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BIOLOGICS STABILITY

LIFECYCLE MANAGEMENT OF DRUG PRODUCTS

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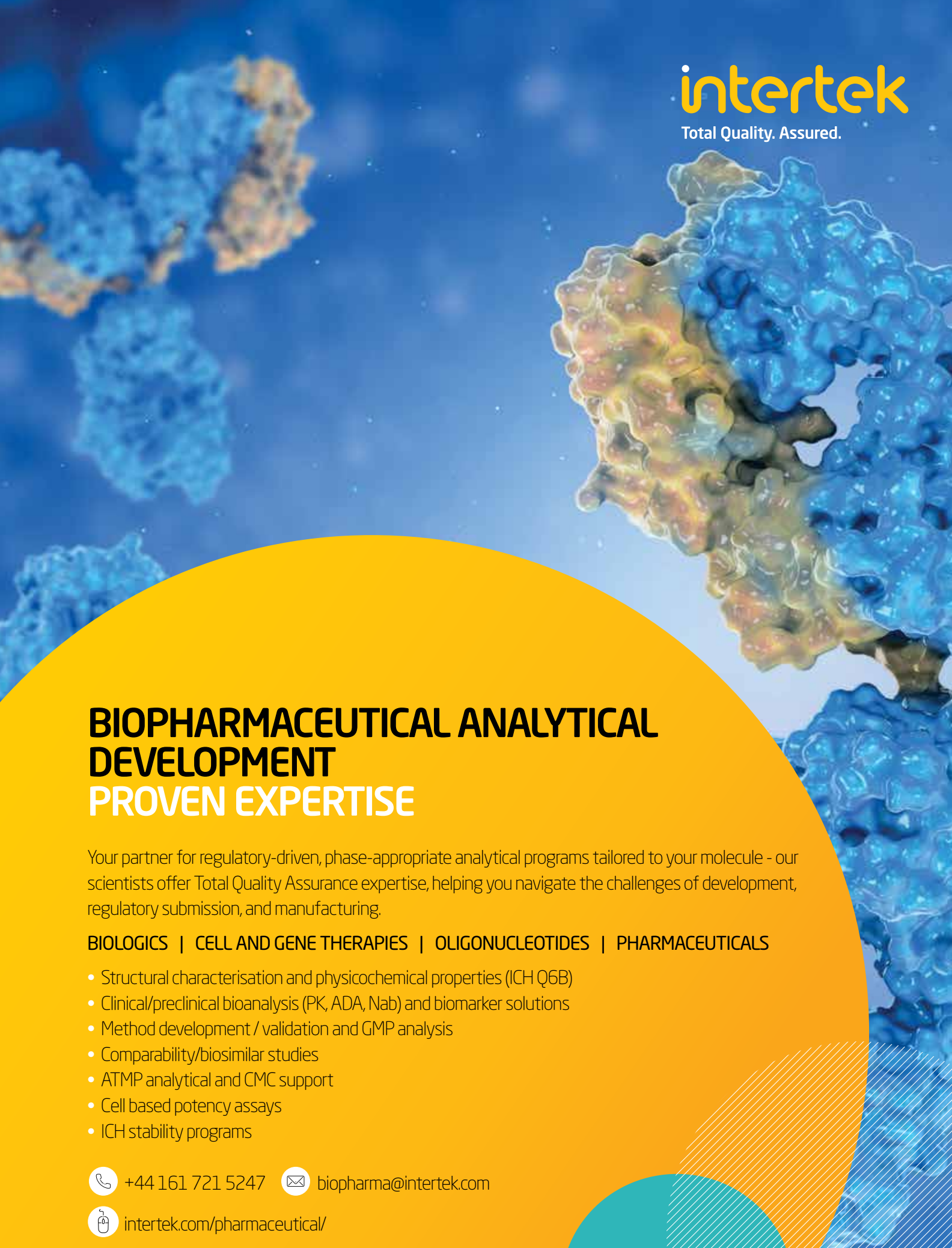

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Biologics Stability

Lifecycle Management of Drug Products

by Maribel Rios

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Biomanufacturers must ensure that their commercialized products remain safe and efficacious throughout the shelf lives of those products and with the same high quality. Stability studies are conducted throughout all phases of product development and manufacturing (Figure 1), and validated potency assays are required for current good manufacturing practice (CGMP) product stability testing. The apparent need to address lifecycle managment issues has made its way into industry guidelines, including the new draft quality guideline Q12 from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and an upcoming *US Pharmacopeia* (USP) general chapter. However, basic information still is needed about forced-degradation studies, the degradation pathways of both traditional and emerging biologics, and the usefulness of existing stability-indicating assays.

Guidelines Focus on Lifecycle Management

The biomanufacturing industry's increased attention to lifecycle management has been driven by different strategies to risk management and mitigation as a result of the FDA's "Pharmaceutical CGMPs for the 21st Century" initiative. Assays conducted at several stages of a biologic's lifecycle include assessment of both protein and drug product stability. Experts have divided these tests into six stages, from early development to follow-up testing (**1, 2**). Stage 1 is stress and accelerated testing with drug substances. Stage 2 includes testing stability of preformulation batches. Stage 3 involves stress testing on scale-up batches. Stage 4 includes accelerated and long-term testing for registration purposes. Stage 5 involves ongoing stability testing. Finally, stage 6 includes follow-up stability testing.

Results obtained during such assessments depend on the stage of development. For example, shelf life is determined during long-term testing, and accelerated testing is conducted to assess product-degradation pathways and develop stability-indicating analytical methods. Prototype testing is performed during early stages to characterize a product or formulation. Stability tests also are conducted after reconstitution of freeze-dried or lyophilized products, including emerging gene therapies (**3**).

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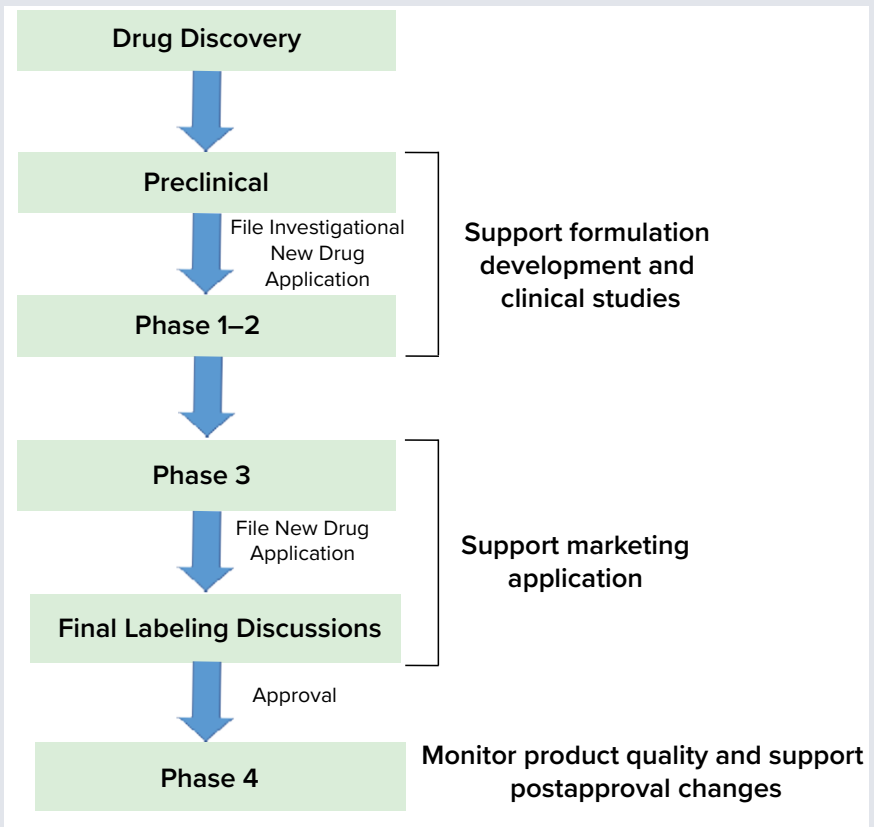
Figure 1: Stability testing throughout a biologic's life cycle (**5**)



Stability assessment is discussed in many industry guidances, including ICH Q1A, ICH Q5C, and Q5E. Stability also is part of the common technical document (CTD, 3.2.S.7 and 3.2.P.8) and discussed in the FDA's guidance for industry *M4Q: The CTD — Quality*. However, the two most recent regulatory documents focused on stability assesment as part of lifecycle management are the May 2018 draft guidance ICH Q12 *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and the upcoming USP general chapter ‹1049.1› *Design of Stability Testing for Biotechnology Products and Lifecycle Management*.

ICH Q12: Section 8.2.1 of this document covers stability data approaches to support evaluation of chemistry, manufacturing, and control (CMC) changes after a drug product has been approved. Whereas ICH Q1A(R2) is used to "establish a useful shelf life and storage conditions for a new, never-marketed drug substance/drug product," the ICH Q12 guideline addresses stability studies that "confirm the previously approved shelf life and storage conditions." The newer document says that approaches to designing such studies should be "appropriately justified." Although what constitutes an "appropriately justified" study is not defined, the guideline does list what the approach may include (e.g., identifying stability-related quality attributes and shelf-life limiting attributes, using appropriate tools to evaluate the effect of proposed changes, and assessing stability risk to determine factors that can affect stability relative to proposed CMC changes). The ICH Q12 guideline also differs from stability approaches discussed in ICH Q5E, which focuses on comparability subject to changes in manufacturing processes.

Reception of ICH Q12 has been mixed. For example, Menezes et al. say that the guideline "provides biomanufacturers incentive to formalize their knowledge assets and improve their lifecycle management strategies. In return, it promises regulatory flexibility with postapproval change management" (**6**). But some experts and organizations remain critical about the potential effects of the guideline's implementation. For example, writing on the *iSpeak* blog for ISPE earlier this year, March F. Witcher opines,

> In a nutshell, the industry should expect additional confusion and more work from a vaguely defined, potentially duplicative system that will likely further inhibit the industry from achieving excellence. . . . Based on the industry's inadequate performance, regulatory agencies are understandably trying to improve the industry's performance by establishing management-based regulatory guidelines such as Q12. However, these guidelines should have a strong focus on both good science and engineering. While regulatory agencies focus on good science and process understanding, they sometime fail to place sufficient emphasis on good engineering principles and practices successfully used by other industries (**7**).

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USP <1049.1> The CASS WCBP Symposium Series has held events about the technical challenges of stability assessments, specifically how such evaluations pertain to CMC development. For example, at the 2018 WCBP conference, panel discussions focused on the stability of frozen drug products, forced degradation, and the upcoming USP ‹1049.1› general chapter, a companion to the established USP ‹1049› general chapter *Quality of Biotechnological Products: Stability/General Information*.

One panel acknowledged that although regulatory guidance for biologic drug products is covered in USP ‹1049› and ICH guidelines, "the complexity of the actual design of expiry-setting studies as well as various other stability studies necessary for product characterization and use are not covered." It was agreed that "the intention of the new companion chapter is to provide further detail regarding the design of stability studies from the earliest stages of the product development lifecycle through product licensure and then postapproval." Thus, USP ‹1049.1› will provide a "holistic approach" for both drug substances and products.

The WCBP session included the following topics (**8**):

- Development of stability specifications (within or separate from lot release)
- Best practices and challenges for stability studies for comparability
- Changing expectations for studies on drug substance attributes that don't change at recommended storage conditions (e.g., frozen drug substance)
- Determining the criticality of attributes that change over time
- Expectations around and stability approaches to products in secondary packaging
- Statistical approaches for trending and reactions for the quality system to signals
- "Time out of temperature" for patient-use products (designing end-to-end studies)
- Optimization of stability studies based on accrued knowledge.

Panelists emphasized that although best practices and points to consider are likely to be discussed in the chapter, it is only a guideline. For example, the chapter will provide "points to consider and guidance with respect to stability of products in devices, allowing for numerous types of devices in the clinic and market . . . ." Detailed notes of this discussion, including industry concerns, can be found elsewhere (**8**).

Table 1: Stability test methods for recombinant proteins, antibodies, and blood products (adapted from BioReliance.com)

Method	Attribute
pH (if liquid)	General quality
Karl Fischer titration (if lyophilized)	Moisture, integrity
Appearance	General quality
UV absorbance	Concentration
SDS-PAGE	Identity, purity, integrity
SEC-HPLC	Identity, purity, integrity
RP-HPLC, IEX-HPLC, HIC-HPLC	Identity, purity, integrity
Peptide mapping	Identity, integrity
Mass spectrometry	Identity, integrity
Isoelectric focusing	Identity, integrity
Capillary electrophoresis	Identity, integrity
Immunoassay/ELISA	Identity, integrity
Ligand-binding assay	Identity, potency, integrity
In vitro bioassay	Identity, potency, integrity

SDS-PAGE = sodium dodecyl sulfate polyacrylamide gel electrophoresis; SEC-HPLC = size-exclusion chromatography high-performance liquid chromatography; RP-HPLC = reversed-phase HPLC; IEX-HPLC = ion-exchange HPLC; HIC-HPLC = hydrophobic-interaction chromatography HPLC; ELISA = enzyme-linked immunosorbent assay

What's Wrong with Stability Studies?

The USP <1049.1> general chapter is likely to include lifecycle management with stability assessment of biopharmaceutical products. I asked Nadine Ritter, president and analytical advisor at Global Biotech Experts and member of BPI's editorial advisory board to provide her perspective on the need for revising methods for existing stability studies.

"The primary practical gap that I see with biologics stability studies (especially with new product modalities) is the assumption that the analytical methods will be stability-indicating for any potential degradation pathway the product could experience from production to patient. For purified monoclonal antibody (MAb) therapeutics, we have a lot of experience with their protein chemistry and relevant methodology for their physical and functional analysis. So the biochemical assumptions we make in early development about their stability profiles frequently (but not always!) prove to have been true. Even so, we conduct comprehensive, systematic forced-degradation studies later in development to confirm the stability-indicating profile of the product and validate the stability methods.

But for novel or complex biological products, we cannot simply assume that the analytics will be capable of detecting the various chemical and physical modes of degradation that they could potentially experience. This is partly because of the diverse nature of the products, and partly to the forms of technologies required to analyze them. We don't have decades of experience with either aspect of these products to make relevant assumptions about their stability profiles or the stability capabilities of these methods. So sooner rather than later in development, it is wise to conduct forced-degradation studies to establish the stability profile of a product and confirm that the chosen methods can monitor any potential degradation of the product. For these products and methods, the risk of delaying such a study is that you can reach the end of development with stability data that have been blind to the actual degradation that has been occurring. Finding later that the stability testing program has had major method gaps can influence decisions in clinically qualified specifications, formulation development, and shelf-life claims that would have been based on deficient historical data."

Stability-Indicating Methods

In general, guidelines do not provide details about how recommended assays should be conducted, and not all assays are stability indicating. Analysts must develop bioassays for specific drug products and drug substances and then validate those assays as stability-indicating. A stability-indicating protocol is developed according to what needs to be determined. The protocol dictates when particular methods must be conducted (Table 1), and the resulting profile must assure that changes in a product's identity, purity, and potency will be detected (**3**).

A *stability-indicating method* is a validated quantitative analytical method that can detect changes over time in the chemical, physical, or microbiological properties of a drug substance or drug product. They allow accurate measurement of the content of active ingredients and degradation products without interference (**9**). Stability-indicating methods are used to monitor results during stability studies to guarantee safety, efficacy, and quality. Such activities also can be used to investigate out-of-trend or out-of-specification results in quality control assessments. Forced-degradation studies conducted under stressed conditions (typically during phase 3 clinical trials, and specified according to the type of product) are used to

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From the BPI Archives at https://www.bioprocessintl.com

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understand degradation pathways and help determine the instrinsic stability of a protein or other drug substance (**9**).

Such studies for well-characterized biologics (such as monoclonal antibodies) often can be conducted with high confidence in methods used and results generated. However, emerging therapies such as cell and gene therapies are far from being well characterized, so their degradation pathways under stressed conditions mostly are determined through much trial and error. The "What's Wrong" sidebar provides one perspective on current problems encountered in conducting stability-indicating strategies.

Advancements in analytical methods and equipment also should be considered when conducting stability studies. Laboratory equipment suppliers are automating commonly used analytical devices (eliminating or reducing operator error), and such systems are being designed with better sensitivity. Efforts are in progress for improving characterization methods for emerging therapies (e.g., Cambridge Healthtech Institute's 4th Annual Cell Therapy CMC and Analytics to Improve Product and Process Analysis and Characterization), including developing alternatives to lyophilization (e.g., aseptic spray drying) (**10**) and stabilizing live biologics (e.g., vaccines) at room temperature (HydRIS platform, Nova Laboratories, Ltd.).

Several conferences in 2020 — such as BPI West, BPI East, and WCBP — will continue to discuss strategies for conducting stability studies, and the USP ‹1049.1› general chapter also is set to be open for industry comments in 2020.

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