Biologics vs Small Molecules

Starting Comments for Discussion Group

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What makes Biologics Different?

- Need to worry about the chemistry AND biology AND biochemistry
  - Temperature sensitivity
  - pH
  - Shear
  - Biochemical diversity (different folding, different glycoforms, biologically derived bioproducts: clipping)
- Not always a clear structure-activity relationship (particularly for vaccines)
- Very dirty early process streams, with lots of other similar components that are difficult to discrminate by facile methods
- Structural diversity (lots of different types of biomolecules)
  - Proteins: MAbs, VLPs, Peptides,
  - Conjugates, Complexes
  - Polysaccharides
  - Nucleic Acids: DNA for gene therapy and vaccines, RNAi
  - Viral Vectors (purified and non; live, attenuated, inactivated)

How are Biologics Similar to Each Other?

- Most have primary components derived from Fermentation or Cell culture
- Most are produced using a handful of unit operations
- Prefer neutral pH and are in general more stable in the cold
- Most have some type of spectroscopic signature in purified form (ie A280/A260)

Synergies between biologics and small molecules

- Incoming Raw Materials
  - Functional analysis of process inputs
- Multivariate process analysis equally applicable to both realms (in many instances more process data is collected from biologics, facilitating development of correlations to yield)
- On-line analyzer tools used for API synthesis can also be used in biologics manufacturing
  - On-line HPLC, on-line UV for monitoring chromatography columns, in-line NIR/FTIR for fermentation/cell culture
- Fill/Finish unit ops identical with sterile small molecule dosage forms
  - Lyophilization
    - On-line mass spec for moisture, automated process data analysis
  - Vial inspection/headspace analysis
  - Spec methods of analysis of final product concentration
  - Excipients are biologically based-frequently
- Cleaning validation toolbox similar
  - On-line TOC, on-line conductivity, VHP monitoring
- Well characterized, therapeutic proteins will be more like pharms that vaccines. However, there still is considerably more heterogeneity in structure and potency assays are more complex.
- Therapeutic proteins products are regulated in the US by CDER as are pharms.

Overall the principles of PAT are the same!

In some cases, there are more off-the-shelf simple PAT tools for biologics manufacturing (sensors/probes, DO, OD, electrolyte/metabolite instruments, flow cytometry etc.)

Is there a systematic approach for PAT of Biologics?

- Process Platform-wide PAT
- Form/Fill PAT that can be applied to sterile pharms should also be applicable to bios (specific checks such as: fill checks, dissolution curves, pH control, lyo monitoring etc.)
- Unit op based: this works great for Upstream!!!!!

What is missing?

- Rapid activity/identity assays that works in a variety of process streams/matrices
- Rapid contaminant detection on line

Backups

PAT of Pharmaceutical Drugs

- Been around for a long time
- Very systematic approach
- Lots of examples of practical and successful application

- The same cannot be said for PAT for Biologics

WHY?