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MONTHLY UPDATE - AUGUST 2021 IN REVIEW

INTERNATIONAL PHARMACEUTICAL QUALITY provides in-depth coverage of emerging drug, biologic and combination product CMC and GMP issues and developments with a mission of helping advance and harmonize the quality regulatory process globally. Headquartered in Washington, D.C., IPQ is read by regulatory agencies, manufacturers, suppliers, consultants, law firms, and universities around the world.

IPQ tracks the industry/regulator dialogue at key international forums along with the developments, initiatives, regulations, guidances and standards in the quality regulatory arena to create a uniquely valuable resource for the intelligence gathering and knowledge management needs of the pharmaceutical community.

IPQ's "actionable intelligence" is particularly valuable for thought leaders and decision makers who need to have a deeper understanding of the issues and their context to help shape regulatory policy and develop implementation strategies. Subscriber support allows IPQ, in turn, to make an important contribution to the efforts of key non-profit associations and public service organizations engaged in addressing the increasingly complex manufacturing and regulatory challenges for medicines in the global context.

IPQ is published online, and the substantial archive at IPQpubs.com is easily searchable through its keyword search indexes. Links to documents referenced and cross-links to related previous IPQ coverage in the area are included, allowing readers to quickly dig as deeply into an issue and its context as needed.

IPQ's **"News Alerts"** provide links to the first few paragraphs of the stories newly posted online. Subscribers and license holders can click through to the full stories.

The **"Monthly Updates"** provide the stories that went online during the month in a print-friendly PDF format, and are an easy way for subscribers to keep up with the critical developments impacting the quality regulatory process worldwide. Included are "Updates in Brief" on recent CMC/GMP developments of note with links to the referenced documents and to our related in-depth analysis. Also included is an annotated listing of FDA drug GMP warning letters and recalls as well as EU GMP non-compliance statements posted during the month.

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Bill Paulson, Editor-in-Chief

NOTE FROM IPQ'S EDITOR-IN-CHIEF: The story featured in the August Monthly Update explores the pressing issues around raw material control in biotech processes and products – how the regulatory expectations and industry control practices are evolving as the knowledge base increases in depth and breadth. A central focus is the rich discussion that took place at a USP workshop on "best practices and quality standards" for raw materials used in biomanufacturing, held virtually in April 2021.

The first part of the story reviews the insights offered by CDER and CBER staffers at the USP workshop on what the agency is seeing and concerned about across the review and inspection landscape regarding raw material use and control practices.

The second and third parts delve more deeply into the workshop discussions on: • how the challenges expand in handling raw materials in the cell and gene therapy context, and • where biomanufacturers are in using and controlling polysorbates. The third part also brings in the significant light shed on the polysorbate issues at a CASSS CMC Strategy Forum on "the impact of excipients and HCPs on the formation of particles in biologics" – held in conjunction with the 2020 CASSS annual WCBP conference.

Developments around the world during August that are highlighted in the *"Updates in Brief"* section of the monthly *(see pp. 85-88)* include new or revised guidelines from WHO on GMPs for investigational products, R&D facilities, and medical gases, and on technology transfer. FDA and EMA updated their general principles of parallel scientific advice to sponsors, and a biosimilar work sharing pilot project was launched by the regulatory agency "Access Consortium."

EMA has released an updated version of its Joint Audit Program, and the agency has endorsed recommendations by the International Coalition of Medicines Regulatory Authorities (ICMRA) to facilitate the use of track and trace systems at the global level. Also in the track and trace arena, FDA announced the extension of the comment period for its June 2021 guidance on the requirements for enhanced drug distribution security at the package level.

After a hiatus in July, FDA posted 11 drug GMP warning letters during August – seven to domestic firms and four to ex-US facilities *(see pp. 89-94)*. Four of the US-based recipients were compounding firms. Three of these didn't meet 503B outsourcing requirements – including GMP, labeling, approval and drug supply chain security requirements, such as adverse event reporting and investigation – and one, the 503A bulk substance requirements. An API repacker was found to be using suppliers that were under import alert and to have a variety of cleaning, handling, storage, and data integrity issues, including unacknowledged repackaging of cytotoxic and beta lactam products. Another letter went to a maker/distributer of hand sanitizers with inadequate contamination controls.

The seventh domestic warning letter recipient was a Utah-based manufacturer of a variety of cellular products for allogenic use deploying human umbilical cords/blood and amniotic membrane. The products, sold directly to health care professional and medial facilities, were intended for injection and purporting to be sterile, but did not qualify for exemption from IND or BLA requirements because they did not meet the homologous use and minimal manipulation definitions. Thirteen CGMP and one good donor practice statutes were cited in the lengthy letter, which is informative on FDA's HCT/P manufacturing expectations.

Among the international warning letter recipients were three OTC product manufacturers and a maker of sterile products. Two of the OTC letters – to manufacturers located in Turkey and Australia – were based on a records review that revealed inadequate release, component and stability testing. The third OTC firm – located in China – was a maker of hand sanitizers. FDA had placed the firm on import alert in September 2020 based on a records review that showed a lack of analytical data supporting drug product release, and then followed up with an inspection in March 2021 to evaluate the disparity in the records provided, which, in turn, were found not to be consistent with the inspection findings. Other data integrity and a variety of CGMP issues were uncovered during the follow-up inspection.

The fourth international warning letter went to a sterile product manufacturer in Japan, where inadequate investigations into recurring intrinsic and extrinsic particle contamination and significant data integrity lapses were found during a February 2021 inspection.

There were three EMA GMP non-compliance reports (NCRs) issued during August, addressing three different facilities of the same API and finished dosage manufacturer located in the Czech Republic, whose agency conducted the inspections. The reports outline numerous critical and major deficiencies found at the facilities – including issues with pest control, material surfaces, sanitation, state of facilities, and quality testing – resulting in the suspension of the firm's manufacturing authorization and GMP certificate withdrawal.

Of the 21 drug recalls on FDA's listings for August *(see pp. 98-99)*, only three were rated Class 1. These included 62 lots of various injectables and a progesterone oil for non-sterility. The third Class 1 was for tea bags in which FDA detected the presence of sibutramine.