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General Commentary

Technical Decision Making With Higher Order Structure Data: Perspectives on Higher Order Structure Characterization From the Biopharmaceutical Industry

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ABSTRACT

Characterization of the higher order structure (HOS) of protein-based biopharmaceutical products is an important aspect of their development. Opinions vary about how best to apply biophysical methods, in which contexts to use these methods, and how to use the resulting data to make technical decisions as drug candidates are commercialized [Gabrielson JP, Weiss WF IV. *J Pharm Sci*. 2015;104(4):1240-1245]. The aim of this commentary is to provide guidance for the development and implementation of a robust and comprehensive HOS characterization strategy. We first consider important concepts involved in developing a strategy that is appropriately suited to a particular biologic, and then discuss ways industry can partner with academia, technology companies, government laboratories, and regulatory agencies to improve the consistency with which HOS characterization is applied across the biopharmaceutical industry.

Introduction

Developing innovative medicines for patients in need is a goal shared by scientists who develop biologics and regulators who approve them. For protein-based therapies, structural properties of the molecule are one crucial element upon which the quality of the medicine depends; consequently, protein structural characterization is an area in which scientists from industry, regulatory agencies, and academic institutions can work together effectively to improve and ensure drug quality. Traditionally, protein structure has been defined as a hierarchy of structural levels beginning with primary structure and culminating with quaternary structure. In this context, the foundational covalent linkages are considered primary structure, the subsequent formation of localized structures facilitated by hydrogen bonding (e.g., helices and sheets) is considered secondary structure, the overall folding of the protein in 3-dimensional space is considered tertiary structure, and any naturally occurring interactions between separately folded polypeptide chains are considered quaternary structure. For the purposes of this commentary, we define higher order structure (HOS) to be all structural elements, beyond primary structure, necessary for the protein product to function as intended. Formation and preservation of HOS, so defined, is potentially critical for both the efficacy and safety of protein-based therapies.[1-3] We acknowledge that elucidating potential links between HOS changes and resulting impacts to safety and efficacy remains elusive. However, in recognition of the importance of characterizing HOS, regulatory agencies have consistently defined HOS characterization expectations in their guidelines, especially in recent guidance.[4,5]

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In light of the need for detailed characterization of protein HOS, a consortium was established to promote open communication and common understanding among industry scientists, academic researchers, and regulatory authorities about the role HOS plays in product quality and the challenges encountered in the application of HOS characterization tools during product development and manufacturing. A commentary by Gabrielson and Weiss[6] introduced key questions and collected general impressions from industry about the use of HOS data in technical decision making. Five case studies published by members of the consortium gave a diverse set of particular decisions influenced to varying degrees by HOS data.[7-11] In this concluding commentary by industry scientists, we return to the central question posed in the introductory commentary in light of the particular case studies: how can HOS methods and data be used most effectively to make technical decisions during development of biologics?

To address this question, we first consider important concepts involved in developing an HOS characterization strategy that is appropriately suited to a particular biologic, and next we discuss ways industry can partner with academia, technology companies, government laboratories, and regulatory agencies to improve how HOS characterization is applied during drug development. By highlighting existing challenges in HOS characterization, we intend to spur continued improvement in how HOS methods are applied during drug development to aid in making informed technical decisions.

Defining an HOS Characterization Strategy

The development of a biologic into a commercial drug product proceeds through an extensive process of clinical trials to determine the drug's safety and efficacy. Coupled to this process is the supporting biophysical, biochemical, and biological analysis that not only establishes the ability of the drug manufacturer to make the drug consistently with high quality, but also provides a comprehensive knowledge base of the molecule's structural and functional characteristics. Thus, along with the clinical data, characterization data are needed in order to understand the attributes of the drug that impact clinical and commercial performance. The role of biophysical characterization in this process is to define the HOS of the biologic and demonstrate that HOS is preserved during drug substance and drug product manufacturing, storage, and delivery to the patient. Furthermore, drug manufacturers must also demonstrate that HOS is maintained following manufacturing changes made during the drug's development and commercial lifecycle.

A careful consideration of Quality by Design principles is likely to be valuable in developing an appropriate HOS characterization strategy. The approach applied to any particular biologic depends on many factors and can include, among others:

- features of the molecule, including its class, scaffold, and critical quality attributes;
- supply chain considerations, including drug substance and drug product container closure systems along with requirements for storage and distribution;
- HOS method lifecycle considerations, including selection of fit-for-purpose methods and demonstration of their capabilities;
- defining the processing step(s) at which the product is sampled for testing (drug substance intermediate, drug substance, or drug product); and
- phase of product development.

Of these factors, this commentary deals with considerations that are largely preserved across most classes of biopharmaceutical products: method lifecycle considerations, method selection criteria, sample type considerations, and development of a phase-appropriate strategy.

HOS Method Lifecycle

It is useful to define a theoretical lifecycle onto which biophysical methods may be placed with respect to their use in supporting biologics research and development (Fig. 1). We begin in

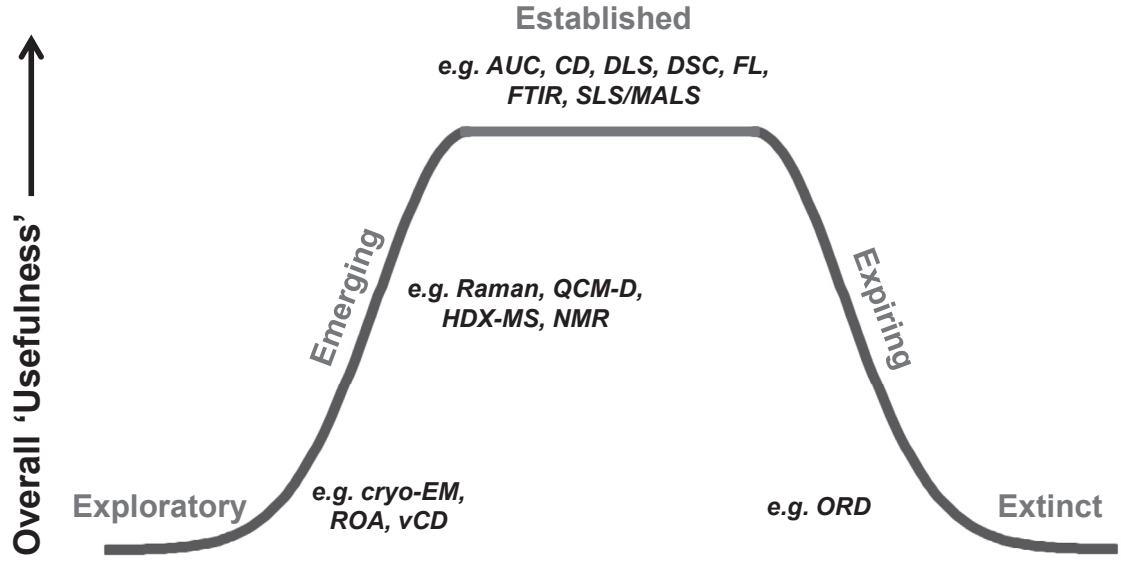

Figure 1. A theoretical lifecycle showing various phases through which a given biophysical method may pass with respect to its use in biopharmaceutical research and development. The overall "usefulness" of the method is greatest in the center and lowest at the extremes. Examples of biophysical methods include: (exploratory) cryogenic electron microscopy (cryo-EM), Raman optical activity (ROA), vibrational circular dichroism (vCD); (emerging) quartz crystal microbalance with dissipation (QCM-D), hydrogen-deuterium exchange mass spectrometry (HDX-MS), nuclear magnetic resonance (NMR); (established) analytical ultracentrifugation (AUC), CD, dynamic light scattering (DLS), differential scanning calorimetry (DSC), fluorescence (FL), Fourier transform infrared (FTIR), static light scattering (SLS)/inline multiangle light scattering (MALS), and (extinct) optical rotary dispersion (ORD).