IPQ
INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue
IPQ.ORG
VOL. 13, NO. 7

MONTHLY UPDATE - JULY 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: Featured in IPQ's July Monthly Update is an in-depth exploration of the dialogue regulators and industry are having on the key CMC issues that are presenting themselves in the development and review of peptides and oligonucleotides and the approaches and expectations for addressing them *(see pp. 4-67).* Central to the story are the discussions that took place on these challenges and expectations at the opening regulatory session of the 2021 USP peptide/oligonucleotide workshop, held in March.

The story in this issue builds on the review provided in IPQ's June 2020 Monthly Update of USP's previous peptide/oligo workshop held in late 2019. The industry, agency, and pharmacopeia experts at the 2021 workshop explored further the CMC/regulatory similarities and differences between the two treatment paradigms in view of the recent developments in this rapidly evolving arena.

Along with a description of the story's four parts, the introductory section provides an overview of the three-day 2021 workshop and an update on the peptide/oligo efforts that are taking place under USP's BIO1 expert committee, which helped organize the meeting.

The first part – on the recent CMC/regulatory challenges of oligonucleotide drugs – focuses on the opening presentation by CDER's Lawrence Perez. He shed light on the issues the agency is seeing in INDs and NDAs regarding the manufacturing, characterization, and control of the oligo drug substance.

Part II continues with a discussion of the comparability challenges that present themselves in developing generic peptide and oligonucleotide drug products. Included is the discussion of the issues at the USP workshop by former CDER reviewer Jeff Jiang. Also provided is a review of the rich dialogue that has been taking place on them recently at FDA workshops and in reports on the agency's generic drug research efforts.

Part III shifts the vantage point to that of a European regulator, BfArM's René Thürmer, who provided insights at the USP workshop on the similarities and differences in the CMC issues that face peptides and oligos regarding the manufacturing process, characterization, impurities, and sterilization.

The fourth part presents an industry perspective on the strategies for setting flexible specifications for oligo synthesis starting materials and controlling impurities, provided at the USP workshop by Roche's Dominik Altevogt.

Developments around the world during July highlighted in the *"Updates in Brief"* section of the monthly *(see pp. 68-72)* include the release for comment by ICH of the Step 2b draft of its Q13 guideline on continuous manufacturing.

PIC/S released a final version of its guidance on data management and integrity in regulated GMP/GDP environments, and guidance to member inspectorates on the COVID-19 risk assessment for routine on-site inspections. Also emerging from the PIC/S pipeline was a guideline on how to evaluate and demonstrate the effectiveness of a pharmaceutical quality system (PQS) and risk-based change management.

There were no FDA drug GMP warning letters nor EMA non-compliance reports posted in July. FDA did post a dozen warning letters to nutritional supplement, OTC and cosmetic firms for misbranding, adding drugs to their products without approval, and/or not meeting the dietary supplement (DS) GMPs *(see p. 73).* Three of these involved unapproved and misbranded products related to COVID-19.

Noteworthy in reviewing the recalls listed by FDA during July *(see pp. 74-76)* was the relatively high percentage of those receiving FDA's most serious Class I rating. Half of the 24 listed were rated Class I.

Five of those rated Class I involved hand sanitizers – recalled for microbial and chemical contamination, and for packaging resembling water bottles. Another four recalls, rated Class II, also involved hand sanitizers – meaning that sanitizers were implicated in over a third of the recalls for the month. Six of the other Class I recalls involved products from different manufacturers containing undeclared tadalafil, sildenafil and/or vardenafil, making them unapproved drugs.