Stalled sequence:
Patents could pose problems for genome-wide diagnostics

Rat race:
Researchers create new rodent disease models

Special delivery:
A combination of two RNAs offers new therapy

Rare opportunities appear on the horizon to treat rare diseases

Clinical trials often involve data from thousands of participants. But, two decades ago, the enzyme replacement therapy Adagen gained US approval solely on the basis of the case history of 12 people. How did Adagen make it through the rigors of approval with so few subjects? The reason, in part, is because it treats an immune disease affecting as few as one in a million people. This rarity made Adagen an orphan product—a drug or device that treats a rare disease.

Back in 1983, as part of the Orphan Drug Act, the US defined rare diseases as those affecting fewer than 200,000 people in the country (which translates into roughly one in 1,500). The bill also set up special government programs to speed up development. Nearly three decades later, however, orphan products continue to be plagued by problems with numbers: many of the nearly 7,000 orphan diseases have affected populations numbering in the hundreds or even dozens, making it difficult to recruit enough subjects for a clinical trial. Moreover, even if researchers can organize a small trial, its limited size can make it hard to see a statistically significant benefit from a drug—which is normally required for regulatory approval.

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Rare treat: Injecting disease with new hope

Recognizing those problems, several groups are looking for ways to improve orphan product development. This past August, the US Institute of Medicine organized a committee to report on how to the country can accelerate this development. Around the same time, the Pharmaceutical Research and Manufacturers of America chartered a similar committee for rare diseases "with the goal of bringing innovative products to patients earlier."

Among those already making strides is the US National Institutes of Health (NIH). The NIH established its Rare Diseases Clinical Research Network in 2003, garnering the help of patient advocate groups and research consortia for rare diseases. During its first phase, the network enrolled more than 5,000 subjects in 37 studies, and, in October 2009, the project was granted $117 million for a second, five-year phase, now covering more than 95 rare diseases. The project is one sign "that we can indeed work with rare diseases—that we can recruit enough patients and move forward with new treatments," says Steve Groft, director of the NIH's Office of Rare Diseases Research.

Making it to market

Besides better recruitment, however, companies and patient groups are looking toward regulatory agencies to help bring drugs for rare diseases to market. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have each learned to walk a fine line when evaluating orphan products. Although both agencies emphasize the need to maintain high standards of safety and efficacy when evaluating drugs for market, they also recognize the special circumstances surrounding rare diseases—and, thus, the need for exceptions.

In 2006, for example, the EMA (at the time known as the EMEA) released an official set of guidelines for small clinical trials. Clearing the air over what was expected from developers, the guidelines set up a hierarchy of evidence, going from the unlikely ideal of a large, placebo-controlled study down through studies based on observation or even just case histories, which tend to be descriptive rather than statistically geared. Although the FDA has no such guidelines, last year the agency's Office of Orphan Products Development began offering a class training investigators in the best possible methods for small trials.

Both agencies are also expanding efforts to communicate early and often with product developers, something they say is key to approval under such difficult conditions. For years, each agency has offered free scientific advice to orphan product developers, allowing companies to receive protocol feedback if they ask for it. But last July, the EMA and FDA announced a joint advice program for all products deemed important enough, granting an audience with both agencies at once. The EMA and FDA are also finalizing harmonized guidelines for the annual reporting done by orphan product developers, which would make communication more efficient. "We both recognize that it's the same science, the same patients and the same companies that we're working with," says Tim Cote, director of the FDA's Office of Orphan Products Development. His office and the EMA's Committee for Orphan Medicinal Products also have monthly teleconferences, allowing for the two agencies to discuss the product pipeline.

Even though the agencies are harmonizing their communication, they remain independent in their approval processes. For the EMA, "the important question becomes whether or not the results of an uncontrolled study are compelling enough," says Eric Abadie, chair of the agency's Committee for Medicinal Products for Human Use. If the data only go so far, the EMA may resort to granting approval under exceptional circumstances (meaning that the perceived benefits greatly outweigh the risks, despite a lack of data showing a statistically significant effect) or granting conditional approval that obligates the product makers to pursue follow-up studies. The FDA has similar options, such as requiring phase 4 studies after approval. "We always look to take the higher road and understand the pitfalls of an approach, as well as the evidentiary benefits," Cote says.

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