



SWITCH Forecast Revisited

The Inevitable Switch and Dual Status of Non-Sedating Antihistamines in the US

*Latest Citizen Petition by Blue Cross Results in
May 11 Advisory Committee Meeting*

A Paradigm Change or Just a Little Sniffle?

Our February 1998 SWITCH Forecast predicted that the excellent safety profile of non-sedating antihistamines would result in Rx-to-OTC switches in the US just as it has in virtually all other world markets. In fact, we were certain that many of these products would gain Dual Status — simultaneous Rx and OTC status with the same brand name and extended time under patent remaining.

However, we did not anticipate that the Citizen Petition would be the mechanism. This initiative by Health Maintenance Organization (HMO) Blue Cross of California is historic and has potentially sweeping implications for the future of Rx and OTC product planning in the US.

The following is the story as it appears today. It will keep on changing for the next few months and merits very close monitoring by all those concerned about the future of the pharmaceutical industry and the future of self-medication.

The Blue Cross of California Rx-to-OTC Switch Initiative

On March 20, the Center for Drug Evaluation and Research (CDER) announced the Tentative List of Meeting Dates for the next few months. These meetings have great importance to the pharmaceutical industry. As such, and given the large opportunities for information leaks within the FDA, the announcements tend to be confirmations to what is already known.

To the great surprise of FDA meeting watchers, the March 20 announcement indicated that there would be a joint meeting of the Pulmonary-Allergy Committee with the Non-Prescription Drugs Committee on May 11. The supporting documents, provided as background, were mostly from Blue Cross of California.

The most important document is dated October 4, 2000. Key ideas are:

1. The Blue Cross petition, referring to specific language in US law, states
“that drugs limited to prescription use under an NDA can be exempted from that limitation if the FDA determines the prescription requirements to be unnecessary for the protection of public health.”
(Code of Federal Regulations, Food and Drug Administration, Title 21, section 10.30)

2. Blue Cross submitted an Evidence Report that compares first generation sedating products (diphenhydramine, chlorpheniramine) with second generation non-sedating Rx products (cetirizine, loratadine, fexofenidine) for the treatment of allergic rhinitis. A meta-analysis attachment provides all data and lists the participation of a number of scientific experts.
3. The petition concludes that “since the second generation antihistamines are less toxic and equally efficacious as the first generation antihistamines, the second generation antihistamines are the preferred antihistamine treatment for allergic rhinitis.”
4. The document asks the FDA to expedite a review of the petition to switch “cetirizine, loratadine and fexofenidine to over-the-counter medication status immediately.”

By way of background, Blue Cross of California has frequently threatened to file a Citizen Petition to switch Claritin. However, no one expected them to go to the trouble and expense of examining public studies and creating a meta-analysis.

The US FDA, on its own, has mentioned several times that it found prescription status of Claritin to be absurd. (It was mentioned to this author as recently as last June when I spoke at an FDA-sponsored switch review.) Again, no one ever thought the FDA would move ahead with a Claritin switch petition or any other switch that was not at the request of the drug sponsor, such as Schering-Plough for Claritin.

In fact, there is abundant evidence that this switch consideration is being sought against the wishes of the drug owner. This is a first in this country. Forced switches, initiated by the Board of Health, are quite common in other countries. Not so, here! The FDA doesn't have the authority.

International Non-Sedating Antihistamines Status

From a pure popularity standpoint the non-sedating antihistamines are one of the most popular switches in the world. Many of them, such as loratadine, have been available in the nonprescription market for years, as can be seen below.

Country	Canada	Denmark	Sweden	UK	Australia	Germany	Holland
Date of Loratadine Switch	1988	1990	1992	1993	1994	1994	1996

In fact, SWITCH's latest count shows that loratadine is now nonprescription in more than 24 countries. There is “significant time and extent” experience from international markets to at least provide directional support for a loratadine switch.

It can be argued that these international markets also have a 3rd Class of Drugs where the pharmacist has a role in insuring that the right drug goes to the right person. However, as anyone knows who has reviewed the 3rd Class of Drugs, that system doesn't work and really is a means to restrict distribution to the pharmacy rather than provide a safety net to the patient/consumer.

Please see our Special Report for more on the legal status of non-sedating antihistamines in international markets.

“Switchability” and Dual Status of Non-Sedating Antihistamines

Claritin, Allegra and Zyrtec are all quite switchable. The success of Claritin has rested on its non-sedating profile and freedom from cardiac side effects and drug interactions. Nevertheless, Claritin was under review by FDA for an extended period of time prior to its approval as a prescription drug. The delay

was attributed to efficacy issues at the non-sedating dose of one 10mg tablet per day. There is a good chance that as an OTC product the 10mg daily dose will stand. The combination of efficacy and lack of adverse effects is good reason to suspect that Claritin could be approved for OTC use as it is currently formulated. Should Schering be forced to reduce the dosage, which is unlikely, efficacy might be jeopardized.

Allegra (fexofenidine), the metabolite version of terfenadine, has been stripped of terfenadine's dangerous side effect profile. The product is apparently very safe. Allegra was launched directly to OTC status in Canada and was switched to non-prescription status in both New Zealand and Australia within months of Rx launch. Allegra was developed and cleared by the FDA for Rx marketing in the US in a record period of three years. Accordingly, we have little doubt that the product is safe for OTC usage.

Pfizer's Zyrtec has been marketed OTC in Canada (as Reactine) since 1994. This product also has a solid safety profile. Therefore it is highly likely that Zyrtec is switchable to OTC status. Moreover, there is a potential low dose available; however, it is currently not sold widely in the US and elsewhere, probably due to its limited efficacy.

Perhaps, quite important as a possible solution, Allegra has a low dose tablet. This could be an alternative if the brand is forced to consider a switch. Dual status becomes a viable alternative — defined as having the same molecule and the same brand name simultaneously in the Rx and OTC markets, but with a different strength or indication from one to the other.

Dual status is not unfamiliar to those who have marketed in other markets, particularly European markets. However, this status is still not that well known or practiced by US domestic Rx marketers. It is ironic that, because of the confluence of liberated DTC advertising and the growth of self-recognition, the US market will discover something much more prevalent in the highly regulated markets of Europe.

As we all know, a simple Rx-to-OTC switch is anathema to the typical Rx marketer: A switch often means that the patent is close to expiration, which is bad news for profits. Moreover, OTC is generally a much lower margin business.

Dual status redefines the shape of the switch: It is a switch that also assumes the continuation of patent protection for the Rx product and the OTC product also. The correct alternative needs to be mapped out and sales and earnings established for the various scenarios.

As can be seen in the chart below, there are no shortages of non-sedating antihistamines currently and planned in the future. Whether all the new ones will make it to the Rx market is hard to decide right now. However, the probability is quite good. That's why the market will continue to change for the foreseeable future.

The May 11 FDA Citizen Petition Advisory Committee Meeting

In principle, every citizen in the US has the right to petition the FDA to review the status of a drug in order to facilitate a change in that legal status. However, the FDA does not need to review the drug if it feels that there is insufficient evidence to justify a review.

A major unanswered question is "Why has the FDA decided NOW to set up an Advisory Committee review of the legal status of non-sedating antihistamines?" Blue Cross of California has petitioned for a review before and nothing has happened. What is new NOW to justify a meeting?

In the FDA docket listing were four additional background documents, one of which could be very important. Apparently, Blue Cross has gone to the trouble of commissioning a "meta-analysis" of existing data

comparing the product profiles of non-sedating antihistamines (second generation antihistamines) and sedating products (first generation antihistamines). A meta-analysis seeks to create common ground, using different studies, in order to provide reliable statistical data as well as meaningful conclusions.

However, current law in the US would only justify a switch if there is sufficient information on the safety of each individual drug for OTC use. A key issue here is the ability to provide adequate labeling for each drug.

The labeling issue is major since, normally, only the sponsor of the drug knows in detail all the performance characteristics of the drug. The sponsor performs numerous studies over the lifetime of the drug and keeps that information private. Therefore, neither Blue Cross nor the FDA could write adequate labeling without the information controlled by Schering-Plough, for example, on Claritin.

Quite simply, a comparative meta-analysis is not enough to create labeling. Moreover, drugs are approved "on their own merits" and therefore individual drug research (efficacy and safety, actual use) is a usual requirement. It is doubtful that Blue Cross would pay for and perform these studies. Maybe material presented for a switch outside the US would be sufficient in the US?

Likely Outcome

In addition to the labeling issue mentioned earlier, there are other issues to overcome before a non-sedating antihistamine could be forcibly switched. The entire area of intellectual property and who gets access to it must be sorted out. There is a due process of law question on how to proceed as well as a need for a formal evidencing hearing to revoke the Rx status.

Finally, for at least cetirizine and fexofenadine there is the patent issue. Their patents expire in several years so forcing an OTC version is technically a violation of their patent protection.

However, and this could be key, Claritin's loratadine patent expires in December 2002. In this case, the patent issue is less concerning since any action would likely be in effect no sooner than January 2003.

In any case, the route to forcing a switch via a Citizen Petition without sponsor support

- Will stretch the already stretched resources (time and money) of the FDA,
- Could require an act of Congress to change the way the laws are currently written, and
- Will not happen overnight.

SWITCH does not believe that Blue Cross will succeed in their desire to force a switch of non-sedating antihistamines. However, we do not pretend to know all the reasons why the FDA has approved the May 11 meeting. There is information missing for us.

The bigger issue is that this new meeting could start a process for an overhaul of the Rx-to-OTC switch system in the US. SWITCH is in favor of that.

There have been very few successful switch submissions in the last few years. However, we do not believe that a cost-oriented company, such as Blue Cross, should be the driver of public health reform. Maybe it's time for additional organizations to take up the challenge.