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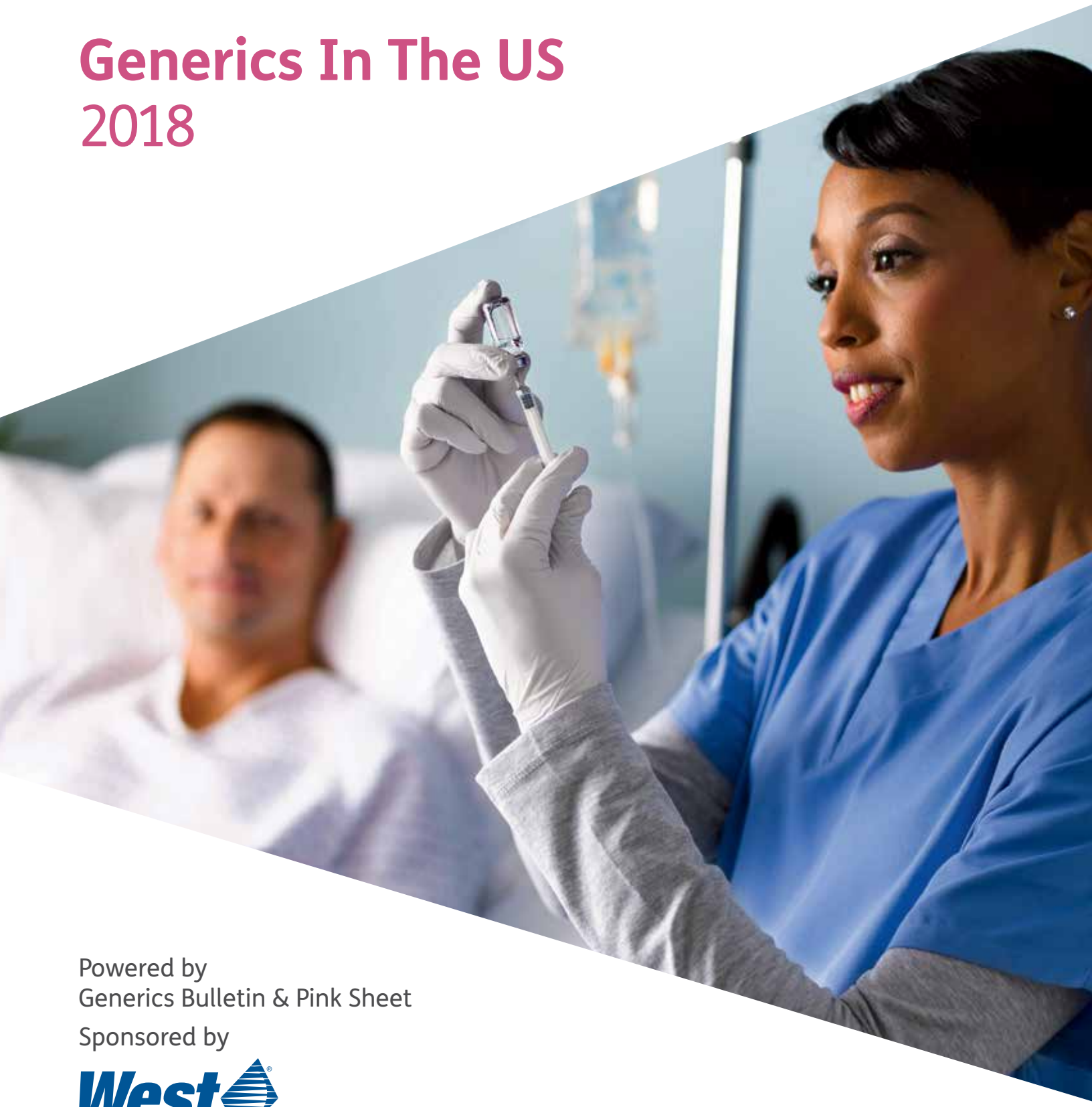
Generics In The US
2018



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More than ever before, generic manufacturers within or exporting to the US market are under significant pressures to get their products to market sooner than competitors with significantly higher quality expectations resulting from the high regulatory standards of the US market to ensure the quality and safety of medical products for the patients that need them. This is evidenced by the increase in warning letters and audits from US regulators. To meet these challenges, generic injectable manufacturers are requiring greater speed and flexibility from their elastomer supply chains in order to help consolidate their stopper SKUs, while being able to get their product to the US market quickly.

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Milagro Eduard Lopez
Global Marketing Director, Generics

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Contents

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Us Firms Find FDA Action On Approvals Is No Panacea

▶ By Aidan Fry

More plentiful approvals have intensified competition in the US generics market. And increasingly powerful buying consortia are taking advantage to drive down prices. Aidan Fry reviews trends discussed at this year's annual meeting of the US industry.

Just two days into this year, the *Washington Post* declared that "generic drugs had a great 2017". But while this message may have resonated in the halls of Capitol Hill and the meeting rooms of the US Food and Drug Administration (FDA), it must have left generics executives spluttering on their coffee as they returned to work after the New Year break to contemplate how to cope with fierce price erosion driven by increasing customer consolidation.

In truth, the *Washington Post*'s proclamation was not entirely unjustified. The article's main focus was on how FDA Commissioner Scott Gottlieb had, since his appointment, identified facilitating generic competition as a key tool to achieve President Donald Trump's goal of reducing drug prices. In its 2017 financial year – the final 12 months of the first five-year iteration of the Generic Drug User Fee Amendments (GDUFA) – the FDA approved a record 767 abbreviated new drug applications (ANDAs). And in calendar 2017, the total was an even more impressive 843 final and 184 tentative ANDA approvals *(see exhibit 1)*, as brands including Asacol HD (mesalamine), Renvela (sevelamer), Strattera (atomoxetine), Truvada (emtricitabine/tenofovir) and Vytorin (ezetimibe/simvastatin) faced generic competition for the first time.

This regulatory progress proved, however, to be a double-edged sword for industry. While faster and more plentiful ANDA approvals provided more opportunities to bring products to market, they also increased the prospect of greater competition to companies' existing portfolios. Product categories in which two or three players had previously enjoyed healthy margins and market shares became increasingly crowded as new players entered, turning attractive niches into commodity battlefields.

And as new entrants sought to capture market share, principally by undercutting incumbent players on price, they found themselves faced with negotiating with one of three purchasing groups formed by wholesalers, retailers and pharmacy benefit managers (PBMs): the Red Oak Sourcing alliance of CVS with Cardinal Health; the Walgreens Boots Alliance Development (WBAD) partnership between WBA and AmerisourceBergen that is set soon to also include Express Scripts' Econdisc group purchasing organisation; and the ClarusOne consortium that was formed by McKesson and Walmart.

> **"Unbranded generics dollar share fell for the third consecutive year, and dollar sales have been down for 19 months in a row through to December 2017."**

Discussing the effects of such customer consolidation in a sustainability white paper published to coincide with its recent 2018 annual meeting, the US Association for Accessible Medicines (AAM) observes that in 1975, there were more than 200 drug wholesalers operating in the US. By 2000, that number had shrunk by more than three-quarters to fewer than fifty, and today the big-three consortia accounted for more than 90% of all US sales of retail generics.

"This consolidation creates an imbalance compared to a highly fragmented generic drug market with more than 200 generic-drug manufacturers, at times with as many as a dozen manufacturers making any given product," the AAM argues in its paper. It cites an analysis of the top 100 drugs by volume under the Medicare Part D social welfare program to show that the average ex-factory price per unit was US$0.10, or US$0.12 to pharmacy after applying a 20% wholesalers' margin.

Observing that generic price deflation has been running at 7% to 8% per year since 2008 and is accelerating amid purchaser consolidation, the AAM says this is causing companies to re-evaluate their US portfolios and to discontinue less

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profitable product lines. “While these trends provide short-term savings to patients and payers,” it acknowledges, “they call into question the market’s long-term sustainability.”

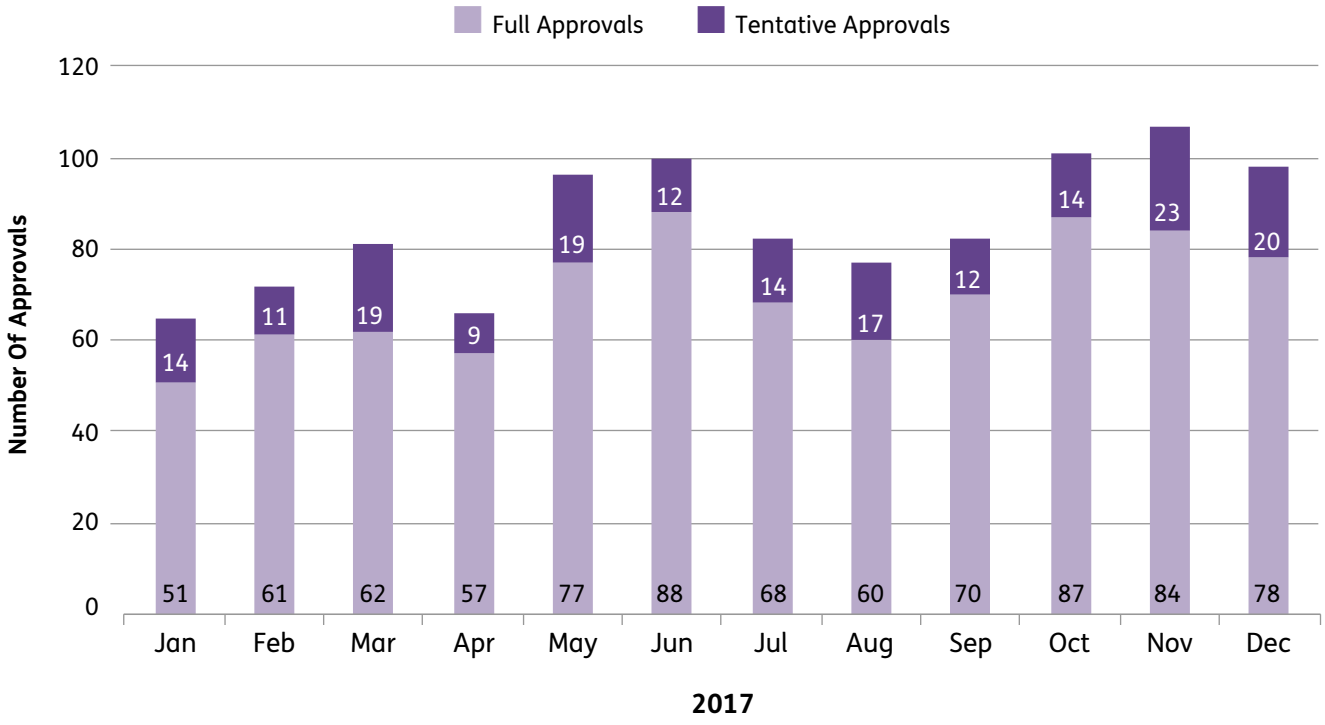
Discussing the industry’s future during a chief executive officers’ round table held during the AAM’s annual meeting in Orlando, Florida, last month, Mylan head Heather Bresch believed the customer consolidation trend had started four or five years ago as retail pharmacy began to link up vertically with wholesalers, PBMs and insurers. “I am not sure the US government or the Federal Trade Commission (FTC) really had a full appreciation of this stream,” she commented, adding that “further disruption is going to happen” as consumer goods giants such as Amazon eyed the healthcare sector.

Bresch insisted that industry was “in a hyper-competitive cycle”. “What is different in the past 18 to 24 months is that we are at an intersection with healthcare delivery in this country,” she said, pointing out how costs were increasingly being shifted from insurers onto patients. In this environment of minimal price transparency, she added, it was not readily obvious that generics offered a solution to rising costs, even though they represented just 26% of drugs spending while supplying 89% of prescription volumes.

Teva’s North American head, Brendan O’Grady, agreed that the market had started to shift in 2012 and 2013, and the latest market rumours of further moves – such as an approach by WBA to take full control of AmerisourceBergen – were “not a surprise”. With more players for each molecule and diminishing returns from first-to-file opportunities for 180-day market exclusivity, companies including Teva were looking for ways to optimise their base portfolios, such as by discontinuing unprofitable lines, he remarked.

Returning to the generics sphere after three years in the brands sector with Allergan, recently-appointed Amneal chief Bob Stewart noted that not only the pricing environment had changed, but also the defensive tactics that originators were using, such as offering increasingly aggressive rebates to retain brand share.

Exhibit 1: Tentative And Final ANDA Approvals In 2017



Source: FDA

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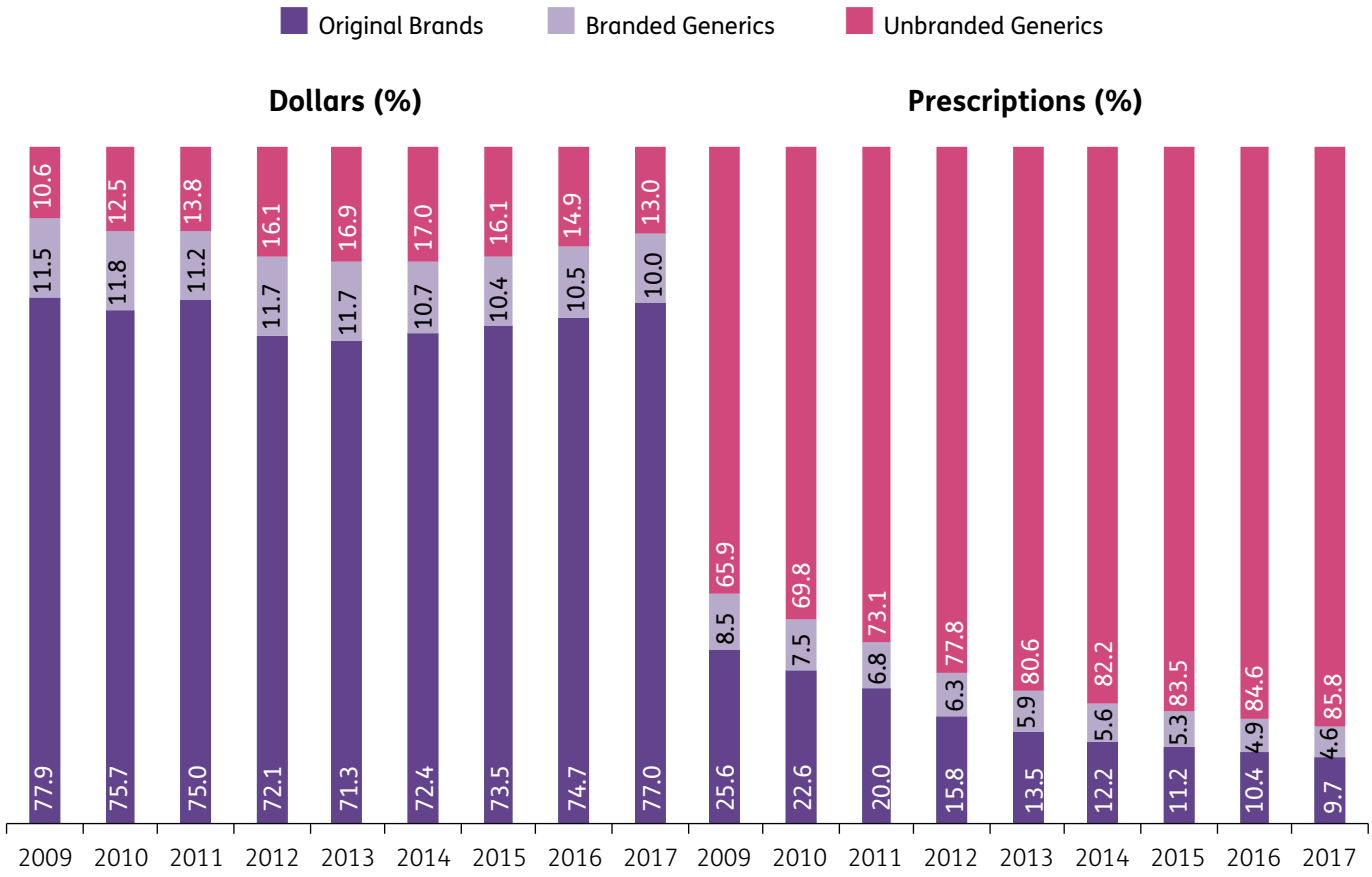
Exhibit 2: US Value And Volume Shares Of Branded And Unbranded Generics



Source: IQVIA

"We have to adapt," he advised, urging a different approach to allocating capital in areas such as research and development. "You are going to see a lot of companies rebalancing their capacities," Stewart forecasted. While this could encourage greater financial responsibility, he argued, a tighter portfolio focus could create drug shortages.

Shortages scare is real

"Shortages are not a scare tactic, this is real," Stewart insisted. "We cannot afford to continue to invest and hold capacity in this pricing environment. This is a fundamental shift in the way that we do business and invest." As Amneal merged with Impax, the two firms would take out capacity in a responsible manner, he pledged.

Both O'Grady and Bresch highlighted how prices of several essential drugs were less than for a cup of coffee, with Bresch pointing out how the US was entirely dependent on imports for antibiotics. Part of the problem on pricing was, she suggested, that co-payments had left consumers and patients ignorant of the true cost of drugs. "This is the only industry where you walk up to the counter with no idea what you will be asked to pay," she said, adding that the US was unique in allowing direct-to-consumer (DTC) advertising to drive demand for certain brands.

O'Grady admitted that both the public and policy-makers at both federal and state levels found it difficult to differentiate between disparate pricing and cost dynamics for brands and generics. Bodies aligned with the originator industry

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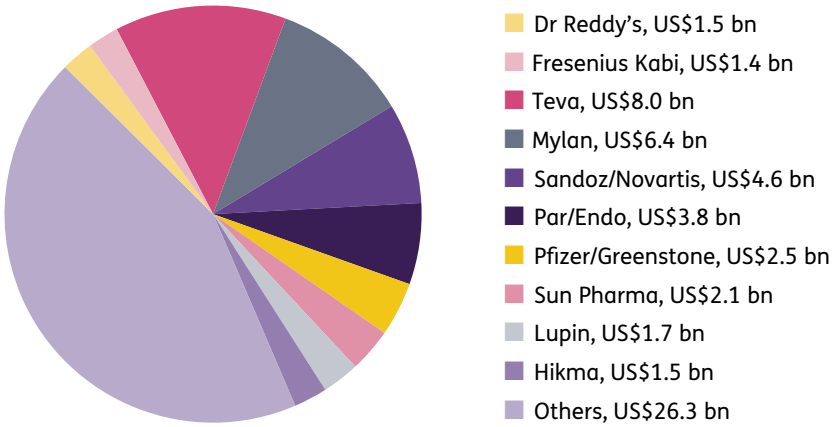
Exhibit 3: The 10 Leading Players By Value In The Us Unbranded Generics Market In The 12 Months Ended November 2017



Source: IQVIA

had, he recognised, been largely successful in putting the spotlight on off-patent price increases in percentage terms, rather than far larger increases for patented brands in terms of absolute dollars.

Accusing legislators of being attracted to "sound-bites that play well and poll well", Stewart argued that industry needed to refine and simplify its story on drug prices to reflect accurately its essential role in healthcare provision. "We have to ensure we get a fair share of voice. We have to change our narrative so we are not seen as second-class citizens relative to the branded side," he proposed.

Questioned on how companies could grow against such headwinds and 90% market penetration, the panel members were united in pointing to the importance of a well-stocked pipeline, including complex generics and biosimilars. Bresch observed that the relatively fragmented nature of the sector, with leading players holding less than a 15% market share in the US, suggested further transactions would follow, while Stewart believed consolidation "has to happen" as firms mopped up "distressed assets" and sought to match the greater scale that customers were achieving. As major players got larger, he recognised, new, often virtual companies would pop up to "place small, opportunistic bets".

Stewart also referenced an earlier presentation made at the AAM meeting during which Doug Long, vice-president of industry relations for market researcher Iqvia, had forecasted volume growth in the US market of around 3% through to 2020.

Long told AAM delegates that while the US branded and unbranded generics market had seen a 1.9% volume uplift in the 12 months ended September 2017, value growth had fallen by 5.0% over the same period due to fierce price erosion.

The volume growth, adjusted for 90-day prescriptions, was being driven by antihypertensives, mental-health therapies, lipid regulators and diabetes drugs, more than offsetting declines for analgesics and antibiotics amid pushes to limit usage of opioids and to combat antimicrobial resistance.

In calendar 2017, Long revealed, unbranded generics accounted for 85.8% of all US prescriptions, and branded generics another 4.6%, leaving brands with less than a tenth of the total market by value. But branded originals were responsible for 77.0% of dollar spending, compared to 13.0% for unbranded generics and a tenth for branded generics such as oral contraceptives *(see exhibit 2)*.

"Unbranded generics dollar share fell for the third consecutive year, and dollar sales have been down for 19 months

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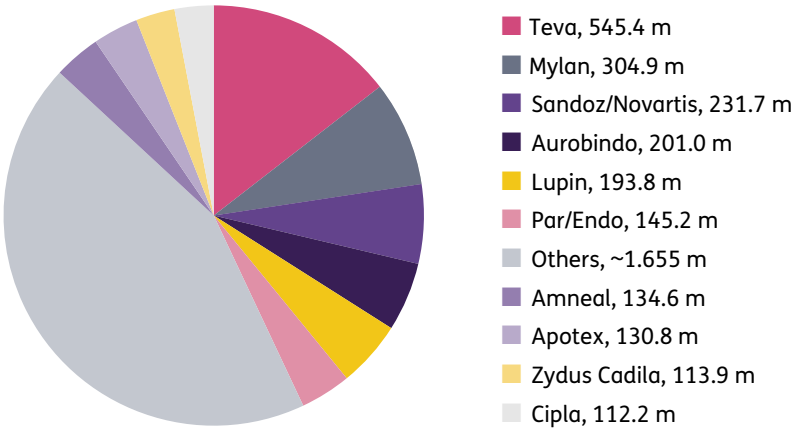
Exhibit 4: The 10 Leading Players By Prescriptions In The US Unbranded Generics Market In The 12 Months Ended November 2017



Source: IQVIA

in a row through to December 2017," Long observed. More ANDA approvals increasing competition on many molecules had led to generic deflation worsening, while originators were defending their brands aggressively, he noted. "This has led to a new wave of portfolio optimisation."

Looking at the 767 final ANDA approvals in financial 2017, Long said 80 were for first-time generics. "A lot of them were the fifth, sixth or seventh player in a molecule, driving down price," he remarked. Citing an analysis at Nephron Research, Long said there appeared

to be a strong correlation between the number of ANDA approvals and the degree of price erosion experienced in the US generics market.

With generic prices declining since late 2015, he observed that the rate had slid into double digits by mid-2017 as the ClarusOne purchasing group had first equalised its terms and then begun a bidding cycle. Other consortia had begun to re-bid during the second half of last year, he noted. "It appears that the trend bottomed out around August 2017," Long commented, adding that pricing seemed to have stabilised in recent months, with erosion on solid-dosage forms running about double the 6% slide experienced by injectables.

The result, Long highlighted, had been that 17 of the top 20 US generics players by value had experienced sales declines during 2017, with only Fresenius Kabi, Zydus Cadila and Alvogen exhibiting positive dollar growth in the 12-month period.

Furthermore, half of the top 20 generics firms had seen lower total prescription volumes in 2017 as the market moved increasingly from 30-day to 90-day scripts, he added.

Industry remains fragmented

Whereas the top three generic purchasing groups controlled around 90% of the market, "it would take 20 or more generics companies just to get up to 75% market share by value", he stressed. As Exhibit 3 shows, the top 10 unbranded generics suppliers by value, before discounts, in the 12 months ended November 2017 held just over a 56% combined share of an almost US$60 billion market, led by Teva with 13.3%, Mylan with 10.7% and Novartis' Sandoz with 7.8%. However, Teva's grip on the top spot weakened as its unbranded generics sales slid by almost a third in the 12-month period, while Mylan and Sandoz suffered single-digit declines.

Long pointed out that Fresenius Kabi was set to cement its place in the value top 10 by acquiring 20th-placed Akorn, while the planned merger between Impax and Amneal would also create a player that could threaten the top five.

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Teva, Mylan and Sandoz also led the way last year in terms of unbranded generics dispensed, but India's Aurobindo – which Iqvia ranked only 16th by value – was their closest volume challenger following double-digit growth, followed by Lupin, Endo's Par, Amneal and Apotex. Two other Indian companies, Zydus Cadila and Cipla, rounded out the volume top 10 *(see exhibit 4)*.

Cipla and Zydus Cadila trailed only Alvogen in terms of absolute dollar growth in the unbranded generics segment during the 12 months ended November 2017, with Kabi, Lannett, Intas' Accord, Alembic, Endo and ANI also among the others to advance in value terms. Cipla, Aurobindo and Citron led the way in terms of absolute prescription growth, while the most commonly dispensed unbranded generic was Lupin's lisinopril, followed by Mylan's levothyroxine and Apotex' atorvastatin.

"We are seeing a significant uptick in efforts by certain branded companies to keep competition from coming to the market."

Looking forward, Long said small-molecule brands with combined US annual sales of almost US$75 billion were at risk of generic competition between 2018 and 2022. Widely disparate forecasts for potential US savings from biosimilars reflected the ongoing uncertainties around the pace of uptake, with Sandoz' Zarxio and Teva's Granix rivals to Neupogen (filgrastim) each taking around a fifth of the US market, while Lilly's Basaglar alternative to Sanofi's Lantus (insulin glargine) had garnered a similar share. But Pfizer's Inflectra biosimilar of Remicade (infliximab) had, to date, made only minor inroads, he observed.

In an exclusive interview conducted during the association's annual meeting, AAM president and chief executive officer Chip Davis told **Generics *bulletin*** that the US could take many lessons from Europe. "We talked a lot while they executed," he acknowledged. "Europe has millions of days of patient experience, and we can learn from that," he stated.

While the FDA remained committed to developing the regulatory pathway for biosimilars, Davis said there was a danger of a "litigation backlog" hampering access. Originators were consistently attempting to weaken incentives to develop biosimilars and bring them to market, or to hamper market uptake, he observed. "We are in the process of finalising a campaign for greater awareness on biosimilars, targeting healthcare providers," Davis revealed.

In the small-molecule generics arena, Davis identified three areas in which industry was facing challenges. Firstly, he said, buyer consolidation was causing concern. "Secondly, we are seeing a significant uptick in efforts by certain branded companies to keep competition from coming to the market," he outlined, not least through contracting strategies on rebates between originators and PBMs that were being struck to keep generics off formularies. "These contractual relationships are a *de facto* extension of the monopoly," he said, noting that Pfizer was fighting similar tactics employed by Johnson & Johnson to hamper the uptake of biosimilar infliximab.

Thirdly, Davis explained, US companies were having to contend with "an increasingly volatile legislative environment" at both federal and state level. Bills were often poorly drafted and failed to appreciate vastly different dynamics in the off-patent and patented sectors, he observed, adding that this trend threatened to chill incentives to bring competition to market.

The AAM's current priority, Davis stated, was ensuring that there was awareness around these issues as the association honed its policy recommendations. One area where the AAM and its allies had already created significant traction was on the draft Creating and Restoring Equal Access To Equivalent Samples (CREATES) Act that could still be passed by Congress this year (**Generics *bulletin***, 23 February 2018, page 8).

"Manufacturers may say they got a record number of ANDAs through the FDA last year," Davis stated. "But if they also set a record for how few of them they launched into the market, that is not efficient for the market, our members or the FDA."

Published in Generics Bulletin, 2 March 2018

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US Companies Should Steer Story On Pricing

▶ By Aidan Fry

Individual member companies within the Association for Accessible Medicines (AAM) can do more to "control the narrative" around drug pricing and access, the US industry body's president and chief executive officer, Chip Davis, told delegates to the AAM's 2018 annual meeting.

Speaking in Orlando, Florida, Davis described the generics and biosimilars industries as "underdogs". "Compared to others in the pharmaceutical supply chain, when it comes to public policy and advocacy, we have far fewer resources," he pointed out, adding that originators spent US$20-25 for every US$1 invested in such activities by generics and biosimilars providers.

Drug costs, he said, were "the number one healthcare issue" in the US at present, and while generics accounted for almost 90% of all medicines dispensed in the US, brand companies held around 90% of "the mind-share" in the public policy debate.

Nevertheless, he said the AAM had registered significant achievements since its rebranding from the Generic Pharmaceutical Association (GPhA) around a year ago. The association had testified several times before Congress during 2017 and had also contributed to both a Food and Drug Administration (FDA) workshop on balances within the Hatch-Waxman legislative framework and a joint FDA/Federal Trade Commission (FTC) forum on competition (**Generics *bulletin***, 3 November 2017, page 13). Furthermore, bills on user fees for both generics and biosimilars had been ratified, while harmful proposed changes to labelling had "gone into the deep freeze" as bad policy. "We got some important wins on biosimilars to ensure there are appropriate incentives in the marketplace," he added.

However, 2017 had been "a very challenging year" for industry, Davis said, with "unprecedented sustained periods of price deflation in the generics sector" and continuing consolidation that was tilting "the negotiating table in favour of buyers". A rumoured takeover approach by Walgreens Boots Alliance for AmeriSourceBergen threatened to further restrict competition in the supply chain, he observed.

Encouraging delegates to band together to "drive our own narrative", Davis warned that, with US mid-term elections this year, "policy-makers are going to prioritise good politics over good policy".

"We have the opportunity to do a lot more to advance the value proposition of the generic and biosimilar sectors of AAM," Davis insisted. "Tell your individual story as a business," he urged, noting how originator firms had mobilised rapidly after President Donald Trump's State of the Union address to deflect blame for rising drug costs onto other parts of the supply chain. "I do not want anyone but the leaders of this industry to be controlling the narrative of this industry," he stated.

"We have an opportunity to help more leaders get out there and explain the value proposition of this industry," he continued. "If we raise the level of engagement now and put more resources in play, there is nothing we cannot accomplish, because we are on the right side, the side of patients, access and affordability."

Companies should cultivate relationships with local media to explain their value proposition and current challenges, Davis proposed. "Invite policy-makers to your offices," he advised, adding that politicians wanted to understand their constituents' problems. "Hundreds of millions of patients around the world rely on this industry for safe, affordable and effective medicines," he concluded. "We have nothing to apologise for."

The AAM will hold its next annual meeting on 4-6 February 2019 in New Orleans, US.

Published in Generics Bulletin, 23 February 2018

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Structured Reviews Will Accelerate ANDAs

▶ By Aidan Fry

Testing and implementing a more structured, computer-aided assessment process for abbreviated new drug applications (ANDAs) will enable the US Food and Drug Administration (FDA) to accelerate approvals on their first review cycle, according to Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER).

Addressing the annual meeting of the US Association for Accessible Medicines (AAM) in Orlando, Florida, earlier this month, Woodcock admitted to delegates that the current trajectory of the ANDA program was "probably not sustainable under current assessment practices".

While the FDA was approving record numbers of ANDAs (**Generics *bulletin***, 16 February 2018, page 10), Woodcock recognised that the number of ANDAs received by the agency rose in its 2017 fiscal year by 54% to 2,849. "We expect this rising trend to continue over the next several years," she said. Over the same period, controlled correspondence increased by 42% as "questions from industry are becoming more pointed and detailed, as well as larger in volume".

"There are still many inefficiencies in the review process under the Generic Drug User Fee Amendments (GDUFA)," Woodcock admitted, stressing the need to achieve more first-cycle approvals and decrease the number of refuse-to-receive notifications (RTRs) to minimise workload on both industry and the FDA. A first-cycle ANDA approval rate of 12.8% in fiscal 2017 was broadly in line with recent trends, meaning a large number of filings were sent back to industry for rectification. And while fiscal 2017's RTR rate of 10.5% was around half of the 20.9% average between fiscal 2015 and 2017, such rejections represented "a waste of time and effort for both you and us".

"The real question for me is how can we revise the program and right-size staffing so we understand the throughput and workload that gives us a steady state?" she said. The key, she outlined, was giving applicants clarity on the agency's expectations and structuring the review process so that it was more standardised.

At present, Woodcock acknowledged, the application assessment process – particularly pertaining to quality – was "labour-intensive", with multiple scientists creating text-based documents that were "not very amenable to knowledge management". "We do not have very good visibility in terms of what we have done before, and it is hard for us to understand the precedents from what we have told similarly situated applicants," she admitted.

To tackle this problem, the agency's Office of Pharmaceutical Quality (OPQ) has developed a knowledge-aided assessment and structured application (KASA) as "a new paradigm for performing quality assessments of applications". By adopting a more tabular, structured approach, Woodcock said this would create "consistency across what we are asking of applicants" and "remarkably improve the efficiency of processing applications."

The agency was, she said, currently testing and improving prototypes of computer-aided interfaces and was piloting a "dashboard interface" that was centred around quality risk-assessment for critical quality attributes and corresponding mitigation strategies, as well as control strategies for drug substances and products. "We are putting a fair amount of investment into testing these prototypes," she explained. "Once we really start utilising and improving them, we will be able to share them with industry."

"Ultimately, maybe some years hence, we would like to have a more structured submission that is more based on data than on text, but we are not there yet," Woodcock concluded.

Published in Generics Bulletin, 23 February 2018

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ANDA Pre-Submission Meetings A 'Challenge' To Integrate Into Development Timelines

▶ By Derrick Gingery

Pre-submission meetings with the US FDA are popular among complex generic sponsors, but there are questions about how best to make them part of the product development process, since it appears even companies are having trouble fitting them into their schedules.

"A current challenge is how industry will integrate product development and pre-submission meetings into a product development timeline," according the minutes of a Jan. 10 meeting between FDA officials and the generic industry to discuss implementation of the user fee agreement.

As part of the generic drug user fee reauthorization, FDA allowed sponsors of complex generics to schedule meetings to discuss drug development issues (called a product development meeting) or to explain the contents of an upcoming ANDA (pre-submission meeting) with agency officials. Ideally, the meetings will allow FDA to offer guidance and other tips to ensure the ANDA meets expectations upon submission. They may prove important for complex product sponsors, since those generics historically have been difficult to develop. *(Also see "Complex ANDAs To Be Allowed Pre-Submission Product Meetings" - Pink Sheet, 24 Oct, 2016.)*

The current iteration of the generic user fee program does not specify how long the agency has to schedule a meeting after sponsor request, but "if industry plans their pre-ANDA interactions with FDA well, then sponsors will not have to delay product development while they are waiting for FDA's input," the agency told the Pink Sheet Feb. 23.

As the agency "holds more of these meetings and gains experience, FDA may be able to make recommendations around the timing of holding these meetings," the meeting minutes noted.

FDA is planning to produce more product-specific guidances for generic development, which it hopes will reduce the need for individual sponsor meetings and help drive the agency's Drug Competition Action Plan's goals on improving ANDA review efficiency to push down drug prices. *(Also see "US FDA Commits To Meeting With Complex ANDA Sponsors, Works Hard To Avoid It" - Pink Sheet, 24 Oct, 2017.)*

Getting In As Early As Possible

Product complexity likely will dictate meeting planning, but sponsors may want to schedule the meetings sooner rather than later in the development program, said Robert Pollock, a former acting director of FDA's' Office of Generic Drugs, who now is senior advisor and outside director to the board of Lachman Consultants.

But sponsors also must be certain that there is enough data for FDA to take the meeting. Meeting packages can be time-consuming to develop and must be submitted with the meeting request. *(Also see "Unhappy With GDUFA II? Note It For GDUFA III, FDA Says" - Pink Sheet, 28 Nov, 2017.)*

"One would think that firms would try to get in as early as possible with preliminary data so they can better understand how the agency expectations will impact their preliminary plans," Pollock told the Pink Sheet. "Historically it has been a learning process for both OGD and the firms, especially with a highly complex product."

Scheduling meetings has been a challenge on the new drug side as well. There was a learning curve when FDA began offering mid- and late-review cycle meetings for NDA sponsors during PDUFA V. After scheduling problems surfaced, agency and industry officials agreed to allow meeting waivers as part of PDUFA VI. *(Also see "Sponsors, FDA Reviewers To Get More Flexibility Under New User Fee Program" - Pink Sheet, 15 Jul, 2016.)*

The agency also missed some scheduling goals under the biosimilar user fee program *(Also see "FDA Met Biosimilar Review Timelines But Missed Meeting Goals In 2015" - Pink Sheet, 25 Apr, 2016.)*, and during BsUFA reauthorization talks, made changes to relieve the pressure.

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(Also see "Biosimilars Will Get PDUFA-Style Reviews Under New User Fee Plan" - Pink Sheet, 28 Sep, 2016.)

Is Meeting Workload Already A Problem?

FDA also wants to build tools to predict its meeting workload as well as when in the timeline they will be requested, said David Gaugh, Association for Accessible Medicines senior VP for sciences and regulatory affairs, who attended the GDUFA II implementation session. Gaugh said there are too many variables to be able to build a successful model.

The agency also wants to create a model that will help determine when and/or whether an ANDA sponsor will address the problems outlined in complete response letters. But variables also may hinder its development.

FDA already may be concerned about the upcoming meeting workload. The agency said in the minutes that first quarter meeting requests for complex products suggest that the total for fiscal year 2018 will be double the annual request rate during GDUFA I. FDA told the Pink Sheet that it had received 25 pre-ANDA meeting requests in FY 2018.

Gaugh said FDA projected during GDUFA II negotiations that it could handle about 60 pre-ANDA meetings per year.

FDA tried to control the workload in draft guidance by limiting product development meeting requests to one per year per product. *(Also see "Complex ANDAs: Early Meetings With FDA Can Generate Bonus Communication" - Pink Sheet, 2 Oct, 2017.)*

Sponsors Must Seek Pre-Assigned ANDA Number Before Sending Meeting Request

Complex product sponsors must request a pre-assigned ANDA number before sending a product development or pre-submission meeting request.The agency said in the minutes the number is necessary to link the meetings and associated material with the actual ANDA once it is submitted.

To receive a pre-assigned ANDA number, sponsors must have a secure email with FDA, then send a message with the pertinent information. FDA said on its website that it cannot accept these requests through the Electronic Submission Gateway.

Pre-assigned ANDA number requests must include basic information such as applicant name, address, US contact information, drug name or master file subject, and the drug trade name, if applicable.

Sponsors also should include the reference listed drug name and RLD number, when NCE exclusivity, if any, will expire, and whether they previously have filed applications containing the active ingredient.

In addition, the sponsor must state whether the pre-assigned ANDA number is for an "old antibiotic," which is an application for a drug with an antibiotic that was the subject of a marketing application received on or before Nov. 20, 1997. The 1997 FDA Modernization Act ended the antibiotic monograph system and exempted "old antibiotics" from patent listing, certification and exclusivity regulations.

Sponsors should receive their pre-assigned number within three business days, according to the FDA website.

Filing a meeting request is more technologically advanced than gaining an ANDA number. FDA rolled out a web portal for those submissions last fall that allows sponsors to track the status of their requests, as well as upload meeting packages. *(Also see "FDA Web Portal Eases Pre-ANDA Meeting Request Process" - Pink Sheet, 9 Oct, 2017.)*

Published online in Pink Sheet, 23 February 2018

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In Switching Generic 'Reviews' To 'Assessments' Is US FDA Changing More Than Just A Word?

▶ By Derrick Gingery

The US FDA's decision to change ANDA "reviews" to "assessments" may represent a sea change in its approach to generic drug reviews. Or it could simply be a more accurate description of the increasingly complicated application evaluation system. Opinions of the significance of the new wording, which was recently rolled out in an internal FDA policy manual, appear to stretch the gamut.

Attorney Kurt Karst, director at Hyman, Phelps and McNamara, said in an interview with the Pink Sheet that it is only a terminology change. He said the agency now is emphasizing how ANDA evaluations always have been assessments. "Assessment sounds more in-depth, which FDA wants to reinforce," Karst said.

But Robert Pollock, senior advisor and outside director to the board of Lachman Consultants, who is a former acting director of FDA's Office of Generic Drugs, said calling evaluations assessments is part of an effort to better ensure staff "stick closer to the regulatory requirements and not go off script because they see something interesting."

Pollock said "it will be a huge change in thinking if it translates into action."

"This has been a long-standing problem – ever since I was there," he said. "Changing the culture of the reviewers/assessors, I believe, will be difficult, but the supervisors must now get tough and not allow the primary reviewers/assessors [to] deviate from the regulatory requirements."

David Gaugh, Association for Accessible Medicines senior VP of sciences and regulatory affairs, took a more middle-of-the-road stance. He acknowledged it was a change in thinking, but did not call it significant.

A Manual of Policies and Procedures document issued Jan. 3 made the change as part of an adjustment to the generic drug application evaluation process. The agency said it would begin calling ANDA reviews assessments "to reinforce the policy and procedural changes," which included dropping the primary, secondary and tertiary review system in favor of a primary assessment and secondary assessment with division directors overseeing staff and consulting as needed.

The MaPP also mandated several streamlining policies, such as focusing on so-called "need to know information" in applications. The new procedures are part of Commissioner Scott Gottlieb's Drug Competition Action Plan, which is FDA's response to problems with rising drug prices. *(Also see "FDA Drug Pricing Policy Offers Short-Term PR Gain, More Long-Term Actual Benefit" - Pink Sheet, 27 Jun, 2017.)*

Gottlieb had signaled that ANDA review process and policy changes were coming as part of efforts to increase generic application evaluation speed. *(Also see "FDA Exploring Whether Public Shaming Can Stop REMS Abuses" - Pink Sheet, 18 Jul, 2017.)*

Definitions Differ Slightly

Brian Malkin, counsel at Arent Fox, thinks assessment and review represent two different ideas. A review is more of an evaluation of the application to determine whether it has met the criteria for approval, while an assessment targets the application components, Malkin said.

"I put assessment more in the application quality bucket," he said.

FDA's definitions of review and assessment are not all that different. (*See table, p. 20.*)

The agency said staff examine submitted data during reviews, while analyze it during assessments, but both definitions indicate the goal is to determine whether the application should be approved.

FDA also included that the agency should document the reasoning for the decision in the definition of assessment, which appears to be a nod to efforts to improve commu-

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Review or Assessment? FDA's Definitions	
"FDA has generally defined review as thoroughly examining all submitted data on the drug and making a decision to approve or not approve it." *– Agency response to Pink Sheet question*	"Assessment means the process of both evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination." *– FDA's Good ANDA Assessment Practices MaPP*

nication between FDA and industry. Among the directives in the MaPP is that staff should "clearly communicate to applicants what deficiencies must be corrected for their ANDAs to be approved."

FDA has also increased the transparency of its new drug review system by requiring reviewers to complete a benefit-risk assessment framework where they outline the reasoning behind approval decisions. *(Also see "US FDA's Benefit/Risk Framework Gets High Marks But Could Be Improved" - Pink Sheet, 20 Sep, 2017.)*

Attorney David Rosen, a partner at Foley and Lardner and a former regulatory counsel at FDA, said the new ANDA communication system seems to be fostering more interaction between FDA and sponsors earlier in the evaluation. "They're trying to get the information out to companies so they can respond and not lose their place in the process," he said.

Indeed, under the generic drug user fee program renewal, FDA agreed to send discipline review letters and information requests by the middle of the first review cycle. *(Also see "FDA To Use New Discipline Review Letters In Communicating ANDA Deficiencies To Generic Drugmakers" - Pink Sheet, 28 Dec, 2017.)*

Will You Say 'Assessment' Instead Of 'Review'?

Rosen said the language in the MaPP is interesting, but implementation will determine whether it will spur substantial change. Another interesting question may be whether assessment will become as integral part of generic drug industry conversations as review now is. Rosen was willing to adjust his vocabulary if it will ensure OGD meets its ANDA evaluation goals and runs in a predictable manner.

"I don't care what you call it," he said.

Karst said as FDA continues to use the term, it eventually will sink in. "Folks will be using assessment over time," he said.

Pollock was less optimistic, predicting review "will stick around. ... Ever try to change the culture of the FDA?" he said. "It is like trying to move an elephant with a feather."

Indeed, Gottlieb seemed to revert to the old vernacular in his statement announcing the MaPP's release. While he said the document "outlines ANDA assessment practices for FDA staff," he also added that it "formalizes a more streamlined generic review process."

Published online in Pink Sheet, 10 January 2018

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Generic Combination Products May Be Permitted Delivery Device Variations

▶ By Derrick Gingery

US FDA officials seem open to some delivery device differences to make it easier for generic combination products to reach the market, but acknowledged the difficulties of balancing product variations with safety concerns.

For example, variation in the sets of instructions for uses of products dispensed through a pharmacy is potentially problematic, Badrul Chowdhury, director of the Division of Pulmonary, Allergy and Rheumatology Products in FDA's Office of Drug Evaluation II, said.

"You would have the instructions for use for the innovator and the generic ... and the patient would walk out with no training," Chowdhury said during the May 3 generic drug user fee program's fiscal year 2018 research workshop. "That's where you need to come in and think would you allow variations on this."

> **"As long as those features are identified and focused in these studies and shown despite those minor differences [that the] devices are equally accepted and used by the patient population, I think that should really serve the purpose here,"**
> **– Amneal's Ravi Harapanhalli.**

Chowdhury said that while some device differences may not matter much, for others, like an auto-injector, FDA may not want variations such as one product operated by applying pressure to the device and the other by a pressing a button.

"In situations where [there is] chronic use, every week you inject ... you may allow the risk-based judgement," he said.

Office of Generic Drugs Deputy Director John Peters was not ready to wholly allow device variations either, because of the increased opportunities for misuse.

"If you give a patient a particular device-drug combination and they could potentially misuse it, they will misuse it," Peters said. "For that reason we have to be very cautious in terms of what kinds of differences are allowable, thinking in terms not only of how they may work well, but also in terms of the failure modes."

Still, the comments suggest that FDA may be more willing to allow some device variation if possible to push generics onto the market and potentially bring down drug costs.

New FDA Commissioner Scott Gottlieb told Senators during his confirmation hearing that changes to the combination product instructions for use regulations may be appropriate to encourage more generic entry and price competition. *(Also see "Complex Generics: Gottlieb Eyes FDA Policy Changes To Speed Approvals" - Pink Sheet, 5 Apr, 2017.)*

Let Companies Justify Device Variations, Amneal Official Says

Ravi Harapanhalli, **Amneal Pharmaceuticals LLC** senior VP of Global Regulatory Affairs, argued during the workshop that there can be situations where the design features of

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the generic can differ from the reference product "as long as everybody agrees there can be some difference."

"It's a humongous task for generic companies to really navigate through all this maze to come with their design that best represents the innovator's product in terms of usability, design features, and patient acceptance while all the time ensuring that critical product attributes for the device are preserved and maintained and bioequivalent with the reference product," he said.

Harapanhalli said companies should be allowed to prove that device differences would not impact the instructions for use.

"As long as those features are identified and focused in these studies and shown despite those minor differences [that the] devices are equally accepted and used by the patient population, I think that should really serve the purpose here," he said.

FDA released draft guidance on generic drug-device combinations in January that said the devices must not require provider intervention or patient retraining, a substantial requirement for substitution. *(Also see "ANDAs For Drug/Device Combos Face High Bar At US FDA; Epipen, Advair May Benefit" - Pink Sheet, 17 Jan, 2017.)*

Among the biggest problems that the industry has had in developing competitors for products like **GlaxoSmithKline PLC**'s *AdvairDiskus* (fluticasone/salmeterol) and **Mylan NV**'s *EpiPen* (epinephrine) is creating an equivalent delivery device.

In many cases, the devices are protected by several patents, which hinder the generic's ability to be ruled bioequivalent, and can force the generic sponsor to gain approval through the new drug pathway, which is much more expensive and time-consuming, often because a clinical trial could be required.

In the case of EpiPen, **Teva Pharmaceutical Industries Ltd.** had filed an ANDA using a delivery device that was similar, but Mylan filed a citizen petition and study that showed the competitor's device may not work the same as the EpiPen device.

Mylan argued that Teva's product could not be substituted for EpiPen because in an emergency if providers followed the instructions for an EpiPen, the medicine would not be administered correctly. FDA ultimately issued a complete response letter for Teva's ANDA. *(Also see "Mylan's EpiPen Exclusivity Saved Again As Teva Reports CRL" - Pink Sheet, 1 Mar, 2016.)*

FDA also raised significant problems with Mylan's proposed Advair generic, which lead to a complete response letter. Mylan said the agency applied updated guidance on human factors studies for use of its device, which was different from an agreement that had been in place. *(Also see "Advair Generic: Mylan Takes Issue With US FDA's 'Major' Concerns" - Pink Sheet, 10 May, 2017.)*

Another Drug Pricing Answer?

FDA and industry acknowledged problems with complex generics during generic drug user fee reauthorization negotiations and expanded communications to help sponsors better understand FDA requirements.

The agency agreed to allow pre-submission meetings for complex generic sponsors, which could help avoid multiple review cycles. *(Also see "Complex ANDAs To Be Allowed Pre-Submission Product Meetings" - Pink Sheet, 24 Oct, 2016.)* The House Energy and Commerce Committee wants to expand the idea to include generics with little or no competition. *(Also see "Breakthrough-Style Program For ANDAs Added To House User Fee Bill" - Pink Sheet, 18 May, 2017.)*

By speeding development and approval of generics, some members of Congress hope the additional competition will help bring down drug costs. While FDA cannot take price into account when it approves drugs, it still can help deal with the problem, Gottlieb told agency staff. *(Also see "Gottlieb Places Drug Pricing Out Front In First Speech To US FDA Staff" - Pink Sheet, 16 May, 2017.)*

Published online in Pink Sheet, 4 June 2017

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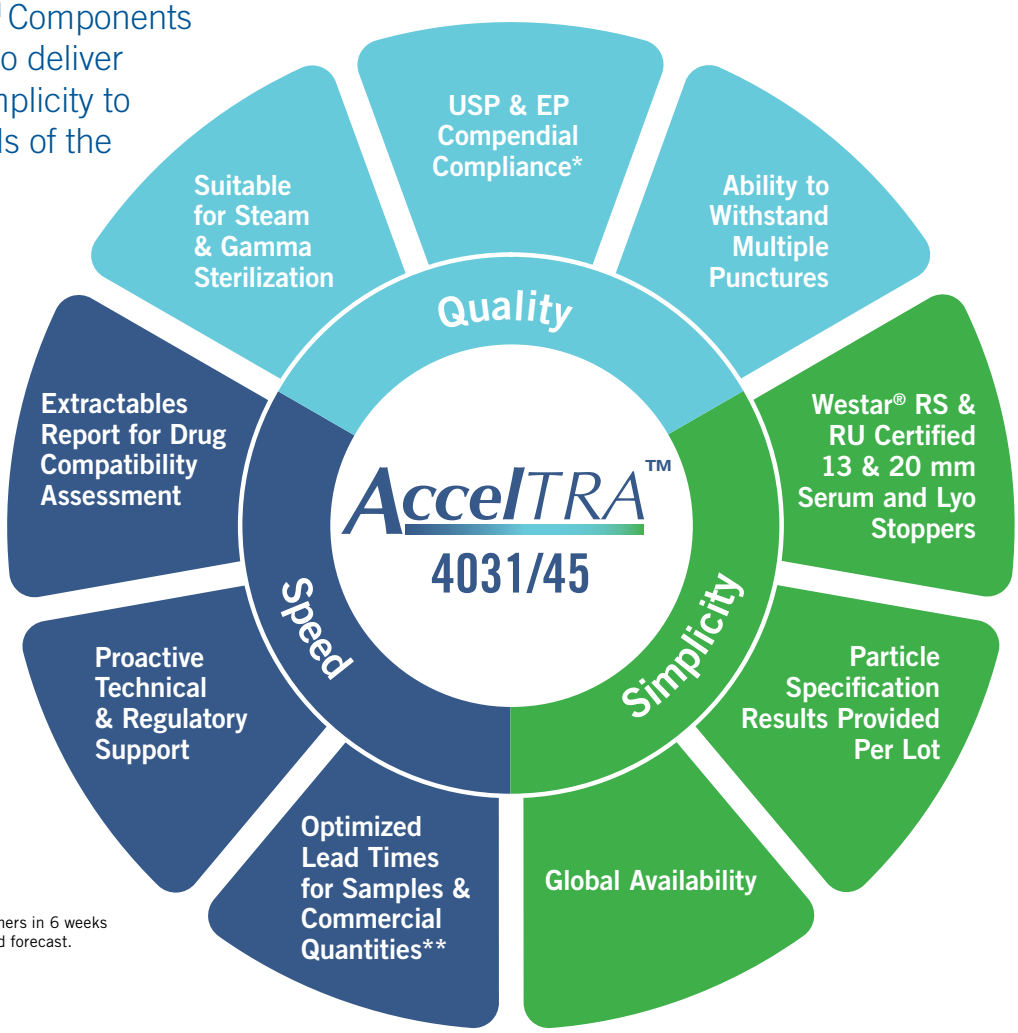

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