

Orphan Drugs Plus REMS: A Perfect Fit?

Biopharma companies have a decidedly mixed view of FDA's new post-marketing safety authorities. But for one industry segment—companies concentrating in serving very small patient populations suffering from rare diseases—the new regulatory model is decidedly good for business. What does that mean for the future of Big Pharma?

By Michael McCaughan

Centric Health Resources CEO Craig Kephart may be the single biggest fan of the Food & Drug Administration's new post-marketing Risk Evaluation & Mitigation Strategies authority.

Creation of the REMS was “a real tipping point” for Centric, Kephart says, triggering an interest in the St. Louis specialty pharmacy/distributor's “high-touch service model” from a range of companies Centric never expected to do business with: Big Pharma companies.

Over the course of two months (June and July), Centric discussed three “large market” opportunities with “the biggest of big pharma” companies, Kephart says. For a small start-up (founded in 2004, Centric has just 85 employees), that is pretty heady stuff.

That's nice for Centric, but why should anyone else care? Because Centric is not just any specialty pharmacy provider—it was founded to focus on the ultimate in niche markets: so-called “ultra-orphan” patient populations. Centric is interested in products intended for populations of 20,000 or smaller—and, in fact, its key product (**Talecris' Prolastin** for Alpha-1 Antitrypsin Deficiency) serves a market of about 7,000.

That is not the type of markets that Big Pharma salivates over.

So has **Pfizer Inc.** decided that their future rests with selling drugs for dozens of patients? Will **Merck & Co. Inc.** make its merger with Schering-Plough pay off by selling a stable of

products for children with rare genetic diseases?

Not exactly. Instead, according to Kephart, Big Pharma is interested in applying the ultra-orphan marketing approach to help adapt to the new regulatory imperatives set up by the FDA Amendments Act.

“People have learned that if you embrace REMS you can get through FDA quicker,” Kephart says, and a specialty pharmacy is “perfect to administer” the types of programs sponsors are looking at.

Big Pharma sponsors still have big market aspirations, but they recognize that “they need intense relationships for launch,” he says, with programs emphasizing physician and patient education, restricted distribution, specialized training, and other support services. In other words, Big Pharma needs the post-market launch and control skills that Centric was built to deliver for a different subset of products.

The Triumph of the Biotech Business Model

The notion of “ultra-orphan” marketing models can sound scary to pharmaceutical companies used to thinking of primary care blockbusters.

But there is a different way to describe essentially the same idea: pharmaceutical companies need to embrace the biotech business model.

That is something virtually every Big Pharma company is eagerly trying to do—though the emphasis is usually on the

drug development side rather than the commercial model.

But Kephart's discussion of why pharmaceutical companies need services like those offered by Centric isn't so different than how then-MedImmune CEO David Mott described **AstraZeneca PLC's** decision to acquire MedImmune for more than \$15 billion in 2007.

The acquisition, Mott explained during Windhover's Pharmaceutical Strategic Alliances conference in September 2007 gave AstraZeneca "biotech in a box:" a "fully built out organization has all the capabilities" of a biotech company. (Mott left AZ/MedImmune in 2008 and is now a general partner at the VC firm NEA.)

"It is a very different model" built on commercializing products for "small patient populations...but high-value added products. So it is a high price per unit, low volume business versus a high volume low price per unit business."

"We know how each patient is going to buy the drug, which distributor is going to get it to them, whether the physician is going to be buying it, whether the patient is going to be buying it. It is just a micro-managed selling process, which hasn't historically lent itself to large primary care products."

Compare that to how Kephart describes the impact of REMS. It "is forcing manufacturers to rethink distribution channels because it requires you to follow patients more closely," he says.

"We are seeing in the review process that the FDA is looking at REMS performance," he says. "But do they really understand the risks?...It becomes about following the marketplace patient by patient."

Short-Term Plans—Long-Term Implications?

There really isn't much need for a "high touch" model for most REMS, since the vast majority of the new programs involve only a requirement for distribution of a consumer medication guide. Even some of the more complicated REMS—programs involving special communication plans like a "Dear Doctor" letter, or some type of advertising restrictions—don't necessarily involve fundamental changes to the typical Big Pharma business model.

But for more tightly restricted products—older medicines like the multiple sclerosis therapy *Tysabri*—or newly approved drugs like **Amgen Inc.'s** *Nplate* or **Lundbeck Inc.'s** *Sabril*—the regulatory requirements can in fact read exactly like the ultra-orphan distribution model, demanding patient-by-patient enrollment and direct, tightly controlled shipments. And it is already clear that sponsors who embrace that model can still find commercial success. (See "The Billion Dollar REMS," *The RPM Report*, February 2009.)

"If they embrace it early they will get their drug through FDA faster," Kephart says. "A robust response to REMS greases the skids."

That doesn't work for every product, of course, but in an era of seemingly perpetual R&D frustration, any shortcut to market bears consideration.

And it is already clear that restricted distribution programs (known by the regulatory acronym ETASU, or Elements to Assure Safe Use) are also becoming more common. FDA has approved eight programs of that type since the REMS authority took effect in March 2008. (That total does not include products like *Tysabri* that are in the process of being converted to the REMS system.) And that is just the tip of the iceberg. David Galardi of the Sharon Hill, Pa. consulting firm **Apogenics Inc.** says that his firm alone is working on 14 ETASU programs for drugs in development.

That statistic is compelling. But, for those interested in the intersection of REMS and orphan drugs, *where* Galardi talked about the growing awareness of REMS programs is at least as important as *what* he said. Galardi made his comments during a conference for stakeholders interested in ultra orphan products hosted by Centric in St. Louis in August.

The conference attracted several start-up companies, VC investors, specialty pharmas and reimbursement/drug development consultants interested in the potential for products focused on very small patient populations. It would not be an exaggeration to say that there were more people in the room than there are potential patients for some of the diseases treated by ultra orphan products.

And, at least in that room, it was clear that it is not just Kephart who sees REMS as potential business opportunity.

REMS or Personalized Medicine?

Of course, Kephart isn't an unbiased observer; Centric is built to capitalize on the opportunity he and his co-founders saw in serving ultra-orphan markets. (The term "ultra-orphan" is short hand: Orphan Drugs are defined by statute in the US as products intended for patient populations of 200,000 or fewer; "ultra-orphan" is not a recognized regulatory concept, but rather an easy way to indicate markets that are an order of magnitude smaller than the maximum to qualify as an orphan.)

All three Centric founders—Kephart, SVP John Fielder, and Chief Operating Officer Michelle Hefley—formerly worked for **Quantum Health Resources**, the initial distributor for *Prolastin*.

Kephart and Hefley joined **Express Scripts** after Quantum was acquired by Accredo, and then left after Express acquired the specialty distributor CuraScript. Centric was founded on

the principle that companies like Accredo (now part of **Medco Health Solutions Inc.**) and Express Scripts are simply too big to provide the level of support necessary for ultra-orphan indications. And the company quickly secured rights to distribute *Prolastin* as its first building block.

So it is easy to dismiss Kephart's contention that the number of ultra-orphan products is about to "explode logarithmically" as wishful thinking.

Several Trends Driving Interest

But it's not so easy to dismiss the many different factors driving sponsors to look at the "high touch" distribution model.

The REMS is just one of several inter-twined factors driving Big Pharma companies to talk to niche market distributors, Kephart says.

In general, sponsors are looking to market "different types of products" than they have in the past, as Big Pharma companies look anew at specialty markets across the board. Rare disease therapies are attractive in general because "they are easy to market, they cost less to support, and there are no huge clinical trials because there aren't that many patients." Kephart isn't the only one making that case—though so far there is scant evidence Big Pharma companies are doing more than talk about those opportunities. (See "*Doing Well by Doing Good*," in this issue.)

But the REMS are also driving use of the "high touch" model for larger market therapies, Kephart says. The company has talked to sponsors about support "in the early days of training and side effect profiles," since "data shows long-term persistence is greater if you have a good start."

In the long run, Kephart sees the REMS authority—and his company's "high-touch" business model—evolving together to support some of the most important trends in drug development.

The first is personalized medicine. The Centric model fits perfectly for medicines whose use is tied to specific testing requirements to identify optimal patient populations, Kephart says. That, in fact, is the *Prolastin* model, where confirmation of diagnosis is part of the distribution system. It's "not an expensive genetic test," but it's also "not so different," Kephart says: "you have to get results with that test to meet the package insert and get reimbursement."

Some healthcare leaders see the advances in genomics leading to a point where all virtually all diseases are viewed as a collection of rare diseases. Francis Collins, the newly installed head of the National Institutes of Health, is a key proponent of that view. (See "*A Rare Opportunity?*" in this issue.)

That is certainly not a unanimous opinion of the future of biomedical research.

However, there is no denying that FDA's new REMS authorities do offer a ready-built regulatory framework for medicines that are brought to market in conjunction with genomic tests or other screening requirements. (See "*FDA and Health Care Reform*," *The RPM Report*, December 2008.)

Sell a Program, Not a Drug

More importantly, though, is the potential for tightly controlled distribution programs to help capture and explain the value of a medicine to support reimbursement.

As Kephart points out, risk sharing agreements like the groundbreaking *Velcade* deal in the UK require close interaction between the manufacturer and the patient. Those agreements involve tracking outcomes with rebates tied to performance of the product in the health system. (See "*The Cost Sharing Solution*," *The RPM Report*, February 2009.)

Kephart argues that payors will increasingly expect proof of value from any reasonably expensive medicine—and notes that a tightly managed distribution model helps both gather the data, and improve the outcomes.

The actual value from the therapeutic impact of the drug is just one component of the overall value a medicine can deliver, Kephart says. There is also the value tied to appropriate management of the medication in actual use—compliance with the prescribed dosing regimen and adherence to therapy. A well designed distribution program can enhance that piece.

And then there is the value tied to actual health outcomes—the potential for a support program to provide counseling and services that help patients live better with their disease. If you already have a REMS, Kephart observes, it doesn't cost much more to "go beyond that and administer some health management to improve quality of lives, manage co-morbidities and manage trips to the hospital." The program can demonstrate "value to the patient that can be tied back to the drug."

"It is not a large market model, so it is not for everyone," Kephart adds, "but in a small market you need to sell program and not a drug to get a therapeutic benefit."

Sell a program, not a drug: those may be words to live by in the REMS era.

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