

MOMENTA



**“Characterization and Equivalence of
Complex Biologic Products”**

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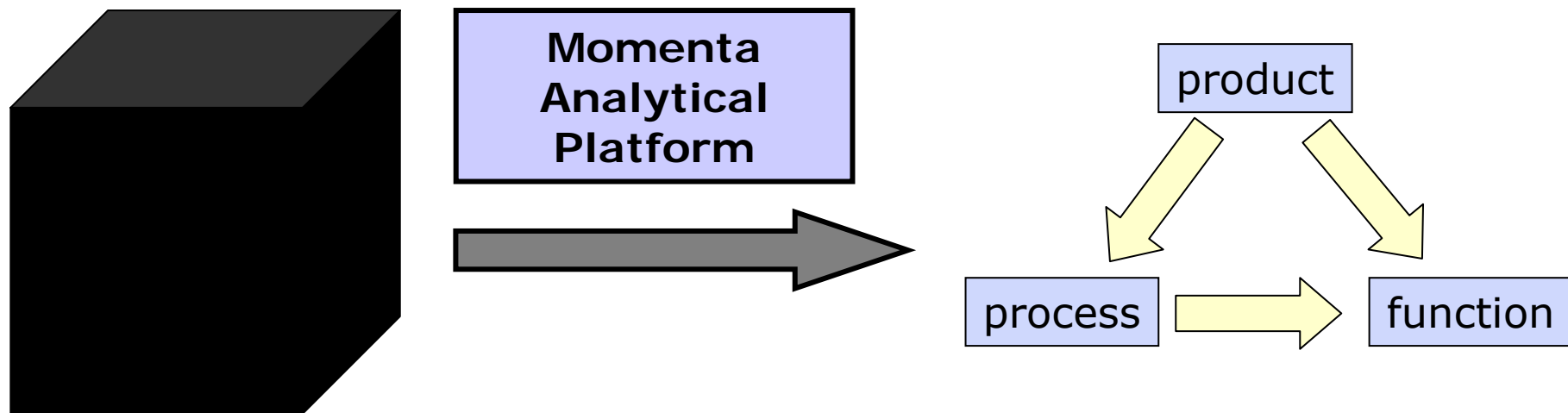
Senior Vice President, Research

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A Historical Time

- **Biopharmaceutical industry is at an exciting cross roads to help redefine generic drug opportunities**
 - Complex products present a continuum of technical, regulatory, and legislative challenges
 - Technology available to enable characterization of complex biologic molecules
 - Opportunity for science to play a role in shaping regulatory pathway for complex biologic products

Complex Mixture Molecules: Using characterization to “demystify” black box



- **Leverage novel analytics to:**
 - achieve thorough characterization of chemical constituents (**Structure**)
 - design and control of manufacturing processes (**Structure-Process**)
 - relate structure to biological and clinical attributes (**Structure-Activity**)
- **Bring Complex Molecules to be on-par with small molecule drugs**

Defining Structure

Must include

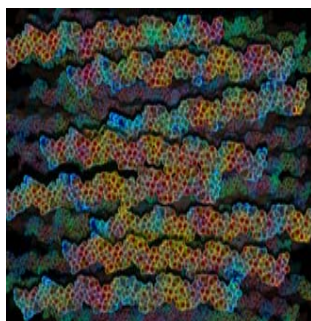
- Chemical characterization
 - Physical characterization (secondary, tertiary, quaternary)
 - Biological characterization
 - Impurities and degradants
 - Stress behaviour
-
- When available, reference standards for RLD can be used. Else, innovator drug product is the standard.

Characterization should define the molecular, chemical and structural attributes of the product

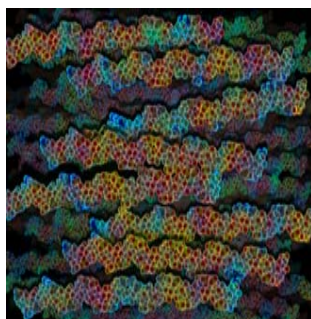
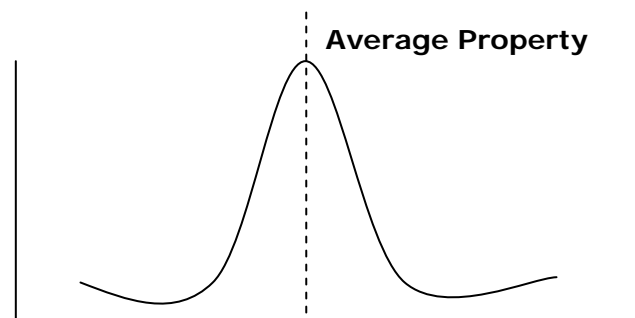
Need to appropriately “integrate” a variety of analytical methods to ensure complete coverage

Defining Structure: Challenges with Complex Mixtures

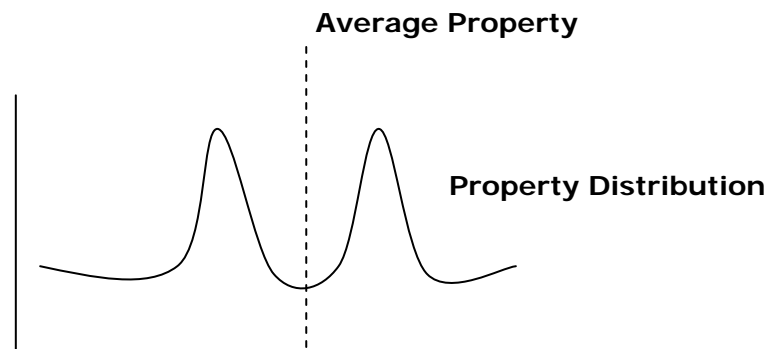
- Advanced analytical techniques offer limited “projections” of the complex mixture
- Structural attributes captured as ensemble averages
- Comparability based on “point to point”



Complex mixture



Complex mixture



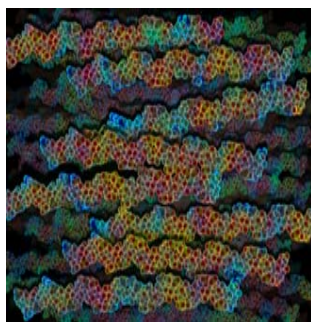
Defining Structure: Thorough Elucidation of Chemical Structures

Approach: Orthogonal Analytical Techniques

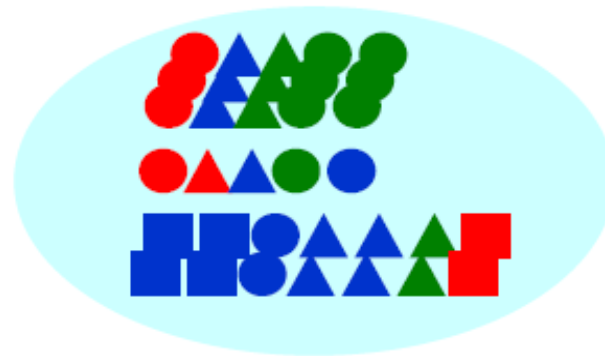
- Use orthogonal analytical techniques to:
 - Characterize components of the ensemble
 - Leverage complementarity of analytical projections
 - Tailor suitability of analytical methods

Result: Thorough Chemical Characterization

- structural identity of species in the mixture: composition, sequence, and abundance of all species above threshold
- mass balance (accounting for all species)



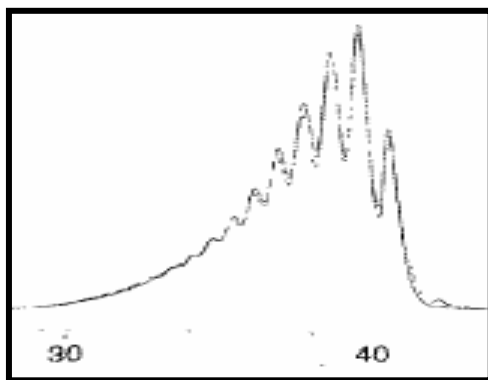
Complex mixture



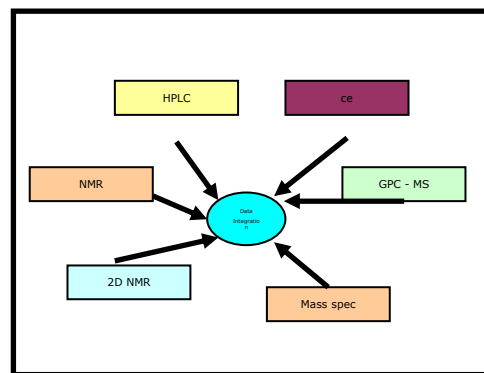
Defining Structure: The Need for Data Integration

Summary of Data Integration Method

- Integration of unique, yet complementary data sets (derived from multiple analytical methods) enables the structural identification of complete mixture
- Analogous to solving an X-ray crystal structure
- Provides a rationale for methods (data sets) that are both necessary and sufficient to demonstrate thorough characterization as well as equivalence



Previous Technology



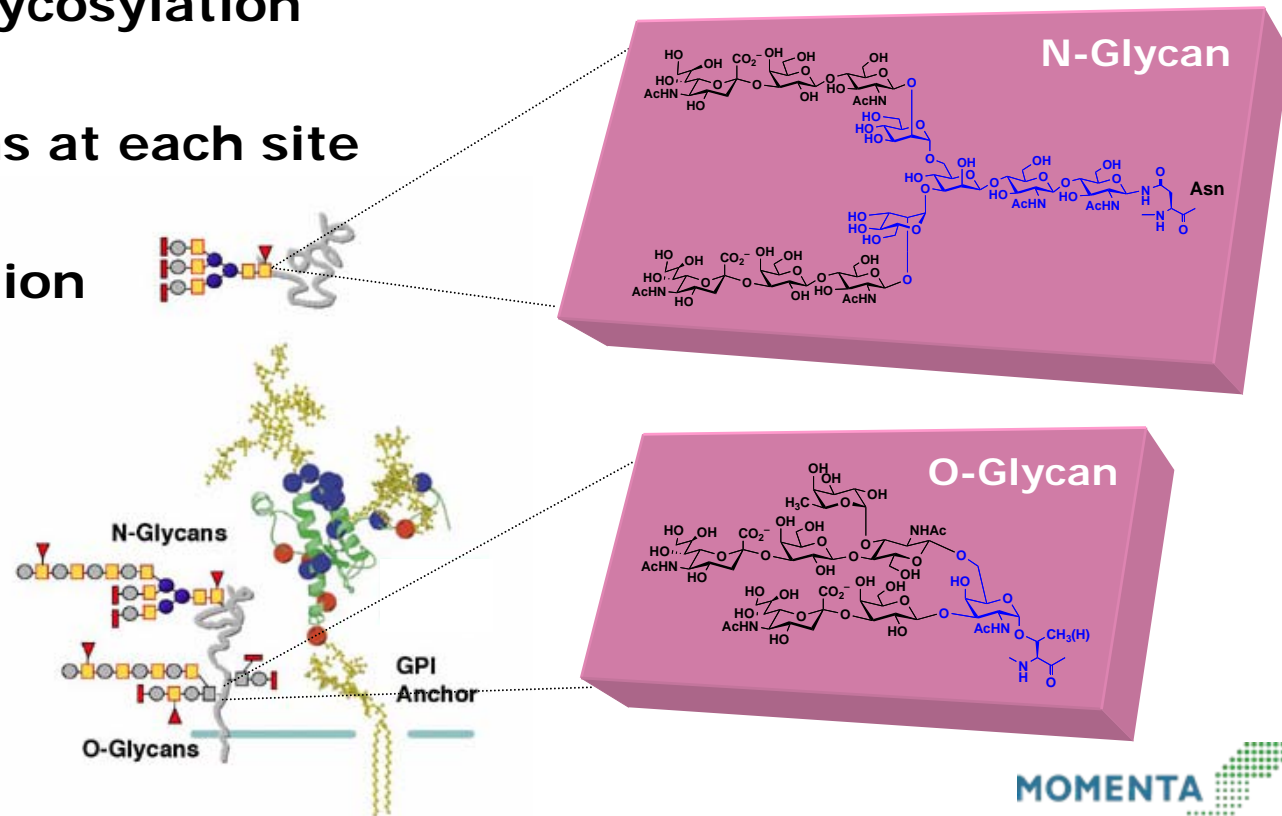
Multiple State-of-the-Art
Characterization Technologies

Sequence	Prevalence
SBN135NY89T6J7	57
GGH13HF68L4N5	63
SDFP	231
23HJKLO99	4
45THQCX8547	71
48DSMX	123
.....	
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Data Integration

Example: Glycoproteins

- Glycoprotein structures exist as complex mixtures
- Same protein backbone
- Multiple sites of glycosylation
- Multiple glycoforms at each site
- N and O glycosylation



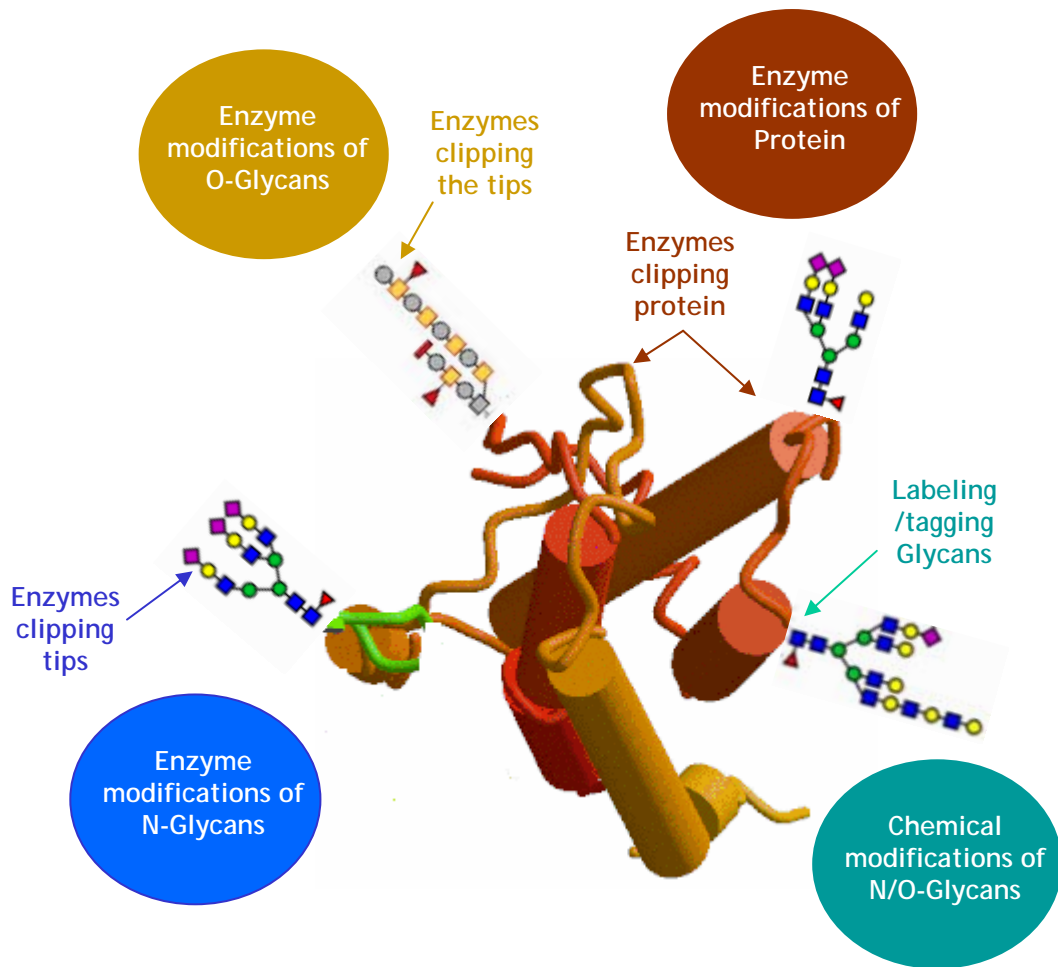
Glycans: Challenges

- Lack of tools to study glycans
- Complex, non-template biosynthesis
- Heterogeneous, polydisperse chemical structures
- Cannot be amplified, low amounts of material
- Partial/non-deterministic information on glycan structures

Current Technology Capabilities

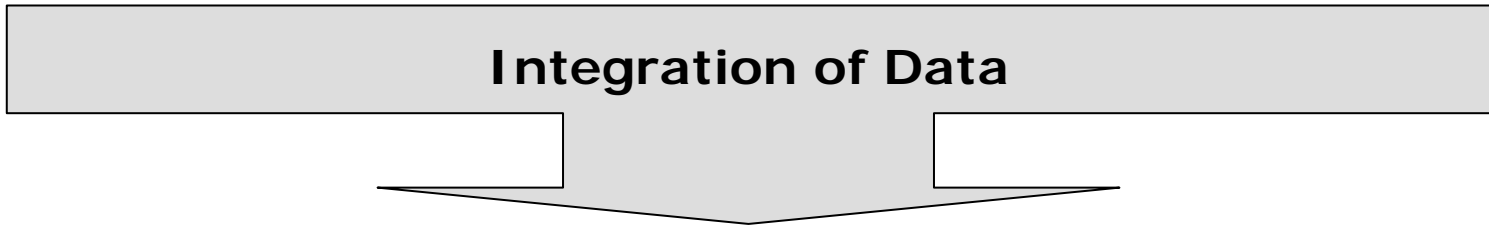
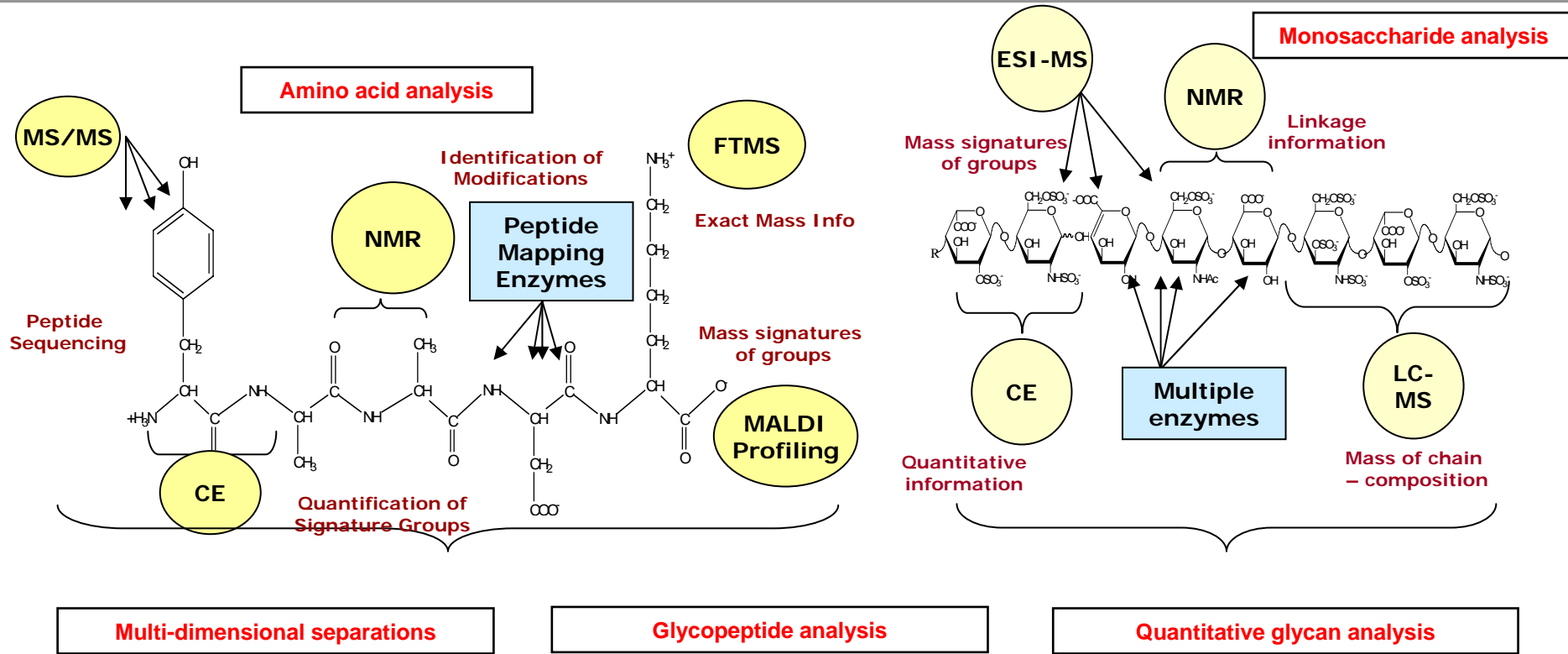
- Non-specific cleavage
 - Chemical methods
 - Enzymatic methods (PNGase-F etc)
 - Loss of site information for multiple glycosylation sites
 - Sample loss and bias introduced
- Separation and resolution challenges due to overlapping peaks
 - Compositional analysis
 - E.g. Monosaccharide analysis
- Distribution analysis
 - Comparison of traces to determine reproducibility in manufacture
 - Calibration with known standards (very limited) to determine identity
 - Co-elution of multiple species in the same peak confounds analysis
 - Isomeric structures (same composition, different linkage) cannot be discriminated
 - Low abundance species often not accounted for – focus on major species

Comprehensive Approach to Structural Characterization



- Release of N/O glycan functional groups by selective enzymes
 - Sialic acids, Fucose etc
- Chemical Modification of Glycans
 - Mass or emission based
- Digestion of the Protein with enzymes to release glycopeptides
 - Tagging Peptides for selective characterization
- Analytical Technologies
 - Mass Spectrometry [MALDI-MS, ESI-MS, AS-MS etc]
 - Capillary Electrophoresis
 - Liquid Chromatography
 - NMR
- Complex Data Integration

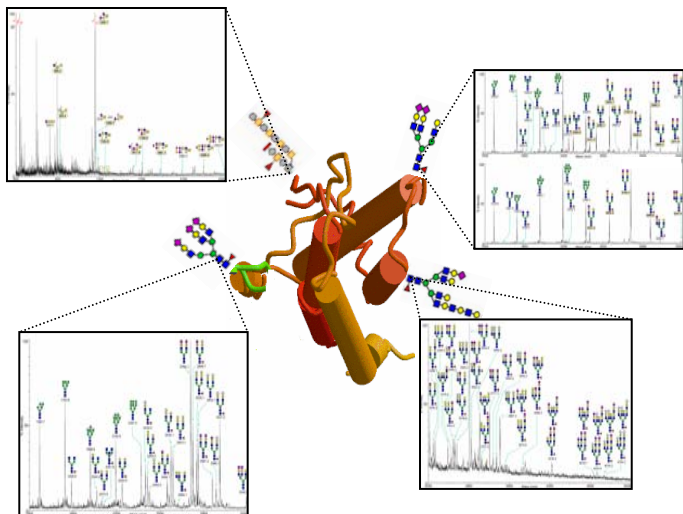
Integrated Approach to Precise Chemical Characterization



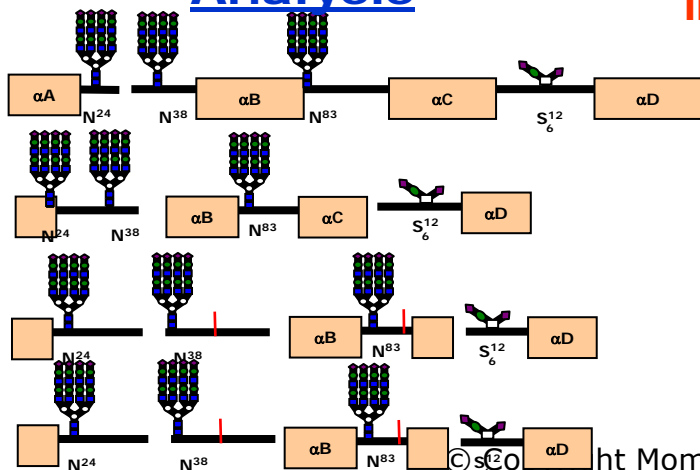
Convergence on unique solution


Solution of Glycoprotein Structures





Glycan Analysis



Glycopeptide Fragment Analysis




**DATA
INTEGRATION**

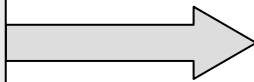
Structure	Prevalence
 Structure 1	7239
 Structure 2	1719
⋮	⋮
 Structure 307	1026
 Structure 308	6127

Illustrative

Developing Equivalence Criteria

Concept of "Equivalence Windows"

Currently Marketed
Complex Products



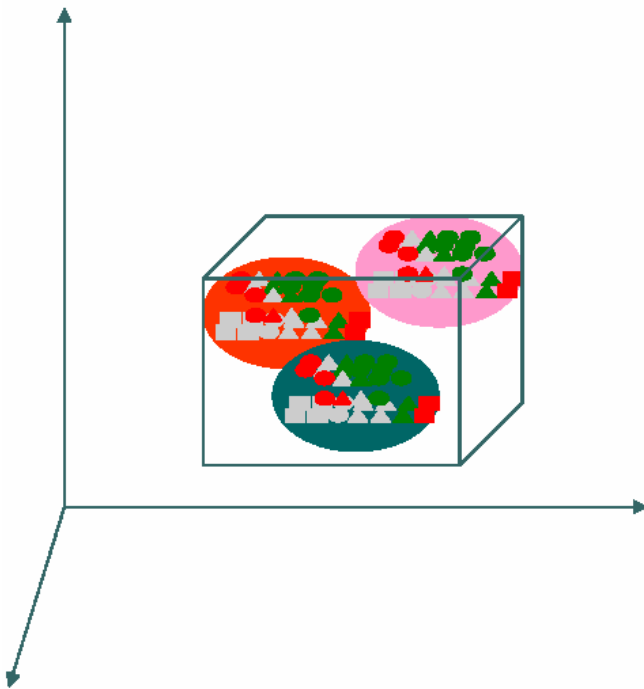
Momenta Analytical Platform

Thorough Chemical Characterization

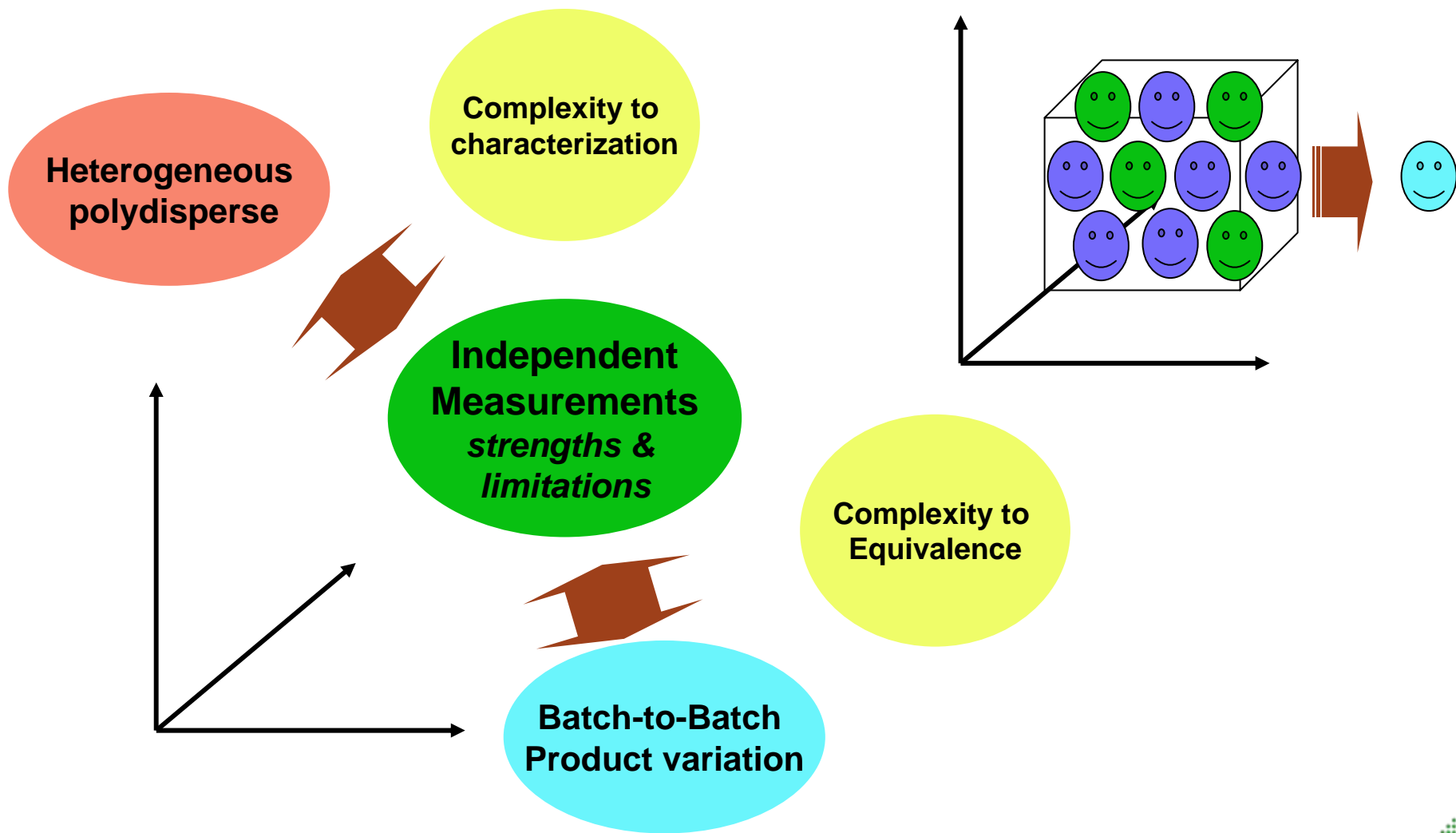
**Define Batch-to-Batch Variability of
Innovator Product**

Develop "Equivalence Window"

- Covers a multi-dimensional area (box)
- Aggregate properties of the entire mixture – not a point to point comparison

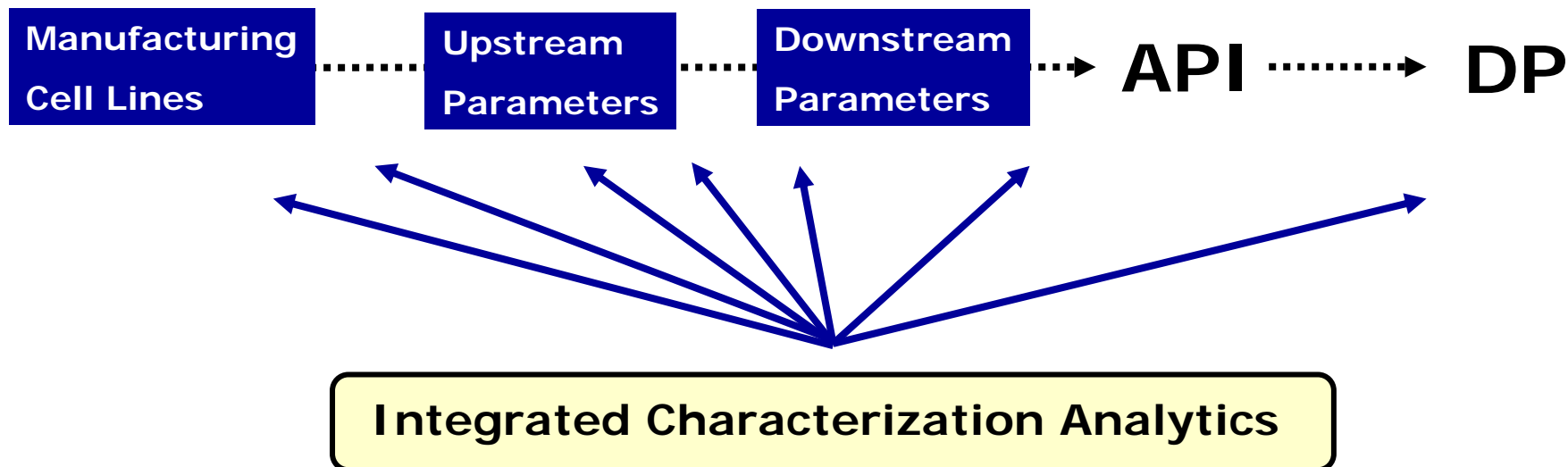


Multivariate Equivalence Windows for Complex Biologics Needs to be Established



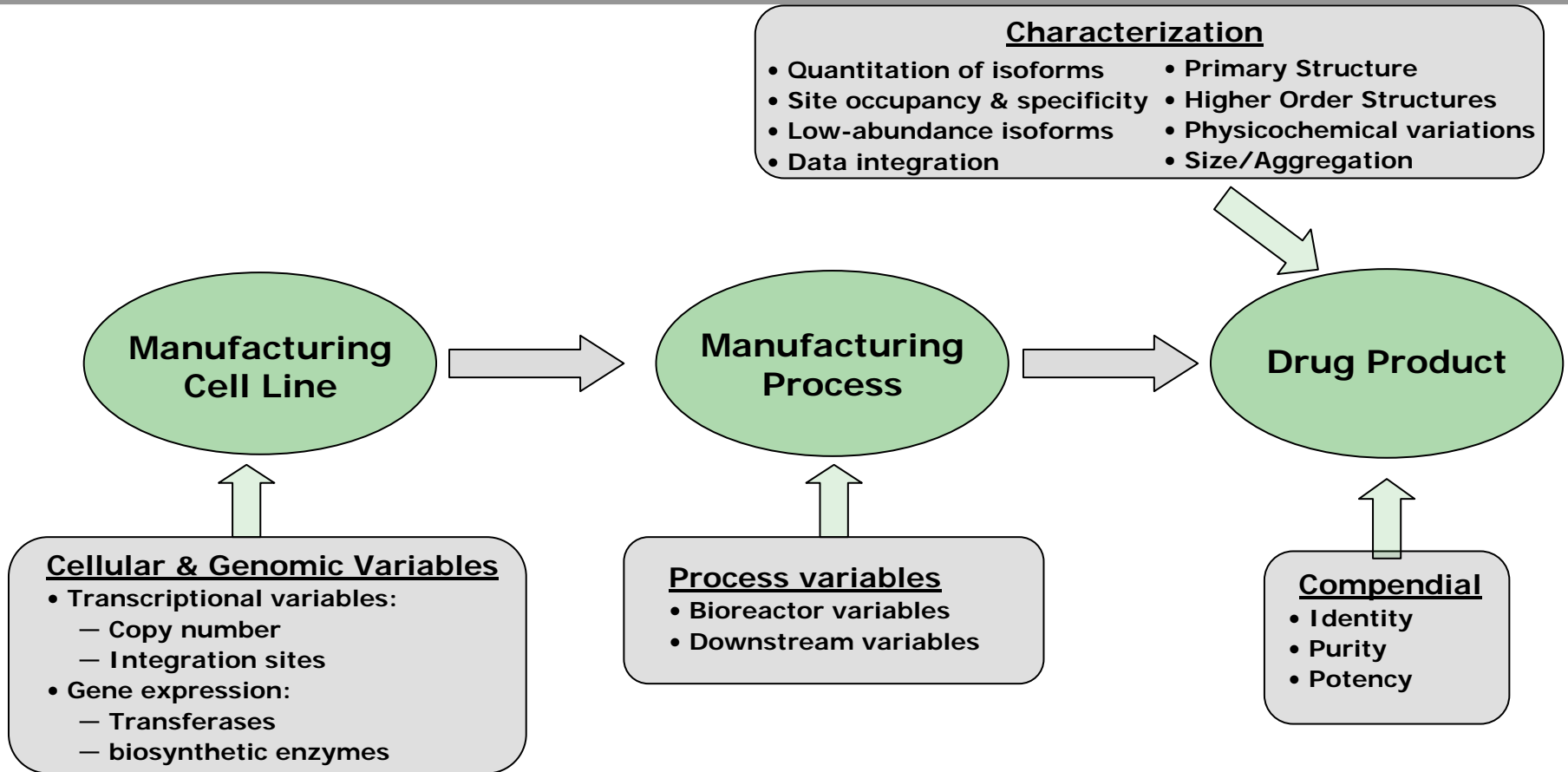
Structure – Process:

Enhanced understanding of complete process



- Product Specifications
- Product Quality Attributes
- Process Parameters and Controls
- Concept of Design Space

Reverse Engineer the Process



Explore multi-dimensional design space to achieve product
within target equivalence window

Summary: Thorough Characterization of Glycoproteins Requires New Levels of Analyses

- Current analytical techniques provide only selected "perspectives" or "projections" of glycoprotein characterization.
- Appropriate integration of analytical techniques can provide thorough characterization of complex biologicals
- For complex biologics there is a need for multiple measurements from orthogonal analytical techniques that provide different "perspectives"; these techniques can be integrated in a multidimensional "equivalence window".
- Defining appropriate design space, in combination with suitable analytics can enable reverse engineering of process

**A New Approach to Complex Molecule
Characterization and Equivalence**

Goal for Complex Mixture Molecules

- **Leverage analytics to:**
 - Achieve thorough characterization of chemical constituents (**Structure**)
 - Design and control of manufacturing processes (**Structure-Process**)
 - Relate structure to biological and clinical attributes (**Structure-Activity**)
- **Bring Complex Molecules to be on-par with small molecule drugs**

Momenta is developing portfolio through characterization of complex mixture products

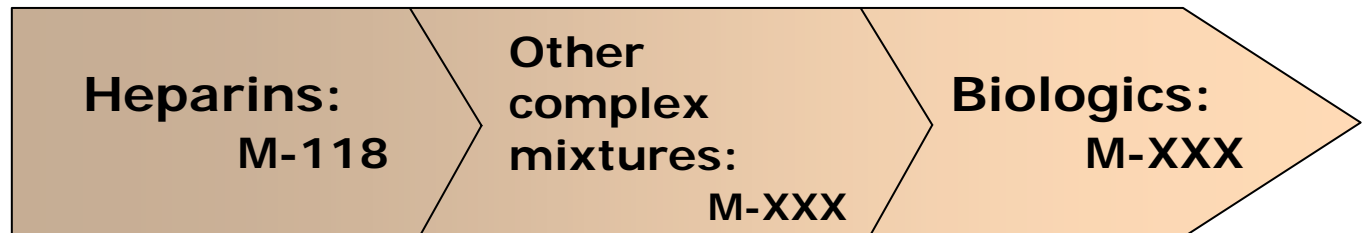
Technology-Enabled Generics

Abridged



Technology-Enabled Improved Drugs

NDA / BLA



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