



Review

Advancing pharmaceutical quality: An overview of science and research in the U.S. FDA's Office of Pharmaceutical Quality



Adam C. Fisher^a, Sau L. Lee^{a,*}, Daniel P. Harris^a, Lucinda Buhse^a, Steven Kozlowski^a, Lawrence Yu^a, Michael Kopcha^a, Janet Woodcock^b

^a Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Silver Spring, MD 20993, United States

^b Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States

ARTICLE INFO

Article history:

Received 7 September 2016

Received in revised form 17 October 2016

Accepted 18 October 2016

Available online 20 October 2016

Keywords:

Pharmaceutical quality

Regulatory science

Emerging technology

Quality standards

Policy

ABSTRACT

Failures surrounding pharmaceutical quality, particularly with respect to product manufacturing issues and facility remediation, account for the majority of drug shortages and product recalls in the United States. Major scientific advancements pressure established regulatory paradigms, especially in the areas of biosimilars, precision medicine, combination products, emerging manufacturing technologies, and the use of real-world data. Pharmaceutical manufacturing is increasingly globalized, prompting the need for more efficient surveillance systems for monitoring product quality. Furthermore, increasing scrutiny and accelerated approval pathways provide a driving force to be even more efficient with limited regulatory resources. To address these regulatory challenges, the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA) harbors a rigorous science and research program in core areas that support drug quality review, inspection, surveillance, standards, and policy development. Science and research is the foundation of risk-based quality assessment of new drugs, generic drugs, over-the-counter drugs, and biotechnology products including biosimilars. This is an overview of the science and research activities in OPQ that support the mission of ensuring that safe, effective, and high-quality drugs are available to the American public.

Published by Elsevier B.V.

Contents

1. Introduction	391
2. Manufacturing science and innovation	392
2.1. Manufacturing and controls for small molecule drugs	392
2.2. Manufacturing and controls for biotechnology products	393
3. Drug quality standards	394
4. Advanced characterization of complex mixtures and biologics	394
5. Physicochemical characterization of complex formulations and dosage forms	395
6. Post-market product quality and public health issues	396
7. Immunogenicity and immunology	397
8. Linking biomarkers and drug attributes to safety and efficacy	398
9. Summary	400
References	400

Abbreviations: ADF, abuse deterrent formulation; API, active pharmaceutical ingredient; T-DM1, Ado-Trastuzumab Emtansine; ADC, antibody-drug conjugate; CDER, center for drug evaluation and research; CBRN/EID, chemical, biological, radiological/nuclear and emerging infectious disease; CMC, chemistry, manufacturing, and controls; DMD, Duchenne muscular dystrophy; DLS, dynamic light scattering; FDA, food and drug administration; FTIR, Fourier transform infrared spectroscopy; GA, glatiramer acetate; IVIVC, *in vivo/in vitro* correlation; MHC, major histocompatibility complex; MVDA, multivariate data analysis; NMR, nuclear magnetic resonance; OBP, office of biotechnology products; OPQ, office of pharmaceutical quality; OTR, office of testing and research; PAT, process analytical technology; QbD, quality by design; SLEP, shelf-life extension program; TNF, tumor necrosis factor; VLP, virus-like particle.

* Corresponding author.

E-mail address: sau.lee@fda.hhs.gov (S.L. Lee).

1. Introduction

For over a decade, the Center for Drug Evaluation and Research (CDER) in the U.S. Food and Drug Administration (FDA) has followed a vision to modernize pharmaceutical development and manufacturing in order to enhance product quality (FDA, 2004). Over the same time span, there have been increasing challenges with regard to drug shortages and recalls that reflect failures in pharmaceutical quality. Nearly two-thirds of all drug shortages can be attributed to quality failures, particularly due to issues in facility remediation and product manufacturing (FDA, 2013b). In addition, there is increasing scrutiny from the industry and lawmakers, coupled with a greater desire for engagement and dialogue among the regulatory agencies, industry, and patients. At the same time, major technical and scientific advancements have challenged existing regulatory paradigms. Such advancements have impacted biosimilars, precision medicine, combination products, emerging manufacturing technologies, and the use of real-world data.

Pharmaceutical manufacturing is globalizing at an unprecedented pace, making product quality surveillance even more challenging. Furthermore, there is pressure to implement new regulatory mandates (e.g., accelerated approval pathways) with limited resources. To strengthen pharmaceutical quality in the face of present and future challenges, the FDA established the Office of Pharmaceutical Quality (OPQ) within CDER on January 11, 2015 (Yu and Woodcock, 2015). The science and research program within OPQ is built to support the mission and priorities of the FDA related to pharmaceutical quality (FDA, 2013a). Science and research in OPQ forms the foundation for risk-based quality evaluation including review, inspection and surveillance, as well as for quality-related standard and policy development for all drug product areas – new drugs, generic drugs, over-the-counter drugs, and biotechnology products. In this review, OPQ science and research includes: (i) testing and scientific investigation of methods and data that aid drug quality evaluation and (ii) proactive research for development of scientific tools and approaches for evaluating the safety, performance and quality of products.

There is a mandate to better utilize science and research to advance public health by improving access to safe, effective, and high-quality drugs. From the product quality perspective, the FDA

needs science and research to keep pace with rapid advances in technology and increasing complexity of FDA-regulated products. For example, since the dawn of OPQ, approvals have been seen for products of new manufacturing paradigms including the first 3D printed product (Norman et al., 2016), the first three biosimilars (FDA, 2016b; Holzmann et al., 2016; von Schaper, 2016), the first new drug product made using continuous manufacturing (Vertex, 2015), and the first switch from a batch process to a continuous process for a previously FDA-approved product (PharmaTech, 2016). OPQ science and research helps the FDA, once perceived as a potential obstacle to innovation, actively promote and support new technology paradigms with the potential to improve overall drug manufacturing quality and reliability (Yu et al., 2016). The information gained supports review and inspection, as well as accelerated development timelines for new drugs and biotechnology products, including biosimilars.

OPQ's designation as a super-office indicates that multiple offices operate within its purview (Fig. 1). Under this organizational structure, OPQ can integrate the science and research findings into review, inspection, and surveillance across the product lifecycle. The laboratories of OPQ – established in the Office of Biotechnology Products (OBP) and the Office of Testing and Research (OTR) – conduct mission-directed, collaborative laboratory-based science and research activities to support the development of scientific standards and policies for safe and effective quality drug products. OPQ also collaborates with other Centers and stakeholders (e.g., academia) to conduct research to advance pharmaceutical quality as appropriate. These efforts collectively build the capacity for evaluation and monitoring, address mission-critical science matters, and maintain a state of research readiness that anticipates FDA needs while allowing for rapid response to emergent regulatory issues. There are seven key areas in OPQ's science and research portfolio:

- Manufacturing Science and Innovation.
- Drug Quality Standards.
- Advanced Characterization of Complex Mixtures and Biologics.
- Physicochemical Characterization of Complex Formulations and Dosage Forms.
- Post-Market Product Quality and Public Health Issues.
- Immunogenicity and Immunology.

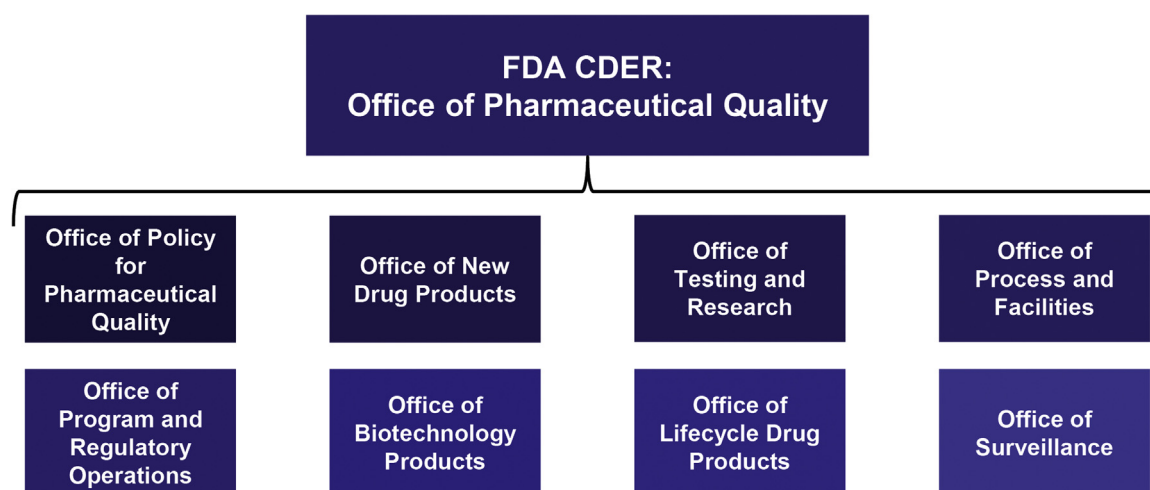


Fig. 1. Organization of CDER's Office of Pharmaceutical Quality (OPQ). There is an immediate office and eight sub-offices within the purview of OPQ. The immediate office consists of Program Management Analysis Staff (PMAS), providing administrative services, and Science and Research Staff (SRS), who help coordinate scientific activities within OPQ. Governance of scientific and research work in OPQ is the mission of OPQ's Research Review Coordinating Committee which supports, promotes, priorities and funds OPQ laboratory research that will have an impact on review and policy decisions. Committee membership is drawn from OPQ's immediate office and 8 sub-offices.

- Linking Biomarkers and Drug Attributes to Safety and Efficacy. Scientific advancements in these areas directly impact the establishment of clear science-based standards and policies for consistent product quality evaluation. Such advancements also facilitate risk-based decision making regarding the product safety and efficacy in relation to product quality. For example, OPQ research has recently:
- Informed regulatory guidance documents (FDA, 2014), product reviews/approvals (Anderson et al., 2015; Holzmann et al., 2016), and congressional testimony (Throckmorton, 2015);
- Provided scientific standards (FDA, 2016c); and
- Tested and screened products resulting in consumer alerts (FDA, 2016e,f).

The FDA's ability to meet public health challenges as a result of science and research in these seven core areas is described in more detail below.

2. Manufacturing science and innovation

Data show that drug shortages and product recalls are commonly related to shortcomings in product or facility quality (FDA, 2013b). To proactively address these issues, it becomes increasingly important for manufacturing technologies to evolve and bring agility, flexibility, and robustness to the manufacture of pharmaceuticals and modernize pharmaceutical manufacturing to be on par with other manufacturing industries (e.g., semiconductors, chemicals, and petroleum) (Rockoff, 2015). The need for advancement of manufacturing technologies is relevant to both drug substances and drug products and both small molecule drugs and biotechnology products. The FDA prepares for the evaluation of novel technologies through the recently established FDA Emerging Technology Program (FDA, 2015a) by promoting manufacturing science and research, including advanced analytics or process analytical technology, process modeling and simulation, and advanced manufacturing methodologies (e.g., 3D printing and continuous manufacturing).

2.1. Manufacturing and controls for small molecule drugs

Batch manufacturing is the predominant method for the production of small-molecule drugs (i.e., drug substances and finished dosage forms). However, there is often insufficient systematic understanding of batch processes, particularly with respect to manufacturing scale up and especially for more complicated unit operations. To address these problems, the FDA's research effort in manufacturing science is focused on improving the understanding of how process parameters affect drug product critical quality attributes across scales for various batch processes.

Recognizing the limitations of current batch manufacturing processes (e.g., difficult scale up, long total processing times due to storage and shipping of intermediates, and large manufacturing facilities needed for large-volume product production), the FDA places an emphasis on advancing new pharmaceutical manufacturing technologies. Advances in manufacturing science have the potential to reinvigorate the pharmaceutical manufacturing sector in the U.S. by stimulating adoption of emerging technologies that are innovative in the pharmaceutical domain and expected to improve product quality (NSTC, 2016). For example, 3D printing technology enables previously inaccessible dosage forms (e.g., rapidly dissolving oral dosage forms) and has the potential to advance precision medicine (e.g., by enabling patient-specific drug manufacturing). Continuous manufacturing can result in better efficiency and improved product quality, benefiting both the industry and patients (O'Connor et al., 2016). The FDA has projects – several in partnership with external collaborators – that focus on emerging technologies including process analytical technology (PAT), advanced process controls, real-time release testing, and process simulation and modeling for continuous manufacturing (FDA, 2016a).

Integrated process models for continuous manufacturing can support a quantitative initial risk assessment through sensitivity analysis by examining the relative magnitude of the impact of variations in process parameters and/or material attributes on quality attributes. Process models can also be tools to assess the

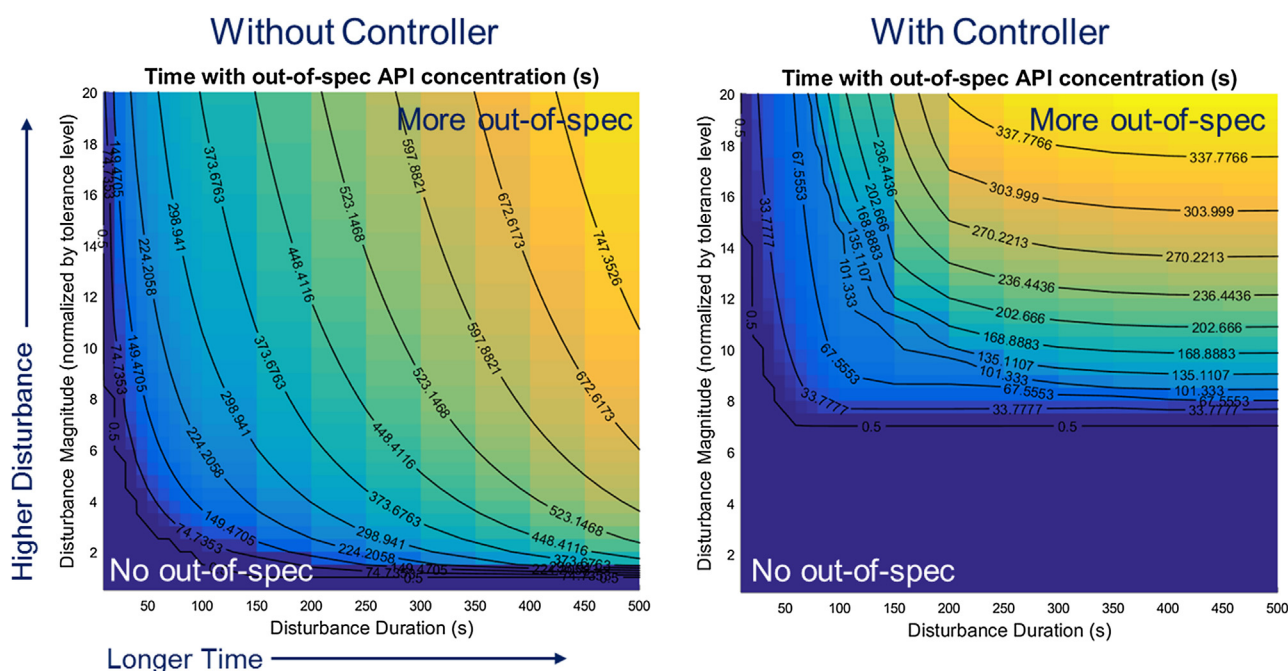


Fig. 2. Modeling robustness of continuous direct compression with respect to the disturbance in the feeding of active pharmaceutical ingredient (API) for two different control strategy approaches. The amount of time for which the blender/tablet API concentration exceeded limits is plotted in relation to the magnitude and the duration of pulse disturbance. The incorporation of ratio feed-rate controls is able to increase the robustness of the system.

effectiveness of a proposed control strategy through the use of case studies, such as examining the ability to mitigate the impact of disturbances (e.g., feeder refills) (Escotet-Espinoza et al., 2015). Therefore, these modeling approaches can aid and streamline regulatory review and inspection activities. For example, the process modeling of continuous direct tablet compression was used to identify: (i) types of disturbances that can have a significant impact on product quality and (ii) the effectiveness of an active control system to minimize these disturbances for a continuous process (Fig. 2). Furthermore, process models may be directly incorporated into the control strategy for a continuous manufacturing process (e.g., models that track non-conforming material to downstream diversion points). Systematic risk assessments and failure mode analysis from process modeling simulations can inform feedback and recommendations to manufacturers during the development of continuous manufacturing processes. This research ensures that advances in small-molecule drug manufacturing will be understood by regulators and can be used to support advanced technology in the industry.

2.2. Manufacturing and controls for biotechnology products

Biotechnology products are large, complex molecules typically produced in living cells. For these products there is a general desire to advance manufacturing, both upstream and downstream, to reduce shortages and variability, allow for cost savings and production flexibility, and simplify scale up procedures (Konstantinov and Cooney, 2015). To this end, the pharmaceutical industry is transitioning toward continuous processes in biomanufacturing to improve product quality, reduce facility footprints, increase productivity, and reduce production costs (Walther et al., 2015). Continuous processes decrease bioreactor residence time and eliminate intermediate hold steps while minimizing manual operations and human decision making. These advancements may reduce the risk of modification or degradation of product, and potentially decrease impurity levels by allowing drug production at high cell densities.

FDA research in biomanufacturing includes work to improve process analytical technology (PAT) for the production of

biotechnology products. Research to develop PAT for bioreactor optimization evaluated a Fourier transform infrared spectroscopy (FTIR) method for measuring key metabolites (Wu et al., 2015) and a dielectric spectroscopy-based method for measuring viable cell density (Lee et al., 2015a). These methods were determined to be suitable for monitoring cell culture process dynamics in real time. Another recent project used a quality by design (QbD) approach to assess specific parameters (e.g., temperature and nonessential amino acid supplementation) that significantly influence glycoform profiles of a monoclonal antibody (Agarabi et al., 2015). Multivariate data analysis (MVDA) of this process was used to correlate product quality attributes (e.g., specific glycan abundance) with process variables, particularly levels of amino acid supplements in the cell culture media (Rathore et al., 2015) (Fig. 3). In addition to work on upstream processes, downstream processes are also a focus of FDA research, especially with respect to the critical area of viral safety. FDA efforts in the area of viral safety include understanding failure modes for viral filters (LaCasse et al., 2016), evaluating new chromatographic methods for viral clearance (Iskra et al., 2015), evaluating viral clearance as a function of resin age, and introducing concepts to assure viral safety for continuous processes (Johnson et al., 2016). FDA efforts on downstream processes also include work on downstream processes such as lyophilization (Awotwe-Otoo et al., 2015) and optimizing formulation buffers for stability (Chavez et al., 2016). Biomanufacturing research in the FDA supports chemistry, manufacturing, and controls (CMC) decisions on biotechnology products, and aids in the formulation of guidance and policy development.

FDA research includes investigations into types of biomolecules other than recombinant proteins. For example, FDA scientists develop chemical methods for the synthesis, purification, and delivery of synthetic nucleic acids. Amphipathic phosphorothioate DNA elements were recently demonstrated by FDA researchers to transporter uncharged nucleic acid sequences into mammalian cells (Jain et al., 2015). This work may enable the development and manufacture of therapeutic uncharged and negatively charged nucleic acid-based drugs and streamline the FDA review process for these products.

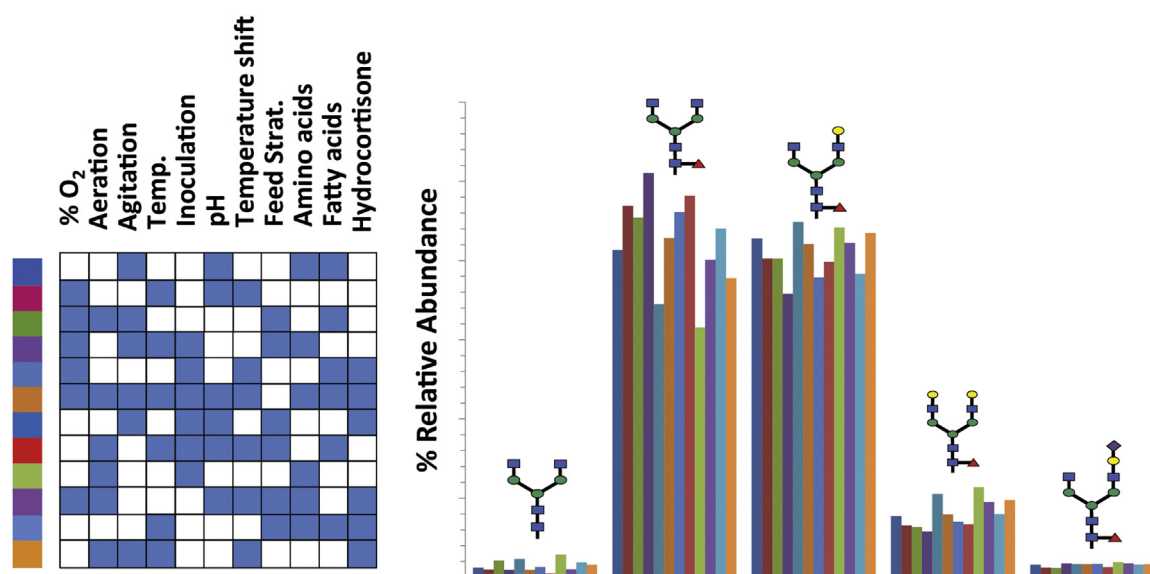


Fig. 3. Quality by design (QbD) optimization of bioreactor manufacturing for monoclonal antibodies. A Plackett–Burman screening design was applied to laboratory-scale parallel cultures to study the effects of 11 process variables on critical quality attributes of a monoclonal antibody. Engineering changes related to culture temperature and nonessential amino acid supplementation significantly impacted glycan profiles associated with fucosylation, galactosylation, and sialylation. Figure adapted from (Agarabi et al., 2015).

3. Drug quality standards

Efficient drug evaluation and lifecycle management require clear standards (*i.e.*, tests or other measures) to ensure product identity, strength, purity, quality, and potency. As such, the development and evaluation of science-based, clinically-relevant standards is a focal point of the FDA product quality assessment. FDA science and research on drug quality standards aims to inform industry, standard setting organizations including compendia, and generates recommendations that facilitate the regulatory quality assessment and product approval.

With respect to drug quality standards, of particular importance is work focuses on providing standards for abuse deterrent formulations (ADF) of opioid products. Such products are important for improving the quality of life for patients who need them, but they can be misused and abused, potentially leading to addiction (Meyer et al., 2014). The issue of drug abuse becomes more prominent when the dosage forms can be readily manipulated to release or extract a high amount of opioid. One approach to deter opioid abuse is by providing scientific standards for ADF properties that make abuse of the product more difficult. For example, as the highest mortality rates for opioid abuse are associated with parenteral and nasal routes, this may include increasing the difficulty of crushing a tablet in order to snort the contents or dissolving a capsule in order to inject the contents (Katz et al., 2011). With limited history and a lack of compendial standards, evaluation of ADF opioid products can be challenging. An FDA laboratory recently developed a risk-based, standardized *in vitro* approach for testing abuse deterrent features for all ADF products, including the solubility in common solvents and assessment of particle size after manipulation which may influence the rate of opioid extraction from a product or the potential for abuse by insufflation (Xu et al., 2016b) (Fig. 4). This and other work on the impact of formulation and process variables on ADF (Rahman et al., 2016) enhances the understanding of ADF and supports guidance development and the quality review of ADF products (FDA, 2016c).

Knowledge surrounding the quality of well-established drugs across the lifecycle is evolving. For example, a new product failure mode was identified for warfarin sodium. A significant FDA research effort has focused on understanding and detecting this undesirable phase transformation of the crystalline solid to a glue-like substance at high humidity (Korang-Yeboah et al., 2015; Nguyenpho et al., 2015; Rahman et al., 2015b; Siddiqui et al., 2015). It is important to understand this phase transformation to properly evaluate the stability of warfarin sodium drug products during use and handling, especially to ensure the consistent therapeutic

efficacy a drug with such a narrow therapeutic index. Research into this failure mode resulted in post-marketing corrections of the approved products, impacted regulatory decisions for pending warfarin sodium applications, and led to a better quality control of this drug product (Rahman et al., 2015a).

FDA researchers are working to provide clinically-relevant specifications for complex dosage forms and formulations, including products containing ophthalmic ointments and transdermal drug delivery systems (*i.e.*, patches). An important scientific challenge for complex products is correlating *in vitro* drug release of a formulation to the *in vivo* drug profile. Such an *in vivo/in vitro* correlation (IVIVC) can be used to ensure product quality and performance during product development and when facing scale-up and post-approval changes. An FDA laboratory recently developed an IVIVC for estradiol transdermal drug delivery systems using *in vitro* skin permeation studies for marketed products (Yang et al., 2015) (Fig. 5). This is the first IVIVC model for transdermal systems using marketed estradiol as a model drug product. The IVIVC may prove useful as a performance predictor for ensuring product quality, as it passed both internal and external validations. An FDA laboratory also developed an *in vitro* release testing method suitable for ointment formulations using acyclovir as a model drug (Xu et al., 2015). This model included a novel transient-boundary layer which challenges the well-established Higuchi model for kinetic release from oily ointment bases. This work provides a needed and improved understanding of product quality and performance for locally acting complex topical drug products, including ophthalmic ointments.

4. Advanced characterization of complex mixtures and biologics

The regulation of drug substances consisting of complex heterogeneous mixtures (Lee et al., 2015b) or biomolecules (Ghasriani et al., 2016) poses a pressing regulatory challenge. In addition, there is a need to keep pace with advancements in analytical technology in the face of accelerated clinical development and approval timelines, such as the breakthrough therapy designation (Sherman et al., 2013). Drug substance characterization is required for all product areas, including new drugs, generic drugs, new biotechnology products, and biosimilars. Equivalence and similarity comparisons by analytical means constitute a significant basis of the evaluation of manufacturing and formulation changes, generic complex drug substances, and biosimilars. In addition, analytics can identify chemical markers that are sensitive to changes in raw materials and manufacturing process



Fig. 4. A risk-based *in vitro* performance assessment of extended release abuse deterrent formulations. A model compound, sotalol, that resembles the physicochemical properties of certain opioids, was manipulated (*e.g.*, splitting, crushing, grinding, etc.) to determine particle size and size distribution. For example, (A) one sotalol test formulation could easily be manipulated into smaller particles; over 20% were below 500 μm . (B) Another sotalol test formulation showed relatively high resistance to physical tampering and was very difficult to break into sizes smaller than 3 mm. Figure adapted from (Xu et al., 2016b).

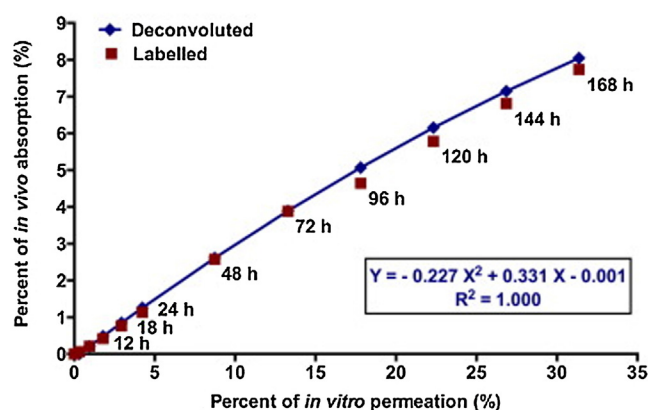


Fig. 5. IVIVC model estradiol transdermal drug delivery systems using *in vitro* skin permeation data created using GastroPlus[®] software. A second order polynomial correlation ($Y = -0.227 X^2 + 0.331 X - 0.001$) was found between the *in vitro* % permeation (X) and the deconvoluted (Fit) *in vivo* % absorption (Y) with a correlation coefficient (R^2) of 1.000, indicating a strong correlation between the two components (diamond). Manually calculated *in vivo* % absorption based on the label information for the product was also shown at each time point for comparison (square). The *in vitro* permeation experiment was conducted using surgically discarded skin and 20% (v/v) ethanol in the receiver medium. Figure adapted from (Yang et al., 2015).

parameters, which allow for improved development of quality controls. Impurities are a significant concern for all product areas, but particularly for generic complex mixture drug substances. Sensitive characterization can provide information on the identity and quantity of individual impurities. Therefore, it is necessary to develop and use an orthogonal set of advanced analytical methods for characterization of complex drug substances and biomolecules, and for linking these attributes to safety, quality, and clinical performance.

In this context, FDA science and research supports equivalence or similarity evaluation by identifying highly specific product attributes and aiming to achieve “fingerprint-like” characterizations of heterogeneous mixtures. Recent FDA research has shown how so-called “modern or advanced analytics” can be used to address challenges in characterizing:

- Biosimilars (e.g., filgrastim (Ghasriani et al., 2016) or monoclonal antibodies (Ferguson and Gucinski-Ruth, 2016; Schiel et al., 2015)),
- Complex mixtures, either naturally derived, (e.g., protamine sulfate (Gucinski et al., 2015)) or synthetic (e.g., glatiramer acetate (Rogstad et al., 2015)), and
- Modifications to therapeutic proteins that are post-translational (e.g., glycosylation (Zhang et al., 2016)) or occur during manufacturing/storage (e.g., oxidation (Kryndushkin and Rao, 2016; Uehara and Rao, 2015)).

For example, the drug substance glatiramer acetate is a mixture of synthetic copolymers consisting of four amino acids marketed for the treatment of multiple sclerosis that is highly heterogeneous (Jalilian et al., 2012). The FDA developed an independent, sensitive analytical method (i.e., LC–MS with digestion) coupled with principal component analysis to characterize the sameness of glatiramer acetate products (Rogstad et al., 2015). The result of this analysis, coupled with orthogonal techniques such as nuclear magnetic resonance (NMR) or multiangle light scattering, together with information from the application helped inform the regulatory decision to approve the first generic glatiramer acetate product in 2015 (Anderson et al., 2015) (Fig. 6).

The FDA was also part of an international collaborative effort to determine the precision and robustness of 2D-NMR for the

structural assessment of filgrastim biosimilars (Ghasriani et al., 2016). This was the first reported interlaboratory study of a high-resolution 2D-NMR method to assess higher-order structure of a biotherapeutic. In this study, the U.S. FDA-approved originator product and three international filgrastim products were compared using six spectrometers in four different laboratories. Results showed that minimal measurement drift was observed over the nine-month period of the study. The resolution of the 2D-NMR method was shown to allow visualization of the degree of similarity between filgrastim products (Fig. 7). In addition, traceable reference values were established which could allow for comparisons to the NMR signature of a comparator product from a validated database. Recently, a filgrastim product became the first U.S. biosimilar approval, followed by an infliximab and an etanercept product in 2016 (FDA, 2016b; Holzmann et al., 2016; von Schaper, 2016). Further, the presence of trace amounts of copper and the presence of ascorbate in protein formulations was found to increase levels of carbonylation, a type of oxidative modification, in therapeutic proteins and, in some instances, lead to aggregation and loss of function (Kryndushkin and Rao, 2016). This research has informed risk assessment strategies on the impact of trace metals, certain excipients, and storage conditions on the stability, purity, and potency of protein therapeutics.

5. Physicochemical characterization of complex formulations and dosage forms

Complex dosage forms and formulations, such as transdermals, ointments, emulsions, and products containing nanomaterials, are developed to achieve specific functionalities including enhanced bioavailability, reduced side effects, and/or improved drug targeting and drug concentration at the site of action. Physicochemical characterization of these products is particularly useful to support the evaluation of equivalence of generic products to their innovator counterparts. For example, for generic drug products with a complex formulation, the goal is to use physicochemical characterization to capture key molecular features that result from unique formulation and process designs to ensure delivery of the same clinical performance as the innovator product (Chang et al., 2013). Such sameness determinations can be particularly important because they may eliminate the need for a

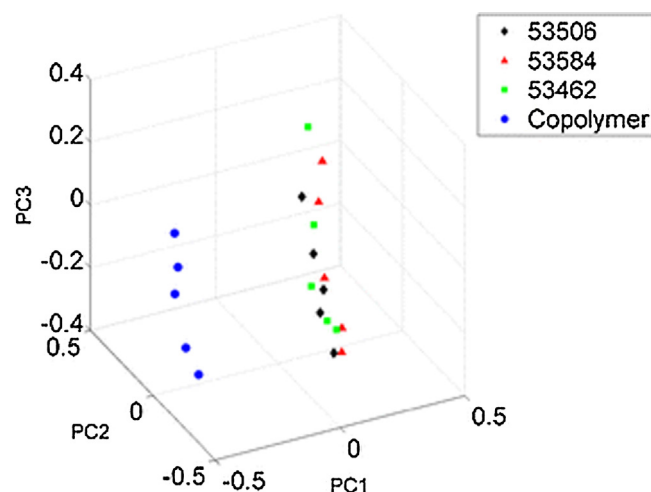


Fig. 6. 3D plot of all data points in space by the three principle components (PC1, PC2, and PC3) from three lots of approved glatiramer acetate (GA) drug product tested prior to expiration (P53462, P53584, and P53506) and non-pharmaceutical Copolymer-1 purchased from Sigma. In the plot, the Copolymer-1 sample was clearly separated from three GA lots, and three GA lots overlap with each other. Figure adapted from (Rogstad et al., 2015).

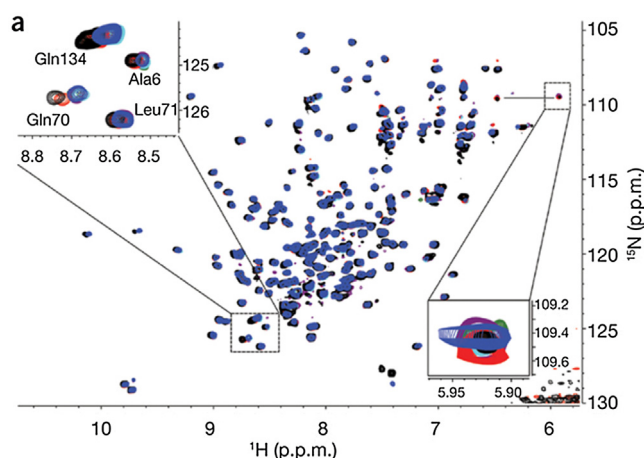


Fig. 7. 2D-NMR overlay plot of the same region of the same U.S. FDA-approved filgrastim sample at four different sites and six different instruments (shown by differing colors). Note that nearly all resonances are overlaid under the blue peaks. An expansion shows the regions containing signals from the amides of Gln134, Gln70, Leu71, and Ala6. Data from two of the spectrometers from one laboratory showed shifts in the peaks (Gln70, Gln134 and Ala6). These were subsequently found to be due to mis-calibrated temperatures of 2 and 4 °C. When the data was re-acquired at the correct temperature, all peaks overlaid. In the lower right, an expansion shows a weak peak observed in all spectra which were not sensitive to temperature. These data illustrate the sensitivity of NMR data to structural changes. Figure adapted from (Ghasriani et al., 2016). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

clinical bioequivalence study for certain complex generic products (e.g., nasal spray suspensions and ophthalmic emulsions). The information from this sameness analysis can also be helpful for the purpose of quality controls, as it helps to identify product attributes relevant to clinical performance and/or sensitive to changes in the manufacturing process or formulation variables (e.g., excipient properties). Tests for such attributes should be included in the drug product specification.

The FDA has taken on the challenge of characterizing complex dosage forms and formulations, including products containing nanomaterials or nanodomains, transdermals, ophthalmic ointments, and amorphous solid dispersions. For example, dynamic light scattering (DLS) is a dispersion-based technique frequently used to determine particle size and particle size distribution for sub-micron particles. As of 2015, ~60% of submissions for drug products that contained nanomaterials included DLS data. Despite the popularity of the technique, there are several limitations to DLS including wide variability due to the ways in which raw data are analyzed and reported. FDA research into best practices for reporting and analyzing DLS data resulted in the production of a reviewer user guide. This document provides standard practices for evaluating DLS data across many product classes, including products containing nanomaterials. In addition, the FDA developed a novel analytical method that couples microscopy with chemical imaging to determine the microstructure and particle or droplet size distribution of complex formulations (unpublished data) (Fig. 8). This method could potentially be used in the future to support biowaivers for certain generic products (e.g., nasal spray suspensions and ophthalmic emulsions).

6. Post-market product quality and public health issues

As the FDA is committed to assuring quality throughout the drug product lifecycle, assessing or monitoring post-market product quality is a key aspect of oversight. FDA laboratory science supports the surveillance of product quality over product

lifecycle, especially when potential safety signals (e.g., patient complaints or abnormal occurrence of adverse events) arise for specific products. FDA laboratories play an important role in investigating the root cause of such signals and determining whether they are related to product quality issues. The result of such investigations helps inform appropriate regulatory actions. In addition to post-market product quality which impacts public health, the FDA's diverse knowledge and expertise are positioned to help address broad public health issues when needed, including providing assistance in the development and evaluation of medical countermeasures. This includes work to minimize domestic vulnerability to chemical, biological, radiological/nuclear and emerging infectious disease (CBRN/EID) threats.

An example of FDA laboratory contributions to the above areas is the maintenance of a national stockpile of oseltamivir phosphate, a critical medical countermeasure for a national influenza pandemic (Patel and Gorman, 2009). The Shelf-Life Extension Program (SLEP), which extends the useful shelf life of federal stockpiles of critical drugs through periodic testing (Khan et al., 2016), saves the federal government large sums of money by reducing stockpile replacement costs (Courtney et al., 2009). In addition to maintaining the stockpile, it is important to eliminate counterfeit products that may contain unapproved antibiotics and analgesics rather than the FDA-approved drug substance (FDA, 2010). The FDA recently developed means to predict qualitative and quantitative critical quality attributes of oseltamivir phosphate using principal component analysis and a Raman spectroscopy-based method that could be deployed in the field (Loethen and Rodriguez, 2015) (Fig. 9). This field-deployable method enables enhanced capability to monitor and assess product quality more rapidly than laboratory-based tests, which require days to transport samples and many hours to perform the analyses (e.g., assay, dissolution, and impurities).

When needed, there is capacity in the FDA to help protect the public by minimizing domestic vulnerability to emerging

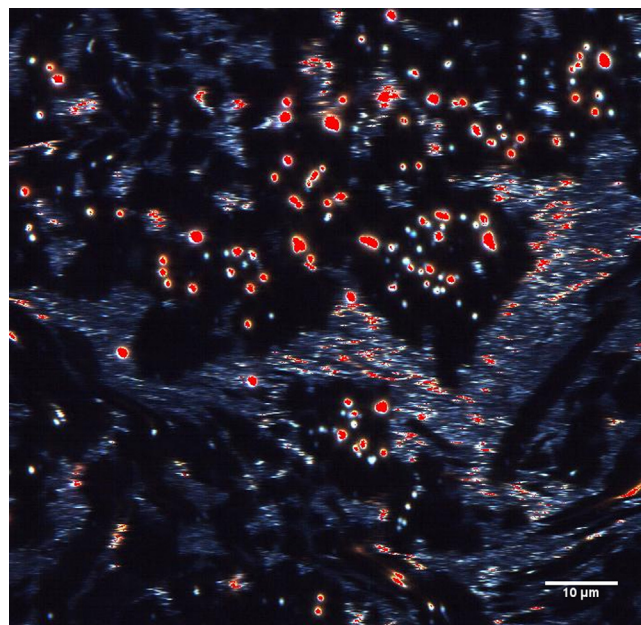


Fig. 8. Physicochemical characterization of drug products containing nanomaterials via hyperspectral images of a cyclosporine ophthalmic ointment. Dark field imaging coupled with hyperspectral analysis can determine the location of drug substance within an emulsion and this information can be used to support the physicochemical equivalence of potential generic emulsion products. High resolution microscopy coupled with chemical analysis captures key information on the microstructure of this and other complex formulations.

infectious disease (EID) threats. Emerging public health threats of infectious disease include Ebola virus and Zika virus (Russek-Cohen et al., 2016). The recent Ebola virus outbreak has emphasized the need to better understand filovirus pathogenesis and the necessity for rapid development and evaluation of preventive and therapeutic agents. The limited number of certified biosafety level 4 (BSL-4) facilities to conduct experiments with filoviruses prompted the FDA to develop replication incompetent virus-like particles (VLPs) with filovirus surface glycoproteins (unpublished data). Since VLPs cannot replicate, they allow scientists to study filovirus entry into cells without the risk of productive infection. VLP studies will be helpful in supporting regulatory submissions for therapeutic proteins against filoviruses, including monoclonal antibodies. In anticipation of the need for assessing therapeutics for Zika virus infections, the FDA has developed a novel mouse model that allows for testing of potential drug candidates (unpublished data). Unlike existing Zika infection models, the new mouse system allows for exploration of long-term effects of the virus on sites where the virus is known to persist in infected patients, such as the central nervous system, the eye, and the reproductive system.

Protecting the public from infectious disease and bioterrorism threats is accomplished in part by developing medical countermeasures to these threats. In the case of anthrax, monoclonal antibodies have been shown to increase survival in animal models and have been approved for use in patients with inhalational anthrax (Fox, 2013). Nevertheless, questions surround the pathogenic effects of anthrax toxin, meaningful biomarkers are needed to assess potential therapeutics, and gastrointestinal anthrax remains unaddressed by therapeutics. Moreover, the FDA recently demonstrated that passive immunotherapy with an anthrax toxin neutralizing antibody also protects against enteric

invasion in a mouse model of gastrointestinal anthrax (Huang et al., 2015) (Fig. 10). This suggests a new medical countermeasure and a potential new role for existing products licensed for treatment of inhalation anthrax in the treatment of gastrointestinal anthrax.

7. Immunogenicity and immunology

A pressing issue with regard to safety and efficacy in relation to pharmaceutical quality is characterizing and predicting potential interactions between components or attributes of drug products and the human immune system (Catalfamo et al., 2015). Proper targeting to and/or avoidance of certain elements of the innate and adaptive immune system is often key to meeting clinical expectations. Within the FDA, immunology research is carried out to better understand the relationship between pharmaceuticals and specific components of the immune system in order to aid the FDA's immunogenicity risk assessment of products. This can be achieved by, for example, deciphering the mechanisms of adverse immune events (Rosenberg et al., 2012). Beyond general mechanisms, human immune responses are a complicated field of study as they are a highly personalized result of an individual's genetic polymorphism and previous exposure to antigens, including both vaccines and pathogens. It is important to understand product attributes that positively or negatively influence immune response by both the innate and adaptive immune systems. Such information is critical for evaluating product quality attributes, particularly for protein therapeutics (e.g., structure, aggregation, posttranslational modifications such as glycosylation, and impurities such as host cell proteins).

Mechanisms that underlie immune responses are an important focus of immunology research in the FDA, including receptors and regulators such as FcγRI (Swisher and Feldman, 2015), the SRC kinase family (Boekhoudt et al., 2015), receptor chain IL-13Rα1 (Sheikh et al., 2015), and Fc receptor-like 5 (Damdinsuren et al., 2016). To this end, an FDA laboratory recently showed the first elucidation of the expression and function of the receptor CD300c on natural killer cells (Dimitrova et al., 2016; Li et al., 2016). Furthermore, peptide loading of major histocompatibility complex class I (MHC-I) molecules is a key to antigen presentation in the immune system and to immune-mediated adverse drug reactions. FDA research recently showed the molecular workings of peptide loading of MHC-I by the TAP binding protein (Morozov et al., 2016). The knowledge gained from this work could have implications for understanding the molecular basis of MHC-linked drug hypersensitivity.

FDA immunology research also aims to develop techniques to predict immunogenicity and modulate immune response. For example, an FDA laboratory developed a cell-based *in vitro* approach, using immune cell lines (human and mouse) to detect receptor-specific agonists, to evaluate impurities that impact immunogenicity risk (Haile et al., 2015) (Fig. 11). Such an approach may allow for an immunogenicity comparison between products by, for example, comparing cellular gene expression fingerprints. This may help in the evaluation of trace impurities with immunogenicity risks, an issue particularly important for generic peptides, naturally-derived products, and biosimilars. FDA research in immunology has highlighted immunological safety issues that need to be addressed during product development and informed the risk assessment for certain products, such as low molecular weight heparin (FDA, 2016d).

Research in immunology also allows the FDA to address potential medical interventions and serious public health issues related to the immune system. With respect to medical interventions, there is a desire to modulate pathological antibody response, for example in patients with adverse responses to

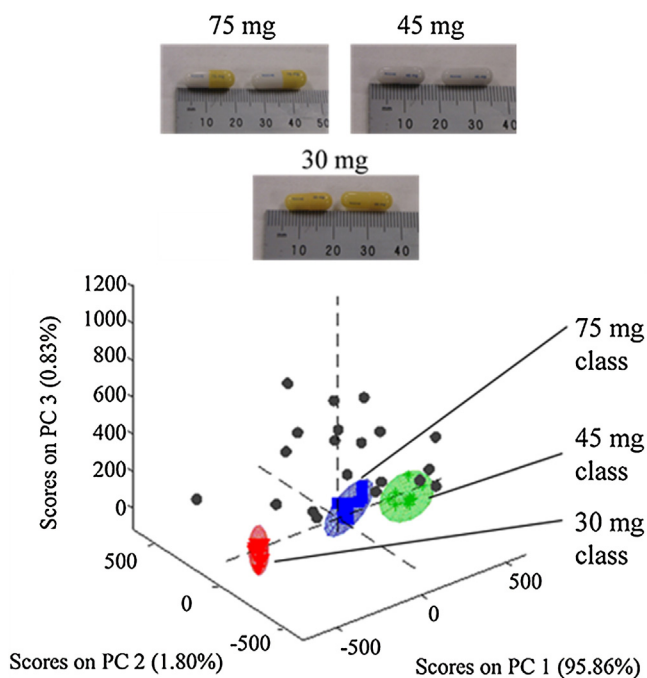


Fig. 9. Simulated counterfeits were used to test the models created from the Raman spectra of oseltamivir phosphate products. PCA models constructed using all dosages were tested with simulated counterfeits and capsule-forms of different drug products. The calibration samples of 30 mg (red), 45 mg (green), and 75 mg (blue) are depicted with 95% confidence limits (shaded ellipsoids). The simulated counterfeits and other drug products are designated as black circles. Figure adapted from (Loethen and Rodriguez, 2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

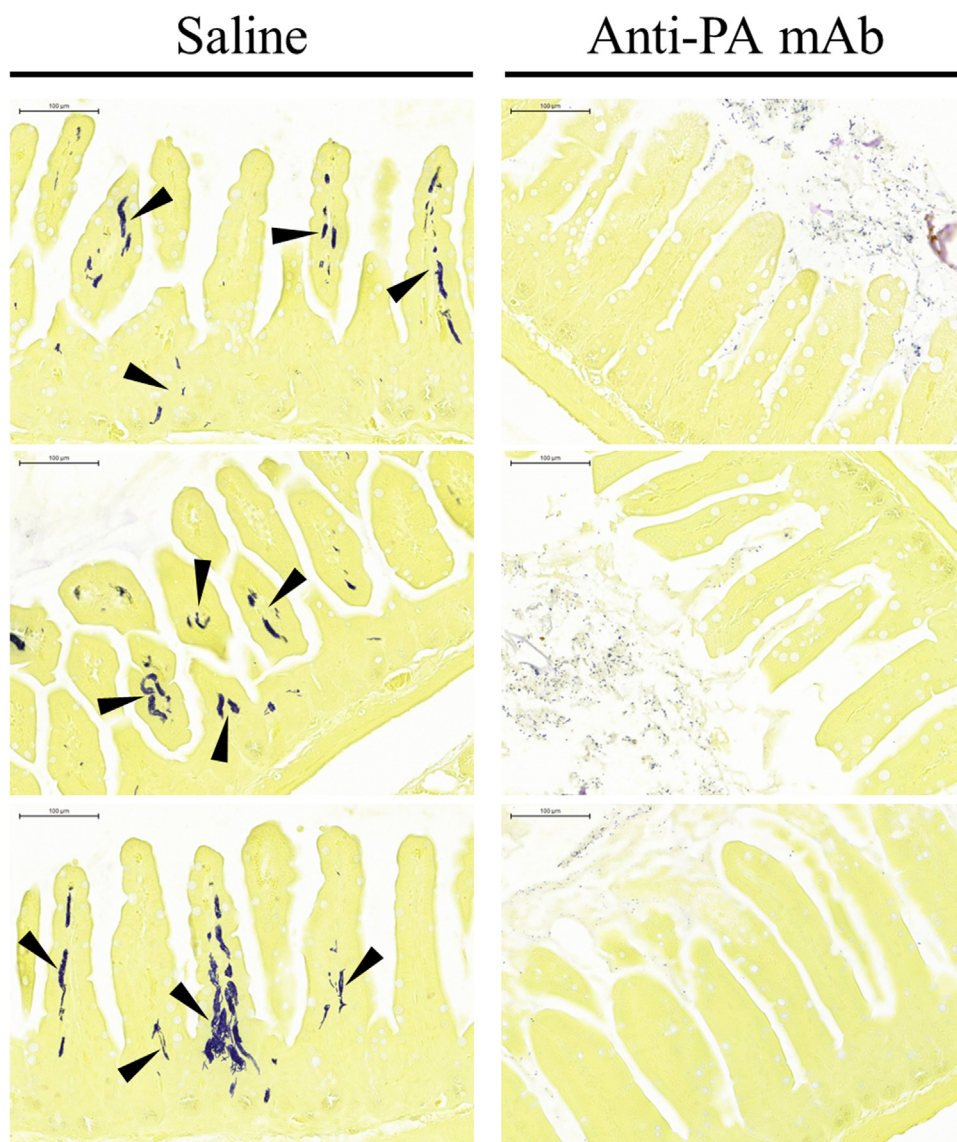


Fig. 10. Passive immunotherapy protects against enteric invasion in a murine model of gastrointestinal anthrax. A monoclonal antibody targeting anthrax toxin prevents *Bacillus anthracis* invasion into intestinal villi in a murine model. Photomicrographs of enteric tissue sections recovered from anthrax-gavaged mice were stained for bacteria concomitantly treated with saline control (left column) or anti-anthrax PA mAb (right column) were fixed, then sectioned for staining by the Brown and Brenn method (representative images shown). Gram + bacilli invading the tissue stain dark blue (arrowheads). Scale bars indicate 100 µm. Figure adapted from (Huang et al., 2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

therapeutic proteins or autoimmune diseases. FDA scientists hypothesized that targeting long-lived plasma cells may result in immune tolerization in several clinical scenarios (Rosenberg et al., 2016). This concept was supported by recent studies of immune tolerance to enzyme replacement therapies (Kazi et al., 2016). With respect to human disease, Duchenne muscular dystrophy (DMD) is a degenerative muscle disorder in boys that eventually leads to paralysis and death. Advancing treatments for patients with DMD is a public health priority because there are currently no treatment options (FDA, 2015b). Research on mechanisms of inflammation have aided in the understanding of the immune-mediated pathology of DMD and clarified opportunities for clinical intervention (Rosenberg et al., 2015). In this context, FDA laboratories contributed by collaborating with internal and external stakeholders to facilitate the development and validation of robust methodologies and assessment criteria for reviewing biomarker data obtained from these methods. Method validation expertise developed through FDA laboratory and

regulatory experiences have been applied to facilitate biomarker and drug development in DMD and other clinical conditions.

8. Linking biomarkers and drug attributes to safety and efficacy

The FDA emphasizes the importance of linking both biomarkers and drug quality attributes to the clinical performance, safety, and efficacy of a drug product. Biomarkers are characteristics measured as an indicator of normal biological processes, pathogenic processes, or responses to exposures or interventions (Robb et al., 2016). Biomarkers can provide insights into, among other things, whether a particular drug will be safe or effective for a particular patient. Precision medicine is an approach to disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles. As precision medicine continues to develop, it will become critical to better understand biomarkers, therapeutic targets, and pathology at the individual patient level.

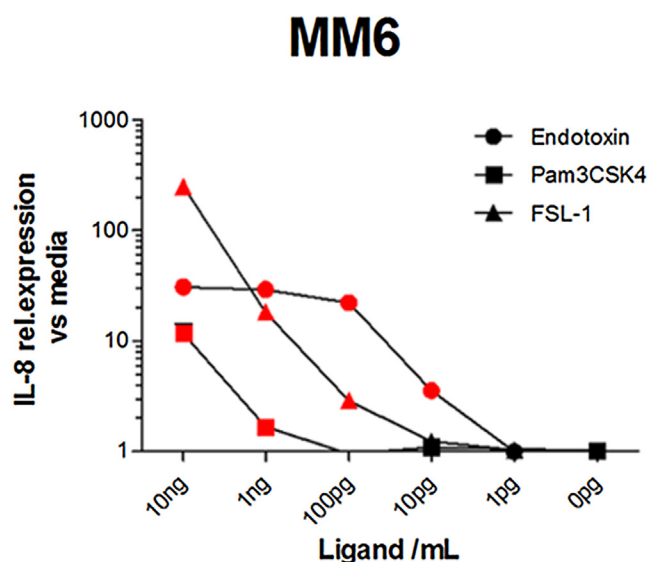


Fig. 11. Detecting complex impurities in therapeutic protein products using human monocytic cell line Macrophage-like-MonoMac6 (MM6) cells stimulated with the indicated concentration of endotoxin, a synthetic triacylated lipopeptide (Pam3CSK4), and a synthetic lipoprotein (FSL-1). Levels of IL-8 mRNA (relative expression vs media) was measured in triplicate. Data points represent mean \pm SD. (* $p < 0.05$ vs media control). Red points show the limit of detection for each individual impurity. Figure adapted from (Haile et al., 2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

A large and rapidly growing number of FDA-regulated products have an oncological indication (Beaver et al., 2015; Casak et al., 2015; de Claro et al., 2015; Khozin et al., 2015; Kim et al., 2015; Miller et al., 2015; Nair et al., 2015; Przepiorka et al., 2015). The use of monoclonal antibodies has proven to be particularly useful in the treatment of cancers, as these drugs can provide a mechanism for targeting treatment on cancerous lesions while sparing normal cells. The approval of trastuzumab, a monoclonal antibody directed against the biomarker HER2, along with a diagnostic kit to detect breast cancers positive for HER2, advanced a new era of precision medicine (Collins and Varmus, 2015). It is anticipated that incorporation of biomarkers into clinical care will facilitate smarter, personalized treatment of individual cancer patients (Blumenthal et al., 2016). With the establishment of the National Cancer Moonshot Initiative, there is an opportunity to change the paradigms of preventing, diagnosing, and treating cancer (Lowy and Collins, 2016). With the dawn of this era come new opportunities to identify cancer biomarkers to ensure that drug products are deployed appropriately. Recent research in the FDA used RNA sequencing to identify a distinct RNA profile of metastatic colorectal carcinoma by comparing colorectal tumor tissue with adjacent healthy tissue from the same patient (Xu et al., 2016a). This biomarker could potentially assist in determining the risk of colorectal carcinoma metastasis. Another FDA study found that a protein expressed in primary breast tumors, RhoGDI, was significantly decreased during tumor progression from benign to malignant and metastatic lesions (Bozza et al., 2015). In addition to identifying a potential cancer biomarker, this study may also suggest that RhoGTPase inhibition could be explored as a therapy for advanced breast cancer. This type of research into cancer biomarkers supports the evaluation and approval of oncological drug products with cancer indications.

FDA researchers also investigate drug quality attributes and their effect on safety and efficacy. For example, the clinical administration of monoclonal antibodies often involves dilution in a 5% dextrose-saline solution for intravenous administration. FDA

research recently identified the cause of monoclonal antibody aggregation when antibody-dextrose solution mixes with human plasma. In this case, pH-dependent precipitation of plasma proteins, including complement proteins, resulted in insoluble aggregates containing antibody (Luo and Zhang, 2015) (Fig. 12). As the aggregation of monoclonal antibodies in human plasma may adversely impact product safety and efficacy (Rosenberg, 2006), this finding improves the ability to assess monoclonal antibody product development regarding compatibility with diluent and human plasma. FDA laboratories also seek to better understand quality attributes relevant to clinical performance, and mechanism of action, to improve the FDA's risk-based approach for evaluating biotechnology products. For example, trastuzumab is a monoclonal antibody indicated for HER2-positive breast and metastatic gastric cancer (Mohan and Wu, 2015). However, trastuzumab has also shown unintended impact to the heart (cardiotoxicity). The FDA investigated the mechanisms underlying trastuzumab-induced cardiotoxicity and revealed that it is due to HER2 expressed by cardiac muscle cells (cardiomyocytes) (Seidman et al., 2002). Binding of the antibody to HER2 expressed on the cell surface dysregulates autophagy in these cells (Mohan et al., 2016). Similarly, FDA scientists have studied unintended liver injury (hepatotoxicity) induced by ado-trastuzumab emtansine (T-DM1), a trastuzumab antibody-drug conjugate (ADC). Hepatotoxicity is a serious adverse event associated with T-DM1 therapy (Dieras et al., 2014). Recent FDA research demonstrates that T-DM1 is internalized in hepatocytes following binding of HER2, leading to damage to the microtubule network, nuclear fragmentation, and

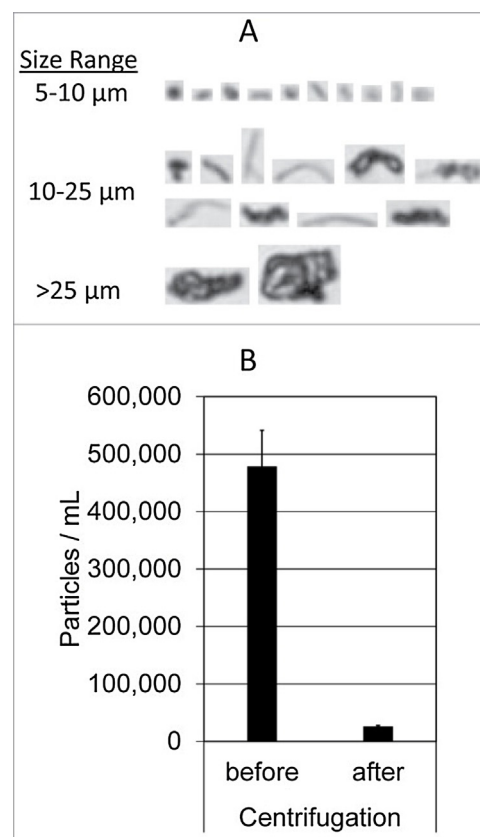


Fig. 12. Micro-flow imaging analysis to examine insoluble aggregates in the mixture of bevacizumab, 5% dextrose, and human plasma. (A) Representative images of particles ($>5 \mu\text{m}$) formed in the mixture. (B) Particle counts in the sizes of $1-70 \mu\text{m}$ were determined for the resulting mixtures before and after centrifugation at $21,000 \text{ g}$ for 3 min . Shown are representatives of 3 independent experiments. Figure adapted from (Luo and Zhang, 2015).

production of tumor necrosis factor (TNF- α) (Yan et al., 2016). Both of these studies unveil mechanisms that explain significant risks associated with the use of trastuzumab therapies and inform the regulatory review of these types of products. These findings may also present insight useful for the development of monoclonal antibody products with fewer associated side effects.

9. Summary

Industry trends are expanding the regulatory challenges pertaining to quality, manufacturing, and drug product development. Manufacturing technologies are becoming more complex (e.g., 3D printing, continuous manufacturing). Clinically-meaningful specifications are increasingly needed to support diverse dosage forms, including abuse deterrent formulations of opioid products, ointments, and emulsions. Analytical methods are advancing and being used for the characterization of complex mixtures, biologics, and complex formulations. The immunogenicity risk for naturally-derived products, protein therapeutics, and biosimilars needs to be better understood so both the regulatory agency and industry can utilize the newly generated knowledge to better manage or mitigate potential safety risks. Science-based informatics systems are needed to analyze “big” datasets to predict manufacturing outcomes, assess equivalence/sameness, and identify sources of risk. Biomarkers need to be identified and qualified to advance the era of precision medicine. Meanwhile, clinical designs are evolving and development timelines are accelerating. The pharmaceutical industry is globalizing at an unprecedented pace. The promising era of biosimilars, precision medicine (National Precision Medicine Initiative), the microbiome (National Microbiome Initiative), and the eradication of cancer (National Cancer Moonshot Initiative) has just begun. The resulting scientific and regulatory challenges must be met with science- and risk-based decisions. In addressing these challenges, OPQ has built its science and research program to: (i) maintain and establish collaborations with external stakeholders, (ii) prepare to understand and evaluate new technologies, (iii) respond quickly to drug-related emergencies or public health issues (e.g., Ebola and Zika viruses), and (iv) provide drug product quality surveillance testing and science-based investigational activities. It is also critical to train and expose the next generation of regulatory scientists to pharmaceutical quality through external collaborations. OPQ science and research is the foundation that underlies the FDA's ability to meet mounting regulatory challenges and supports the mission of ensuring that safe, effective, high-quality drugs are available to the American public.

References

- Agarabi, C.D., Schiel, J.E., Lute, S.C., Chavez, B.K., Boyne, M.T., 2nd Brorson, K.A., Khan, M.A., Read, E.K., 2015. Bioreactor process parameter screening utilizing a Plackett-Burman design for a model monoclonal antibody. *J. Pharm. Sci.* 104, 1919–1928.
- Anderson, J., Bell, C., Bishop, J., Capila, I., Ganguly, T., Glajch, J., Iyer, M., Kaundinya, G., Lansing, J., Pradines, J., Prescott, J., Cohen, B.A., Kantor, D., Sachleben, R., 2015. Demonstration of equivalence of a generic glatiramer acetate (Glatopa). *J. Neurol. Sci.* 359, 24–34.
- Awotwe-Otoo, D., Agarabi, C., Read, E.K., Lute, S., Brorson, K.A., Khan, M.A., 2015. Product and process understanding to relate the effect of freezing method on glycation and aggregation of lyophilized monoclonal antibody formulations. *Int. J. Pharm.* 490, 341–350.
- Beaver, J.A., Amiri-Kordestani, L., Charlab, R., Chen, W., Palmby, T., Tilley, A., Zirkelbach, J.F., Yu, J., Liu, Q., Zhao, L., 2015. FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen Receptor-Positive, HER2-Negative metastatic Breast cancer. *Clin. Cancer Res.* 21, 4760–4766.
- Blumenthal, G.M., Mansfield, E., Pazdur, R., 2016. Next-generation sequencing in oncology in the era of precision medicine. *JAMA Oncol.* 2, 13–14.
- Boekhoudt, G.H., McGrath, A.G., Swisher, J.F., Feldman, G.M., 2015. Immune complexes suppress IFN- γ -induced responses in monocytes by activating discrete members of the SRC kinase family. *J. Immunol.* 194, 983–989.
- Bozza, W.P., Zhang, Y., Hallett, K., Rosado, L.R., Zhang, B., 2015. RhoGDI deficiency induces constitutive activation of Rho GTPases and COX-2 pathways in association with breast cancer progression. *Oncotarget* 6, 32723–32736.
- Casak, S.J., Fashoyin-Aje, I., Lemery, S.J., Zhang, L., Jin, R., Li, H., Zhao, L., Zhao, H., Zhang, H., Chen, H., 2015. FDA approval summary: ramucicromab for gastric cancer. *Clin. Cancer Res.* 21, 3372–3376.
- Catalfamo, M., Mawle, A., Verthelyi, D., 2015. Immunology careers at the NIH, FDA and CDC: different paths that focus on advancing public health. *Nat. Immunol.* 16, 129–132.
- Chang, R.-K., Raw, A., Lionberger, R., Yu, L., 2013. Generic development of topical dermatologic products: formulation development, process development, and testing of topical dermatologic products. *AAPS J.* 15, 41–52.
- Chavez, B.K., Agarabi, C.D., Read, E.K., Boyne, M.T., 2nd Khan, M.A., Brorson, K.A., 2016. Improved stability of a model IgG3 by doE-based evaluation of buffer formulations. *BioMed Res. Int.* 2016, 2074149.
- Collins, F.S., Varmus, H., 2015. A new initiative on precision medicine. *N. Engl. J. Med.* 372, 793–795.
- Courtney, B., Easton, J., Inglesby, T.V., SooHoo, C., 2009. Maximizing state and local medical countermeasure stockpile investments through the Shelf-Life Extension Program. *Biosecur. Bioterror.* 7, 101–107.
- Damkinsuren, B., Dement-Brown, J., Li, H., Tolnay, M., 2016. B cell receptor induced Fc receptor-like 5 expression is mediated by multiple signaling pathways converging on NF- κ B and NFAT. *Mol. Immunol.* 73, 112–121.
- de Claro, R.A., McGinn, K.M., Verdun, N., Lee, S.-L., Chiu, H.-J., Saber, H., Brower, M.E., Chang, C.G., Puma, E., Habtemariam, B., 2015. FDA approval: ibrutinib for patients with previously treated mantle cell lymphoma and previously treated chronic lymphocytic leukemia. *Clin. Cancer Res.* 21, 3586–3590.
- Dieras, V., Harbeck, N., Budd, G.T., Greenon, J.K., Guardino, A.E., Samant, M., Chernyukhin, N., Smitt, M.C., Krop, I.E., 2014. Trastuzumab emtansine in human epidermal growth factor receptor 2-positive metastatic breast cancer: an integrated safety analysis. *J. Clin. Oncol.* 32, 2750.
- Dimitrova, M., Zenarruzaiteia, O., Borrego, F., Simhadri, V.R., 2016. CD300c is uniquely expressed on CD56bright Natural Killer Cells and differs from CD300a upon ligand recognition. *Sci. Rep.* 6.
- Escotet-Espinoza, M.S., Singh, R., Sen, M., O'Connor, T., Lee, S., Chatterjee, S., Ramachandran, R., Ierapetritou, M., Muzzio, F., 2015. Flowsheet models modernize pharmaceutical manufacturing design and risk assessment. *Pharm. Technol.* 39.
- FDA, 2004. Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach.
- FDA, 2010. FDA Warns About Fraudulent Tamiflu.
- FDA, 2013. Center for Drug Evaluation and Research (CDER) Strategic Plan 2013–2017.
- FDA, 2013. Strategic Plan for Preventing and Mitigating Drug Shortages.
- FDA, 2014. Draft Guidance on Conjugated Estrogens.
- FDA, 2015. Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base: Guidance for Industry.
- FDA, 2015. Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry.
- FDA, 2016. Advancing Continuous Flow Reactor Technology through Real-Time Control and Product Isolation for Improved Quality Assurance and Consumer Safety.
- FDA, 2016. FDA approves Erelzi, a biosimilar to Enbrel.
- FDA, 2016. General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry.
- FDA, 2016. Immunogenicity-Related Considerations for Low Molecular Weight Heparin: Guidance for Industry.
- FDA, 2016. Tainted Sexual Enhancement Products.
- FDA, 2016. Tainted Weight Loss Products.
- Ferguson, C.N., Gucinski-Ruth, A.C., 2016. Evaluation of ion mobility-mass spectrometry for comparative analysis of monoclonal antibodies. *J. Am. Soc. Mass Spectrom.* 27, 822–833.
- Fox, J.L., 2013. Anthrax drug first antibacterial mAb to win approval. *Nat. Biotechnol.* 31, 8.
- Ghasriani, H., Hodgson, D.J., Brinson, R.G., McEwen, I., Buhse, L.F., Kozlowski, S., Marino, J.P., Aubin, Y., Keire, D.A., 2016. Precision and robustness of 2D-NMR for structure assessment of filgrastim biosimilars. *Nat. Biotechnol.* 34, 139–141.
- Gucinski, A.C., Boyne II, M.T., Keire, D.A., 2015. Modern analytics for naturally derived complex drug substances: NMR and MS tests for protamine sulfate from chum salmon. *Anal. Bioanal. Chem.* 407, 749–759.
- Haile, L.A., Puig, M., Kelley-Baker, L., Verthelyi, D., 2015. Detection of innate immune response modulating impurities in therapeutic proteins. *PLoS One* 10, e0125078.
- Holzmann, J., Balser, S., Windisch, J., 2016. Totality of the evidence at work: the first US biosimilar. *Expert Opin. Biol. Ther.* 16, 137–142.
- Huang, B., Xie, T., Rotstein, D., Fang, H., Frucht, D.M., 2015. Passive immunotherapy protects against enteric invasion and lethal sepsis in a murine model of gastrointestinal anthrax. *Toxins* 7, 3960–3976.
- Iskra, T., Sacramo, A., Gallo, C., Godavarti, R., Chen, S., Lute, S., Brorson, K., 2015. Development of a modular virus clearance package for anion exchange chromatography operated in weak partitioning mode. *Biotechnol. Prog.* 31, 750–757.
- Jain, H., Verthelyi, D., Beaucage, S., 2015. Amphipathic trans-acting phosphorothioate DNA elements mediate the delivery of uncharged nucleic acid sequences in mammalian cells. *RSC Adv.* 5, 65245–65254.
- Jalilian, B., Einarsson, H.B., Vorup-Jensen, T., 2012. Glatiramer acetate in treatment of multiple sclerosis: a toolbox of random co-polymers for targeting

- inflammatory mechanisms of both the innate and adaptive immune system? *Int. J. Mol. Sci.* 13, 14579–14605.
- Johnson, S.A., Brown, M.R., Lute, S.C., Brorson, K.A., 2016. Adapting viral safety assurance strategies to continuous processing of biological products. *Biotechnol. Bioeng.*
- Katz, N., Dart, R.C., Bailey, E., Trudeau, J., Osgood, E., Paillard, F., 2011. Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions. *Am. J. Drug Alcohol Abuse* 37, 205–217.
- Kazi, Z.B., Prater, S.N., Kobori, J.A., Viskochil, D., Bailey, C., Gera, R., Stockton, D.W., McIntosh, P., Rosenberg, A.S., Kishnani, P.S., 2016. Durable and sustained immune tolerance to ERT in Pompe disease with entrenched immune responses. *JCI Insight* 1.
- Khan, S.R., Mohammad, A., Khan, M.A., Faustino, P.J., 2016. Critical importance and quality evaluation of drug delivery autoinjectors in the FDA-DOD shelf life extension program (SLEP). *AAPS J.* 18, 801–803.
- Khozin, S., Blumenthal, G.M., Zhang, L., Tang, S., Brower, M., Fox, E., Helms, W., Leong, R., Song, P., Pan, Y., 2015. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. *Clin. Cancer Res.* 21, 2436–2439.
- Kim, G., Ison, G., McKee, A.E., Zhang, H., Tang, S., Gwise, T., Sridhara, R., Lee, E., Tzou, A., Philip, R., 2015. FDA approval summary: olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. *Clin. Cancer Res.* 21, 4257–4261.
- Konstantinov, K.B., Cooney, C.L., 2015. White paper on continuous bioprocessing may 20–21, 2014 continuous manufacturing symposium. *J. Pharm. Sci.* 104, 813–820.
- Korang-Yeboah, M., Akhtar, S., Siddiqui, A., Rahman, Z., Khan, M.A., 2015. Application of NIR chemometric methods for quantification of the crystalline fraction of warfarin sodium in drug product. *Drug Dev. Ind. Pharm.* 1–11.
- Kryndushkin, D., Rao, V.A., 2016. Comparative effects of metal-catalyzed oxidizing systems on carbonylation and integrity of therapeutic proteins. *Pharm. Res.* 33, 526–539.
- LaCasse, D., Lute, S., Fiadeiro, M., Basha, J., Stork, M., Brorson, K., Godavarti, R., Gallo, C., 2016. Mechanistic failure mode investigation and resolution of parvovirus retentive filters. *Biotechnol. Prog.* 32, 959–970.
- Lee, H.W., Carvell, J., Brorson, K., Yoon, S., 2015a. Dielectric spectroscopy-based estimation of VCD in CHO cell culture. *J. Chem. Technol. Biotechnol.* 90, 273–282.
- Lee, S.L., Dou, J.H., Agarwal, R., Temple, R., Beitz, J., Wu, C., Mulberg, A., Yu, L.X., Woodcock, J., 2015b. Evolution of traditional medicines to botanical drugs. *Science* 347, S32–S34.
- Li, H., Borrego, F., Nagata, S., Tolnay, M., 2016. Fc Receptor-like 5 expression distinguishes two distinct subsets of human circulating tissue-like memory B cells. *J. Immunol.* 196, 4064–4074.
- Loethen, Y.L., Rodriguez, J.D., 2015. Field-deployable raman anti-counterfeit screening of tamiflu capsules. *Am. J. Anal. Chem.* 6, 559.
- Lowy, D.R., Collins, F.S., 2016. Aiming high—changing the trajectory for cancer. *N. Engl. J. Med.* 374, 1901–1904.
- Luo, S., Zhang, B.L., 2015. Dextrose-mediated aggregation of therapeutic monoclonal antibodies in human plasma: implication of isoelectric precipitation of complement proteins. *Mabs Aust.* 7, 1094–1103.
- Meyer, R., Patel, A.M., Rattana, S.K., Quock, T.P., Mody, S.H., 2014. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. *Popul. Health Manage.* 17, 372–387.
- Miller, B.W., Przepiorka, D., de Claro, R.A., Lee, K., Nie, L., Simpson, N., Gudi, R., Saber, H., Shord, S., Bullock, J., 2015. FDA approval: idelalisib monotherapy for the treatment of patients with follicular lymphoma and small lymphocytic lymphoma. *Clin. Cancer Res.* 21, 1525–1529.
- Mohan, N., Wu, W.J., 2015. Trastuzumab is not a tyrosine kinase inhibitor. *Nat. Rev. Cardiol.* 12, 669.
- Mohan, N., Shen, Y., Endo, Y., ElZarrad, M.K., Wu, W.J., 2016. Trastuzumab, but not pertuzumab, dysregulates HER2 signaling to mediate inhibition of autophagy and increase in reactive oxygen species production in human cardiomyocytes. *Mol. Cancer Ther.* 15, 1321–1331.
- Morozov, G.I., Zhao, H., Mage, M.G., Boyd, L.F., Jiang, J., Dolan, M.A., Venna, R., Norcross, M.A., McMurtrey, C.P., Hildebrand, W., 2016. Interaction of TAPBP, a tapasin homolog, with MHC-I molecules promotes peptide editing. *Proc. Natl. Acad. Sci. U. S. A.* 113, E1006–E1015.
- NSTC, 2016. Advanced Manufacturing: A Snapshot of Priority Technology Areas Across the Federal Government.
- Nair, A., Lemery, S.J., Yang, J., Marathe, A., Zhao, L., Zhao, H., Jiang, X., He, K., Ladouceur, G., Mitra, A.K., 2015. FDA approval summary lenvatinib for progressive, radio-iodine-refractory differentiated thyroid cancer. *Clin. Cancer Res.* 21, 5205–5208.
- Nguyenpho, A., Ciavarella, A.B., Siddiqui, A., Rahman, Z., Akhtar, S., Hunt, R., Korang-Yeboah, M., Khan, M.A., 2015. Evaluation of in-use stability of anticoagulant drug products: warfarin sodium. *J. Pharm. Sci.* 104, 4232–4240.
- Norman, J., Madurawe, R.D., Moore, C.M., Khan, M.A., Khairuzzaman, A., 2016. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. *Adv. Drug Deliv. Rev.*
- O'Connor, T.F., Yu, L.X., Lee, S.L., 2016. Emerging technology: a key enabler for modernizing pharmaceutical manufacturing and advancing product quality. *Int. J. Pharm.* 509, 492–498.
- Patel, A., Gorman, S., 2009. Stockpiling antiviral drugs for the next influenza pandemic. *Clin. Pharmacol. Ther.* 86, 241–243.
- PharmaTech., 2016. FDA approves tablet production on Janssen continuous manufacturing line. *Pharm. Technol.*
- Przepiorka, D., Ko, C.-W., Deisseroth, A., Yancey, C.L., Candau-Chacon, R., Chiu, H.-J., Gehrke, B.J., Gomez-Broughton, C., Kane, R.C., Kirshner, S., 2015. FDA approval: blinatumomab. *Clin. Cancer Res.* 21, 4035–4039.
- Rahman, Z., Korang-Yeboah, M., Siddiqui, A., Mohammad, A., Khan, M.A., 2015a. Understanding effect of formulation and manufacturing variables on the critical quality attributes of warfarin sodium product. *Int. J. Pharm.* 495, 19–30.
- Rahman, Z., Mohammad, A., Akhtar, S., Siddiqui, A., Korang-Yeboah, M., Khan, M.A., 2015b. Chemometric model development and comparison of raman and ¹³C solid-state nuclear magnetic resonance-chemometric methods for quantification of crystalline/amorphous warfarin sodium fraction in the formulations. *J. Pharm. Sci.* 104, 2550–2558.
- Rahman, Z., Yang, Y., Korang-Yeboah, M., Siddiqui, A., Xu, X., Ashraf, M., Khan, M.A., 2016. Assessing impact of formulation and process variables on in-vitro performance of directly compressed abuse deterrent formulations. *Int. J. Pharm.* 502, 138–150.
- Rathore, A.S., Kumar Singh, S., Pathak, M., Read, E.K., Brorson, K.A., Agarabi, C.D., Khan, M., 2015. Fermentanomics: relating quality attributes of a monoclonal antibody to cell culture process variables and raw materials using multivariate data analysis. *Biotechnol. Prog.* 31, 1586–1599.
- Robb, M.A., McInnes, P.M., Califf, R.M., 2016. Biomarkers and surrogate endpoints: developing common terminology and definitions. *JAMA* 315, 1107–1108.
- Rockoff, J.D., 2015. Drug making breaks away from its old ways. *Wall Street J.*
- Rogstad, S., Pang, E., Sommers, C., Hu, M., Jiang, X., Keire, D.A., Boyne II, M.T., 2015. Modern analytics for synthetically derived complex drug substances: NMR, AFFF-MALS, and MS tests for glatiramer acetate. *Anal. Bioanal. Chem.* 407, 8647–8659.
- Rosenberg, A.S., Verthelyi, D., Cherney, B.W., 2012. Managing uncertainty: a perspective on risk pertaining to product quality attributes as they bear on immunogenicity of therapeutic proteins. *J. Pharm. Sci.* 101, 3560–3567.
- Rosenberg, A.S., Puig, M., Nagaraju, K., Hoffman, E.P., Villalta, S.A., Rao, V.A., Wakefield, L.M., Woodcock, J., 2015. Immune-mediated pathology in Duchenne muscular dystrophy. *Sci. Transl. Med.* 7, 299rv294.
- Rosenberg, A., Pariser, A., Diamond, B., Yao, L., Turka, L., Lacana, E., Kishnani, P., 2016. A role for plasma cell targeting agents in immune tolerance induction in autoimmune disease and antibody responses to therapeutic proteins. *Clin. Immunol.* 165, 55–59.
- Rosenberg, A.S., 2006. Effects of protein aggregates: an immunologic perspective. *AAPS J.* 8, E501–E507.
- Russek-Cohen, E., Rubin, D., Price, D., Sun, W., Cox, E., Borio, L., 2016. A US Food and Drug Administration perspective on evaluating medical products for Ebola. *Clin. Trials* 13, 105–109.
- Schiell, J.E., Rogstad, S.M., Boyne, M.T., 2015. Comparison of traditional 2-AB fluorescence LC-MS/MS and automated LC-MS for the comparative glycan analysis of monoclonal antibodies. *J. Pharm. Sci.* 104, 2464–2472.
- Seidman, A., Hudis, C., Pierri, M.K., Shak, S., Paton, V., Ashby, M., Murphy, M., Stewart, S.J., Keefe, D., 2002. Cardiac dysfunction in the trastuzumab clinical trials experience. *J. Clin. Oncol.* 20, 1215–1221.
- Sheikh, F., Dickensheets, H., Pedras-Vasconcelos, J., Ramalingam, T., Helming, L., Gordon, S., Donnelly, R.P., 2015. The interleukin-13 receptor- α 1 chain is essential for induction of the alternative macrophage activation pathway by IL-13 but not IL-4. *J. Innate Immun.* 7, 494–505.
- Sherman, R.E., Li, J., Shapley, S., Robb, M., Woodcock, J., 2013. Expediting drug development—the FDA's new breakthrough therapy designation. *N. Engl. J. Med.* 369, 1877–1880.
- Siddiqui, A., Rahman, Z., Korang-Yeboah, M., Khan, M.A., 2015. Development and validation of X-ray diffraction method for quantitative determination of crystallinity in warfarin sodium products. *Int. J. Pharm.* 493, 1–6.
- Swisher, J.F., Feldman, G.M., 2015. The many faces of Fc(RI): implications for therapeutic antibody function. *Immunol. Rev.* 268, 160–174.
- Throckmorton, D.C., 2015. Cannabidiol: Barriers to Research and Potential Medical Benefits.
- Uehara, H., Rao, V.A., 2015. Metal-mediated protein oxidation: applications of a modified ELISA-based carbonyl detection assay for complex proteins. *Pharm. Res.* 32, 691–701.
- Vertex, 2015. FDA Approves ORKAMBI™ (lumacaftor/ivacaftor) – the First Medicine to Treat the Underlying Cause of Cystic Fibrosis for People Ages 12 and Older with Two Copies of the F508del Mutation.
- von Schaper, E., 2016. Celltrion's infliximab copy shows path to biosimilars in US. *Nat. Biotechnol.* 34, 454–455.
- Walther, J., Godawat, R., Hwang, C., Abe, Y., Sinclair, A., Konstantinov, K., 2015. The business impact of an integrated continuous biomanufacturing platform for recombinant protein production. *J. Biotechnol.* 213, 3–12.
- Wu, H., Read, E., White, M., Chavez, B., Brorson, K., Agarabi, C., Khan, M., 2015. Real time monitoring of bioreactor mAb IgG3 cell culture process dynamics via Fourier transform infrared spectroscopy: implications for enabling cell culture process analytical technology. *Front. Chem. Sci. Eng.* 9, 386–406.
- Xu, X., Al-Ghabeish, M., Krishnaiah, Y.S., Rahman, Z., Khan, M.A., 2015. Kinetics of drug release from ointments: role of transient-boundary layer. *Int. J. Pharm.* 494, 31–39.
- Xu, L., Ziegelbauer, J., Wang, R., Wu, W.W., Shen, R.F., Juhl, H., Zhang, Y., Rosenberg, A., 2016a. Distinct profiles for mitochondrial t-RNAs and small nucleolar RNAs in locally invasive and metastatic colorectal cancer. *Clin. Cancer Res.* 22, 773–784.

- Xu, X.M., Gupta, A., Al-Ghabeish, M., Calderon, S.N., Khan, M.A., 2016b. Risk based in vitro performance assessment of extended release abuse deterrent formulations. *Int. J. Pharm.* 500, 255–267.
- Yan, H., Endo, Y., Shen, Y., Rotstein, D., Dokmanovic, M., Mohan, N., Mukhopadhyay, P., Gao, B., Pacher, P., Wu, W.J., 2016. Ado-trastuzumab emtansine targets hepatocytes via human epidermal growth factor receptor 2 to induce hepatotoxicity. *Mol. Cancer Ther.* 15, 480–490.
- Yang, Y., Manda, P., Pavurala, Khan, N.M.A., Krishnaiah, Y.S., 2015. Development and validation of in vitro–in vivo correlation (IVIVC) for estradiol transdermal drug delivery systems. *J. Control. Release* 210, 58–66.
- Yu, L.X., Woodcock, J., 2015. FDA pharmaceutical quality oversight. *Int. J. Pharm.* 491, 2–7.
- Yu, L.X., Akseli, I., Allen, B., Amidon, G., Bizjak, T.G., Boam, A., Caulk, M., Doleski, D., Famulare, J., Fisher, A.C., Furness, S., Hasselbalch, B., Havel, H., Hoag, S.W., Iser, R., Johnson, B.D., Ju, R., Katz, P., Lacana, E., Lee, S.L., Lostritto, R., McNally, G., Mehta, M., Mohan, G., Nasr, M., Nosal, R., Oates, M., O'Connor, T., Polli, J., Raju, G.K., Ramanadham, M., Randazzo, G., Rosencrance, S., Schwendeman, A., Selen, A., Seo, P., Shah, V., Sood, R., Thien, M.P., Tong, T., Trout, B.L., Tyner, K., Vaithiyalingam, S., VanTrieste, M., Walsh, F., Wesdyk, R., Woodcock, J., Wu, G., Wu, L., Yu, L., Zezza, D., 2016. Advancing product quality: a summary of the second FDA/PQRI conference. *AAPS J.* 18, 528–543.
- Zhang, L., Luo, S., Zhang, B.L., 2016. The use of lectin microarray for assessing glycosylation of therapeutic proteins. *Mabs Aust.* 8, 524–535.