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FDA Panel Signs Off on Sandoz's Biosimilar Application on Neupogen

An FDA advisory committee has thrown its support behind the first publicly acknowledged biosimilar application in the United States.

Industry experts on the FDA's oncologic drugs advisory committee voted 14-0 earlier this month to recommend the agency approve Sandoz's bid to produce its own version of Amgen's Neupogen (filgrastim), which Sandoz plans to market in the U.S. as Zarxio.

FDA staff had already given Sandoz's application their own stamp of approval with a finding that the firm's version was highly similar and showed no clinically meaningful differences to Amgen's reference version.

*(See **Neupogen Biosimilar**, Page 2)*

Celgene Unable to Dismiss Lawsuit in First Written REMS Opinion

In a closely watched case, a federal judge has denied Celgene's motion to dismiss a lawsuit alleging the brandmaker engaged in anticompetitive conduct by refusing to turn over product samples for ANDA bioequivalence testing.

The New Jersey District Court federal judge ruled late last month that Mylan could proceed with claims that Celgene's actions willfully excluded the generics maker from the market. The judge did, however, dismiss Mylan's claims alleging a conspiracy by Celgene and its distributors to deny testing samples of its cancer therapies Thalomid (thalidomide) and Revlimid (lenalidomide).

The ruling appears to be the first written opinion that could help settle the dispute over the brand industry practice of using REMS protocols to block access to sample drugs that generics need to prepare their applications, legal experts say.

Other REMS cases have been dismissed or settled out of court, Hyman, Phelps & McNamara attorney Kurt Karst said. The case

*(See **Celgene Lawsuit**, Page 4)*

Neupogen Biosimilar, *from Page 1*

The committee gave its recommendation in part because of the hundreds of thousands of European patients who've shown the same outcomes with the biosimilar as Neupogen across millions of exposure days. That data helped to override lingering concerns with differences in the pharmacodynamic parameters presented in the application (*see story, page 10*).

CDER Director Janet Woodcock called the meeting a historic occasion, the culmination of years of work and the first of many meetings for different biosimilars.

Observers had expected the meeting to help set the tone for future FDA consideration of biosimilars. The agency is expected to continue dealing with applications on a case by case basis, initiating similar advisory committee meetings for each new proposed biosimilar for the foreseeable future.

Lingering over the meeting was the question that first drove Congress's 2010 creation of a biosimilar approval pathway: whether or not biosimilars will lower costs and improve patient access.

Sandoz's head of biopharmaceuticals, Mark McCamish, assured the committee that the biosimilar would cost less than the brand. However, the price may at times be at parity with the reference, he cautioned. Other factors, such as rebates, will ultimately drive down the cost to the end-payer patient or insurance provider, he said.

Committee member James Liebmann was not as confident with the cost-saving assessment. He specifically asked about pricing for the therapy and noted that while Sandoz's biosimilar version, marketed as Zarzio in Europe, has created savings, European and U.S. drug costs are radically different, he said.

The committee heard the application as EP2006 because the brand name Zarzio, spelled with an "x" in the U.S., has not yet been approved by the FDA. The FDA heard the application as a biosimilar rather than on the higher regulatory burden of an interchangeable therapy.

The difference in theory would be that interchangeables could be directly swapped from the prescribed reference therapy at the pharmacy, although that will depend on state-by-state substitution laws. — Bryan Koenig

EMA Adopts Final Guideline on Biosimilarity Clinical Considerations

The European Medicines Agency wants biosimilar makers to use pharmacodynamic markers alongside pharmacokinetic data to demonstrate biosimilarity.

In a final guideline that takes effect July 1, the agency says it will accept comparative PD/PK studies when the surrogate biomarkers sufficiently affect patient outcomes. For example, an early cut in viral loads may be used to demonstrate the effectiveness of alpha interferons on hepatitis C.

When these biomarkers are not effective surrogates, but multiple doses are known to have relevant effects on the active substance, a single or multiple dose-exposure-response study at two or more dose levels is sufficient to waive a clinical efficacy study.

Manufacturers should test surrogate efficacy endpoints in randomized, double-blind, parallel group comparative trials using an equivalence design and patients who align with the approved therapeutic indication for the reference product. Deviations from this model will be considered when factors dictate, the agency says.

The EMA also will accept extrapolations of safety and efficacy data when the reference product carries multiple approved indications. However, when an endpoint is not established as an acceptable marker for all indications, agency reviewers will request additional data.

When it comes to safety monitoring, sponsors need to include postmarket pharmacovigilance and risk monitoring plans in their applications and continue monitoring their biosimilars postapproval.

View the guideline at www.fdanews.com/01-12-15-EMAguideline.pdf. — Lena Freund

Hospira Announces Epogen/Procrit Biosimilar Application, Fourth in U.S.

Hospira has submitted a BLA for anemia drug Retacrit, a proposed biosimilar to Amgen's Epogen and Janssen's Procrit — making it the fourth company to announce submission of a biosimilar application to the FDA.

Hospira announced the filing for epoetin alfa Jan. 12. The application was sent to the FDA on Dec. 16, 2014, the firm said. The drugmaker told *Generic Line* it expects FDA notification of acceptance of the submission within 60 days of filing. The FDA has committed for this fiscal year to acting on at least 80 percent of biosimilar applications within 10 months.

The announcement came a week after an FDA advisory committee considered the first biosimilar application. The Oncologic Drugs Advisory Committee voted unanimously to recommend approval of Sandoz's Zarxio, a biosimilar to Amgen's Neupogen (filgrastim) (*see story, page 1*).

Celltrion and Apotex are the other two companies with announced biosimilar applications

(*Generic Line*, Jan. 7). Hospira has a partnership with Celltrion giving it exclusive U.S. marketing rights to the South Korean firm's biosimilar, if approved. No biosimilars have yet been approved under the 2010 pathway, and all are likely to face uphill patent battles against the brandmakers.

Hospira has long touted itself as a major international biosimilars firm, with products in Australian and European markets, including Retacrit, which Hospira launched in Europe in 2008 and Australia in 2011.

Amgen's branded version of epoetin alfa, Epogen, earned the firm \$518 million in worldwide sales in the third quarter of last year, according to an SEC filing. For Janssen, Procrit brought in \$307 million in the same period.

Epoetin alfa is approved in the U.S. to treat anemia in patients with chronic kidney disease who are on dialysis. It is also indicated for anemia in HIV-infected patients and cancer patients undergoing chemotherapy.

— Bryan Koenig

NICE Updates Process for Reviewing Biosimilars

The UK's healthcare cost watchdog has updated its methods for reviewing biosimilar applications in anticipation of the products' increasing availability in the country.

Biosimilar applications for national coverage generally will be reviewed under a multiple technology appraisal process along with the reference product, according to a Jan. 6 position statement from the UK's National Institute for Health and Care Excellence.

Positive appraisals of biosimilars will use the name of the active drug substance, including the reference product and brand name, to inform clinical decisions, NICE says.

In other circumstances, where the agency does not make a recommendation, NICE says it will issue an "evidence summary: new medicine." Evidence summaries of the biosimilar will

include the therapy's brand name because substitutability and interchangeability cannot be assumed, the agency adds. Such summaries will leave the decision to use the biosimilar or originator biologic up to the physician.

Biosimilars already are covered to some extent by the National Health Service, and NICE has included biosimilars in its technology appraisal on the human growth hormone somatotropin. Their availability and use is expected to become more widespread over the next few years, NICE says.

Several top-selling biological medicines have lost or will soon lose patent protection, especially monoclonal antibodies for use in patients with cancer, rheumatoid arthritis and other inflammatory diseases, as well as insulins for diabetes, NICE says.

Read the updated position statement at www.fdanews.com/01-07-15-NICEbiosimilar.pdf.

— Neal Learner

Uhl Named Permanent Director of Office of Generic Drugs

The FDA has named Kathleen Uhl permanent director of the Office of Generic Drugs (OGD), where she has served as acting director since March 2013.

Uhl was named acting director of the office, which is charged with overseeing and approving all generic drug products, after the departure of Gregory P. Geba, who was OGD director for only about nine months (*Generic Line*, March 26, 2013).

Uhl has more than 30 years of regulatory and medical policy, scientific, and government experience. She was an integral part of OGD's reorganization and expansion, and oversaw implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA).

Uhl joined FDA in 1998 as a medical officer in clinical pharmacology review. She has served in several leadership roles, including senior advisor to OGD director, OMP deputy director, and assistant commissioner of women's health and director of the Office of Women's Health, Office of the Commissioner.

Celgene Lawsuit, from Page 1

between Mylan and Celgene stands to be the first to go to a final decision at trial, which could set a significant legal precedent for other generics makers seeking to circumvent REMS barriers to product samples, Karst told *Generic Line*.

Mylan expressed satisfaction with the ruling, calling it an important step in the firm's efforts to bring generic versions of the two therapies to market.

Court documents trace the dispute between the two firms to 2003, when Mylan first requested Thalomid samples from Celgene for bioequivalence testing. Celgene balked at the request, citing product safety protocols meant to carefully limit distribution of drugs that are prone to abuse.

The two companies entered protracted negotiation that stretched into 2009, with Celgene continuously pushing back on Mylan's requests. Finally, after attempting to engage with Celgene for almost five years to procure samples, Mylan recognized that further engagement with Celgene would be fruitless, the judge said in her ruling.

A similar squabble emerged over Mylan's efforts to acquire Revlimid samples in a series

of requests and countered protocol requirements that stretched from 2009 to 2012, according to the documents.

The FTC this summer sided with Mylan in an amicus brief, and has weighed in on similar cases, arguing that in the individual instances, refusal to sell sample batches amounted to anti-competitive behavior that threatened to stifle generic competition (*Generic Line*, July 15, 2014).

Celgene has argued that it is free to determine with whom it does business. Brandmakers in similar instances have voiced fears they could be held liable for noncompliance with their REMS protocols.

Nearly 40 percent of all new drugs now come with REMS restrictions, and generics makers say these protocols are often abused by brandmakers to hinder bioequivalence testing and head off potential competition. A bill was introduced in the last Congress aimed at prohibiting such conduct. The FDA also recently issued draft guidance codifying its longstanding practice of issuing letters to generics makers certifying them to be REMS compliant in their bid for samples (*Generic Line*, Jan. 5).

Celgene told *Generic Line* that it does not comment on ongoing litigation. — Bryan Koenig

2015 Guidance Expected on Social Media, Biosimilars and Quality Metrics

The FDA this year aims to answer key questions on which quality metrics it will collect from drugmakers, how to develop biosimilars and how to use social media to promote products.

CDER issued a list of 91 new and revised guidances it plans to publish throughout the year. Highlights of the list include:

- Guidance on quality metrics and risk-based inspections, which CDER delayed after deciding to include biologics in the program. Guidance on the eight to 10 metrics CDER would collect from drugmakers was supposed to be released by now;
- Four guidances on biosimilars, covering labeling, a Q&A on biosimilars, demonstrating interchangeability to a reference drug, and statistical approaches to show biosimilarity;
- Six guidances on advertising, including links to third-party sites and promoting off-label uses, properly disclosing risk information in TV ads, and promotional labeling;
- Four guidances for compounding pharmacies, including a set of good manufacturing practices for large compounders, properly registering for federal oversight as an outsourcing facility, and how pharmacies can properly repackage drug products. FDA will also finalize guidance on how outsourcing facilities can submit adverse events;
- Guidance on modifications of risk evaluation and mitigation strategies;
- A Q&A guidance on data integrity, which comes in the wake of a slew of problems discovered at international sites; and
- Six guidances on implementing the federal track-and-trace law, including verification systems for drugs, getting a waiver from product tracing requirements, and products eligible for grandfather status.

CDER does not provide a timeline on when guidances are expected to be released. To read the full list, visit www.fdanews.com/01-06-15-GuidanceList.pdf. — Robert King

FTC Tracks Slight Downturn in Pay-for-Delay Deals in FY 2013

The Federal Trade Commission counted 29 pay-for-delay deals in fiscal year 2013 out of a total of 145 patent litigation settlements between brand and generic drugmakers — a slight decline from 2012, but in line with the two previous years.

In FY 2012, there were 40 pay-for-delay deals out of 140 final infringement settlements, the FTC says in a study released last month. While that is significantly higher than the number of pay-for-delay agreements recorded in FY 2013, it proved an outlier from earlier years, with 31 such deals in FY 2010 and 28 in FY 2011. The government's fiscal year runs from Oct. 1 to Sept.30.

The study drew on data from pharma settlements reported to the Department of Justice and the FTC under the Medicare Modernization Act of 2003.

The 29 potential pay-for-delay deals in FY 2013 were settled over 21 different therapies with a total of \$4.3 billion in annual sales in the U.S., the FTC says. Included were 13 first-filer generics. Fourteen of the 29 included a cash payment to the generics firm that was billed as reimbursement for attorney fees, while another 11 came with some other side business deal compensation. Four of the settlements came with a promise by the brand manufacturer not to introduce an authorized generic version.

Of the 145 total deals counted, 75 showed no explicit or possible compensation and 31 did not create any barriers to generic entry, according to the FTC.

The FTC offers no explanation for the recent downtrend in settlements.

See the FTC study here: www.fdanews.com/12-23-14-FTC-Patent-Settlements.pdf. — Bryan Koenig

Judge Sides With FDA Over Colchicine 505(b)(2) Approval

Hikma Pharmaceuticals will launch its gout treatment, Mitigare, after a federal court rejected Takeda's arguments to block the product, which would compete with Takeda's drug Colcris.

The D.C. district court judge denied several motions for summary judgment that would have automatically awarded Takeda a permanent ban on Mitigare's (colchicine) approval. The court gave the company until Jan. 23 to show why the case shouldn't be dismissed outright. Takeda has already moved to appeal.

The ruling stems from Takeda's October suit against the FDA for allowing Hikma to cite another colchicine product, ColBenemid, in its 505(b)(2) application for approval, thus skirting a patent infringement lawsuit over Colcris.

Takeda charged that the FDA decision would create a public health risk because

Hikma couldn't cite Colcris' safety warning on toxicity of colchicine when mixed with other drugs, as its application was based on another product.

Hikma defended the drug's approval, pointing out that Mitigare is not an exact copy of Colcris because it is a capsule while Colcris is a tablet. Mitigare's approval also does not include all of Colcris' indications.

As for the safety concerns, Hikma says Mitigare's label specifically warns against using the drug with other products known to cause harmful reactions with colchicine (*Generic Line*, Oct. 22, 2014).

Meanwhile, Takeda seems to be trying to mitigate the damage a competitor might cause by launching an authorized generic version of Colcris with Prasco. The copy will be marketed under the Prasco label. Colcris' patent doesn't expire until 2029. — Bryan Koenig and Jonathon Shacat

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Indian Court Blocks Cipla From Selling Novartis Generic

India appears to be working somewhat on its reputation as being unfriendly to foreign drug patents, with a court temporarily blocking Cipla from marketing its own generic version of Novartis' COPD therapy Onbrez.

The Delhi High Court ruled this month that India-based Cipla cannot be allowed to infringe the valid patents protecting Onbrez (indacaterol).

The ruling bars Cipla from marketing its Onbrez generic at least until a final decision is rendered in the case. Further arguments aren't expected until at least March.

Novartis praised the ruling, noting that Onbrez is patent-protected in India until 2020. The drug is licensed in India by Lupin. In the U.S., Novartis markets the therapy under the brand name Arcapta Neohaler.

Court Challenge

Cipla asked the court in October to invalidate five patents protecting Onbrez, launching its own version of the drug for about one-fifth the brand price in the process. At the time, Cipla argued not that the patents were invalid but that,

under Section 66 of the Indian Patents Act, they should be struck down to serve a public need. Specifically, Cipla said Novartis was supplying only enough Onbrez in India for a few thousand people despite a population of roughly 15 million that suffers from chronic obstructive pulmonary disorder (*Generic Line*, Nov. 5, 2014).

Novartis maintains that it has met the demand for Onbrez in India and says Cipla has inflated the need for the drug, according to the recent decision.

Intellectual Property

While disappointed with the ruling, Cipla said it will comply and will decide on a course of action once it reads the judgment.

Patients will continue to get the generic version of the therapy while the old stocks last, the company added.

Observers have speculated that Cipla faces an uphill battle in its bid to invalidate Onbrez's patents. That's in part due to recent efforts by the Indian government and domestic generics companies to reform their image in the eyes of foreign brand makers who have complained of a lack of patent protections in the subcontinent (*Generic Line*, Oct. 22, 2014). — Bryan Koenig

Actavis Gets Expedited Review in Namenda Appeal

A federal appeals court is expected to rule next month in a dispute over Actavis' plan to pull an older formulation of its blockbuster Alzheimer's drug Namenda from the market and replace it with a newer version.

Actavis confirmed this month that the U.S. Court of Appeals for the Second Circuit would expedite its appeal of a district court's ruling that temporarily mandated Namenda IR (memantine) stay on the shelves.

The drugmaker said it has requested a ruling by Feb. 16.

The company also expressed confidence that the appellate court would overturn the Southern District of New York judge's temporary ruling in the case, which stemmed from Actavis and subsidiary Forest Laboratories' bid to switch patients to extended-release Namenda XR.

New York state Attorney General Eric Schneiderman sued Actavis in September. He claimed the switch was designed solely to prolong market exclusivity through the newer, patent-protected version.

Actavis has countered that the XR version is superior because it needs to be administered just once a day compared with twice daily for the older formulation (*Generic Line*, Jan. 7). — Bryan Koenig

Actavis Keeping Namenda on Shelves, But Notification Mandate Waived

Actavis must keep its Alzheimer's drug Namenda on the market for now, but a recent agreement with the New York Attorney General will let the company avoid notifying more than half a million people of that fact.

A federal judge in December blocked Actavis from pulling its original formulation of Namenda (memantine) from the shelves to make way for a new longer-acting formulation.

However, the drugmaker will not have to fulfill another part of the judge's ruling: that it inform pharmacists, patients and others that supplies of Namenda would remain uninterrupted.

Mass Notification

Actavis argued that such a requirement would have forced it to send out more than 500,000 notices nationwide, according to court filings.

The notification requirement will remain lifted until at least January, when the U.S. District Court for the Southern District of New York

is expected to rule on Actavis's challenge that it continue supplying Namenda for the length of a lawsuit contesting the company's planned drug switch (*Generic Line*, Jan. 7).

The notification requirement was lifted in part to prevent Actavis from needing to send two separate notices in case it won its bid to pull Namenda, according to the Attorney General's office.

Anticompetitive Accusations

The latest development stems from a September antitrust lawsuit filed by New York Attorney General Eric Schneiderman.

Schneiderman claims Actavis and its subsidiary Forest Laboratories intended to replace Namenda with extended-release Namenda XR purely to hinder generic competition and artificially maintain market exclusivity.

Actavis contends that its XR version, which has longer-lasting patents, is a superior product, requiring administration once a day compared with twice daily for the original formulation.

Namenda generated \$1.5 billion in sales in fiscal year 2014. — Bryan Koenig

Mylan, Abbott Submit Merger Proposals to Ease EU Antitrust Concerns

Mylan and Abbott have submitted proposed commitments to the European Commission's competition oversight body to allay anti-competitive concerns over a proposed merger that would reincorporate Mylan in the Netherlands.

The commission currently is investigating any potential antitrust issues in light of the commitments, an EC spokesperson told *Generic Line*.

Details of the companies' commitments were not publicly available.

Under the \$5.3 billion merger, announced last summer, Mylan would acquire Abbott's non-U.S. branded generics business in developed markets, including cardiac and gastrointestinal products.

The deal would allow Mylan to benefit from a significantly lower corporate tax rate in the Netherlands, a move the drugmaker is pursuing despite U.S. regulatory actions against other so-called inversion mergers (*Generic Line*, Nov. 5, 2014).

A decision is expected from the commission by the end of the month. — Bryan Koenig

Gilead Denied Sovaldi Patents in India, Paving Way for Generic Competition

Unauthorized knock-offs of Gilead's pricey blockbuster hepatitis C therapy, Sovaldi, may soon hit the market in India after the government refused to grant it patent protection.

The Director General of Patent Designs and Trademarks sided last week with a challenge by Indian drugmaker Natco Pharma and the Initiative for Medicines, Access & Knowledge, a U.S.-based nonprofit devoted to challenging nonmeritorious patents in developing countries. According to I-MAK cofounder Tahir Amin, the patent office agreed that Gilead's bid failed to meet the stringent IP requirements of Indian patent law to qualify as brand new and not simply an improvement on existing science.

Gilead had argued that Solvadi (sofosbuvir) was a wholly new therapy not anticipated by the existing science, according to the patent ruling.

With the patent bid denied, there is now nothing blocking generic entry of Sovaldi copies,

Amin tells *Generic Line*. He expects unauthorized generic versions from Natco and others could hit the market in six months.

Those competitors would join seven others that have signed nonexclusive licenses with Gilead to sell generic Sovaldi in the developing world—an effort to limit the sticker shock of a drug that costs \$84,000 for a full treatment in the U.S. Six of those seven firms are based in India.

Ongoing Fight

Gilead promised to appeal the ruling, arguing the decision was improper. The generic licensing program with its Indian partners continues as normal, the company said, noting that sofosbuvir was granted regulatory approval Jan. 13.

The patent office is still considering a challenge to another Sovaldi patent application. However, until India actually recognizes any of the protections sought by Gilead, there is nothing stopping generic entry, Amin says.
— Bryan Koenig

Depomed Decision Doesn't Force FDA to Change Orphan Drug Program

The FDA will maintain its policy on determining when an orphan drug product is entitled to market exclusivity, saying a recent federal court ruling that overruled the agency's policy applied to just one drug and established no precedent.

Drugmakers seeking orphan status for a rare disease therapy that is the same as a previously approved drug must still prove their product is clinically superior, the agency said last month.

The three-page policy restatement stemmed from a court ruling that forced the agency to grant seven years of market exclusivity to Depomed's post-shingles pain drug Gralise (gabapentin) in a case involving whether the drug was clinically superior to Pfizer's Neurontin (gabapentin).

The FDA had granted Gralise orphan drug status in 2010, but withheld marketing exclusivity when it launched in January 2011, claiming

that Depomed presented no definitive proof that Gralise was better than Neurontin in treating post-herpetic neuralgia.

Depomed argued in a 2012 lawsuit that a drugmaker must prove clinical superiority only when the other product with the same active ingredient also is an orphan drug, a status Neurontin never obtained. The U.S. District Court for the District of Columbia in September sided with Depomed and the FDA granted the exclusivity a month later.

One legal expert says he anticipated the FDA would change its policies to reflect the court's decision. The agency may be seeking a way to draw out another lawsuit to relitigate the issue in court, says Kurt Karst, an attorney with Hyman, Phelps & McNamara, of the decision to maintain the status quo.

To read the *Federal Register* notice, visit www.fdanews.com/12-22-14-OrphanDrug-Decision.pdf. — Robert King

Groups Use Neupogen Biosimilar Vote to Highlight Outstanding Issues

An FDA advisory committee may have given its unanimous approval for a biosimilar application this month, but industry and patient groups contend the regulatory pathway still has many potholes and unanswered questions.

Advocacy groups reacted to the Jan. 7 oncologic drugs advisory committee meeting on Sandoz's application for a biosimilar version of Amgen's Neupogen (filgrastim) by pointing out unresolved issues with the biosimilars approval process.

BIO assailed the FDA's current focus on looking at biosimilars on an almost exclusively case-by-case basis rather than creating industrywide guidance.

For example, the agency has not yet addressed the issue of naming. GPhA has called for biosimilars to be given the same international non-proprietary name as those given to generics. Distinguishing between biosimilars using different names will confuse patients and impede adoption of the cheaper therapies, GPhA and others argue.

But patient advocates and others at the meeting called for some kind of distinguishing feature to be applied to biosimilar names. Patient advocates were joined by some in industry, including Amgen, which has nine biosimilars in development. Non-proprietary names should be distinguishable for every biologic, brand or biosimilar, to inform patient use and aid in adverse event tracking, said Richard Markus, Amgen's vice president of global biosimilars development.

Another major point of concern was over the extent of clinical trials required for biosimilar

applications. Some groups, including the Immune Deficiency Foundation, called for all biosimilar applicants to have to perform full clinical trials, instead of clinical analytics on a smaller scale.

The FDA has so far treated biosimilar trials on a case-by-case basis. Under the 2010 statute on the biosimilar approval pathway, the agency requires applicants to prove only that their products are at least highly similar and have no clinically meaningful differences to the reference therapy, with the assumption that the reference has demonstrated safety and efficacy.

Biosimilar guidance on clinical pharmacology data notes that the FDA can determine at its discretion whether developers may be exempt from some testing requirements (*Generic Line*, May 20, 2014).

CDER Director Janet Woodcock noted in opening remarks at the meeting that Sandoz's Neupogen biosimilar required limited clinical trials because it is a relatively simple biologic with well-established pharmacodynamic endpoints, unlike some other therapies.

Evercore ISI financial analyst Mark Schoenebaum cautioned that more complicated biosimilars will face a more difficult road. That means agency views on Neupogen probably shouldn't be assumed to extend to other biosimilar applications, Schoenebaum said.

The committee voted 14-0 to recommend approval for Sandoz's product on all five U.S. indications for Neupogen. Action on Sandoz's application is expected by as soon as May (*see story, page 1*). — Bryan Koenig

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DAY ONE

8:00 a.m. – 8:30 a.m.

REGISTRATION/CONTINENTAL BREAKFAST

8:30 a.m. – 10:00 a.m.

Understanding The Basics of Human Error On The Manufacturing Floor

- How human errors intersect with manufacturing regulations
- Examples of applicable FDA requirements and what the FDA expects companies to be complying with
- A review of other industry standards that apply to drug and device manufacturing
- What FDA investigators look for during inspections and the most common violations found in Form 483s and Warning Letters
- Which violations tied to human errors and manufacturing are trending up
- The various types of human errors are commonly found on manufacturing floors
- How we got here — why is human error reduction such an important topic

Interactive Exercise! Do we also err?

Attendees will be broken into groups and asked to describe the most common human errors within their facilities. The workshop will then reconvene and break-out group leaders will describe what they uncovered. A list of the most common problems will be tallied to help focus the future discussion.

10:00 a.m. – 10:15 a.m. **BREAK**

10:15 a.m. – 12:00 p.m.

Human Error In Context — What Are the Factors That Drive Human Errors?

- The taxonomy of human error; how and why drug and device companies need to focus on this in their investigation processes
- Why administrative and management systems factor so prominently into deviations and non-conformances
- The role of innovative operational controls and their role in reducing human errors

- Simple procedures that prevent human error -- how they should be described and presented to maximize human error reduction
- Common examples of poor human factors engineering and workplace conditions that contribute to human error
- When training is appropriate and when we should stop
- Learn how common day-to-day communication gaps contribute to human error
- How supervision can be one of the best human error reduction strategies at your site
- When is individual performance responsible for human error and when does it become a root cause
- How to address cognition, attention, and memory failures at your site

12:00 p.m. – 1:00 p.m. **LUNCH**

1:00 p.m. – 2:30 p.m.

Internal vs. External Factors

- How our biology affects our thinking process and individual performance
- Understanding the latest on cognitive load and attention, memory, and decision making errors — how they commonly occur on the manufacturing floor
- How our senses control how we react — it's more important that you think
- Best practices for controlling human factors for optimum people performance
- How to create an organizational environment that supports human error reduction initiatives — from senior management to floor level staff
- Why our culture with regards to human error has to change; it's not an easy process but vitally necessary for drug and device companies

2:30 p.m. – 4:30 p.m.

Corrective and Preventive Action (CAPA) — FDA's #1 Manufacturing Compliance Problem

- How to develop corrective actions that make sense — what's working and not working
- Creating preventive actions that truly prevent; how to stop errors that have not yet happened
- Understanding the human error prediction process and tools

- Prevention and human error control: proven ways to measure improvement and on-going trend analysis
- When to use detection mechanisms instead of preventive mechanisms — the pros and cons of each
- Human error detection and recovery rate — are you really uncovering all the errors within your facilities?
- Assuring for the FDA your CAPA program is effective and you've adequately focused on human error

Interactive Exercise! When to do what?

DAY TWO

8:30 a.m. – 10:00 a.m.

Human Error Reduction Techniques

- Discussion of insights from day 1
- When is human error a human resources issue?
- How and when to apply engineering controls to correct and prevent human error deviations
- What to do when individual performance is the major contributor
- Human error and documentation: from design, construction, change management and implementation
- Additional Contributors for human errors will be discussed

Interactive Exercise! Practice identifying techniques to be applied

10:00 a.m. – 10:15 a.m. **BREAK**

10:15 a.m. – 12:00 p.m.

Human Error Investigation

- Human Error investigation process defined from beginning to end
- How to gather data in the human error investigation process
- How to perform an effective interview
- Important steps for effective human error investigations

- How to report issues to make sure management listens

12:00 p.m. – 1:00 p.m. **LUNCH**

1:00 p.m. – 2:30 p.m.

Root Cause Analysis Tools

- A brief review of common tools used in determining root cause
- Hierarchy and use of the root cause determination tool for human error investigations
- How to perform a cognitive load assessment
- The interview process and interview techniques for human error root cause analysis
- When and how to use the human error prediction tool
- When to perform a Process vs. procedure analysis and why it is so important to do so before establishing procedure revision as a CAPA for human error

Interactive Exercise! Brainstorm root causes for real cases with peers. Using the situations identified in the first exercise we will try and apply the applicable tool.

2:45 p.m. – 4:45 p.m.

Metrics and Human Error

- KPI's
- Human Error rate
- 1st time pass rate
- Overall equipment effectiveness (OEE)
- Trending /Tracking

Interactive Exercise! Work with various common metrics and benchmarks. Determine what constitutes acceptable and non-acceptable results.

4:45 p.m. – 5:00 p.m.

Review and Key Insights/Materials

- Copies of the presentations
- Current FDA regulations
- Pertinent guidance documents
- Articles on Human Error
- Manual Tools
- Interviewing guide
- Report Example
- Root Cause Determination Tool

5:00 p.m. **WORKSHOP ADJOURNS**

WHO SHOULD ATTEND

- QA/QC directors and managers
- Process improvement/excellence professionals
- Training directors and managers
- Manufacturing operations directors
- Human factors professionals
- Device engineering
- Compliance officers
- Regulatory professionals
- Executive management

COURSE BINDER MATERIALS

- Root cause determination tool
- Interviewing guide – you can take back and use immediately
- Example of well-documented HE report
- Complete copy of slide deck materials
- Copies of applicable FDA regulations referenced in the course
- Copies of pertinent FDA guidance documents
- Articles focused on human error reductions

YOUR EXPERT SPEAKER

GINETTE COLLAZO, PH.D.,
— has spent more than 15 years in technical training, organizational development and human reliability. She has worked with Bristol-Myers Squibb, Johnson & Johnson, Schering-Plough, Wyeth and Medtronic, and many more small and mid-sized drug and device companies. An active researcher in specialized studies related to human reliability, she is the author of numerous publications on these topics.

“The topic is very relevant to the needs of our business at the moment. I learned several things associated with how to train and use lean techniques to reduce the opportunity for human error. It also reaffirmed the things we are doing well that are working.”

—Richard Leach,
Director of Quality, Nosco

“[Ginette is] very passionate [and] high energy. A lot of take aways. Reduction of human error has been a challenge and the tools provided will be put to the test.”

—Alex Masso, QA In-Process Supervisor,
Mylan Institutional Inc.

“[Ginette is] very knowledgeable with great industry examples. Very spunky! Great delivery.”

—Irene Rockwell, Manufacturing
Compliance, Biogen Idec

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Sept. 16-17, 2015
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