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Product Liability Litigation Playbook: Pros And Cons For Pharma

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One significant development is more frequent exclusion of testimony from plaintiffs' expert witnesses. Rulings excluding expert witness testimony in Zoloft and Lipitor litigation led to the dismissal of thousands of suits.

Johnson & Johnson's recent experience shows how uncertain product liability litigation is for drug makers. After winning jury verdicts in three *Xarelto* (rivaroxaban) bellwether trials, the company was hit with a $417m verdict in a talcum powder lawsuit last month.

Despite the divergent outcomes in personal injury complaints for J&J, pharma companies are seeing some positive trends. One significant development has been the more frequent exclusion of testimony from plaintiffs' expert witnesses. Rulings excluding expert witness testimony in *Zoloft* and *Lipitor* litigation led to the dismissal of thousands of suits.

At the same time, plaintiffs' attorneys have been narrowing their claims to win a jury verdict. That was evident in a jury's award of $150m in punitive damages against **AbbVie Inc.** in *AdroGel* litigation. While the jury rejected claims of strict liability and negligence for the plaintiff's heart attack, it found that AbbVie made false representations about the testosterone replacement therapy in its promotion. *(Also see "AbbVie AndroGel Jury Verdict Targets 'Low T' Promotion" - Pink Sheet, 24 Jul, 2017.)*

The drugs that are subject to the most complaints tend to be those in multidistrict litigation (MDL). When numerous cases involving similar facts are filed in federal courts, the Judicial Panel on Multidistrict Litigation often transfers them to one district for consolidated pre-trial proceedings. However, the MDL docket does not convey a complete picture of the drugs subject to personal injury suits. For example, approximately 13,800 plaintiffs have filed claims against J&J's *Risperdal* (risperidone) but they were not transferred to an MDL. And many mass tort cases are pending in state courts.

The MDL docket currently includes 26 drugs in product liability litigation, several of which have largely been settled. The most recent litigation transferred to an MDL involves **AstraZeneca PLC**'s *Farixga* (dapagliflozin), Bristol-Myers Squibb Co./Pfizer Inc.'s 's *Eliquis* (apixaban), J&J's *Invokana* (canagliflozin), and a second MDL involving Pfizer's *Nexium* 24HR and *Protonix* proton pump inhibitors. (*See chart at the end of this article.*)

JURY REJECTS XARELTO CLAIMS

The Xarelto litigation is the biggest, with approximately 20,000 plaintiffs who have filed claims in the MDL and state courts. J&J and **Bayer AG** won the first bellwether trial in the MDL in May, the second in June and the third in August. Bellwether trials, a small group of lawsuits chosen to be tried first, give an indication of what will happen with future litigation.

The Xarelto complaints are similar to those

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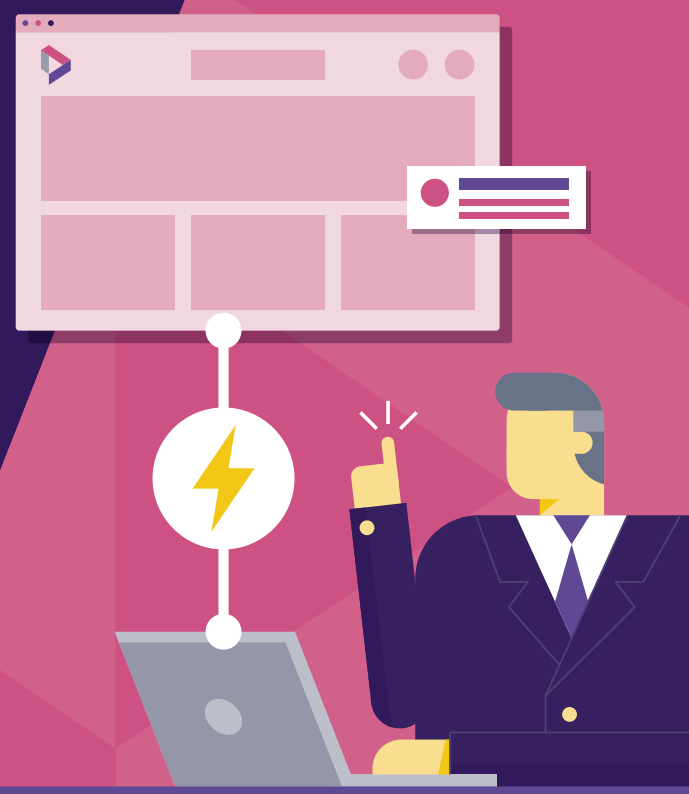

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There were passionate testimonies from patients affected by Sanofi's anti-epileptic drug valproate at the European Medicines Agency's first public hearing on medicines safety. There was almost full agreement among those who testified that existing risk reduction measures are not working.

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FDA is sued by Public Citizen after failing to make a decision on a 2014 citizen petition urging the agency to remove an infant teething indication for OTC benzocaine products. The complaint asks a federal court to order a response from the agency within 30 days.

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brought against **Boehringer Ingelheim Corp.**'s blood thinner *Pradaxa* (dabigatran). The Xarelto cases were consolidated in multidistrict litigation after Boehringer entered a $650m settlement agreement in May 2014 covering 4,590 claimants alleging Pradaxa caused severe bleeding and other injuries. BI reached a settlement before a trial was held. *(Also see "Product Liability Suits: Testosterone, Lipitor Grow While Yaz, Pradaxa Settle" - Pink Sheet, 19 Jan, 2015.)*

The plaintiffs in the Xarelto litigation allege that they or their family members suffered severe bleeding and other injuries due to the anticoagulant's allegedly defective design and inadequate warning label. In the third bellwether trial, the plaintiff did not allege that the defendants failed to warn of Xarelto's bleeding risk, which is on the label, but claimed they failed to instruct physicians about the need to evaluate the drug's anticoagulant effect on individual patients with standard laboratory testing. Specifically, the plaintiff alleged the defendants failed to adequately instruct physicians about Xarelto's clinically significant inter-patient variability, whereby certain patients will have a higher bleeding risk.

Asked about these claims, J&J's **Janssen Pharmaceutical Cos.** unit said it is continuing to defend against the plaintiff's theories as they contradict years of scientific data, FDA's repeated confirmation of Xarelto's safety and efficacy, and how the medicine should be used as described in its prescribing information.

"Specifically, there is: no FDA-approved method for measuring the amount of any Factor Xa non-vitamin K antagonist oral anticoagulant, including Xarelto, in a patient's blood; no FDA-approved or scientifically validated test to predict who is at high risk for bleeds from any anticoagulant medicine, including Xarelto; and no scientific evidence supporting the use of PT testing to make clinical decisions," the company said in an email.

Plaintiffs' attorney Brent Wisner, of Baum, Hedlund, Aristei & Goldman, noted that there has been a narrowing of claims in cases where an adverse event is on the label. He said there are two types of cases: those in which changes are later made to a product's label, and those in which FDA hasn't said anything about an adverse event. In the latter, you must argue not just that a company failed to warn "but didn't do something important scientifically that FDA wasn't aware of," said Wisner, who was not involved in the Xarelto litigation.

Wisner noted that the defense side often argues that there is no good evidence that the plaintiff injury was cause by the product. But he said there may be "evidence there was something shady, that they did something wrong." He added that that is why plaintiffs won a verdict in the testosterone trial.

KESSLER TESTIFIES AGAINST ANDROGEL PROMOTION

The jurors in that case, Mitchell v. AbbVie, faulted AbbVie for its promotion of AndroGel as a treatment for low testosterone, known as "Low T." The case is the first bellwether trial in testosterone replacement therapy multidistrict litigation. Approximately 4,260 claims are consolidated in the MDL and approximately 240 claims are pending in state courts naming AbbVie, **Allergan PLC**, **Endo Pharmaceuticals Inc.**, **Eli Lilly & Co.**, and Pfizer as defendants.

> "Plaintiffs' increasing focus on promotion is part of the "reptile theory" of prosecution in which plaintiffs "appeal to the reptilian brain of the juror," that is, to their emotions and fears rather than their rational side. – Reed Smith's James Beck

Following the Mitchell trial, the plaintiff filed a motion seeking an additional award of $136,408 in economic damages. The plaintiff's attorneys said the testimony at trial showed AbbVie knew there was no evidence that AndroGel was safe and effective for "age-related hypogonadism." They cited the testimony of former FDA Commissioner David Kessler that the agency had told AbbVie at the time of the drug's initial approval that it would be misleading to promote it for that condition.

"Dr. Kessler noted that the growth of the TRT [testosterone replacement therapy] market generally and AndroGel sales specifically were not due to an increase in diagnosis of FDA-approved conditions for AndroGel," the Aug. 21 filing states. "Ultimately, Dr. Kessler opined that AbbVie's marketing and promotional efforts for AndroGel were 'false and misleading.'"

AbbVie filed a motion for a judgment as matter of law before the verdict arguing that there is no clear and convincing evidence that the plaintiff, Jesse Mitchell, and his prescribing physician saw or relied on any false representation. Mitchell claimed he suffered a heart attack from taking AndroGel.

Kessler "did not identify a single purportedly 'false' branded AndroGel ad during his direct exam" and identified "no instance where the FDA told the company it was marketing off-label or 'over-promoting,'" the filing states.

AbbVie filed an Aug. 30 motion asking the court to reconsider the admissibility of marketing materials and post-injury evidence, arguing that it led to the jury verdict that found no compensable loss but awarded punitive damages "that were tethered to nothing."

AbbVie noted that a Cook County Court ruled against the admission of such evidence in a state court case, Couch v. AbbVie, and in August the jury issued a verdict for AbbVie. Judge Matthew Kennelly, of the US District Court for the Northern District of Illinois, denied AbbVie's motion in a Sept. 13 order.

Plaintiffs have been targeting a drug's promotion more often in product liability cases. James Beck, counsel at Reed Smith, said it is part of the "reptile theory" of prosecution in which plaintiffs "appeal to the reptilian brain

of the juror," that is, to their emotions and fears rather than their rational side.

Plaintiffs' attorneys "try to convince jurors that rules were broken" and that there is a safety issue, he said.

EXPERT TESTIMONY HURDLE

On the winning side of the ledger for pharma, in January, a district court granted Pfizer's motion for summary judgment in Lipitor (atorvastatin) litigation, dismissing substantially all the cases pending in the MDL. Plaintiffs claimed that Lipitor caused their diabetes. South Carolina District Judge Richard Gergel excluded plaintiffs' expert general causation testimony on three of four Lipitor dosages. Plaintiffs have appealed to the US Court of Appeals for the Fourth Circuit.

Pfizer won a similar ruling in Zoloft (sertraline) litigation. In April 2016, a district judge granted Pfizer summary judgment, dismissing most of the remaining cases, after excluding plaintiffs' expert witness. In a June opinion, the US Court of Appeals for the Third Circuit affirmed the decision. The court concluded that the plaintiffs' general causation witness, Dr. Nicholas Jewell, applied different techniques to subsets of the data and inconsistently discussed statistical significance and thus did not reliably analyze the weight of the evidence.

"As a gatekeeper, courts are supposed to ensure that the testimony given to the jury is reliable and will be more informative than confusing," the appeals court stated. "Dr. Jewell's application of his purported methods does not satisfy this standard."

Beck said that while there has been an uptick in the exclusion of witness testimony, it is an individual case-by-case occurrence.

Wisner stated that the standards for expert witness testimony are applied differently in different courts. "You see forum shopping because the law is applied differently," he said.

That may change with a recent US Supreme Court decision restricting where cases can be filed. In June, the court ruled that state courts cannot exercise specific jurisdiction over personal injury claims against companies brought by out-of-state residents. The case, Bristol-Myers Squibb v. Superior Court of California, involved a mass tort suit in which plaintiffs alleged BMS misrepresented the safety of *Plavix* (clopidogrel). *(Also see "Liability Win For Industry As US Supreme Court Curtails Forum-Shopping" - Pink Sheet, 19 Jun, 2017.)*

> On the winning side of the ledger for pharma, a district court granted Pfizer's motion for summary judgment in Lipitor litigation, dismissing substantially all the cases pending in the MDL.

Beck said the ruling will benefit pharma as it will result in smaller mass torts so plaintiffs will be less likely to hide weak cases in the litigation.

POST-VIOXX CASES REMAIN SMALLER

Except for the Xarelto MDL, the cases currently in multidistrict litigation are much smaller than a decade ago when **Merck & Co. Inc.**'s *Vioxx* (rofecoxib) and **Eli Lilly & Co.**'s *Zyprexa* (olanzapine) were each the subject of more than 25,000 lawsuits.

The size of the litigation was driven by the large population taking the drugs and the background rate of the adverse event. The withdrawal of Vioxx from the market in 2004 due to increased cardiovascular events contributed to the huge number of cases. Merck settled the bulk of the litigation in November 2007 for $4.85bn and Lilly paid $1.2bn to resolve most of the Zyprexa litigation. *(Also see "Product Liability Forecast: More Suits, Smaller Scale" - Pink Sheet, 1 Jul, 2009.)*

At the time, they were the largest settlements following the record-setting $21.1bn that **Wyeth** (now Pfizer) set aside to resolve litigation over its fen-phen diet drugs *Redux* and *Pondimin*. More recently, in 2014, Bayer reached agreements to settle approximately 9,200 claims alleging venous clot and other injuries from its contraceptives *Yasmin* and *Yaz* (drospirenone/ethynyl estradiol) for about $1.8bn. And in 2015, Takeda agreed to settle most suits alleging its diabetes drug *Actos* (pioglitazone) causes bladder cancer for approximately $2.4bn. *(Also see "Takeda Offers $2.4bn No-Fault Settlement Of Actos Suits" - Scrip, 29 Apr, 2015.)*

Companies are also embroiled in cases outside federal multidistrict litigation that can be costly. For example, in June an Illinois jury issued a verdict against AbbVie ordering it to pay $15m in compensatory damages to a boy with spina bifida whose mother took *Depakote* (dvalproex) during her pregnancy. And this month, the Missouri Supreme Court upheld a $38m jury award to a girl with spina bifida. AbbVie noted in a recent SEC filing that approximately 675 claims are pending in federal and state courts alleging the company did not adequately warn about certain injuries, primarily birth defects, arising from use of Depakote.

GlaxoSmithKline PLC has faced litigation alleging injuries from use of its antidepressant *Paxil* (paroxetine) during pregnancy. The company has reached agreements to settle the majority of US claims, while several cases have been dismissed and several others are pending in state courts. On Sept. 14, US District Judge William Hart of the Northern District of Illinois affirmed a jury verdict ordering GlaxoSmithKline to pay $3m to the widow of an attorney who committed suicide after taking a generic version of Paxil. *(Also see "FDA Label Decisions On Paxil Don't Deter Verdict Against GSK In Suicide Case" - Pink Sheet, 22 Apr, 2017.)*

In over-the-counter product litigation, juries have issued a string of verdicts against J&J for injuries alleged be caused by its talcum powder products. Most recently, a Los Angeles jury awarded $417m to a terminally ill patient who claimed her ovarian cancer was caused by long term use of the talcum powder.

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Top Pharma Product Liability Cases

When numerous suits alleging similar facts are pending in various federal courts, the US Judicial Panel on Multidistrict Litigation often consolidates them in one court for pre-trial proceedings. Below is a list of prescription drug products in multidistrict litigation.

DRUG PRODUCT	HISTORY	STATUS
Bristol-Myers Squibb/ Otsuka Pharmaceutical Co.'s Abilify (aripiprazole)	In May 2016, FDA issued a warning that compulsive or uncontrollable urges to gamble, binge eat, shop and have sex have been reported with use of aripiprazole and to have stopped when the medicine was discontinued or the dose reduced. FDA added new warnings about these compulsive behaviors to the labeling and patient medication guides.	More than 270 cased have been filed in federal and state courts alleging the atypical anti-psychotic caused compulsive gambling behaviors. In July, BMS and Otsuka filed a motion for summary judgment on general causation and a motion to exclude expert witness testimony.
Daiichi Sankyo and Forest Labs' Benicar (olmesartan)	In July 2013, FDA warned that the blood pressure drug can cause intestinal problems known as sprue-like eteropathy and approved label changes to include this concern.	Daiichi announced on Aug. 1 that it has agreed to settle the litigation on behalf of Daiichi and Forest (now Allergan). There are almost 2,300 cases pending. The settlement requires at least 95% of all eligible litigants and claimants to opt-in to the settlement program, which is capped at $300m.
Bristol-Myers Squibb/ Pfizer's Eliquis (apixaban)	Plaintiffs allege the anticoagulant was defectively designed, the label failed to warn of bleeding risk, and that there is lack of a reversal agent. As of July 17, there were more than 100 cases pending in state and federal courts and 61 cases had been dismissed from the MDL.	In May, Southern District of New York Judge Denise Cote dismissed the lead case, Utts v. Bristol-Myers Squibb, finding that its claims are preempted by federal law and that the Eliquis label is adequate. She requested plaintiffs in remaining 55 cases to file amended complaints. In June, she dismissed 24 cases for failing to do so and plaintiffs voluntarily dismissed 14 actions. Several other plaintiffs dismissed their complaints and refiled in Delaware state court.
AstraZeneca's Farxiga (dapagliflozin)	In June 2017, FDA strengthened the warning about risk of acute kidney injury with Farxiga and J&J's Invokana. *(Also see "FDA Warning On SGLT-2 Drugs Raises Specter Of Labeling Change" - Pink Sheet, 15 May, 2015.)* In December 2015, FDA added a warning of the risk of detoacidosis and serious urinary tract infections to the label of all SGLT2 inhibitors and required manufacturers to conduct a post-marketing study. *(Also see "SGLT2 Inhibitors' Warning On Ketoacidosis Recommends Drug Holidays" -Pink Sheet , 4 Dec, 2015.)*	Court will conduct four bellwether trials. The parties are to submit a list of proposed bellwether cases by Nov. 6.
Fluoroquinolone	In August 2013, FDA required the drug labels and medication guides for all fluoroquinolone antibacterial drugs to better describe the side effect of peripheral neuropathy.	Approximately 267 cases are pending in the MDL in Minnesota district court, 182 of which involve only Bayer. Actions allege that fluoroquinolone antibiotics – principally Bayer's Cipro and Avelox and Janssen's Levaquin – cause or substantially contribute to the development of irreversible peripheral neuropathy and that defendants' warnings were inadequate. Discovery is underway. Plaintiffs dispute the number of treating physician depositions Bayer is seeking for each bellwether case.
Merck's Fosamax (alendronate)	In 2005, FDA requested all oral bisphosphonate manufacturers to include a precaution about the risk of osteonecrosis of the jaw (ONJ) and musculoskeletal pain. In October 2010, FDA required labeling of bisphosphonates to state the uncertainty of the optimal duration of use for osteoporosis and required a REMS medication guide that described the risk for atypical fractures of the thigh.	In 2014, Merck and Plaintiffs' Steering Committee finalized a $27.3m master settlement agreement for 1,200 plaintiffs claiming Fosamax caused ONJ. Approximately 15 cases are pending in federal and state courts.

DRUG PRODUCT	HISTORY	STATUS
Incretin-Based Therapies	In March 2013, FDA issued a drug safety communication about the drug class, saying it was evaluating unpublished new findings by a group of academic researchers. In February 2014, FDA and European regulators wrote a piece in the New England Journal of Medicine that available data were "inconsistent" with assertions of a causal link between these drugs and pancreatic adverse events.	Plaintiffs allege one or more of four anti-diabetic incretin-based medications – Merck's Janumet and Januvia, Bristol-Myers Squibb/AstraZeneca's Byetta and Novo Nordisk's Victoza – caused pancreatic cancer. In November 2015, the MDL and California state court granted summary judgment to defendants on grounds of preemption. These rulings resulted in dismissal of approximately 1,175 of 1,215 claims. Plaintiffs are appealing the preemption rulings.
J&J's Invokana (canaglifozin)	In June, FDA strengthened the warning about risk of acute kidney injury with Invokana and AstraZeneca's Farxiga.	As of July 2, approximately 800 plaintiffs had filed claims with respect to Invokana. The first trial is expected to be scheduled for September 2018.
Bristol-Myers Squibb/ Sanofi's Plavix (clopidogrel)	In November 2014, FDA announced it was evaluating preliminary data from a clinical trial showing treatment for 30 months with aspirin plus either Plavix or Effient (prasugrel) following implantation of drug-eluting coronary stents decreased the risk of heart attacks and clot formation in stents, but increased overall risk of death compared to 12 months of treatment. In October 2015, FDA said its review found that long-term use of Plavix does not increase or decrease overall risk of death in patients with, or at risk for, heart disease.	More than 5,300 claims have been filed in federal and state courts. Plaintiffs allege firms falsely touted Plavix as providing superior cardiovascular benefits to those of aspirin and misrepresented or failed to disclose serous risks of heart attack, stroke, internal bleeding or death. Discovery in MDL in New Jersey is ongoing. The first case scheduled to begin on Jan. 16, 2018.
Merck's Propecia and Proscar (finasteride)	Plaintiffs allege use of the male pattern baldness treatment causes persistent sexual dysfunction in a subset of men.	Approximately 1,190 federal and state lawsuits have been filed by plaintiffs alleging they experienced persistent sexual side effects following cessation of treatment with the drugs and approximately 40 plaintiffs allege the drugs caused or can cause prostate cancer, testicular cancer or male breast cancer. The first bellwether tranche in the MDL is to be ready for trial by March 2018.
Proton-Pump Inhibitor Products (No. II)	Plaintiffs allege they developed kidney-related injuries as a result of ingesting certain proton pump inhibitors.	In August 2017, federal actions against Pfizer, involving its Nexium 24HR and Protonix, and other manufacturers were transferred to an MDL in New Jersey District Court.
Taxotere (docetaxel)	Plaintiffs in more than 200 actions allege they experienced permanent hair loss as a result of using the chemotherapy drug and that defendants failed to warn patients of this possible side effect and marketed Taxotere as more effective than other chemotherapy drugs when other drugs were equally effective without the associated permanent hair loss. Defendants include Sanofi, Sandoz, Accord Healthcare, Hospira, Sun Pharma and Actavis.	First phase of discovery regarding the design, testing, manufacturing, marketing and labeling of Taxotere is to conclude on Feb. 6, 2018. Four cases will then be nominated to proceed to the second phase of discovery and the court will select one plaintiff for the first trial date and three alternative plaintiffs. A jury trial is to begin the week of Sept. 24, 2018.
Testosterone Replacement Therapy	In January 2014, FDA announced it was investigating the risk of stroke, heart attack and death in men taking testosterone products after two observational studies suggested an increased risk of cardiovascular events in men prescribed the drugs. In September 2014, FDA advisory committees recommended that manufacturers be required to conduct randomized controlled trials to assess CV risk and that trials should be conducted for a "Low T" indication.	AbbVie, Allergan, Endo, Lilly and Pfizer are the subject of more than 4,000 claims alleging TRT caused injuries, primarily heart attacks, strokes and blood clots. In the first bellwether case to go to trial, a jury issued July 24 verdict finding Abbott made false representations about AndroGel and awarding plaintiff $150m in punitive damages.

DRUG PRODUCT	HISTORY	STATUS
Pfizer's Viagra (sildenafil) and Lilly's Cialis (tadalafil)	Plaintiffs allege the erectile dysfunction drugs increase the risk of developing melanoma and that defendants failed to warn of the risk.	Initial complaints against Pfizer were transferred to the Northern District of California in April 2016. Cases against both Lilly and Pfizer were transferred to the MDL in December. Litigation is now in discovery.
Janssen and Bayer's Xarelto (rivaroxaban)	Plaintiffs allege they suffered severe bleeding and other injuries from the blood thinning drug, which was approved in 2011.	As of July 2, approximately 20,000 plaintiffs had filed claims in the MDL and state courts. Janssen won jury verdicts in the first three bellwether trials.
Bayer's Yasmin and Yaz (drospirenone/ethinyl estradiol)	An FDA epidemiologic study found that contraceptives containing drospirenone have a higher risk for blood clots but in December 2011 two FDA advisory committees concluded that the benefits of the drugs outweigh the risks.	Cases were transferred to an MDL in 2009. In 2015, Bayer settled approximately 9,200 claims for about $1.8bn with approximately 4,000 claims left pending. 33 cases were to proceed to trial.
GlaxoSmithKline's Zofran (ondansetron)	In September 2011, FDA issued a safety communication that abnormal heart rhythms may be associated with the anti-nausea drug. In June 2012, it announced that preliminary results from a clinical study suggested that a 32 mg IV dose may affect the electrical activity of the heart (QT interval prolongation), which could pre-dispose patients to develop an abnormal and potentially fatal heart arrhythmia. In December 2012, the agency announced the 32 mg IV dose would no longer be marketed.	Plaintiffs claim GSK failed to warn of risk of birth defects with use of the drug during pregnancy and marketed it off-label. As of July 12, there were 381 federal cases and 15 state court cases. 130 MDL cases have been voluntarily dismissed. Discovery is underway. In April, a Massachusetts district court judge denied defendants' motion to dismiss fraud-based claims.
Pfizer's Zoloft (sertraline)	In December 2011, FDA issued a drug safety communication saying there were conflicting findings in studies evaluating the risk of persistent pulmonary hypertension of the newborn from use of a selective serotonin reuptake inhibitor (SSRI) during pregnancy. It advised health care professionals not to alter their current clinical practice of treating depression during pregnancy.	Plaintiffs allege the antidepressant causes birth defects in children born to women who took the drug while pregnant. In April 2016, a district court granted Pfizer's motion for summary judgement, dismissing most remaining claims that had not been voluntarily dismissed. In June 2017, the Third Circuit affirmed the district court's decision.

EMA Paints Nightmare Scenario Of EU System 'Unraveling' If Relocation Goes Wrong

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If the European Medicines Agency is relocated to any one of the eight EU candidate cities that its staff believe do not meet the agency's requirements and cannot ensure business continuity, fewer than 30% of existing employees would move with it to the new location.

In such a case, the EMA has warned, the agency would be unable to operate, there would be "permanent damage" to the regulatory system and the EU single market for medicines would "unravel."

On the other hand, if it were to go to one of five candidate cities that are deemed to meet its requirements, more than 65% of staff would potentially go along too, with the result that new drug approvals and safety monitoring would be largely maintained, albeit with some delays possible.

The conclusions come out of a staff survey EMA conducted in early September to help it work out how to compensate for varying degrees of loss of staff when the agency has to leave its London HQ for another EU member state as a result of Brexit. "The results of the survey emphasize the importance of the upcoming decision on the EMA's future seat as the retention of skilled and experienced staff is crucial for the agency's continuity of operations," the EMA commented. The European Commission is due to publish its assessment of the 19 bids to become EMA's new host country by the end of this week (deadline Sept. 30).

None of the 19 candidate countries is identified in the results published by the EMA.

"The outcome that was shared with staff earlier this month revealed that for certain locations staff retention rates could be significantly less than 30%. This would mean that the agency is no longer able to function and, as there is no backup, this would have important consequences for public health in the EU. In a best-case scenario, EMA could keep up to 81% of its workforce."

If staff losses exceed 70%, the EMA "would be unable to operate, causing a public health crisis and permanent damage."

LOCATION A KEY FACTOR FOR 65%

Staff were asked to say whether they were "very likely," "likely," "unlikely" or "very unlikely" to move to each of the 19 candidate cities, based on their assessments of the cities' official bids and whether they would meet their (and their family's) needs and expectations. A total of 92% of staff completed the survey, and of those, 65% said the new EMA location would be a "determining factor" in whether they relocated.

To reach their decisions, people used information provided by member states but were also "highly motivated" to do their own research into factors such as the availability and quality of housing, educational possibilities, and job opportunities for partners in the candidate cities.

The results showed that if the agency were to move to the most popular candidate country (not named by the EMA), 81% of staff would relocate, while the second and third most popular cities would allow the agency to retain 76% and 73% of staff, respectively.

At the other end of the scale, a move to the least popular destination city would see the agency lose 94% of its current staff, while the second and third least favored cities would result just 8% and 10% of staff staying, respectively.

FOUR KEY SCENARIOS

The 19 cities were organized into four groups based on likely staff retention rates and taking into account the priority activity categories outlined in the agency's business continuity plan last month. *(Also see "EMA Suspends Some Activities & Warns That High Job Losses Could Halt Its Operations" - Pink Sheet, 2 Aug, 2017.)*

This produced the following scenarios for each of the four groups:

Group 1 – retention rate of 65% or more (five cities). Cities in group 1 are judged to meet EMA requirements, ensuring it is operational on time. Depending on the extent of staff loss, new drug approvals and monitoring are largely maintained, possibly with some delays. Progress on public health initiatives like antimicrobial resistance and cooperation with health technology bodies would slow.

Group 2 – retention rate of 50%-64% (five cities). The location meets the requirements but there are some concerns about getting the agency up and running on time. Patients may have to wait longer for new medicines, and safety monitoring may have to be ring-fenced and resources re-routed. "Public trust in the system starts to erode," Europe risks losing its appeal and its cutting edge in research, and new legislation on clinical trials, veterinary medicines and medical devices will be "significantly delayed."

Group 3 – retention rate of 30%-49% (one city). The location only partially meets EMA requirements and raises "major concerns as regards EMA business continuity." Patients are at "serious risk" due to delays in medicines access and poor safety monitoring, some life-saving medicines may not be available in some countries, and there would be a "loss of innovation."

Group 4 – retention rate below 30% (eight cities). The city does not meet EMA requirements and does not ensure business continuity. The agency would be unable to operate, causing a public health crisis. The EU single market would "unravel" as there would be no centralized marketing authorizations and medicines would have to be imported from third countries such as the US and Japan. Patients would be "exposed to side-effects – deaths – litigation." This scenario would require emergency legislative measures at both EU and national levels. "Permanent damage" would be caused to the regulatory system.

NAMING NO NAMES

While none of the candidate countries is identified in the results published by the EMA, there are suggestions that staff may be less willing to move to one or another of the eastern European countries that have put in a bid to host the agency.

A number of LGBT (lesbian, gay, bisexual, trans) employees recently wrote to EMA Executive Director Guido Rasi, European Council President Donald Tusk, European Commission President Jean-Claude Juncker and European Parliament President Antonio Tajani saying they were worried about their rights and those of their partners being affected in certain EU member states. *(Also see "EMA's Future Home: Assessment Of Bids Nears Completion Amid Growing Staff Concerns" - Pink Sheet, 21 Sep, 2017.)* Member states such as Bulgaria, Poland, Slovakia and Romania, which have all submitted bids, do not recognize formal same-sex relationships. Slovakia and Bulgaria, among others, have been making much of the fact that they do not currently host an EU agency, saying this should make them a priority candidate.

Rasi and other EMA delegates have been visiting various EU cities on the bidding list, including the Greek capital Athens, as well as Amsterdam, Barcelona, Copenhagen, Malta, Milan, and Vienna, according to the EU Observer. The other EU agency that must leave London because of Brexit – the European Banking Authority – has reportedly made no such visits.

From the editors of Scrip Regulatory Affairs. Published online September 26, 2017

Patient Experience Data May Require Separate Label, Genentech Suggests

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The increasingly patient-centric approach to drug development and regulation may necessitate the development of separate product labeling for patients, one industry researcher believes.

Speaking at a Sept. 18 workshop on the US FDA's benefit/risk assessment framework, Alicyn Campbell, global head of Patient-Centered Outcomes Research for Oncology Product Development at **Genentech Inc.**, questioned whether the time has come for separate, patient-friendly labeling to reflect the growing body of patient-reported data on drug side effects, efficacy and overall experience in a way that is understandable to those likely to use the treatment.

Data on patient experiences, outcomes and preferences is "descriptive, it's analytic. It's large," Campbell said. "We kind of have a space problem" fitting it into the current product labeling framework.

Presenting such data in a way that is understandable to patients also is important, she said, noting for example that bar charts with descriptive information are a more patient-friendly approach than hazard ratios.

Systematic inclusion of the patient voice in clinical trials creates large amounts of data that frequently requires descriptive analysis and presentation at the item/concept level "because if I'm a patient who really cares about those side effects of interest, we do need to get into that level of detail," she said.

HEALTH LITERACY POSES A COMMUNICATIONS HURDLE

Campbell said there often is an expectation that although patient-reported data may not make it into labeling, such information is accessible to patients through published manuscripts.

However, "there's a cost associated with downloading a manuscript. There's health literacy and understanding how to search PubMed, and also just the way we present data. I really like hazard ratios, too, but when we talk to patients they tend to tell us it's not intuitive to them."

> Systematic inclusion of the patient voice in clinical trials creates large amounts of data that frequently requires descriptive analysis and presentation at the item/concept level, Genentech's Campbell said.

"We do need to have a better way … to communicate this to patients in a way they understand and not expect them, when they have a lot going on in their lives and a short amount of time to choose your treatment, … to have the health literacy ability to really find and interpret a purely academic manuscript."

FDA and stakeholders have long struggled with how to communicate drug information to patients precisely but accessibly, especially in the context of material that would be dispensed along with a prescription. *(Also see "US Patient Medical Information Rule: Will It Be Delayed Again?" - Pink Sheet, 1 Mar, 2017.)*

MORE DATA COMING WITH CURES ACT

Another reason to start thinking now about separate patient labeling is because of a 21st Century Cures Act provision that highlights the role of patient experience data in FDA's drug approval decisions.

Under Section 3001 of the statute, which was signed into law Dec. 13, following approval of a new drug application (NDA) or biologic license application (BLA) FDA "shall make public a brief statement regarding the patient experience data and related information, if any" reviewed as part of the application. The provision applies to NDAs and BLAs submitted on or after June 12.

"With 21st Century Cures, we're only going to be seeing more information," Campbell said.

It is unclear how FDA intends to implement Sec. 3001; the agency's chart of 21st Century Cures Act deliverables does not reflect any details about the agency's plans.

However, the agency has previously said it is working to figure out how to present patient-reported outcomes (PRO) data within the existing confines of its current labeling regulations as well as through other formats. *(Also see "Will Patient-Reported Data Require New Drug Labeling Framework?" - Pink Sheet, 5 May, 2017.)*

HYCELA LABELING AS A MODEL?

Labeling for Genentech's new formulation of *Rituxan* could serve as an early example of how FDA might handle patient experience data under Sec. 3001.

Rituxan Hycela (rituximab/hyaluronidase) is a subcutaneous form of the CD20-directed cytolytic antibody that previously was approved only for intravenous infusion. FDA approved the BLA June 22

for treatment of follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia. *(Also see "Keeping Track: Cardio, Antibiotic Approvals Put FDA Over Last Year's Novel Drug Count" - Pink Sheet, 26 Jun, 2017.)*

The Clinical Trials section of Hycela labeling includes a subhead for "Patient Experience" that reflects data from a dedicated patient preference study in previously untreated adult patients outside the US. The study evaluated patient preference and satisfaction for the subcutaneous route of administration compared to intravenous infusion. The data were included in Genentech's briefing document for an FDA advisory committee review of the new formulation. *(Also see "Subcutaneous Rituximab Seems Headed For US FDA Advisory Panel OK" - Pink Sheet, 28 Mar, 2017.)*

In the preference study, patients were randomized to standard chemotherapy regimen and either Rituxan Hycela at treatment cycles 2-4 or rituximab by intravenous infusion at cycles 1-4. After the fourth cycle, patients crossed over to the other route of administration for the remaining four cycles.

"After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of Rituxan Hycela over intravenous rituximab and the most common reason was that administration required less time in the clinic," labeling states.

> In the patient preference study, 77% of subjects favored subcutaneous administration with Rituxan Hycela over intravenous rituximab, with the most common reason being less time in the clinic.

"After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration," labeling states. "Forty-eight of 620 patients (7.7%) had no preference for the route of administration. Twenty-nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire."

Genentech told the Pink Sheet that Hycela is the first time that a "Patient Experience" section has been included in a US product label.

"These data were part of an overall package of data submitted to the FDA for their review of the Rituxan Hycela BLA," the company said in a statement. "The data are presented in a text format, which was considered the most appropriate format for the US [prescribing information] during the assessment of the BLA."

However, at the FDA meeting on the benefit/risk framework, Campbell presented more data from the patient preference study in the form of a bar chart showing more reasons why patients preferred subcutaneous rituximab over intravenous.

While the top-line preference data were included in the Hycela labeling "in a verbal, descriptive format rather than in a bar chart format. … It's just something to think about as we continue to collect this data," she said. "There needs to be careful consideration not only about how to incorporate it into the framework, but also how we're communicating it to patients because in the end they're also making an individual risk/benefit assessment about the best treatment choice for themselves and their family."

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The Return of The Pazdur Moment

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The meeting was going smoothly for Pfizer. Then came the "Pazdur moment."

The "Pazdur moment," of course, refers to those times when Oncology Center of Excellence Director Richard Pazdur decides to turn on his microphone to weigh in on the key issue at hand during an Oncologic Drugs Advisory Committee meeting. What he says and how he says it typically has an impact on the direction of the meeting.

For **Pfizer Inc.**, the "Pazdur moment" came Sept. 19 just before the panel was getting ready to vote on expanding *Sutent's* (sunitinib) label for adjuvant use post nephrectomy.

Richard Pazdur, director of FDA's Oncology Center of Excellence

Talk shifted from the main voting question on benefit-risk to consensus treatment guidelines. Pazdur's microphone came on and he cut the conversation off with his special knack for directness.

"That's somewhat tangential to this whole meeting, what goes into consensus reports. I really want to emphasize that that should not go into your decision-making, what outside groups do. We have no control over that. We don't know what their meeting schedules are. Those are totally extraneous, so let's put that aside."

Pazdur was not done. He pursued the discussion that Mayo Clinic's Lance Pagliaro had offered on "non-pre-specified, non-randomized subgroup sets" of exploratory analyses from a trial that showed no benefit on the surrogate of disease-free survival and giving those results more weight than they deserve.

"This is *very* dangerous territory to go into," he said. "We had a great deal of internal debate of whether or not to present these findings here because it is a non-randomized population in terms of these subgroups so you can't make any inferences as far as treatment effect on these populations."

Then Pazdur turned to the key question in his mind for the committee: why is a substantial disease-free survival (DFS) effect in renal cancer different from other oncology settings where FDA has approved drugs with similar efficacy profiles?

"The thing I have to hear from the committee is, we've used DFS in multiple adjuvant disease settings of similar magnitude. If you're planning on voting 'no' or have some qualms on this, I have to know from you what's different about this disease setting from colon cancer, melanoma, breast cancer."

"We have to have a consistent regulatory policy here. We have to know if there's a difference with this disease that would preclude us from using DFS that was seen in a well-controlled randomized trial."

From that point, the advisory committee took a sharp turn (maybe inadvertently) and resulted in an even split on approvability of the new indication (6-6). *(Also see "Pfizer's Sutent Expanded Indication: 'Hope' Or 'False Hope'?" - Pink Sheet, 19 Sep, 2017.)*

That tie vote in itself is noteworthy, ending a streak of eight consecutive ODACs that ended with a recommendation for approval – an astonishing turn from the pattern of the last five years, where ODAC voted "yes" a total of just four times. *(Also see "Puma Breaks A Long Losing Streak For Sponsors At ODAC" - Pink Sheet, 3 Jun, 2017.)*

Coincidentally or otherwise, the *Sutent* meeting was also the first time in 2017 where Pazdur spoke up to opine on a key point of the discussion. So it was nice to hear his voice again.

ANOTHER BOB TEMPLE?

The Pazdur Moment was also a refresher of just how good Pazdur is at what he does. The only other FDA official who seems to share the same gravitas when it comes to discussing key regulatory concepts and precedents in the context of advisory committees is Bob Temple, the drug center's deputy director for clinical science.

Temple and Pazdur have very different styles. Pazdur will tell a sponsor or panel member to cut to the chase or reject an argument out of hand while Temple has always seemed to relish a lengthy debate that may digress from the issue at hand.

> Like his colleague Bob Temple, Pazdur has a fundamental love of the job as both gatekeeper for the newest most exciting advances in medicine and protector of the public health.

But there is a deeper and more important similarity that goes beyond advisory committees and more to the core of FDA's mission and how they view drug development. On FDA's organization chart, Pazdur has recently ascended to head the new congressionally chartered Oncology Center of Excellence. But after nearly 20 years at the agency, Pazdur is also joining that special position that Temple has held as something like an internal FDA oracle: the protector and explainer of FDA review policies.

In that role, Pazdur and Temple share some important commonalities. For example, Pazdur has always stressed the importance of the randomized clinical trial as the bedrock of a strong oncology application. Randomized clinical trial design and different strategies to enhance them is Temple's joie de vivre.

Still, both Temple and Pazdur have also embraced FDA's fundamental flexibility under its statutory authorities. In recent years, Pazdur has welcomed small randomized "home run" trials and single-arm trials where large response rates are demonstrated as adequate for FDA approval. In the same vein, every time there is a new law or idea presented with the goal of accelerating approval, Temple has said repeatedly in different settings: "we can already do that."

They also share a fundamental love of the job as both gatekeepers for the newest most exciting advances in medicine and protectors of the public health.

When Temple has been asked why he has remained at FDA, he often says because the job is "fun." *(Also see "FDA's Temple of Wisdom: The Dean of Drug Development" - Pink Sheet, 1 May, 2007.)* Pazdur also clearly has fun at the job and has been thinking through what FDA should look like over the long-term. The Oncology Center of Excellence is part of that academic model he talks about from time to time.

In fact, Pazdur's new role likely explains his more hands-off role at advisory committee meetings this year; he has been deferring to others on the team of review managers he has built over the years.

But he has also joined Temple as the voice and intellect of FDA drug reviews in a larger sense. That's the larger importance of those "Pazdur moments."

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Humira Biosimilar Settlement Could Be Model For Other Disputes

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AbbVie Inc.'s agreement with **Amgen Inc.** clears the way for Amgen to launch its biosimilar to AbbVie's *Humira* (adalimumab) in Europe next year and in the US in 2023. While the deal appears similar to classic patent settlements between brand-name and generic companies, the terms are unknown and it is uncertain whether other biosimilars disputes will follow this path.

Under the settlement, announced Sept. 28, AbbVie will grant non-exclusive patent licenses to Amgen for the use and sale of its Humira biosimilar worldwide, on a country-by-country basis. Amgen said it expects to launch the biosimilar in Europe as *Amgevita* on Oct. 16, 2018 and in the US as *Amjevita* (adalimumab-atto) on Jan. 31, 2023.

Amgen will pay AbbVie royalties but the amount, as well as other terms of the agreement, were not disclosed. All pending litigation between the companies will be dismissed. AbbVie said in a release that Amgen acknowledged the validity of its intellectual property related to Humira.

"We are pleased to have reached this settlement with Amgen which respects the breadth and strength of our intellectual property portfolio," AbbVie Exec VP External Affairs and General Counsel Laura Schumacher said.

Approved for several inflammatory conditions, including rheumatoid arthritis and psoriasis, Humira is the world's top-selling drug with worldwide revenue of $16.1bn in 2016.

FDA approved Amjevita in September 2016. Just before the approval, AbbVie filed suit against Amgen claiming the biosimilar infringes 61 of the more than 100 patents that cover its anti-TNF-alpha monoclonal antibody. Amgen opted to limit the number of patents to be litigated in the first wave of litigation and only 10 were cited in the complaint. They have expiration dates ranging from 2022 to 2033. *(Also see "AbbVie v. Amgen Round One: Humira Biosimilar Infringes 10 Patents, Suit Claims" - Pink Sheet, 5 Aug, 2016.)*

While the agreement delays Amgen's marketing until seven years after approval, it provides time to iron out biosimilar market access challenges.

Last month, the agency approved **Boehringer Ingelheim GMBH**'s Humira biosimiar *Cyltezo* (adalimumab-adbm) and AbbVie filed a similar suit against BI. At the time, BI said it could not speculate on the launch timing of Cyltezo or comment on the litigation with AbbVie. *(Also see "Humira Biosimilar: Boehringer Faces Same Launch Hurdles As Amgen" - Pink Sheet, 28 Aug, 2017.)*

It is unclear how the settlement will impact BI and if BI and other Humira biosimilar sponsors will pursue a similar deal with AbbVie.

In a same-day email to investors, Evercore ISI analyst Umer Raffat questioned whether AbbVie and Amgen have an understanding that Amgen will have certain lead time over additional settlements down the road. "In a more classic ANDA settlement setting, you would have expected that," he said. But he noted that there are no "first to file" 180-day market exclusivities here as there are in ANDA litigation.

Elaine Herrmann Blais, a partner at Goodwin Procter, said it would be surprising if the agreement limits Amgen's entry if another Humira biosimilar enters before 2023 and she could imagine it includes an accelerant to move the date forward in such a situation.

Blais said the agreement offers a test case to see if the Federal Trade Commission takes an interest in biosimilar settlements as it has with Hatch-Waxman litigation deals. Brand and generic companies are required to submit their patent dispute settlements to the FTC, which assesses whether they are anticompetitive. The agency has filed numerous so-called "pay-for-delay" suits alleging the deals blocked other generics from entering the market.

Chad Landmon, a partner at Axinn, Veltrop & Harkrider, said the worldwide nature of the settlement is different than settlements in the pharma space, which almost always carve out patent disputes outside the US.

One question, he said, is whether other Humira biosimilar sponsors will get similar deals. "In the pharma space, once one generic company settles, you typically see the rest of them settle on similar terms," Landmon said. "Here we don't know if that will be the case."

He noted that while pharmaceuticals lose about 90% of their market when generics enter, that market drop is not expected to occur with biosimilars and inno-

vators may care more about limiting how many biosimilars get on the market.

LAUNCH DATE AND LITIGATION TIMELINE

Amgen has previously said it did not plan to launch Amjevita until at least 2018 given the complexity and pace of the litigation. Amgen was unsuccessful in its efforts to knock out two key Humira formulation patents through inter partes review (IPR) petitions. The Patent Trial and Appeal Board (PTAB) issued final written decisions upholding both patents, Nos. 8,916,157 and 8,916,158.

Raffat said the PTAB's findings on these patents were a key factor in Amgen's decision to settle. He stated that since Amgen filed IPR petitions on them it is a safe assumption that Amgen's Humira formulation infringed them.

Raffat also pointed out that the current litigation could have extended out until 2021 with an appeal and AbbVie could have filed suit on additional patents lengthening the litigation timeline further. Thus, the January 2023 entry date is not far off from when Amgen might have launched if the litigation was resolved in its favor.

Barclays analysts said in a Sept. 28 note that they conservatively estimate US biosimilar competition in the 2019/2020 timeframe, though they noted that this could be pushed out a few years depending on the outcome of other litigation, including potential settlements.

Several companies have biosimilars under development hoping to carve out a piece of Humira's lucrative market, including **Momenta Pharmaceuticals Inc.** and **Coherus BioSciences Inc.**

Coherus has sought to invalidate Amgen patents through the IPR process and has had mixed results. PTAB has issued final written decisions finding patents on a method of treating rheumatoid arthritis are unpatentable. *(Also see "PTAB Tosses Two More Humira Patents; Will Supreme Court Eliminate IPR Proceeding?" - Pink Sheet, 14 Jun, 2017.)*

But in November 2016, the board declined to institute review of formulation patent No. 9,114,166. And earlier this month denied review of four Coherus petitions challenging the validity of formulation patent No. 9,085,619, which covers a non-buffer formulation and is a more critical patent in the Humira portfolio. Coherus contends that its Humira formulation does not infringe the two formulation patents Amgen challenged.

FDA has approved seven biosimilars, three of which have launched in the US: **Sandoz Inc.**'s *Zarxio* (infliximab-sndz), a biosimilar to Amgen's *Neupogen* (filgrastim); **Celltrion Inc./Pfizer Inc.**'s *Inflectra* (infliximab-dyyb), a biosimilar to **Janssen Biotech Inc.**'s *Remicade* (infliximab); and **Samsung Bioepis Co. Ltd./Merck & Co. Inc.**'s Remicade biosimilar *Renflexis* (infliximab-abda).

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FDA Ends Regularly Scheduled Patient-Focused Drug Development Meetings

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FDA's Sept. 25 session on hereditary angioedema was its 24th patient-focused meeting over the past few years.

The schedule of formal patient-focused drug development meetings will end along with PDUFA V later this month, but the US FDA is planning more patient engagement efforts – and the big public meetings might not disappear entirely.

FDA conducted the last of its planned meetings seeking opinions from patients on various diseases Sept. 25 with a session on hereditary angioedema. It was the 24th that the agency has held during the five-year prescription drug user fee program cycle.

Theresa Mullin, who directs the Office of Strategic Programs in the Center for Drug Evaluation and Research, said as resources permit and topics emerge, the agency could schedule additional meetings. But going forward she said FDA does not expect to repeat the formal scheduling process of selecting disease topics and scheduling meetings for the next five years. Instead, she said the meetings will be held on an as-needed basis.

Mullin told attendees of the hereditary angioedema meeting that PDUFA VI, which begins Oct. 1, will include a lot of additional patient-focused drug development work. "We've learned so

much in these meetings that we are proceeding to do a bunch of follow-on work," she said.

The additional work includes writing guidances. The 21st Century Cures Act passed last year mandates that the agency issue guidance on collecting patient and caregiver input on the burden of disease and methods for measuring patient impact that will facilitate collection of meaningful patient input in clinical trials. *(Also see "FDA's 21st Century Cures Plan Gives Patient-Focused Drug Development A Boost" - Pink Sheet, 10 Jul, 2017.)*

Also among the issues for the agency to tackle following the success of the patient-focused drug development meetings is determining how the information could be quantified and incorporated into FDA decisions and drug development. *(Also see "You Just Have To Wait: FDA Can't Hurry PDUFA VI Guidances" - Pink Sheet, 15 Aug, 2016.)*

MEETINGS 'HUGE STEP' IN HELPING FDA GAIN PATIENT INPUT

The end of the formal meetings was expected. Eric Gascho, VP of policy and government affairs for the National Health Council, said in an interview with the Pink Sheet that the meetings were just one step of a larger process and more important than FDA learning about the individual diseases was for the agency to understand how to engage with patients.

"In helping FDA learn to seek the patient perspective and incorporate it into decision-making, it has been a huge step in that direction," Gascho said. "It also helped shift the culture at FDA as well. Having reviewers in the room with patients really puts them in a different mindset."

At the start of PDUFA V, which launched in October 2012, the agency committed to holding 20 disease-focused meetings to solicit patient input on unmet needs and available treatments. FDA conducted a formal selection process to determine which diseases warranted meetings using a variety of criteria. *(Also see "20 Is The Loneliest Number: FDA Disease Meeting Schedule Leaves Some Worried About Exclusion" - Pink Sheet, 23 Oct, 2012.)*

The agency wound up conducting four more meetings than expected because they were extremely helpful, Mullin said. "It gives us an enormous amount of insight that we otherwise wouldn't get," she said. "We usually hear things that are not in literature or anywhere else during these meetings."

Each meeting is followed by a Voice of the Patient report that describes the input received and illustrates how it could be incorporated into reviewers' benefit-risk decisions.

STAKEHOLDER MEETINGS BECOMING MORE IMPORTANT?

Going forward, stakeholders hoping to get their message out about specific diseases may rely more on patient-focused drug development meetings organized by groups outside FDA, but it does not appear that the meeting host is as important as the substance of the discussion.

Pat Wildman, Lupus Foundation of American VP of advocacy and government relations, said FDA engagement is most important. He said the meeting host does not matter as long as the proper people are involved and the data collected is valuable to FDA and the patient community.

Agency officials have encouraged advocacy groups for diseases that were not selected by FDA to conduct their own meetings and have offered planning help and said that FDA staff would try to attend and contribute, if possible.

The Lupus and Allied Diseases Association, Lupus Foundation of America and Lupus Research Alliance partnered to conduct a meeting in Hyattsville, Md., the same day as the hereditary angioedema meeting. CDER Director Janet Woodcock and Nikolay Nikolov, clinical team leader in the Division of Pulmonary, Allergy and Rheumatology Products, spoke at the event. Kathleen Arntsen, president and CEO of the Lupus and Allied Diseases Association, said planning the meeting took several years.

Several other groups also have conducted their own meetings and published reports of the findings for FDA's use. Among the first was Parent Project Muscular Dystrophy, which conducted a meeting on Duchenne muscular dystrophy drug development in 2013. *(Also see "FDA's Patient-Focused Drug Development Meetings Inspire Imitators" - Pink Sheet, 19 May, 2014.)* The group used the information to write a proposed draft guidance on drug development in the disease. *(Also see "Group Submits Duchenne Muscular Dystrophy Guidance, Hoping To Direct FDA Policy" - Pink Sheet, 7 Jul, 2014.)*

FDA OFFICIALS WHO ATTENDED HEREDITARY ANGIOEDEMA PFDD MEETING

- **Jonathan Goldsmith,** Associate Director for Rare Diseases, Center for Drug Evaluation & Research
- **Theresa Mullin,** Director, Office of Strategic Programs, CDER
- **Meghana Chalasani,** Office of Strategic Programs, CDER
- **Christine Mueller,** Medical Officer, Office of Orphan Product Development
- **Tejashri Purohit-Sheth,** Director, Division of Clinical Evaluation & Pharmacology / Toxicology, CBER
- **Diane Maloney,** Associate Director for Policy, Center for Biologics Evaluation & Research
- **Wilson Bryan,** Director, Office of Tissues and Advanced Therapies, CBER
- **Ross Pierce,** Medical Officer, Clinical Review Branch, Division of Hematology, CBER
- **Larissa Lapteva,** Associate Director, Division of Clinical Evaluation & Pharmacology / Toxicology, CBER
- **Donna Lipscomb,** Office of Communication, Outreach and Development, CBER (facilitator)

PATIENT INVOLVEMENT AT FDA CONTINUES TO EVOLVE

FDA reviewed the document and created its own draft guidance on DMD drug development. *(Also see "Duchenne Muscular Dystrophy: FDA Supports Broader Outcome Measures, Biomarkers" - Pink Sheet, 10 Jun, 2015.)*

And while that approach is many respects a model for how the agency hopes to work with patient communities, the subsequent review of **Sarepta Therapeutics Inc.**'s exon-skipping DMD drug *Exondys 51* (eteplirsen) exposed a fair bit of tension between agency reviewers and patient advocates, potentially setting back the cause of tighter interactions.

FDA has a number of avenues to receive patient input outside of patient-focused drug development meetings, including a planned Office for Patient Affairs that Commissioner Scott Gottlieb has said will help coordinate agency policy on patient engagement. *(Also see "US FDA's Centralized Patient Affairs Office Aims For No Disruption" - Pink Sheet, 13 Sep, 2017.)*

Agency staff also have consulted patients during a review to gain perspective on potential risks and benefits. *(Also see "FDA Quietly Consults Patients To Understand Vimizim's Six-Minute Walk Significance" - Pink Sheet, 1 Dec, 2014.)*.

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FDA's NDA And BLA Approvals: Xhance, Trelegy Ellipta, Clorotekal, Verzenio

Below are FDA's original approvals of NDAs and BLAs issued in the past week. Please see key below chart for a guide to frequently used abbreviations

SPONSOR	PRODUCT	INDICATION	CODE	APPROVAL DATE
New Drugs				
Optnose US	*Xhance* (fluticasone propionate)	Nasal spray for treatment of nasal polyps in patients 18 years of age or older.	S, 5	9/18/2017
GlaxoSmithKline	*Trelegy Ellipta* (fluticasone furoate/ umeclidinium/ vilanterol)	Inhalation powder for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are on a fixed-dose combination offluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations, in whom additional treatment of airflow obstruction is desired, or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.	S, 5	9/18/2017
Sintetica	*Clorotekal* (chloroprocaine HCl)	Intrathecal injection for the production of subarachnoid block (spinal anesthesia) in adults undergoing surgical procedures.	S, 5	9/26/2017
Lilly	*Verzenio* (abemaciclib)	Kinase inhibitor used in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy, or used as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.	S	9/28/2017

KEY TO ABBREVIATIONS

Review Classifications	NDA Submission Classification
P: Priority review **S:** Standard review **O:** Orphan Drug	**1:** New molecular entity (NME); **2:** New active ingredient; **3:** New dosage form; **4:** New Combination; **5:** New formulation or new manufacturer; **6:** New indication; **7:** Drug already marketed without an approved NDA; **8:** OTC (over-the-counter) switch; **9:** New indication submitted as distinct NDA – consolidated with original NDA; **10:** New indication submitted as distinct NDA – not consolidated with original NDA

UnitedHealth 2018 Formulary Updates Broaden Exclusions, Deter Copay Coupons

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UnitedHealthCare's commercial insurance formulary policies for 2018 take a broader approach to coverage exclusions and aim new strategies at discouraging the use of manufacturer-sponsored copay coupons. The policies were announced recently to brokers as part of United's 2018 formulary updates. They apply to fully-insured and self-funded plans.

The insurer will remove four branded drugs from its formularies beginning Jan. 1, 2018 using an approach that allows for exclusions when there are less expensive drugs with equivalent clinical benefit available.

Previously, UnitedHealth only excluded drugs in two situations -- when a therapeutically equivalent drug became available OTC or when another product with same active ingredient became available through the pharmacy benefit.

The drugs impacted by the new policy are **Merck & Co. Inc.**'s *Dulera* (mometasone fumerate/formoterol fumerate), **PTC Therapeutics Inc.**'s *Emflaza* (deflazacort), **Kowa Pharmaceuticals America Inc.**'s *Livalo* (pitavastatin) and **Lundbeck Inc.** and **Takeda Pharmaceutical Co. Ltd.**'s *Trintellix* (vortioxetine).

Dulera's exclusion comes amid other changes in United's coverage of the asthma category. The moves follow the April launch of **Teva Pharmaceutical Industries Ltd.**'s *AirDuo RespiClick*, which contains the same active ingredients as **GlaxoSmithKline PLC**'s *Advair* (fluticasone/salmeterol) but in a different inhaler device. *(Also see "Teva's AirDuo Authorized Generic Priced At A 70% Discount To Advair" - Scrip, 20 Apr, 2017.)*

UnitedHealthcare will cover AirDuo RespiClick but not the higher-priced authorized generic of the product that has also been introduced by Teva. And other brands besides Dulera will be covered, likely reflecting hefty rebates from the manufacturers. They include Advair, GSK's *BreoEllipta* (fluticasone/furoate/vilanterol) and **AstraZeneca PLC**'s *Symbicort* (budesonide/formoterol fumarate).

Emflaza became one of the more egregious examples of drug pricing abuses when it was approved in February for Duchenne muscular dystrophy and priced at $89,000 per year. *(Also see "Marathon Gets Long-Known Duchenne Treatment On-Label, But Will Payers Respond?" - Scrip, 10 Feb, 2017.)*

The drug, a corticosteroid, had been used abroad as a much less expensive generic off-label for years before officially gaining the DMD indication. PTC acquired it in March from its developer, **Marathon Pharmaceuticals LLC**, and lowered the price to $35,000 a year. But UnitedHealthcare still consider the price excessive and has decided not to cover it.

Livalo, a branded statin for reducing cholesterol, will not be covered because it is significantly more expensive than the widely-available generic statins. Similarly, Trintellix is considered more expensive but not necessarily more effective than other options available for depression.

UnitedHealthcare will further modify its formulary exclusion practices next year by removing branded drugs from coverage as soon as a generic version becomes available. Currently, brand are excluded when generics launch only when the insurer implements its biannual formulary updates on Jan. 1 and July 1.

That shift should ensure swift market access for generics, and seems aligned with a suggestion from FDA Commissioner Scott Gottlieb that payors reserve some market share for biosimilars in an effort to encourage their development.

NEW ACCOUNTING FOR COPAY COUPONS

UnitedHealthcare has also developed a new program to deter members from using copay coupons. Manufacturer coupons have been an ongoing concern for payers because though they can be a good deal for individual members, they also lead to the use of more expensive drugs, higher utilization and an increase in payer costs.

UnitedHealthcare has had a program in place for some years in which specialty pharmacies in its network decline to redeem copay coupons for non-preferred products. The new program will expand on that by addressing the increasing numbers of members in high-deductible plans or those with coinsurance linked to out-of-pocket maximums.

Currently, both the member copay and the amount covered by the manufacturer coupon are applied to the deductible or out-of-pocket cap, mainly because the coupon is processed after a claim has been electronically sent to the insurer.

Next year, United's specialty pharmacy, BriovaRx, will rapidly send back information regarding coupons that have been used, allowing the insurer to more accurately reflect only what the member pays. The change will likely cause deductibles and out-of-pocket limits to be met more slowly, which is expected to cause members to more proactively choose less expensive options when they are available.

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Single Payor And Drug Pricing: High Stakes, But Better Debate For Pharma

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The formal legislative introduction of Sen. Bernie Sanders' "Medicare-for-All" bill on Sept. 13 is best viewed as a very early kick-off to what is likely to be a core component of the next national election cycles: whether the Democratic party will decide to back a single-payor health care model in the US.

The proposal, clearly, is not a viable legislative effort in the current GOP-controlled Congress – where rolling back the federal role in health care is the overriding priority. But while Sanders has long supported a single-payor health care system, the attention given to the event was warranted by the unusually long list of co-sponsors in the Senate –16 of the 48 Democrats – and especially by the endorsements of many of the perceived leaders in the race for the party's Presidential nomination in 2020.

In addition to Sanders – who just ran a surprisingly close challenge to Hillary Clinton for the 2016 nomination – co-sponsors include Massachusetts Democrat Elizabeth Warren and several less well-known but emerging leaders of the Sanders/Warren wing of the party, including New York's Kirsten Gillibrand, New Jersey's Cory Booker, and California's Kamala Harris.

For biopharma companies, the potential that the Democratic Party would embrace a single-payor health care system as a core priority would significantly raise the stakes in the health care debate: a single-payor system would be a direct step to price controls for innovator drugs.

However, to the extent the Democratic Party campaigns on creating a single-payor health care system, there may be less direct political energy expended on enacting meaningful price controls under the current hybrid (or hodge-podge) US system.

The hoopla around Sanders' bill introduction is still a long way from any assurance that single payor will be a dominant campaign theme next year. But it already has shifted the ground in a manner that may actually benefit biopharma companies.

To the degree that Sanders (and those who want to court the "Sanders voters") is promoting a single-payor health care system as a top priority, the focus on immediate action to curb drug pricing is demoted to a secondary theme.

The attention to single payor as the end goal of health reform also helps biopharma companies rally support from Republicans (and many Democrats) who reflexively oppose "socialized" medicine. The headlines generated by Sanders already served as a useful foil for Senate Republicans to rally behind in their last-ditch, but ultimately unsuccessful, effort to repeal and replace the Affordable Care Act before the budget reconciliation shortcut authority expires Sept. 30.

Regardless of how that debate plays out, biopharma companies should be able to count on more receptive responses to arguments against proposals to interfere in the "free market" for pharmaceuticals.

For the 2018 mid-term elections, a campaign that highlights support or opposition to single payor would be a huge improvement versus a campaign that focuses more directly on high prescription drug costs. And there is essentially no scenario where single payor is actually enacted into law during the Trump Administration no matter how those elections play out.

To the extent a single payor platform is a key part of the 2020 presidential election, the risks are much higher. However, as much of the media coverage of the "Medicare for All" proposal noted, for now the support is coalescing around the goal – universal coverage – and not around the disruptions and costs inherent in the single payor approach. In other words, unless single payor becomes a dominant theme that drives a Democratic landslide in 2020, it isn't really on the table in the US.

WHAT WOULD A NATIONAL FORMULARY LOOK LIKE?

Sanders' "Medicare-for-All" proposal also offers a starting point for thinking through how a US single-payor system would treat prescription drug coverage.

Even at the initial rallying-cry stage, it is interesting to note how the political dynamics that have protected innovator prices in the US so far may continue to mitigate the generally negative impact of a single-payor system.

At a baseline level, Sanders' bill would make both inpatient and outpatient prescription drugs a covered benefit with no excluded classes as currently exists in the Medicaid and Medicare Part D programs.

The bill includes a short section on payment for prescription drugs (and other medical supplies), declaring that prices will

be negotiated annually. In addition, the bill would establish a prescription drug formulary "which shall encourage best-practices in prescribing and discourage the use of ineffective, dangerous, or excessively costly medications when better alternatives are available." The formulary would be specifically directed to promote the use of generic medicines. Finally, it would also include a right to petition so "clinicians and patients" may seek "to add new pharmaceuticals or to remove ineffective or dangerous medications from the formulary."

Those broad outlines are also included in the House version of "Medicare for All," introduced to much less fanfare in January.

The Sanders bill includes two additional provisions that were not in the House bill. The first is an explicit and separate directive for HHS to "promulgate rules regarding the use of off-formulary medications which allow for patient access but do not compromise the formulary" – a directive that reflects the sensitivity of even the modest ardent critics of drug pricing to the allegation that they are denying necessary treatments.

Second, the Sanders bill authorizes cost-sharing for pharmaceuticals – the only benefit other than a newly created long-term care benefit that would not be completely free to beneficiaries.

While that serves to single out prescription drugs for cost containment attention, the "Medicare for All" formula also reflects the tension between encouraging cost-consciousness by consumers while also assuring that on-formulary medicines are in fact affordable to beneficiaries.

The section on cost sharing would require that the schedule for copays be "evidence-based and encourage the use of generic drugs." In addition, "preventative drugs" would not be subject to copays. Finally, there would be a co-pay cap of $200 per year for each beneficiary.

As a stand-alone law, that copay section would probably garner widespread support in the biopharma industry.

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New HTA Methodology Could Solve Value Conundrum

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Health policy experts at the London School of Economics have developed a new methodology for evaluating the benefits of medicines to inform funding decisions. The idea behind the Advance Value Framework is to bring more transparency and structure to healthcare decision making, which should in turn improve trust in evaluation procedures and decision outcomes, said Aris Angelis, from the LSE and one of the architects of the new methodology.

The methodology offers an alternative to current health technology appraisal (HTA) processes that are used to assess the value of new drugs and whether they should be funded, and also brings a new approach to the concept of value in the context of drug evaluations, something that the HTA world has long struggled with.

THE PROBLEM

Aging populations are demanding more from health services and new technologies are becoming increasingly expensive. As such, budgets are stretched and concern is growing about the sustainability of health services. Among the preferred methods used by HTA bodies are economic evaluations techniques, such as cost effectiveness analyses. Nevertheless, such evaluation models fail to properly incorporate and reflect all value-related concerns. For example, cost utility analysis does not capture the value of a product's level of innovation or the value of its socio-economic impact. Furthermore, in a bid to simplify complex processes, decision makers may under use or omit certain important information – such as data on societal impact – which leads to "choices based on an ad-hoc priority setting process," says the study that sets out the Advance Value Framework.. This can undermine consistency and credibility in these processes, the study adds.

> The methodology aims to "capture all the dimensions of value that typically go under the radar, and which may not be explicitly considered"
> - Panos Kanavos, LSE

A SOLUTION?

The new methodology seeks to improve the situation by ensuring that decision making processes are more structured and transparent. "That way, the decision outcome could become more reasonable and well received, and therefore more legitimate across society," said Angelis in an interview with the *Pink Sheet*.

Core to the methodology is a value-based model known as a "value tree" (called the Advance Value Tree) that sets out decision maker concerns for assessing value, explained the LSE's Panos Kanavos, who developed the framework alongside Angelis. Based on multiple criteria decision analysis (MCDA), the framework aims to "capture all the di-

mensions of value that typically go under the radar, and which may not be explicitly considered," said Kanavos. For example, an appraisal committee may discuss socioeconomic benefit in a meeting, but exactly how much weighting or influence that benefit has in the final decision remains unclear as it is not overtly explained in the decision reasoning.

The methodology therefore looks beyond more traditional interpretations of value, which are cost and therapeutic effect, and the value tree incorporates five "key domains" that can be explicitly measured and assessed. These are: burden of disease, therapeutic impact, safety profile, innovation level and socioeconomic impact. It offers "a more structured way of assessing value drivers and their trade-offs in an explicit manner," said Kanavos.

Key to the value framework, says Kanavos, is the weighting, or the level of importance assigned to the different evaluation criteria within the value tree. This means that the methodology is adaptable and that decision makers can structure their preferences and concerns regarding the value of a product. This is important because different HTA organizations have different value concerns, for example, Sweden's TVL may be more interested in some socioeconomic gains than England's NICE.

According to Angelis, the Advance Value Framework consists of "a generic value model incorporating different evaluation criteria for assessing the value of new medicines while allowing for a set of Multi Attribute Value Theory (MAVT) modeling approaches for preference elicitation and aggregation." More precisely, various MAVT techniques can be used to appropriately adapt the evaluation model to score alternative treatment options and assign relative weights of importance to the criteria. "Overall, the combination of these MCDA modeling techniques for the elicitation and construction of value preferences across the generic value tree provides a new value framework (Advance Value Framework) enabling the comprehensive measurement of value in a structured and transparent way," says the study.

The results of the first case study that tests the methodology are due to be published soon. This pilot appraised three treatments for colorectal cancer and adopted an expanded scope of the NICE's evaluation remit. The methodology has also been tested in collaboration with other HTA bodies in Spain, Poland, Sweden and Belgium, this time looking at prostate cancer drugs. More pilots will follow, according to Angelis. Feedback from HTA bodies has so far been positive and the new methodology has garnered much interest among HTA stakeholders, which want more evidence to show how well it works and how it might be applied in practice, he said.

The methodology was formulated following extensive research and rounds of consultation with different stakeholders as part of a large EU-funded grant called Advance-HTA.

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REGULATORY UPDATE

"We Regulators Need To Get Our Heads Round Big Data": EU Task Force Chair

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The EU task force mandated with exploring opportunities and challenges associated with the use of big data in regulatory decision-making has launched two surveys – one for pharmaceutical companies and the other for national competent authorities - to ascertain the current landscape on how big data is being used across the drug development pathway.

The task force, which was jointly formed by the European Medicines Agency and the EU Heads of Medicines Agencies in March this year, appears to have made good progress over the last five months towards delivering its final goal of issuing a big data strategy for the EU medicines network in 2018. *(Also see "Denmark Leads New EU Task Force Exploring Use Of Big Data In Medicines Assessment" - Pink Sheet, 23 Mar, 2017.)*

The two surveys were launched earlier this month and will run until October. The industry is being asked to identify, among other things, the key challenges faced by companies in the use of big data. National competent authorities, on the other hand, are be-

> "When it comes to social media and m-health, it is a bit like starting from scratch because this has really never been a part of what the regulators tend to look at"
> – EU big data task force chair Thomas Senderovitz

ing asked whether they have the necessary staff, infrastructure and procedures in place to analyze raw data, said Thomas Senderovitz, the head of the Danish Medicines Agency (DKMA) and the co-chair of the EU big data task force.

The task force comprises six "tracks" or sub-groups covering various topics, such as social media and mobile health data, genomics and other 'omics – such as proteomics, metabolomics and lipidomics – clinical trial data including imaging datasets, observational data, and adverse drug reaction (ADR) data. The scope of an earlier seventh track on IT is in the process of being re-defined. *(Also see "Interview: EU Big Data Task Force Is 'Not Just Another Discussion Forum', Says Chair Thomas Senderovitz" - Pink Sheet, 4 May, 2017.)*

SOCIAL MEDIA IS CHALLENGING, BUT CAN'T BE IGNORED

Senderovitz said that the task force had gathered the information to successfully complete its first objective of mapping data sources and identifying obstacles in acquiring data within each of the six tracks. During this exercise, the task force had found some of the tracks to be more difficult than others. The track on social media and mobile health data for example, he said, is "more challenging for us regulators."

This, Senderovitz explained, is because regulators pretty much know the data sources for genomics, clinical trials, and spontaneous and observational ADRs. When it comes to social media and m-health, however, it is a bit like "starting from scratch because this has really never been a part of what the regulators tend to look at," he told the *Pink Sheet*.

As the task force moves forward with its next objective of identifying the applicability of big data, Senderovitz suspects that "we are still going to end up with some unanswered questions" on how exactly regulators can utilize social media and m-health data in regulatory decisions.

Nevertheless, Senderovitz believes regulators cannot ignore the fact that social media and health apps can generate big data that can influence regulatory decision-making. "I think, we just have to accept this fact… and at least come up with proposals on how we are going to relate to that," he said.

DENTIFYING GAPS

In June, the task force attended a major workshop on big data that had around 70 participants, including regulators from the US, Canada, Switzerland and Brazil, as well as industry representatives. At the workshop, there were discussions on the challenges faced by regulatory authorities in using big data, concerns around data validity, and the applicability of big data in the development of medicines, particularly for rare diseases. Senderovitz thinks "the workshop was excellent and really paved the way" for the task force to help realize its next objective of identifying the usability of big data.

He explained that the mapping exercise, the feedback from the workshop as well as the results the two surveys, when available, will help the task force understand the current picture regarding the use of big data in drug development. This will help "us understand the gap between where we are currently and where we want to be" and will form the basis of final recommendations on the EU-wide strategy.

IDEAL TIMING

When the DKMA first put forward the idea for an EU-level big data strategy, Senderovitz said not everyone realized that big data was a regulatory challenge. He feels the topic is gaining attention now for many reasons, including the recent focus on finding new ways to accelerate the approval of innovative medicines, especially for unmet medical needs.

Initiatives such as the EMA's PRIME scheme for getting innovative medicines to patients faster means regulators will now have to look at big data more comprehensively, in addition to post-approval data. Senderovitz said: "It is interesting to see how more and more regulatory agencies… are struggling with this and thinking about how they are going to handle this. So, I feel that the [establishment of the] EU [big data] task force was extremely timely and it is really key that we get our heads around this."

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EMA Argues Pre-Submission Activities Under Ombudsman's Radar Are A Legal Requirement

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The European Medicines Agency, which is undergoing an inquiry by the EU Ombudsman into whether it might be influenced during the pre-submission meetings it holds with drug developers, maintains that having these early interactions with companies is a legal obligation that the agency must fulfil to facilitate timely patient access to promising innovative medicines.

In an Aug 29 letter to Ombudsman Emily O'Reilly, EMA executive director Guido Rasi said that pre-submission activities touch upon "all major operational processes" of the agency, and that providing a detailed statistical overview of all these activities over the past five years "would be a challenging exercise" as it would potentially cover thousands of exchanges.

The EMA has offered to meet the Ombudsman on Sept. 28 in London to have an "initial exchange" on the matter. The Ombudsman's inquiry was launched in July.

Specifically, the EMA is worried that the scope of the inquiry is too broad-ranging. The agency has been asked to prepare and submit to the Ombudsman's office, among other things, a detailed statistical overview of all its pre-submission activities between 2012 and 2016. *(Also see "Ombudsman Probes Whether Industry Can Influence EMA In Pre-Submission Meetings" - Pink Sheet, 21 Jul, 2017.)*

Rasi is hoping that the "initial exchange" with the Ombudsman will help the EMA to identify the precise scope of the inquiry and result in an agreement on a "reasonable timeline" for the agency to provide further information that would supplement the inquiry.

Regarding the questions the Ombudsman wants the EMA to address, Rasi said that some of these could be initially answered based on information already published on its website, while others would "require a careful analysis as to their scope and purpose."

The EMA is already under pressure as a result of Brexit. Rasi explained that over the next 18-24 months, the agency will be "extremely busy" relocating its offices from London to another EU city. 19 countries have put themselves forward as the ideal candidate for hosting the EMA when it moves out of London. The agency has also suspended some of its activities to free up staff to support the re-location. *(Also see "EMA's Future Home: Assessment Of Bids Nears Completion Amid Growing Staff Concerns" - Pink Sheet, 21 Sep, 2017.)(Also see "EMA Suspends Some Activities & Warns That High Job Losses Could Halt Its Operations" - Pink Sheet, 2 Aug, 2017.)*

Rasi told the Ombudsman that the agency obviously needs to limit what it can undertake. He said the EMA had to plan its activities "with extreme care to ensure that the huge disruptions linked to Brexit, affecting both the Agency as a whole and our staff individually, do not have an adverse impact on public health."

LEGAL OBLIGATION

The EMA is maintaining that its pre-submission-activities are required by law and are organized in accordance with the necessary legal framework. "They exist in strict fulfilment of the Agency's primary public health priorities, namely to facilitate timely access by patients and healthcare professionals to promising innovative medicines whilst maintaining their quality and safety in use," it said.

Early dialogue can help optimize a medicine's development plan, provide methodological direction and discourage the production of irrelevant or substandard data. The process is beneficial for both companies and the regulators, the agency said.

It increases the likelihood that a medicine will be developed "in a way that generates the evidence we need to properly evaluate its benefits and risks," Rasi said. It also allows EMA assessors/experts/scientific secretariat (who are to be involved in the evaluation) "to gain an overview of the product and its development so that their assessment can be performed more efficiently and minimise any unnecessary administrative delay."

The EMA's pre-submission activities include various early development advice services. These services relate to such things as providing scientific advice for human medicines. They also involve dealing with pediatric development issues, and applications for orphan designation, the priority medicines (PRIME) scheme and the qualification of novel methodologies. Interactions by the agency's Innovation Task Force also fall under pre-submission activities, as does the work the EMA does to support micro-, small- and medium-sized enterprises (SMEs), and the work it does under its adaptive pathways approach.

Also, there are opportunities for early interaction with companies developing advanced therapy medicinal products (ATMPs) to support the classification of such products, and to issue ATMP certification to SMEs. In addition, the agency holds pre-submission meetings with companies prior to the submission of a marketing authorization application.

To remove the potential for bias during such interactions, Rasi said the agency has a robust and rigorous assessment processes in place, "which separate the advice function from the final decision." Commenting on the inquiry, the EMA chief said he welcomed any opportunity to further clarify and foster public trust in these important operations.

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India's Draft Plan To End API Reliance On China 'Needs Work'

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Back in January 2016, the government set a 2020 deadline to end the country's heavy dependence on neighboring China for raw materials to make medicines, especially key antibiotics and painkillers, and it announced ambitious plans to ramp up production of bulk drugs.

Since then, though, India's progress toward achieving self-reliance has been minimal and chances of meeting the 2020 target look increasingly elusive. Now, the government of Prime Minister Narendra Modi has come up with an umbrella draft pharmaceutical policy that includes promise of "an enabling environment" to promote domestic active pharmaceutical ingredient (API) production. But the document, which speaks of creation of "end-to-end indigenous drug manufacturing," is sketchy in its proposals for creating the right supportive climate, experts say. *(Also see "Indian Policy Shifts Could Force Firms To Abandon 'Second Brand' Strategies" - Pink Sheet, 22 Aug, 2017.)*

"Beyond the government calling out the problem (of API dependence on China), I don't think we've gotten much further" toward reducing the country's reliance, Sujay Shetty, life sciences leader and partner at consulting firm PwC India, told Scrip. "I think everyone agrees the draft needs work," he said.

India is known as "pharmacy to the world," accounting for 20% of global generic drug exports by volume, making the country the biggest supplier of copycat drugs globally. Pharmaceutical exports totaled $16.4bn in the financial year 2016-17, according to Pharmexcil, the pharmaceuticals export promotion council. But over 60% of raw materials – APIs and intermediates -- used to make the medications are imported with the bulk coming from China.

Indeed, for 12 "essential drugs" --- including the painkiller paracetamol, the anti-diabetic metformin, the antacid ranitidine, antibiotics such as amoxicillin, acetylsalicylic acid and the anti-amoebic metronidazole, there's a "significant dependence" on imports of which "approximately 80%-to-90%" are from China," the government told Parliament.

CHINA SERVES AS INDIA'S API 'LIFELINE'

"The country has become dependent on China for its lifeline," said Dilip Shah, secretary general of the Indian Pharmaceutical Alliance, which represents 20 major domestic drug producers.

The issue of Indian reliance on Chinese bulk drug imports was brought into sharp focus recently when a territorial dispute in the remote Himalayas threatened to explode into open conflict. Indian and Chinese troops in August pulled back from their military standoff, ending a two-month crisis.

It was one of the most serious confrontations between the neighbors since China won a border war in 1962. But tensions remain high between the nationalist-minded governments and the latest flare-up was a reminder of India's vulnerability on the drug import front. The Indian government in July held a meeting with

local drug-makers to draw up an emergency plan to deal with any halt in Chinese API shipments. The Indian Drug Manufacturers' Association (IDMA) noted in a submission that at present "India is not able to manufacture many important drugs due to low-priced imports from China." *(Also see "India's API Build-Up Plan To Bridle The Dragon" - Scrip, 4 Oct, 2015.)*

The government's new draft proposal says its aim is "to address the ways and means to restore and revive" manufacturing capabilities indigenously. It proposes "mega drug parks where benefits of scale can be availed of by using common facilities for pollution control…provided by the central government." The policy says India's "states would be encouraged to set up (the zones) in a public-private partnership mode." These PPPs have a mixed success track record in India.

The plan also calls for slapping "peak customs duty" on all APIs that can be manufactured domestically to spur local drug-making and proposes formulations made from local APIs get preference in government contracts and be exempted from price controls for five years.

PLAN LESS AMBITIOUS

The scheme is less far-reaching than the government's initial January 2016 scheme which involved setting up six drug and two medical device industrial parks in three years. The government had said then its plan would require $6bn investment from public and private sources without giving a breakdown.

Months later, the government scaled back, telling Parliament it was considering "providing assistance for three green-field bulk drug/API parks to the extent of INR2bn ($30m) each." And in June, the government, which is straining to meet fiscal deficit targets amid sharply showing economic growth, mentioned a rider in a court filing that "financial sanctions for the scheme" would hinge on the "overall financial structuring of the government," The Indian Express newspaper reported.

The draft policy spells out the problem but offers "sketchy

proposals" and little by way of concrete incentives to persuade domestic manufacturers to produce more APIs, said Amit Sengupta, an international coordinator of the global Jan Swasthya (people's health) movement. Also, any shift away from Chinese raw material imports could make medicines more expensive – an outcome that would run directly counter to the government's aim of making drugs more affordable for Indians, 80% of whom have no form of health insurance, experts say.

In addition, higher input prices could affect Indian competitiveness in increasingly challenging world markets, noted Kanchana TK, director general of the Organization of Pharmaceutical Producers of India. And now, rather than investing in APIs, large Indian drug-makers are focusing on diversifying into complex generics to grow sales as they contend with an ever more crowded and competitive plain-vanilla generics market.

CHINA'S API SUCCESS DRIVEN BY ECONOMIES OF SCALE

India's API industry became unviable under government-controlled prices that companies complained were often below production costs. Many manufacturers shut down and drug formulators ended up importing cheaper APIs, mainly from China. China's API success has been driven by economies-of-scale and government support involving cluster-based development, a dependable supply of cheaper power, water and labor, effluent treatment facilities – drug production is one of the most polluting industries – as well as subsidies in the form of tax holidays and low-interest loans.

But low-cost Chinese imports have also played in favor of Indian firms, helping them migrate up the value chain to focus on value-added formulations with higher margins that they have been able to sell at prices far cheaper than those prevailing in the West. Just under a quarter of Indian drug producers make APIs.

Now, though, as the neighbors jockey for regional influence, India's government has flagged the country's API dependence on China. Indian national security advisor Ajit Doval has called the reliance on China "a national threat." Yusuf Hamied, **Cipla Ltd.**'s chair, said last month "there are selected (critical) items which we should produce irrespective of the cost… We cannot be dependent (on China) for penicillin." He suggested revival of public sector drug companies for that purpose.

"It's not that there's not the local capability, but it would take a bit of time to meet indigenous requirements. I don't see much planning," said Shetty.

There have been indications of what might happen if Chinese API shipments were curtailed for some reason and India had made no preparations. Last year, supplies of China-sourced API D-penicillamine were disrupted, resulting in a lack of drugs in India to treat Wilson's disease, a rare inherited illness. Also, during the 2008 Beijing Olympics, China closed API plants to cut pollution and Indian manufacturers ran short of some bulk drugs, resulting in price rises of up to 20% of certain products, the industry says.

"There are ways to manage the costs" of reducing India's API import dependence, Shetty said. Experts say, however, India can't afford to duplicate China's subsidy regime and that one move to help diversify suppliers would be to assist other Asian and African nations in developing API production.

"The private sector alone cannot reverse the damage (to the API sector), there need to be concerted policy initiatives," Shah said.

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Gottlieb's Tweets: Skirting The Rules Or Advancing Policy?

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US FDA Commissioner Scott Gottlieb and his predecessor Robert Califf are no strangers to Twitter, as each publishes tweets almost daily about a variety of public health issues. But the reason that Califf didn't really tweet when he was in the post while Gottlieb does, it seems, is that Gottlieb chooses to ignore the agency's legal advice discouraging use of the social media platform.

The two most recent FDA heads engaged in a friendly dialogue about Twitter at a National Academies of Sciences, Engineering, and Medicine meeting examining the impact of real-world evidence on medical product development on Sept. 19. Following a question from Califf to Gottlieb about electronic health data, Gottlieb jokingly pointed out that Califf has been "liberated" on Twitter since he left the agency in January.

"When Dr. Califf was at FDA, the lawyers wouldn't let him tweet," Gottlieb said, laughing. "When I got to FDA, the lawyers wouldn't let me tweet, but I decided not to take legal advice on that matter," he said.

Califf confirmed he received the same legal advice, noting that he "obeyed or-

ders." He then pointed to former Centers for Medicare and Medicaid Services (CMS) Acting Administrator Andy Slavitt's use of Twitter, suggesting there were consequences.

"I noticed Andy Slavitt was tweeting, I mean he has gone completely crazy in tweeting since," Califf said. "But he was tweeting while he was at CMS [and] … I did ask him why he got to tweet and I didn't. He said 'I was told I couldn't. I just did it anyway.' Then he said there was entire team at the White House to clean up behind his tweets. So, maybe it was not a good resource use."

For its part, FDA insisted that Gottlieb wasn't actually breaking the rules, even if he thinks he is. "Dr. Gottlieb knows how much Dr. Califf likes Twitter, and took the opportunity to have a playful exchange," an agency spokesperson said. "The two of them are friends. Dr. Gottlieb wasn't told that he couldn't use Twitter, but worked through a legal review process to ensure it was properly stood up."

Regardless of whether his tweets are illicit or completely above board, Gottlieb has been using the handle @SGottliebFDA since his taking the commissioner post in May, tweeting about a range of issues, including opioids, vaccines, generic drugs, and enforcement, over 700 times. That handle was created specifically for his communications as commissioner; he previously tweeted from the handle @ScottGottliebMD, where he has tweeted over 10,000 times since joining in 2009.

[*Editor's note: Commissioner Gottlieb will be speaking at Informa's FDA/CMS Summit on Dec. 4.*]

BENEFITS OF PUBLIC COMMUNICATION?

Although the legal ramifications of an agency head using Twitter could be significant, as evidenced by the advice provided to the commissioner, Gottlieb's social media use could ultimately benefit industry beyond just the 140-character bursts of information about agency activity.

To many, the FDA commissioner's use of Twitter could be overshadowed by his boss' – President Trump's – use of the platform. *(Also see "Industry In The Middle: Merck's Frazier Takes A Stand, Trump Tweets Back" - Scrip, 14 Aug, 2017.)* However, Gottlieb's knowledge of Twitter could inform final guidance on industry's use of Twitter as a promotional tool.

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In a 2014 draft guidance on presenting product information through social media platforms, FDA recommends that each individual message or tweet should include the product name, its indication, the most serious risks associated with the product and a hyperlink to a destination that is devoted exclusively to the communication of risk information about the product. *(Also see "FDA's Twitter Formula Allows Tweets About Products Without Excessive Risks" - Pink Sheet, 17 Jun, 2014.)*

The Pharmaceutical Research and Manufacturers of America (PhRMA) complained that the draft guidance is "inconsistent with the agency's own responsible communications about medicines using Internet and social media platforms with character space limitations."

"FDA's recommendations would significantly burden companies' communications using character-limited platforms, which would be expected to decrease transparency and the beneficial flow of information about their medicines to healthcare professionals and patients," PhRMA said in its comments on the draft guidance.

"Specifically, FDA now uses character-limited platforms to announce information about drugs and does it in a responsible, truthful way, including providing safety overviews after Twitter links. Yet FDA proposes to restrict manufacturers from using the same social media tools that FDA uses."

FDA's historic policies on off-label communication have also made it difficult for drugmakers to engage on Twitter beyond carefully crafted press release teasers. *(Also see "Finally, An FDA Commissioner Who Tweets" - Pink Sheet, 31 May, 2017.)*

Gottlieb's use of Twitter has also served as a tool for the commissioner to communicate directly with the press. *(Also see "What Trump's FDA Commissioner Could Teach Trump About Twitter" - Pink Sheet, 23 Aug, 2017.)* It has also shown his determination to get out in front of the issues on FDA's agenda, in addition to his large number of public appearances. *(Also see "US FDA To Publish Own Datasets In Latest Signal Of Enhanced Transparency" - Pink Sheet, 18 Sep, 2017.)*

Peter Pitts, president of the Center for Medicine in the Public Interest and a former FDA associate commissioner for external relations, gives Gottlieb a thumbs up for tweeting as head of the agency.

"Scott's a great communicator," Pitts tells the Pink Sheet. "Denying him the use of Twitter would be like taking away Avogadro's abacus."

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Recent And Upcoming FDA Advisory Committee Meetings

TOPIC	ADVISORY COMMITTEE	DATE
PTC Therapeutics' *Translarna* (ataluren oral suspension) for treatment of patients with dystrophinopathy due to a nonsense mutation in the dystrophin gene	Peripheral and Central Nervous System Drugs	Sept. 28
Selection of strains to be included in an influenza virus vaccine for the 2018 southern hemisphere influenza season	Vaccines and Related Biological Products	Oct. 4
Spark Therapeutics' *Luxturna* (voretigene neparvovec) for treatment of vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy	Cellular, Tissue, and Gene Therapies	Oct. 12
Aerie Pharmaceuticals' netarsudil ophthalmic solution 0.02% for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Dermatologic and Ophthalmic Drugs	Oct. 13
Clinical development plan for Pfizer's *Staphylococcus aureus* vaccine intended for pre-surgical prophylaxis in elective orthopedic surgical populations	Vaccines and Related Biological Products	Nov. 7
Bayer HealthCare Pharmaceuticals' ciprofloxacin inhalation powder for reduction of exacerbations in non-cystic fibrosis bronchiectasis adult patients (≥18 years of age) with respiratory bacterial pathogens	Antimicrobial Drugs	Nov. 16
Discussion of patient selection criteria and clinical trial design features, including acceptable endpoints, for demonstrating clinical benefit for drugs intended to treat interstitial cystitis and bladder pain syndrome. Also discussion of whether bladder pain syndrome and interstitial cystitis reflect overlapping or different populations, and whether it is appropriate to assess efficacy in the same way for both conditions	Bone, Reproductive and Urologic Drugs	Dec. 7

Correction: An article in the June 19 issue of The Pink Sheet, "Regulators Accepting Predictive Stability Data In Lieu of Long-Term Studies" incorrectly stated that regulators are accepting predictive stability data in lieu of long-term stability studies. Regulators are accepting predictive stability data at the time of submission to support new drug applications but still expect these drugs to be placed on full stability studies.

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