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Food and Drug Administration perspective: Advancing product development for non-healing chronic wounds

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Abstract

The US Food and Drug Administration (FDA) understands that innovative product development is essential to addressing the unmet medical need of non-healing chronic wounds. Barriers to product development for non-healing chronic wounds may involve but are not limited to a dearth of biological models, challenges in drug delivery, challenges in clinical trial execution, and limited commercial viability. This perspective article discusses FDA's renewed focus on non-healing chronic wounds and outlines efforts to address identified barriers to product development for non-healing chronic wounds. In collaboration with key wound healing stakeholders including academia, professional associations, patient groups, reimbursement organizations and industry, FDA intends to help advance product development for non-healing chronic wounds for the ultimate betterment of patients.

Keywords

FDA perspective; non-healing chronic wounds; product development

The US Food and Drug Administration (FDA) understands that innovative product development is essential to addressing the unmet medical need of non-healing chronic wounds. This editorial discusses FDA's renewed focus on non-healing chronic wounds and outlines efforts to address identified barriers to product development for non-healing chronic wounds.

Non-healing chronic wounds – wounds that have failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure

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CONFLICT OF INTEREST

The authors declare no competing interests for this work.

– present a significant public health burden. More than 6.5 million patients are affected annually in the United States, and it is estimated that an excess of US $25 billion is spent annually on treatment. Rising rates of obesity and diabetes are resulting in increased cases, and the number of adults over 65 years of age (at higher risk of non-healing chronic wounds) is expected to double over the next 20 years.[1,2]

Despite the public health burden, innovative products aimed at the treatment of non-healing chronic wounds are lacking. Although more than 70 products, including wound dressings, are cleared by the FDA for the management of wounds so that the natural healing process can take place, they are not intended for the treatment of non-healing chronic wounds. Most potential drug and/or biologic products aimed at the treatment of non-healing chronic wounds fail to demonstrate efficacy in Phase 2 and 3 trials. Only one biologic (becaplermin gel) and two moderately effective cell-based therapies (Dermagraft and Apligraf, Organogenesis, Canton, MA) have been FDA approved for the indication of treating (i.e. healing) a non-healing chronic wound. Furthermore, no small-molecule drug has received FDA approval for the treatment of non-healing chronic wounds.[3–7]

From 2020 to 2021, the Division of Dermatology and Dentistry (DDD), through a Science Strategies program launched by the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER), collaborated with experts from the Center for Biologics and Evaluation Research (CBER), Center for Devices and Radiological Health (CDRH), and OND's Division of Clinical Outcome Assessment (DCOA) to assess areas of unmet need and activity in the product development pipeline for wound healing. OND's Science Strategies program develops tools and resources to systematically assess the drug development landscape by therapeutic area to identify barriers to drug development in areas of unmet patient needs. The goals of the program are to support FDA subject matter experts to systematically assess unmet need (e.g. prevalence, disease burden, treatment burden), evaluate the state of clinical development (e.g. pipeline activity), identify challenges and barriers to drug development, and explore opportunities for purposeful FDA scientific leadership. Due to high unmet need with relatively limited research and funding, non-healing chronic wounds was identified as an area of priority.

Landscape analyses performed through the Science Strategies program by subject matter experts across FDA indicate that barriers to product development for non-healing chronic wounds may involve but are not limited to: a dearth of biological models, challenges in drug delivery, challenges in clinical trial execution, and limited commercial viability. Regarding a dearth of biological models, though a tremendous body of basic science research on wound healing exists, chronic wounds are uncommon in animals and challenging to simulate. Thus, a lack of optimal preclinical animal models that are capable of properly recapitulating human wounds remains a significant translational challenge.[8–10] Regarding challenges in drug delivery, the hostility of the wound environment presents unique complexities (e.g. degradative enzymes, hypoxia, ischemia, oxidative stress, bacterial infection, a critical role played by inflammatory cells), which are obstacles to developing therapeutics which maintain efficacy.[11,12] Regarding challenges in clinical trial execution, difficulties with patient enrollment, heterogeneous study designs with varying standard of care protocols and study populations, and difficulty achieving the most commonly utilized primary efficacy

endpoint of complete wound healing result in high rates of trial failure, singly as well as collectively further impeding the development of innovative products.[4,5,7,13,14] Regarding limited commercial viability, reimbursement for wound care management is highly complex and dependent on a multitude of factors, which may impede patient access to products and discourage sponsors from innovative wound care product development.[15–17]

Through the Science Strategies group, specific activities where FDA can have the most direct impact, particularly focused on clinical trial issues, were identified as priorities to address the identified barriers to product development for non-healing chronic wounds. These activities, outlined below, have the overarching goals of enhancing awareness of unmet needs and barriers, supporting data sharing, and evaluating innovative trial designs and tools.

All proposed activities to advance innovative product development for non-healing chronic wounds begin with identifying and building collaborations with key wound healing stakeholders (e.g. patient groups, academia, professional associations, industry, reimbursement organizations). Internally, the FDA's Inter-Center Wound Healing Working Group (ICWHWG) convenes CDER, CDRH, and CBER staff involved in wound care product regulation on a quarterly basis. Externally, FDA stakeholders have engaged with the Wound-care Experts/FDA-Clinical Endpoints Project (WEF-CEP) through a Critical Path Innovation Meeting on clinically meaningful endpoints for wound healing clinical trials and have begun collaborating with the recently formed Wound Care Collaborative Community (WCCC).[18–20] This multi-stakeholder engagement will help identify key considerations for trial standardisation, endpoints, drug development tools, and/or innovative trial designs (e.g. utilizing real-world evidence and patient registries, virtual/decentralized trials).

To further engage multiple stakeholders involved in product development for non-healing chronic wounds, the FDA will host a wound healing scientific workshop in April 2022. The overarching objectives of the workshop are to discuss and gather input on the current barriers to product development for non-healing chronic wounds, codify root causes of barriers, and align on the highest priority barriers. The meeting summary will be published on the FDA website, and we are optimistic that the workshop will serve as a foundation to help direct future activities.

Ultimately, the FDA's goal is to improve the pathway to developing products that make a clinically meaningful difference to patients with non-healing chronic wounds. Beyond hearing from patients and caregivers during the April 2022 workshop, future patient-focused drug development (PFDD) meetings and/or dedicated patient listening sessions will be beneficial to improve understanding of the patient factors influencing clinical trial participation and risk of non-adherence, as well as identify steps and initiatives sponsors can take to promote trial participation (e.g. expanding eligibility, increased patient outreach) and address non-adherence (e.g. adherence reminders, increased caregiver support).

The FDA understands that there is external stakeholder interest to provide updated guidance to the 2006 Guidance for Industry: *Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment*.[21] When published, guidance documents represent the Agency's

current thinking on a particular topic, which may evolve with time, and the evolution of Agency thinking may be informally communicated in various settings separate from guidance documents (e.g. conferences, public workshops, and editorials such as this). The Agency also acknowledges that updating such guidance is a complex process requiring input from multiple FDA centers and subject matter experts. Stakeholders are reminded that guidance documents are a set of recommendations. An alternate approach other than one proposed in guidance documents may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Sponsors are encouraged to communicate with the Agency if they wish to discuss an alternate approach to obtain Agency feedback.

A longer-term priority for advancing product development for non-healing chronic wounds includes enabling data sharing across industry, academia, Centers for Medicare & Medicaid Services (CMS), medical centers, and other key stakeholders. For example, the Critical Path Institute (C-Path) has previously established collaborations with various industry sponsors to support sharing of clinical trial data with stakeholders for a range of meta-analyses (e.g. endpoint evaluation, trial size optimization, evaluation of disease natural history). A future data-sharing deliverable may be modelled off these prior collaborations.[22–24]

In addition to the activities outlined above identified through the Science Strategies program, current opportunities exist for stakeholders to engage with FDA on innovative product development for non-healing chronic wounds.[25] The breakthrough devices program allows prioritized review for eligible products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.[26] The Medical Device Development Tools (MDDT) program and Drug Development Tool (DDT) program allow the FDA to qualify clinical outcome assessments (including patient-reported outcomes), biomarker tests and non-clinical assessment models for use in the development and review of medical devices, drugs and biologics.[27–30] Finally, the Critical Path Innovation Meeting (CPIM), while not a substitute for formal pre-IND or other regulatory meetings, is a means by which CDER and investigators from industry, academia, scientific consortia, patient advocacy groups, and government can communicate to improve efficiency and success in drug development.[18,31]

The US FDA remains deeply committed to protecting and promoting public health and recognizes the public health burden of non-healing chronic wounds and the lack of available innovative products. Through specific activities which have been identified as priorities to address barriers to product development for non-healing chronic wounds, and in collaboration with key wound healing stakeholders including academia, professional associations, patient groups, reimbursement organizations and industry, FDA intends to help advance product development for non-healing chronic wounds for the ultimate betterment of patients.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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