INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 2, No. 26
June 27, 2016

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FDA Provides Blueprint for Extrapolating Adult Clinical Data for Pediatric Use

FDA is clarifying how and when existing adult clinical data may be extrapolated to support marketing approval and labeling of medical devices for use in pediatric patients.

Sponsors are encouraged to engage FDA early on when considering whether existing clinical data might support pediatric claims.

The agency notes in final guidance released June 21 that there is a dearth of scientific evidence to substantiate submissions for devices that diagnose or treat pediatric patients.

The guidance provides sponsors a roadmap on:

- How to leverage relevant existing clinical data to increase availability of safe and effective pediatric devices;
- When it may be appropriate to leverage this data to support pediatric device indications and labeling;
- How to determine whether extrapolation is appropriate, and to what extent the data can be leveraged; and

(See **Pediatric***, Page 4)*

FDA Outlines Strategy to Increase Diversity in Clinical Studies

Manufacturers need to increase diversity of subpopulations when designing clinical trials to obtain an unbiased estimate of treatment effect, the FDA says.

New draft guidance assists sponsors in developing strategies for evaluating and reporting age, race and ethnicity data on device safety, effectiveness, benefit-risk profile, study design and device labeling.

The guidance shows sponsors what demographic variables should be considered in study designs. It covers collection and consideration of subpopulation data during clinical study design, outlining how to interpret subgroup data, pointers on how to enroll diverse populations and to maintain clinical follow-up.

(See **Diversity***, Page 2)*

Diversity, *from Page 1*

To better evaluate clinically meaningful differences across patient subpopulations, sponsors need to enroll patients that are representative of the intended-use population of the investigational device, the guidance says.

Barriers to Diversity

The guidance lists several barriers to diversity in trials, including inclusion/exclusion criteria that unintentionally exclude different age, race, or ethnic groups.

Potential barriers also occur during the enrollment process when researchers may run into language, cultural and health literacy gaps between investigators and patients.

Additional barriers can be caused by pressure on trial investigators to quickly recruit regardless of demographic characteristics, increased expense or trial logistic challenges, along with disproportionate dropout rates.

Certain devices or diseases may effect certain subpopulations more than others, the FDA acknowledges.

For example, some orthopedic devices would likely have different considerations for use in specific age groups. And, mortality rates of patients on dialysis have been shown to differ across race and ethnicity groups, the guidance notes.

Similary, older patients and pediatric patients often have co-morbidities, concomitant therapies, or development considerations that could interact with the investigational device effects and impact device performance.

FDA recommends sponsors identify specific information about a subpopulation and the disease associated with the intended use of the device.

Sponsors should also document any known clinically meaningful age, race, and ethnicity differences in disease course, outcomes, or benefit-risk profile to be included in 510(k) summary and labeling.

Unless the investigational device is intended for use in only one age, race or ethnic group, it is important that the variation in data across age, race, and ethnic groups be accounted for both in study design and analysis of results, the guidance states. If co-morbidities or other characteristics are found, sponsors should base their analysis on demographic subgroups.

Although analysis of specific subgroups with inadequate sample sizes can't be generalized as safe and effective across populations when labeling the device, the data would be useful for considering the overall benefit-risk profile of the device, the FDA said.

More Trials Needed?

If analysis points to a lack of demographically diverse data, negating clinically meaningful differences in outcome, FDA may request additional clinical data and modify trial design to address pre- or post-market questions.

The FDA encourages sponsors to use decision trees when considering various age, race or specific statistical recommendations for different clinical study designs.

Sponsors should also describe how any clinically meaningful differences across subgroups may contribute to differences in benefit-risk profiles in certain subpopulations.

The guidance applies to 510(k), PMA applications, de novo requests, HDE applications, as well as post-approval and post-market surveillance studies.

When finalized, the guidance will extend policy in the FDA's Evaluation of Sex-Specific Data and complement Collection of Race and Ethnicity Data in Clinical Trials Guidance.

Interested parties can comment on the guidance until Sept. 19.

The draft guidance can be found here: www.fdanews.com/06-20-16-ReportingMedicalDeviceClinicalStudies.pdf. — Joya Patel

CAPAs, Change Controls Bring Warning for Medtronic Firm

Several issues with CAPA investigations and change controls netted a warning letter for TYRX, a Medtronic subsidiary that makes absorbable antibacterial envelopes.

For example, the Monmouth Junction, N.J., company had no procedures to control and take action on devices suspected to have nonconformities, according to the June 2 warning letter posted online June 21.

It cited the company for closing a 2015 CAPA on seven lots of envelopes that were out of specification for drug content without taking action because three out-of-specification results had a "suspected common root cause." The company's form for nonconformance procedures doesn't require it to verify or validate the effectiveness of CAPAs being documented.

The letter points to a November 2015 OOS event where an impurity substance was above specification in one lot and the possible root cause could not be determined. TYRX's retest analysis was reintegrated and recalculated based on new chromatographic integration. After the reintegration, all retest results were within specification.

Failure to Investigate?

The company's investigation found that "due to the change in the integration of the chromatograms, the raw data is the source of the error," the letter says.

The quality assurance disposition stated that no further investigation was needed and the OOS investigation was closed without TYRX knowing the root cause of the original failure, the letter notes. The company did not verify that the updated test method would mitigate future incidents.

Similarly, a 2014 CAPA was opened to address low molecular weight of the Tyrosine polymer, which can cause higher drug elution. The company took corrective actions with the supplier related to material handling and closed the CAPA. However, two subsequent CAPAs were opened for the same issue, with one stating that the root cause was related to impurity and inconsistencies in a process. That CAPA was still open at the time of the FDA inspection.

Validation, Qualification Lacking

The letter also raised issue with validations and performance qualifications for the large TYRX Antibacterial Envelope. The letter notes that the firm failed to validate the device for drying conditions as well as the polyarylate polymer production process.

Additionally, batch records for certain validation lots that support the polymer production process documented deviations from the instructions in the batch records.

For example, one lot failed for water content due to a deviation from instructions related to mixing, and one lot had a deviation related to the company's efforts to make up for leak detection and repair time.

Another process validation issue related to a lot manufactured under an approved process qualification protocol. The lot failed the content uniformity test for Minocycline and the process qualification report states that lots were released to commercial inventory. However, one lot was later documented as being rejected and not for commercial use.

TYRX had not performed a validation to support a device master record deviation for TRX Absorbable Antibacterial Envelopes that allowed polymer molecular weight specifications to be changed due to a change in the way the company processed molecular weight analyses.

Medtronic is committed to working with the FDA to resolve these issues in a timely manner, a spokesperson told *IDDM*. "We do not expect the warning letter to have a significant financial impact to the company."

The warning letter is available at www.fdanews.com/06-23-16-MedtronicWarning.pdf.
— April Hollis

Pediatric, *from Page 1*

- How to describe statistical methodology that can be used to leverage data for pediatric indications.

The guidance notes that conducting device clinical trials in children has presented numerous challenges, and adult devices are often used in children off-label as a result.

The guidance clarifies that the appropriateness of extrapolation largely depends on the similarity of existing data and the characteristics to the intended pediatric sub-population.

Industry Comments

Industry comments on the May 2015 draft version of the guidance prompted the FDA to clarify how and when extrapolation may be appropriate, and to include de novo requests in the final guidance.

Advamed supported the move to extrapolate data, and said in its comments that leveraging existing clinical data "will have the important added benefit of reducing the number of pediatric human subjects needed to participate in clinical trials to demonstrate safety and effectiveness in a particular device."

Advamed and other industry stakeholders also sought clarification on the extent of extrapolation across pediatric subpopulations as well as what the agency meant by "borrowing strength."

In response to those requests, the final guidance provides additional explanation of the concept of extrapolation, defines pediatric subpopulations and includes data collected for de novo applications.

The guidance also explains "borrowing strength" as a means to bolster data sources. The agency notes that the extent of leveraging depends on the similarity "between borrowed data and any pediatric data that will be collected."

The guidance also notes that study design could be different for different endpoints, and there could be different considerations in the pediatric population for safety versus effectiveness. "Therefore, safety is considered

(See **Pediatric**, *Page 6)*

Power Morcellation Containment Systems Now Class II Devices

FDA is classifying gynecologic laparoscopic power morcellation containment systems as Class II, special control devices.

Devicemakers submitting a premarket notification for these morcellation containment systems will need to comply with the special controls named in the final order issued on June 21.

On April 8, the FDA approved Advanced Surgical Concepts' PneumoLiner, the first containment system for use in conjunction with laparoscopic power morcellators intended to isolate uterine tissue that is not suspected to contain cancer.

The gynecologic laparoscopic power morcellation containment systems create a working space allowing for direct visualization during a power morcellation procedure for removing benign tissue that is not suspected to contain malignant tissue.

Morcellators used to shred tumors have been on the market for more than 20 years. The FDA issued a safety alert for the devices in 2014, warning against their use in most women undergoing myomectomy or hysterectomy for treatment of fibroids. The alert said that morcellator blades could spread unsuspected cancers in as many as one in 350 cases.

The controversial devices have received much scrutiny over the past few years, with Congress and the FBI investigating whether devicemakers failed to notify the FDA of suspected risks (*IDDM*, Nov. 25, 2015).

The FDA required the manufacturer of the containment system to warn patients and healthcare providers that the PneumoLiner has not been proven to reduce the risk of spreading cancer during morcellation procedures (*IDDM*, April 8).

The Class II designation was based off of the devicemakers' recommendation for its PneumoLiner device. Subsequent gynecologic laparoscopic power morcellation containment systems will fall under the same classification, according to the final order.

The special controls required to mitigate risk associated with the containment systems include:

- Biocompatibility;
- Sterilization must be validated, and data must support shelf life;
- Non-clinical performance data must meet design specifications;
- Contraindication for use in gynecologic surgery in which tissues to be morcellated is known or suspected to be malignant; and
- Training must be developed and validated to ensure users can follow instructions for use.

The containment systems are not safe for use except under the supervision of a licensed practitioner, and devices must satisfy prescription labeling requirements, the FDA noted.

The agency determined that premarket notification is necessary to ensure safety and effectiveness of these types of devices.

The final order can be found here: www.fdanews.com/06-20-16-PowerMorcellationSystemClassification.pdf. — Joya Patel

Supplier Control Failures Bring Warning, for UK Probe Maker

Berwickshire Electronic Manufacturing, a UK contract manufacturer, did not set requirements to evaluate suppliers and fell short on several other supplier control measures, according to an FDA warning letter.

Its purchasing procedure did not require records of acceptable suppliers, quality benchmarks that suppliers must meet, or documented agreements that suppliers will notify BEM of changes when possible.

Further, BEM had not set purchasing control requirements for certain suppliers of components for its Helica Thermal Coagulators and Helica LT/LTC Probes, according to the Feb. 4 letter posted June 21 on FDA's website. Berwickshire lacked incoming product acceptance records for

(See **BEM Warning**, *Page 8)*

China FDA Allows Self-Inspections For Device Distributors

China FDA is requiring distributors of Class II and III devices to conduct self-inspections and report on their business activities.

Manufacturers with distribution hubs in China will need to conduct audits of their distributors to ensure they are compliant.

The move is yet another measure the agency is taking to consolidate the market, because it believes the reports will expose non-compliant manufacturers.

"There could be a significant amount of disruption at the end of this go-to-market process," Helen Chen, managing director and partner at L.E.K. Consulting in Shanghai, told *IDDM*.

CFDA will review self-inspection reports on three types of distributors: foreign device distributors, those with noted poor management and cold supply chains.

According to Katherine Wang, partner at Ropes & Gray LLP, subsidiary distributors acting as domestic agents for imported medical devices are key targets of the current enforcement campaign.

As second- and third-level distributors are common in China, a given manufacturer may have a high portion of their sales come from small distributors several steps away from their audited distribution partner, adds Chen.

Thus, manufacturers at highest risk are those with only a sole national distributor that is non-compliant with good supplier guidelines and invested in the labeling, warehousing and record keeping requirements.

Manufacturers with first-level distributors are most likely to control their product distribution and will likely be less impacted, she said.

Chen recommends that manufacturers of Class II and III devices review their own distributor audit records against the listed criteria, and reconfirm qualifications with their distribution partners.

Manufacturers that already track product sell-outs should review the list of their lower level distributors and sales exposure.

Distributors will need to check their distribution records going back to June 1, 2014 and report on Class II and III devices which:

- Lack CFDA registration certificates;
- Do not meet mandatory standards or technical requirements of their registrations;
- Lack qualified and valid documentation and licensure;
- Do not have an established stock inspection records policy;
- Have insufficient labels and/or indications for use that do not comply with current CFDA regulations; and
- Show any instances where instructions and label indications for transport and storage of a device were not followed.

If distributors refuse to report, conceal self-inspection findings, or fail to take self-inspection seriously, they may face revocation of medical device distribution permits, Wang said.

Distributors are required to submit their reports to provincial officials by July 15, who will review the self-inspection reports and submit their findings to CFDA by Sept. 30.

Read CFDA's update here: www.fdanews.com/06-23-16-CFDAInspectionUpdate.pdf. — Joya Patel

Pediatric, *from Page 4*

independently from effectiveness in deciding whether or not extrapolation may be appropriate."

Advamed and industry stakeholders also questioned why the guidance did not apply to 510(k) devices. The FDA reiterated that it only applies to devices subject to premarket approval applications, human device exemptions and de novo premarket requirements. The FDA noted that future guidance may address issues related to the 510(k) regulatory pathway.

Read the guidance here: www.fdanews.com/06-20-16-UsingExistingDataPediatricUsesofMedicalDevices.pdf. — Joya Patel

Ethicon Issues Worldwide Withdrawal of Physiomesh

Ethicon is voluntarily withdrawing its surgical mesh product, Physiomesh due to higher than average revision rates after use.

The J&J subsidiary decided to withdraw the flexible composite mesh following analysis of data from two large independent hernia registries that showed higher than average rates of recurrence after laparoscopic ventral hernia repair compared to other meshes.

Patients already implanted with the product should be followed as usual, the company said. The withdrawal does not involve any other Ethicon meshes.

The field safety notice with the affected product codes can be found here: www.fdanews.com/06-23-16-EthiconMeshWarning.pdf. — Joya Patel

Analogic Settles Foreign Bribery Charges Against Distributor

Massachusetts medical device maker Analogic, agreed to pay nearly $15 million to settle civil and criminal actions involving Foreign Corrupt Practices Act violations.

The SEC found the company's Danish subsidiary, BK Medical, ran hundreds of phony transactions with distributors to funnel roughly $20 million to third parties, "including individuals in Russia and apparent shell companies in Belize, the British Virgin Islands, Cyprus, and Seychelles."

"Analogic's subsidiary, BK Medical, allowed itself to be used as a slush fund for its distributors, funneling millions of dollars around the world at its distributors' direction without knowing the purpose of the payments or anything about the recipients," the SEC said.

Analogic agreed to pay $7.67 million in disgorgement and $3.8 million in prejudgment interest to settle the charges that it failed to keep accurate books and records and maintain adequate internal accounting controls. BK Medical agreed to pay a $3.4 million criminal fine in a non-prosecution agreement with the U.S. Department of Justice.

BK Medical's former CFO Lars Frost agreed to pay a $20,000 penalty to the SEC to settle charges that he knowingly circumvented the internal controls in place at BK Medical and falsified books and records.

From 2008 to 2011, Frost personally approved roughly 150 of the faked invoices and submitted false quarterly sub-certifications to Analogic. Analogic discovered the violations and voluntarily divulged them to U.S. and Danish authorities in 2011. — Joya Patel

Appeals Court Denies Review Of Ethicon's Loss Against Covidien

Ethicon's petition for an *en banc* hearing was rejected 10-1 by the Federal Circuit after the J&J subsidiary appealed a final decision by the PTAB in its patent battle with Medtronic over surgical stapler patents.

Ethicon appealed a U.S. Patent and Trademark Office's Patent Trial and Appeal Board final decision, arguing the decision was invalid because the same panel made both the threshold decision and the decision to conduct an *inter partes* review.

"The current practice of assigning the same PTAB panel to both institute and conduct an *inter partes* review is not only contrary to the statute, but has the taint of prejudgment," Circuit Judge Newman wrote in the June 22 dissenting opinion.

In March 2013, Covidien asked the U.S. Patent & Trademark Office for an *inter partes* review of 14 patent claims covering surgical stapling devices that produce formed staples having different lengths.

Following a challenge by Medtronic, a federal appeals court upheld in January the patent board's decision to invalidate some claims in J&J's surgical stapler patent.

The final decision can be found here: www.fdanews.com/06-23-16-USPTODenialDecision.pdf. — Joya Patel

BEM Warning, *from Page 5*

components, including parts that are manufactured and supplied according to specifications.

The letter cites a host of other problems with procedures, noting the procedure for final inspection of probes did not ensure finished devices are quarantined or adequately controlled until their release. The agency said it would not allow the firm's devices entry into the U.S. until violations are corrected.

BEM's procedure for controlling nonconforming product did not properly address identification, documentation, evaluation, segregation and disposition. One employee told the inspector that the firm doesn't document nonconformities identified during manufacturing operations and related activities for the Helica Thermal Coagulators and Helica LT/LTC Probes, the letter says.

It also cited Berwickshire for not establishing production and process control procedures, such as:

- Monitoring and control of process parameters, components and device characteristics during production;
- Approval of processes and process equipment;
- Documented criteria for workmanship; and
- Authorized release by a designated individual.

Meanwhile, the procedure to control monitoring and measuring devices did not include:

- Specific directions and limits for accuracy and precision;
- Provisions for remedial action when accuracy and precision limits are not met; and
- Documentation of remedial actions.

The letter points out that equipment used in final acceptance testing for some Helica Thermal Coagulators was out of calibration.

Another citation notes the corrective and preventive action procedures lacked key provisions, including requirements to use statistical methodology, when necessary, to detect recurring quality problems. BEM had not conducted and documented analyses of quality data at the time of the inspection. The firm's CAPA also was not validated to ensure that corrective actions were effective and didn't adversely affect the finished device.

The firm also was cited for failing to maintain device master records.

In addition to the GMP violations, the company has not fulfilled its annual registration requirements, making all of its products misbranded, the letter says.

The company did not respond to a request for comment by press time. The warning letter is available at www.fdanews.com/06-24-16-BEMWL.pdf. — April Hollis

Stryker Issues Worldwide Recall Of Select Target Nano Neuro-coils

Stryker is initiating a voluntary global recall for a select number of Target Nano neurovascular coil over issues with substandard stretch resistance.

The sutures inside the coil that provide stretch resistance may have been damaged due to prolonged exposure to heat during manufacturing. If a coil is stretched during procedure, the coil should be removed and replaced.

There is a remote potential of thrombus formation when the stretched coil is left exposed in the blood flow, but there are no long-term adverse events after a stretched coil is removed from the body, Stryker said. The issue does not affect patients with implanted coils.

The units come from five different lines of products, including the rHead, uHead, Sigmoid Notch, Remotion and Radio Capitellum devices. The recall covered 1,500 lots.

Stryker has notified the FDA and other regulatory bodies of the issue. The company has received 10 customer complaints related to the issue, but no adverse events have been reported.

The urgent medical device recall notice can be found here: www.fdanews.com/06-23-16-StrykerRecall.pdf. — Joya Patel

BRIEFS

John Sheets Takes Over at ODE

Industry veteran John Sheets has been appointed as the new director of the FDA's Office of Device Evaluation, which is responsible for premarket review of devices.

Sheets, who began his new duties on June 12. Previously he was the chief scientific officer at device and biotech firm Anika Therapeutics.

William Maisel had served as acting director of ODE since September 2014, in addition to his CDRH deputy director for science duties.

MHRA Updates Quicksite, Quickflex Alert

MHRA has updated a 2012 medical device alert for Quicksite and Quickflex devices manufactured by St. Jude Medical, recommending discontinuation of prophylactic replacement.

Certain models with damaged lead insulation could potentially worsen heart failure symptoms after implantation.

MHRA recommends that cardiologists and cardiac physiologists return patients to a six-month follow-up period, and withdraw certain models and remotely monitor patients in collaboration with St. Jude.

The April 2012 alert advised UK hospitals not to implant QuickSite and QuickFlex leads, and to follow up every three months on all patients already implanted with these leads.

Read the updated alert here: www.fdanews.com/06-23-16-MHRALeadAlert.pdf.

Hologic's Zika Virus Assay Scores EUA

Hologic has won an emergency use authorization from the FDA for its Aptima diagnostic to detect Zika virus.

The Aptima assay detects Zika RNA in human serum and plasma. The molecular diagnostic tool runs on the Hologic Panther system.

Under the EUA, the Aptima assay is exempt from GMP requirements as well as labeling requirements for cleared, approved and investigational devices.

The emergency use authorization sets certain reporting and documentation requirements on Hologic and its distributors. It also requires that the assay be available only in authorized laboratories.

FDA Approves Procleix Zika Assay

The FDA has approved the Procleix Zika virus screening assay using the Procleix Panther System to screen donated blood in potential endemic areas of the U.S. under an IND.

Co-developed by Hologic and Grifols, the Procleix Panther system automates nucleic acid testing (NAT)-based blood screening on a single, integrated platform, eliminating the need for batch processing.

The American Red Cross will participate in the Procleix Zika Virus assay investigational study, which will begin testing donated blood for Zika virus early this summer to ensure patients receive safe blood transfusions in targeted endemic areas.

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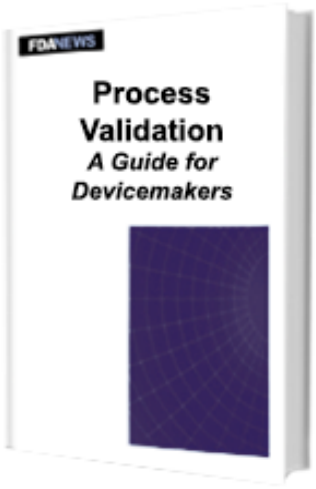

Process Validation
A Guide for Devicemakers

When must a process be validated? That is the first crucial question devicemakers must answer. But with no clear guidance from the CDRH, finding the answer can be difficult.

The new FDAnews management report — **Process Validation: *A Guide for Devicemakers*** provides you with the answers. This report will walk you through each point in the decision-making process, including how to determine if a product can be "fully verified," and how FDA inspectors define that term.

In it, you'll also find a valuable in-depth overview of all of the currently applicable regulatory guidelines that have an impact on process validation for devices, including those from three key sources: the FDA, the International Organization for Standardization (ISO) and the Global Harmonization Task Force (GHTF).

Process Validation: *A Guide for Devicemakers* teaches the proper application of the regulatory requirements that lead to successful process validation, and also offers advice on the practical issues confronting validation compliance by using real-life anecdotes and scenarios.

You also get invaluable extras, such as checklists for IQ, OQ and PQ — and hundreds of pages of appendices, including the invaluable *Medical Device Quality Systems Manual: A Small Entity Compliance Guide*, which is no longer available from the FDA.

But, most importantly, throughout the report, you'll find real-life examples that illustrate relevant concepts … show when processes need to be validated … identify the kinds of evidence you need to collect and maintain to demonstrate proper validation … and actual FDA warning letters to help you learn from others' mistakes.

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