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Regulatory Newsletter
Special US Edition – June 2016

Introduction

CROMSOURCE, a full service, ISO-certified Contract Research Organization, publishes a quarterly regulatory newsletter prepared by its regulatory team as a service to its colleagues in the pharmaceutical, medical device and biologics industry.

This Special Edition of the newsletter is dedicated to US Regulatory Affairs. The articles presented in the newsletter provide a summary of the topic and contain hyperlinks should the reader desire additional information.

This newsletter is distributed via email and is also posted on the CROMSOURCE website. Please feel free to send feedback to the regulatory team at regulatory.services@cromsource.com

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CROMSOURCE Opens New North American Headquarters

CROMSOURCE is pleased to announce the opening of its new North American Headquarters located at 309 Waverly Oaks Road, Suite 101, Waltham, MA, 02452. In addition to the new Waltham location, Cromsource also has US offices in Manhattan Beach, CA and Cary NC.

North American Headquarters

Cary, NC

Manhattan Beach, CA

The Regulatory Affairs Profession in the US

In the US, the Regulatory Affairs profession developed from public health initiatives enacted to protect consumers from unsafe products such as pharmaceuticals, medical devices, biologics, food and cosmetics. The Federal Food, Drug, and Cosmetic Act (FD&C Act), which is the basis of current FDA regulations, was enacted in 1938, one year after the Sulfanilamide Tragedy in which more than 100 individuals died after ingesting elixir in which Sulfanilamide was dissolved in poisonous diethylene glycol.

Regulatory affairs professionals assist companies in marketing their products by advising on regulatory strategy and on the most expeditious path to market. Since most companies develop drugs, biologics and medical devices for marketing in more than one country, a cohesive global regulatory strategy and planning can minimize the time to approval. Regulatory professionals provide input on product design and development, clinical trial design, manufacturing processes, advertising and labelling requirements, nonclinical testing requirements and postmarket surveillance requirements. Regulatory professionals gather and evaluate all information, including safety and efficacy data, available about a product and present it in a concise and meaningful fashion to the FDA in order to gain marketing approval for the new product.

Regulatory professionals employed by CROs can represent the sponsor in meetings and negotiations with FDA. It is best practice to involve regulatory professionals at the very beginning stages of product development and to keep them informed of the process so they in turn can provide advice to keep product development on the appropriate regulatory track resulting in eventual product approval. Regulatory professional can review documents such as the clinical protocol, ICF, IB, IFU and the CSR or CIR for GCP compliance. Regulatory professionals can provide input into manufacturing practices ensuring those practices are in compliance with cGMP regulations and the latest FDA/ICH guidance documents. If the regulatory professional is engaged during the conduct of clinical trials and kept informed of the activities, they can provide valuable advice to sponsors to ensure the clinical study is conducted according to GCP thus ensuring the integrity of the database. Regulatory professionals not only interpret the regulations but guide sponsors on how best to transverse the landscape when there is no clear cut statutory requirement available.

Regulatory affairs is a diverse and global profession with many subspecialties such as Regulatory Strategy, Regulatory Intelligence, Regulatory Compliance, and Regulatory Submission Management. Regulatory professionals must keep current on all new legislative developments occurring on the global landscape. Continuing education and continual professional development are critical attributes of the regulatory professional. There are several professional organizations for regulatory affairs that provide training to their members on the latest regulatory developments.

Abbreviations:	CIR, clinical investigation report; CRO, contract research organization; CSR clinical study report; cGMP/GMP, current good manufacturing practices; FDA, Food and Drug Administration; GCP, good clinical practice; IB, investigator's brochure; ICF, informed consent form; ICH, International Conference on Harmonisation; IFU, instructions for use.

Happenings at the FDA

The New FDA Commissioner

The US Food and Drug Administration has started 2016 with a new leader at the helm. Robert Califf, M.D., was confirmed by the US Senate in February as the next commissioner of the FDA. Califf, a cardiologist by training, previously served as FDA's Deputy Commissioner for Medical Products and Tobacco.

Dr. Califf outlined his priorities for FDA in a post on FDA Voice, the official blog site for FDA. Dr. Califf's top priority is developing a workforce and working environment so that FDA will be able to recruit and to retain top scientific and medical professionals to participate in the decision process for the advancement of healthcare products for patients, providers and consumers.

https://blogs.fda.gov/fdavoice/

http://www.fda.gov/aboutfda/centersoffices/ucm452317.htm

In addition to the workforce initiative, Califf is focused on several other issues including the opioid overdose epidemic and tobacco product deeming. The opioid action plan has been launched and the tobacco deeming rule has been passed.

Early in 2016 FDA created a 7-step action plan with projected outcomes to address the opioid crisis. Those steps include a review of policies on opioid approvals along with strengthening postmarket requirements and developing label changes for immediate-release products.

http://www.fda.gov/newsevents/newsroom/factsheets/ucm484714.htm

http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm491739.htm

In May, FDA finalized the rule "Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco". This rule extends FDA's authority to regulate any product that meets the definition of a tobacco product such as electronic cigarettes, cigars, pipe tobacco and nicotine gels. This rule does not extend FDA's authority to the accessories of newly deemed tobacco products. The rule goes into effect on August 8, 2016.

http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm388395.htm

http://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm394909.htm

User Fees - Reauthorization

Both the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee Amendments (MDUFA) expire September 2017 and need to be reauthorized. Funding from PDUFA and MDUFA is fed back into the applicable center (CDER for PDUFA and CDRH for MDUFA) and is used to support staff development and the review process. Along with user fees, each center is given performance objectives to meet. Stakeholder meetings have started and will continue throughout 2016. FDA, Industry and Congress must agree on the priorities for the Agency before PDUFA and MDUFA will be reauthorized.

Like their more famous cousins PDUFA and MDUFA, both the Biosimilar User Fee Act (BsUFA) and the Generic Drug User Fee Amendments (GDUFA) which were first instituted in 2012 are expiring September 2017 and also need to be reauthorized.

EDITOR'S NOTE: If past reauthorizations provide insight into future reauthorizations, sponsors can expect, at the very least, increased user fees and a set of new processes to follow for FDA submissions. The Food and Drug Administration Safety and Innovation Act (FDASIA) which included both the PDUFA V reauthorization and the MDUFA III reauthorizations was signed in 2012 and brought along with increased user fees, electronic submission requirements for certain INDs, NDAs, BLAs and ANDAs, eCopy requirements for most medical device submissions and refuse to file or refuse to accept checklists for Pre-Submission meetings, IDEs and 510(k)s.

These Acts not only impact sponsors but also impact FDA as they established performance goals for FDA which in turn benefits Industry. A 2016 report prepared by California Life Sciences Association found that FDA review times for new drugs are, for the most part, decreasing, although there are still some therapeutic areas (endocrine, gastrointestinal, genitourinary and CNS) that are lagging behind. The last quarterly update for MDUFA III found that, for the most part, review times for devices are decreasing.

Abbreviations:	ANDA, abbreviated new drug application; BLA, biologics license application; CNS, central nervous system; IDEs, investigational device exemption; IND, investigational new drug application; NDA, new drug application.

Additional Information
http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm446608.htm
https://califesciences.org/2016fdadrugreport/

http://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM495919.pdf
http://www.fda.gov/forindustry/userfees/medicaldeviceuserfee/ucm452535.htm
http://www.fda.gov/forindustry/userfees/medicaldeviceuserfee/ucm452535.htm

http://www.fda.gov/downloads/forindustry/userfees/biosimilaruserfeeactbsufa/ucm478276.pdf
http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm476940.htm

Strategic Priorities for CDER and CDRH

Both the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) have released their 2016 priorities. Staffing and workforce development are important priorities for each center as is fostering collaboration with external parties. The goals for both centers align well with the priorities and issues Dr. Califf is championing.

CDER Priorities

In December 2015, Janet Woodstock M.D., Director for CDER, outlined the 2016 priorities for CDER in a presentation given at the FDA/CMS Summit for Biopharma executives. Dr. Woodstock presented a list of more than 40 activities CDER will be working on throughout 2016. Some of the more notable entries include negotiating PDUFA VI, GDUFA II, and BsUFA II agreements, developing drug label initiatives including training on the pregnancy/lactation label rule, refining policies concerning personalized medicine, continuing to advance the patient-focused drug development program, continuing to develop policies for approaching antimicrobials to treat drug-resistant organisms, developing ways to include children in clinical trials, and developing new approaches to clinical trial design.

EDITOR'S NOTE: Unfortunately Dr. Woodstock did not provide the details behind each of these initiatives. Cromsource will keep on top of CDER's activities and will report the outcomes in future newsletters.

http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm477299.pdf

CDRH Priorities

CDRH released 2 reports late last year describing the Center's goals and priorities for 2016. The first report outlined the Center's top 10 regulatory science priorities. Several of these priorities such as leveraging 'big data' (i.e., human genome project, clinicaltrials.gov database, healthcare databases) , incorporating patient experience data and using patient reported outcome data in regulatory decisions compliments Dr. Califf's goals with respect to his blog post 2016: The Year of Diversity in Clinical Trials. Other priorities such as enhancing the security of medical devices and incorporating human factors testing into the device design have experienced forward motion with the release of guidance documents.

The second report from CDRH discussed 3 objectives: Establish a National Evaluating System for Medical Devices, Partner with Patients, and Promote a Culture of Quality and Organizational Excellence. These objectives link well with the regulatory science priorities and increasing diversity in clinical trials. A national evaluating system for medical devices would provide real-world evidence to FDA for use in regulatory decision making. The Partner with Patients objective would weave patient experiences into the regulatory decision. The Promote a Culture of Quality and Organization Excellence goal supports Dr. Califf's goal of developing a highly-trained FDA workforce that is able to provide top level scientific and medical oversight to innovative medical device technologies while still assuring the devices are safe and effective.

http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhvisionandmission/default.htm
http://www.fda.gov/downloads/MedicalDevices/ScienceandResearch/UCM467552.pdf

Banned Medical Devices

The Code of Federal Regulations, 21 CFR 895 allows FDA to ban a device intended for human use if that device presents a substantial deception or an unreasonable risk of illness or injury.(21 CFR 895.1) If a medical device is banned, that means there is a total prohibition on sales, distribution and manufacturing of that device.

A medical device ban is a very rarely imposed option by FDA. To date, FDA has only banned one device, prosthetic hair fibers. This device was banned in 1983. "Prosthetic hair fibers are devices intended for implantation into the human scalp to simulate natural hair or conceal baldness. Prosthetic hair fibers may consist of various materials; for example, synthetic fibers, such as modacrylic, polyacrylic, and polyester; and natural fibers, such as processed human hair". (21 CFR 895.101)

In 2016, FDA proposed 2 additional medical device bans. In March, FDA proposed a ban on Powdered Surgeon's Gloves, Powdered Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon's Glove and in April, FDA proposed a ban on Electrical Stimulation Devices Used to Treat Self-Injurious or Aggressive Behavior.

FDA determined that Powdered Surgeon's Gloves, Powdered Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon's Glove presented an unreasonable and substantial risk of illness or injury that could not be corrected or eliminated by labeling. (Federal Register - https://www.federalregister.gov/articles/2016/03/22/2016-06360/banned-devices-proposal-to-ban-powdered-surgeons-gloves-powdered-patient-examination-gloves-and).

The Massachusetts Department of Developmental Services and the state of New York contacted FDA with concerns about Electrical Stimulation Devices. FDA reviewed the use of these devices and determined they presented a risk to public health. There is only one facility in the US, located in Massachusetts that uses these devices on individuals with Self-Injurious or Aggressive Behavior.

(Federal Register - https://www.federalregister.gov/articles/2016/04/25/2016-09433/banned-devices-proposal-to-ban-electrical-stimulation-devices-used-to-treat-self-injurious-or).

Next Steps At the time of publishing, the public comment period for both devices was open. Once the comment period closes, FDA will evaluate any comments received and determine if the proposal to ban should be affirmed or modified. The final ruling will be published in the Federal Register.

Industry NewsBriefs

Semler Research Data Suspect and Must Be Repeated

FDA conducted an inspection of Semler Research Private Limited (SRC) bioanalytical facility located in Bangalore, India in the fall of 2015. The inspection revealed several infractions which according to the FDA's website included "the substitution and manipulation of study subject samples." FDA issued a 4831 to the facility at the conclusion of the inspection. In an Untitled Letter to the facility dated April 19, 2016, FDA acknowledged that although a written response to the 483 observations was provided and that a subsequent letter detailing the results of a retrospective investigative audit were also provided, FDA deemed the responses to be inadequate. The Untitled Letter further states "The manner in which Semler conducted the studies noted above causes FDA to have significant concerns with the reliability and validity of all bioequivalence data generated by Semler".

FDA sent a letter to NDA and ANDA sponsors on April 20, 2016 notifying them that clinical and bioanalytical studies conducted by the Bangalore facility were not acceptable and will need to be repeated. "FDA concludes that the integrity and accuracy of data generated at SRC, including the data generated by SRC that you submitted in this application, cannot be assured. Therefore, FDA will not accept data generated at SRC as a basis to approve your application. You must therefore re-conduct those (bioequivalence/bioavailability) studies (both bioanalytical and clinical) at an alternate contract research organization".

The situation with Semler Research has impacted the global community. The European Medicines Agency (EMA) recently announced it is reviewing all EU-authorized drugs that relied on studies conducted by Semler Research. The World Health Organization (WHO) recently issued a Notice of Concern to Semler Research expressing concern over the validity of data and recommending "an immediate stop for all submissions of dossiers relying in whole or in part on involvement from Semler until the underlying issues have been verified to have been adequately resolved."

Additional Information

FDA
http://www.fda.gov/Drugs/DrugSafety/ucm495778.htm

[1] A 483 is an FDA form that is issued to management at the conclusion of an inspection if an inspector has observed any conditions that may constitute violations of the Food, Drug and Cosmetic Act.

EMA
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Semler/human_referral_000403.jsp&mid=WC0b01ac05805c516f

WHO
http://apps.who.int/prequal/info_applicants/NOC/2016/NOC_Semler12April2016.pdf

EDITOR'S NOTE: The unfortunate situation with Semler Research should serve as a reminder to any company that outsources testing. Best practice is to have procedures in place that will allow vendors and third party providers to be thoroughly vetted. Data integrity issues are costly line items in terms of product funding and time to market.

This is not the first time FDA has refused to accept testing results from a contract laboratory. Five years ago FDA notified pharmaceutical companies that bioanalytical studies conducted by Cetero Research, Houston, TX may need to be repeated due to data integrity issues identified as a result of two FDA inspections.

Sponsors should also be aware that, according to FDA's 2016 Annual Report on Inspections of Establishments in Fiscal Year (FY) 2015, GMP/Quality Systems (QS) inspections of both foreign and domestic drug and device establishments are increasing.

http://www.fda.gov/downloads/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/UCM483994.pdf

Compliance Deadlines Approaching for Electronic Submissions

The Food and Drug Administration Safety and Innovation Act (FDASIA) requires that all NDAs and ANDAs along with certain INDs and BLAs be submitted in an electronic format according to FDA guidances.

FDA has released final guidance documents for providing standardized study data in electronic format and for providing submissions in electronic common technical document (eCTD) format. FDA does have the option of granting waivers and may do so for the data standard requirement as long as the data standard has been previously supported by FDA. FDA has not indicated if waivers will be issued for the eCTD requirement.

Electronic documents are submitted through the Electronic Submission Gateway. Users must have an Electronic Submission Gateway account prior to using the Gateway.

Failure to comply with these guidance documents may result in receiving a refuse to accept/file letter.

EDITOR'S NOTE: CDRH does not require the use of a specific format for clinical trial data.

Timeline to Compliance

Submission Type	Must be in eCTD format	Clinical and Nonclinical studies starting after (date) must use standards specified in the Data Catalog
Commercial IND	May 5, 2018	Dec 17, 2017
NDA, ANDA, BLA	May 5, 2017	**Dec 17, 2016**

Additional Information

Electronic Submissions Gateway

http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm2005551.htm

Guidance: Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications –Final May 2015

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf

Guidance: Providing Regulatory Submissions In Electronic Format — Standardized Study Data –Final December 2014
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf

Guidance: Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act – Final December 2014

http://www.fda.gov/downloads/Drugs/Guidances/UCM384686.pdf

Study Data Standards Resources

http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

CDRH

http://www.fda.gov/medicaldevices/deviceregulationandguidance/datastandardsmedicaldevices/default.htm

Good News for Medical Device Manufacturers

The 2.3% medical device tax has been suspended for 2 years. Manufacturers or importers of taxable medical devices will not have to pay taxes on their sales during the period beginning January 1, 2016 and ending on December 31, 2017.

Additional Information

https://www.irs.gov/uac/Medical-Device-Excise-Tax:-Frequently-Asked-Questions

Improving Medical Device Innovation Act

A new medical device bill was presented to Congress on March 17, 2016. The Improving Medical Device Innovation Act would give FDA the authority to eliminate the required premarket submission for certain low risk Class I and II medical devices. FDA will notify industry of the applicable devices by publication of a list in the Federal Register. The bill is currently under committee review.

Additional Information

https://www.congress.gov/bill/114th-congress/senate-bill/2737/text

2016: The Year of Diversity in Clinical Trials

Section 907 of FDASIA directed FDA to determine how well demographic subgroups were represented in applications submitted to the FDA. FDASIA further directed FDA to develop an action plan outlining how it intended to improve the situation so that clinical trial populations accurately represent the end users.

In January 2016, Dr. Califf post a blog entry in FDAVoice entitled 2016: The Year of Diversity in Clinical Trials. This post describes the approach the Agency as a whole is taking towards ensuring that clinical trial participants are representative of the patients who will eventually use the product. The post goes onto explain that FDA has noted there are several underrepresented groups in clinical trials; the elderly, women, and racial/ethnic minorities. This underrepresentation can have consequences as certain groups may respond differently to therapies necessitating the need to have different labelling to compensate for the different responses.

FDA is addressing this underrepresentation on several fronts. The Office of Minority Health is encouraging clinical trial participation through a multi-media campaign highlighting the importance of clinical trial participation. The Office of Women's Health launched an initiative, Diverse Women in Clinical Trials with the aim to raise awareness about clinical trial design, subject recruitment and subpopulation analyses. The Office of External Affairs is planning to publish educational materials describing what it is like to participate in a clinical trial and to encourage clinical trial participation.

Additional Information

http://blogs.fda.gov/fdavoice/index.php/2016/01/2016-the-year-of-diversity-in-clinical-trials/

FDASIA Section 907

http://www.fda.gov/regulatoryinformation/legislation/significantamendmentstothefdcact/fdasia/ucm389100.htm

Lesser Administrative Actions Updated for Non Compliance for IRBs

On April 4, 2016 FDA published a final rule in the Federal Register amending the regulation describing lesser administrative actions for institutional review boards (IRBs). This rule modifies administrative actions that may be imposed on an IRB that has failed to comply with FDA's IRB regulations (21 CFR 56). Specifically, this rule amends 21 CFR 56.120(b) to read," in addition, until the IRB or the parent institution takes appropriate corrective action, the Agency may require the IRB to withhold approval of new studies, direct that no new subjects be added to ongoing studies, or terminate ongoing studies. This will ensure that those activities are suspended until the IRB takes appropriate corrective action to address its noncompliance." This rule becomes effective August 17, 2016. Interested parties have until June 20, 2016 to submit comments.

EDITOR'S NOTE:

This is not a new rule but clarifies existing regulation. Nonetheless, it behooves sponsors and CROs to be aware of the IRB's standing with respect to compliance to FDA regulations.

Additional Information

https://www.gpo.gov/fdsys/pkg/FR-2016-04-04/pdf/2016-07523.pdf

Spotlight on FDA Guidance Documents

This section showcases a few of the nearly 50 guidance documents that were released by FDA since the beginning of 2016. The selected guidance documents discuss developments in both the pharmaceutical and medical device arenas. If you would like a specific guidance document showcased, please email regulatory affairs at regulatory.services@cromsource.com

January 2016 Guidance Documents

Title	**Guidance: Submission and Review of Sterility Information in Premarket Notification (510 (k) Submissions for Devices Labeled as Sterile - Final**
Date	January 2016
Summary	The purpose of this guidance is to clarify the information about sterilization processes and information about pyrogenicity that the FDA recommends be included in 510(k) submissions. Section V of this guidances includes a list of the information that should be included in a 510(k) for both established sterilization methods and novel sterilization methods. FDA has defined established sterilization methods as **"**methods that have a long history of safe and effective use as demonstrated through multiple sources of information such as ample literature, clearances of 510(k)s or approvals of premarket approval (PMA) applications, and satisfactory QS inspections" and as methods "for which there are no FDA-recognized dedicated consensus standards, but for which published information on development, validation, and routine control is available" and novel sterilization methods as "a method that FDA has not reviewed and determined to be adequate to effectively sterilize the device for its intended use". **EDITOR'S NOTE:** Manufacturers using novel sterilization methods should be aware that FDA has indicated in this guidance that it intends to inspect the manufacturing facility before clearing a 510(k) for a device that is sterilized by a novel sterilization process. "Therefore, we intend to inspect the manufacturing facility before clearing a 510(k) for a device that is sterilized by a novel sterilization process. Inspecting the manufacturing facility for devices sterilized using these sterilization technologies will help ensure the safety and effectiveness of these devices and mitigate the risks to human health."

Link	http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm109897.pdf
Title	**Guidance: Postmarket Management of Cybersecurity in Medical Devices *(draft)***
Date	January 2016
Summary	The purpose of this guidance is to inform industry of the Agency's recommendations for creating and managing a postmarket cybersecurity program. This guidance applies to medical devices that contain software (including firmware) or programmable logic, and software that is considered a medical device. FDA encourages manufacturers to be proactive with detecting and managing cybersecurity vulnerabilities by beginning the process in the early development phase. FDA further suggests that professional collaborations will be part of a successful strategy to identify and resolve cybersecurity vulnerabilities. Membership in an ISAO (Information Analysis Sharing Organization) such as the National Health Information Sharing & Analysis Center, (NH-ISAC) is suggested as is adoption of the National Institute of Standards and Technology's (NIST) guideline "Framework for Improving Critical Infrastructure Cybersecurity". This guidance explains the reporting requirements when cybersecurity vulnerabilities are detected. FDA notification will not be necessary for the majority of cases requiring minor or routine action by the manufacturer such as deployment of a software patch. Other situation where clinical performance could be jeopardized will require FDA notification. The guidance provides examples of each situation. There is one Appendix to this guidance which describes the elements the Agency believes should be included in a postmarket cybersecurity program. **EDITOR'S NOTE:** FDA has indicated in this guidance that it will exercise enforcement discretion for those companies that join an ISAO and follow other recommendations in this guidance.
Link	http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm482022.pdf http://www.nist.gov/cyberframework/upload/cybersecurity-framework-021214-final.pdf

	PreMarket Guidance http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM356190.pdf

February 2016 Guidance Documents

Title	**Guidance: Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations – Final**
Date	February 2016
Summary	The purpose of this guidance is describe how to implement selective safety data collection during late-stage premarket and postapproval clinical investigations when the drug's safety profile is well-established. Before implementing selective safety data collection, a sponsor should consult with the applicable FDA review division for input and agreement. Selective safety data collection is either not collecting certain safety data or less frequent collection of certain safety data. This safety data could be certain routine laboratory test results, patient history, physical exams, or information on concomitant medications or non-serious adverse events that are not associated with dose modification, drug discontinuation or withdrawal from the trial. Data on all serious adverse events, on non-serious adverse events that lead to dose modification, drug discontinuation, or withdrawal from the trial and data on unscheduled study visits, hospitalizations, and accidental injuries because these events may reflect serious adverse events of the drug should always be collected. The guidance goes on to further state that "In general, selective safety data collection may be appropriate for certain types of safety data when the following conditions are met: The number of patients and their characteristics, the duration of exposure, and the dose range used in previous clinical investigations are sufficient to adequately characterize the safety profile of the drug for common, non-serious adverse events. The occurrence of common, non-serious adverse events has been generally similar across multiple clinical investigations."

	EDITOR'S NOTE: This guidance states that "FDA is also aware that some of the recommendations in this guidance may not align with the expectations of safety data collection in other regions or countries, which may lead to difficulty in implementing this guidance in some clinical investigations. However, we believe this guidance will give sponsors the flexibility to design and implement protocols with selective safety data collection where appropriate."
Link	http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291158.pdf
Title	**Guidance: Applying Human Factors and Usability Engineering to Medical Devices – Final**
Date	February 2016
Summary	The purpose of this guidance is to assist industry in following human factors engineering (HFE) and usability engineering (UE) processes during the development of their medical device. This guidance suggests that manufacturers focus specifically on the user interface. The user interface "includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, instructions for use, etc." According to the guidance, "HFE/UE considerations in the development of medical devices involve the three major components of the device-user system: (1) device users, (2) device use environments and (3) device user interfaces." The guidance further explains that "Preliminary analyses and evaluations are performed to identify user tasks, user interface components and use issues early in the design process. These analyses help focus the HFE/UE processes on the user interface design as it is being developed so it can be optimized with respect to safe and effective use." A discussion on frequently-used HFE/UE analysis and evaluation methods along with a discussion on the elimination or reduction of use-related hazards is present. Industry is reminded that risk management, HFE/UE testing, and design optimization processes should be documented in the design history file as part of design controls and that by doing so provides evidence that the needs of the intended users were considered and that the device has been determined by the manufacturer to be safe and effective for the intended users, uses and use environments.

	Appendix A contains a report template which outlines the required information that should be included in a human factors engineering and usability engineering report submitted with premarket applications. Appendices B, C and D contain supporting information for industry such as sample size determinations and how to analyze the results of human factors validation testing. **EDITOR'S NOTE:** At the same time of this final guidance's release, FDA released a companion draft guidance 'List of Highest Priority Devices for Human Factors Review'. This guidance lists 16 device types for which FDA expects to see human factors data in premarket submissions. The guidance and list is available at the following link - http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm484097.pdf
Link	http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm259760.pdf

March 2016 Guidance Documents

Title	**Guidance: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans *(draft)***
Date	March 2016
Summary	The purpose of this guidance document is to provide clarification regarding the submission of an initial pediatric study plan (iPSP) and any amendments to the iPSP. This guidance document discusses who must submit an iPSP, timing of an iPSP, suggested content and the review cycle. **Who**: Sponsors must submit an iPSP if they are planning to submit a marketing application for a drug that has • a new active ingredient, • a new indication , • a new dosage form, • a new dosing regimen or • a new route of administration,

	• a biosimilar product that is not interchangeable with the reference product, unless the drug has been granted orphan designation for the proposed indication. **Timing:** In general, the submission of the iPSP should be as an amendment to the IND and should not be later than 60 calendar days after the end-of-phase 2 meeting, before the initiation of phase 3 studies or no later than 210 calendar days before submission of a marketing application. **Content**: The iPSP should include an outline of the planned studies. The guidance provides recommendations for the contents of each section of the iPSP along with a template that should be completed and submitted with the iPSP. **Review:** The review cycle for an iPSP is 210 days. FDA will review and provide comments to the sponsor within 90 days. The sponsor has 90 days to submit a revised iPSP to the FDA. The FDA has 30 days to review and respond either by confirming agreement or by stating it does not agree. A sponsor should not submit a marketing application until agreement has been reached on the iPSP. FDA may grant a waiver and/or a deferral of the required pediatric assessments. This information will be included in the FDA's feedback to the initial iPSP review.
Link	http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf
Title	**Guidance: Labeling for Biosimilar Products *(draft)***
Date	March 2016
Summary	The purpose of this guidance is to describe how to prepare draft labeling for proposed biosimilar products. FDA believes biosimilar product labels should incorporate relevant data and information from the reference product labeling along with appropriate information about the biosimilar product. "The labeling for the biosimilar product should be specific to the conditions of use (e.g., indication(s), dosing regimen(s)) sought for the biosimilar product and should be consistent with language previously approved for the reference product for those conditions of use." FDA recommends including a biosimilarity statement on the label stating that the product is biosimilar to the reference product. The guidance provides suggested wording and format for this statement.

	In addition, this guidance notes that biosimilar product labeling must also comply with both the physician labeling rule (PLR) and the pregnancy and lactation rule (PLLR). For additional information refer to 21 CFR 201.56(d) and 21 CFR 201.57(c)(9)(i)through(iii).
Link	http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm493439.pdf

April 2016 Guidance Documents

Title	**Guidance: Data Integrity and Compliance With CGMP - *Draft***
Date	April 2016
Summary	The purpose of this guidance is to assist industry in complying with CGMP requirements of data handling as outlined in 21 CFR parts 210, 211 and 212. This guidance is presented in the format of questions and answers on several topics such as audit trails, access to computer systems, control of blank forms, use of electronic copies and electronic signatures and if detecting data integrity should be part of routine CGMP training. This guidance also includes definitions to terms such as data integrity, audit trail, static, dynamic and metadata. **EDITOR'S NOTE**: This guidance was released shortly before FDA announced the actions it was taking against Semler Research. In the Background section of this guidance, FDA notes that "FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections" and that these violations have led to "numerous regulatory actions, including warning letters, import alerts, and consent decrees".
Link	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf

Late Breaking Guidance Documents Releases

Title	**Guidance: Technical Considerations for Additive Manufactured Devices - *Draft***
Date	May 2016

Summary	The purpose of this guidance is to "outline technical considerations associated with AM processes, and recommendations for testing and characterization for devices that include at least one AM fabrication step". Additive Manufacturing (AM) is category of manufacturing that encompasses 3-dimentional (3D) printing. The guidance is split into two sections; Design and Manufacturing Considerations and Device Testing Considerations. The Design and Manufacturing section discusses issues that should be addressed by the Quality System requirements. The Device Testing section discusses information that should be included in premarket submissions such as IDE, 510(k), PMA, HDE and de Novo.
Link	http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM499809.pdf

EDITOR'S NOTE: One of the more unique applications of 3D printing has been in the manufacturing of drugs. In 2015 FDA approved the first drug manufactured using 3D printing. Readers interested in more information on 3D printing can refer to the following link.

http://www.fda.gov/medicaldevices/productsandmedicalprocedures/3dprintingofmedicaldevices/default.htm

Title	**Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act - Final**
Date	May 16, 2016
Summary	Section 522 of the FD&C Act gives FDA the authority to require postmarket surveillance of certain Class II and Class III devices. FDA will assign a postmarket surveillance (PS) number to each 522 order it issues. This guidance lists the recommended content to include in a postmarket surveillance submission. A manufacturer is required to submit a postmarket surveillance plan within 30 days after receiving the order. FDA will review the order and respond within 60 days. The surveillance plan must be started no later than 15 months after the day on which the order was issued. Failure to comply with section 522 may result in an FDA enforcement action which can include product seizure, prosecution and/or fines.
Link	http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM268141.pdf

Concluding Remarks

The articles and guidance documents included in this newsletter were selected with the interests and needs of our clients in mind. All of the regulatory developments reported in this issue of the regulatory newsletter will impact companies developing and marketing drugs and medical devices in the US. CROMSOURCE's regulatory team keeps fully informed of recent initiatives that may impact our clients' activities during the pre and post market phases so we can advise our clients accordingly and assist them in preparing for and incorporating the anticipated regulatory changes.

CROMSOURCE News

OmniComm Systems Signs Five-Year Agreement with CROMSOURCE

Fort Lauderdale, FL, April 26, 2016 - OmniComm Systems, Inc. (OmniComm) (OTCQX: OMCM), a global leading provider of clinical data management technology, today announced the signing of a five-year, multi-million dollar agreement with CROMSOURCE, a leading contract research organization (CRO), headquartered in Verona, Italy, with offices throughout Europe and North America. OmniComm's TrialMaster electronic data capture (EDC) suite will be used for the collection of clinical data during this five-year term in trials spanning all clinical phases and therapeutic areas.

For more information: http://www.cromsource.com/omnicomm-systems-signs-five-year-multi-million-dollar-trialmaster-edc-agreement-with-cromsource/

CROMSOURCE Expands Operational Footprint and Management Team

CROMSOURCE, an international contract research organization (CRO) providing a comprehensive portfolio of services to the pharmaceutical, biotechnology, and medical device industries, announced today the appointment of four senior executives to its Management Team. The appointments include: Dr. Troy W. McCall as Chief Operating Officer (COO), Debbie Kent as Global Head of TalentSource Life Sciences staffing solutions, Dr. Kerry Dyson as Global Head of Clinical Research Division and April McCall as Vice President of Commercial Operations. Additionally, CROMSOURCE announced the expansion of its North American presence with the opening of an office in Research Triangle Park in North Carolina

For more information: http://www.cromsource.com/cromsource-expands-operational-footprint-and-management-team/