VAMAS

Synthetic Biomaterials

Technical Work Area 40

Project 6

Comparability in the thermal stability of a protein antibiotic

Objectives

The aim of this study is to validate the thermal stability of a pharmaceutically relevant protein antibiotic in native and near native environments by chiroptical spectroscopy, e.g. Circular Dichroism (CD) spectroscopy.

Background

There is an increasing shift in industry towards protein biologics – 30% of total sales and 50% of top 100 pharma sales in 2022 – with oncology and infectious diseases accounting for the most significant activity.

Proteins undergo structural transitions in response to changes in their environments, while their activity depends on conformational stability and reversibility. These require routine monitoring to support QA in product development. Regulatory agencies emphasise the need for higher-order structural characterization using CD spectroscopy to ensure comparability of biological products for pharmaceutical development (e.g. ICH Q5E).

However, achieving reproducibility in measurements is hampered by the lack of high-order reference materials and methods to benchmark the performance of protein biologics. This is further supported by international comparability studies performed to date (e.g. CCQM P59.1), which revealed the need for suitable reference materials to ensure the repeatability of CD measurement results. The proposed biologic is a protein antibiotic that folds in aqueous media into a highly stable tertiary structure exhibiting complete reversibility under thermal denaturation conditions.

Standardisation needs

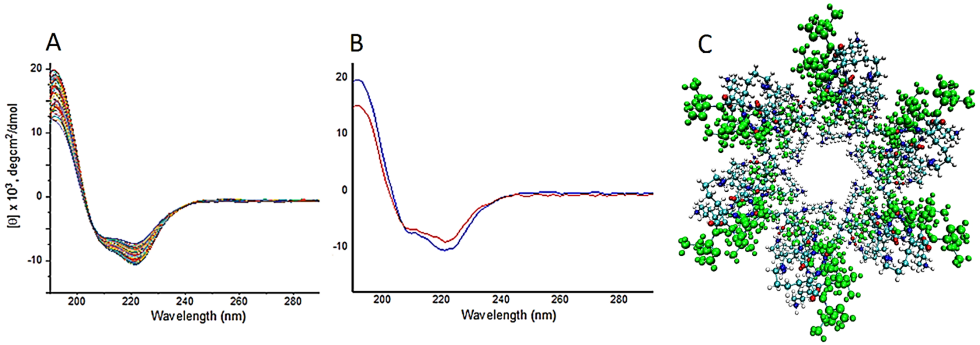
The pre-standardisation needs focus on:

- far-UV CD spectra comparability between laboratories
- transition temperature evaluation upon thermal denaturation
- comparability in cooperativity and reversibility of the transition
- instrument performance validation and measurement variabilities as a function of temperature and concentration

Relevant Standards

- ISO Guide 35:2017
  Reference materials
- ISO 15189:2012
  Medical Laboratories
- ISO 29301:2010
  Microbeam Analysis
- ISO 15194:2009
  In-vitro diagnostic medical devices
- EU 2017/746
  IVD regulation
- ICH Q5E
  Guidelines for comparability of biological products.

Call for Participation



(A) CD spectra of the antibiotic at set time points during thermal denaturation showing cooperativity of unfolding. (B) CD spectra before and after the thermal denaturation showing the reversibility of folding. (C) Model antimicrobial pore formed in bacterial membranes.

Relevant Committees

ISO/TC 276 - Biotechnology
ISO/TC 229 - Nanotechnologies
CIPM CCQM – CAWG, PAWG

Work Programme

- the antibiotic will be distributed to participants as a lyophilised powder
- protocols for sample preparation and measurements will be disseminated
- collected CD spectra will be compared with full uncertainty evaluations

Second stage analysis

- procedures developed will be repeated by a smaller group of participants to determine the effect of test parameters on the repeatability and reproducibility of the measurement results.

Knowledge Transfer

International intercomparison exercise, good practice guidelines, peer-review publications and presentations in conferences and standardisation events.

Status

Study In progress since February 2023.

Volunteers Welcome

Participants fund their own study in the project.

For more information on participation, please contact:

Project Leader
Dr. Liqing Wu
National Institute of Metrology, China
qwu2006@126.com

TWA Chair
Prof. Max Ryadnov
National Physical Laboratory, UK
max.ryadnov@npl.co.uk

www.vamas.org

September 2023