The Alchemy of Process control: regulatory flexibility and supply robustness

Kim Wolfram Director, Regulatory CMC

National Academy of Sciences Identifying Innovative Technologies to Advance Pharmaceutical Manufacturing

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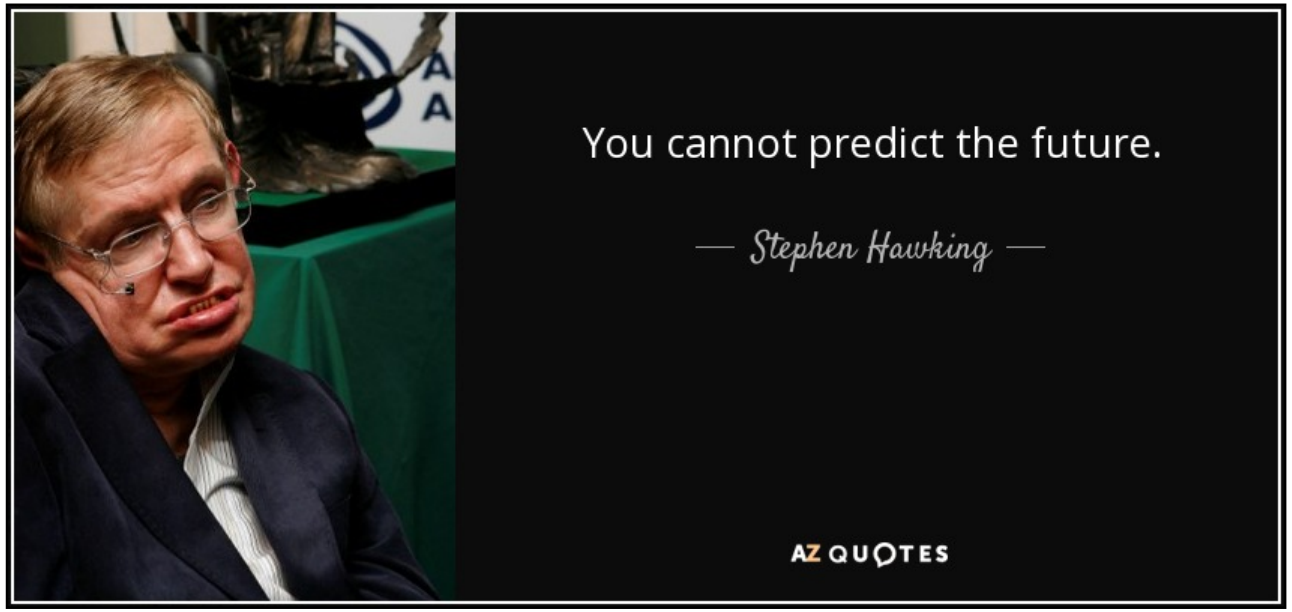
Can you predict the future?

Why thinking about the future is a good idea:

- Build robustness and sustainability
- Better design
- Creativity
- Reduce impact of disruption



Challenges:

- Black swan events
- Predicted harms can also have unanticipated benefits
- Failing to account for exponential change

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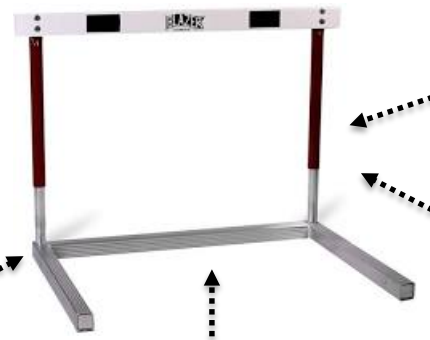
Current and predicted future ‘hurdles’ (not barriers)

Affiliation and trust building in virtual settings

Inability to predict the future

Increased complexity: modalities, patient demographics, and supply chains



Paradox of opposites

Bias (e.g. narrative)

Globalism (convergence) vs Nationalism (divergence)

Increasing number of technology and social disruptions

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How does this relate to Alchemy and Process Control ?

Alchemy: the medieval forerunner of chemistry, based on the supposed transformation of matter. It was concerned particularly with attempts to convert base metals into gold or to find a universal elixir (cure all).

Control Strategy : A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10).

Alchemy of process control: the transformation of planned set of process controls into a control strategy that is derived from prior knowledge and product & process design that assures process performance, product quality, sustainable supply, regulatory flexibility, and is built on a foundation of trust, diversity &inclusion and patient centricity.

Let's start with shared definitions

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Current and predicted future opportunities

Supply robustness by design

Advanced analytics

Control strategy design (science and risk-based approach)

Patient Centricity

Diversity& Inclusion

Structured submissions (KASA) & Prior Knowledge

ICH Q12

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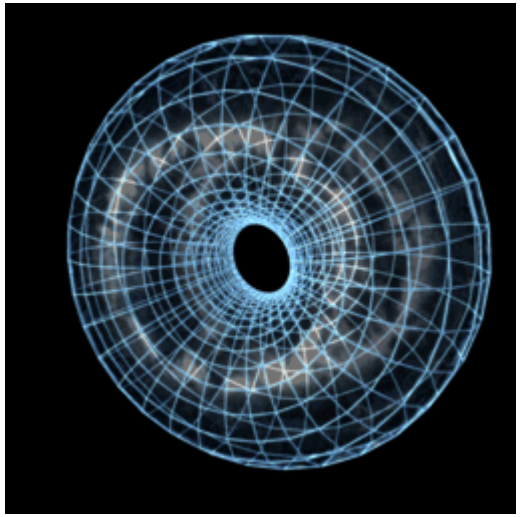

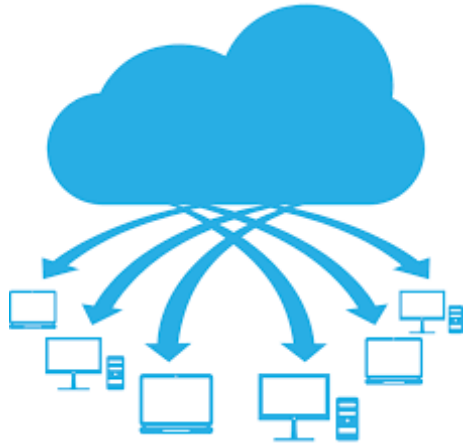

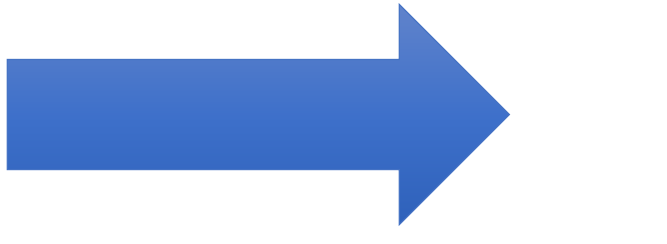

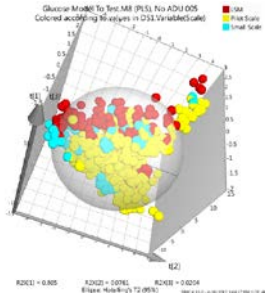

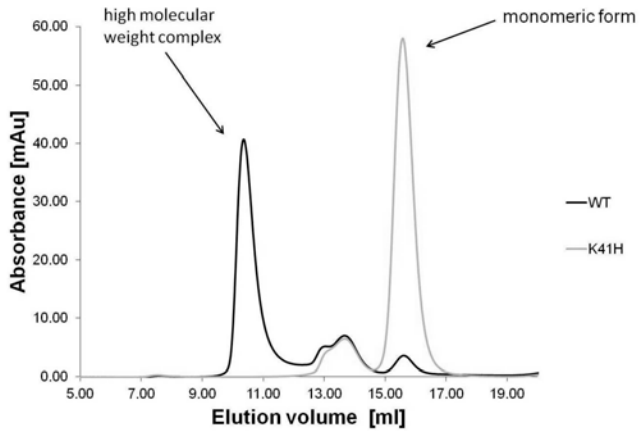
high molecular weight complex
monomeric form
60.00
50.00
40.00
30.00
20.00
10.00
0.00
Absorbance [mAu]
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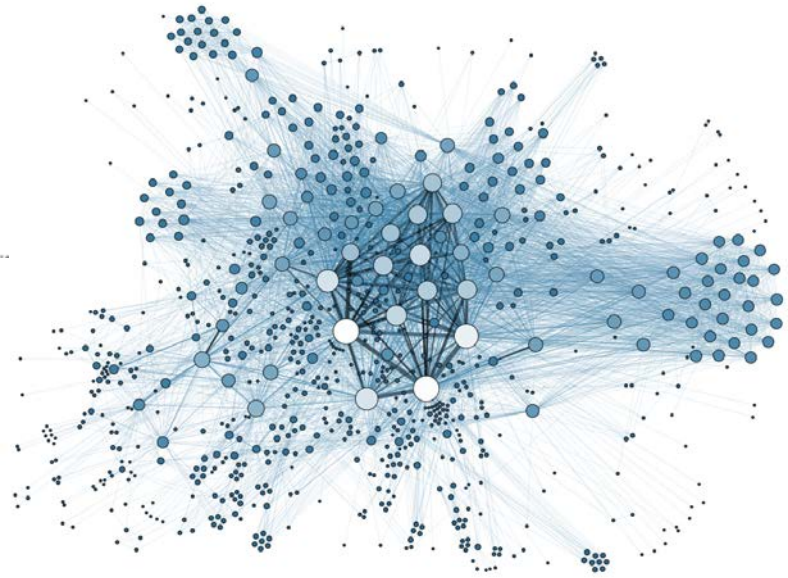

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ICH Q12: Looking forward

The optimist: Q12 will increase the global use of PACMPs and eCPs, support alignment between Sponsor and Regulator (for ECs/non-ECs), increase visibility to planned changes via PLCM, and increase the number of notification changes (based on science and risk-based application). Local regulations and guidance will converge with ICHQ12.

The pessimist: The lack of harmonization of established conditions will promote regional differences and supply chain fractions (resulting in additional supply challenges). Local guidelines/laws will not be changed to align with ICH Q12 and confusion will persist.

The idealist: Regulatory flexibility is a means to a larger end. The primary benefits of ICH Q12 will be broader adoption of ICH guidelines globally, resulting in science & risk-based approaches. This will increase the robustness of submissions & supply chains and enable future technology, transparency, and alignment on what CMC elements are critical for patients.

The realist: A combination of the above. Challenges will continue for non-ICH countries that represent the longest review/approval timelines and in some cases the smaller patient populations. Global alignment of core elements of the dossier will reduce supply complexity and increase access to therapies for all.

Post-approval changes that increase supply robustness

How to balance the risk of implementing the change compared to the risk of not carrying out the change?

- Improved analytical methods
- Advanced analytics
- Additional manufacturing sites
- Use of PACMP and expanded change protocols
- Dual/additional vendors for raw materials or starting materials
- Modification of control strategy in response to increased data (statistical analysis)
- Continuous manufacturing

In some cases these changes are not pursued as a result of the regulatory complexity and long global approval timelines (e.g. 3-5 years). This could impact the ability to supply patients in the long term.

A paradigm shift would benefit patients and reduce risk of supply shortage.

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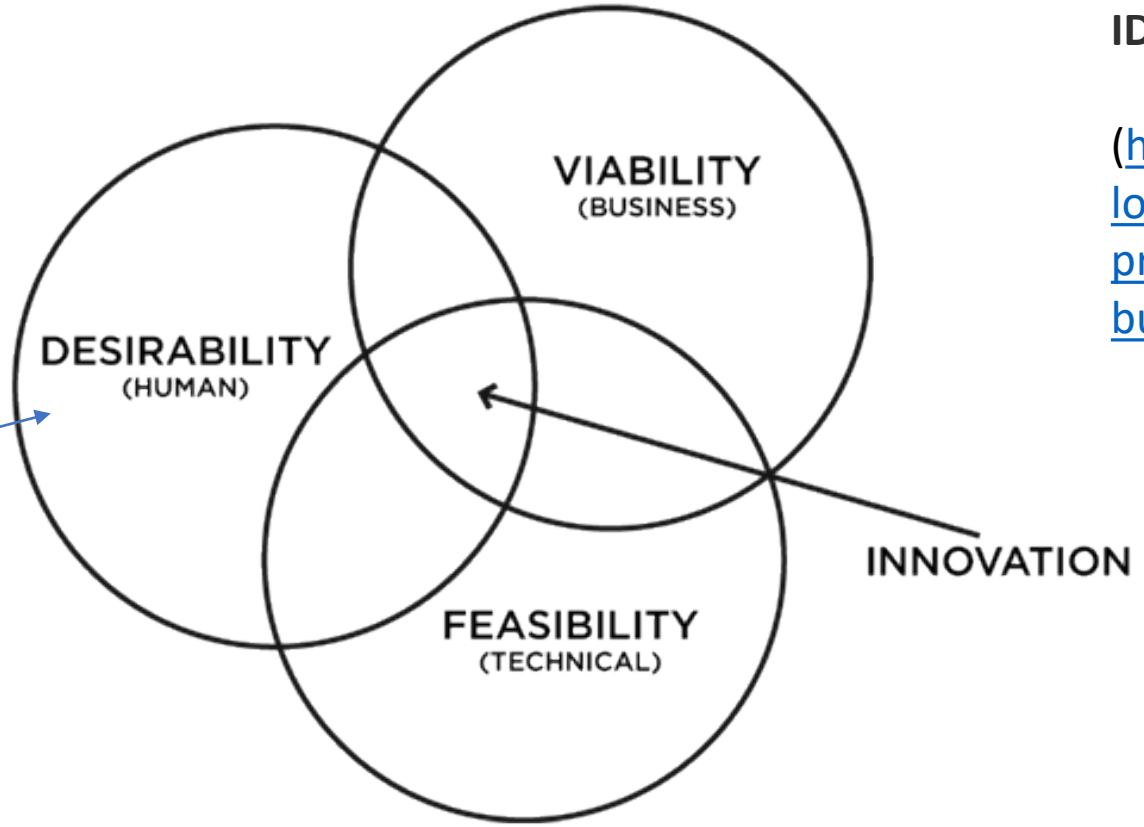
Desirability, Viability, and Feasibility

"Deep understanding of the problems and realities of the people you are designing for"



IDEO Design Thinking:

(https://www.ideou.com/blogs/inspiration/how-to-prototype-a-new-business).

Feasibility: implementation: the distribution channels, the capabilities you need for pulling off the solution and the potential relationships you can form with external partners.

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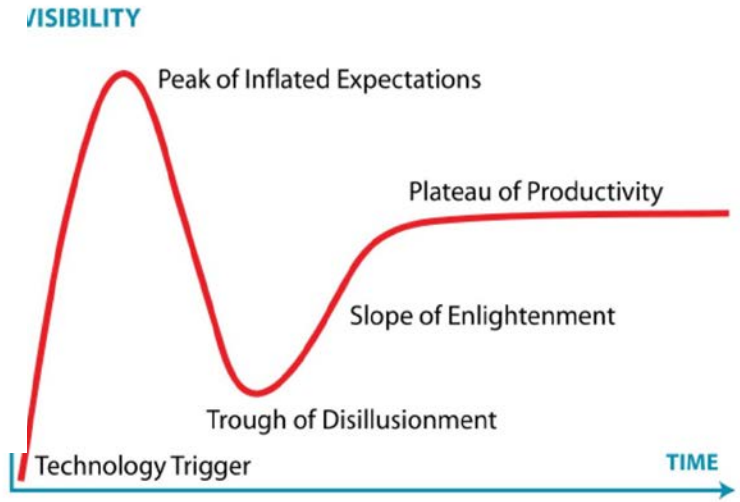
A JOURNEY: WHERE ARE YOU, THE PATIENTS, and YOUR PRODUCTS?

Patient Journey

Gartner Hype Cycle



CONTEXT MATTERS!

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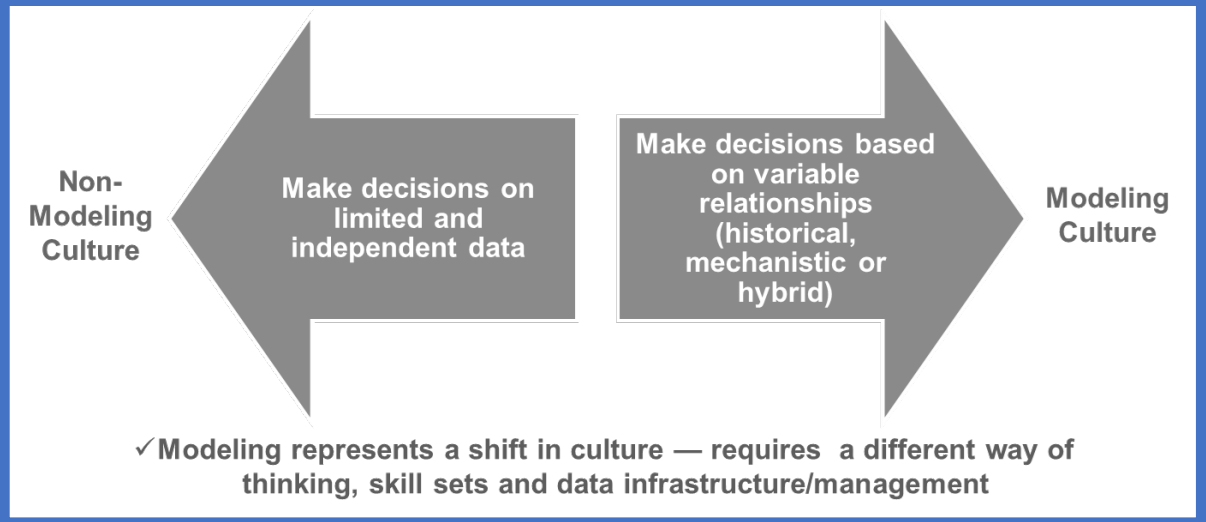
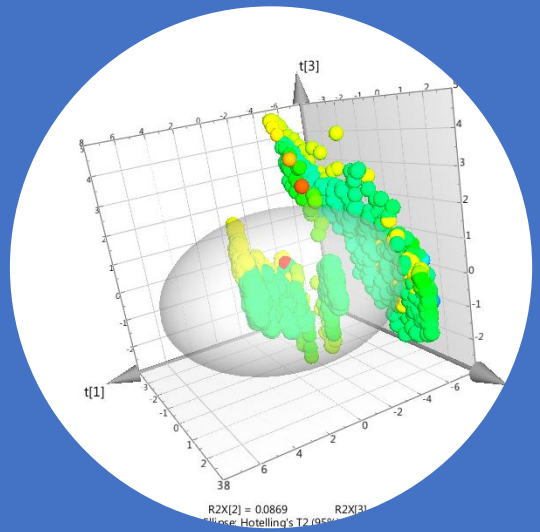
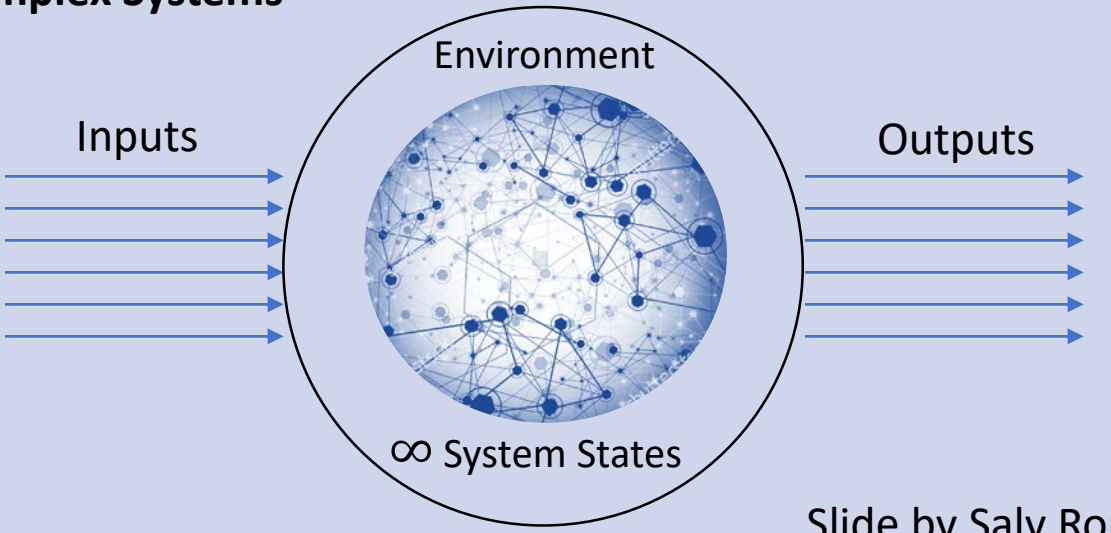
Modeling as a Part of your Culture





Complex Systems



Slide by Saly Romero-Torres et al

"I can do things you cannot, you can do things I cannot; together we can do great things"

Mother Theresa

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Biopharmaceutical Process Model Evolution- Enabling Process Knowledge Continuum from an Advanced Process Control Perspective

Saly Romero-Torres, Kimberly Wolfram, John Armando, Syed Kaschif Ahmed, Jun Ren, Chao Shi, Dan Hill and Rob Guenard

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As the pharmaceutical industry moves into the cyber-physical era, sometimes referred to as Industry 4.0, it will be imperative to harmonize terminology and expectations when developing advanced manufacturing technologies to accelerate their successful adoption and maturity. One of the main pillars of Industry 4.0 is automation intelligence through advanced and cognitive controls.[1] Intelligent process control strategies are also known as Advanced Process Controls (APC)– *see glossary of terms in Table 1 for more information on control terminology*. APC strategies enable process state/condition visibility and process self-optimization which translates to better variation management and higher process capabilities.[2,3] Most APC strategies employ process models at their core.[4]

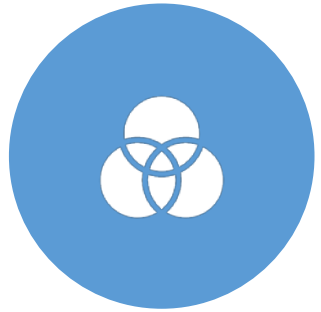
Even though many industries are already realizing the benefits of APC, intelligent control concepts are not yet widely adopted in pharma, with very few published applications.[5,6] Most pharmaceutical plants still operate in a very manual mode without the data infrastructure required for real-time process modeling (from a data synchronization and aggregation standpoint).[7] This makes model development and maintenance for APC applications very challenging. Even when the data infrastructure is sufficient, questions regarding regulatory impact, global acceptance, intended use, risk versus benefit, cost and model maintenance frequency may lead to strong headwinds to adoption of the technology and many hours of interesting debate. This debate becomes exacerbated by three constraints. The first constraint being that it is not possible to determine the final intended use of most process models until their performance has been assessed. The second constraint is finding resources with the right combination of domain knowledge, modeling and control competencies. This interdisciplinary combination is key when developing models for APC applications.[8] The third constraint is the general lack of deep process understanding in support of model optimization and justification at the time of filing. For many processes, it is difficult to identify/develop robust models that describe the process dynamic states and outputs with the precision and accuracy of an analytical technique early in the commercial process lifecycle. This is particularly true when dealing with complex dynamic systems such as a bioreactor. This however doesn't mean that modeling activities do not have a place or should be avoided for early stages of the commercial lifecycle of complex processes. In fact, it should be the opposite and process modeling should be started early in development to begin to build the necessary data and knowledge

Alchemy of Process Control

PATIENT CENTRICITY & DESIGN

SUSTAINABILITY AND SUPPLY ROBUSTNESS

KNOWLEDGE AND ADVANCED TECHNOLOGY



QUALITY. DIVERSITY AND INCLUSION AND TRUST

Calls to action:

Empathy and patient centricity: Deeply understand the dynamic needs of the patient development (via TPP, QTPP, control strategy, supply chain, and planned post-approval changes).

Ask questions to learn context about where people and products stand in their journey. Modify your approach based on where people and products stand.

Advocate for regulatory convergence and inclusion (ICH Q12, language standardization, mutual reliance, and digital regulatory information tools).

Mitigating supply chain risk by designing for supply robustness and changing paradigm (ICH Q12) for post-approval changes that mitigate supply risks.

Create diverse teams with cross-functional (end to end) mindsets

Acknowledgements

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Biogen Regulatory CMC Team

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