Setting the Standard for Automation™

Data Integrity and CPV for Cell Therapy and Personalized Medicines

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Presenter

- Dr. James Blackwell is President and a Principal Consultant for The Windshire Group in the area of CMC. He has been a prominent (bio)pharmaceutical industry consultant for 12 years. He has graduate degrees in chemical engineering, microbiology, business and technology management. He is a member of ISPE, PDA, RAPS, and AAPS.

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What are Personalized Medicines and Cell Therapy Products- PMCTP?

- “Personalized medicine, also termed precision medicine, is a medical procedure that separates patients into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease.”
- Examples of personalize medicine and cell therapy products
  - Allogeneic cell therapy
  - Stem cell therapy
  - Autologous cell therapy
  - Personalized vaccines (e.g. cancer)- peptide and mRNA
  - Cell based fertility treatment

The Promise- A Few Examples

- **“Terminal cancer patients in complete remission after one gene therapy treatment”,** Kite Therapeutics: Sarah Knapton, The Telegraph, 28 February 2017
- **“Teenager’s sickle cell reversed with world-first therapy”,** DisabledGo News and Blog Prince April 23, 2017
- **“Stem cell therapy halves deaths from heart failure”**, http://www.telegraph.co.uk/science/2016/04/04/stem-cell-therapy-halves-deaths-from-heart-failure/

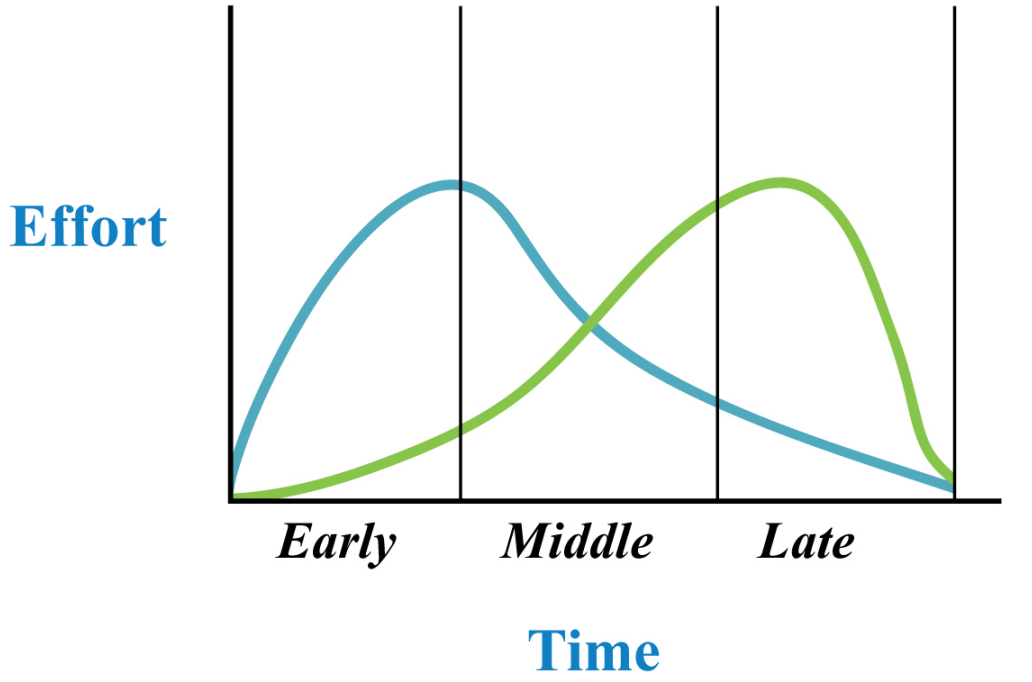
Challenges

- Cell based personalized medicines are highly complex and difficult to characterize
- Linkages to patient outcomes
- Small batch sizes
- Fast cycle times
- Scale up not more cells or products, but in parallel
  - Simultaneous multiple batch processing
- Timely delivery and zero batch failure rate
- Manually intensive (high labor cost) operations
- Batch record requirements
- Process fixed early in product life cycle
- Economics- driving COGS down per patient
- Patient to process to patient data integrity

Development Cycle- Cell Therapy Products

Development Effort

for Cell Therapy vs. Pharmaceuticals



General Approach

- Begin with the end in mind!
- Major and critical aspects cell culture (and similar biological based) personalized medicines should be fixed early. Why?
  - The process is highly linked to the process because the product can not be characterized like traditional pharmaceuticals
  - Changes late are expensive and impact control and data systems and should be minimized
    - Regulatory and technical hurdles become steep
      - “Prove or show the change doesn’t impact patients”
    - Change control, re-validation, system changes are expensive and time consuming

Batch records

- Batch records need to clearly capture all essential processing steps and data
- Create batch records that are as simple as possible, but not one bit simpler. Why?
- Paper batch records usually a necessity early in lifecycle
  - but become a compliance and logistical nightmare when scaling up product to large clinical trial and commercial requirements
  - Paper gets lost, difficult to track, data buried, requires manual handling
- The conversion to an electronic batch record (EBR) will be greatly simplified when the paper batch record needs to become an electronic batch record

Electronic Batch Records

- EBRs can greatly reduce the likelihood of deviations:
  - Errors can often be caught before they become permanent
  - Raw materials, buffers, intermediate, etc. can be tracked with barcodes
  - Data entry can be checked against criteria
  - Sequencing and forced field entry
  - Limits can be automatically checked
  - Review and error checking is greatly simplified
  - Easily integrated with hand-held or mobile computing devices
  - Trending and alerting can warn of problems in advance

Desired Attributes of Electronic Batch Records

- System chosen needs to be flexible and not an undue hindrance to making changes
- Integration with hand-held devices, e.g. bar code readers
- Aspects of EBRs that can assist with flexibility:
  - Intuitive tools that minimize programming to make changes
  - Ability to develop and reuse standardized libraries
  - Lifecycle features and support for change control
    - Flexibility to repeat steps, perform additional cleaning or equipment set-up with authorization
    - Real-time parameter modifications and modifications to future steps
      - Permission based

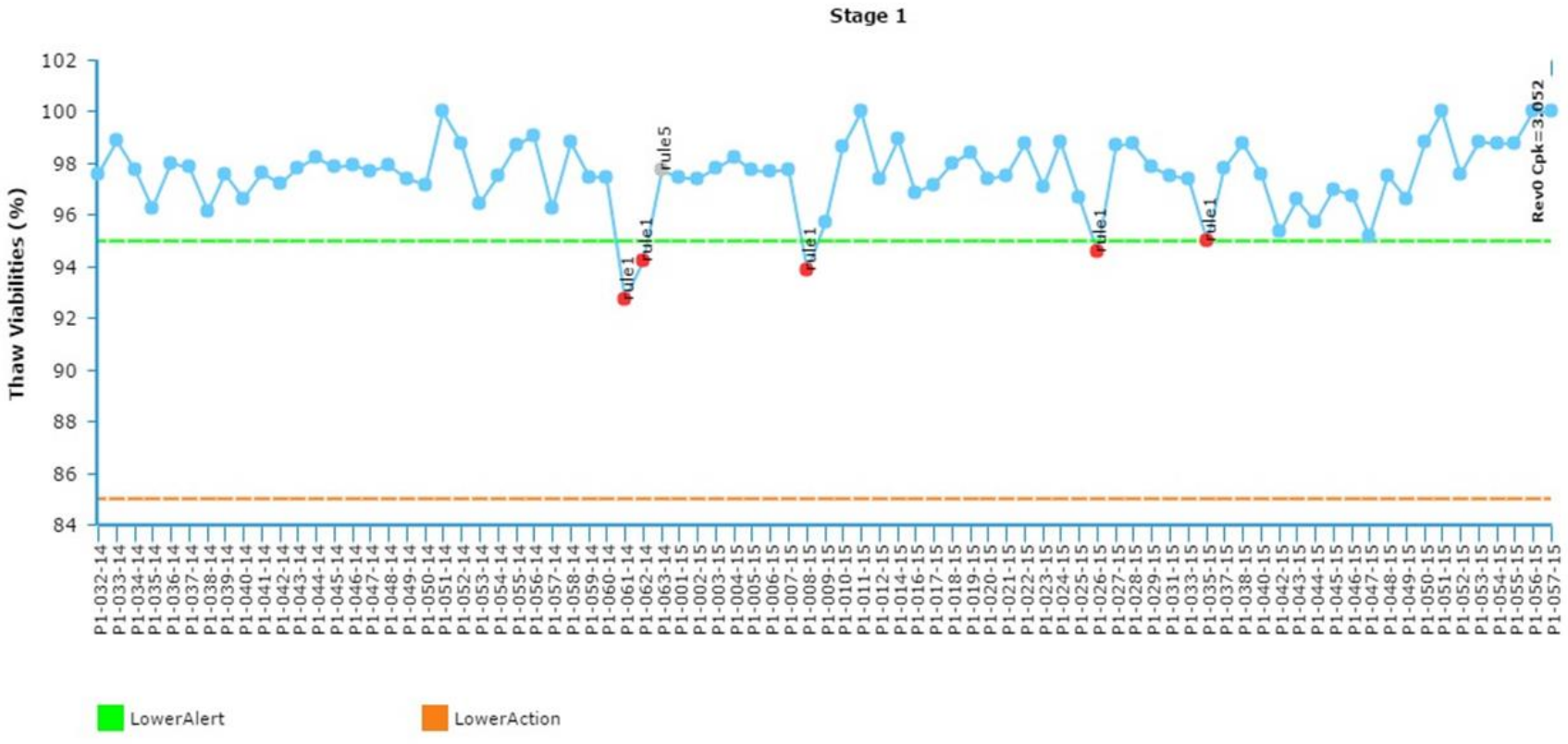
- Lifecycle features and support for change control
  - Change number tracking
  - Specific signing authority levels
  - Ability to N/A future steps
  - Authoring environment
  - Ability to annotate
  - Link to documentation for change rationale
- If you need to fly in experts to make changes, look else where

Continued Process Verification

- A CPV solution is vital for:
  - Driving down labor costs and COGS
  - Monitoring product quality and reacting to quality issues
  - “Get it right the first and second time”
  - Link process performance to patient outcomes
  - It is a lifecycle tool, not just for commercial products
  - Compliance (e.g. FDA Guidance)
- Unifying data from QC/LIMS, batch record, MES, ERP, BMS, and QMS, etc. data into a common environment provides:
  - Significant ROI* just from labor savings alone without consideration of: improved investigations (e.g., process deviations, complaints); yield improvements; saved batches; prevention of recurrence, etc.
  - For PMCTP, CPV is essential

* “A Roadmap for the Implementation of Continued Process Verification” PDA J Pharm Sci and Tech 2016, 70 282-292

CPV Example* Viability for a Cell Therapy Product



*Generated using ProcessPad

Manufacturing and Automation

- Map data flows, control points, and alarms during process development and as part of conceptual design and
- Critical aspects for manufacturing and automation
  - Chain of custody and traceability for product and samples must never be lost
    - Open processing suites mean means many opportunities for potential mix-up or cross contamination
  - Hand-help computing devices and bar codes readers will be common
- Alarm strategy must be aligned with process control strategy and not produce nuisance alarms, false negatives and false positives

  - Multiple processing steps and multiple batches in same suite will create an alarm “forest”
  - Critical alarms need to be selected with care. Note: Not everything is critical and action needed as a result of an alarm needs to be determined in advance
- Get all process data and relevant data from unit operations, e.g. synthesizers, cell factories, into a data historian to aid CPV
- Metadata from some unit operations and QC lab testing equipment (HPLC, UPLC, mass spec) may need to be extracted for data historian and CPV purposes due to larges amounts of data generated, e.g., extraction of peak retention times, height, area

- Closed and automated/robotic processes should be used where possible
  - Reduce environmental controls and risks
  - Reduces manual labor and cleaning requirements
- Data connectivity with data historians and bar code options should be assessed
- Minimize transfers and manual operations/manipulations
- Use tracking system with continuous updates

- Use MES to:
  - Monitor all manufacturing steps
  - Manage an electronic batch record system
  - QC testing
  - Execute certain processing and tracking procedures
- Together with EBR and CPV, cycle times can be significantly reduced and manual date entry eliminated
  - Especially important for scaling to commercial operations

In Conclusion

- Start with end in mind- the patient, data integrity, and integrated systems for right first time, on time
  - Product release by exception and real time testing
- Develop control and data strategies starting with conceptual design
- Integrate data for continued process verification and data integrity
- Design in controls as much as possible and use closed automated systems
- Think simplicity and for flexibility

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