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Review

Hydrogen deuterium exchange mass spectrometry in biopharmaceutical discovery and development – A review

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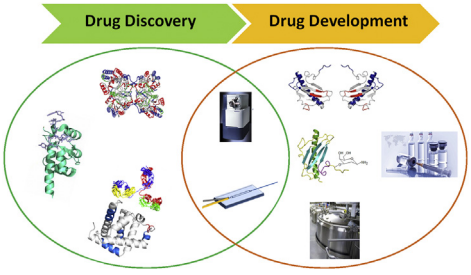
HIGHLIGHTS

- The pharmaceuticals industry is increasingly shifting to protein therapeutics.
- Hydrogen deuterium exchange mass spectrometry is uniquely well suited to support biopharmaceutical development.
- Applications for hydrogen deuterium exchange span drug discovery, development and manufacturing.
- Future developments will allow improved sensitivity, structural resolution and a broader range of dynamics to be monitored.

GRAPHICAL ABSTRACT



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ABSTRACT

Protein therapeutics have emerged as a major class of biopharmaceuticals over the past several decades, a trend that has motivated the advancement of bioanalytical technologies for protein therapeutic characterization. Hydrogen deuterium exchange mass spectrometry (HDX-MS) is a powerful and sensitive technique that can probe the higher order structure of proteins and has been used in the assessment and development of monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs) and biosimilar antibodies. It has also been used to quantify protein-ligand, protein-receptor and other protein-protein interactions involved in signaling pathways. In manufacturing and development, HDX-MS can validate storage formulations and manufacturing processes for various biotherapeutics. Currently, HDX-MS is being refined to provide additional coverage, sensitivity and structural specificity and implemented on the millisecond timescale to reveal residual structure and dynamics in disordered domains and intrinsically disordered proteins.

Contents

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1. Introduction

1.1. Pharmaceutical industry

By 2015, worldwide pharmaceutical sales reached a milestone of $1 trillion with a minimum growth rate of 3% within the preceding decade (Fig. 1) [1]. At the same time, the cost of bringing a typical new drug to market is increasingly high, currently in the range of $1.3 billion over an average development period of 12–15 years [2]. This cost also incorporates a relatively high rate of failure that has been a long-term feature of the drug approval process. The rate of approval for new drugs has been at a relatively stable average of 15%–25% for decades [3]. The global pharmaceutical industry is also seeing a rapid growth in applications (and approvals) for biological macromolecules, such as monoclonal antibodies (mAbs) [4,5].

In contrast to small molecules, protein higher order structure and conformational dynamics are intimately linked to their efficacy as therapeutic agents [6,7]. The rise of protein therapeutics therefore brings about unique challenges that motivate the development of new analytical tools capable of characterizing protein structure, dynamics, and interactions in the context of a robust drug discovery and development environment [8]. For instance, X-ray crystallography [9] and nuclear magnetic resonance (NMR) spectroscopy [10] provide high-resolution measurements of protein structure. However, some limitations to X-ray crystallography include extensive optimization of crystallization conditions, and ultimately a 'static' (albeit high resolution) structure of the protein. On the other hand, NMR can provide dynamic data in the solution phase but suffers from sensitivity issues and inherent analyte size limitations well below that of a typical antibody. While surface plasmon resonance (SPR) [11] and bio-layer interferometry (BLI) [12] allows sensitive detection of structural changes and binding kinetics of protein interactions, they can only provide a 'global' structural picture, without detailed and localized information.

1.2. HDX-MS

Among the many different separation-based or spectroscopy-based strategies [13], hydrogen-deuterium exchange mass spectrometry (HDX-MS) is one of the most robust and promising analytical methods for the study of protein conformation and dynamics [14–16]. The use of HDX as a 'gentle' structure-dependent

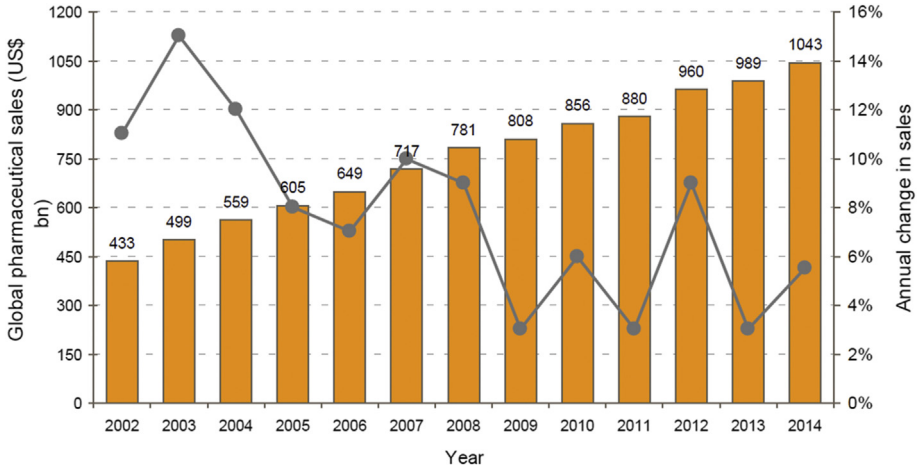

Fig. 1. Global Pharmaceutical Sales, 2002–2014, from 2015 CMR International Pharmaceutical R&D Factbook [1]. Bars represent annual total sales, filled gray circles represent the annual change in sales. Reproduced with permission from Thomson Reuters© 2015.