Manufacturing Logistical and Capacity Considerations For Cell and Gene Therapy Products

Cell & Gene Therapy Products (CGTP): Manufacturing, Quality and Regulatory Considerations
CASSS

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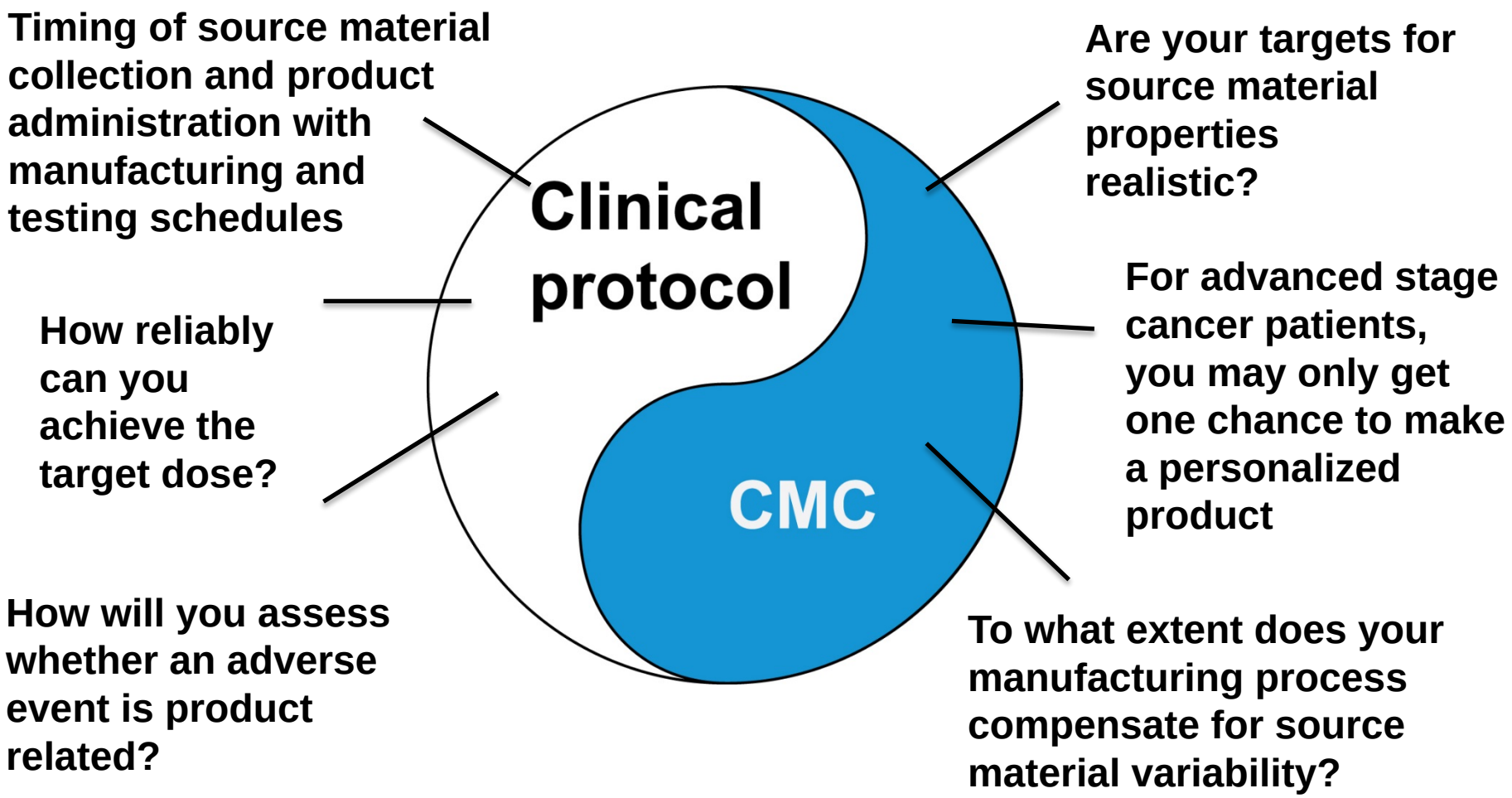
Tom Finn, Ph.D.
CMC Reviewer
Office of Tissues and Advanced Therapies
FDA/CBER

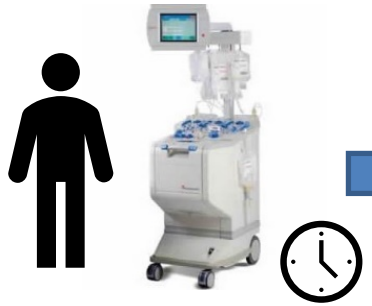
For cell and gene therapy immunotherapies, tight coordination between the clinical protocol and manufacturing are often needed



Coordination of patient's clinical care, donor, manufacturing, and testing

QA oversight

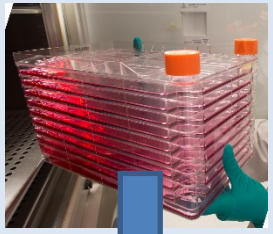
Arrangement for autologous or allo donation



Coordinate manufacturing schedule with availability of source material

Evaluate source material:
- Minimum amount
- Donor eligibility
- Consent from donor
- Analytical testing
- Possible genetic testing

Manufacture product



In-process testing

Harvest and final product testing

Formulation and packaging

Deliver product

Coordination of patient conditioning

Coordinate with treatment schedule

Administration schedule

Examples of logistical concerns

- Medical professionals are rushed because courier shows up early to pick up source material, and proper documentation is not followed
- Expired lot of cytokine is used in manufacturing because no other reagent lots have been qualified yet
- Manufacturing step exceeds holding time because results from in-process testing were not provided quickly enough or there was a delay in processing
- Generating largest dose for a dose escalation study means additional source material must be collected and pooled with first batch, altering patient treatment schedule
- Product arrives at clinical site with little time left before it expires because of a shipment delay
- DP shelf life not long enough to cover all the planned repeated doses
- MCB will expire before replacement is generated – what if it is not comparable to the last one?

Considerations for manufacturing logistics

Source material

- You can't always go back and grab more source material when the patient or a donor is the source - source material is precious
- Perform stability studies on source material to ensure adequate quality
- Shipping, storage, and handling conditions
- Tracking and chain of custody responsibilities

Proper material management

- Have rigorous material tracking system in place
- Verification of inventory
- Adherence to first-in first-out
- Why is expired material still on the shelf?
- Suggest qualifying multiple lots of the same material

Adherence to step and holding times

- Establish step/holding times based on stability studies and manufacturing experience
- Monitor adherence to step/holding times – check before you move on to next step in process – build into SOPs and forms
- Launch investigations when you have deviations, and take appropriate corrective actions, such as revising times

Manufacturing challenges related to capacity and logistics are not just a risk for the manufacturer

Risk to donor

- Procedures such as mobilization, apheresis, surgical tissue collection are not risk-free
- Tissues used as source material are in limited supply

Risk to patient

- Options for reprocessing are often not practical
- In situations involving lengthy and complex manufacturing process, patient may die before treatment, or patient may drop out of study due to deteriorating health status
- Conditioning of patient to receive a product may put them at risk – importance of making sure you can successfully manufacture product

Risk to clinical study

- Manufacturing deviations can lead to clinical protocol deviations, which can complicate evaluation of safety and efficacy (example: not achieving the intended dose)

Cryopreservation of source material, intermediates, and DP can often help because it provides more flexibility on when manufacturing can start/stop and when a patient can be treated, but does not solve all problems (recovery issues, thawing procedures at clinical site, long term stability, etc.), .

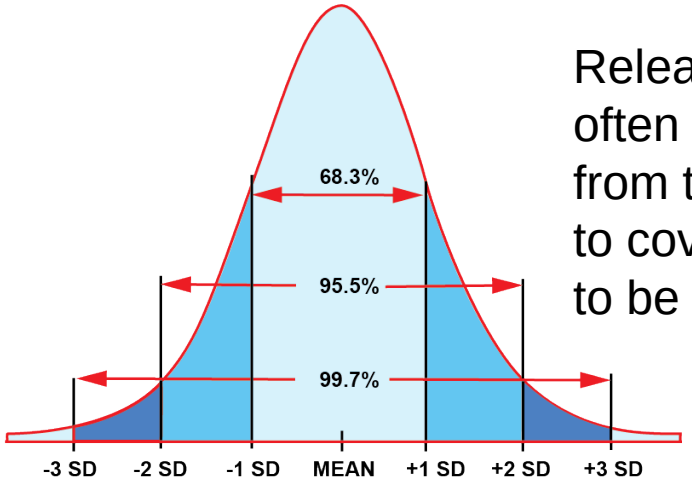
Holistic evaluation of system functionality is important when considering the adequacy of logistics and capacity

Using your manufacturing process as a guinea pig

Have a failure upstream and decide to see if, by chance, it will meet lot release anyway: “there was a serious deviation, but the product still met product release criteria **so there was no consequence.**”

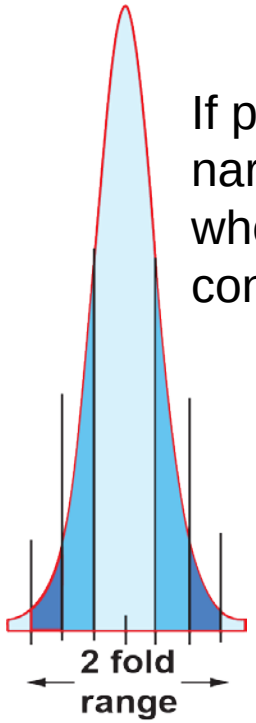
Please consider:

- The process is the product – specifications can only tell you so much
- These products are typically for treating serious, often life-threatening medical conditions – how much do you know about the disease, mechanism of action, and minimum product properties needed to help ensure benefit to the patient and to draw a proper conclusion?
- Cell and gene therapies are typically not well-characterized using rigorous testing:
  - How carefully have you looked for an impact?
  - A potency assay may not be in place until late stage
  - Lot release criteria often have very wide tolerances – meeting release criteria may not be a high bar

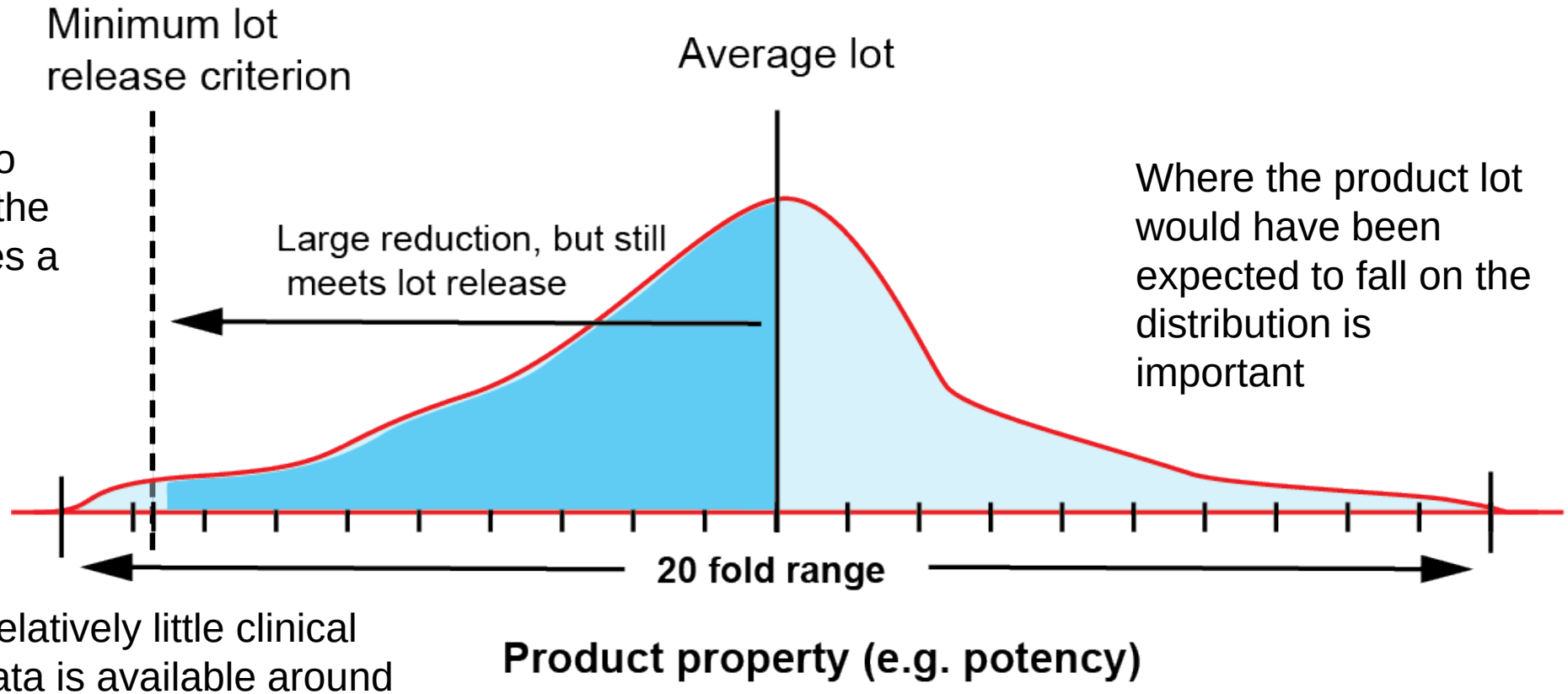


Release criteria are often based on 3 SD from the mean in order to cover all lots likely to be produced (99%)

But cell and gene therapies are often not normally distributed and typically have very wide tolerances. For the average lot being produced a product deviation could drastically reduce a product property and still meet lot release



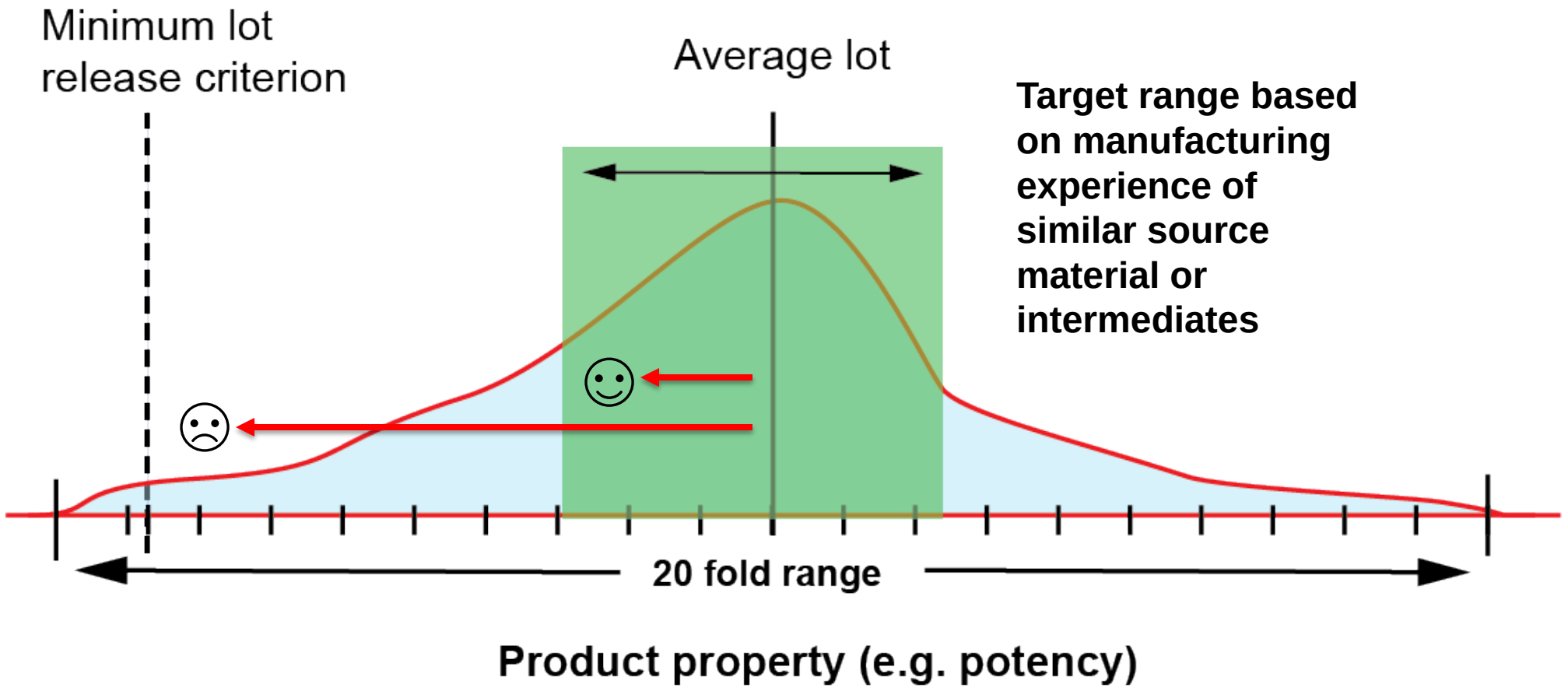
If product is made to narrow tolerances, the whole range ensures a consistent product



Where the product lot would have been expected to fall on the distribution is important

Relatively little clinical data is available around the cut-off

A more useful analysis might be how this lot compares to similar lots you have made before



Evaluating deviations and potential impact- a multistep analysis

Did the DS/DP meet minimum release criteria?

How did this lot compare with all historical lots?

How did this lot compare with historical lots with similar starting/intermediate properties?

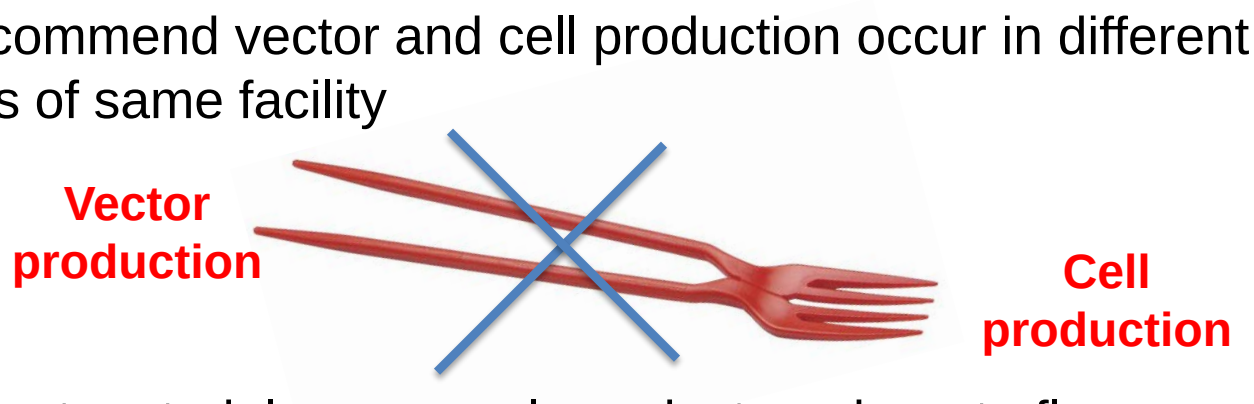
Have there been other incidents and has there been a trend or drift in one direction or another?

Especially important when you are making multiple lots at once, because a shift in quality could occur quickly

Multiproduct manufacturing

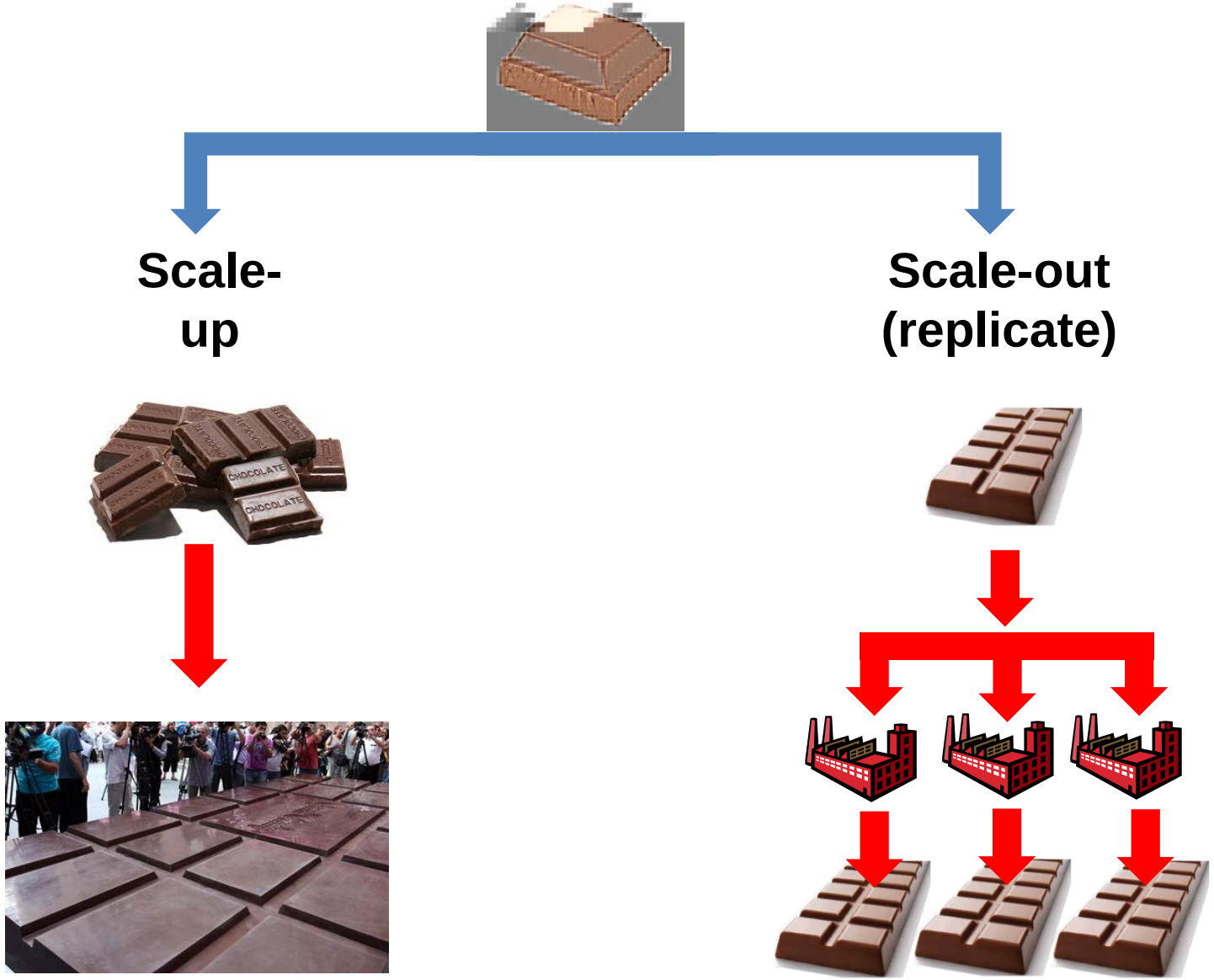
Manufacturing multiple products in the same facility is not the same thing as multi-tasking. Please consider:

- Appropriate segregation of materials, equipment, different products
- Generally recommend vector and cell production occur in different facilities or different parts of same facility



- Concerns about material, personnel, product, and waste flow
- Want to minimize the potential for cross-contamination and mix-ups
- Drug product release specifications must include an identity assay:
  - The assay must distinguish each product made in the facility
  - Identity for patient-specific cell and gene therapies involve identity for the correct cell type, and chain of identity for the specific patient

Different strategies to increase manufacturing scale

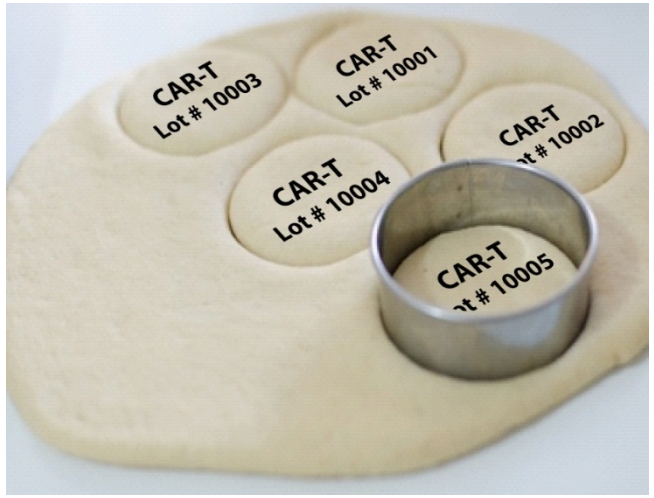


Logistical scale-up considerations

- Length in time in culture and the number of passages can, in some cases, profoundly impact product properties
- Cells can be sensitive to cell density and ratio of cell types, so it can be important to monitor
- Not all processes scale well:
  - Working with huge numbers of flasks can be problematic
  - Time-sensitive steps (such as enzymatic treatment) can be challenging
  - Equipment and material management
  - Adequate personnel, training up to date

Scale-out manufacturing considerations

- While it may be easiest to process all lots identically from a logistical standpoint, remember each lot has unique properties and may react differently to the same conditions – **could contribute to product variability**
- There can be **increased risk when processing multiple lots simultaneously** – e.g., a problem with culture medium or a critical reagent could impact multiple lots at the same time and before you have a chance to notice or intervene. **Material qualification and process monitoring are critical**



- Impact to other products made in same facility
- Recommend that, in addition to aseptic process validation and process validation, a capacity study is performed to identify bottlenecks and **ensure that adequate resources are available**

Difference between process validation and capacity studies

Purpose of process validation

- Manufacturing process is under a state of control
- Each unit operation is performing as intended
- Produces a consistent product

Purpose of capacity studies

- Demonstrate you can successfully execute process as intended while operating at full production scale
- Demonstrates adequate resources are available
- Conforms to manufacturing and clinical schedules

Process validation (required for licensure)

Concerned about:

- Process variability
- Meet all in process and final product release criteria

Involves:

- Process Performance Qualification (PPQ) studies
- Typically 3+ lots
- Consecutive lots (not best 3 out of 5)
- Usually done at full scale for each lot (though can add additional data at smaller scale)

Capacity (may be asked to perform depending on situation)

Concerned about:

- Large increase in production scale over previous production levels (e.g 10X for P3 or commercial product) where there is a lack of experience working at that level
- Process step and holding times might not be adhered to or, or be heavily shifted within range (e.g. held overnight instead of directly processed)
- Logistics and bottlenecks (equipment, rooms, waiting for QC results)
- Delivery of product to clinical site during normal business hours and avoiding patients/health care professionals being rushed
- Potential for mix-ups with many more lots being produced
- Potential for increased product deviations as a result of many lots being produced at one time

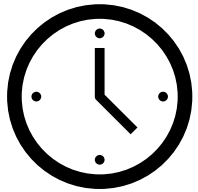
Capacity study design

- Calculations and estimates of needed materials, storage, clean room space, equipment, personnel, QC, etc. taking into account logistics – at the very least it should work on paper
- Evidence from previous studies where perhaps over a short period of time you manufactured at that level
- Successfully manufacturing a small number of new lots at full capacity (full throughput) on a subset of available equipment/rooms/personnel (e.g. full throughput in 2 of 5 cleanrooms)
  - Demonstration of appropriate segregation and tracking
  - Appropriate material management
  - Environmental monitoring
  - Proper Quality System oversight
  - Adequacy of software and computer systems

Recommendations

- Moving fast inside of product corridors and clean rooms, and going quickly in and out of biosafety cabinets creates air currents which can interfere with good aseptic technique – work in sloth mode
- Environmental monitoring should factor in maximum number of personnel in a given area

- Maximum step/hold times:
  - Source material can vary substantially lot-to-lot in terms of volume or number of cells – larger quantities take more time to process. Consider worst case (which may change with experience)
  - As additional stability and product characterization data is acquired, consider impact on time limits and whether they are still accurate



  - As more experience is gained and changes to procedures are introduced, periodically review how long procedures are actually taking versus predicted – just because a maximum time is allowed doesn't mean it is in the best interest of product quality or for safety/efficacy of the patient – setting targets in addition to limits can be useful
  - Monitor adherence to step/hold times during procedures and with batch record review, and not just record stop/end times

Note: These different factors can be at odds with each other

Summary

- For patient-specific products, cell and gene therapies often involve careful coordination between the clinical site and manufacturing/testing/shipping: logistics can be challenging
- Late-stage clinical studies and commercial manufacturing often involve a substantial increase in production level that can stress production/testing and raise concerns about adequacy of available resources
- Careful consideration of manufacturing logistics and capacity can mitigate the potential for an increase in product deviations, shift in product quality, or failed lots
- Manufacturing failures are not just relevant to the developer, but could present a risk to the patient

Contact Information

- **Tom Finn**

  thomas.finn@fda.hhs.gov

- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov

FDA Headquarters

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