Drug Development & Delivery

Analytical Testing in Drug Development

eBook
Analytical Testing Edition
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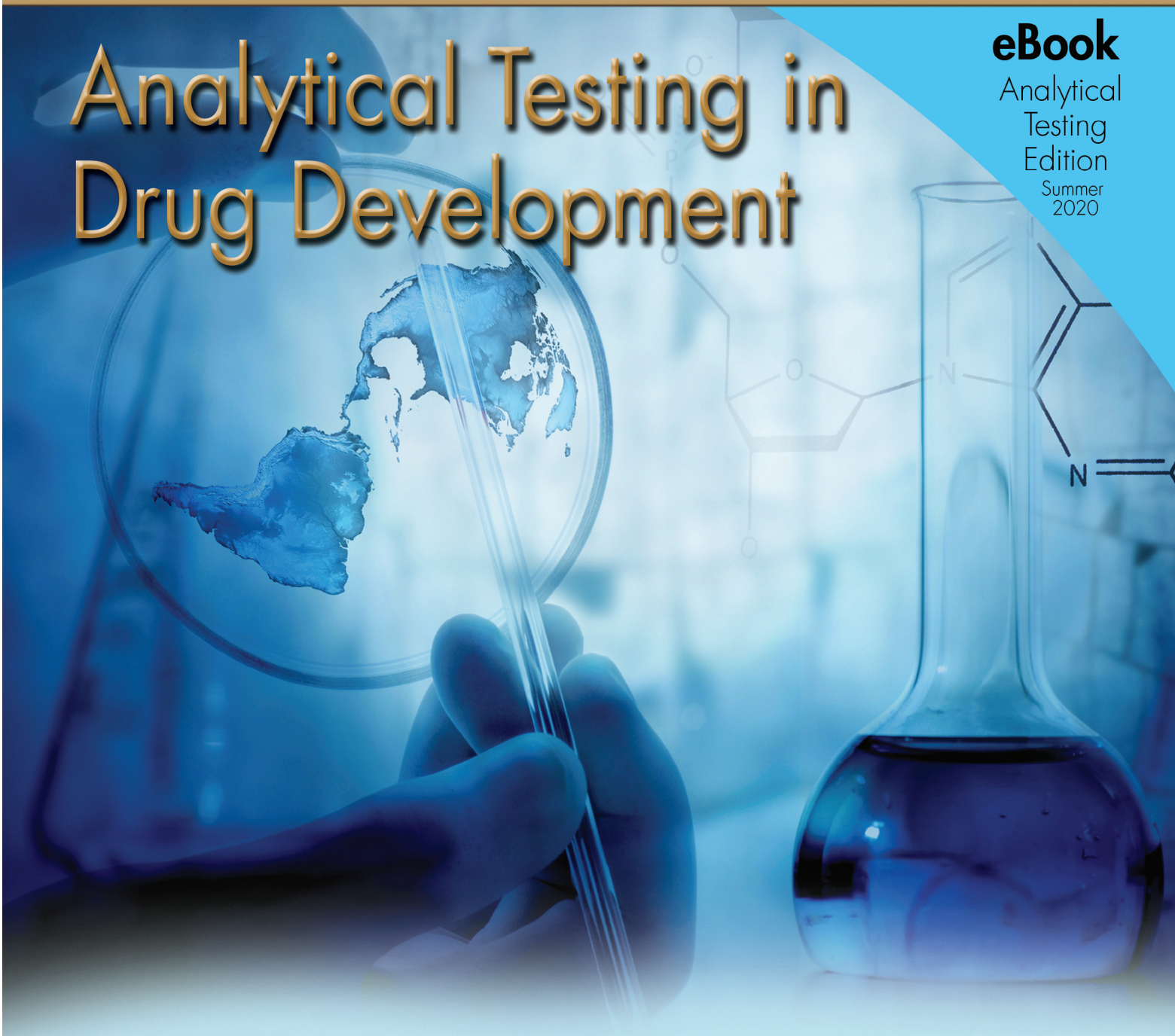

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Analytical Testing eBook

A Critical Role in End-to-End Drug Development

The global pharmaceutical analytical testing outsourcing market is expected to rise to an estimated value of $10.42 billion by 2026[1], up from $3.82 billion in 2018.[2] The market is being driven by a few key factors:

- Increasing usage of pharmaceuticals and therapeutics requiring specialized manufacturing capabilities;
- Growth in modernization and innovations requiring reduction of operating costs of manufacturing and development;
- Increasing investments in R&D;
- Rising demand for product safety and quality, and changing regulations for *in vivo* and *in vitro* tests; and
- Strict regulations and requirements.

The market is segmented into bioanalytical testing services, physical characterization services, method development & validation services, raw material testing services, stability testing services, microbial testing services, environmental monitoring services, and batch-release testing services. The latter is projected to grow at the highest CAGR through 2025. And within the batch-release testing services segment, dissolution testing services is projected to grow at the highest rate during the same period.[3]

In addition to batch-release testing, bioanalytical testing services is a fast-growing sector within analytical testing. The global bioanalytical testing services market is poised to reach $3.72 billion by 2025, from an expected $2.13 billion this year.[3] Within this segment, oncology is the largest application, primarily due to the increasing number of clinical trials and the rising prevalence of cancer worldwide. The growth in this market is attributed to the rising focus on the analytical testing of biologics and biosimilars, increasing preference for outsourcing analytical testing, growing R&D expenditure in the pharmaceutical and biopharmaceutical industries, and the rising adoption of the Quality by Design approach.[4]

This second annual *Drug Development & Delivery* magazine Analytical Testing eBook shines a light on analytical outsourcing providers that are optimizing testing solutions to ensure more robust results, speed time to market, and characterize methods earlier in development.

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The Importance of Crystal Structure Solution in Drug Development

By: Steef Boerrigter, PhD, Senior Research Scientist II, AMRI

Steef Boerrigter, PhD, In addition to teaching crystallography at Purdue University, Steef Boerrigter, PhD, is a Senior Research Scientist II at AMRI who works as a group leader in Materials Science for the Solid Form Development group.

The term *crystallography* has practically become synonymous with single crystal structure solution using X-ray diffraction analysis (SC-XRD). This powerful technique plays an important role in drug development.

For small molecules, SC-XRD is usually first applied during the synthesis of the first batches of a new drug substance. A successful structure solution fully elucidates the molecular structure and is the most compelling evidence for the successful chemical synthesis.

Absolute Configuration

Many drug molecules are chiral. SC-XRD is the only generally applicable and most reliable method to determine the absolute configuration, i.e. the three-dimensional structure of the molecular bonds as opposed to just atomic connectivity. Although technically not a strict requirement in all regions, and though alternative approaches exist, it is most practical to specify a chiral API by its absolute configuration for filing purposes.

With modern equipment and current computational methods, today the absolute configuration can almost always be determined unambiguously from a routine SC-XRD analysis – even for molecules where the heaviest atoms are carbon, nitrogen, and oxygen.

Recent Advances in X-Ray Diffraction Technology

Semiconductor-based technology used at the Large Hadron Collider to detect the Higgs boson is now used in the pharmaceutical laboratory. The so-called hybrid pixel "single photon counting" detector is capable of exactly that. It is noiseless and provides read-outs within a nanosecond.

The sensitivity improvement allowed X-ray intensities to be reduced by more than an order of magnitude. The absence of noise in the read-out of the diffraction signal significantly reduced the collection time needed for sufficient photon count statistics for successful structure solutions. Using shutterless, continuous operation, data acquisition usually requires only a few hours.

Single Crystal Growth

The advances in SC-XRD equipment allow for smaller crystals in structure determination than were required for previous generations of equipment.

A modern microfocus X-ray source projects a 100µm beam. Ideally, the single crystal should not be much larger than that. Smaller crystals can often be used, especially if heavier atoms such as chlorine or sulfur are present.

Generally, smaller crystals are easier and quicker to grow than the larger crystals that were required historically and, therefore, the success rate of SC-XRD has increased. Depending on size, flexibility, and hydrogen-bonding properties of the molecule, crystal growth can sometimes be achieved overnight but can, at times, require several months.

Indexing

Given high resolution powder X-ray diffraction (PXRD) data, most often the unit cell parameters and space group can be determined by finding an indexing solution to the observed peak positions, thereby circumventing the need for a single crystal. This computational routine is usually shorthanded to indexing.

Despite best efforts, some crystalline phases do not produce good quality crystals. During polymorph, salt, or cocrystal screening, it is also not necessary to perform SC-XRD on each discovered form. The unit cell volume from an indexing solution, combined with the known molecular volumes, can quickly reveal the unit cell contents in most instances.

An indexed PXRD pattern readily reveals extraneous Bragg peaks indicating form impurities. The absence thereof indicates the powder sample consists of a single, crystalline phase. This, combined with the confirmation of the integrity of the molecular structure, is used as the criterion for a new form designation as part of solid form screening activities.

Intellectual Property Considerations

Solid forms are usually claimed by listing prominent or characteristic peaks in the PXRD. A single crystal can typically not be sampled from a drug product, so infringement of a claim based on SC-XRD would be impossible to prove. PXRD data is often readily identifiable, albeit in linear overlay with the PXRD signal of the formulated excipients.

Collecting PXRD data is relatively easy and basing a claim structure on it therefore appears relatively straightforward. However, numerous claims for new forms are encountered in the patent literature for which the claimed forms are actually mixtures of previously known forms. Peak shifting due to variable solvent content also often leads to erroneous claims of new forms. Such patent claims will typically not hold up in court.

It is therefore important to ensure that PXRD data used for a patent claim is representative of a single, crystalline phase, either supported by a SC-XRD structure or by an indexing solution to the PXRD.

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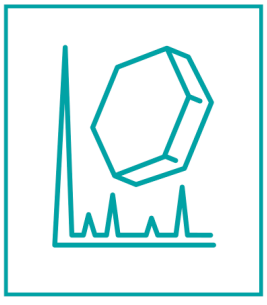

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Avoiding Chromatography Method Development Pitfalls

By: Dr. Daniel Kirschner, Senior Director of Analytical Services, Cambrex

Dr Daniel Kirschner joined Cambrex following the acquisition of Avista Pharma Solutions in January 2019. He has more than 10 years in various analytical roles within fast-paced CDMO and biopharmaceutical companies working in all stages of clinical development from pre-IND through to registration on small- and large-molecule chemistries. Dr Kirschner holds a PhD in Bioanalytical Chemistry from the University of Alaska at Fairbanks.

Column and mobile phase selection screening with systematic optimization enables rapid and data-rich method development.

The development of accurate and robust analytical methods for assay and impurity profiling of new chemical entities (NCEs) is a complex task. New drug substance high-performance liquid chromatography (HPLC) methods must resolve a wide range of potential degradants and manufacturing impurities with appropriate levels of sensitivity.

Because expertise can vary widely among analytical staff in method development workflows, a systematic approach has the potential to streamline the development process. And while there is no single approach to method development that is always successful, there are factors that are always essential to establishing an appropriate method:

- Understanding of the NCE's molecular structure;
- Tuning the chromatographic stationary and mobile phases; and
- Optimizing separation parameters.

Being aware of three common pitfalls in method development also facilitates the development of robust methods and avoids costly delays:

1. Educated guesswork that bases the choice of stationary/mobile phase on a previous method; the generic structure of the NCE; or because a certain detection method is preferred can have long range negative impacts on effectiveness, time, and cost.
2. Superhero antics focused on trying to achieve too much with one method generally have high cost with little reward.
3. Jerry rigging methods to "make do" with the incorrect stationary/mobile phase because it is out of stock or requiring very tight operating windows for success generally creates robustness challenges and lifecycle issues.

Successful method development requires an understanding of the goals for the method and defining a relevant starting point. Changing goals as the method development workflow proceeds often leads to delays and higher costs. Knowledge of key chromatographic interactions and the relevant molecular landscape is also important for enabling rapid development of selective methods.

Robustness should be built in so the method is unaffected by small variations like alternative columns, range of parameters, etc. Streamlining methods and incorporating forced degradation studies early in the development workflow also minimize development time.

Cambrex takes a systematic approach to unbiased method development with semi-automated screening to rapidly develop and optimize robust methods. The latest HPLC technology is coupled with a photodiode array (PDA) as the primary detector. The multi-column configuration of the HPLC system allows for rapid screening of chromatography phases and multiple mobile phase combinations under a range of operating conditions. Mass spectrometry (MS) and charged aerosol detection (CAD) are also available for molecules that lack good UV responses.

Before any runs are performed, the chemistry of the NCE is evaluated to help select the initial mobile and stationary phases for screening. This includes determining whether the molecule is acidic, basic, or neutral, and whether any functional/reactive groups could interact with the mobile/stationary phase and lead to degradation, or if there is a special need for a specific category of mobile phase modifier to either improve detection sensitivity or significantly alter peak shape.

With this information in hand, preliminary gradient and wavelength evaluations are performed, usually on a porous silica or silica hybrid C18 column (2.1 x 100 mm). Once the behavior of the sample is determined and a good response for the detector confirmed, screening runs are initiated.

Typically, 6-20 columns are screened, including various C18 columns with unique surface chemistries and a few alternative phases (phenyl, fluorophenyl, polar-embedded, cyano). Mobile phase screening generally includes tetrahydrofuran (THF), methanol (MeOH) and acetonitrile (ACN). The lead columns that exhibit the greatest performance in terms of separation and resolution are then subjected to further systematic screening to determine the impact of temperature, gradient ramping, pH, flow rate screens and the use of different additives (buffers, ion pairing agents, acids, bases) and identify the conditions that give the best separation of all peaks. The final optimization occurs once parameters that impact resolution are identified and systematically combined.

Forced degradation studies are conducted (oxidation, heat, acid, base, and photolysis) to confirm that any new degradants are well resolved using the lead columns/optimized conditions. MS can be highly useful here for tracking peaks that emerge as the result of forced degradation.

By taking an unbiased, systematic, step-wise approach to column screening, mobile/stationary phase, additive selection and operating parameter optimization, combined with incorporation of forced degradation studies, common pitfalls are avoided. The best performing method can be optimized and taken through pre-validation, and the resulting methods are more robust.

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Strategic Outsourcing of Analytical Testing Solutions to Speed Up Time-to-Market

By: Ramesh Jagadeesan, PhD, Sr. Director, Analytical Development, Recipharm

Ramesh Jagadeesan, PhD, in Pharmaceutical Analysis is currently heading the Analytical Excellence Centre at Recipharm, Bangalore, India. He has 20 years of experience in analytical research and development. He has authored numerous research publications in the areas of analytical development, controlled release technology, and stability studies. He is an expert in stability studies for NCE, ANDA, commercial, and clinical stability.

The way that drug development teams approach analytical testing can have a marked impact on the speed at which a product reaches the market. As regulatory agencies continue to impose increasingly stringent requirements that call for more analytical information on medicines and process development, developers are being charged with identifying innovative solutions that can meet growing demands. Today, optimized approaches to method development, automation, and new technologies are transforming analytical testing and helping to reduce development times.

Automation of Analytical Instrumentation

The automation of instrumentation has progressively become more simplified, and while the volume of data being generated is increasing, the resource needed to achieve this data is reducing, creating time, and cost savings. While analyses have traditionally been used to quantify the active ingredient and the impurities in a product, technology is now at a point where it can also estimate unexpected additions to a formulation, including elemental impurities that may be present through transfer from manufacturing vessels or reactants.

Advancing Technology

Newer analytical techniques are helping to increase assurance of product efficacy and reduce the time required for quality testing. These include:

- Raman spectroscopy
- Inductively coupled plasma mass spectrometry (ICP-MS)
- Optical emission spectroscopy (OES)
- Nuclear magnetic resonance (NMR) spectroscopy
- Ultra-performance liquid chromatography (UPLC)

Different detectors are also be employed, for example refractive index detectors, fluorescence detectors, evaporative light scattering detectors (ELSD), and Quadrupole Dalton (QDa) detectors.

In addition to offering greater reassurance, the incorporation of these technologies during method development is making more substantial data available to regulatory authorities.

Stability testing has also undergone its own transformation with simulating chambers now being used for freeze thaw, the introduction of photostability testing, and the use of chambers for all temperature zones. Better optimization of packaging selection has also been made possible with the introduction of extractables and leachables (E&L) testing and the compatibility testing of materials. Additionally, technology is helping development programs to meet guidelines relating to Quality by Design (QbD), elemental impurities, and data integrity requirements.

Appropriate Method Validation

Efficient responses to regulatory queries are reliant on the quality of validation documents. The use of specialist teams to design validation protocols based on regulatory guidelines is key to minimizing queries. A strict GMP environment, custom field calculation, and electronic data back-up can also ensure error-free data, while QbD-based validations can offer enhanced understanding of an analytical method's critical parameters throughout a product's lifecycle.

Growth in Outsourcing

The escalating costs of running a laboratory is driving many developers to choose to outsource the analytical testing elements of their programs to contract development and manufacturing organizations (CDMOs). Highly equipped, with the expertise and resources to run different analyses in parallel, CDMOs are leading the way in developing shorter/fewer methods, which is in turn driving down testing times.

The breadth of experience accessible via a CDMO means that programs benefit from having specialists on board who have worked with many different molecules and can apply insight gained across the development of multiple formulations. By assuring that the extensive needs of analytical testing are met to the fullest, CDMOs can help their customers to optimize lifecycle management.

A Leading Analytical Solutions Partner

In response to industry demand for outsourced analytical testing, Recipharm Analytical Solutions™ supports customers with stand-alone analytical requirements, providing extensive chemistry services, as well as the capacity, experience, and flexibility to handle both small- and large-scale projects.

Our analytical development team oversees the development of hundreds of analytical methods every year for a range of formulations covering powders, capsules, IV solutions, extended-release (ER) tablets, and dry powder inhalers, freeing up customer QC and analytical laboratories. Recipharm's 160-strong team of chemists solve customer challenges with a 'can-do' approach, while our extensive analytical equipment and several state-of-the-art laboratories and stability chambers enable more than 250 concurrent ongoing stability studies. By utilizing Recipharm's vast expertise, clients can combat their resource challenges while reducing their development timelines and costs.

Working with Recipharm enables development programs to benefit from a QbD approach that guarantees high quality, robust, and transferable methods. With a focus on innovation, we can help customers approach analytical testing with a strategic mindset and assist them in increasing their speed to market.

For more information, please visit:
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Benefits of Integration of Characterization Into Early Method Development

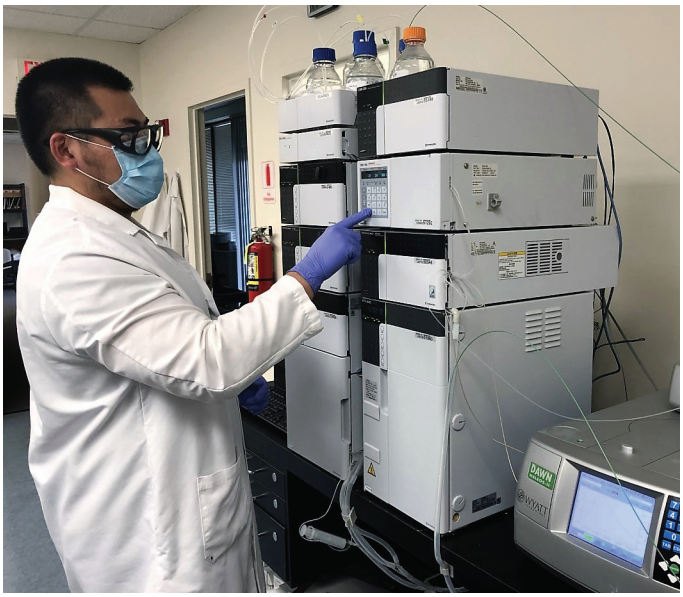
By: Edward R. Zartler, PhD and Rebecca E. Strawn, PhD,
SGS Life Sciences

Size Exclusion Chromatography with UV detection (SEC-UV, or just SEC) is a staple technique in pharma, due to its throughput, accessibility, and analytical power. SEC separates molecules based upon their interaction with a solid phase, and then detects the absorbance of chromophores in the sample. The solid phase has defined pore sizes that retards the molecules by temporarily sequestrating in these pores. This fundamental principle implies that larger molecules migrate faster due to less residence time in the pores, so a chromatographic profile of biomolecules separated based on size is generated, typically reporting species as Main Peak and High Molecular Weight Species (HMWS). In practice, the size of the species separated by SEC cannot be directly determined by the migration time; molecular shape, protein-solid phase interactions, and protein-protein interactions can all affect the resultant chromatogram. Multi-Angle (Laser) Light Scattering [MA(L)LS] detectors can be added in-line with SEC to yield a plethora of information about the particle(s) in solution and to better understand elution profiles. MALS signals can be analyzed to determine absolute molar mass and the Radius of gyration of particles in solution. Thus, chromatographically distinct species can be analyzed and fully characterized as to their nature, i.e. dimer, trimer, etc., which is critical knowledge when characterizing products in solution.

Chromatographic methods are robustly validated and thus are considered primary release methods for biologics. SEC is a "must-have" release method due to its facile ability to characterize HMWS, as HMWS and aggregates can induce an adverse immune response (*J. Immunotoxicol*. (2014) 11:99), even at very low quantities. Most biologics approved over the past 30 years are monoclonal antibodies. This long history has produced a wealth of experience with these molecules, especially with regards to anticipated HMWS and their expected SEC profiles. Thus, the SEC method output has typically not been fully characterized at the early phases of development. Delaying the full characterization of the SEC output — which is a necessary, but time-consuming activity — until much later in the drug development process has historically provided little risk due to the wealth of knowledge about the HMWS of "standard molecules." This approach also means there is less risk of resources being expended in a full characterization for a molecule that may not progress. However, biologics now encompass far more than antibodies, and the industry finds itself knowing less than it once did about the molecules it is developing.

Today's biologics portfolio is increasingly composed of novel molecules, such as mRNA, viral vectors, non-native proteins, and cell-based therapies. Speed-to-clinic is a driving force for many companies who are developing therapeutics in 2020. This is even more urgent with the COVID-19 pandemic and the need to develop vaccines to prevent the disease or therapies to help heal those stricken with it. With so many novel therapeutic modalities, the use of institutional knowledge built up over many decades is no longer relevant. Even with heightened urgency to bring medicines to patients, safety cannot be compromised. The desire for speed and safety reinforces the strategy that methods need to be fully characterized much earlier in development than has been typically done. While there is certainly an added initial cost, and therefore potential financial burden overall if the molecule does not progress clinically, in today's fast-paced market characterizing products early is becoming vitally important. Outside of COVID-19, we are also living in the days of FDA Fast-Track, Break-Through Therapy, Accelerated Approvals, and Priority Reviews. This can mean that a molecule advances very quickly to Phase 3 trials.

As therapeutic strategies change, it is important to constantly re-evaluate historical approaches and methodologies. A "work-horse" release method like SEC should be fully characterized as soon as possible in development. Fully characterizing SEC should include MALS detection at a minimum. Pre-investing in fully characterizing the output from a key release method like SEC also has the benefit that the identity of the peaks can be tracked throughout method changes during development. This confers the distinct advantage that data can be compared from the earliest testing through to the final version of the method. With the fast-paced world of novel molecules, full and early characterization should be the new paradigm.



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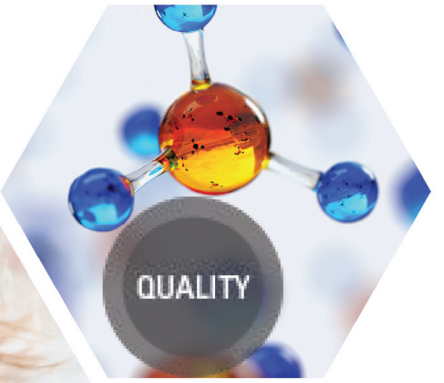

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