Regeneron's PCSK9 program. But it means that PCSK9 inhibitors should remove a natural block on statin function and make statins much more effective. As *Nature Biotechnology* goes to press, complete results for two Regeneron REGN727 phase 2 combination trials with Lipitor (atorvastatin) were to be announced at the American College of Cardiology scientific session taking place in Chicago, March 24–27.

The best way to target PCSK9 is not yet clear. The Regeneron and Amgen mAbs have both shown efficacy, but Alnylam argues that blocking PCSK9 transcription using RNA interference, thus mimicking the dramatic effects of PCSK9 mutations, will be a more powerful approach than inhibiting the protein because this will block PCSK9 intracellularly, not just secreted PCSK9. "We're turning off the tap at the faucet rather than mopping up the floor," says Alnylam chief medical officer Ashkay Vainshaw in a January conference call. Orally available small-molecule PCSK9 inhibitors would eliminate the injection problem, but they're very hard to find because the active site of PCSK9 is very hard to access, except when PCSK9 undergoes autocatalysis in the endoplasmic reticulum (ER). So a typical catalytic site inhibitor would have to penetrate the ER membrane. Such small molecules otherwise wouldn't interfere with PCSK9 degradation of the LDL receptor, which is nonenzymatic.

For all these reasons, biologics are the obvious drug approach (no specific anti-PCSK9 small molecules have yet been reported). Whether companies can sustain their momentum through phase 3 will determine whether statins will remain the last word in LDL lowering, or if targeting this strange protease will provide a new way forward.

Ken Garber *Ann Arbor, Michigan*

Hemacord approval may foreshadow regulatory creep for HSC therapies

The first license for a cord blood product has been granted to the New York Blood Center (NYBC) for Hemacord, hematopoietic stem/progenitor cells (HSCs) isolated from human cord blood for use in allogeneic transplantation in certain blood disorders or malignancies. The approval has reignited a long-simmering debate over whether such products need additional regulation. "This has been a very long story, and it's not clear that this [license] will have the intended effect," says Joanne Kurtzberg, director of Carolinas Cord Bank, and the Pediatric Blood and Marrow Transplant Program at Duke University Medical Center, Durham, North Carolina. There is also concern that the US Food and Drug Administration (FDA) will now move to further regulate HSC therapies derived from peripheral blood.

Hemacord is prepared by drawing blood from the umbilical cord or placenta of a newly born infant. The HSCs in the cord blood are then purified, concentrated and frozen for future use. Once transplanted into an allogeneic recipient, Hemacord progenitor cells migrate to the bone marrow, which has been depleted of endogenous cells by radiotherapy. Donor HSC cells then seed themselves and mature, finally moving to the bloodstream where they can partially or fully reconstitute the complement of adult blood cells and restore immune function.

The Hemacord registration signals that the FDA will now require licenses for all cord blood products from public banks if they are being stored for potential use by a patient unrelated to the donor. Cord blood stored for future use must "meet the definitions of drug under the Food, Drug & Cosmetic (FDA&C) Act and biological product under Section 351 of the Public Health Service Act," writes Paul Richards, public affairs specialist at the FDA's Center for Biologics Evaluation and Research, in an e-mail. But some institutions with established cord banking programs disagree.

Legislation issued in 2000 set up a National Cord Blood Coordinating Center to support unrelated-donor-blood stem cell transplants and establish a single point of access for patients and providers to search for the best available cells, among other things. The latest layer of licensure for these products "was meant to create a higher quality product," Kurtzberg says, "But all it has done is put obstacles in the way of the banks."

Colleen Delaney, director of the Program in Cord Blood Transplantation at the Fred Hutchinson Cancer Research Center in Seattle, agrees. Although centers can still offer the products under an investigative new drug application (INDs), that is a cumbersome and complex process for smaller centers to maneuver, she says. "Big centers like ours have more resources to deal with INDs and more expertise in regulatory affairs."

Cord blood is selected based upon finding the optimal match, so burdening blood centers with new regulations could restrict access. "I don't think that was taken into consideration," Delaney says. Concerns have also been raised that insurers will start to treat nonlicensed cord blood products as inferior, and therefore will not cover them. "If you are a patient who can't travel, getting to a center that is licensed could be a problem," Delaney says. There is no sign yet that insurers are planning to take that tact.

Cells isolated from human cord blood now require a license.

Over 30,000 unrelated-cord-blood transplants have occurred around the world, according to Kurtzberg, and both she and Delaney consider the current accreditation process sufficiently stringent.

It's also unclear how much licensure is going to cost. "It was a very expensive process and required a lot of resources and man hours, and we had to change a lot of processes," says Eva Quinley, senior vice president of quality at the NYBC. "I've heard people estimate the cost at anywhere between $2 and $3 million." But the NYBC went through the process because "licensed products will be the product of choice when a match is available."

The initial regulations also did not cover the use of cord blood transplantation for certain indications, such as sickle cell anemia, in which the blood centers felt there is a sufficient body of data to support use. "Transplantation can cure these patients, but FDA originally said there wasn't enough data," Kurtzberg says. Complaints from the banks led the agency to revise its guidance and include more conditions. Kurtzberg also objects to the agency's insistence on an expiration date. If collected properly, she says, "no one knows the expiration date yet."

Others argue that licenses granted only cover cells processed after licensure, and existing banks have many units already on hand. The biggest question, however, will be whether the agency extends licensure to peripheral stem cells as well. NYBC's Quinley argues that cord blood cells are more drug-like because they are manipulated more than peripheral stem cells. "There is huge fear and dissent against FDA licensing peripheral stem cells," Kurtzberg says.

Malorye Allison *Acton, Massachusetts*