Chimeric antigen receptor T-cell (CAR-T) therapies are groundbreaking, potentially curative treatments that genetically engineer patients' blood cells to target tumors. While CAR-T therapies represent a notable therapeutic advance, their high prices pose a significant barrier to access for patients and a financial strain for hospitals. These prices are set by pharmaceutical companies that commercialize and manufacture CAR-T therapies under patent-protected exclusivity. However, the more proximal reason for high prices—the true driver—may be that CAR-T therapies are regulated as drugs in the first place, thus influencing which entities commercialize CAR-T therapies and shaping the care delivery model. Could CAR-T therapies instead be regulated outside of the “drug” paradigm?

CAR-T therapies are regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps), which are sorted into one of 2 regulatory pathways established in sections 351 and 361 of the Public Health Service Act. Therapies that meet the core criteria for “361 products,” based on the minimal level of manipulation of the cells and their intended use, face relatively limited US Food and Drug Administration (FDA) regulation. Therapies that fail to meet any of the core criteria, or the exceptions outlined in 21 CFR §1271.15 (such as the “same surgical procedure” exception made for autologous tissues removed and implanted without processing), are classified as “351 products” and are subject to largely the same regulatory and premarket approval standards as drugs. The genetically modified T cells in CAR-T therapies do not meet the core criteria—because they are more than minimally manipulated—nor any of the exceptions; thus, they are regulated as 351 products (ie, drugs).

Pharmaceutical companies are the entities best equipped to navigate the costly premarket approval process for 351 products. Thus, in the existing pipeline, pharmaceutical companies control the commercialization and centralized manufacturing of CAR-T therapies. An alternative to this paradigm lies in the manufacture of CAR-T therapies at the point of care (eg, hospitals), the feasibility of which hinges on the regulatory environment. Hospitals have demonstrated the capability to produce and deliver CAR-T therapies in house. Aside from antigen receptor manipulation, CAR-T therapy is similar to autologous stem cell transplants, which are not regulated through the drug pathway but rather as 361 products. A regulatory shift could eliminate the burden of FDA approval, lower barriers to entry for entities such as hospitals, and enable such entities to commercialize, manufacture, and deliver CAR-T therapies directly at the point of care, thereby increasing access and potentially lowering costs.

Within the existing regulatory framework, 2 options exist to shift regulation of CAR-T products, both of which use FDA's rulemaking authority and discretion: (1) adding a specific clause to 21 CFR §1271.10 so that hospital-manufactured CAR-T therapies are regulated solely under less stringent section 361 requirements; or (2) creating a new exception under 21 CFR §1271.15 for hospital-manufactured CAR-T therapies so that they fall outside of both sections 351 and 361 and establishing new regulations addressing quality, safety, reporting, and the like.

Such approaches to CAR-T therapy regulation would not be dissimilar from those adopted abroad. In the European Union, for example, cell and gene therapies are exempt from certain regulatory requirements if they are for use in a hospital, prepared on a nonroutine basis according to specific quality standards, and used within the same member state in a hospital under the exclusive professional responsibility of a medical practitioner. Such products must not be intended for...
commercialization and are subject to manufacturing, pharmacovigilance, traceability, and quality requirements that are set by the national authorities of each member state.

In Australia, recently revised policy excludes from regulation autologous human cell and tissue products (HCTs) that are manufactured and used in an accredited hospital if the following criteria are met: the HCT is (1) collected from a patient under the care of a registered medical or dental practitioner; (2) manufactured for that patient by that practitioner, or by person(s) under their supervision, in a hospital; and (3) not advertised directly to consumers. Accordingly, under certain circumstances, CAR-T therapy produced in hospitals is excluded from specific regulation, with quality and safety protections provided through existing regulations governing hospitals and clinicians.

Thus, both the European Union and Australia provide for a different regulatory pathway for HCT/Ps manufactured and used in hospital settings. Neither pathway is without debate, which primarily focuses on the ability of hospitals to follow quality standards as well as concerns related to competition and fairness if some entities are exempt from following regulatory and manufacturing standards while others are not. Still, they provide an alternative model for regulation in the US.

A more permissive regulatory landscape would enhance competition within the CAR-T therapy market, with multiple health care systems and hospitals taking therapies from bench to bedside, like other hospital services. This competition, coupled with elimination of the costs of premarket approval, could lower the prices of CAR-T therapies. Notably, preliminary implementation of a point-of-care model in Switzerland has hospitals expecting to offer CAR-T therapies at prices between 150 000 ($151,026) and 200 000 Swiss francs, approximately half the price in the US. A regulatory shift would also have potential implications for safety and efficacy. Currently, physicians and patients have some confidence in the safety, reliability, and efficacy of each CAR-T therapy that receives FDA approval. Under more permissive regulations, CAR-T therapies could encounter similar challenges faced by stem cell therapies today, with stem cell clinics increasingly touting procedures with unproven benefits and unknown risks.

These tradeoffs beg the question: is there a regulatory middle ground for CAR-T therapies that promotes the benefits of a point-of-care paradigm while maintaining confidence in safety and efficacy? In March 2018, the FDA proposed a streamlined clinical trial process to facilitate accelerated development of regenerative medicine products by smaller entities, such as individual physicians and physician groups. Multiple sites entering into a cooperative development agreement could be issued site-specific biologic (ie, drug) licenses on the basis of facility-specific manufacturing information and combined clinical trial efficacy data. Such a regulatory approach could offer a tenable middle ground for CAR-T therapies—one in which they are still regulated as drugs, but approval is offered to multiple hospitals rather than 1 commercial entity, and the costs to meet regulatory requirements are shared across parties.

The regulation of CAR-T products as drugs creates a centralized, monopoly model of commercialization and manufacturing by a few pharmaceutical companies, driving high prices. Thus, serious discussion and consideration of regulatory alternatives is merited to increase access and lower costs. Regulating CAR-T therapies either under the existing 361 products regime or by creating a new hospital-based exception could lower prices by enhancing competition and eliminating the costs of premarket approval. Such change is not out of the realm of possibility, considering analogous regulation abroad and the FDA’s willingness to innovate through regulation.
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Conflict of Interest Disclosures: None reported.

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REFERENCES


