The Pharmaceutical and Healthcare Sciences Society (PHSS) GMP Update April 2016

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INTRODUCTION
During the last 4 weeks there have been a number of developments in the regulation of the pharmaceutical industry. This month reported issues have come from the EU, USA, Canadian and Chinese regulatory authorities.
The topics covered in this edition of the "Update" include:

Europe
- **Potential presence of mutagenic alkyl sulfonates in active substances**

USA
- **Environmental Assessment: Q&A Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity**
- **Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act**
- **Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products**
- **Labeling for Biosimilar Products**
- **Recommendations to reduce the risk of Zika virus transmission by human cell and tissue products**

International
Canada
- **Post-Notice of Compliance (NOC) Changes**

China
- **SFDA requires Generics to obtain brand-name drug quality**

Documents
- **The Responsible Person for GDP – Code of Practice**

RECENT DEVELOPMENTS IN GMP AND REGULATORY REQUIREMENTS

Europe
EDQM
Potential presence of mutagenic alkyl sulfonates in active substances
The last of five general methods, elaborated by the European Pharmacopoeia's Mesilate Working Party, were implemented on 1st April 2016 (Supplement 8.7). This working party had been appointed by the Ph. Eur. Commission in 2008 to assist users in determining mutagenic impurities potentially present in mesilate-, besilate- or tosilate salts of active substances. In addition to the elaboration of these methods, the Ph. Eur. Commission had also decided to revise the Production section of the monographs to inform users of the risk related to the potential presence of such mutagenic impurities.
See:- ***press release***

United States of America
The US Food and Drug Administration (USFDA)

Environmental assessment: Q&A regarding drugs with estrogenic, androgenic, or thyroid activity
This guidance is intended to supplement FDA's guidance for industry on Environmental Assessment of Human Drug and Biologics Applications, issued July 1998 (the EA Guidance), by addressing specific considerations for drugs that have potential estrogenic, androgenic, or thyroid hormone pathway activity (E, A, or T activity) in the environment.
FDA regulations at 21 CFR part 25 specify that EAs must be submitted as part of certain NDAs, abbreviated new drug applications (ANDAs), biologic license applications (BLAs), supplements to such applications, and investigational new drug applications (INDs), as well as for various other actions, unless the action qualifies for a categorical exclusion. Failure to submit either an EA or a claim of categorical exclusion is sufficient grounds for FDA to refuse to file or approve an application (21 CFR 25.15(a), 314.101(d)(4), and 601.2(a) and (c)). This guidance focuses on the categorical exclusion for actions on NDAs and NDA supplements that would increase the use of an active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment would be below 1 part per billion. Although an action that qualifies for this exclusion ordinarily does not require an EA, FDA will require "at least an EA" if "extraordinary circumstances" indicate that the specific proposed action (e.g., the approval of the NDA) may significantly affect the quality of the human environment.
See:-***final guidance***

Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act
This guidance describes FDA's approach to implementation of the provision of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) under which an application for a biological product approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) on or before March 23, 2020, will be deemed to be a license for the biological product under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) on March 23, 2020. Specifically, this guidance describes FDA's interpretation of the "deemed to be a license" provision in section 7002(e) of the BPCI Act for biological products

that have been or will be approved under section 505 of the FD&C Act on or before March 23, 2020. This guidance also provides recommendations to sponsors of proposed protein products intended for submission in an application that may not receive final approval under section 505 of the FD&C 26 Act on or before March 23, 2020, to facilitate alignment of product development plans with FDA's interpretation of section 7002(e) of the BPCI Act.

See:- procedural guidance

Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products

This draft guidance is intended to assist a potential applicant who plans to develop, and submit an abbreviated new drug application (ANDA) to seek approval of, a generic version of a solid oral opioid drug product that has the potential for abuse and which references an opioid drug product with abuse-deterrent properties described in its labeling. The guidance recommends studies, including comparative in vitro studies, that should be conducted by the potential ANDA applicant and submitted to FDA in an ANDA to demonstrate that a generic solid oral opioid drug product is no less abuse-deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse.

See:-***draft guidance***

Labeling for Biosimilar Products

This draft guidance is intended to assist applicants in developing draft labeling for submission in applications for proposed biosimilar products under section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)). The recommendations for prescription drug labeling in this guidance pertain only to the prescribing information (commonly referred to as the package insert), except for recommendations in section V pertaining to FDA-approved patient labeling (e.g., Patient Information, Medication Guide, and Instructions for Use).2 Specific labeling recommendations for interchangeable biological products are not provided.

To meet the standard for interchangeability, an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or 50 diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider (see section 351(i)(3) of the PHS Act). An application submitted under section 351(k) of the PHS Act must contain, among other things, information demonstrating that "the biological product is biosimilar to a reference product" based upon data derived from:

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity); and
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

FDA has the discretion to determine that an element described above is unnecessary in a 351(k) 72 application. Under FDA regulations, prescription drug labeling must provide adequate information to enable health care practitioners to use the drug safely and for the purposes for which it is intended and to this end, the approved prescribing information summarizes the essential scientific 77 information needed by health care practitioners for the safe and effective use of a drug. This labeling reflects FDA's finding of safety and effectiveness5 for the drug under the labeled conditions of use and facilitates prescribing decisions, thereby enabling the safe and effective use of drugs (including biological products) and reducing the likelihood of medication errors.

See:***draft labeling guidance***

Recommendations to reduce the risk of Zika virus transmission by human cell and tissue products

FDA has issued new guidance for immediate implementation providing recommendations to reduce the potential transmission risk of Zika virus from human cells, tissues, and cellular and tissue-based products (HCT/Ps). The guidance addresses donation of HCT/Ps from both living and deceased donors, including donors of umbilical cord blood, placenta, or other gestational tissues.

See:***press release***

International

Canada

Post-Notice of Compliance (NOC) Changes

This guidance document applies to sponsors intending to make changes to new drugs that have received a NOC pursuant to Section C.08.004 of the Food and Drug Regulations This may include pharmaceuticals, biologics and radiopharmaceuticals for human use and pharmaceutical, radiopharmaceutical and certain biotechnological products for veterinary use. In the absence of a guidance specific to Quality changes to drugs which were approved through a Drug Identification Application - Biologics (DIN-B drugs), the Quality guidance document applies to those products. This guidance also applies to those submissions for which a NOC has been recommended but issuance of the NOC has been placed on hold.

See:- ***PNC guidance***

China

China (SFDA) requires Generics to obtain brand-name drug quality

Pharmaceutical companies have been ordered to make sure the quality and efficacy of their drugs are on par with brand-name drugs, a move that aims to improve the nation's pharma industry.

According to a circular issued by the State Council General Office, generic drugs already available on the market should be assessed on whether they are consistent with brand-name drugs, and if they could be used clinically.

This circular strengthens the previous 2013 requirements for bioequivalence. It now requires bioequivalence to be determined against the brand name version of the generic drug or should this no longer be available then against an imported, globally recognised generic version internationally recognised

See:-***summary***

Documents

The Responsible Person for GDP – Code of Practice

A Task Force initiated by the ECA Foundation has developed a Guidance document which aims to support Responsible Persons (RPs) for Good Distribution Practice (GDP). The Code of Practice Version 01 is available on the ECA GDP Group webpage. The document is available at no costs after registration.

See:***ECA news***

And finally…

We hope that our readers find our reviews to be both informative and helpful in keeping up to date with pharmaceutical legislation and regulatory guidance.

GMP Update is compiled by Malcolm Holmes an independent GMP Consultant

Useful website addresses / Links

Warning – some of the addresses include underscored spaces, which may be difficult to see as they appear in "Word" documents. You will also need to use Adobe Acrobat Reader, which can be downloaded from: http://www.adobe.com/products/acrobat/readstep2.html

British Pharmacopoeia (BP): http://www.pharmacopoeia.gov.uk/

Health Canada Compliance: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index-eng.php

The European Commission DG Enterprise – Pharmaceuticals: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/index_en.htm

European Commission DG Enterprise – Medical Devices Sector http://ec.europa.eu/enterprise/medical_devices/index_en.htm

European Medicines Agency (EMA): http://www.ema.europa.eu/

European Medicines Agency Regulatory and Procedural Guidance: http://www.ema.europa.eu/htms/human/raguidelines/intro.htm

European Medicines Agency Inspections Sector: http://www.ema.europa.eu/Inspections/index.html

European Chemical Industry Council – Active Pharmaceutical Ingredients Sector (CEFIC/APIC): http://apic.cefic.org/

European Guide to GMP: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-4/index_en.htm

European Compilation of Procedures for GMP Inspections: http://www.ema.europa.eu/Inspections/GMPCompproc.html

European Federation of Pharmaceutical Industries and Federations (EFPIA): http://www.efpia.org/

European Guidelines on Quality, Safety, and Efficacy for Human Use Products: http://www.ema.europa.eu/htms/human/humanguidelines/background.htm

European Guidelines on Quality, Safety, and Efficacy for Veterinary Products: http://www.ema.europa.eu/htms/vet/vetguidelines/background.htm

European Pharmacopoeia (Ph Eur): http://www.pheur.org/

FDA Home Page:http://www.fda.gov/default.htm

FDA GMP Regulations (CFR21): http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr211_01.html

FDA Inspections Operation Manual: http://www.fda.gov/ICECI/Inspections/IOM/default.htm

FDA Inspection Guides: http://www.fda.gov/ora/inspect_ref/igs/iglist.html

FDA CBER Guidance / Guidelines / Points to Consider: http://www.fda.gov/cber/guidelines.htm

FDA Guidance on Drugs: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Global Harmonization Task Force (GHTF): http://www.ghtf.org/

International Conference on Harmonisation (ICH): http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254

International Society of Pharmaceutical Engineers (ISPE): http://www.ispe.org/

International Pharmaceutical Federation (FIP): http://www.fip.nl/www/

International Pharmaceutical Excipients Council (IPEC): http://www.ipec.org/

Japanese Ministry of Health, Labor and Welfare (MHW): http://www.mhlw.go.jp/english/

Mutual Recognition Agreements (MRAs): http://www.emea.europa.eu/Inspections/MRA.html

Pharmaceutical Inspection Co-operation Scheme (PIC/S) -GMP Guide and basic standards: http://www.picscheme.org/

Pharmaceutical and Research Manufacturers of America (PhRMA): http://www.phrma.org/

Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century – Table of contents: http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm

The Irish Medicines Board: http://www.imb.ie/

The Pharmaceutical Quality Group (PQG): http://www.pqg.org/

The UK Medicines and Health Care Products Regulatory Agency (MHRA): http://www.mhra.gov.uk/

The MHRA Pharmaceutical Industry Pages: http://www.mhra.gov.uk/Pharmaceuticalindustry/index.htm

UK GMP (Orange) Guide: https://web110.secure-secure.co.uk/phss.co.uk/?cart=yes&do=item&cid=142

UK Official Documents including Medicines Legislation: http://www.tso.co.uk/bookshop/bookstore.asp

United States Pharmacopoeia (USP): http://www.usp.org/

World Health Organisation GMP Information (WHO): http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html