Process Performance Qualification (PPQ) for cell-based products

(process validation)

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General Considerations

FDA validation guideline 2011:

- With a lifecycle approach to process validation that employs risk based decision making throughout that lifecycle, **the perception of criticality as a continuum rather than a binary state is more useful.**

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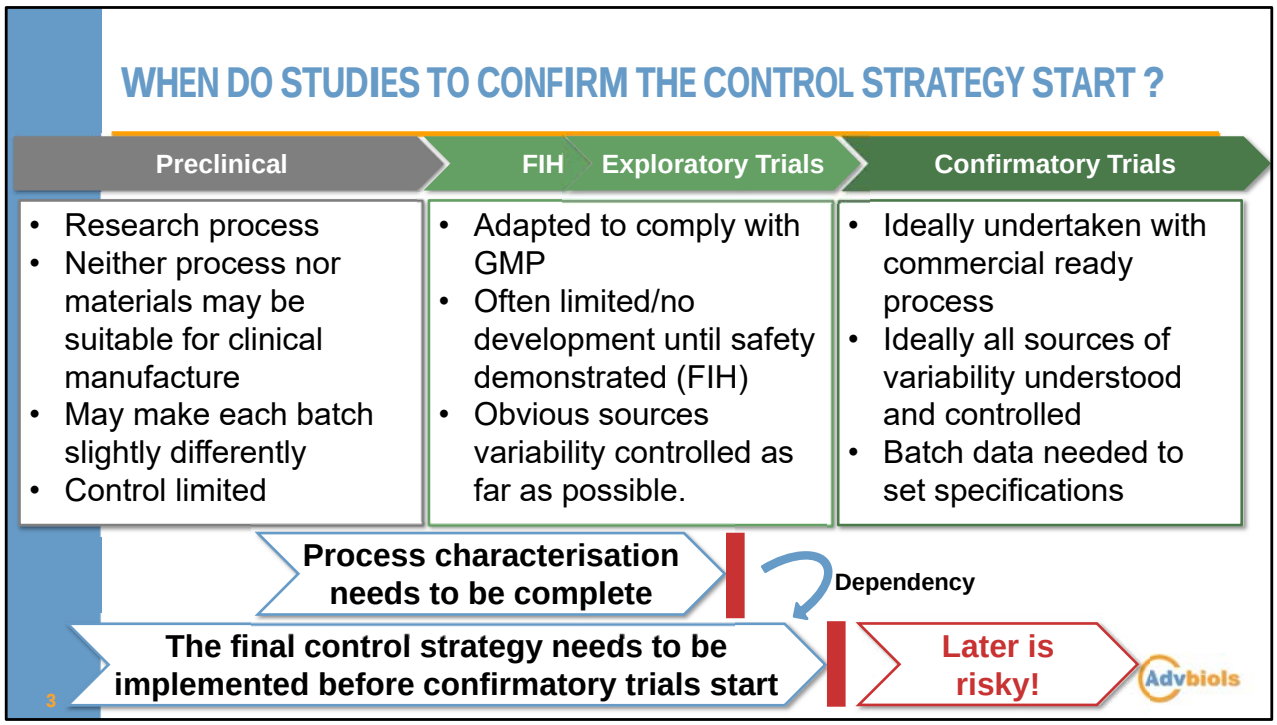
I rather like this phrase/concept, it is indeed a more appropriate way of looking at it.



This is to make the point that the work cannot wait until you've started pivotal studies, you need to start before they start or you may not have time. The approach described here takes considerable resources, but the benefit should be a well-controlled process for which you have the understanding to implement changes. Where data are more limited, the operating ranges at approval will be tighter than development because you have no data to prove otherwise. This risks batch failures in the commercial phase due to tight operating parameters, and not enough knowledge to implement process changes.

STAGE 1: PROCESS DESIGN

The commercial process

- Clearly you don't want to validate the development process (unless its suitable for commercial)
- Ideally the commercial or commercial ready (designed to easily be adapted to commercial) process is used for confirmatory clinical trials (pivotal).
  - Comparability risk
- So this needs to be designed and implemented before the pivotal study/ies start.
  - It might be very different, e.g. automation, and might be a new site.
- This part is not discussed further here.
  - But you will also need to establish comparability with the preceding development process.

STAGE 1: PROCESS DESIGN (COMMERCIAL PROCESS)

Considerations for development studies

FDA, Process validation, 2011:

- "…early process design experiments do not need to be performed under the CGMP conditions..."
  - But operate as if GMP where this impacts the process, e.g. time it takes.
- "Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability."
  - This needs to be demonstrated, either that it behaves the same and/or the limitations of the model. Fine-tuning will likely be required on the full-scale process as there will be limitations.
- "Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained."
  - Try and maximize the information collected; OFAT might work for simple unit operations, but most will be multifactorial.

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While in stage 1 of the guideline they apply more broadly to development and process characterisation studies.
DoE – design of experiments, a statistical design that allows multiple parameters to be explored with fewer experimental conditions.
OFAT – one factor at a time.
The key here is to learn as much as you can about the process in smaller scale models of unit operations or steps, rather than the whole full scale process. While PPQ (stage 2) is conducted on the full scale commercial process (GMP), these process characterisation studies do not have to be under GMP.
Even with model systems there will be a lot of parameters to explore so these can be prioritised through a risk assessment approach;
Multidisciplinary team essential
Consider if risk needs to be assessed just with respect to the impact on the process, e.g. feeding during culture expansion; or the risk to the patient, e.g. removal of impurities; or both.

STAGE 2: PPQ

Part 1: Qualification of utilities and equipment

- Briefly, you need to show the facilities and equipment are qualified as suitable for use (relative to design specification), e.g.
  - Suitable capacity, e.g. water, waste etc; constructed of correct materials
  - Calibration of equipment (reference materials may be needed)
  - Etc……see guideline
- This should include **challenging the equipment or system functions while under load comparable to that expected during routine production**. *See next slide for example*
- It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. Operating ranges should be shown capable of being held as long as would be necessary during routine production.

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The guideline provides more detail, here I merely want to note that this needs to be done and more on to other points.

An example of the highlighted point is provided in the next slide.

FDA BLA OBSERVATIONS

Kymriah – CAR-T product, autologous

Early review question:

Process Validation

Each patient lot is a separate manufacturing operation with several manual manipulations and incubation steps over a span of <redacted>. Have you performed capacity studies (actual or simulated) to determine the number of lots that the facility/ equipment/QC and personnel can handle and sustain per day, week, etc…? Please provide a detailed description and results.

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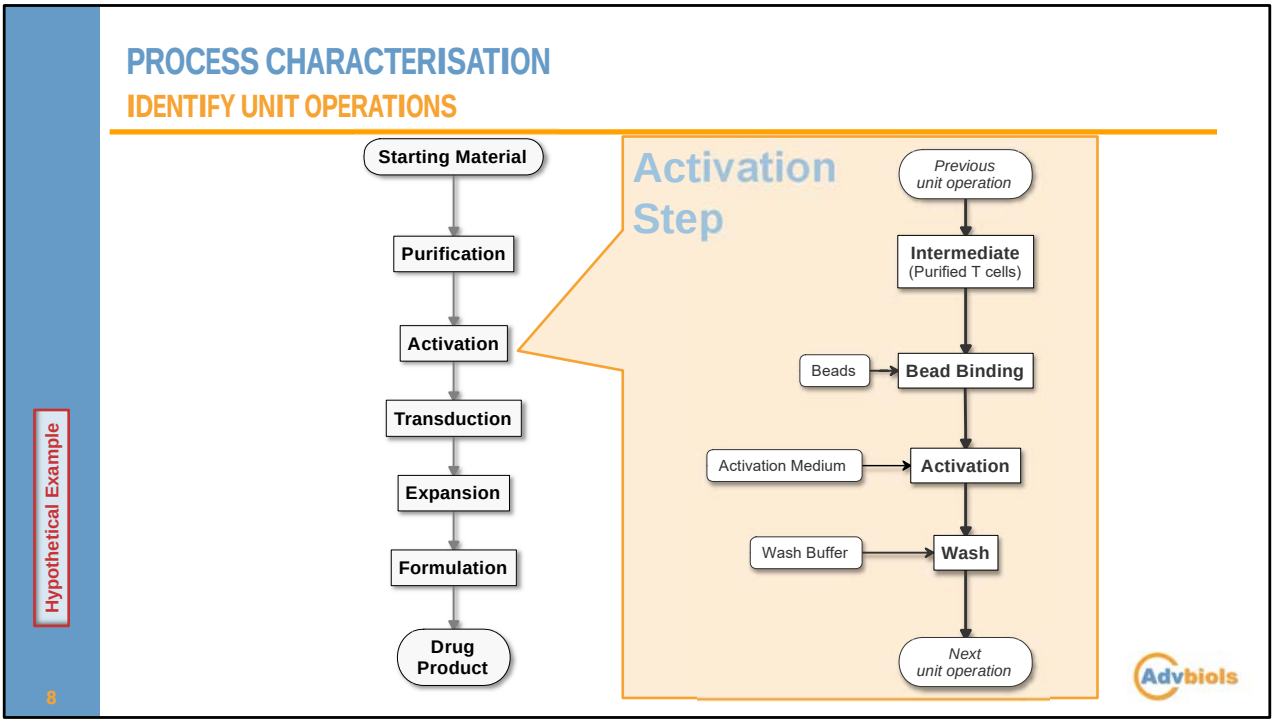
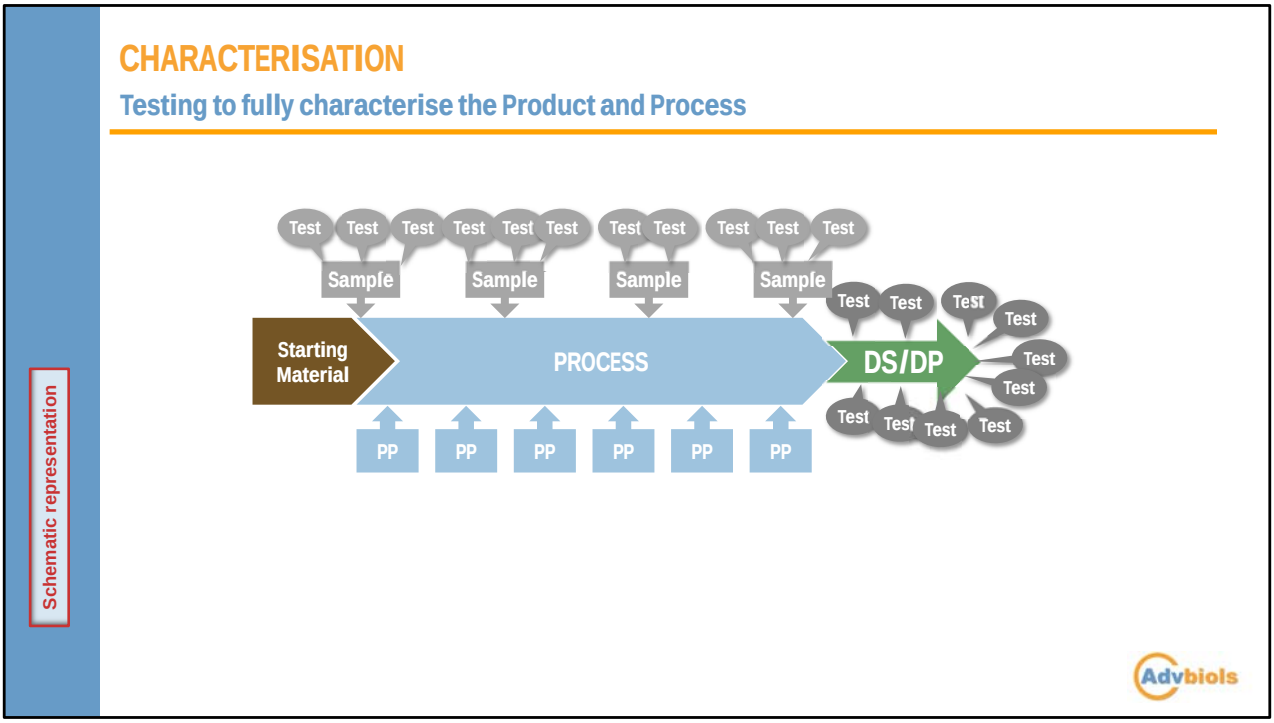
This comes from the published BLA documents, which are redacted versions of the actual documents. <redacted> indicates some text was redacted, this may have been a single word, part sentence, paragraph and in some cases many pages.

This seems to relate to stage 2, part 1 of PPQ, relating to qualification of the facilities. It's a good point as this will have been done during development, and for an autologous cell product in particular the number of parallel products being manufactured is likely to be small in development compared to commercial (depends on indication/market size and penetration of course).

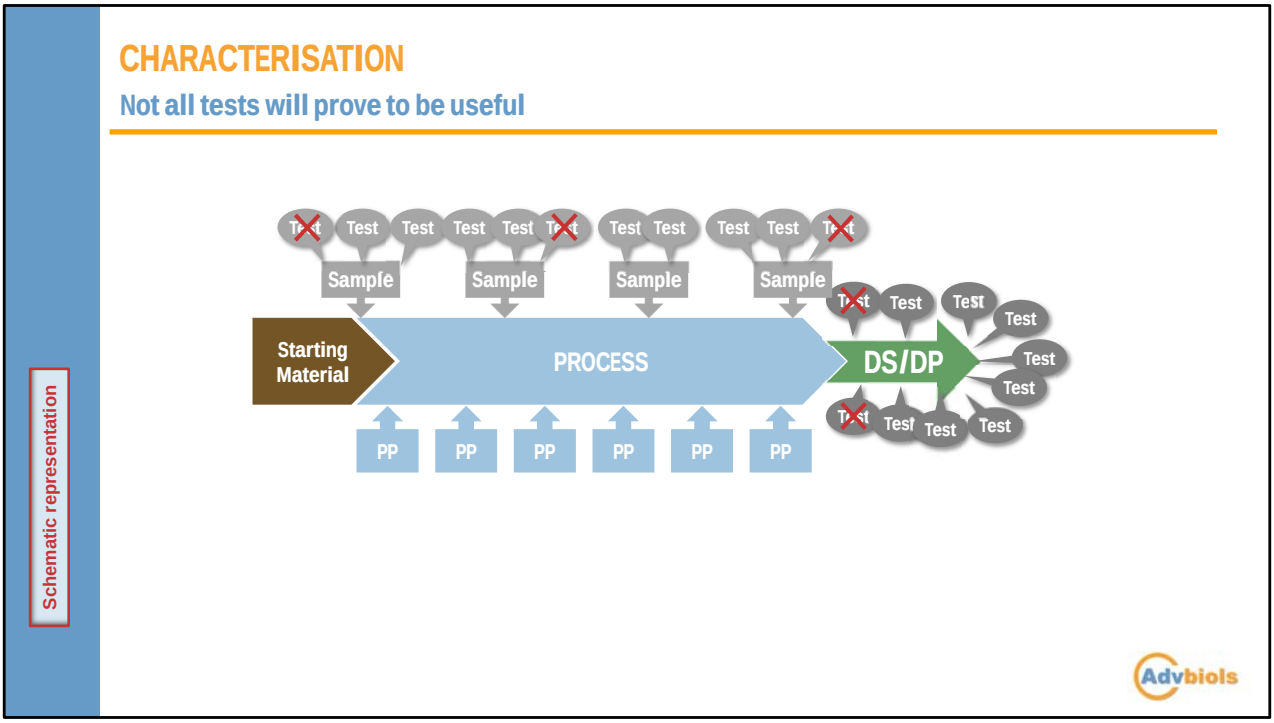


Please note this is a hypothetical example, so please allow artistic license its merely to make some points.
From my work I have found some would call each step on the left of this figure a unit operation; whereas I think they are better described as steps as each contains one or more unit operations (right hand side for example). Each of these unit operations will have different critical parameters, e.g. concentration of raw material (reagent) or change of temperature, volume, duration etc.



Obviously this (and next slides) is a schematic representation, so please don't over-interpret, the number of samples and tests shown is random. No distinction is made between DS or DP to keep it simple (also many cell-based product processes are continuous without releasing a DS).

The first stage is to complete characterisation of the product (if not complete); then for stage 2 of PPQ the process (earlier processes should still have been characterised, but likely to a lesser degree). The likely useful process testing will have been identified from experience (e.g. prior process, prior experience) and risk assessments of which QA of the samples (intermediates) are likely critical. Here the QA tested may relate to their importance to the unit operation (not shown), the importance of the QA to the next unit operation, and/or relevance of the QA to patient safety (e.g. impurity) and efficacy (e.g. biological activity/potency).

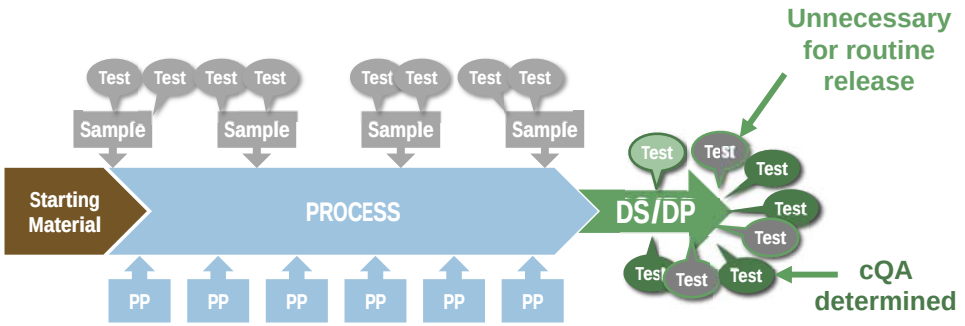


The order as presented is not necessarily the order you do these, indeed they are iterative. Clearly characterisation of the DS/DP should start during the preclinical phase and continue throughout development and to some degree beyond approval.
Some of the tests applied to the various samples may prove not to be useful, so these methods would have no further use. These could be alternative QA that prove to be of no relevance. Characterisation should apply orthogonal methods (different measurement principle) for the same QA; some of these methods will be suited to routine use, others may not be. Those that are not suited to routine release can still be useful for extended characterisation (e.g. for PPQ, comparability etc).

CHARACTERISATION

The set of tests that fully characterises the process and product

Schematic representation



Before you can complete characterisation of the process, it is necessary that the critical quality attributes of the product (DS/DP) are determined. This requires understanding of the mechanism of action.

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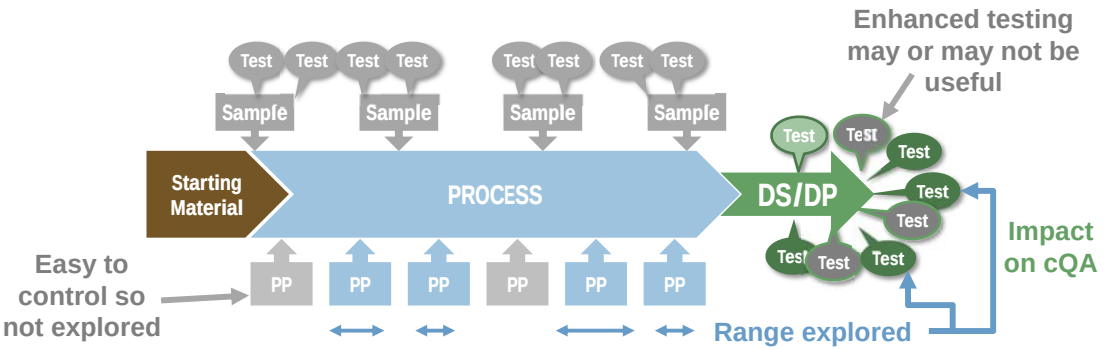
Release testing is a sub-set of the testing required to completely characterise the product, but they are shown to be sufficient for a controlled process.
Note: changes to the process require full re-characterisation (product and process), i.e. comparability.

CHARACTERISATION

Understanding the impact of PP on cQA



Schematic representation

Studies should be conducted to understand the impact of process parameters (PP) on the cQA in order to determine which PP are critical (cPP) and to set a normal operating range (NOR)

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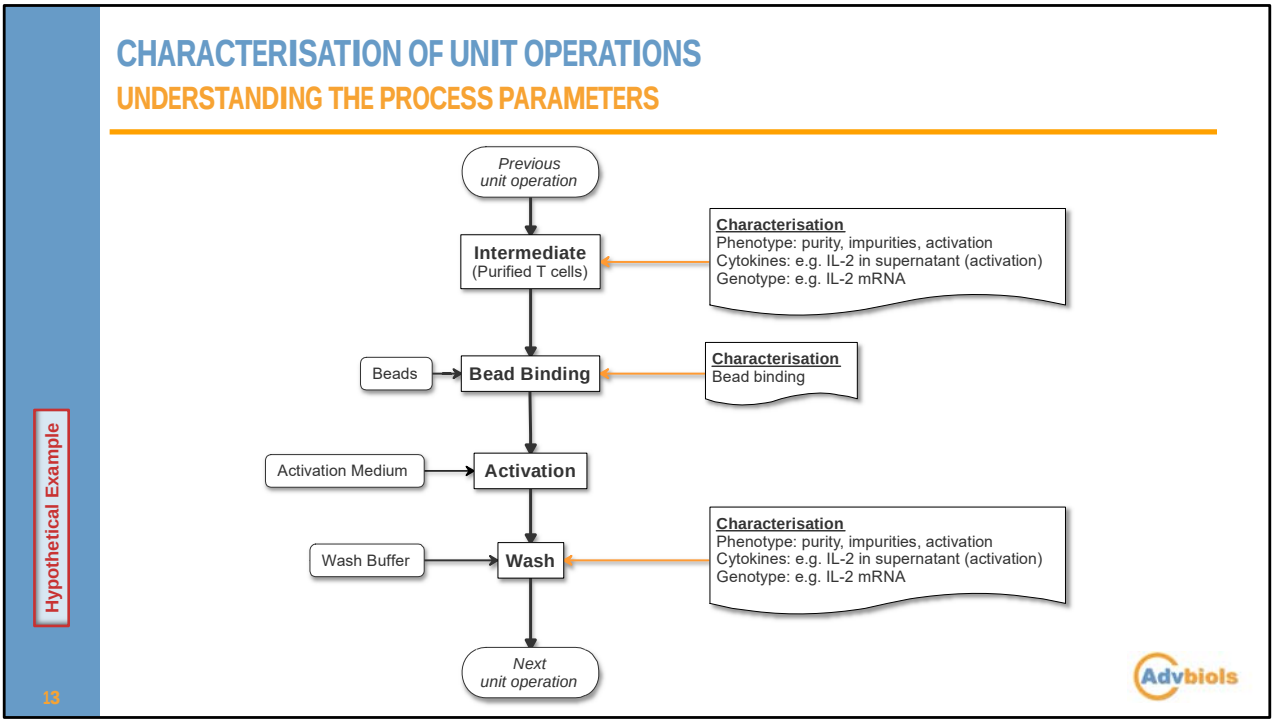
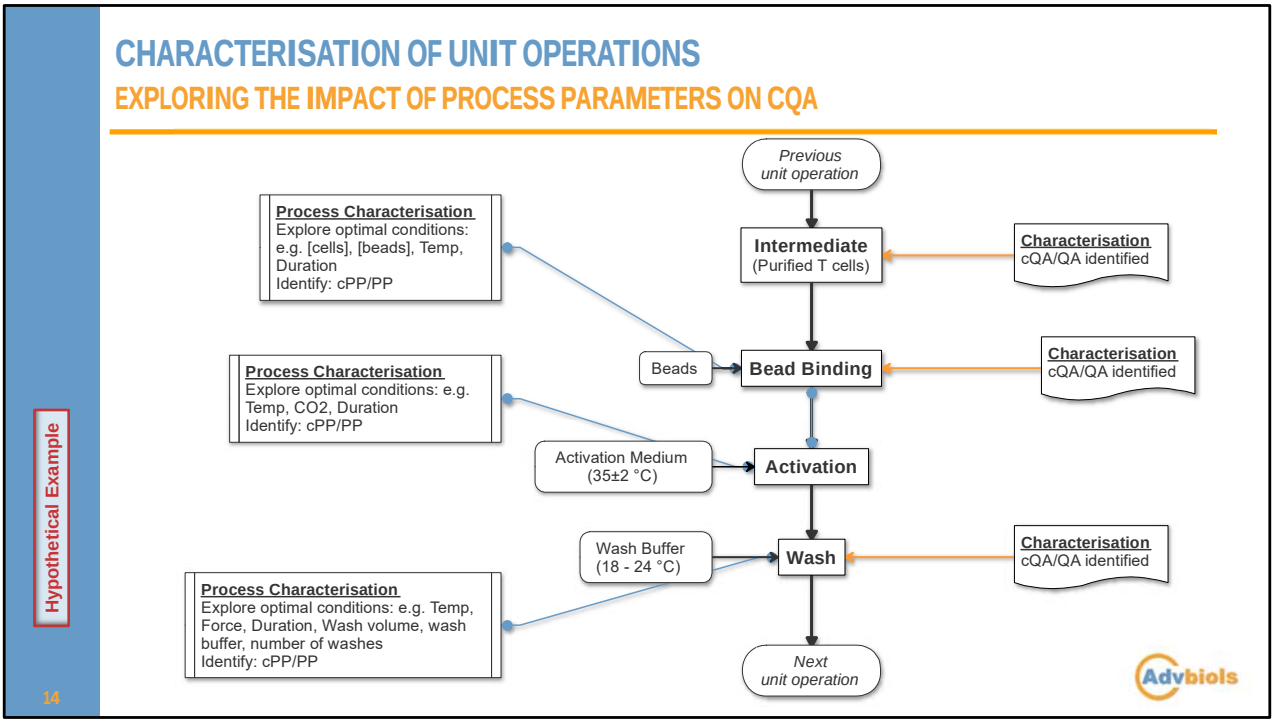
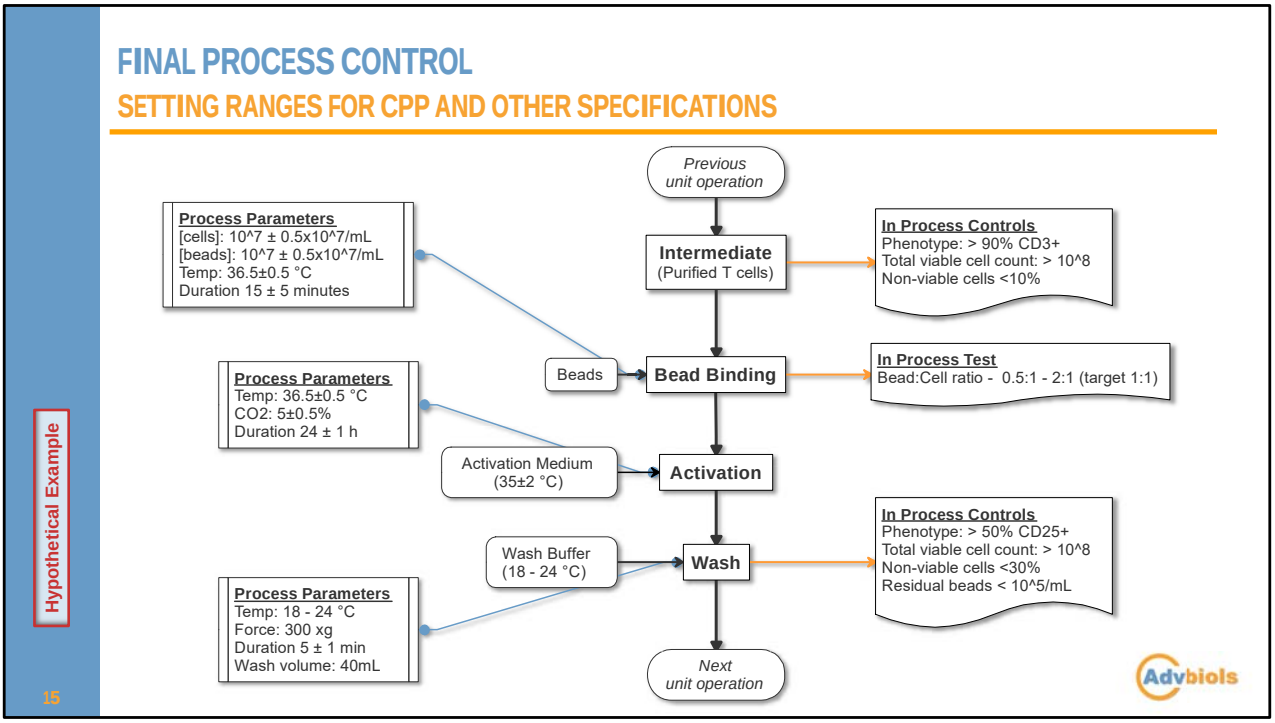
Once the cQA are determined, the impact of the process parameters on the cQA can be evaluated experimentally to determine a normal operating range (NOR). You may also identify the proven acceptable range (PAR) and possibly the edge of failure (can be very useful). The range explored is sometimes called the characterisation range.



To understand which process parameters are critical, it may be necessary to characterise the intermediates from the unit operations to identify their cQA, e.g. to find the optimal concentration of activation beads (here assumed to be c.4-5um) you might assess the proportion of cells bound to 1 or more beads and evaluate what the optimal cell:bead ratio is (potential cPP). This might require a method to confirm the T cell is activated (potential cQA of intermediate), e.g. here I have suggested that IL-2 might be used (not a recommendation, just made-up as an example). Too many beads and it may be hard to remove them later (process impurity, patient-related risk), too few and the cells will not be fully activated, the result may be lower transduction efficacy (process-related risk) in the next step.

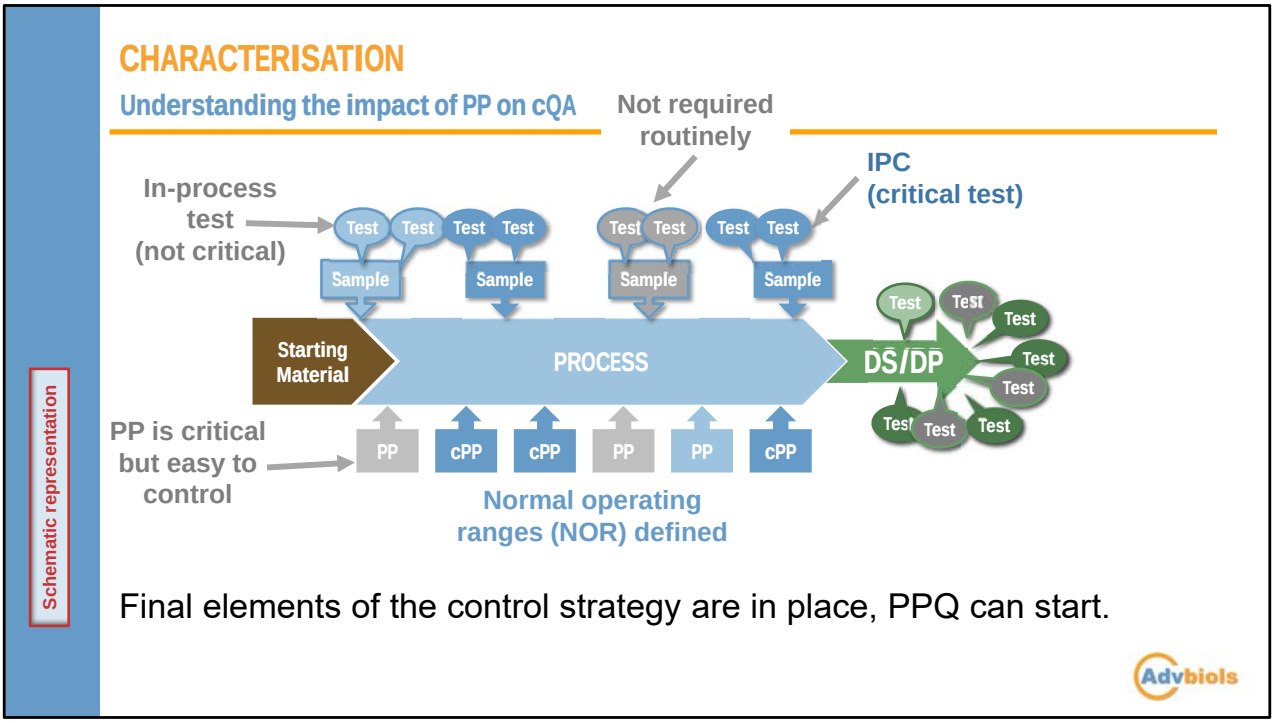


Once you have established the cQA of the intermediate of each unit operation, likely cPP can be explored to understand their impact on the cQA of the intermediate. This assumes those QA assumed to be critical include those that are critical in downstream unit operations, e.g. presence of the T cell activation marker means the cell is optimised for transduction (a unit operation of the next step) in this hypothetical example.



Once these data are combined a control strategy can be implemented, setting normal operating ranges (NOR) for the cPP identified, and implementing any in-process testing needed to confirm each unit operation was successful, or justify that no in-process tests are needed. It might be the testing described above is considered full characterisation, but the routine testing is more limited; this needs to be justified from the data. However, this full (extended) characterisation might be applicable for the PPQ batches, and when undertaking comparability studies. Some tests may not be needed for process control, but useful to collect for process monitoring.

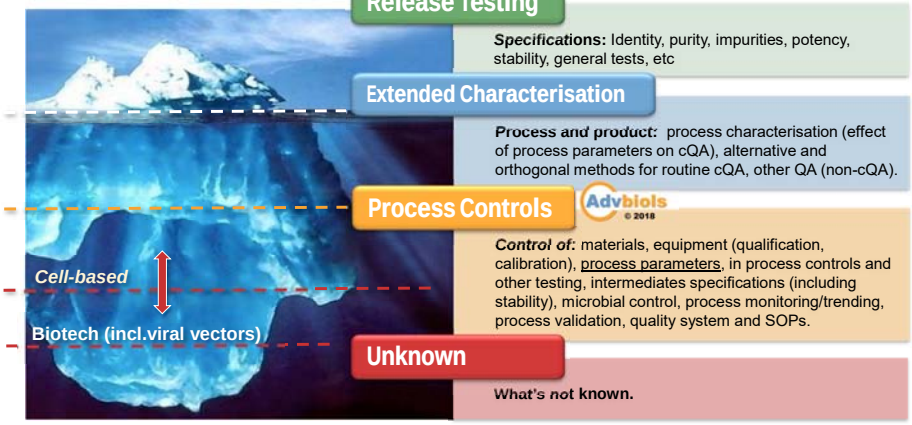
Note: I didn't consider microbial control in this example.



Characterising the process will involve more samples being taken and more tests done of those samples. From those results you decide which samples are critical, and which tests are critical or useful (e.g. process monitoring). But those samples and tests not conducted routinely, may be useful for enhanced testing for PPQ and comparability studies.

PROCESS CONTROL

Before you can validate, you need to have the process under control



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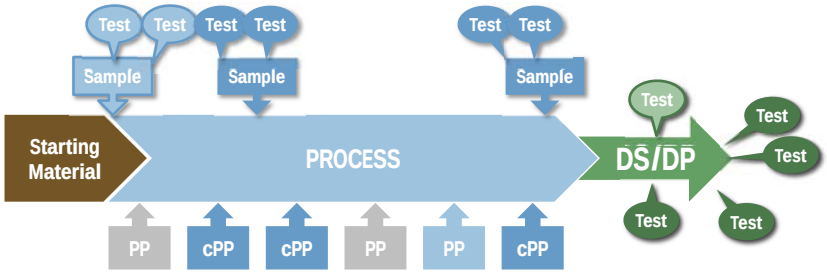
This is a modified version of a figure from and ICH presentation which makes the point that release testing is just the tip of the iceberg. Full characterisation requires more tests than used for release, which is why comparability is not demonstrating the product meets the final release specifications. Release testing even with extended characterisation can only confirm a process was successful, it does not control the process. The elements of process control are what ensure the process will be successful. There are always unknowns, the lifecycle approach to PPQ aims to continue to reduce these unknown even in the commercial phase.

CHARACTERISATION

The set of tests for routine use

Schematic representation

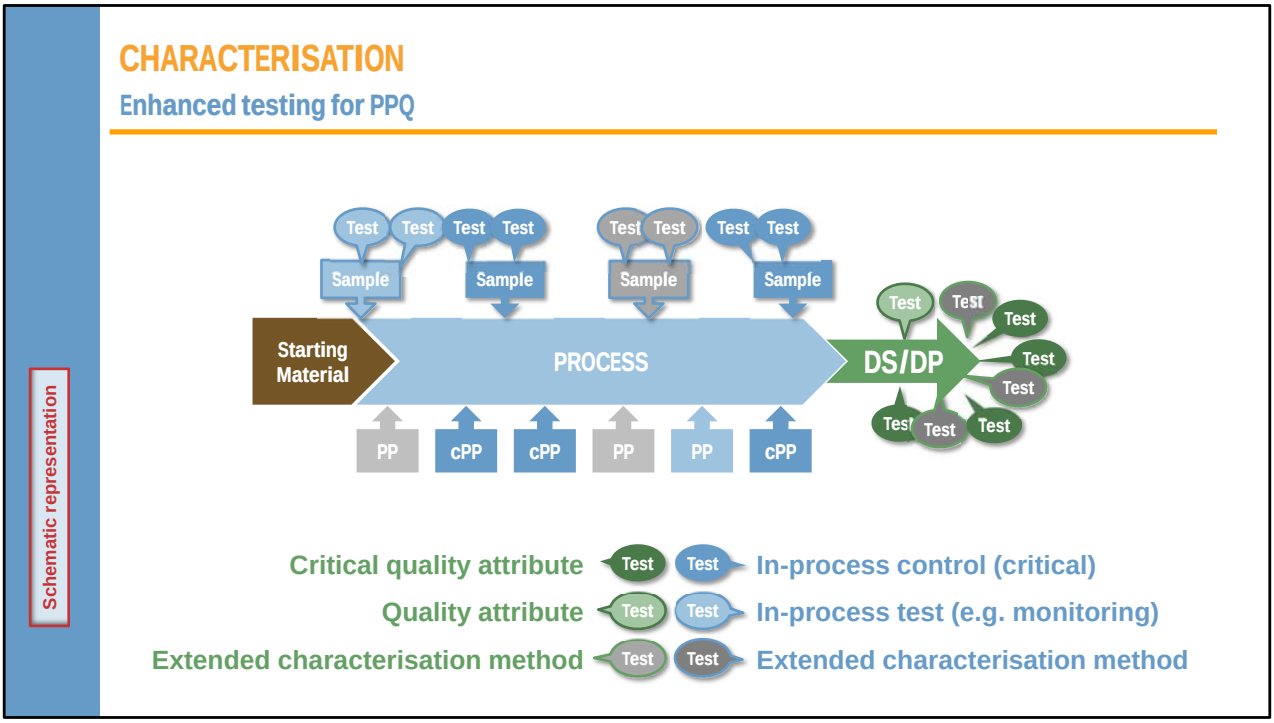


Critical quality attribute — In-process control (critical)

Quality attribute — In-process test (e.g. monitoring)

Extended characterisation method — Extended characterisation method

This is what the routine testing would be.



This might be the enhanced testing used for PPQ runs.
Enhanced testing is expected because routine testing assumes a stable robust process so is a sub-set of full characterisation. This can include additional samples as well as additional testing.

STAGE 2: PPQ

Considerations

- FDA, Process validation, 2011:
  - "…it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by process design data"
  - Where possible it is cheaper and easier to undertake such studies in pilot/small scale model processes.
  - Use intended set points/mid points for PPQ where possible.
  - Cumulated experience from PPQ runs (pre and post-approval) together with process characterisation studies (e.g. model process) should eventually cover the range.

EMA MAA OBSERVATIONS

Kymriah – CAR-T product, autologous

The Applicant has provided an overview of the process validation approach. This included a summary of the process characterisation that formed the basis of the setting of process parameters, in addition to PARs and NORs. The Applicant has undertaken a process risk assessment to identify high-risk parameters followed by a process capability analysis of clinical batches manufactured so far to designate high-risk parameters as key or critical. Lastly, PARs and NORs were set based on previous manufacturing experience.

The Applicant produced **several process validation batches covering both manufacturing sites and both patient and healthy donor material**. Batches were **deliberately chosen to display a variety of starting material compositions**, in particular varying B-cell content. The approach taken for the starting material selection and the number of batches used are endorsed.

The Applicant has provided data on processing times for individual culturing steps, results for CPPs and IPCs, information on yield and Population Doubling Levels (cPDLs). Based on the data provided, the process appears overall consistent.

Aseptic process validation was conducted at both MP and FH IZI. Results were satisfactory. Adequate results from shipping validation studies have also been provided.

The Applicant has presented a continuous process verification (CPV) plan that outlines monitoring activities planned for the future. The explanation of the CPV approach has been provided and is acceptable.

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The European public assessment report (EPAR) for Kymriah is a summary of the observations, omitting any details that are confidential/proprietary so provides limited detail. It seems the EMA were happy with the approach taken – this approach is entirely consistent (as far as can be determined) with the FDA guideline discussed in this talk.

EMA MAA OBSERVATIONS

Yescarta – CAR-T product, autologous

A major objection was identified during the procedure and was related to the fact that consistency of transduction of the autologous cells had not been fully demonstrated.

On the basis of the comprehensive responses and clarification provided by the applicant, together with various commitments, the issue was considered resolved.

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The European public assessment report (EPAR) for Yescarta is a summary of the observations, omitting any details that are confidential/proprietary so provides limited detail.

It appears they questioned the consistency of the transduction, its difficult to know what aspect wasn't satisfactory, it might have been insufficient process characterisation resulting in poor control of that step. Unfortunately the EPAR gives no data to know what the EMA considered to be too variable. The issue was resolved sufficiently to approve the product, but they seem to have had some follow-up measures which were likely to fill whatever gaps were considered present.

Of note this product was approved after the FDA and received PRIME support; so the concern was either not identified by FDA, or seen a little differently by EMA.

FDA BLA OBSERVATIONS

Kymriah – CAR-T product, autologous

3. Novartis did not run any batches **with leukapheresis materials that contained high levels of monocytes as advised by the FDA** during the pre-BLA discussion.

4. FDA questioned the acceptance criteria for CPPs and KPPs used in the PPQ studies. **Some of the CPP and KPP ranges are quite wide, and were based on data not submitted in the BLA.** These ranges would not help define a validated and controlled commercial manufacturing process. During the discussion with Novartis during the inspection, the FDA has recommended that the acceptable ranges for CPPs and KPPs should be revised to reflect the accumulative manufacturing data and experience. FDA indicated that **a simple 3 times of standard deviation may not be a suitable approach given the wide ranges of the available data**.

5. Some unit operation holding time was not defined (e.g. *<redacted>*)

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From a late review cycle report, but at the end acknowledges new data were submitted and were under review.
I left out Q2 as it simply expanded on the issue that the PPQ batches were not from the commercial process.
Point 6 was:
6. As the result, the FDA issued a 483 letter to capture these issues. Novartis has responded to the 483 letter and proposed to submit additional validation data by June 7, 2017 to address the 483 issues. Novartis indicated that new batches for validation PPQ runs have been identified and the new commercial batch records will be submitted by June 7, 2017. The CMC review team will review the new validation data as they become available.
Note the dossier was submitted end of March 2017 and approved in Aug 2017 – seems to suggest they were still doing PPQ runs……

POST APPROVAL ISSUES

Kymriah – CAR-T product, autologous

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Manufacturing

Novartis, still struggling with Kymriah manufacturing, is providing some out-of-spec doses to patients who ask

by Eric Palmer | Dec 18, 2018 12:11pm

https://www.biopharmadive.com/news/in-car-t-manufacturing-a-hurdle-novartis-has-yet-to-clear/543624/

Yet, about eight months on from securing a second approval for Kymriah (tisagenlecleucel), the company is still delivering the CAR-T treatment to some patients for free, unable to charge for a product that — while OK for use in patients — doesn't meet stricter specifications established for commercial use.

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Considering the previous observations (development process, previous slide) and the late submission of the commercial phase PPQ runs – it seems possible Novartis didn't take enough time to ensure they had developed an appropriate control strategy and collected enough PPQ data to set appropriate specifications. If the FDA took a similar approach for the commercial data, they may have pushed Novartis into tighter specifications than were appropriate. This slide might be the consequence of errors by both parties.

Please note I am only presenting a possible explanation, I do not know enough details to know if this is the explanation or not. But clearly such a situation could be the reason, so I wanted to emphasise how important it is to get PPQ right.

VALIDATION

What to include

- Should I include different donors?
  - Yes, a clear objective is to demonstrate the process is sufficiently robust to cope with variation in the starting material (donor, allo or auto).
  - Feels unlikely you could be sure of the impact across the whole process just with process characterisation.
- Should I include different batches of vector for a GM-cell?
  - Possibly, depends how consistent the vector is and perhaps more importantly, how consistently it works in the process, e.g. model process, trending across routine clinical batches.
- Should I include different batches of complex (e.g. biological) raw materials?
  - No (unless you have to), it would increase the number of batches needed and make validation more complex
  - Study at unit operation level, at scale/scaled-down to understand the CMA
  - Control raw material quality based on CMA, e.g. tighten acceptance criteria and/or undertake additional raw material testing (expand specification).
  - Consider additional process monitoring (e.g. test relevant to performance of raw material in the process) to collect additional information for trending across batches of the raw material.

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A few thoughts from me.

PLATFORM KNOWLEDGE

Knowledge or Belief?

- Guidelines discuss 'platform knowledge'
  - Don't mistake experience with the current and/or similar products as knowledge if its not based on (relevant) experimental data.
  - I've been told "we know the difference between patient variability and process variability"
  - When I asked to see the data…….
  - It didn't exist, they just 'knew' they could tell the difference.
- Until you have >1 similar product approved (e.g. CAR-T), you probably don't have platform knowledge, just experience.
  - Even then, are they really similar enough?

A personal concern of mine, platform know I would say means multiple licensed products from a platform, not just in development.

THANK YOU FOR LISTENING

Questions?

In God we trust, all others bring data.

William Edwards Deming
(October 14, 1900 – December 20, 1993)

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FURTHER READING

EMA guidance

EU GMP

EurdaLex volume 4

Annex 15: Qualification and Validation

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

EMA

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

Guideline on process validation for finished products - information and data to be provided in regulatory submissions (not specific for biological products)

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Other than the GMP for ATMP these are not specific to cell and gene (ATMP), and the DP validation isn't even specific for biological products, but mentions the same principles apply.

FURTHER READING

FDA Guidance

GMP

21 CRF 211

Guidance

Guidance for Industry Process Validation: General Principles and Practices

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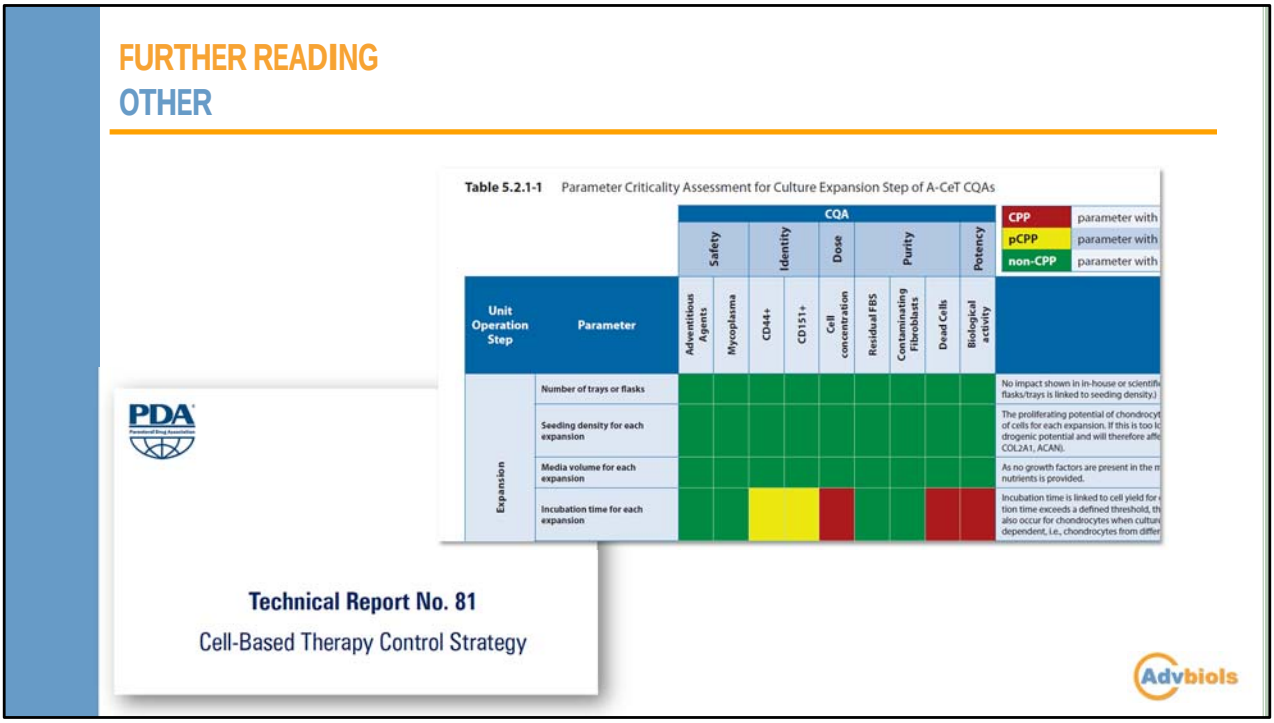
I focussed on this guideline for this talk.

FURTHER READING
OTHER



PDA – parenteral drug association
They produced a commonly cited document for mAbs called the A-mab study, it presents in some detail how to develop a control strategy for a mAb. Based on that, more recently they produced this report. The report is available from PDA.org