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Quick Pulse

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When Can Withdrawn Drugs Be Re-Launched?

When a drug is pulled from the U.S. market for safety reasons, that is usually the end of that drug. However, it is possible, in rare circumstances, for drugs to return to the market. Currently, companies are trying to bring back two drugs – Merck's Cox-2 inhibitor Vioxx (rofecoxib) and Biogen Idec/Elan's multiple sclerosis therapy Tysabri (natalizumab). To better understand the regulatory path for a re-launch of these and other withdrawn drugs, Dr. John Jenkins, Director of the FDA's Office of New Drugs, was interviewed.

The door was opened for a Vioxx re-launch when the FDA determined in April 2005 that the cardiovascular (CV) side effects with Vioxx are, at least to some extent, a class effect for all NSAIDs. Tysabri's superior effectiveness over other available multiple sclerosis therapies is the main reason there is any hope for a return of that drug. Vioxx and Tysabri are both likely to get restricted labels, but the FDA may require either regular monitoring or some form of restricted distribution as well for Tysabri. However, the FDA does not appear to be convinced yet that there is an accurate test to monitor Tysabri patients for progressive multifocal leukoencephalopathy **(**PML). Neither drug is likely to be on the market again soon, and the timeframe for Tysabri is at least 9-12 months.

Other Drugs with Safety Problems

A number of drugs have been pulled from the market for safety reasons, including:

- Merck's Vioxx (rofecoxib), a Cox-2 inhibitor.
- Biogen Idec/Elan's Tysabri (natalizumab, antegren), for multiple sclerosis.
- GlaxoSmithKline's Lotronex (alosetron), for irritable bowel syndrome in women.
- Warner Lambert's Rezulin (troglitazone), for Type 2 diabetes.
- Roche's Posicor (mibefradil), a calcium channel blocker for hypertension.
- Purdue Pharma's Palladone (extended release hydromorphone), an extended release narcotic painkiller.
- Pfizer's Bextra (valdecoxib), a Cox-2 inhibitor.

Of these, only Lotronex actually made it back onto the market, and Lotronex use is highly restricted. Several other drugs were initially launched with restricted access or restricted distribution systems, including:

➢ **Celgene's Thalomid (thalidomide),** a cancer agent. The S.T.E.P.S. program is designed to prevent fetal exposure to thalidomide, so the question is not really managing the toxicity of thalidomide to the patient who is getting it.

All thalidomide prescribers must be licensed and they must register in the S.T.E.P.S. Prescriber Registry. Patients must be given counseling materials outlining the teratogenic risks, other side effects and precautions associated with the drug, and the selection of ***two*** contraceptive methods. Patients must sign a consent form, take a quiz to verify they understand the risks and requirements of therapy, and undergo regular pregnancy tests. Thalidomide survey forms also must be completed by both the prescriber and the patient.

- **Novartis's Clozaril (clozapine),** an antipsychotic.
- **Roche's Accutane (isotretinoin),** for acne.

Accutane

On August 12, 2005, the FDA announced that the SMART risk management program is being replaced with a new program, iPLEDGE, designed to make sure women do not become pregnant while taking Accutane, which can cause serious birth defects. Starting December 31, 2005, the following must register and agree to carry out the iPLEDGE program in order to participate: wholesalers who distribute it, doctors who prescribe it, pharmacies that dispense it, and patients who take it.

- Starting November 1, 2005, only wholesalers registered with iPLEDGE will be able to obtain isotretinoin from manufacturers.
- Starting November 1, 2005, only pharmacies registered with iPLEDGE will be able to receive isotretinoin from registered iPLEDGE wholesalers.
- Starting December 31, 2005, iPLEDGE pharmacies must obtain authorization from the iPLEDGE system before filling any Accutane prescription. If the patient is registered, the pharmacist will receive an iPLEDGE authorization. For females of child bearing potential, this authorization is based on a current, valid negative pregnancy test result. Only prescriptions from prescribers registered in iPLEDGE will be accepted.
- iPLEDGE prescribers must agree to assume the responsibility for pregnancy counseling of female patients of childbearing potential. Prescribers must obtain and enter into the iPLEDGE system negative pregnancy test results for female patients of childbearing potential prior to prescribing isotretinoin.
- The manufacturers will implement a reporting and collection system for serious adverse events associated with the use of isotretinoin through iPLEDGE. All pregnancy exposures to isotretinoin must be reported immediately to the FDA.
- The manufacturer must provide educational programs and materials for all parties in iPLEDGE regarding the risks of isotretinoin and program requirements.
- Manufacturers and the FDA will assess pregnancy rates and compliance with program requirements to monitor the success of the program.

Clozaril

Clozaril was first approved outside the U.S. in 1970, but in 1975 it was withdrawn from the worldwide market following 16 cases of agranulocytosis, eight of which were fatal. Clozaril sales resumed in a limited fashion outside the U.S. shortly after that, and usage grew over time with the introduction of strict patient monitoring systems.

The FDA approved Clozaril in 1989, specifying it could be sold only with a patient monitoring system in place to prevent fatalities due to agranulocytosis. For many years, providers who dispensed clozapine had to ensure that a patient's white blood cell count was monitored weekly. The use of clozapine also was restricted to three sub-populations: (1) treatment-resistant schizophrenics, (2) patients who cannot tolerate the extrapyramidal symptoms of conventional antipsychotics, and (3) patients with evident tardive dyskinesia that was not suppressed. Clozapine therapy also had to be initiated in an inpatient setting, where the dose could be titrated to reduce the risk of agranulocytosis.

Today, weekly monitoring is only required for the first six months of Clozaril use. After that, white count monitoring can be reduced to once every two weeks. Clozaril is only available through a distribution system that ensures the patient's white blood cell count is in an acceptable range.

Lotronex

Lotronex originally was approved by the FDA in February 2000 for use in women with diarrhea-predominant irritable bowel syndrome (IBS). By November 2000, the FDA had received numerous reports of severe adverse effects associated with the drug, including ischemic colitis, severely obstructed or ruptured bowel, and death, and the FDA concluded that unrestricted marketing posed a substantial risk to patients. However, the FDA and Glaxo were unable to agree on a risk management program for alosetron, and Glaxo voluntarily withdrew the drug from the market.

Subsequently, the FDA and Glaxo both received numerous complaints from patients whose quality of life was adversely affected by the withdrawal of Lotronex. In April 2002, an FDA advisory panel recommended that access to the drug be restored through development of a restricted distribution program that Glaxo proposed. The FDA approved a supplemental New Drug Application (sNDA) for alosetron on June 7, 2002, permitting the remarketing of the drug under restricted conditions of use.

Under the new prescribing program, physicians must enroll in a special Lotronex Prescribing Program, must attest to having certain qualifications, and must agree to fulfill specific responsibilities. Physicians enrolled in the Prescribing Program agree to inform patients of the risks and benefits of Lotronex and to have patients sign a Patient-Physician Agreement indicating that they understand these risks and benefits. Enrolled physicians must then affix a sticker, which identifies the physician as a participant in the Prescribing Program for Lotronex, to each Lotronex prescription. This sticker allows the pharmacist to identify that the prescription was written by a physician enrolled in the Prescribing Program for Lotronex.

Tysabri

On February 28, 2005, Biogen Idec and Elan stopped all clinical trials of Tysabri and voluntarily withdrew it from the market. Tysabri has been associated with several suspected cases – but only three confirmed cases – of PML, of which two were fatal. Two PML cases occurred in multiple sclerosis (MS) patients also taking another Biogen Idec drug, Avonex (interferon beta-1a), but one case occurred in a Crohn's Disease patient on Tysabri monotherapy. A Biogen Idec official said, "Those cases of patients were by no means the typical patients that we see in MS. These were certainly patients that had more significant issues than the average relapsing/remitting patient."

Researchers are working to try to identify a test that could predict development of PML, perhaps through measuring the level of JC viral DNA titers in the serum, white cells, and urine. However, a Biogen Idec official indicated the data so far are inconclusive on the utility of a serum JC virus test to predict and monitor for PML. PML apparently can be detected in cerebrospinal fluid, but that is not a viable monitoring test. The National Institutes of Health (NIH) have developed a CLIA-certified and validated assay to detect JC virus, if that proves a predictive test for PML.

Biogen Idec would like to restart the clinical trial program for Tysabri even before the drug returns to the market. However, an official said patients could not be assured they are not going to contract PML, though the company is pledging a "high degree of clinical vigilance." A Biogen Idec official commented, "What we have found already, and the literature supports this, is that early detection and early immune reconstitution improves prognosis." Another official promised that doctors and patients would be given a "very accurate understanding of what the risks" could be and that doctors would be encouraged not to give Tysabri to patients with "significant immune dysfunction."

Biogen Idec/Elan are expected to re-submit Tysabri to the FDA, along with all the safety data on MS, Crohn's, and rheumatoid arthritis (RA) patients, by fall 2005. The CEO of Biogen Idec said, "In the U.S., they need to have adequate time to deliberate around the information and for us to discuss with them what would be the appropriate new labeling, as well as any appropriate risk mitigation measures. Certainly, we don't intend to do anything unilaterally on that front. In Europe, we are…in the process of the approval reviews…The additional efficacy data would complete the answers to the current consolidated list of questions. We hope to do that in the fall…We obviously need to update the label for the incidence of PML and the warnings relative to PML and monitoring and things like that, in terms of people just being aware of PML. I am not referring to any specific monitoring …Other than that, we don't expect that we would change it from what the label is, which is for relapsing and remitting patients."

Vioxx

Vioxx, an arthritis and acute pain medication, was approved in the U.S. in 1999 and was marketed in more than 80 countries. Safety questions started being asked about Vioxx in March 2000 when the VIGOR trial showed a higher rate of cardiovascular events with Vioxx than with the comparator, naproxen. In September 2004, Vioxx was voluntarily withdrawn from the market worldwide after the APPROVe trial confirmed an increased cardiovascular risk, particularly heart attack and stroke, with the drug.

In February 2005, an FDA Advisory Committee reviewed the safety of all Cox-2 inhibitors, and the panel opened the door for Merck to bring Vioxx back to the market in a restricted way. There was a bare majority in favor of resuming marketing of Vioxx. At that time, an FDA official said, "Currently, Vioxx is voluntarily withdrawn…If Merck continues to have interest (in re-introducing Vioxx), we will welcome them to come talk to us about various pathways forward…We consider committee member comments, and we factor in the comments of people who voted no…If we decided to keep (Vioxx) on the market, we would try to incorporate a mechanism to address those concerns."

Even though Vioxx, like Tysabri, was voluntarily withdrawn, Merck would still need FDA approval to re-launch it, and FDA officials indicated they would have to approve a new label first. The Advisory Committee recommended a black box, an indication for second-line therapy, and perhaps other restrictions. At the panel meeting, Dr. Jenkins said, "Vioxx could not just reappear back on the market (immediately)…There would need to be substantial agreement on moving forward on labeling, which we would have to approve."

In April 2005, the FDA determined that Pfizer's Cox-2 inhibitor Celebrex (celecoxib) and all prescription-strength NSAIDs were getting a black box label warning about the potential risk of cardiovascular events and gastrointestinal bleeding. On April 7, 2005, Pfizer also voluntarily withdrew another Cox-2 inhibitor, Bextra (valdecoxib), from the market at the FDA's request. The FDA had determined that the benefit with Bextra did not outweigh the risk. The FDA also

requested that all over-the-counter (OTC) NSAIDs (e.g., ibuprofen, naproxen, etc.) include more information about the potential gastrointestinal and cardiovascular adverse side effects of the drugs, a warning about potential skin reactions, as well as information about safe use of the drugs (such as duration and dosage).

The FDA April 2005 opinion concluded: "After carefully reviewing all the available data, we believe that the data are sufficient to support a conclusion that celecoxib, rofecoxib, and valdecoxib are associated with an increased risk of serious adverse CV events when compared to placebo…We conclude that the three approved Cox-2 selective drugs are associated with an increased risk of serious CV events, at least at some doses, with reasonably prolonged use…We believe that it is reasonable to conclude that there is a 'class effect' for increased CV risk for all NSAIDs (selective and non-selective)."

The April 2005 guidance document also specified what Vioxx would have to do to return to market, including:

- **A revised label.**
- **Submission of an sNDA.** The FDA specified: "The supplemental NDA would require FDA review and approval prior to implementation of the new labeling since the changes would not be of the type allowed under FDA regulations for a 'Changes Being Effected (CBE)' labeling supplement. The supplemental application should specifically outline the sponsor's proposal for revised labeling designed to provide for safe and effective use of the drug in populations where the potential benefits of the drug may outweigh potential risks."
- **Consultation with an Advisory Committee** and the FDA's Drug Safety Oversight Board (DSB).

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THE FDA PERSPECTIVE

There is little precedent for returning a drug to the U.S. market that was withdrawn for safety reasons. The most recent example is Lotronex. In an April 6, 2005, memo on Cox-2 inhibitors, the FDA outlined the pathway by which Vioxx could possibly return to the market. Dr. Jenkins said that this is pretty much the process for any of the other drugs – e.g., Palladone, Tysabri – that might try to return, "The sponsor would have to submit an sNDA, outlining what data they have and what the proposed labeling would be, the risk management plan, and the justification for a favorable risk:benefit profile. We would review that and take it to a public advisory committee for discussion. Any time a drug is withdrawn for safety, when it is remarketed that warrants an advisory committee, as we did with Lotronex. And now with the Office of Drug Safety Oversight, after the advisory committee it is likely we would like to hear from them before the Agency takes final action. That meeting is not public. There is no guarantee that we would always go to the Drug Safety Oversight Board because we still have to work out how that operates and consider the timelines and the review clocks."

To get permission to re-launch a drug would require an sNDA, Dr. Jenkins explained. He outlined these timelines: "If it were an efficacy supplement, then the PDUFA clock would apply – meaning a decision within 6 to 12 months depending whether it is standard or priority review. If it is just a labeling supplement, which is hard to imagine, there is no PDUFA clock, but we have internal goals of six months."

Understanding risk

From the FDA's perspective, understanding the risk is critical to managing it. Dr. Jenkins said, "There are lots of factors in play, including the nature of the adverse event and how predictable it is so you can manage the risk – whether you can avoid the risk or identify those developing adverse events to stop them in time to prevent a serious adverse event or death. We also have to look at what benefits the drug provides over other therapies. So, it is a complex equation. We left Rezulin on the market until Actos (Lilly/Takeda, pioglitazone) and Avandia (GlaxoSmithKline, rosiglitazone) were approved, and we felt pretty comfortable a year after those were approved, and we were not seeing the same liver toxicity signal. Then, we felt Rezulin was not offering anything more in effectiveness, and the others didn't have the same risk. The Rezulin risk seemed idiosyncratic, and even though we monitored liver function to pick up early toxicity, there were cases that developed so rapidly that the monitoring would not have prevented them from going on to serious toxicity…so monitoring was not the answer."

For a risk factor to be acceptable, it doesn't have to occur predictably or with symptoms. Dr. Jenkins said, "There could be scenarios where a drug is so important to have that even unpredictable and unmonitorable risk might be acceptable. In that case, we would want to get to a situation where doctors and patients were as well informed as possible – and possibly have informed consent – to make sure patients were aware they were being prescribed a drug that is very effective but also carries a risk, and then let patients and doctors decide if it is right for them."

QT prolongation has been a hot button with the FDA, but early testing appears to be successfully identifying this problem before drugs get approved. Dr. Jenkins said, "On QT prolongation, we have good screening in animal and early human studies, so it is less and less likely that drugs with QT prolongation will get approved. Those are being screened out. There are ICH guidelines on how to look for that, so we are unlikely to approve a drug that significantly prolongs QT unless there is a significant benefit because we really can't monitor that effectively in an individual patient."

If a very effective drug had a QT prolongation problem, it might still be able to get approved. Dr. Jenkins explained, "Some QT prolongation problems are from interaction with

other drugs. Some of the QT prolongation is not at recommended doses but in combination with a drug that inhibits its metabolism. If you have a drug without drug interactions and no QT signal at the usual recommended dose, and it takes 10-100x the usual dose to get into trouble, and there are no interactions with ketoconazole, etc., that is a different scenario. That is different from Seldane (Hoechst Marion Roussel, terfenadine) and Hismanol (Johnson & Johnson, astemizole)."

Restricted distribution

Restricted distribution – as with thalidomide or Accutane – is one solution, but this is an option that the FDA uses very, very sparingly. Dr. Jenkins said, "In general, we try to avoid restricted distribution programs if possible because they are very burdensome to the healthcare system. We hear a lot of feedback from patients, pharmacists, and everyone else on restricted distribution programs. If you think about a large number of drugs with different restricted distribution programs, that gets burdensome on the healthcare system. Right now, there are only a handful (of restricted distribution systems) – Clozaril with a blood test, S.T.E.P.S. for thalidomide, and SMART for Accutane with a sticker on the prescription. *(NOTE: This was replaced with the iPLEDGE program shortly after Dr. Jenkins' comment.)* What we hear from stakeholders is it is confusing, complicated, and burdensome. We hear that and try to limit distribution."

Questions also have been raised about the FDA's authority to impose restrictions on distribution and restrictions on prescribing. Dr. Jenkins said, "Our primary authority is over the sponsor. We have very limited authority over physicians. Why not just limit Palladone to pain specialists? There are a lot of practical issues to limiting a drug to a specific group of doctors – how to select the doctors to be allowed to prescribe, what is our authority to tell licensed physicians that they can or cannot prescribe a drug – and it is a big question whether we have the authority to do that…When we hear calls for limiting a drug to pain specialists, for example, there are practical and legal questions."

If a restricted distribution system is the only way to assure the safe use of a drug, it is up to the sponsor, not the FDA, to propose the restricted distribution program. Dr. Jenkins said, "The sponsor is responsible for setting up a certain pharmacy or a program where they don't let a drug be dispensed without a white blood cell count, etc., so, we have to operate through sponsors." That's what GlaxoSmithKline did with Lotronex.

Lotronex and Clozaril are both models that might be used for re-introducing other drugs. Dr. Jenkins said, "FDA lives a lot by precedent, so all these current risk management programs are precedents that we established and could use again. What we are all struggling with and saw when we wrote the guidance on the risk management programs for giving broad advice on designing and implementing these programs is to try to pick the program that best fits the needs for the case at hand. At the same time, we have to realize people don't like different programs for each drug. They don't want a sticker for Lotronex, a sticker for Vioxx, and a sticker for Palladone. Too many stickers get confusing, are hard to track, and are hard for us to monitor and assess if the programs are being implemented correctly and effectively."

For Tysabri, the two models that appear to have the most appeal for the FDA appear to be:

- **Monitoring with a Clozaril-type program.** Dr. Jenkins said, "That is definitely one model to look at. It is a very effective drug for a subset of patients who have not responded to other therapies. If it (Clozaril) were just another drug equal to its peers, we might not be willing to accept the risk of agranulocytosis to keep it on the market, but since it is so effective in refractory patients, that warranted keeping it on the market despite a significant but rare risk that can be fatal. And we found the monitoring program can effectively manage the risk…We have to consider if the benefit offsets the risk and how to manage the risk. With Clozaril, we found monitoring is effective, so we were imposing a burden on the system, but it (monitoring) is effective."
- **Restricted distribution with a Lotronex-type program.** Dr. Jenkins said, "The Lotronex program is one where doctors are signing up to be in the Lotronex Prescribing Program and attesting that they have the knowledge and expertise to use the drug. That is basically a program run by the sponsor. FDA does not certify which doctors are certified (to prescribe it). And it (the program) is not limited to just gastroenterologists but to doctors who sign up and read materials and are qualified to prescribe it."

Monitoring tests

Monitoring tests need to be validated. If the monitoring test being proposed is not a standard test – such as ALT for liver failure – the test would need to be validated. Dr. Jenkins said, "If it is not a commonly available test and not really validated for how effective it is at early detection of the adverse event so that the adverse event could be picked up in time to stop a serious event, we might ask for a study to be done to try to help convince us that the test can do that. Then, we get into an ethical issue – doing a study to see if the test is adequate, but those people in the study may not be protected because they don't know if the test works. In the past, where we ended up was with what was done in clinical trials that seemed to be helpful. With Rezulin, the experience was in some part based on monitoring in clinical trials done to get the drug approved. There was also an Abbott drug several years ago (similar to Singulair) that never went anywhere. It was approved but not used. It had liver toxicity as well. We based the recommendations for monitoring and labeling on what was done in the clinical trials."

Some experts have suggested that a viremia test could be used to monitor Tysabri patients for PML. Dr. Jenkins said, "That

requires a lot of analysis of the data to see if we can feel comfortable that the test is a valid predictor – the sensitivity and specificity of that test for the results you are getting. Then, you get into false positives and false negatives. Often, you don't have the data you like. In the case of Tysabri, we will have to look very carefully at retrospective data on all the patients exposed in the trials and then try to assess whether there are any monitoring tests or procedures that can be utilized to try to pick up people early when they become at risk for PML but hopefully before there can't be recovery. That will be the challenge with the Tysabri experience."

Patient population

For a drug to return to the market after a safety problem, it most likely would have to have some advantage over other drugs in the class, but that advantage needs to be proven, not just speculation. Dr. Jenkins said, "We would probably want to see data that a drug is uniquely effective in patients who did not respond to the other drugs in the class before we would be interested in entertaining the idea of bringing a drug back. We are not comfortable about bringing a drug back on the hypothetical that someone who doesn't respond (for example) to Actos or Avandia might respond to Rezulin. We would want data on that…In clinical trials it appears Tarceva (Genentech, erlotinib) has much more impressive results on survival, on all the outcome measures than Iressa (AstraZeneca, gefitinib). A lot of people are saying, 'What about Tarceva failures? Shouldn't they have access to Iressa?' We would like to see data on those patients who fail Tarceva, and if they respond to Iressa. We would like to see that in a trial setting."

However, it is also likely that any drug with a safety problem that is allowed back on the market would have an indication in a more narrow patient population than was in the original label – even if that new patient population had not been directly studied in the clinical trials. For example, with Tysabri, patients might be required to try one or more interferons or Copaxone (Teva, copolymer-1) first. Dr. Jenkins said, "Sometimes we are forced to make a decision on limiting use of a drug even though there are not good data. I don't know all the patient populations studied with Tysabri, but if, in fact, there were ever a decision to allow it to come back, we would have to carefully weigh what patients to recommend it for, given the significant risk…We can't always be in a situation to require data because sometimes it is not ethical to do the study. Sometimes we just have to make decisions on where it appears the risk:benefit profile is acceptable. We can't always make decisions based on data."

The final decision

Some stakeholders argue it is not the FDA's role to restrict drugs to anyone – that they should be approved and doctors and patients should make up their own minds. Dr. Jenkins said, "We try to balance in the middle…Congress charged FDA with making a risk:benefit judgment from a population based on statute, but a lot of libertarians would like no restrictions…We have to thread the needle and find the right balance…In the case of restricted access, we have to struggle with the issues that come into play, including our legal authority – what our authority is to impose restrictions…If we felt the only way to use a drug safely is with restrictions, and the company is not willing to voluntarily agree to restrictions, and we didn't feel we had the authority to impose them, then we will not approve that drug. Our ultimate risk management tool is not to approve the drug. We try not to use that often because, at the same time, you are denying patients a drug."

THE OUTLOOK FOR TYSABRI AND VIOXX

It appears that the FDA is open to allowing both Vioxx and Tysabri back on the market, but in both cases, the market size for the product is likely to be considerably smaller and more restricted, and the path does not look quick. Before any re-launch, the FDA will:

- Require submission of an sNDA application.
- Hold a public FDA Advisory Committee meeting and probably consult with the Drug Safety Oversight Board.
- Negotiate a narrower label.

In the case of Vioxx, the return path is not really complicated. The problem is the size of the market for the drug when it did return and whether that is commercially feasible for Merck.

In the case of Tysabri, there are more issues and the outlook is cloudier. If Tysabri does return to the market, it is likely to:

- **Be restricted** to patients who have failed other therapies – even though there are no data on those patients.
- **Require some type of monitoring.** If a monitoring test can be developed, that would make the FDA much more comfortable with allowing Tysabri back on the market, and probably would assure it does return, at least for some patients. However, the FDA appears very dubious about a monitoring test for PML, and validating a new test has ethical problems.
- ***Not* have a restricted distribution system.** The FDA is loathe to introduce a new restricted distribution program just for Tysabri, noting that this would be very burden-some for the healthcare system.
- **Include strong patient education and a patient consent form.**
- **Not be restricted only to neurologists.**

If Biogen Idec/Elan do not actively promote a plan for monitoring and/or restricting Tysabri usage, then the FDA will essentially do it by not approving the re-launch. Any attempt to make Tysabri broadly available is likely to cause the FDA to refuse to re-approve it.

The most likely scenarios for a Tysabri return are with either (a) a Clozaril-type monitoring program (assuming the FDA can be convinced the viral test works) or (b) a Lotronex-type program that qualifies doctors to prescribe Tysabri. The FDA's goal with either of these will be to restrict usage and minimize PML cases. The FDA cannot and will not impose either of these scenarios, so it will be up to Biogen Idec/Elan to propose a program. The FDA likes both these programs because they work – they have limited use of both Clozaril and Lotronex and minimized the serious adverse events that can occur with those drugs. At this point, a Lotronex-type program appears to be the approach the FDA is most likely to approve for Tysabri.

If Biogen Idec/Elan were to get Tysabri back on the market with a Lotronex-type program and then widespread use of Tysabri occurred off-label, it could lead to an excess of PML cases. The FDA might then respond by pulling Tysabri again, with no hope of another return.

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