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Beyond "Breakthrough": FDA, Industry See Benefits For Drugs Outside Expedited Pathway

by Sue Sutter

Pharmaceutical manufacturers and FDA have enthusiastically embraced the “breakthrough therapy” program as a way to more quickly bring new drugs with substantial effects to patients in need. With two years of program experience now under their belts, agency and industry representatives talk about learnings and best practices that could be applied to the development and review of drugs outside the program.

- Under breakthrough, FDA commits to bring an “all hands on deck” approach to help expedite the efficient development and review of therapies for serious conditions when early clinical evidence suggests there may be a substantial advance over existing treatments.
- Benefits realized by sponsors to date include a seemingly unprecedented level of interaction with agency reviewers and senior staff, answers to questions and resolution of problems in almost “real time,” and smaller clinical data packages to support approval.
- More broadly, the program has changed how FDA reviewers interact with sponsors, making them a participant in the drug development process rather than an observer.
- The next PDUFA reauthorization in 2017 will create an opportunity to make large or small changes to the program and, potentially, extend its learnings across a broader range of products.

FDA’s “breakthrough” designation has been the breakout star of the review changes ushered in under the last user-fee reauthorization. With enthusiastic adoption and positive reviews, stakeholders are eager to replicate the program’s success. The early experience with the breakthrough therapy program could serve as a model for transforming and improving the development and review of drugs and biologic products that do not carry the expedited

regulatory pathway designation.

Pharmaceutical and biotechnology sponsors have enthusiastically embraced the breakthrough program. They have swarmed the agency with more than 200 requests for designation – a number far more than agency and industry reps expected at the time the program was enacted as part of the 2012 FDA Safety and Innovation Act. (*See online sidebar "A Primer On FDA's "Breakthrough Therapy" Program*.)

from large and small companies with breakthrough-designated products have lauded the agency's management of the program and its intensive engagement with sponsors aimed at expediting the development and review of highly innovative and effective therapies. They also are quick to point out the advantages realized under the program, ranging from reduced clinical development time, quick resolution of problems that could potentially delay an approval, and increased visibility, both within FDA and externally, of rare diseases and other conditions with unmet medical needs.

Primer On FDA's "Breakthrough Therapy" Program

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A look at the genesis of the US expedited regulatory pathway for drugs and biologics, its benefits, and how the program is working today.

Read the full article here

With more than two years of breakthrough program experience under their belt, FDA and industry are now starting to talk about ways in which lessons from the breakthrough program could inform the development and FDA review of new products that do not carry the special designation.

> ***Breakthrough has changed the dynamic of how FDA interacts with sponsors, making the agency more of an active participant, and less of an observer, in the drug development process.***

Breakthrough has changed the dynamic of how FDA reviewers and senior officials interact with sponsors, making the agency more of an active participant, and less of an observer, in the drug development process. In addition, it has forced FDA and sponsors to work together to develop

creative clinical trial designs and novel data packages that could support approval of new treatments, and to reach agreement on what data are required pre-approval and what can be pushed back into the post-approval setting.

"The real benefit is not only to the [breakthrough] sponsor but really to the FDA, and that is for us to start thinking a little bit differently of how we interact with sponsors," FDA Office of Hematology and Oncology Products director Richard Pazdur, MD, said at a recent industry meeting. "I view this as a very positive aspect of the program."

The expedited program has opened the door for sponsors to have an improved dialogue – one that is continuous, rigorous, and scientifically enriched – with FDA, *Portola Pharmaceuticals Inc.*CEO William Lis said at a recent Biotechnology Industry Organization meeting. "If this could expand into other areas beyond breakthrough designation, I think it would be a great day for the industry."

Speaking at the same meeting, *Catalyst Pharmaceuticals Inc.*chairman and CEO Patrick McEnany said breakthrough is "an important, innovative program that allows us to get people who are very sick important medicines quicker, and that's a good thing. We hope that we can see this program expanded in a … broader sense within the agency to help everybody that is submitting NDAs and treating these diseases."

Cartier Esham, executive VP of BIO's emerging companies section, said the trade association wants to understand how FDA and sponsors are working to expedite development and application review "and look at it from a point of view of what criteria did they utilize to allow novel endpoints or non-traditional clinical trials."

"Is that the kind of information that could be utilized to modernize or perhaps expedite the regulatory and development process more broadly in the long view?" she asked during a panel discussion at the October 7 *BIO Investor Forum*.

The quinquennial reauthorization of PDUFA is the usual time for stakeholders to work on ways to improve drug development and FDA review, and the breakout success of the breakthrough program could become a target for applying the model more broadly as planning begins for the next round.

Early Bolus Of Requests

Breakthrough is intended to expedite the development and review of drugs and biologics for serious or life-threatening diseases or conditions when preliminary clinical evidence indicates they may demonstrate a substantial improvement over existing therapies. The designation comes with a number of benefits, including intensive interaction and advice from FDA on an efficient drug development program.

As of September 30, 64 of 227 requests for breakthrough designation had been granted by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. (*See online sidebar, "FDA Offers Clues, But No Clear Standards, On "Breakthrough"-Worthiness, for a discussion of requests and lack of official standards for the program.*)

Speaking at the *BIO Investor Forum*, Esham said that of 52 designated products for which information is available, one-fourth were from small companies. About 43% of the designations were in oncology and 56% were for products targeting rare diseases, she said.

As of November 10, 10 novel products and four supplemental indications with breakthrough designation have been approved.

Many of the novel products approved to date received the designation late in development or even after NDA/BLA submission. Yet, the breakthrough program is expected to be most impactful for those products that gain the designation early in clinical development.

Given the late designations for many of the drugs and the still youthful nature of the program itself, determining whether breakthrough drugs uniformly come to market months or years faster than they would have without the designation will be difficult until the program matures.

Nevertheless, interviews with, and public comments by, industry representatives and current and former FDA officials consistently reflect a number of key advantages that breakthrough products have enjoyed, even those that received the designation late in development. *(See sidebar, "Should You Request "Breakthrough" Status? Sponsors, FDA Give Their Advice.)*

"The program is a remarkable success," said Rachel Sherman, MD, a principal in the consulting firm Greenleaf Health and former director of CDER's Office of Medical Policy, where she was responsible for implementing the breakthrough program. She added that "there's no question" that drugs are getting to the market faster under the designation.

FDA Offers Clues, But No Clear Standards, On "Breakthrough"-Worthiness

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Although officials say "breakthrough therapies" are "transformative" treatments that "hit you in the face" with their efficacy, the agency has yet to release clear guidelines to help industry determine when a product is worthy of the coveted designation.

Read the full article here

Should You Request "Breakthrough" Status? Sponsors, FDA Give Their Advice

Communication And Coordination

FDA staff and sponsors repeatedly stress the benefits of increased and intensive communication in moving a product through the development and regulatory process faster.

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Companies need to be selective in seeking the designation and certain that they'll be able to keep up with the accelerated pace of development and manufacturing expected under the expedited pathway.

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In the development phase, such communications, which include input from FDA senior staff, have had the effect of clearly and quickly giving sponsors guidance on a development plan. During the NDA/BLA review of breakthrough products, the interactions have served as a channel through which potential issues that could threaten a timely, or even early, product approval were quickly resolved.

Communication is a cornerstone of a CDER "best practices" document – officially known as a Manual of Policies and Procedures – that outlines the actions its staff will take from the time a designation is granted until a marketing application has been submitted. (*See (Also see "CDER Takes A Micro/Macro Approach To Monitoring 'Breakthrough' Programs*" - Pink Sheet, 11 Aug, 2014.).) Such actions include convening a comprehensive, multidisciplinary meeting with the sponsor shortly after designation to discuss the drug development plan and to establish a communication plan for efficient management of future interactions. (*See* (Also see "*'Breakthrough' Drugs Get 'Road-MaPP' – Complete With Communication Timetable*" - Pink Sheet, 29 Jul, 2014.).)

Novartis AG cited speedy and efficient communication as among the key advantages provided under the breakthrough program as it pursued approval of the lung cancer drug *Zykadia* (ceritinib).

The Breakthrough Advantage: FDA Expedites Zykadia Name Review

Novartis' breakthrough designation for the lung cancer drug aided its ability to quickly get a new proprietary name approved after the agency rejected the company's original proposals. Review documents indicate FDA expedited the review process to provide preliminary analyses of alternative names, including Zykadia, in an effort to meet the agency's internal goal date for product approval.

Genentech Inc.'s leukemia drug *Gazyva* (obinutuzumab) was the first novel product approved under the breakthrough pathway. In an interview, Genentech VP of US regulatory affairs Michelle Rohrer said it's important to have an early conversation with the review division about each party's expectations once the designation has been granted, and not just with regard to

clinical issues.

"I think that sponsors need to get clarity from FDA right at the beginning, assuming that this will move quickly, [about] FDA's expectations with regard to the CMC specifications and material, the quality plan, [and] validation plan," she said.

In the case of Gazyva, an enhanced level of communication was integral to a speedy approval even though breakthrough designation was not awarded until after BLA submission.

FDA review documents indicate that agency and Genentech personnel had regular, almost weekly teleconferences on CMC and product quality issues with the goal of ensuring an adequate supply of product would be available at the time of approval. FDA approved Gazyva on November 1, 2013, almost two months ahead of the December 20 PDUFA date.

Rohrer said the frequent teleconferences reflected the speed at which FDA's product quality reviewers were working. "They wanted to work quickly and so that meant that they needed a channel where they could have real-time dialogue as opposed to a more paper-based dialogue, and those weekly telecons afforded it."

Regular conference calls on CMC issues also were a hallmark of the Zykadia review and showed the agency-wide commitment to these products. Novartis noted that "the calls were not always weekly, but a close relationship was maintained, which helped to truly resolve any issues/questions almost in real time."

The early involvement of senior review division staff also has had a noticeable impact.

At the *BIO Investor Forum*, Catalyst CEO McEnany described the company's first meeting with FDA after receiving breakthrough designation for amifampridine phosphate in the treatment of patients with Lambert-Eaton myasthenic syndrome.

"In that meeting … the senior staff was there, so it wasn't like you asked a question and somebody had to get back to you," he said. "There was a lot of dialogue, a lot of interaction at that meeting. It was very constructive to coming away with a conclusion, and I think that compresses a lot of the time that you spend typically" in drug development.

BIO's Esham said that looking at the types of interactions that are occurring between FDA and breakthrough product sponsors could help improve such interactions outside the program.

> *BIO is looking at "how these interactions are working well and how, when appropriate, might they be applied and should be promoted more broadly." - Cartier Esham, BIO*

"Are people outside of breakthrough having different kinds of conversations" than what would normally be expected "because they realize it's productive and time effective? I think one of the things we want to look at this program for is how these interactions are working well and how, when appropriate, might they be applied and should [they] be promoted more broadly," she said.

The emphasis on meetings and intensive communications between FDA and sponsors is inherent in the statutory language that created breakthrough. However, the program's goal of expedited development and the "all hands on deck" approach promised by FDA also has required that different review disciplines within the agency communicate and work more effectively with each other on a given product.

"One of the things that we noticed was that … everyone of the FDA review divisions was reviewing at the same pace, and that's not always true under non-breakthrough therapy conditions," Genentech's Rohrer said. "It was very clear that because of the breakthrough therapy designation that the whole FDA team, I like to say, was marching to the beat of the same drummer."

Such internal improvements in communication and alignment of goals among review functions are being hailed within the agency as a major benefit of the breakthrough program.

"The biggest benefit of breakthrough is not for the breakthrough drugs, it's for the subsequent drugs that come through, and I'm not even talking about the subsequent drugs that are breakthrough drugs because it really changes our thought process in terms of how we look at applications," FDA's Pazdur said at an FDA/Product Quality Research Institute conference in North Bethesda, MD, September 16."The key to this … is the importance of breakthrough therapy, not necessarily for the drug, but for the process, for the internal FDA organization as far as communication, not only with the sponsor but also internally at the FDA."

Like other large organizations, FDA has its challenges when it comes to internal communications, Pazdur said. However, the breakthrough program "helps us to … improve these communication patterns not only with the sponsors but also internally [to] take a look at what really do we need for a drug approval."

Pazdur said breakthrough is a "major cultural shift" because it has required FDA reviewers to think differently about how they interact with sponsors. With breakthrough, review team members have become participants in the drug development process, Pazdur said, explaining that this is different from the traditional view of "I'm the reviewer and this is a review issue and I don't know what the right thing to do is, this is going to be your problem."

Breakthrough also has provided a platform for CDER's Medical Policy Council, which vets all designation requests, to consider broader policy issues that impact drugs both inside and outside the program, according to Sherman, who previously chaired the council.

Navigating Manufacturing Landmines

Since the start of the program, there has been widespread concern in FDA and industry that manufacturing issues, particularly the challenges of scaling up for commercial-level production, would become a rate-limiting step for breakthrough products. Simply put, while a novel product might be ready for approval from a clinical perspective, a sponsor's manufacturing operations might not be able to keep up with the accelerated clinical development and review anticipated under breakthrough.

Review documents for some of the early breakthrough approvals reflect such concerns about sponsors' manufacturing readiness and capacity. For example, CMC issues stand out in the Gazyva review documents, reflecting the tension created when speed must be balanced by product quality and manufacturing capability.

Rohrer said one of the key elements of the review was whether the clinical material met Genentech's specifications for commercial material. "It was determined, through the work that we did together with FDA, that the clinical material met all specifications of the commercial material," she said.

In a reflection of the type of flexibility FDA is willing to show under breakthrough, Genentech launched Gazyva with commercial material that was sourced from the clinical supply – a move necessitated by the speed of the drug's review and approval, Rohrer said.

"If we had been approved on the action date, then we would have had commercial material to supply to launch, but because we were approved in advance of the action date the commercial material hadn't quite gone through all the necessary checks and the work that needs to be done," the Genentech exec said. "So we leveraged the fact that we could source the commercial supply from the clinical material given that it met all of the specifications."

However, Rohrer was emphatic that Genentech did not receive any breaks on CMC requirements resulting from Gazyva's breakthrough status. "There were no special allowances given and I think that that's something that FDA is quite clear on, especially on the CMC side, that they

won't be cutting sponsors any breaks, just because their product has breakthrough therapy designation, on the quality of the manufacturing."

In a May 2014 guidance on breakthrough and three other expedited regulatory programs, FDA said it may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components, such as stability updates, validation strategies, inspection planning, and manufacturing scale-up. (*See* (Also see "*"Breakthrough" Flexibility: FDA Answers Industry Call On Manufacturing Data*" - Pink Sheet, 9 Jun, 2014.).)

At the FDA/PQRI meeting, Pazdur emphasized the agency's willingness to be flexible on manufacturing issues for breakthrough drugs – to a certain extent.

> ***When it comes to product quality issues, "there is a difference between regulatory flexibility and contortionism." - Richard Pazdur, MD, FDA***

With breakthrough drugs, "we really have to work in concert to get that drug out and we will take the appropriate flexibility of doing that from a manufacturing standpoint, including even the release of study materials that have been seen with some of these applications," he said. However, "there is a difference between regulatory flexibility and contortionism," Pazdur said. "There is just a point where it becomes impossible for us to make that leap of flexibility."

Sponsors who request breakthrough designation need to understand it's not just clinical issues that will go through the expedited process. Rather, consideration needs to be given to how a company will accelerate manufacturing so as to ensure an adequate supply of drug at the time of approval.

"I really would emphasize for our colleagues in the chemistry divisions and manufacturing divisions … to get their senior people involved very early into these applications both from the company perspective as well as from the regulatory perspective," Pazdur said.

The agency also has paid special attention to getting on top of potential manufacturing compliance issues before they become a hurdle to a breakthrough approval.

Among the early breakthrough approvals, compliance-related manufacturing issues have arisen late in the review for several drugs, including *Gilead Sciences Inc.*'s hepatitis C treatment *Sovaldi* (sofosbuvir), Novartis' Zykadia, and *Merck & Co. Inc.*'s melanoma treatment *Keytruda* (pembrolizumab).

In the case of Sovaldi, manufacturing compliance issues forced Gilead to withdraw two facilities from the NDA late in the review process, leading to questions about the company's ability to meet expected patient demand. (*See* (Also see "*Sovaldi NDA Review Marred By Manufacturing Compliance Issues*" - Pink Sheet, 22 Apr, 2014.).)

Just weeks before Zykadia's approval, CDER director Janet Woodcock was consulted about a compliance issue at a manufacturer involved in the production of the ceritinib active pharmaceutical ingredient – a problem that potentially could have delayed the drug's expedited approval. (*See* (Also see "*Zykadia Expedited Timeline Challenged By Late-Breaking GMP Concern*" - Pink Sheet, 7 Jul, 2014.).) Merck removed a facility from its Keytruda BLA after it became apparent that the biologic's approval would be held up until the site could be inspected.

Clinical Time Saved

Much of the promise of breakthrough is tied to the notion that with early identification of a potentially substantial efficacy benefit, a sponsor and FDA can work together to devise a clinical program that is more efficient in both time and number of subjects than would normally be required to support a regulatory filing.

"The earlier you could get the breakthrough designation, I think, the more helpful it's going to be," Pazdur said. "We could start discussing plans for the initial submission of the drug [and] what are going to be the required studies. That's going to be the area where you see the most significant impact."

Pharmacyclics Inc./*Janssen Pharmaceutical Cos.*' *Imbruvica* (ibrutinib) received accelerated approval for mantle cell lymphoma November 13, 2013, making it the second novel drug approved under the breakthrough program, just 12 days after the Gazyva approval. However, it gained breakthrough designation earlier in the course of development than Gazyva did and the impact was evident in the clinical program ultimately submitted to support approval.

The Breakthrough Advantage: Sovaldi Gains Broader Label Thanks To New Data

FDA's Division of Antiviral Products directed Gilead to request breakthrough status late in the NDA review because it believed the designation was necessary to evaluate a large volume of new clinical data ahead of the hepatitis C drug's user-fee goal date – without the breakthrough program, FDA couldn't have reviewed that late submission of data in the initial review period. Reviewers analyzed efficacy data for more than 500 subjects from two trials with just two months

left in the review cycle, culminating in sofosbuvir's on-time approval in early December 2013 with the broad indication requested by Gilead.

In an interview, Pharmacyclics senior VP of global regulatory affairs Urte Gayko said the designation led to an NDA submission at least six to nine months earlier than originally anticipated. Coupled with a speedy FDA review that lasted just four and one-half months, the company ultimately saved about one year total in development and review time.

"In our particular case, we really did change the package that was submitted for the NDA for the approval of the drug" because of its breakthrough status, she said.

In the MCL indication – one of three areas where ibrutinib holds breakthrough status – the sponsor and FDA agreed on a different pivotal study than originally anticipated, which meant that clinical data were available sooner and the time line for submission was moved up, Gayko said. Pharmacyclics was able to use a Phase II study as the primary basis of its submission, she said.

Novartis also saw some time savings with Zykadia, thanks to an abbreviated clinical program. Zykadia received breakthrough designation in March 2013, more than nine months before completion of a rolling NDA in December. The lung cancer drug received accelerated approval on the basis of a Phase I trial that was also a first-in-human study. The company used an adaptive design to collapse the traditional functions of Phase II and Phase III – dose finding and safety and efficacy – into Phase I. (*See (Also see "Dose Finding At Breakthrough Speed: FDA Found A Role For Anecdotal Reports On Zykadia*" - Pink Sheet, 18 Jun, 2014.).)

"All areas of our program were expedited based on the Phase I study and as a result we went to market with the formulation that was tested in that study," Novartis said. "Considering the urgent patient need and early efficacy signals, we filed based on the Phase I data and received conditional FDA approval based on this study."

The company said it was able to shave off more than a year in development time, with some clinical obligations shifted to the post-approval setting. "Novartis is now working to complete extensive post-marketing requirements for Zykadia to be granted full approval by FDA, which includes a large-scale, multi-year clinical development program."

The pre-approval clinical program for Keytruda also was abbreviated. The first anti-PD-1 to clear FDA received accelerated approval on the basis of a single randomized, open-label, dose-ranging, multicenter cohort of 173 patients within a large, multi-stage, multiple cohort, dose-finding, activity-estimating, safety and tolerability trial.

In some cases, it's not just about the clinical time saved but also about the creative approaches to

designing a clinical program that can support a breakthrough approval.

Portola's andexanet alfa holds breakthrough designation as a direct reversal agent for patients receiving a Factor Xa inhibitor who suffer a major bleeding episode or require emergency surgery. Portola CEO Lis told the *BIO Investor Forum* that the company hopes to move from IND to BLA filing "in less than three years, and in our space that's absolutely unheard of."

The company is currently conducting Phase III trials to evaluate the safety and efficacy of andexanet alfa in reversing the effects of various Factor Xa inhibitor anticoagulants in older healthy volunteers. Efficacy is being evaluated using biomarker endpoints, including anti-Factor Xa levels. The company is targeting a BLA submission for accelerated approval in late 2015.

"In the field of thrombosis, we're going to get approval based on data from healthy volunteers," Lis said. "It's absolutely unheard of in the field that I've been working in in the last 30 years."

Looking Ahead To PDUFA VI

Although the breakthrough program was created in FDASIA, it was not part of the Prescription Drug User Fee Act V reauthorization agreement contained within that legislation, and the agency did not receive any additional resources or user fees for its implementation. Given the program's popularity and the lack of dedicated resources, there has been concern that the added workload might overwhelm the agency.

The PDUFA VI reauthorization in 2017 would seem to provide a natural opportunity for industry and FDA to make changes to the breakthrough program given the knowledge that will come with a few more years of experience with the expedited regulatory pathway.

Some in industry already have highlighted areas that they would like to see tweaked, either in legislation or in FDA policy.

For example, Pharmacyclics' Gayko suggested that mandatory mid-cycle communication and late-cycle meetings for new molecular entities and novel biologics should be optional for breakthrough therapies because trying to squeeze those meetings into the compressed review time frames has proven challenging. (*See* (Also see "*"Breakthrough" Review: FDA And Sponsors Discuss Ways To Improve Efficiency*" - Pink Sheet, 12 May, 2014.).)

BIO's Esham and Andrew Emmett, its managing director of science and regulatory affairs, said the trade group will continue to "look for ways to ensure that any barriers to expedited access to these products, such as expediting manufacturing validation or cross-center review of companion diagnostics or combination therapies, are addressed early in the process."

The influx of breakthrough designation requests and the number of designations granted to date

– coupled with FDA's always-limited resources – raises the possibility of a legislative tightening of the criteria for breakthrough therapy.

Another possibility that might be on the table – although surely one that will not garner much support from industry – is a dedicated user fee to support the program. The UK's recently launched Promising Innovative Medicine designation was inspired by FDA's breakthrough program, but includes a fee of about $6,800 for a designation assessment. (*See* (Also see "*The UK's Early Access Scheme: Breakthrough Or Mixed Blessing?*" - In Vivo, 5 Aug, 2014.).) BIO said it has not discussed a user-fee model to support the breakthrough therapy program. However, the group is intent on looking at how best practices from breakthrough can inform modernizing approaches to drug development and review more broadly.

The program could serve an even greater purpose than just getting designated new medicines to people in need, Esham told the *BIO Investor Forum*.

"This could be a learning process," she said. "It could help inform how certain interactions enable expedited development or enable the ability to utilize more modern approaches, novel endpoints, non-traditional clinical trial designs. And by studying those interactions and learning from them it can and should be an iterative process that informs the ability to use those things more broadly outside of the breakthrough program."

Greenleaf's Sherman said it seems a sure thing that the concept of breakthrough, including any expansion or reevaluation, will become fodder for discussions in the course of the PDUFA VI reauthorization or sooner as part of the House Energy and Commerce Committee's 21st Century Cures Initiative, which is focused on accelerating the pace of cures from discovery through development to delivery. Committee leaders expect to have a discussion draft of legislation ready by January 2015. (*See (Also see "Biomedical Reform Legislation Draft Could Be Released By January*" - Pink Sheet, 11 Sep, 2014.).)

However, Sherman sees little need for legislative tinkering at this time, and she credits the statute's focused scope for much of the program's success to date. Breakthrough is "a remarkably good piece of legislation," she said, describing its drafting in FDASIA as a "very targeted, very succinct, laser sharp piece of law."

"It's doing exactly what it was intended to do, and it seems to be doing it extremely well," Sherman said. "In my personal opinion, at the moment, changes are not warranted."