‘Next Generation’ Biotechnology Product Development, Manufacturing and Control Strategies July 16-17th 2018
Day 1 Morning Panel Session: Continuous and Advances in Manufacturing - Upstream
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

Perfusion/ATF Systems
Perfusion scale down clone screening model appears to have benefits as occasionally one can see a cell line that doesn’t respond well to perfusion in both scale down and in the actual ATF.
Perfusion can result in increased product consistency as it uses refreshed media (i.e. more consistent content over time).
Assuring product quality vital for perfusion/high density batch fed and important to screen at the clone stage, not just for productivity. Glycosylation can be impacted by these systems.
Continuous usually means perfusion in upstream but not necessarily totally continuous.
Implementing perfusion/new technology at the N-1 stage is an easier start in adopting the technology.
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**Shear/Sieving**

Is there shear stress in ATF processes – declining viability can be seen at end of runs but it is not clear it is due to stressing cells. However, this is not usually an issue with new cell lines as they are selected for optimal performance in ATF but could be for older cell lines.

In scale down models there can be shear through increased aeration. Sieving/clumping – are small scale ATFs predictive? This can be seen as high at the start of the run (sieving coefficient 30%) but then goes down later.

Fouling can occur in these systems and cells lyse. Oligosaccharides have been seen to be impacted and HCPs will go up due to cell lysis. Additives to cell culture medium or change out membranes can mitigate the issue.
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Analytics
Stainless to disposable really has no impact on the number/type of analytics but removing serum has allowed reduction in analytics due to less complex media. Using QbD also allows for reduction (e.g. clearance studies) allowing reductions to occur.

PAT/dynamic control influences the frequency of testing – one wants to get in front of an issue before it is too late. Statistics need to be standardized across industry for models to compare. Currently Raman evaluates every 15 minutes but some vendors have quicker ones.

In gene therapy one needs to enrich for ‘full’ particles (ion exchange or centrifugation). A suitable full/empty particle quality attribute can require to extra steps in processing. There is a need to understand the dynamics to understand where to include viral activation steps then can use traditional clearance once well understood.
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Analytics

Raman – RMS in models as good as precision of assays themselves (single digit percent's of averages) however some variability in models depending on what they are testing (e.g. amino acids).

Validation expectations for RAMAN – generic model is a stretch but for simple things such as glucose, cell density or same analytes it may work. Otherwise need specific models for product specific attributes.

The effort required to use advanced sensors for product quality depends on the application – if it is just another probe it is not as much (e.g. glucose or lactate) but product quality attributes often require a different level of validation.

Real time release should come only after one has thorough control of the process as part of the overall control strategy.

Modeling one day could replace a release test but needs stringent validation.
What are the advantages and disadvantages of utilizing Continuous Manufacturing or other newer technologies for upstream processes

**Advantages**

Higher productivity
Lower COGM
Process robustness
Improved viral safety
Shorter production times
Decrease footprint (scale out rather than scale up)
Continuous version for large molecule not the same as SM. Step-wise-fed batch – semi continuous – but is encouraged by agency
Efficiency better as long as not impacting quality
Using at N-1 stage allows to keep existing large tanks
What are the advantages and disadvantages of utilizing Continuous Manufacturing or other newer technologies for upstream processes

Disadvantages/Challenges

Trade off is batch definition – what happens with a deviation in a long process – what do you do? Batch requires risk for impact depending on when found etc.
Still uses a lot of media with the volumes required during perfusion.
Asset utilization – what do you do with fully depreciated tanks that are still useful?
How to purify large volumes of material/product coming out of higher productive bioreactors.
Larger perfusion residence time longer in tank can impact product quality.
How to dispose of disposables.........
How to do PPQ runs.........
What are the unique challenges, technical or regulatory, associated with advances in technologies for upstream processes?

Platforms of legacy/well known processes offer faster and efficient execution, reduced headcount, effective use of asset, fewer deviations, simplified supply chain/management – however new processes don’t always lend themselves to platforms as no ‘platform yet’.

Suppliers of materials – often we aren’t a huge part of their market so can pose challenges for supply of unique reagents/equipment/bags etc. For viral vectors it is mindset – one needs to consider the whole supply chain – how to get supplier agreements for critical reagents (plasmids etc).

Comparability - Any movement to the more advance processes needs comparability which can be complex and may even need clinical trials. It is also not just the number of analytical tools but lots of replicates helps.

Minor differences but with lots of replicates to show inherent variability can still show comparability.
What are the unique challenges, technical or regulatory, associated with advances in technologies for upstream processes?

**Comparability** – If changing a cell line for a marketed product there is naturally a higher requirement for comparability postmarketing. One company just provided a new BLA rather than show comparability, including new clinical data. One needs to show comparability in longer production processes to ensure that product quality is appropriate all the way through to the end, including end of production cell line testing etc. Changing only at the N-1 stage is less risky on several fronts, including comparability.
What are the unique challenges, technical or regulatory, associated with advances in technologies for upstream processes?

**Regulatory** - FDA has new emerging technology group – the ETT is a useful interaction with FDA – positive and get good feedback. Interaction with the agency important. It is optimal to go to agency for advice in advance of starting a comparability program. Often there are more questions in filings with new technology – so collaborate and use industry forums as well.

**PPQ** – With advanced process changes one needs to do PPQ and lots of process characterization but can process control replace the need for more lots and shorten the development timeline of process that is shown to be well controlled?

How can we compress process characterization and PPQ when clinical timelines are so rapid?
Day 1 Afternoon Panel Session:
Continuous and Advances in Manufacturing - Downstream
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**New models to help design processes** – It would be optimal to have feedback control – a mechanistic model based feedback control i.e. to predict what would happen in a column and then sensors to see what is actually happening thus a need for the right in line or at line sensors. FDA is open to modeling but one needs to demonstrate how the model is comparable to what goes on in ‘real life’ and where it fits into the control strategy.

Overall so far good experience in translating small scale models to large scale – especially impurity clearance.

**Downstream continuous processes** – The cost of primary capture has driven the most focus in chromatography – but continuous processing could be done elsewhere.

In series processing can be done and has been done is small scale to date.

The chromatography mode dictates the type of continuous processing – e.g. mode bind/elute or gradient.
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Implementation of Continuous Downstream Manufacturing

Why are we not seeing more of the continuous manufacturing? Currently available systems don’t always suit what is needed (gradients, only two column set ups etc.). We need to identify the ‘problem’ before companies willing to invest – no driver and only risk however, if you are starting from scratch with a new process/facility it can be of value.

There are new Protein A versions – more cost effective but convincing anyone is hard to implement due to risk and inertia for material that works.

To make the change need to invest in time too, people, building etc before results come into the company while using traditional technology – when to make the switch.

Vendors build demonstration versions into their business models and this can facilitate adoption.
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Definition of a batch
Where you test and stop/separate?
Break point where you change a virus filter or where you fill a container – a discrete place/stop. There is usually a place where you clean something or change things out.
A place where you segregate.
Not all continuous columns have same flow and have surge tanks so might have mixing that confuses what a batch is.
Needs to be prospectively defined…..traceability is important – how one batch links to another.
In perfusion many reactors feeding a single downstream train - many ‘batches’ feed on DS batch.
Define as time and amount of material?
Advantages of continuous manufacturing in downstream

Reduced size of columns
Time to purify product
Cost of resins
Higher productivity
Less buffer (this helps manufacturing capacity/throughput)
Storage costs and repacking time etc.
Reduces microbial risk through storage and packing
Can right-size to feed variability – 25% more resin utilization
Less issues with huge, heavy columns from a personnel and facility perspective. OPEX savings from clinical products that don’t work – fail early and cheaper.
Enables single use chromatography skids.
Practicalities mean likely to have hybrid approach and product dependent
Pseudo continuous offerings have just duplicated equipment and switch batch and forth (e.g. 2 tanks for viral inactivation) or switching UF skids - new technologies required for true continuous processing.
Needs of continuous manufacturing in Downstream

Batch to continuous requires comparability.
Complex unit operations inevitably require more monitoring.
Analytical methods nearer to process and faster turn around times.
Failure of long processes are more impactful - need to find stop steps.
Materials need to have strong microbial control as longer processing.
In line/at line analytics for downstream – moving in that direction.
Dynamic light scattering getting there. HCPs going to be much more difficult - MAM on line might get there. Not much use for batch process as can test at end and extraneous data.
For continuous processing what if you want to reprocess but have used up the life of the resin – what to do?
What happens if there is an unexpected hold in a continuous process........how to build into validation.
Microbiology Considerations
More complex processing systems can be harder to clean and might get contaminated.
Risk assessments sent to FDA lack supplier qualification for single use connections. How to deal with leaks and mitigation of failures and how to detect contamination downstream – ie can contaminate the whole downstream bit.
Design aspects to be considered ‘closed’ - single use technologies, defined ports of entry, closed to microbial ingress, validated connectors. Could still be SIP pipework free from microbial ingress.
Companies are wanting to work in ISO-9/CNC if using closed systems however leaks can impact entire downstream processes so need monitoring. However what does truly ‘closed’ mean - we need UF/DF membrane changes, resin changeover/packing so any ‘open’ steps should be under controlled conditions.
Need to consider how one segregates clinical from commercial systems – since for clinical there will be little development knowledge especially around microbial limits that are controlled by procedure.
Day 2 Morning Panel Session:
Modelling and Control Strategies
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

**Driver and utility for big data analysis** - key was underutilizing data being generated. CPV was still reactive and not translating process data to process knowledge.

The process allows for better utilization of data and real time analysis thus more eyes on the process and better documentation. Drives continuous improvement for more reliable and productive processes.

Big data is not just about gathering data – you could end up with a data swamp – but on the other hand you need to have data before you can analyze it. It isn’t too costly to simply collate data into one place. Once you have the data, then you can develop tools to analyze it.

Benchmarking against other industries they actually gain more data than the pharmaceutical industry. We lag in the ‘big data’ space. Standard multivariate approaches are starting to be unable to analyze the volume and complexity of our data so we need new approaches.
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Gathering Data

When do you bring in data about product, upstream impacting downstream during process development etc.

Starting to use process development data from the start into the data systems to integrate LIMS and product characterization data into process development.

There is a need to look at sources of variability for process capability – analytical methods themselves have variability that can impact the data. You must be able to parse out data from what is method versus process. Looking at signal to noise for all measurements and applying fitting to ‘signals’ such as smoothing are valuable. Also need to understand fitness of use of the equipment actually providing data.

Data systems can take several years and have big resource impact – best to be designed by both IT and business users together.

Need to attach metadata to data for analysis and make sure it is in the right place thus need data discipline.
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**Developing models**

Using high impact models can replace traditional analytics. Process engineers gaining more knowledge with statisticians gives the best models. Data scientists knowing the process more successful. Capabilities very important.

This can reduce Quality lead time, help develop PAT thus less sending samples to labs and testing actually more in real time.

To generate models that are predictive you need to operate in control to reduce the complexity of the model. If in control, RRT is less risky. RRT is a benefit of having a process under control. Models can also help show performance of the process.

When collecting loads of data, how do you assess what is useful or not? There will likely be less valuable data in a total data set but when consolidated and under holistic analysis the data will eventually show its own utility.
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Developing models
Data driven modeling is not enough and we always need process understanding and success depends how much confidence you have in your control strategy. For example, a data driven model is easier to use for chromatography if you can justify the associated variables. Yet degrees of freedom are almost infinite for a bioreactor. If you don’t have data as not enough lots what to do? In future still learn from previous products. How to link to molecular information in the future. Therefore bridge prior knowledge from other products. Plus are you manufacturing enough to show value of the investment. Model base control costs money but not huge incremental change as overall control strategy should control process. How many batches for incremental improvement? Platform based knowledge to supplement data. How to integrate clinical and preclinical data into our products/process. Looking at stability data to see how attributes might impact patients (plus exposure to increase limits).
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Using Models
What if outcome of in silico DOE doesn’t agree with the traditional approach risk assessment – do you need more confirmation? Models don’t always fit the data exactly. It is an iterative process – predict, validate, refit model, predict etc. Models rarely totally off if we have product and process understanding – e.g. standard chromatography – however more complex chromatography will be more challenging.

Can we move totally to in silico data and not wet experiments? It is unlikely we can replace totally but we can reduce the amount of testing – especially when you have prior knowledge. Some models can’t describe all aspects of the process so can focus experiments on those aspects the models can’t yet work on.

Can one over model? Don’t think so as part of gaining knowledge – can’t have too much data. However, tools can show overfitting and need statistical/process experts to check overinterpretation/assumptions. No escape from expertise…..
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Using Models
Modeling can simply be automated analysis of data without complex models.
Models can break down and you may need to go back to zero and start from scratch.
There are examples where process understanding gained through models has adjusted the supply chain and solved non obvious problems – thought to be raw materials – where a sub component was shown to be the issue through data analytics.
If a model doesn’t fit, it could be that new aspects of variation were not understood. Thus there is a need to go back and identify that new source of variability - e.g. work with raw material suppliers for example to understand what those new variables could be.
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**Using Models**

Models are good at showing shifts and changes but when things go way out, model based process controls can’t cope well with total failures. If you know the process is not performing comfortably, don’t trust sensors as they can hurt more than correcting it. There are grey zones that depend on the state of process. Even if there is a failure there is usually some event prior to it that a model can detect.

There can be a three-pronged approach to control systems - full detection, model based and self-sensor systems.

At the end of the day, it is hard to use models when working outside data ranges used to create the model.
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Replacing experiments with models and getting them approved
Can you replace experiments with models in filings for process characterization? It is possible to replace some experiments with modeling - but they need to go hand in hand together first until you have confidence in your model. Best to approach FDA to discuss.

In Q12 there is discussion about lifecycle management - one could prespecify in filing how to monitor lifecycle of the model upfront in a filing and monitor within the quality system. The agencies want to know there is a quality system to allow for things that are going well or not and what action you would take.

How do you document big data and models in a filing? You can show the how the model is suitable for use and how you would update model etc. You don’t want to send too much data to regulators but they may ask for relevant portions of it. You will need to describe model validation and lifecycle maintenance.
Day 2 Afternoon Panel Session: Emerging Analytical Technologies
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

**mRNA nanoparticles** – can be formed by precipitation techniques. Can encapsulate through microfluidics and two phase solvents approach (lipids/mRNA solution). Large polydispersities can occur so they are part of the control strategy.

Size is characterized via scattering – DLS, LS etc.

Made by series of methods, both synthetic and biologic.

When cleaning up remove both product and process related impurities and can reduce immune responses.

10 programs in clinic and 10 in development – VEGF mRNA for cardiac tissue regeneration.

Designed from initial sequences so have function relative to route of administration.
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**Status of new nanoanalytical technologies**
Nanosensors are in development to see how they work in the field. Factors affecting binding/signal depends on the type of ligand used but you can get very sensitive signal detection. Work is underway to increase affinities of coatings. Polymer coating is the most costly part – the nanotube itself isn’t too expensive.

**Characterization assays**
Requirements less than ones required for lot release but should be shown to be qualified to be ‘fit for purpose’ so there should be enough assay characterization to understand the data it provides. MAM has been used for process characterization.
What is critical to approval of new analytical technology?

Appropriate method development, characterization/qualification and validation – the more complicated the technology the more data is expected.

Need to show comparability/bridging to traditional methods.

There can be phase appropriate ‘qualification/validation’ but even then, might need more detail at early stages than a more traditional method (e.g. things like intermediate precision).

Qualification focuses on a ‘fit for use’ assessment.

Understand sensitivity, accuracy and precision.

Ensure no sample prep/assay artefacts.

Complex software needs to be properly validated and understood.

Lifecycle management of new technology may not be as well understood as traditional methods.

Ensure you interact with the agencies ahead of submission – can use ETT. Also speak at conferences in presence of regulators and industry.
What is critical to approval of new analytical technology?

After approval for one product, any relaxing of regulatory stringency for new technology depends on how similar the second molecule is. The mechanism of action of the molecule may also dictate the amount of information required.

The amount of information needed for attributes can depend on their criticality and ability to have process control.

Knowing your product is key – understanding what is a CQA or not can allow a non critical CQA to not require testing after characterization studies.

Whether orthogonal methods required for a single attribute depends on whether the method is truly orthogonal (e.g. fragments, HMS etc.)

For MAM, FDA OTR are themselves working on the method to help speed its development and OTR expert sits on ETT for MAM.
Are new modalities also driving new analytics?

Yes – more complex modalities are requiring methods beyond the traditional to characterize and measure structure and function

How can we make regulators confident about new technologies

Data!
Showing comparability with original technology plus analysis of materials used in clinical studies or other relevant reference standard/s
Often industry uses the new technology for characterization before moving it to QC to give more familiarity
What are the requirements where new species are found?
If you find new impurity but have no clinical samples to go back to you likely have sufficient patient use post-marketing, so should go back as far as you can. One needs to understand if any process changes created the new species or the method itself or if it is truly ‘new’. If you have a new species it should then be well characterized.

What are the risks when new technologies measuring different quality attributes?
Depends on the attribute, its criticality, is it new and what the assay is measuring.
What reference materials would be useful to help with new technology adoption?

They are needed should different species be found with a new method and can bridge back to clinical material.

A reference material forms a foundation/benchmark for testing rather than using different lots – specifically during method development to understand variability of the method versus the material. NIST Mab is an example of a class specific public reference material useful for Mab method development and would be useful to have for other modalities.
Thank you for coming to

CMC STRATEGY FORUM
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July 16-17, 2018
Gaithersburg Marriott Hotel
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