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Quick Pulse

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The Ongoing Taxus Stent Recall

The recall of Boston Scientific's Taxus (paclitaxel-eluting) stents keeps expanding, and sources still aren't sure the bad news is over. Concern remains that the rest of the "old" stents in the pipeline – or even the "new" stents with a manufacturing "fix" – could still face a recall in the near future. FDA officials deny the company has lost credibility or that any additional recall is imminent or likely, but the agency is still investigating. Boston Scientific certainly won't win any awards for the way it has handled this problem.

Taxus was launched in Europe in February 2003 and in the U.S. on March 4, 2004. It quickly took market share from Johnson & Johnson's sirolimus-eluting Cypher stent, and some sources had estimated that Taxus had ~70% of the drug-eluting stent market when the first recall was announced.

However, the stent has been plagued with problems almost from Day One. Two issues became apparent as early as April 2004: (1) retraction/deflation problems and (2) stickiness. The recalls have all been related to the deflation problems, and company officials have indicated they do not believe they can fix the stickiness, but they discount its importance.

April 2004: The First Reports of Problems

Interventional cardiologists and cath lab managers started reporting problems with Taxus stents a month after they hit the U.S. market. There were rumors of deployment issues, and an unconfirmed report that up to five patients receiving a Taxus stent sustained adverse events caused by an inability to separate the balloon from the expanded stent. At least two of the affected patients were sent to surgery for bypass procedures. While Boston Scientific acknowledged that one or two cases of failed balloon retraction did in fact occur and prompted surgical repair, the company claimed that these were issues that also occurred on occasion with bare metal stents, that the rate of occurrence was in line with conventional products, and that no design changes were planned as a result of these problems.

Company officials implied any problems were "operator" issues and suggested it was an over-the-wire (OTW) problem, but three French doctors reported both retraction and stickiness issues with Taxus at a medical conference on April 8, 2004. Two U.S. doctors who experienced retraction problems in their labs didn't think it was due to operator error. One said, "This is a real issue. We've had many stents where it felt like the polymer was sticking to the balloon. The company says that is not the case, but that's what it feels like. We've had many cases with major problems and two serious consequences. Both patients did okay, but it was not pleasant. We are still using Taxus, but I'm nervous about it…Boston Scientific says that if you deflate the balloon carefully and slowly, you won't have the problem, but I can't say I'm convinced."

MAY 2004: A MANUFACTURING CHANGE DESIGNED TO FIX THE PROBLEM

Boston Scientific announced in early May 2004 that it had gotten FDA approval for a small design change to laser welded balloon bond on the Taxus stent, following reports of problems with retraction. In late May 2004, a Boston Scientific official insisted that the change had already been made and that stents with the change incorporated already were being shipped. He insisted there were no additional changes to the stent planned in the near future. The change that was made was not intended to address a stickiness issue, for which the company reportedly has not been able to find a solution, and U.S. doctors appear to be learning to live with the stickiness.

JULY 2004: THE FIRST RECALL

On July 2nd Boston Scientific announced the first Taxus recall – of just 200 stents shipped to 99 U.S. and three Canadian hospitals. The company said the problem was due to "characteristics in the delivery catheters that have the potential to impede balloon deflation during a coronary angioplasty procedure," noting that impeded balloon deflation could result in significant patient complications, including CABG and death. A narrowing in the area where the catheter and balloon are laser welded was blamed for impeding deflation and removal of the balloon after stent placement. Boston Scientific claimed the problem was limited to two manufacturing lots, which were identified by a quality monitoring program – and all of the stents were made before the manufacturing change. At the time, the FDA had reports of at least one death and 16 serious injuries associated with Taxus balloon deflation as well as at least eight reports of balloon malfunction not associated with patient injury.

Cardiologists were concerned with the recall, but the recall did not appear to be affecting their willingness to use Taxus to any significant degree. A cardiologist said, "We haven't had any additional problems. It seems to be business as usual. But I expected the company to be more pro-active. The company is acting like it is not a big deal, but to me it has been very disturbing. But I'm still using Taxus stents."

JULY 2004 – TWO WEEKS LATER: THE RECALL EXPANDS SIGNIFICANTLY

On July 16, 2004, Boston Scientific expanded the recall to encompass 85,000 Taxus stents and 11,000 bare Express[2] stents. By this time, about 500,000 Taxus stents had been shipped, and the company admitted to three deaths and 53 serious injuries: one death and 28 serious injuries with Taxus, and two deaths and 25 serious injuries with the bare Express[2]. Federal Express packages with detailed explanations were sent out to all hospitals.

U.S. hospitals were expected to be fully re-supplied within three to four weeks, and European hospitals within four to six weeks. A Boston Scientific official said, "We cast a broad net…to remove all product from the field that had any chance of no deflation…There are six lots of OTW Taxus affected …All other OTW Taxus will be left in the field…The bare metal Express has been affected to a much smaller degree…but we did find some lot numbers in Monorail Express that had a similar issue as Taxus. OTW Express (bare) is not affected."

It was possible for the company to replace 96,000 stents this quickly, a company official explained, because: "We have maintained – in each manufacturing facility – enough capacity to supply the entire DES market…And we have manufactured at a rate 40% higher than sales...in the event something like this happened."

Boston Scientific officials called this a "significant recall" and did a webcast to inform doctors about the problem. They carefully avoided calling this a stent problem, repeatedly referring to this as a "catheter" problem. Some of the key points out of that discussion include:

- **Deflation cause.** The deflation problem was believed due to a combination of a manufacturing defect (occasional excessive heat in spots that weakens the polymer) plus at least one pound of force. "No deflation" was defined as a failure of the delivery catheter balloon to deflate within one minute after deployment of the stent. This was believed to be caused by "focal neckdown" (a narrowing of the inflation/deflation lumen, which restricts the flow of contrast media out of the balloon). An official said, "We've known the catheter could manifest focal neckdown for some time…but until a few weeks ago we thought it occurred randomly in the field at low rate of <1:10,000…and we felt that everything was good as it left the plant…We are recalling ~85,000 systems due to one bad system found in inventory…It is logical that we can build fences around the good and bad product…The vast majority of those stents being recalled probably would function normally, but we can't be certain."

- **Identification of problem stents.** The company was able to determine which stents were "good" and which were potentially risky and needed to be recalled because of three things: (1) inspection under magnification, (2) a process change to avoid future laser hot spots, and (3) a laser software monitoring program. However, the software monitoring program was only installed in the Maple Grove MN facility, not the plant in Ireland.

- **FDA.** Officials characterized the FDA as "reasonably comfortable" that there won't be a continuing problem. However, a ***Wall Street Journal*** article suggested that the FDA was still investigating the situation.

- **Modified stents.** There had been no complaints about any of the 65,000 "revised" or "new" stents in circulation.

- **Recalled product.** All recalled product was to be destroyed.

➢ **Stickiness.** The company was distinguishing between the deflation and stickiness issues. An official said, "The sticky balloon phenomenon is something we are taking extremely seriously, but it is not linked quite frankly to the same severity…Right now, we have a very clear root cause analysis with No Deflate, but that is not true with sticky balloon. We have been able to identify some procedural characteristics, such as acute angulation of the vessel or presence of calcification on the vessel that correlates to balloon withdrawal issues, but no device-specific or manufacturing-specific change we can make at this time that might limit the sensation of withdrawal stickiness…My sense is there may be some balloon stickiness that is caused by slow or very slow deflation…It might well be that when we remove from the field all the product at risk of No Deflate that we positively influence the rate of stickiness sensed by the clinician...but that remains to be seen."

Doctors and hospitals were much more concerned about this recall. Several major U.S. cath labs suspended use of Taxus stents entirely until they knew more about the situation. Sources predicted Boston Scientific's market share would drop by about 10% within 30 days, but would probably stabilize at that level – unless additional recalls or problems were announced.

- *New England cardiologist:* "We have suspended all Taxus use and Express[2] use. I am not sure what will make us use them again, but I am confident that we will. Prior to the recall we were split evenly between Taxus and Cypher."

- *Cardiologist who suspended use of Taxus in his lab for a week:* "I'm not sure that the problem has been rectified, and that 85,000 is the last recall. This recall will impact the market share…There will be slower adoption of the stent."

- *Florida cath lab manager:* "We won't be changing from our 60% Cypher/40% Taxus use that I can see. We still get a slight price break on Cypher…I feel that some of this is technique. (Our) interventionalists…are not having issues…I don't see much difference (with the Taxus problem) from the subacute thrombosis issue with Cypher… My doctors are very comfortable with using the (Taxus) stents, perhaps because they have not had any deliverability issues with them. They do not seem to be as concerned over legal implications as I thought they would be. If there are more incidents with new product, that may change their mind quickly."

- *A Midwest cardiologist:* "I'll continue to use Taxus, although when deliverability is not an issue, I'm now going to be more likely to consider Cypher…I think this entire saga hurts Boston Scientific's credibility. This is not the first time they've had safety issues with a device (Nir with Sox and rotablator recalls, for example), and their approach was similar – stonewall…If there is not a good reason to use Taxus over Cypher (deliverability, for instance, or availability), then one might be at risk for a lawsuit. However, this is not a big issue here."

European doctors initially were less worried about the recall. A German cardiologist said, "We will still be using Taxus because I personally have not seen any problems." A French cardiologist said, "I have no specific concerns as all companies experience technical problems once in a while."

Another worry was whether Johnson & Johnson would be able to supply the entire drug-eluting stent market if all Taxus stents were recalled. A J&J official said, "We have the capacity to make as many stents as needed, and we will ramp up production to meet any additional customer needs…We can ramp production, but, depending on customer needs, there may be some back orders because it will take some time to ramp up production." Another J&J source said, "We are taking steps to be able to do that…We've been operating in a different mode for the past several months. That would be a big change in the market dynamic, and you would have to get yourself set up for the other kind of dynamic...If you can't get Taxus, and can't get all of the Cypher when you want it, you still can reach for a bare metal stent. While that may not be the way you desired to go, you are not compromising patient care. So there will be plenty of people, including Boston Scientific which would say, 'Well, just use our bare metal stents.'"

AUGUST 2004: EUROPEAN RECALL

On August 6, 2004, the European watchdog agency (MRHA) issued a recall of ***all*** old Taxus and bare Express[2] stents – by date and not by lot number. The MRHA advised European doctors and hospitals:

- ➢ Do not implant any:
  - Taxus Express² stents labeled with "use by" dates earlier than October 2005.
  - Express² stents labeled with "use by" dates before June 2006.
- ➢ Review stocks of coronary stents and identify those affected.
- ➢ Immediately segregate all affected product and return to Boston Scientific in accordance with their instructions.

The explanation included the MRHA's announcement:

"Virtually all products distributed in the U.K. pre-date this manufacturing improvement (implemented in May 2003 for Express² and in April 2004 for Taxus Express²) are affected by this recall. Therefore, MHRA is advising that identification of products to be returned to the manufacturer should be based upon the product 'use by' date, since this can be correlated with the manufacturing date. Express² stent systems have a three-year shelf-life and Taxus Express² stent systems have an 18-month shelf-life. The 'use-by' date for both products is printed on the outer box label and on the inner pouch label in the format: YYYY-MM…A revised analysis by the manufacturer indicates that this recall now covers approximately 23,000 Express² and approximately 16,000 Taxus Express² stent systems distributed in the U.K., and a total of 162,000 stent systems worldwide."

AUGUST 2004: THE FDA PERSPECTIVE

On August 6, 2004, several hours after the MRHA action, the FDA held a press conference to explain to reporters its view of the expanded Taxus recall. Dr. Daniel Schultz, Director of the FDA's Center for Devices and Radiological Health, said there have been no additional deaths since the July 16th recall. He could not say precisely how many "old," unmodified stents were in the pipeline (inventory and shipped), but he estimated the number to be between 100,000 and 200,000. He also advised reporters that:

➢ **No additional recall.** The FDA had decided not to further expand the recall at this time. Dr. Schultz said, "Given what the company has done and given the systems that they have in place, some of which are redundant systems, and none of which is 100%, until we have further information, we feel that at this particular time it would be unwise to initiate any further recall…At this particular time, our belief is that the product that has been recalled is – was – appropriately recalled. The product that is currently on the shelves or has already been shipped is safe, and the additional actions being taken by the company and the agency will continue to assure that safety."

➢ **FDA still has concerns.** Dr. Schultz said, "The preliminary indication that we have from (our) discussions is that these quality assurance measures are adequate to assure the safety of the product. We are, however, continuing to look at this information extremely carefully. There is data regarding these quality systems that haven't yet been completely reviewed, and we are reviewing that as we speak…If we determine that there are problems that we have not seen at this particular time, we will take the appropriate steps." He predicted the agency would have all the information it needs by August 9th and should be able to look at it by August 11th-13th, though the complete inspection in Ireland may take longer.

➢ **European recall.** He was unaware of the European agency's actions further expanding the Taxus recall in Europe.

➢ **Ireland plant.** The FDA never inspected Boston Scientific's Ireland plant after this problem arose and now realizes that it made assumptions about that plant which may not be true and will be inspecting it soon. Dr. Schultz said, "We did have an inspection at the facility in Minnesota, and we have not found any serious problems identified during that inspection. We have not up until this time inspected the manufacturing facility in Galway, Ireland…We felt that the processes at the two plants were very similar, if not identical. It turns out there are or have been some difficulties in terms of at least the way the quality system has been implemented at those two facilities, so we are going to be inspecting the Galway facility as soon as we possibly can…But I think it's somewhat reassuring that the inspection that has occurred so far has not turned up any significant problems."

➢ **Meetings.** No additional meetings scheduled with Boston Scientific, but the agency is in ongoing discussions with the company, and a meeting is possible.

➢ **Cypher impact.** Broader availability of Johnson & Johnson's Cypher stents would not have impacted this decision/process or made it more likely that the FDA would have ordered a larger Taxus recall.

➢ **Acceptable failures.** The FDA is willing to accept a certain percentage of failures. He commented several times, "Nothing is 100% perfect." He added, "The company is…adding redundancies to the system in order to be as sure as humanly possible that these devices are safe…I have no reason to believe that there is an undue risk associated with the use of either the pre-manufacturing-change product or the post-manufacturing-change product."

➢ **Credibility.** Boston Scientific still had credibility with the agency. Dr. Schultz said, "At least up until this point, we feel that the company has been open and has been sharing information with us as that information has become available to them. Obviously, they were not happy – that's sort of an understatement – to have to report this latest incident…but I think that they did identify this problem and reported it as soon as it was made available to them…We all have to be honest and recognize that no system is perfect…As of today, I am confident in…our decision not to do anything at this particular time."

➢ **Stickiness.** The FDA did not consider the stickiness problem to be a safety issue. Dr. Schultz said, "My best understanding is that the issue of stickiness is really sort of a misnomer. I think people had the idea that the balloon actually sticks to the polymer or the drug. It appears that is not the case. There have been some instances, depending on how the device is positioned, where there can be some difficulty in dislodgement of the balloon once it's been deflated…That's something that the company is looking into certainly, and I suspect that future generations of this product will attempt to correct that problem. We don't believe that this constitutes an imminent danger to patients as opposed to the deflation problem which certainly caused some deaths and patient injuries."

THE FUTURE

Cardiologists and cath labs are waiting to see if there will be:

1. ***Another recall of more "old" Taxus stents?*** Sources said they would not be surprised to see this.
2. ***A complete recall of all the "old" Taxus stents?*** This also would not surprise some sources, and one suggested it is what should have been done initially.
3. ***A recall of any or all of the new, modified Taxus stents?*** This, sources agreed, would be a disaster for Boston Scientific. ♦