BioCentury
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THE 21CC SOLUTION

BY STEVE USDIN, WASHINGTON EDITOR

The U.S. House of Representatives is in the middle of its effort to create legislation intended to promote biomedical innovation, and the Senate is just starting a similar effort, but it is already possible to anticipate the provisions that could be in any law that results from the efforts, and with greater confidence, the proposals that will not be included.

As the House Energy and Commerce Committee (E&C) works to pare down its sweeping 21st Century Cures legislation, the Senate Health, Education, Labor and Pensions Committee (HELP) is embarking on a less ambitious "innovation initiative" that is intended to produce companion legislation.

In the end, it all will come down to a simple equation: Start with a large number of policy options, subtract any that don't appeal to Republicans, remove any that Democrats adamantly oppose, delete any that industry hates, and kill or revamp those that FDA says it cannot live with. Then examine the product and punt any FDA-related provisions that require money or manpower to implement into upcoming user fee negotiations, and scale back any others that are expensive.

There are several ways to solve the equation.

The solution set could include the creation of a pathway for approving antibiotics for limited populations based on small, pathogen-specific studies.

If the criteria are tightly defined, it is also possible to persuade Congress to provide extended market exclusivity for drugs for serious unmet needs such as Alzheimer's disease (AD), and to add exclusivity to drugs approved for common conditions if sponsors conduct research that leads to the addition of an Orphan indication.

It also would be possible to reach consensus on some policies to improve the development of medicines for children, including the creation of global pediatric clinical trials.

It is far from certain, however, that Congress will produce a solution that satisfies all of the criteria for success, or that it will do so in time to avoid the legislative paralysis that will afflict Washington early next year as the presidential race heats up.

Even if the efforts to create a new law ultimately fail, the debate and thinking that are going into the 21st Century Cures and innovation initiatives will live on in the drug and device user fee reauthorization legislation that will be enacted in 2017.

Moreover, many of the topics that have been included in a discussion draft of 21st Century Cures legislation could be effectively addressed without legislation, either by FDA or NIH acting alone, or through collaboration between government and representatives from medical product manufacturers, patients and patient advocates, and academic scientists.

Areas that are ripe for action outside the legislative arena include patient-driven drug development and biomarker and surrogate endpoint validation.

INNOVATION INITIATIVE

The House and Senate processes are a study in contrasts.

The House E&C Committee has sought maximum publicity, launching a social media campaign and making bold claims about Congress' ability to transform medical product discovery and development. E&C has held 19 round table discussions and eight hearings. Stakeholders have invested a massive amount of time in the 21st Century Cures process.

The initial result of all of this work is a 393-page discussion draft that is a mash-up of hundreds of proposals from a number of bills that have been introduced over the last year, most poorly or incompletely drafted, many contradictory, and none vetted with the agencies responsible for implementation.

The Senate HELP Committee is taking a more traditional, low key approach and pursuing more modest goals.

Speaking at the first hearing on the innovation initiative last Tuesday, Sen. Lamar Alexander (R-Tenn.) made it clear that the effort is a lower priority for him than 21st Century Cures is for E&C Chairman Fred Upton (R-Mich.).

Alexander, who is the HELP chairman, did not convey a sense of urgency, saying he plans to have a bill passed by the Senate in "about a year," a timetable that would not allow Upton to meet his objective of having legislation on President Obama's desk by year end. That means the entire effort would land in the legislative dead zone that will form in the wake of the presidential campaign.

Alexander started the hearing by saying the committee's first priority is "fixing" the No Child Left Behind Act; its second is reauthorizing the Higher Education Act; "and third, one we're all looking forward to without exception, improving biomedical innovation, including the Food and Drug Administration and the National Institutes of Health."

None of the HELP members at the hearing presented a clear vision for the innovation initiative, and their questions and comments indicated a tenuous grasp of the regulatory and scientific issues at the core of FDA's and NIH's missions.

Sen. Orrin Hatch (R-Utah), the HELP Committee member with the deepest knowledge of FDA and the best track record of pushing ambitious medical products legislation through Congress, was conspicuous by his absence.

DIY PATIENT ENGAGEMENT

The House Energy & Commerce Committee captured the biomedical public policy zeitgeist by putting patient-focused drug development at the top of the 21st Century Cures discussion draft.

It missed the essence of the concept, however, by attempting to legislate in an area where by definition patients and their advocates should be taking the lead.

Almost everyone involved with medical product development and regulation already agrees that steps should be taken to better integrate patient perspectives throughout development and regulation. The open question is what steps can advance the goal.

One place to start is for patient advocacy groups and drug developers to collaborate on a set of proposed draft guidance documents and submit them to FDA.

The guidances would set standards for the scientific collection and analysis of patient preference data, specify how such data could be submitted to FDA, and indicate how the agency should integrate it into assessments of benefit-risk.

The draft guidances could also identify best practices for companies to interact with individual patients and patient advocacy groups in ways that do not run afoul of prohibitions against promotion of experimental drugs or off-label uses.

The Medical Device Innovation Consortium, a partnership that includes FDA, medical device companies, patient groups and academic researchers, is laying some of the groundwork. It is assembling a catalog of methods for assessing patient preferences about benefits and risks and creating a framework to incorporate preferences into benefit-risk assessments.

Patient advocacy groups and drug companies could start working on draft guidances immediately, with no intervention by Congress. By starting the drafting process, patients and drug developers would have more control over the outcome than they would if they were responding to a document drafted by FDA.

— STEVE USDIN

Alexander implicitly criticized E&C's unruly discussion draft, saying, "We don't want to waste our time in the next year; we can't do everything."

The lawmaker asked outgoing FDA Commissioner Margaret Hamburg and NIH Director Francis Collins to identify "one or two or three things we should focus on in order to make the greatest contribution to the goal of moving medicines, devices and treatments to the medicine cabinet and doctor's office."

POLITICAL REALITIES

Upton stresses bipartisanship every time he discusses the 21st Century Cures initiative, but so far has failed to gain the public support of a single Democrat. The discussion draft is being reworked to make it palatable to the other side of the aisle.

Alexander also said his innovation initiative will be bipartisan.

But beating any legislation into a form congressional Democrats and the Obama administration will accept will not be easy. To obtain support from Democrats and the White House, numerous provisions in the House discussion draft that set FDA's hair on fire will have to be dropped or revamped.

FDA has briefed E&C staff on scores of specific items the agency opposes, including some it views as existential threats to its ability to protect the public from unsafe medical products, and others that the agency believes would paralyze medical product reviews.

These include provisions that would require FDA to make decisions based on peer-reviewed journal articles and bar it from requesting the underlying data, and others that lower standards for the kinds of data that support regulatory decisions.

The House committee's efforts to accelerate the validation of biomarkers could suck up vast amounts of time from product reviewers and require the agency to make decisions on timetables that its senior leaders believe are completely unrealistic.

Given the close relationships between Republican lawmakers' staffers and pharma companies, anything industry strongly opposes, such a proposal in the discussion draft to fund NIH and patient assistance programs through levies on drug sales, is certain to be vaporized.

Provisions that would harm influential Democratic constituencies, such as the generic drug industry, also are unlikely to make it to President Obama's desk. This means any new market exclusivities will have to be narrowly focused and framed in ways that do not make them seem to be giveaways to big pharma.

At last week's HELP hearing, every Democrat who attended, as well as several Republicans, said that increasing NIH's budget is a high priority. House Democrats on the E&C Committee have made increased NIH funding a prerequisite for their support of 21st Century Cures legislation.

However, unless some creative new revenue source other than taxpayer dollars is identified, increased appropriations for NIH would have to be negotiated with appropriations committees in both the House and Senate. Appropriators are likely to want any increases to be paid for with equivalent cuts to programs under the jurisdiction of E&C and HELP. This robbing Peter to pay Paul approach would limit the size of any increase and put the legislation at risk from constituencies that would be hurt by the cuts.

There also will be strong pressure to defer action on any proposals that require new funding for FDA, leaving them for negotiations over drug and device user fees, which have become a relatively transparent and collegial process.

The need to avoid contentious issues means Congress is unlikely to tackle one of pharma's most pressing concerns, making FDA's regulation of commercial speech, including the use of social media, consistent with the First Amendment to the U.S. Constitution.

Congress is also unlikely to tackle the ticklish issue of oversight of laboratory developed tests, though it might find a way to delay FDA from moving ahead with its plans to regulate LDTs.

> "WE DON'T WANT TO WASTE OUR TIME IN THE NEXT YEAR; WE CAN'T DO EVERYTHING."
>
> SEN. LAMAR ALEXANDER (R-TENN.)

SOLVING THE EQUATION

When everything that doesn't fit into the political equation is stripped out, a few items remain.

They wouldn't be revolutionary, but they would allow politicians to honestly claim that they are helping Americans get access to new and better medicines.

Creating a public-private partnership that would advance patient-driven drug development is non-controversial. Its agenda could include conducting research on methods for determining patient preferences that can be used to choose endpoints and evaluate benefit-risk trade-offs; setting standards for patient-reported outcomes and other patient-centered research, and elucidating best practices for patient engagement. Funding and a mandate from Congress would make it easier to achieve the scale needed to make progress quickly, but this work could start without legislation.

Measures to reduce the red tape wrapped around clinical trials by reforming informed consent and IRB procedures are good candidates for making it through the political process. This could increase participation in trials and facilitate research using electronic health records and databases of genomic information.

Congress and the White House understand the threat posed by antibiotic-resistant bacteria, so FDA's proposal to create a new pathway to speed antibiotics to market for limited populations will be included in 21st Century Cures legislation, or if doesn't make it over the finish line, in PDUFA reauthorization.

The broad, generous extensions of market exclusivity proposed in the House discussion draft will not pass muster with Democrats, but it could be possible to achieve consensus on exclusivity provisions that are tightly defined, for more modest time periods and clearly designed to serve very specific goals. These include incentives for adding Orphan indications

to drugs approved for common diseases, and developing compounds for public health priorities such as Alzheimer's.

New market monopolies would be more politically acceptable if they are created as pilot projects, with short expiration dates. Experience with the Orphan Drug Act and PDUFA demonstrates the value of reconsidering and reauthorizing policies on a periodic basis.

There is broad support for creating a pathway for approving antibiotics based on small data sets for limited populations.

NIH Director Collins has asked Congress to reduce administrative burdens on NIH-funded extramural researchers, and to ease oversight of and restrictions on travel by NIH intramural scientists. These are small common sense requests that are not likely to be opposed. They would boost morale on the NIH campus and free resources that now are being wasted on paper-pushing.

Advocates for pediatric drug development have good arguments supporting the need for legislation and have sympathetic ears in Congress.

> "TREATMENTS CAN BETTER MEET THEIR NEEDS IF WE CAN CAPTURE SCIENCE-BASED, DISEASE-SPECIFIC PATIENT INPUT TO INCORPORATE IN THE DEVELOPMENT AND REVIEW PROCESS."
>
> MARGARET HAMBURG, FDA

Possibilities for helping children in 21st Century Cures/innovation legislation include supporting the establishment of global pediatric clinical trial networks, which would widen access to small patient populations and facilitate harmonized data requirements.

Congress could also act on proposals to reform the Pediatric Research Equity Act — which requires companies to study drugs for some conditions in children — to make the law more applicable to pediatric cancer. Key issues are modifying a waiver for Orphan conditions and classifying cancer therapies by targeted genomic mutation rather than tumor location.

The breakthrough therapies program has been wildly popular, so efforts to extend the concept could be successful.

In a letter to the HELP Committee, PhRMA proposed the creation of an Expedited Breakthrough Approval (EBA) authority. The authority would "enhance the existing Breakthrough designation for qualified new medicines by authorizing FDA and sponsors to convert strong, early stage clinical trial results to full approvals for cases of serious, life-threatening diseases where there is no adequate available treatment for patients."

PhRMA's letter added, "EBA approval would entail sponsor and FDA post-market confirmation of safety and effectiveness and enhanced safety monitoring by FDA."

MOVING AHEAD WITHOUT CONGRESS

Given the limited chances that 21st Century/innovation initiative legislation will actually make it into law, and the lengthy lead time for enactment of new policies tied to user fees, it makes sense to look for opportunities to advance key priorities without waiting for Congress.

Hamburg, in her last testimony before Congress as FDA commissioner, mentioned some areas where steps could be taken to improve the way drugs are developed and regulated. Major advances could be made in each of them without legislation through actions FDA can take on its own or through cooperation with academic scientists, patient groups and industry.

"Treatments can better meet their needs if we can capture science-based, disease-specific patient input to incorporate in the development and review process," Hamburg said. A great deal of progress could be made in this arena through structured collaborations involving patient advocates, industry and FDA (see "DIY Patient Engagement," page 2).

Hamburg also said, "More attention needs to be given to the development of biomarkers and surrogate endpoints." She suggested this could be accomplished through the "establishment of strong public-private partnerships to develop the science that we need." Indeed, FDA already participates in many PPPs that were not created by Congress.

Although the 21st Century Cures biomarker validations provisions were poorly drafted, they reflect enormous frustration among drug developers about the lack of progress in getting FDA to validate biomarkers for a variety of purposes, ranging from inclusion criteria for clinical trials to approval endpoints and data included on product labels. Industry would support, and pay for, approaches that could make real progress on biomarker validation.

Hamburg noted that FDA has made progress in using real-world data to monitor product safety, notably through its Sentinel Initiative, which accesses data on more than 170 million lives. However, she added, the "science of using big data to establish product effectiveness is still in its infancy. Real progress demands that we develop the methodologies needed to harness the promise of real-world data."

The use of real-world data is clearly an area where academic and industry scientists can work with FDA, without congressional involvement.

Hamburg also touched on one of the most important problems facing FDA: its difficulty in recruiting and retaining "talented scientists to review cutting-edge products." She did not propose any solutions, and it isn't clear how to solve it, with or without help from Congress. bc

COMPANIES AND INSTITUTIONS MENTIONED

Medical Device Innovation Consortium, St. Louis Park, Minn.
National Institutes of Health (NIH), Bethesda, Md.
Pharmaceutical Research and Manufacturers of America (PhRMA), Washington, D.C.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

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