs at lower cost to patients
- Success stories of commercial implementation of Continuous Manufacturing – testament to great collaboration between industry, agency and academia

Challenges- global acceptance, submission requirements, PQS updates

Key Points from Talk #1 – Art Herwig (Amgen)

Transforming Biopharmaceutical Production Through the Deployment of Next Generation Manufacturing: Opportunities and Challenges

- The changing business landscape is requiring agility, flexibility, modularity, and dematerialization of biomanufacturing networks.
- A 'Biology First' strategy is driving a significant increase in the number of modalities being pursued.
- Portfolio diversity, increased competition, and uncertainty will continue to challenge the industry to adapt to deliver the following:
  - *Product heterogeneity* – maintain modality independence
  - *Flexibility to manage greater demand uncertainty* - expand global presence
  - *Lower per product volume* – develop products more targeted to specific patient populations

A one size-fits all manufacturing approach is not suitable for a diverse portfolio of molecules and an integrated approach between manufacturing and process development are essential for efficient deployment of a polymodal pipeline.

Key Points from Talk #1 – Art Herwig (Amgen)

Transforming Biopharmaceutical Production Through the Deployment of Next Generation Manufacturing: Opportunities and Challenges

- Industry will need to respond to these pressures by using existing plants/technologies where they make most sense, build new capabilities, and evolve the definition of a platform.
- Intensified and integrated processing can help to transform the current bio-manufacturing paradigm:
  - Some elements are continuous but not fully continuous
  - Flexibility and scalable capacity
  - Smaller footprint
  - Use of modular facilities
- Example: Flexible/reconfigurable next-gen Amgen biomanufacturing facility in Singapore with ~80% reduction in size but same throughput as conventional 750K sq. ft facility. Emphasizes higher productivity in smaller reactor vessels, single-use equipment, and connected/continuous purification process.

Key Points from Talk #1 – Art Herwig (Amgen)

Transforming Biopharmaceutical Production Through the Deployment of Next Generation Manufacturing: Opportunities and Challenges

- Dedicated modality-specific platforms are not an efficient solution to advance a polymodal portfolio. Industry should adopt a modular approach to platform expansion that is modality-agnostic and allows for efficiency and facility fit.
  - Like a subway system, distinct modalities would go through production but meet at common points based on molecular properties and needs, such as speed, quality and program requirements (e.g., cell line, expression strategy, bioreactor format capture step, etc.).

By applying modular process platforms and developing revolutionary new manufacturing platforms we can continue to both utilize the existing network and create processes suitable for all modalities

Key Points from Talk #2 – Paul Collins (Eli Lilly)

Continuous Manufacturing- Framing a Future for Patients

- Focused on Small drug substance manufacturing
- Emerging modalities present new challenges – low volume and niche synthesis
- Industry is trending towards smaller batches and unconventional formulations to meet demands for personalized medicine.
- Industry needs to continue to embrace Quality by Design (QbD), defined as *a maximally efficient, agile, flexile, pharmaceutical manufacturing sector that reliable produced high-quality drug products without extensive oversight.*
- Applying the current Synthetic Unit Operations approach to new small batch, small molecule DS or DP would have a high cost and present control strategy challenges.
- Dr. Collins proposed a shift in pharma manufacturing structure that would allow companies to experiment with new, limited-use therapeutic modalities in one place, while also limiting footprint and investment.
- In this approach, volume would no longer be the driver for building equipment technology and continuous manufacturing concepts would be applied to allow unit operations to be flexible and designed for purpose.

Key Points from Talk #2 – Paul Collins (Eli Lilly)

Continuous Manufacturing- Framing a Future for Patients

- Eli Lilly Small Molecule Continuous (SVC) API Facility - Small footprint, CM API facility in Ireland
  - Facility designed for throughput of 10 kg/day
  - Production contained in dual-access fume hoods.
  - Applies the use of modular skids that plug into distributed control system to support wide range of unit operations.
  - Whenever possible, uses standard dimensions and components (flexible and adaptable) (i.e., “bricks”, 24 bricks – fume hood).
    - New process is viewed as types and numbers of bricks
  - PAT is key component of manufacturing control
  - Automated systems for sampling, analysis, and transfer of results.

Conclusions:

- Next wave of medicines requires industry to change – CM framework allows industry to meet those needs
- SVC Facility is a start but new unit operations are needed
- QbD should never have been about multivariate PARs, risk and control strategies –it’s about *design*

Key Points from Talk #3 – Sharmista Chatterjee (FDA)

Novel Technologies to Support Patient Centric Drug Product Development: FDA Perspective

- Emerging technologies offer the promise of novel therapies for developing patient centric dosage forms and modernizing pharmaceutical manufacture
- Dr. Chatterjee offered three examples of innovative technologies FDA has experience with that might support development of patient-centric dosage forms and associated quality considerations:
  - On-demand 3D printing on finished dosage forms – Portable 3D printing unit that could be used at the bedside to deliver on-site, on-demand, customized drug products.
    - Quality Considerations – Labeling for personalized dosing, raw materials controls, process parameter settings, monitoring equipment performance criteria, and managing environmental factors.
  - Portable Manufacturing Units – DARPA funded effort to make a "pharmaceutical plant in a briefcase"; portable continuous manufacturing unit to make finished products, on-demand, anywhere in the world.
    - Quality Considerations – Ensuring cGMP compliance, establishing methods for assessing quality of finished products, and detection and removal of non-conforming batches.
  - Digital Pill – FDA approved in 2017, it is a pill embedded with a sensor that can tell doctors when and whether a patient has taken their medication.
    - Quality Considerations – Ensuring that the sensor is placed in every pill, defining acceptance criteria, and confirming functionality across formulations.

Key Points from Talk #3 – Sharmista Chatterjee (FDA)

Novel Technologies to Support Patient Centric Drug Product Development: FDA Perspective

- Continuous Manufacturing - Flexibility in batch sizes based on size of patient population and market demand.
  - Five small-molecule CM processes have been approved
  - ETT (Emerging Technologies Team) program.enabled approvals
  - ETT allows for early FDA-industry interaction before IND and allows for frequent discussion with agency during development, which facilitates first cycle approval.

- CM Quality Considerations – FDA DRAFT Guidance for CM
  - Quality Control Unit
    - *Integrated team based approach (technical and quality) is recommended for establishing quality decision metrics for CM systems*
    - Needs to adapt quality processes for CM requirements (i.e., alarms, alerts, change control) and have established metrics for overall batch quality (criteria for batch rejection).
    - Quality Systems much be programmed into automation. Equipment should be validated and qualified.

Key Points from Talk #3 – Sharmista Chatterjee (FDA)

Novel Technologies to Support Patient Centric Drug Product Development: FDA Perspective

- CM Quality Considerations – Cont'd
  - Process Validation
    - Must be able to demonstrate that process can achieve and maintain a state of control over duration of run. Must also be aware of potential failure modes.
    - Assess process robustness during PPQ (Process Performance Qualification). PPQ study should be representative of intended commercial run time, including interventions that could occur during routine operation.
  - Lifecycle Considerations
    - Define plans for continuous process verification and collect product and process monitoring data for trending and analysis
  - Model Implementation
    - Implementation of CM warrants some specific PQS considerations
    - Should document plans for model maintenance including plans to verify model performance, triggers for updates, and validation process post-update

Panel Discussion and Q&As

Q: For Art Herwig (Amgen), what factors informed your decision to build facility in Singapore?

A: Talent pool, financial aspects, and changes in US tax law

Q: For Art Herwig (Amgen), in you presentation you mentioned that quality control needed to adapt to continuous manufacturing. What did you mean?

A: Quality control needs to adapt to unique needs. You have many ways to remove non-conforming product but need to have ways with CM to identify and define the "batch" that needs to be removed.

Q: For Paul Collins (Eli Lilly), how does Eli Lilly define batch for their semi-continuous process?

A: Batch is defined by two ways – (1) run time or (2) the amount of material being processed.

Q: For Paul Collins (Eli Lilly), what did you mean when you said that we need to put the "Design" back into QbD?

A: When Eli Lilly started to discuss continuous API several year ago, they focused on running reactions that they would not have been able to be run on a larger scale or in batch form for safety, stability, and/or other reasons. We since moved away from running reactions that would give us what we wanted and focused instead on the reaction rather than designing the process to fit whatever reaction we wanted to conduct.

Panel Discussion and Q&As

Q: With respect to FDA's experience with 3D Printing – the pod may be CM but is lacking the resources and raw materials needed to make it run. How do you make sure you don't have contaminations and other errors introduced into the process, particularly at the patient's bedside?

A: The Technologies presented are no where near the level of maturity level they need to be for approval but they are early ideas and the technology may evolve that would allow this to be a reality. The objective of presenting these cases was to demonstrate the quality considerations that will need to be taken into account and addressed as these technologies develop.

Overall Conclusions

- To meet demand for patient-centric and personalized medicines, industry is transforming manufacturing processes
  - allow flexibility in batch sizes based on size of patient population and market demand
  - These systems are modular, have a smaller footprint, are flexible (can adapt to several different modalities), and are much more agile.
- Elements of continuous manufacturing are baked-in to the design but don't offer complete solution.
- Implementation of new process including CM warrants specific PQS considerations