

2018

The FDA's Priority Review Voucher Program's Role in Bringing Benznidazole to Chagas Disease Patients in the United States

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Recommended Citation

Cline, Lisa (2018) "The FDA's Priority Review Voucher Program's Role in Bringing Benznidazole to Chagas Disease Patients in the United States," *Cybaris®*: Vol. 9 : Iss. 2 , Article 3.

Available at: <https://open.mitchellhamline.edu/cybaris/vol9/iss2/3>

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**THE FDA’S PRIORITY REVIEW VOUCHER PROGRAM’S ROLE IN
BRINGING BENZNIDAZOLE TO CHAGAS DISEASE PATIENTS IN THE
UNITED STATES**

BY LISA CLINE, MD

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I. Introduction

Chagas disease is a serious parasitic infection that affects at least 6 million people in the world.¹ An estimated 300,000 Chagas disease patients live in the United States.² Until recently, no FDA approved treatment for Chagas disease existed.³ The FDA's Priority Review Voucher incentive program was a key factor in the recent FDA approval of benznidazole for the treatment of Chagas Disease.⁴

¹ *Chagas Disease (American Trypanosomiasis)*, WORLD HEALTH ORG. (last updated Mar. 2017), <http://www.who.int/mediacentre/factsheets/fs340/en/> [hereinafter WHO] (fact sheet) (stating that Chagas disease is “also known as American Trypanosomiasis”).

² *Chagas Disease*, FOOD & DRUG ADMIN. (last updated Oct. 12, 2017), <https://www.fda.gov/ForConsumers/ByAudience/MinorityHealth/ucm466121.htm>.

³ Thomas Morrow, MD, *FDA Gives First-Ever Approval of Drug to Treat Chagas Disease*, (Nov. 2017), <https://www.managedcaremag.com/archives/2017/11/fda-gives-first-ever-approval-drug-treat-chagas-disease> (“Until recently, there was no treatment bearing the FDA’s stamp of approval for Chagas’ [*sic*] disease.”).

⁴ *See* Press Release, FDA, FDA Approves First Treatment for Chagas Disease (Aug. 29, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573942.htm> [hereinafter Press Release FDA Approves] (explaining that the FDA granted a priority review voucher to the drug sponsor of benznidazole and that “[t]he FDA is committed to making available safe and effective therapeutic options to treat tropical diseases”).

This article describes the role of the FDA Priority Review Voucher program in the recent FDA approval of benznidazole for Chagas disease. This article's first section details the background and current status of the FDA Priority Review Voucher program.⁵ The next section explains the sale of priority review vouchers.⁶ This article then explores the impact, benefits, and limitations of the Priority Review Voucher Program.⁷ Part II ends with a brief description of the FDA's Orphan Drug status designation.⁸

Part III begins by describing Chagas disease and its discovery.⁹ This part then addresses the history of Chagas disease treatments.¹⁰ This article then explains the events surrounding the recent FDA approval of benznidazole for the treatment of Chagas disease.¹¹ This article concludes by assessing the FDA Priority Review Voucher program's role in the benznidazole approval and addresses legislative concerns going forward.¹²

II. History and Background Section

A. *Relationship Between Patent Law and Pharmaceutical Companies*

Many diseases in developing countries are untreated because patent law monopolies price the necessary medications out of the financial reach of poor countries' inhabitants.¹³ Although many

⁵ See *infra* Parts IIA., B., C.

⁶ See *infra* Part IID.

⁷ See *infra* Parts IIE., F.

⁸ See *infra* Part IIG.

⁹ See *infra* Parts IIIA., B.

¹⁰ See *infra* Part IIIC.

¹¹ See *infra* Part IV.

¹² See *infra* Part V.

¹³ Robert C. Bird, *Developing Nations and the Compulsory License: Maximizing Access to Essential Medicine While Minimizing*

factors contribute to the lack of available medications in developing countries, the tight relationship between U.S. governmental patent law and multinational pharmaceutical corporations provides the cornerstone to “this global health crisis.”¹⁴ Multinational pharmaceutical corporations utilize government-approved monopolies to control medications’ use and sale.¹⁵ Patents to medications allow pharmaceutical corporations to raise prices into the unaffordable range for patients who need the medications the most.¹⁶ Multinational corporations claim that high research and development costs impede their ability to lower medication prices.¹⁷ Additionally, multinationals cite the potential for trafficking of

Investment Side Effects, 37 J.L. MED. & ETHICS 209, 209 (2009) (“Many of the health problems facing the developing world do not arise from a lack of understanding of complex diseases. Rather, the problem arises from a striking lack of availability of life saving medications for the consumers that need these medicines the most.”).

¹⁴ *Id.* (stating that “the publicity spotlight . . . has shined largely on the alliance of strong, government-legislated patent law and the multinational corporation” as a cause of poor medication access in developing countries).

¹⁵ *Id.*; Marcia Angell, *The Truth About Drug Companies*, THE N.Y. REV. OF BOOKS (July 15, 2004),

https://alojamientos.uva.es/guia_docente/uploads/2013/478/46299/1/Documento2.pdf (stating that the pharmaceutical industry is “utterly dependent on government-granted monopolies—in the form of patents and Food and Drug Administration (FDA)-approved exclusive marketing rights”).

¹⁶ Bird, *supra* note 13 at 209 (stating that “[m]ultinationals owning patents to medicines raise prices” such that the needed treatments “become unaffordable to the poorest consumers who need them”).

¹⁷ Bird, *supra* note 13 at 209; Angell, *supra* note 15 at 1 (quoting a pharmaceutical company spokeswoman as explaining that “[p]rice increases are not uncommon in the industry and that allows us to invest in R&D” (research and development)).

medications from developing countries to wealthier nations.¹⁸ However, critics believe that multinationals sacrifice impoverished countries' citizens' health to increase profit margins.¹⁹

¹⁸ Bird, *supra* note 13 at 209.

¹⁹ Bird, *supra* note 13 at 209; Angell, *supra* note 15 at 3 (stating that research and development costs comprise a minor portion of (pharmaceutical corporations' spending and that "the prices drug companies charge have little relationship to cost of making drugs and could be cut dramatically without coming anywhere close to threatening [research and development]").

B. United States Food and Drug Administration Priority Review

In 2006, a trio of Duke University faculty members published a paper suggesting the use of priority review vouchers to incentivize drug companies to manufacture “essential drugs in developing countries.”²⁰ The paper proposed that the FDA grant transferrable vouchers that would significantly decrease FDA approval times for drugs treating neglected tropical diseases (“NTDs”).²¹ The voucher idea “caught the attention” of members of Congress, and in 2007, President Bush signed the Food and Drug Administration Amendment Act (FDAAA) that included provisions for priority review vouchers (“PRVs”).²² The Act states that the FDA may issue a PRV to a pharmaceutical company that receives approval for a new drug application (“NDA”) or a biologics license application (“BLA”) for a new chemical entity (“NCE”) to treat an NTD.²³ The pharmaceutical company may then apply the PRV toward a different medicine that the company wishes to market.²⁴ Conversely, a pharmaceutical company may sell its PRV to another drug manufacturer.²⁵ As of 2016, the average sale price for a PRV was \$200 million.²⁶ Thus, the PRV acts as a “prize” to encourage pharmaceutical companies to complete the required steps for FDA approval.²⁷ In 2012, President Barack Obama signed the Food and Drug Administration Safety and Innovation Act (FDASIA), which provided the FDA with authority to grant PRV for treatments of rare pediatric diseases.²⁸

²⁰ David B. Ridley et al., *Developing Drugs for Developing Countries*, 25 HEALTH AFFAIRS 313, 313 (2006), <https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.25.2.313> [hereinafter Ridley, *Developing Drugs*] (listing Chagas disease as an example of a “neglected disease”).

²¹ *Id.* at 322 (explaining that “[i]n a well-functioning voucher market,” priority review vouchers would “speed access to highly valued treatments,” allowing drugs for treating diseases in developing countries to reach patients more quickly); David Ridley, *Priority Review Vouchers*, PRIORITY REV. VOUCHERS (last visited Dec. 16, 2017), <http://priorityreviewvoucher.org> [hereinafter Ridley, *Priority Review Vouchers*] (listing the NTDs eligible to PRVs including blinding trachoma, cholera, dengue, leprosy, malaria, tuberculosis, as well as Chagas disease, which the FDA added in 2015); *Why are some tropical diseases called “neglected”?*, WORLD HEALTH ORG. (Jan. 2012), <http://www.who.int/features/qa/58/en/> (“Neglected tropical diseases persist in under conditions of poverty and are concentrated almost exclusively in impoverished populations in the developing world.”).

²² Jonathan Berman, *The Tropical Disease Priority Review Voucher: A Game-Changer for Tropical Disease Products*, 96 AM. J. TROPICAL MED. HYGIENE 11, 12 (2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5239674/>; Alexander Gaffney, *Regulatory Explainer: Everything You Need to Know About FDA’s Priority Review Vouchers*, REG. AFF. PROFS. SOC’Y (Nov. 29, 2017), <http://www.raps.org/Regulatory-Focus/News/2015/07/02/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA’s-Priority-Review-Vouchers/>; Ridley, *Priority Review Vouchers*, *supra* note 21; see Food and Drug Administration Amendment Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, <https://www.gpo.gov/fdsys/pkg/STATUTE-121/pdf/STATUTE-121-Pg823.pdf>.

²³ 21 C.F.R. § 314.108 (2016) (“New chemical entity means a drug that contains no active moiety that has been approved by the FDA in any other NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.”); Berman, *supra* note 22 at 12; *Biologics License Applications (BLA) Process (CBER)*, U.S. FOOD & DRUG ADMIN. (last updated Nov. 5, 2015), <https://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/default.htm> (“The Biologics License Application (BLA) is a request for permission to introduce . . . a biologic product into interstate commerce (21 CFR 602.1).”); *New Drug Application (NDA)*, U.S. FOOD & DRUG ADMIN. (last updated March 29, 2016), <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm> (“The NDA application is a vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S.”).

²⁴ Berman, *supra* note 22 at 12.

²⁵ *Id.* (“The PRV is transferrable and can be sold for use with any other product.”).

²⁶ David B. Ridley, *Priorities for the Priority Review Voucher*, 96 AM. J. TROPICAL MED. HYGIENE 14, 15 (2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5239680/> [hereinafter Ridley, *Priorities*] (explaining that as of June 2016, 4 out of the 10 PRV recipients had sold their vouchers); *see also* Gaffney, *supra* note 22 (stating that as of June 2017, PRV sale prices have ranged from \$ 67 million to \$350 million).

²⁷ Ridley, *Developing Drugs*, *supra* note 20 at 316–18 (explaining “push” and “pull” mechanisms for stimulating drug development and describing the PRV strategy a “pull mechanism”); Ridley, *Priority Review Vouchers*, *supra* note 24 (referring to a PRV as a “prize” in the context of discussing the limitations of the PRV program).

²⁸ 21 U.S.C. §§ 360bb, 360ff (2012), <https://www.gpo.gov/fdsys/pkg/USCODE-2012-title21/pdf/USCODE-2012-title21-chap9-subchapV-partB-sec360bb.pdf>; <https://www.gpo.gov/fdsys/pkg/USCODE-2012-title21/pdf/USCODE-2012-title21-chap9-subchapV-partB-sec360ff.pdf> (defining a “rare pediatric disease” as one that “primarily affects individuals aged birth to 18 years” and “which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 persons in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug”); *FDA: Recently Signed PDUFA 5 Provisions to Address Drug Shortages*, POL’Y & MED. (July 18, 2012), <http://www.policymed.com/2012/07/fda-recently-signed-pdufa-5-provisions-to-address-drug-shortages.html>; *Rare Pediatric Disease Priority Review Voucher Program*, U.S. FOOD & DRUG ADMIN. (last updated Nov. 2, 2017), <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm>.

C. FDA's Priority Review Vouchers

All prescription medications marketed in the United States must receive FDA approval.²⁹ To receive approval, each drug must undergo the FDA's review process.³⁰ The review process is a "two-tiered" system that includes *standard review* and *priority review*.³¹ Drugs with a standard review designation normally receive an FDA decision concerning approval 10 months after a manufacturer submits an NDA.³² In contrast, the decision time for drugs with a priority review designation is 6 months.³³ The FDA grants a standard review or a priority review designation for all NDAs and BLAs.³⁴ Additionally, a drug manufacturer may request a priority review designation.³⁵ PRVs provide yet another mechanism by which a drug may receive priority review designation.³⁶

²⁹ *What is the Approval Process for a New Prescription Drug?*, U.S. FOOD & DRUG ADMIN. (last updated Nov. 11, 2017) <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194949.htm>.

³⁰ *Priority Review Vouchers*, U.S. FOOD & DRUG ADMIN. (last updated Sept. 9, 2014), <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm> [hereinafter *FDA Priority Review*].

³¹ *Id.*

³² *Id.*; *Step 4: FDA Review*, U.S. FOOD & DRUG ADMIN. (last updated Apr. 26, 2017), <https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405570.htm>.

³³ *FDA Priority Review*, *supra* note 30.

³⁴ *Id.*

³⁵ *Id.*

³⁶ Gaffney, *supra* note 22 (detailing the differences between “What the Priority Review Designation Process Normally Looks Like” and “How the Priority Review Voucher System Works” in a chart).

The FDA provides priority review designations to drugs that “would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.”³⁷ A priority review designation does not decrease the clinical trial period’s length, nor does it “alter the scientific standard for approval or the quality of evidence necessary.”³⁸ Instead, the priority review designation “is intended to direct overall attention and resources to the evaluation of such applications.”³⁹ The FDA also grants priority review designation to treatments for pediatric patients and for infectious diseases.⁴⁰ Priority review is one of four FDA approaches that strive to increase the speed with which drugs become available in the United States.⁴¹

³⁷ FDA *Priority Review*, *supra* note 30 (listing “elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of patient compliance,” and “evidence of safety and effectiveness in a new subpopulation” as examples of “significant improvement”);

³⁸ *Id.*

³⁹ U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 24 (2014), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf> [hereinafter GUIDANCE].

⁴⁰ *Id.* (describing a “supplement that proposes a labelling change pursuant to report on a pediatric study” and an “application for a drug that has been designated as a qualified infectious disease product”).

⁴¹ *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, U.S. FOOD & DRUG ADMIN. (last updated Sept. 4, 2015), <https://www.fda.gov/ForPatients/Approvals/Fast/default> (noting that although “each of [the four] approaches implies speed,” they constitute “four distinct and successful approaches to making such drugs as rapidly as possible”).

D. Sale of PRVs

Another beneficial characteristic of PRVs is their transferability.⁴² Instead of utilizing the PRV to obtain priority review for one of its own products, a PRV holder may sell the PRV to another drug manufacturer.⁴³ To illustrate the potential economic value of a PRV, consider a small pharmaceutical company with a PRV for an NTD.⁴⁴ The PRV's value may be essentially equivalent to the company's value.⁴⁵ Not surprisingly, new business models have come into existence with the goal of utilizing the PRV program as a valuable financial tool.⁴⁶

⁴² Ridley, *Priority Review Vouchers*, *supra* note 21.

⁴³ Gaffeny, *supra* note 22 (explaining that a PRV holder can either redeem the voucher for its own use or sell the voucher to “another company, which might to have its own drug reviewed in a six-month timeline”).

⁴⁴ See David B. Ridley, *Fuqua Research into Action: The Priority Review Voucher*, <https://faculty.fuqua.duke.edu/~dbr1/voucher/> [hereinafter Ridley, *Fuqua Research*] (video) (giving an example of a company who held a voucher from the manufacturing of a drug for leishmaniasis).

⁴⁵ *Id.* (describing bankers seeking information concerning the value of a PRV to determine the value of a company).

E. Impact and Benefits of PRVs

A PRV provides a drug manufacturer with a priority review designation for use with a future drug.⁴⁷ The manufacturer does not use the PRV for the NTD medication; instead, the manufacturer uses the PRV for a different drug.⁴⁸ Although the PRV-qualifying NTD drug does not utilize a PRV, the NTD drug must also qualify for priority review “on its own merit.”⁴⁹ A PRV allows a new drug to arrive on the U.S. market sooner than its competitors, thus increasing the potential for a pharmaceutical company to release a blockbuster drug.⁵⁰

⁴⁶ Chris Bialas, *Analyzing the FDA Priority Review Voucher Programs Stimulation of Research and Public Health Impact*, 3 TECHNOLOGY TRANSFER & ENTREPRENEURSHIP 131, 137 (2016), https://www.researchgate.net/profile/Dennis_Gross/publication/305823499_Analyzing_the_FDA_Priority_Review_Voucher_Program%27s_Stimulation_of_Research_and_Public_Health_Impact/links/5874ef4308ae6eb871c97e36/Analyzing-the-FDA-Priority-Review-Voucher-Programs-Stimulation-of-Research-and-Public-Health-Impact.pdf (“This interest has even spawned new business models based on the development of target designation treatments in order to acquire and sell PRVs.”)

⁴⁷ Gaffeny, *supra* note 22; Ridley, *Priority Review Vouchers*, *supra* note 21.

⁴⁸ Ridley, *Priorities*, *supra* note 26 (“Thus, two drugs are involved: the drug that wins a bonus priority review and the drug that uses the bonus priority review.”).

⁴⁹ Ridley, *Priorities*, *supra* note 26 at 15.

⁵⁰ *Id.*; David B. Ridley, *Fuqua Research*, *supra* note 44.

Three value sources for PRV holders exist.⁵¹ First, a PRV allows a manufacturer to release its product into the market sooner than standard review would allow.⁵² Second, a PRV provides a longer on-market experience for the pharmaceutical company's product.⁵³ Third, a PRV provides a drug manufacturer with "competitive benefits" that may allow the voucher holder to "launch" their product closer to or even before a competitor's product.⁵⁴

⁵¹ Ridley, *Fuqua Research*, *supra* note 44.

⁵² *Id.* (noting that reaching the market earlier increases the "time value of money").

⁵³ *Id.* (explaining that "you launch earlier and have the same effective patent expiration date, in many cases").

⁵⁴ *Id.*

The PRV program provides two important benefits to healthcare.⁵⁵ First, PRVs encourage drug companies to complete the necessary research and development for rare and neglected disease treatments.⁵⁶ Without the attraction of a PRV, few drug companies would invest in medicines to treat NTDs.⁵⁷ Accordingly, before the PRV program, few pharmaceutical companies applied for patents on their “essential medicines” distributed to low-to mid-income countries.⁵⁸

⁵⁵ Ridley, *Priority Review Vouchers*, *supra* note 21.

⁵⁶ GUIDANCE, *supra* note 39 (requiring clinical trials, clinical testing, “randomized trials, other types of controls . . . for example, historical controls” as “an attempt to show superiority relating to either safety or effectiveness”); Ridley, *Priority Review Vouchers*, *supra* note 21.

⁵⁷ Gaffeny, *supra* note 22 (“FDA’s priority review vouchers . . . are incentives meant to spur the development of new treatments for diseases that would otherwise not attract development interest from companies due to the cost of development and the lack of market opportunities.”).

⁵⁸ Amir Attaran, *How Do Patents and Economic Policies Affect Access to Essential Medicines in Developing Countries?* 23 HEALTH AFFAIRS 155, 155, 159 (2004), <https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.23.3.155> (finding that pharmaceutical companies usually did not seek patents in developing countries, even when they legally had the option).

Second, PRV program allows “potential blockbuster” drugs to reach U.S. patients more quickly.⁵⁹ Data suggests that priority review status increases a drug’s likelihood of obtaining blockbuster status.⁶⁰ While some drugs achieve blockbuster status without priority review designation, pharmaceutical companies and patients lose the benefits of expedited FDA approval.⁶¹ Because the FDA “direct[s] overall attention and resources” to drugs with priority review status, the voucher holder must pay a fee to redeem the PRV.⁶² This user fee allows the FDA to obtain the necessary resources to expedite the review of the PRV drug without delaying the review of other medications.⁶³ Thus, the PRV program provides sources of medications to treat NTD without incurring U.S. taxpayer costs or delayed FDA review of other medications.⁶⁴ The PRV program inspired the United States Patent and Trademark Office to create an awards competition to recognize “innovators who use game-changing technology to meet global humanitarian challenges.”⁶⁵

⁵⁹ Ridley, *Priority Review Vouchers*, *supra* note 21; *What Is a Blockbuster Drug?*, THE MOTLEY FOOL (last visited Dec. 18, 2017), <https://www.fool.com/knowledge-center/what-is-a-blockbuster-drug.aspx> (“Blockbuster drugs are those that generate at least \$1 billion in revenue a year for the pharmaceutical companies that produce them.”).

⁶⁰ Ridley, *Developing Drugs*, *supra* note 20 (noting that during the 1990s, “fourteen of the twenty-nine ‘blockbuster drugs’ . . . were classified as priority”).

⁶¹ *Id.* (listing Zocor, Norvasc, Cozaar, and Zyprexa and examples of drugs that “[h]ad priority review vouchers been available, these drugs could have helped patients sooner and earned higher returns”).

⁶² Notice, Fee for Using a Tropical Disease Priority Review Voucher in Fiscal Year 2017, 81 Fed. Reg. 67356
<https://www.federalregister.gov/documents/2016/09/30/2016-23623/fee-for-using-a-tropical-disease-priority-review-voucher-in-fiscal-year-2017> (stating that the fee category for an “[a]pplication submitted with a tropical disease priority review voucher in addition to the normal PDUFA fee” was \$2,706,000 for the fiscal year 2017); *Tropical Disease Priority Review Voucher Program*, U.S. FOOD & DRUG ADMIN. (last updated May 24, 2017), <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm> (noting in a table that fees for tropical disease PRV have ranged from \$2,325,000 to \$5,280,000 from 2011 to 2018 and that the Tropical Disease PRV User Fee for the 2018 fiscal year will be \$2,830,000; Ridley, *Priority Review Vouchers*, *supra* note 21 (“By moving one drug to faster review, there is the potential to slow other drugs.”)).

⁶³ Ridley, *Priority Review Vouchers*, *supra* note 21.

⁶⁴ Berman, *supra* note 22 at 13.

⁶⁵ Request for Comments on Incentivizing Humanitarian Technologies and Licensing Through the Intellectual Property System, 75 Fed. Reg. 57261 (Sept. 20, 2010)
<https://www.federalregister.gov/documents/2010/09/20/2010-23395/request-for-comments-on-incentivizing-humanitarian-technologies-and-licensing-through-the>; *Patents for Humanity*, UNITED STATES PAT. & TRADEMARK OFF. (last updated Nov. 17, 2017), <https://www.uspto.gov/patent/initiatives/patents-humanity/learn-more>; Ridley, *Priority Review Vouchers*, *supra* note 21.

F. Limitation, risks, and criticisms of the PRV Program

The PRV program contains inherent risk and limitations.⁶⁶ Most importantly, the FDA is not required to approve a PRV holder's product.⁶⁷ The FDAAA and FDASIA state that the FDA will come to a decision on a PRV holder's NDA—not that the FDA is obligated to approve the drug.⁶⁸ Additionally, although the FDA pledges to allocate resources to expedite the review of a priority review drug, the FDA does not guarantee completion of review in the six-month time frame.⁶⁹

⁶⁶ Gaffeny, *supra* note 22.

⁶⁷ *Id.*

⁶⁸ U.S. FOOD & DRUG ADMIN., TROPICAL DISEASE PRIORITY REVIEW VOUCHERS: GUIDANCE FOR INDUSTRY 6 (2016), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf> [hereinafter TDPRV GUIDANCE] (“Note that an FDA review within a specific time frame does not mean an application will be approved within that time frame. The term *review and act on* is understood to mean the issuance of an approval or complete response letter after the review of a filed application.”); *Id.* (noting that an action letter may not contain approval); Gaffeny, *supra* note 22 (“As Novartis proved in the first-ever use of a priority review voucher, FDA will not necessarily approve a product just because its sponsor used a voucher. Priority review . . . will not save a bad drug from being rejected.”).

⁶⁹ GUIDANCE, *supra* note 39 at 25 (“A priority review designation means the FDA’s goal is to take action on the marketing application within 6 months of receipt (compared with 10 months under standard review).”); TDPRV GUIDANCE, *supra* note 68 at 5 (stating that the FDA has “committed to a goal to review and act on 90 percent pf priority new molecular entity (NME) NDA and original BLA submissions within 6 month of the 60-day filing date, and 90 percent of priority non-NME original NDA submissions within 6 months of receipt”); Gaffeny, *supra* note 22 (describing the FDA’s lack of obligation to meet a fixed deadline for approval as a “little-known limitation”).

Critics of the PRV program highlight several weaknesses of PRVs.⁷⁰ First, the drug applying for a PRV must itself earn a priority review designation.⁷¹ Second, the costs for completing clinical trials are often higher for NTDs than for rare pediatric diseases, thus making PRVs less valuable to drug manufacturers developing NTD treatments than those developing rare pediatric disease treatments.⁷² Third, Congress could decide not to renew the voucher program, thus exposing drug companies to investment risk.⁷³ Additionally, variables such as timing, supply, and competition make predicting a PRV's sale value challenging.⁷⁴ Fourth, drug manufacturers may receive PRV for drugs that are currently available outside the United States, thus defeating the program's goal of developing novel treatments.⁷⁵ Finally, the PRV program does not ensure that the drugs for treating NTDs will be available or affordable.⁷⁶

⁷⁰ See Berman, *supra* note 22 at 13; Ridley, *Priorities*, *supra* note 26 at 15.

⁷¹ TDPRV GUIDANCE, *supra* note 68 at 2 (stating that a drug application sponsor is eligible for a tropical disease PRV if “[t]he application might otherwise be eligible for a priority review”); Berman, *supra* note 22 at 11 (stating that the requirement the NDA product must itself have priority review has “at least three important ramifications”); Ridley, *Priorities*, *supra* note 26 at 14.

⁷² Berman, *supra* note 22 at 12 (“Unlike rare pediatric diseases . . . tropical diseases . . . require large-scale trials”); Ridley, *Priorities*, *supra* note 26 at 14.

⁷³ Berman, *supra* note 22 at 12 (“There is legislative risk around the programs very existence or the rules around its application.”).

⁷⁴ *Id.* (explaining that “the timing of a voucher sale is more art than science”).

⁷⁵ Helen Branswell, *How a System Meant to Develop Drugs for Rare Diseases Broke Down*, STAT (Nov. 28, 2015), <https://www.statnews.com/2015/11/28/priority-review-vouchers-rare-diseases/> (explaining the first PRV recipient was a drug manufacturer of a malaria treatment that “had been licensed outside the U.S. since 2001 and was already widely in use”); *see also* David Ridley, *How to Put an Ebola Treatment on Drugmakers’ Radar*, SFGATE (Oct. 12, 2014), <http://www.sfgate.com/opinion/openforum/article/Congress-should-offer-vouchers-to-develop-ebola-5818174.php> (stating that “Congress should restrict eligibility for the voucher to novel products that have not been approved in other countries more than two years prior to FDA submission”).

⁷⁶ Ridley, *Priorities*, *supra* note 26 at 14; Branswell, *supra* note 75 (“Drug makers that earn priority review vouchers don’t have to guarantee that the drugs will actually be available, or sold at an affordable price.”).

G. The Orphan Drug Development Program

In 1984, President Ronald Reagan signed the Orphan Drug Act.⁷⁷ The Act provided incentives for pharmaceutical companies to market treatments for rare diseases.⁷⁸ These incentives include tax credits, market exclusivity, and fast-track designation.⁷⁹ A drug may obtain orphan status in two ways.⁸⁰ First, the FDA may grant a drug orphan status if the drug provides a treatment for a rare disease.⁸¹ Second, the FDA may grant orphan status to a drug for which “there is no reasonable expectation that the sales of the drug will be sufficient to offset the costs of developing the drug.”⁸² While critics of the Orphan Drug Act have voiced concerns about drug manufacturers’ abuse of orphan drug status, the Act has contributed to FDA approval of important blockbuster drugs.⁸³ Under the FDA’s Accelerated Approval Pathway,⁸⁴ the FDA may grant priority review designation and orphan drug status to the same medication.⁸⁵

⁷⁷ *FDA Marks Orphan Drug Law Milestone*, U.S. FOOD & DRUG ADMIN. (last updated Oct. 24, 2017), <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/OOPDNewsArchive/ucm333527.htm>.

⁷⁸ DEP’T OF HEALTH & HUMAN SERVS., *THE ORPHAN DRUG ACT: IMPLEMENTATION AND IMPACT 1* (2001), <https://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf>.

⁷⁹ *Id.* at 4 (listing the Act’s incentives as “(1) 7-year market exclusivity . . . (2) a tax credit of 50 percent of the cost of conducting human clinical trials, and (3) Federal research grants for clinical testing”); *id.* (“In 1997, Congress created an additional incentive when it granted companies developing orphan products an exemption from the usual drug application or “user” fees charged by the Food and Drug Administration (FDA).”); *Orphan Drugs in the United States*, ORPHANET (last updated Dec. 19, 2017), http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_USA (describing additional orphan drug sponsor incentives as “some written recommendations provided by the FDA concerning clinical and preclinical studies to be completed in order to register the new drug” and “a fast-track procedure for the FDA to evaluate registration files”).

⁸⁰ Aarti Sharma, *Orphan Drug: Development Trends and Strategies*, 2 J. PHARMACY & BIOALLIED SCI. 290, 290 (2010), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996062/>; *Designating an Orphan Product; Drugs and Biological Products*, U.S. FOOD & DRUG ADMIN. (last updated Dec. 19, 2017), <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm>; *Developing Products for Rare Diseases & Conditions*, U.S. FOOD & DRUG ADMIN. (last updated Dec. 19, 2017), <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm>.

⁸¹ 21 C.F.R. § 316.21(a)(1) (2013), https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=718f6fcbc20f2755bd1f5a980eb5eed&mc=true&n=sp21.5.316.c&r=SUBPART&ty=HTML#se21.5.316_120 (defining the a rare disease as one “that the number of people affected by the disease or condition for which the drug is developed is less than 200,000”); Sharma, *supra* note 80 at 290 (“A medicinal product designated as an orphan drug is one that has been specifically developed to treat a rare medical condition, the condition itself being referred to as an ‘orphan disease’”).

⁸² 21 C.F.R. § 316(a)(2) (describing the parameters for orphan status regarding the drugs development to sales cost ratio in the United States).

⁸³ James Bohan, *Orphan Drugs and Why Everybody Wants One!*, IDEA PHARMA (Mar. 15, 2017), <http://ideapharma.com/junkie/orphan-drugs-and-why-everyone-wants-one>; Sarah Jane Tribble, *Drugs for Rare Diseases Have Become Uncommonly Rich Monopolies*, NPR (Jan. 17, 2017), <https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies> (reporting information demonstrating that “the system intended to help desperate patients is being manipulated by drugmakers to maximize profits and to protect niche markets for medicines already taken by millions”); *id.* (listing Humira, Enbrel, Remicade, and Rituxan as examples of orphan drugs that became blockbusters); Sarah Jane Tribble, *FDA Moves to Rein in Drugmakers’ Abuse of Orphan Drug Law*, NPR (Sept. 13, 2017), <https://www.npr.org/sections/health-shots/2017/09/13/550700062/fda-moves-to-rein-in-drugmakers-abuse-of-orphan-drug-law> (stating that “many drugs that now have orphan status are not entirely new” and that the FDA “plans to close a loophole that allows manufacturers to skip pediatric testing requirements when developing a mass-market drug for treating rare diseases in children”). *But see* Walter Armstrong, *Pharma’s Orphans*, PHARMEXEC.COM (May 1, 2010), <http://www.pharmexec.com/pharmas-orphans> (“The legislation is almost universally viewed as a roaring success.”)

⁸⁴ *Accelerated Approval*, U.S. FOOD & DRUG ADMIN. (last updated Sept. 15, 2014), <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm>.

⁸⁵ *See* Press Release FDA Approves, *supra* note 4 (stating that the treatment for Chagas disease received priority review and orphan status).

III. History of Chagas Disease Treatment

A. *Description of Chagas Disease*

Chagas disease (American Trypanosomiasis) results from the infection of the protozoan parasite *Trypanosoma cruzi*.⁸⁶ Contact with the urine or feces of triatomine bugs infects humans.⁸⁷ Infected insects emerge at night from their daytime hiding places in the cracks of walls and roofs to bite humans.⁸⁸ When the person rubs or itches the bite area, parasite-infected feces and saliva enter the wound.⁸⁹ Additionally, the Chagas parasite may infect patients via blood transfusions, contaminated food consumption, laboratory accidents, organ transplants, and mother-to-unborn child transmission.⁹⁰

⁸⁶ TINTINALLI'S EMERGENCY MEDICINE, 1102 (Judith Tintinalli, ed., 2016).

⁸⁷*Id.* (indicating that triatomine bugs are also known as “kissing bugs” and “assassin bugs”); WHO, *supra* note 1.

⁸⁸ WHO, *supra* note 1; TINTINALLI, *supra* note 86 at 1102.

⁸⁹ TINTINALLI, *supra* note 86 at 1102; WHO, *supra* note 1 (stating that the “parasites enter the body when the person instinctively smears the bug feces [*sic*] or urine into the bite, the eyes, the mouth, or any skin break”).

⁹⁰ TINTINALLI, *supra* note 86 at 1102; WHO, *supra* note 1.

Persons infected with the parasite first experience inflammation around one eye (Romaña's sign) or painful swelling at the bite site.⁹¹ Chagas disease sufferers typically experience two phases of the illness: an acute and a chronic phase.⁹² During the acute phase, which typically lasts two to 4 weeks, infected persons may experience "fever, headache, enlarged lymph glands, pallor, muscle pain, difficulty in breathing, swelling, and abdominal or chest pain."⁹³

After the acute phase, the untreated disease enters a latent, chronic stage, in which the infected person experiences few symptoms.⁹⁴ During the chronic phase, the parasite remains dormant in heart, nerve, and muscle cells.⁹⁵ The disease gradually destroys nervous and cardiac tissue, which can lead to heart disease, gastrointestinal malfunction, and sudden death.⁹⁶

⁹¹ TINTINALLI, *supra* note 86 at 1102 (describing the swollen area around the bite as a "chagoma").

⁹² TINTINALLI, *supra* note 86 at 1102; WHO, *supra* note 1.

⁹³ TINTINALLI, *supra* note 9 at 1102 (noting that acute-phase may "last up to 3 months" and may involve high levels of the parasite in the blood stream, as well as swelling of the liver and spleen); WHO, *supra* note 1.

⁹⁴ TINTINALLI, *supra* note 86 at 1102; WHO, *supra* note 1; *see Latent infection*, THE FREE DICTIONARY (2017), <https://medical-dictionary.thefreedictionary.com/latent+infection> (defining a latent infection as one that is "asymptomatic" but "capable of manifesting symptoms under particular circumstances," and that "does not produce visible signs of a disease but may be transmitted to another host").

⁹⁵ TINTINALLI, *supra* note 86 at 1102; WHO, *supra* note 1.

⁹⁶ TINTINALLI, *supra* note 86 at 1102 (stating that "Chagas-induced heart disease is the leading form of congestive heart failure in much of Latin America"); WHO, *supra* note 1.

Physicians diagnose acute-phase Chagas disease by taking blood samples or muscle biopsies.⁹⁷ To diagnose Chagas disease in the chronic phase, physicians may utilize specialized blood tests or targeted organ tissue biopsies.⁹⁸

Two medications successfully kill the *Trypanosoma cruzi* protozoan—benznidazole and nifurtimox.⁹⁹ These medications have an almost one hundred percent cure rate for patients in the acute phase of Chagas disease.¹⁰⁰ However, this exceptional efficacy rate is only applicable if the infected person receives the medication “soon after infection at the onset of the acute phase.”¹⁰¹ The continued efficacy of the treatment decreases in a manner inversely proportional to the length of time the person has been infected.¹⁰² Thus, the longer the delay in treatment, the less effective the medications are against Chagas disease.¹⁰³

⁹⁷ TINTINALLI, *supra* note 86 at 1102 (noting that the blood or tissue samples may demonstrate “motile parasites”).

⁹⁸ *Id.*

⁹⁹ *Id.* at 1102 (stating that these medications “are available in the United States through the Centers for Disease Control”); WHO, *supra* note 1.

¹⁰⁰ WHO, *supra* note 1 (adding that benznidazole and nifurtimox “are almost 100% effective in curing the disease if given soon after infection . . . [in] cases of congenital transmission”).

¹⁰¹ *Id.*

¹⁰² *See id.* (noting that the treatments’ efficacy also decreases with increased length of infection time in cases of post-natal maternal-fetal transmission).

¹⁰³ *Id.*

No vaccine exists to prevent Chagas disease.¹⁰⁴ Thus, controlling transmission through triatomine bugs, transfusions, and transplants is the mainstay of Chagas disease prevention.¹⁰⁵ The World Health Organization's Chagas disease prevention and control measures include insecticide use, improved food-preparation hygiene, structural home improvements, and blood donor screening.¹⁰⁶

¹⁰⁴ *Id.*

¹⁰⁵ *Id.* (explaining that “[o]riginally . . . *T. cruzi* only affected wild animals” and that the “large reservoir of *T. cruzi* parasites in wild animals in the Americas means that the parasite cannot be eradicated”).

¹⁰⁶ WHO, *supra* note 1 (suggesting “spraying of houses and surrounding areas with residual pesticides,” repairing cracked walls and roofs in houses, using bednets, “testing of organ, tissue, or cell donors and receivers,” and “screening of newborns and other children of infected mothers”).

Chagas disease is epidemic in twenty-one Latin American countries, affecting between six and seven million persons worldwide.¹⁰⁷ Although Chagas disease has historically been confined to Latin America, recent decades have seen the Chagas disease distribution expand to include the parts of the United States, Canada, Europe, and western Pacific countries.¹⁰⁸

¹⁰⁷ *Id.* at n.1 (listing countries with endemic areas of Chagas Disease as Argentina, Belize, Bolivia, Brazil, Chile, Columbia, Costa Rica, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, and Venezuela); *Data & Statistics*, CTRS. FOR DISEASE CONTROL & PREVENTION (last updated Oct. 25, 2017) (providing data for endemic-level diseases in the United States, including Lyme disease, tuberculosis, and viral hepatitis); *Principles of Epidemiology in Public Health Practice, Third Edition: An Introduction to Applied Epidemiology and Biostatistics*, CTRS. FOR DISEASE CONTROL & PREVENTION (last updated May 18, 2012), <https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section11.html> (describing an endemic level of disease as one that is the “baseline” level that is the “observed level” that is “usually present in a community,” and that “[i]n the absence of intervention and assuming that the level is not high enough to deplete the pool of susceptible persons, the disease may continue to occur at this level indefinitely”).

¹⁰⁸ TINTINALLI, *supra* note 86 at 1102 (“The protozoan *Trypanosoma cruzi* is found in up to 5% of emigrants from endemic parts of Latin America”); WHO, *supra* note 1 (stating that “Chagas disease occurs principally in the continental part of Latin America and not in the Caribbean isles” and that the spread of Chagas disease to other parts of the world “is due mainly to population mobility between Latin America and the rest of the world”).

B. *History of Chagas Disease*

In 1908, a scientist named Carlos Justiano Ribiero de Chagas began dissecting “large blood-sucking insects” as part of an effort to combat malaria in railway construction camps in Brazil.¹⁰⁹ Chagas discovered “numerous trypanosomes” in the insects and gave the pathogen the name *Trypanosoma cruzi*.¹¹⁰ Chagas allowed infected insects to bite laboratory animals and learned that “the parasite was infective to several . . . laboratory animals.”¹¹¹ Chagas deduced that the trypanosomes caused an unidentified human illness.¹¹²

¹⁰⁹ Dietmar Steverding, *The History of Chagas Disease*, U.S. NAT’L LIBR. MEDICINE 1, 3 (Jul. 10, 2014), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4105117/> [hereinafter Steverding, *History*] (stating that Carlos Chagas (1879–1934) was “a Brazilian hygienist and bacteriologist” who “was made aware by a railroad engineer of large blood-sucking insects which lived en masses in local dwellings and bit sleeping people preferentially in the face”).

¹¹⁰ *Id.* at 3 (explaining that Chagas “named *T. cruzi* in honor of his mentor, the Brazilian physician and bacteriologist Oswaldo Cruz (1872–1917)); See *An Introduction to Molecular Parasitology and Trypanosomes*, ROCKEFELLER U. (last visited Dec. 20, 2017), http://trysp.rockefeller.edu/trypsru2_introduction.html (describing Trypanosomes as “microscopic unicellular protozoa that are ubiquitous parasites of . . . mammals” and cause diseases such as Chagas disease).

¹¹¹ Steverding, *supra* note 109 at 3–4.

¹¹² *Id.* at 4 (“Chagas was sure he had found a pathogenic organism of a human infectious disease but he did not know what kind of sickness it was.”).

In 1909, Chagas examined a feverish two-year old girl named Bernice whose spleen, liver, and lymph nodes were enlarged.¹¹³ Although Chagas did not find *T. cruzi* in Bernice's blood during his first examination, four days later, Chagas discovered "numerous trypanosomes" in her blood.¹¹⁴ Chagas described the illness's acute phase and "linked the infection with some chronic symptoms of the illness."¹¹⁵ Although Bernice never developed the chronic phase of the disease, she was infected with *T. cruzi* her entire life.¹¹⁶

¹¹³ *Id.*

¹¹⁴ *Id.* (stating that the trypanosomes in Bernice's blood were of "similar morphology" to those found in the infected laboratory animals' blood).

¹¹⁵ *Id.* (noting that Chagas's ability to connect the two phases of the disease "was remarkable considering that the chronic phase of American trypanosomiasis usually appears decades after the first inoculation with *T. cruzi*"); Aluizio Prata, *Evolution of the Clinical and Epidemiological Knowledge of Chagas Disease 90 Years After its Discovery*, 94 MEMORÍAS DO INSTITUTO OSWALDO CRUZ 81, 82 (1999), <https://pdfs.semanticscholar.org/f513/a6c4bc9ea465663cebe3fcee395a92aa8631.pdf> (stating that in a preliminary note dated July 5, 1910, Chagas "stated that there were three modalities of the disease: one acute and two chronic").

¹¹⁶ Steverding, *History*, *supra* note 109 at 4 (noting that Bernice died at the age of 73 "on unrelated causes"); See M. de Lana et al., *Characterization of Two Isolates of Trypanosoma Cruzi Obtained from the Patient Bernice, the First Human Case of Chagas' Disease by Carlos Chagas in 1909*, <https://www.ncbi.nlm.nih.gov/pubmed/8801560/> ("Two isolates of *Trypanosoma cruzi* were obtained from the patient Bernice . . . when she was 55 and 71 years old, respectively.").

Although Chagas contributed significantly to the identification of the disease which now bears his name, other scientists played important roles in the description and understanding of Chagas disease.¹¹⁷ Chagas's discovery aroused keen interest in the international scientific community at the time.¹¹⁸ Chagas received many international recognitions, including two Nobel Prize nominations.¹¹⁹ However, Chagas's rapid rise to fame brought "animosity and envy in his own country."¹²⁰ After experiencing sabotaging actions from his own lab,¹²¹ scientists and colleagues from Brazil claimed that Chagas disease was only a local phenomenon and that the parasite was of "little virulence."¹²² Some of Chagas's opponents even accused Chagas of falsifying his findings and of being unpatriotic.¹²³ Historians speculate that Chagas's countrymen's animosity toward him "may have cost [Chagas] the Nobel Prize."¹²⁴ Additionally, the anti-Chagas group's actions likely resulted in a twenty-year period in which Chagas disease was all but "forgotten," causing research and interest in the disease to grind to a halt.¹²⁵

¹¹⁷ Prata, *supra* note 115 at 84 (mentioning that the Brazilian scientist and physician Eurico de Azevedo Villela (1883–1962) "always worked with Chagas"); Steverding, *supra* note 109 at 4 (listing Oswaldo Cruz, the Czech zoologist and parasitologist Stanislaus von Prowazek (1875–1915), the Brazilian pathologist Gaspar de Oliveira Vianna (1885–1914), and the French pathologist Alexandre Joseph Émile Brumpt (1877–1951) as contributors to early Chagas disease research). *But see* Marillia Coutinho et al., *The Noble Enigma: Chagas' Nominations for the Nobel Prize*, 94 MEMORÍAS DO INSTITUTO OSWALDO CRUZ 123, 127 (1999),

<http://www.scielo.br/pdf/mioc/v94s1/ultimo.pdf> ("Chagas had just performed the perfect algorithm from vector to disease within a few months and alone.").

¹¹⁸ Steverding, *History*, *supra* note 109 at 5; Rachel Lewinson, *Prophet in His Own Country: Carlos Chagas and the Nobel Prize*, 46 PERSPECTIVES IN BIOLOGY & MED. 532–40 (2003), <http://repositorio.unicamp.br/bitstream/REPOSIP/102650/1/2-s2.0-1542598939.pdf> (stating that “Chagas’s discovery brought him immediate, worldwide acclaim” and that “[h]onors were showered upon him”);

¹¹⁹ Coutinho, *supra* note 117 at 123 (stating that “Chagas was twice nominated for the Nobel Prize—in 1913 and in 1921–, [*sic*] but never received the award”); Lewinson, *supra* note 118.

¹²⁰ Coutinho, *supra* note 117 at 128 (describing the “surreptitious actions of the early anti-Chagas group” that led to “an unpleasant incident involving Rudolph Kraus, Director of the Institute of Bacteriology at Buenos Aires and Chagas’s own laboratory at Manuinhos”); Lewinson, *supra* note 118 (noting that “the overwhelming success of the young scientist from the backwoods of Minas Gerais set off a reaction of a different kind in some of his colleagues at Manguinhos, the Faculty and National Society of Medicine” and that “antagonism against [Chagas] . . . began to flare up”); Steverding, *History*, *supra* note 109 at 5.

¹²¹ Coutinho, *supra* note 117 at 128 (“It was clear that someone from Manguinhos had been feeding . . . contentions against Chagas.”); Lewinson, *supra* note 118 (describing Chagas’s reaction at finding slides from his own laboratory at the Institute of Bacteriology).

¹²² Coutinho, *supra* note 117 at 128; Lewinson, *supra* note 118 at 544 (listing some of Chagas’s opponent’s “preposterous accusations” including that the disease “was restricted to a small area in Minas Gerias where [Chagas] had found his first cases” and that “the number of cases did not exceed some 40 patients”).

¹²³ Coutinho, *supra* note 117 at 128 (quoting the Brazilian physician and university president Júlio Afrânio Peixoto as saying: “You could have found some mosquitos, you could have invented a rare and unknown disease . . . a disease that you could magnanimously distribute among your countrymen”); Lewinson, *supra* note 118 at 542 (noting that “a grotesque accusation was in store for Chagas: because he openly discussed the disease and its implications . . . he was reproached with being unpatriotic; this stupid, pointless charge was to haunt him for many years.”).

¹²⁴ Coutinho, *supra* note 117 at 128–29 (suggesting that “it was this local opposition that actually prevented Chagas from being awarded the Nobel Prize in 1921”); Steverding, *History*, *supra* note 109 at 5.

¹²⁵ Lewinson, *supra* note 118 at 547–48 (quoting Chagas’s son, Carlos Chagas Filho, as saying that “[t]o this day, we do not know how many of our faculties of medicine [at the National Academy of Medicine in Brazil] never taught Chagas disease”); Carlos M. Morel, *Chagas Disease, from Discovery to Control—and Beyond: History, Myths, and Lessons to Take Home*, 94 MEMÓRIAS DO INSTITUTO OSWALDO CRUZ 3, 4 (1999), <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.326.2200&rep=rep1&type=pdf> (stating that the “strong opposition against Chagas “had a devastating effect”); Steverding, *supra* note 109 at 5.

In the 1930s, Argentine physician and epidemiologist Salvador Mazza described thousands of cases of Chagas disease in Argentina.¹²⁶ In 1935, Cecilio Romaña described the periorbital swelling that is commonly present in Chagas disease patients during the acute phase of the illness.¹²⁷ Because Romaña's sign was so distinctive, the number of reported cases of Chagas disease increased dramatically after 1935.¹²⁸ By 1940, thousands of cases of Chagas disease had been diagnosed.¹²⁹

¹²⁶ Morel, *supra* note 125 at 4 (stating that “[t]he ‘resurrection’ of Chagas disease is mainly due to the work of Salvador Mazza in Argentina” and noting that Mazza was “the first one to raise the possibility of transfusion-transmitted Chagas disease”); Prata, *supra* note 115 at 85 (stating that “under the guidance of Mazza, the reports . . . started to appear, with many acute cases also detected, especially in Chile and Uruguay”); Steverding, *History*, *supra* note 109 at 5.

¹²⁷ *What is Chagas disease?*, CTRS. FOR DISEASE CONTROL & PREVENTION (last updated Dec. 19, 2017), https://www.cdc.gov/parasites/chagas/gen_info/detailed.html (describing Romaña's sign as “the most recognized marker of acute Chagas disease”).

¹²⁸ Prata, *supra* note 115 at 85 (noting that Ezequiel Dias and Evandro Chagas (Carlos Chagas's son) considered the “discovery of the Romaña sign” to be “the most valuable foreign contribution to the disease” and that “thanks to the Romaña sign [*sic*] which permits suspecting the disease at a distance, more than 500 cases were detected in Argentina and about 100 in Uruguay” between 1934 and 1938)

¹²⁹ François Delaporte, *Romana's Sign*, 30 J. HISTORY BIOLOGY 357, 357 (1997), <https://link.springer.com/article/10.1023/A%3A1004221722554> (“Once thought to be a provincial affliction limited to the state of Minas Geres, Chagas disease was now seen to be an endemic malady throughout Latin America.”).

C. *Development of Chagas Disease Treatments*

In the years following his description of Chagas disease, researchers attempted to find a treatment for Chagas disease.¹³⁰ These efforts were unsuccessful, leading Chagas and his son Evandro to state in 1935 that “there was no specific treatment” for Chagas disease.¹³¹ Between 1912 and 1962, researchers experimented with a variety of chemical agents in their endeavors to find a treatment for Chagas disease.¹³² Beginning in 1918, researchers employed various methods to obtain vector control of the Chagas disease-transmitting insect.¹³³

¹³⁰ José Rodrigues Coura & Solange L. de Castro, *A Critical Review on Chagas Disease Chemotherapy*, 97 MEMÓRIAS DO INSTITUTO OSWALDO CRUZ 3, 4 (2002), <http://www.scielo.br/pdf/mioc/v97n1/review.pdf> (stating that in 1912 and 1914, Mayer and Rocha Lima experimented with several agents, including arsenical, rosanilin dye, antimony potassium, and mercury chloride); Steverding, *History*, *supra* note 109 at 5.

¹³¹ Coura & Castro, *supra* note 130 at 4 (stating that Carlos and Evandro Chagas reported that “[d]rugs with trypanocidal activity have been assayed by a great number of researchers, but without success”); Steverding, *History*, *supra* note 109 at 5.

¹³² Coura & Castro, *supra* note 130 at 4 (listing some of the “chemotherapeutic agents employed until 1962,” including quinolein derivatives, bismuth, gentian violet, nicotinic acid hydrazide, cortisone, and “more than 30 antibiotics and some nitrofurans”).

¹³³ WORLD HEALTH ORG., HANDBOOK FOR INTEGRATED VECTOR MANAGEMENT 1 n.1 (2012), http://apps.who.int/iris/bitstream/10665/44768/1/9789241502801_eng.pdf (“ ‘Vector-borne disease’ is the collective term for infectious diseases transmitted by insects, snails, or rodents, which act as vectors of the actual pathogens.”); João Carlos Pintos Dias, *The Beginning of Chagas Disease Control (Homage to Dr. Emmanuel Dias, the pioneer of Chagas Disease Control, in the Year of His Birth Centenary)*, 44 REVISTA DA SOCIEDADE BRASILEIRA DE MEDICINA TROPICAL 12, 12 (2011), <http://www.scielo.br/pdf/rsbmt/v44s2/a03v44s2.pdf> (listing housing improvements, DDT, fire throwers, and cyanidric gas as agents used in early attempts at Chagas disease vector control).

I. Nifurtimox

The first drugs to demonstrate efficacy against Chagas disease were those belonging to the nitrofurans class.¹³⁴ The Eaton laboratory marketed a type of nitrofurans called nitrofurazone in Brazil.¹³⁵ In 1967, the Bayer pharmaceutical company introduced the empirically-discovered drug nifurtimox to treat Chagas disease under the trade name Lampit.¹³⁶ In 1997, Bayer ceased production of nifurtimox due to “lack of profitability.”¹³⁷ However, in 2000, Bayer recommenced nifurtimox production as part of the treatment of African sleeping sickness.¹³⁸ In 2004, Bayer agreed to provide the World Health Organization 500,000 tablets a year at no cost.¹³⁹ In 2011, Bayer increased this amount to one million tablets a year, making this “donated drug . . . the primary source of nifurtimox worldwide.”¹⁴⁰ Nifurtimox is not FDA approved for distribution in the United States, but the Centers for Disease Control (CDC) dispenses the drug under its Expanded Access program.¹⁴¹

¹³⁴ José Rodrigues Coura, *Present Situation and New Strategies for Chagas Disease Chemotherapy—A Proposal*, 104 MEMORÍAS DO INSTITUTO OSWALDO CRUZ 549, 549 (2009), <http://www.scielo.br/pdf/mioc/v104n4/02.pdf>; *Nitrofurans*, GOLD BIO (last visited Dec. 21, 2017), <https://www.goldbio.com/category/nitrofurans> (Nitrofurans are a class of drugs typically used as antibiotics or antimicrobials. The defining structural component is a furan ring with a nitro group.”); Steven Perez, *Nitrofurans Analyses (FAQ)*, ADPEN LABORATORIES, INC. (May 26, 2010), <http://adpen.com/2010/05/nitrofurans/> (“Nitrofurans are a class of drugs that have the ability to kill microorganisms [*sic*].”).

¹³⁵ Coura, *supra* note 134 at 550 (noting that the drug was sold in Brazil “as Furacin ointment for topical use”).

¹³⁶ Johathan D. Alpern et al., *Access to Benznidazole for Chagas Disease in the United States—Cautious Optimism?*, PLOS NEGLECTED TROPICAL DISEASES 1, 3 (2017), <http://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0005794&type=printable>; Riza Theresa Bautista-Navarro, *Drug Discovery*, ENCYCLOPEDIA SYSS. BIOLOGY, https://link.springer.com/referenceworkentry/10.1007%2F978-1-4419-9863-7_1340 (last visited Dec. 21, 2017), (“Empirical drug discovery involves finding a compound that produces a desired therapeutic effect in vitro. Initially, there is no understanding of the candidate drug’s mechanism of action.”); Dietmar Steverding, *The Development of Drugs for Treatment of Sleeping Sickness*, 3 PARASITES & VECTORS 1, 5 (2010), <https://parasitesandvectors.biomedcentral.com/track/pdf/10.1186/1756-3305-3-15?site=parasitesandvectors.biomedcentral.com> [hereinafter Steverding, *Development*].

¹³⁷ Alpern, *supra* note 136 at 3; *see also* Coura & Castro, *supra* note 130 at 5 (“Since the 1980s, [nifurtimox] had its commercialization discontinued, first in Brazil, and then in Chile, Argentina, and Uruguay.”). *But see* Steverding, *History*, *supra* note 109 at 5 (stating that “the production of nifurtimox was suspended in 1997 due to lack of demand”).

¹³⁸ Steverding, *Development*, *supra* note 136 at 5 (explaining that nifurtimox has shown success in treating a form of late-stage African sleeping sickness when combined with eflornithine); Steverding, *History*, *supra* note 109 at 5.

¹³⁹ Alpern, *supra* note 136 at 3; Colin J. Forsyth et al., *Safety Profile of Nifurtimox for Treatment of Chagas Disease in the United States*, 63 CLINICAL INFECTIOUS DISEASES 1056, 1061 (2016), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5036918/pdf/ciw477.pdf> ;

¹⁴⁰ Alpern, *supra* note 136 at 3; Forsyth, *supra* note 139 at 1061.

¹⁴¹ Alpern, *supra* note 136 at 3; *Antiparasitic Treatment*, CDC (last updated Aug. 31, 2017), https://www.cdc.gov/parasites/chagas/health_professionals/tx.html (stating that nifurtimox is “currently available under investigational protocols from the CDC”); *Expanded Access (Compassionate Use)*, U.S. FOOD & DRUG ADMIN. (last updated Oct. 3, 2017), <https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm> (explaining that expanded access “is the use outside of a clinical trial of an investigational medical product”).

2. *Benznidazole*

1966, the pharmaceutical company Hoffman La-Roche developed the drug benznidazole.¹⁴² In 1971, Roche began marketing the drug in several South American countries under the names Rochagan, Radanil, and Ragonil.¹⁴³ In 2003, Roche transferred its rights to benznidazole to the Brazilian government.¹⁴⁴ Roche and Brazil then agreed to subcontract the marketing and production of benznidazole to “a public Brazilian agency” called the Laboratório Farmaceutico do Estado de Pernambuco (LAFEPE).¹⁴⁵ In August 2004, Roche delivered an adequate amount of the active ingredient in benznidazole for LAFEPE to register the drug with the Brazilian Drug Regulatory Authority (ANVISA).¹⁴⁶ In November 2006, ANVISA authorized LAFEPE to market benznidazole in Brazil.¹⁴⁷ Roche then withdrew its registration for benznidazole, leaving LAFEPE as the sole manufacturer of benznidazole in the world.¹⁴⁸

¹⁴² Steverding, *History*, *supra* note 109 at 5.

¹⁴³ SUMMARY REVIEW: NDA 209570 BENZNIDAZOLE, CTR. DRUG EVALUATION & RES. 8 (2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/2095700rig1s000SumR.pdf [hereinafter SUMMARY REVIEW] (stating that “Roche obtained registration of [benznidazole] in Brazil, Argentina, Bolivia, Uruguay, Peru, and Nicaragua”).

¹⁴⁴ SUMMARY REVIEW, *supra* note 143 at 8; *Shortage of Benznidazole Leaves Thousands of Chagas Patients Without Treatment*, MÉDECINS SANS FRONTIÈRES (Oct. 1, 2011), <http://www.doctorswithoutborders.org/news-stories/briefing-document/shortage-benznidazole-leaves-thousands-chagas-patients-without> (explaining that Roche “transferred the manufacturing technology and the license to produce to Brazil’s Pernambuco state”); *Critical Shortage of First-Line Therapy for Chagas: The Story of Benznidazole*, MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN (last updated Apr. 10, 2012), <https://www.msfaccess.org/content/critical-shortage-first-line-therapy-chagas-story-benznidazole> [hereinafter MSF *Critical*].

¹⁴⁵ Briefing Document, Médecins Sans Frontières, *The Shortage of Benznidazole Leaves Thousands of Chagas Patients Without Treatment 1* (Oct. 2011), <http://www.doctorswithoutborders.org/sites/usa/files/Chagas%20briefing%20paper%20Final.pdf> [hereinafter MSF Briefing Document); *see* SUMMARY REVIEW, *supra* note 143 at 8.

¹⁴⁶ MSF Briefing Document, *supra* note 145 at 1 (giving the Brazilian name of ANVISA as Agência Nacional de Vigilância Sanitária); *see* SUMMARY REVIEW, *supra* note 143 at 8.

¹⁴⁷ MSF Briefing Document, *supra* note 145 at 1; SUMMARY REVIEW, *supra* note 143 at 8.

¹⁴⁸ Alpern, *supra* note 136 at 2; MSF *Critical*, *supra* note 144; MSF Briefing Document, *supra* note 145 at 1–2 (adding that “products previously produced by Roche continued to be available until their expiration date, with stocks available up to October 2010”); SUMMARY REVIEW, *supra* note 143 at 8.

Because Roche was no longer producing benznidazole, LAFEPE need to obtain a source of the drug's active pharmaceutical ingredient ("API").¹⁴⁹ By 2010, Roche had provided the necessary documentation to allow a company called Nortec Química to manufacture benznidazole's API.¹⁵⁰ Although a manufacturer and an API supplier were now in place, various administrative problems arose that created a delay in benznidazole production.¹⁵¹

¹⁴⁹ MSF Briefing Document, *supra* note 145 at 2; Kathlyn Stone, *What Is an Active Pharmaceutical Ingredient (API)?*, THE BALANCE (last updated June 20, 2017), <https://www.thebalance.com/api-active-pharmaceutical-ingredient-2663020> (explaining that an API "is the part of any drug that produces its effects" and that some drugs "have multiple active ingredients").

¹⁵⁰ MSF Briefing Document, *supra* note 145 at 2.

¹⁵¹ Alpern, *supra* note 136 at 2 (describing the reasons for the ensuing worldwide benznidazole shortage as "multifactorial"); MSF *Critical*, *supra* note 144 (stating that there was "a lack of coordination between the API supplier Nortec, LAFEPE and the Brazilian Ministry of Health");

Meanwhile, the need for benznidazole was increasing.¹⁵² This increasing demand arose from various factors.¹⁵³ First, evidence had recently demonstrated that benznidazole was effective in treating Chagas disease patients in the chronic stage.¹⁵⁴ Previously, researchers believed that the drug was only able to treat the acute form of Chagas disease.¹⁵⁵ Second, recent research indicated that patients up to age 60 could benefit from benznidazole treatment.¹⁵⁶ Formerly, concerns about the safety to administering benznidazole to adults had limited the drug's use in older patients.¹⁵⁷ These changes in prescribing recommendations expanded benznidazole's use to treat chronic Chagas disease patients and older patients.¹⁵⁸

¹⁵² Alpern, *supra* note 136 at 2; MSF Briefing Document, *supra* note 145 at 2.

¹⁵³ See MSF Briefing Document, *supra* note 145 at 2 (“Clear signs showed that the demand for benznidazole was set to increase.”).

¹⁵⁴ Alejandro M. Hasslocher-Moreno et al., *Safety of Benznidazole Use in the Treatment of Chronic Chagas Disease*, 67 J. ANTIMICROBIAL CHEMOTHERAPY 1261, 1261 (2012), <https://academic.oup.com/jac/article/67/5/1261/980974> (noting in 2012 that “[d]espite the controversy over the efficacy of [benznidazole] treatment for adult patients in the chronic phase” that “some centres advocate using [benznidazole] in order to reduce the morbidity and mortality of the disease” and that benznidazole was “recommended for all cases of acute, congenital, reactivated, and chronic Chagas disease in children under 12 years of age”); MSF Briefing Document, *supra* note 145 at 2.

¹⁵⁵ Coura & Castro, *supra* note 130 at 5 (noting in 2002 that “[i]n relation to chronic [Chagas disease] cases, results [using benznidazole] have been poor”); MSF Briefing Document, *supra* note 145 at 2 (“Initially, treatment with benznidazole was intended only for people in the acute phase of the disease.”); Steverding, *History*, *supra* note 109 at 5 (stating that originally, benznidazole was “primarily used for treatment of acute cases of Chagas disease because [it] was considered less effective in the chronic phase”).

¹⁵⁶ MSF Briefing Document, *supra* note 145 at 2. Compare Maria-Jesús Pinazo et al., *Tolerance of Benznidazole in Treatment of Chagas' Disease in Adults*, *ANTIMICROBIAL AGENTS & CHEMOTHERAPY* 4896, 4896 (2010), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2976114/pdf/0537-10.pdf> (finding in 2010 that “the unwanted side effects [of benznidazole] are more frequent and severe in adults than in children”), with Hasslocher-Moreno, *supra* note 154 at 1265 (finding in 2012 that “[t]reatment with benznidazole was considered safe” for Chagas disease patients up to 65 years old).

¹⁵⁷ MSF Briefing Document, *supra* note 145 at 2; Pinazo, *supra* note 156 at 4896 (noting in 2010 that “[i]n adults, benznidazole has a high rate of adverse effects”).

¹⁵⁸ Oliver Yun et al., *Feasibility, Drug Safety, and Effectiveness in Etiological Treatment Programs for Chagas Disease in Honduras, Guatemala, and Bolivia; 10-Year Experience of Médecins Sans Frontières*, 3 *PLOS NEGLECTED TROPICAL DISEASES* 1, 7–8 (2009), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2700957/pdf/pntd.0000488.pdf> (“Over the past decade, treatment for Chagas disease has expanded from children <12 years old, to < 15, then to <18, and finally adults.”); MSF Briefing Document, *supra* note 145 at 2; see R. Viotti et al., *Towards a Paradigm Shift in the Treatment of Chronic Chagas Disease*, 58 *ANTIMICROBIAL AGENTS & CHEMOTHERAPY* 635, 635 (2014), <http://aac.asm.org/content/58/2/635.full.pdf+html> (reviewing “the paradigm shift” and “argu[ing] in favor of antiparasitic treatment for all chronic [Chagas disease] patients”).

Concurrent with the expansion of benznidazole's recommended use, various agencies "launched campaigns to raise awareness of Chagas disease."¹⁵⁹ Médecins Sans Frontières (MSF),¹⁶⁰ the Drugs for Neglected Disease Initiative (DNDi),¹⁶¹ the World Health Organization (WHO), and the Pan American Health Organization (PAHO) set forth guidelines or passed resolutions concerning Chagas disease awareness, diagnosis, and "demand forecasting" for benznidazole.¹⁶² The combination of expanding prescribing recommendations and increasing international concern about Chagas disease led to increased demands on the world's single supplier of benznidazole.¹⁶³ In 2011, when LAPEFE was unable to fill orders for benznidazole, a "global shortage ensued."¹⁶⁴

¹⁵⁹ MSF Briefing Document, *supra* note 145 at 2.

¹⁶⁰ *About MSF*, MÉDECINS SANS FRONTIÈRES (last visited Dec. 22, 2017), <http://www.msf.org/en/about-msf>.

¹⁶¹ *Neglected Patients*, DRUGS FOR NEGLECTED DISEASES INST. (last visited Dec. 22, 2017), <https://www.dndi.org/>.

¹⁶² Chagas R&D Accelerator Initiative, World Health Organization ¶ 13 (2009), http://www.who.int/phi/implementation/chagas_R_D_accelerator_initiative.pdf (describing "demand forecasting" as estimating "Chagas treatment needs of endemic countries"); MSF Briefing Document, *supra* note 145 at 2; MSF *Critical*, *supra* note 144 (stating that the "demand forecasting tool has been created to estimate demand for benznidazole"); see *Neglected Infectious Diseases and Other Poverty-Related Diseases in the Americas*, PAHO (last visited Dec. 22, 2017), http://www.paho.org/pahobranding/wp-content/uploads/2013/08/NCD_Opt1_v1.pdf (providing public information about NTDs—including Chagas disease—based on a resolution from the 2009 Directing Council of PAHO).

¹⁶³ MSF Briefing Document, *supra* note 145 at 2.

¹⁶⁴ Alpern, *supra* note 136 at 2 (“In 2011, a [benznidazole] shortage occurred in the face of increased demand due to improved recognition and screening efforts worldwide.”); MSF Briefing Document, *supra* note 145 at 2; MSF *Critical*, *supra* note 144; *see* Miriam Navarro et al., *Short Report; Benznidazole Shortage Makes Chagas Disease a Neglected Tropical Disease in Developed Countries; Data from Spain*, 87 AM. J. TROPICAL MED. & HYGIENE 489, 489 (2012), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3435352/pdf/tropmed-87-489.pdf> (“The current shortage of benznidazole makes Chagas disease a neglected tropical disease also in developed countries.”).

The benznidazole shortage affected several countries, including developed countries such as Spain.¹⁶⁵ Many traditionally Chagas-endemic countries suffered significant deficits of benznidazole during this time.¹⁶⁶ Additionally, global migration from Chagas-endemic areas brought new cases of Chagas disease to regions such as Europe and the United States.¹⁶⁷ These areas suddenly needed a drug no one seemed to have.¹⁶⁸

¹⁶⁵ Alpern, *supra* note 136 at 2; Navarro, *supra* note 164 at 489 (stating that [i]n Spain alone, at least 5,003,460 benznidazole tablets [were] needed” and that “more than 23,000 [would] not receive the treatment they need[ed]”).

¹⁶⁶ Press Release, Médecins Sans Frontières, Treatment Ends for Chagas Patients (Oct. 5, 2011), <https://www.msfaccess.org/about-us/media-room/press-releases/treatment-ends-chagas-patients> [hereinafter Press Release] (stating that Chagas disease in “endemic in several Latin American countries” and that the shortage of benznidazole was creating situations that were “not acceptable” in Brazil, Bolivia, and Paraguay); MSF Briefing Document, *supra* note 145 at 4 (stating that in 2011, LAFEPE “informed MSF” that LAFEPE would be unable to fill MSF’s orders for benznidazole in Bolivia, Paraguay, and Columbia).

Some relief arrived in 2012, when an Argentine company, Maprimed, became a benznidazole API supplier to an Argentine pharmaceutical company, ELEA.¹⁶⁹ ELEA distributed its benznidazole product, Abrax, to Latin American countries, including Bolivia, Paraguay, Chile, and Argentina.¹⁷⁰ Currently, LAPEFE and ELEA are the only sources of benznidazole in the world.

¹⁶⁷ Mauizio Bonati & Valeria M. Confalonieri, *Global Rights for Global Diseases: The Shortage of Benznidazole Case*, 22 EUR. J. PUB. HEALTH (2012), https://academic.oup.com/eurpub/article/doi/10.1093/eurpub/el_316/2547684 (noting that “as a result of migration and travel from [Latin America], [Chagas disease] is now also present in non endemic [*sic*] countries, including those in many European regions (in Belgium, France, Italy, Spain, Switzerland, the United Kingdom)”); Press Release, *supra* note 166 (stating that “Chagas disease . . . is a highly important but little-addressed public health issue, not only in Latin America but also increasingly in non-endemic, developed countries, due to globalization and population flows”); *see* Navarro, *supra* note 164 at 489–90 (stating that Bolivia has the “highest [Chagas] disease burden in the world” and that in 2011, 206,635 registered migrants from Bolivia lived in Spain—25,080 of whom were adults infected with *T. cruzi*).

¹⁶⁸ *See* Bonati & Confalonieri, *supra* note 167 (“Such an illogical situation, in which lifesaving treatment for millions of people depends wholly on a single pharmaceutical company . . . should make everyone think.”).

¹⁶⁹ SUMMARY REVIEW, *supra* note 143 at 8; Alpern, *supra* note 136 at 2–3.

¹⁷⁰ SUMMARY REVIEW, *supra* note 143 at 8 (noting that Abrax “is also available in Spain”); Alpern, *supra* note 136 at 3.

III. The Road to FDA Approval

On August 20, 2015, the FDA set forth an order describing the criteria by which a disease may be added to the list of NTD eligible for a PRV.¹⁷¹ The Food, Drug, and Cosmetic (FD&C) Act originally contained a list of sixteen tropical diseases for which the FDA could grant a PRV.¹⁷² Section 524 of the FD&C Act provided the authority under which the FDA could designate another tropical disease as PRV-eligible.¹⁷³ The FDA's order also "opened a docket to receive recommendations from the public for future additions to the list."¹⁷⁴ Additionally, the FDA order added Chagas disease and neurocysticercosis to the list of NTDs in the FD&C Act.¹⁷⁵

¹⁷¹ 21 U.S.C. § 360n (2008), https://www.kidsvcancer.org/wp-content/uploads/2008/05/FDCActChapter-V_DrugsandDevices-Priority-Review-to-Encourage-Treatments-for-Tropical-Diseases.pdf; Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act, 21 C.F.R. § 317 (2015), <https://www.federalregister.gov/documents/2015/08/20/2015-20554/designating-additions-to-the-current-list-of-tropical-diseases-in-the-federal-food-drug-and-cosmetic>.

¹⁷² 21 U.S.C. § 360n (2008); Ridley, *Priority Review Vouchers*, *supra* note 21; *cf.* 21 U.S.C. § 360n (2017) (including Filovirus diseases and Zika virus diseases on the list of NTDs, both of which legislation added in 2014).

¹⁷³ 21 U.S.C. § 360n(a)(3)(S) ("Any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by order of the Secretary."); 21 C.F.R. § 317; TDPRV GUIDANCE, *supra* note 67 at 4.

¹⁷⁴ 21 C.F.R. § 317; TDPRV GUIDANCE, *supra* note 67 at 4.

¹⁷⁵ 21 C.F.R. § 317; TDPRV GUIDANCE, *supra* note 67 at 4; Ridley, *Priority Review Vouchers*, *supra* note 21.

A. *The Race for the Benznidazole PRV*

Once the FDA added Chagas disease to list its list of NTD, interest in acquiring FDA approval for benznidazole soared.¹⁷⁶ In November 2015, Martin Shkreli, former hedge fund manager and founder of Turing Pharmaceuticals, became CEO of the California biotechnology company KaloBios.¹⁷⁷ On December 3, 2015, KaloBios announced its purchase of the rights to benznidazole from Savant Neglected Diseases.¹⁷⁸ In a press release, KaloBios stated its intent to “file for Orphan Drug Designation and Fast Track Designation for benznidazole in Chagas Disease.”¹⁷⁹ Additionally, KaloBios expected to receive a PRV if the FDA approved benznidazole.¹⁸⁰

¹⁷⁶ JEREMY BAROFSKY & JAKE SCHNEIDER, PROMOTING PRIVATE SECTOR INVOLVEMENT IN NEGLECTED TROPICAL DISEASE RESEARCH AND DEVELOPMENT 11 (2017), https://www.brookings.edu/wp-content/uploads/2017/12/br_health4_optimized_final.pdf (“Following the addition of Chagas disease to the list of PRV eligible conditions, market activities for Chagas disease increased substantially.”); Courtney Columbus, *Drug for ‘Neglected’ Chagas Disease Gains FDA Approval Amid Price Worries*, NPR (Sept. 10, 2017), <https://www.npr.org/sections/health-shots/2017/09/10/547351794/drug-for-neglected-chagas-disease-gains-fda-approval-amid-price-worries> (explaining that benznidazole was “the best of the two available options for treating Chagas” because benznidazole is “more toxic” than nifurtimox); *id.* (referring to a PRV as a “potential gold mine” and a “golden ticket” for pharmaceutical companies); Daisy Hernández, *A New Strategy to Undermine Big Pharma’s Price Gouging Actually Worked*, SLATE (Sept. 7, 2017), http://www.slate.com/articles/health_and_science/medical_examiner/2017/09/inside_the_battle_to_approve_a_chagas_treatment.html (stating that “[w]ith its inclusion on that federal list in 2015, Chagas became a cash cow in the pharma world”).

¹⁷⁷ Damian Garde, *Shkreli's KaloBio Buys an Old Drug with Eyes on a Lucrative FDA Voucher*, FIERCE BIOTECH (Dec. 4, 2015), <https://www.fiercebiotech.com/financials/shkreli-s-kalobios-buys-an-old-drug-eyes-on-a-lucrative-fda-voucher> (describing KaloBios as “a once-doomed company brought back from the brink by biotech entrepreneur Martin Shkreli”); David Goldman, *Who is Martin Shkreli? A Timeline*, CNN MONEY (Dec. 18, 2015), <http://money.cnn.com/2015/12/18/news/companies/martin-shkreli/index.html> (“Shkreli formed Turing Pharmaceuticals in February 2015, which bought the rights to Daraprim, a toxoplasmosis treatment used by AIDS patients.”); *see id.* (“Turing caught fire in September 2015 for hiking the price of Daraprim. A single pill, which had cost \$13, was raised 5,000% to \$750.”); Andrew Pollack, *Drug Goes From \$13.50 a Tablet to \$750, Overnight*, N.Y. TIMES (Sept. 20, 2015), <https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html>.

¹⁷⁸ Press Release, KaloBios, *KaloBios Announces Agreement to Acquire Benznidazole Program for the Treatment of Chagas Disease* (Dec. 3, 2015), <https://ir.humanigen.com/press-releases/detail/71/kalobios-announces-agreement-to-acquire-benznidazole> [hereinafter *KaloBio Press Release*] (stating that KaloBios was to pay Savant “an upfront payment of \$ 2 million, plus regulatory milestones and a royalty based on sales”).

¹⁷⁹ *Id.*; Garde, *supra* note 177 (“KaloBios plans to file to the FDA’s fast-track designation in hopes of scoring a quick approval for benznidazole without running any clinical trials of its own.”).

¹⁸⁰ KaloBios Press Release, *supra* note 178; Garde, *supra* note 177 (“And, because [Chagas disease] is on the FDA’s list of neglected tropical ailments, winning approval would grant KaloBios a tradeable coupon that shortens drug reviews by four months.”).

After forming the agreement with Savant, Shkreli told KaloBios investors that the price of benznidazole would be similar to the price of hepatitis C drugs.¹⁸¹ KaloBios's price for benznidazole would have cost Chagas disease patients between \$60,000 and \$100,000 per treatment.¹⁸² On December 17, 2015, the FBI arrested KaloBios CEO Martin Shkreli on securities fraud charges.¹⁸³ That same day, KaloBios fired Shkreli.¹⁸⁴ The value of KaloBios's stock plunged after news of Shkreli's arrest became public.¹⁸⁵ However, KaloBios continued to pursue FDA approval of benznidazole following Shkreli's dismissal.¹⁸⁶

¹⁸¹ Laura Bult, *Martin Shkreli Plans to Raise Price of Drug for Parasitic Infection Chagas Disease*, N.Y. DAILY NEWS (stating that during a public conference call with investors “Shkreli gleefully announced the purchase of the Chagas treatment and said that he would price the drug, benznidazole, similarly to hepatitis C drugs”); Andrew Pollack, *Martin Shkreli's Latest Plan to Sharply Raise Drug Price Prompts Outcry*, N.Y. TIMES (Dec. 11, 2015), <https://www.nytimes.com/2015/12/12/business/martin-shkrelis-latest-plan-to-sharply-raise-drug-price-prompts-outcry.html?mcubz=3> [hereinafter Pollack *Outcry*]; see Forward Looking Statements, KaloBios Pharmaceuticals (Dec. 2015), https://www.sec.gov/Archives/edgar/data/1293310/000110465915082792/a15-24519_1ex99d1.htm (stating under the heading “Commercial Opportunities” that benznidazole “[p]ricing expected to be similar to Hepatitis C antivirals”).

¹⁸² Pollack *Outcry*, *supra* note 181.

¹⁸³ Chris Isidore & Aaron Smith, *Reviled Drug CEO Martin Shkreli Arrested*, CNN MONEY (Dec. 18, 2015), <http://money.cnn.com/2015/12/17/news/companies/martin-shkreli-arrest-reports/index.html> (noting that the federal case against Shkreli “center[ed] on his time as CEO of Retrophin, . . . another biotech company that ousted him last year”).

¹⁸⁴ *KaloBios Fires Shkreli as CEO*, REUTERS (Dec. 21, 2015), <https://www.reuters.com/article/us-usa-crime-shkreli/kalobios-fires-shkreli-as-ceo-idUSKBN0U41R720151221>.

¹⁸⁵ Laura Lorenzetti, *KaloBios Just Fired Martin Shkreli as CEO*, FORTUNE (Dec. 21, 2015), <http://fortune.com/2015/12/21/martin-shkreli-kalobios/>.

¹⁸⁶ See *BRIEF—KaloBios to Have FDA Meeting for Using Benznidazole for Treating Chagas Disease*, REUTERS (Dec. 5, 2016), <https://www.reuters.com/article/idUSFWN1E00AT> [hereinafter *BRIEF*]; Beth Mole, *In Comeback Bid, Shkreli's Old Company Gets OK to Buy Life-Saving Drug*, ARS TECHNICA (Feb. 27, 2016), <https://arstechnica.com/science/2016/02/in-comeback-bid-shkrelis-old-company-gets-ok-to-buy-life-saving-drug/> (stating that a Delaware bankruptcy court authorized KaloBios to continue its purchase of benznidazole rights from Savant).

The U.S. and international medical communities reacted to KaloBios's possible price-jacking of benznidazole with considerable concern and apprehension.¹⁸⁷ The price of benznidazole in many Chagas disease-endemic countries was \$50 to \$100 per treatment.¹⁸⁸ Further, the CDC had been dispensing benznidazole at no cost to patients participating in investigational protocols.¹⁸⁹ To allow KaloBios to obtain FDA approval of benznidazole and then drastically raise its price was unacceptable to public health care advocates.¹⁹⁰ Consequently, two non-profit groups and a pharmaceutical company formed a partnership and "set out . . . to register the drug where its [*sic*] needed, including the U.S."¹⁹¹

¹⁸⁷ Press Release, Drugs for Neglected Diseases initiative, DNDi statement on KaloBios' [*sic*] Intention to Raise Price of Chagas Drug and File for FDA Priority Review (Dec. 14, 2015), <https://www.dndi.org/2015/media-centre/press-releases/dndi-statement-on-kalobios-intention-to-raise-price-of-chagas-drug-and-file-for-fda-priority-review-2/> [hereinafter Press Release DNDi] (quoting Dr. Bernard Pécoul, Executive Director of Drugs for Neglected Diseases initiative (DNDi) as saying that "[a]t this point, we see the move by KaloBios as a direct threat to affordable benznidazole both in the U.S. and in Latin America"); Mole, *supra* note 186 ("When KaloBios and Shkreli first revealed the plan late last year, it sparked public outcry from public health experts and infectious disease doctors who feared that the new cost would make it difficult for the millions of patients in Central and South America to get the drug."); Pollack *Outcry*, *supra* note 181 (" 'It's caused a lot of angst in the Chagas community,' said Dr. Sheba Meymandi . . . 'Everyone's in an uproar.' ").

¹⁸⁸ Press Release DNDi, *supra* note 187; Pollack *Outcry*, *supra* note 181.

¹⁸⁹ Alpern, *supra* note 136 at 3; Pollack *Outcry*, *supra* note 181. *But see* Hernández, *supra* note 176 (noting that "between 2007 and 2013 the [CDC] only released 422 doses of both benznidazole and [nifutimox]").

¹⁹⁰ See Press Release DNDi, *supra* note 187 (“We could face a nightmare situation for Chagas patients and healthcare providers in the US: the drug will finally be registered, but it could be even less accessible than it is today.”); Hernández, *supra* note 176 (“What Shkreli didn’t count on were the people—physicians and advocates—who would be outraged over his tactics.”); *DNDi, Mundo Sano, and Chemo Team Up to Register Benznidazole in US and Latin America*, INSUD PHARMA (June 9, 2016), <http://www.insudpharma.com/dndi-mundo-sano-and-chemo-team-register-benznidazole-us-and-latin-america> [hereinafter DNDi, Mundo Sano, and Chemo] (quoting DNDi’s Executive Director as saying: “Our ambition is to put an end to a scandalous and unjustifiable situation where almost none of the people living with Chagas has access to existing treatments”).

¹⁹¹ John Carroll, *A Non-Profit Group’s Chagas Drug Beat Out Martin Shkreli’s Old Rival to FDA OK, Valuable PRV*, ENDPOINT NEWS (Aug. 30, 2017), <https://endpts.com/fda-oks-nonprofit-groups-old-chagas-drug-handing-out-prv-and-clearing-way-to-cheap-price/>; DNDi, Mundo Sano, and Chemo, *supra* note 190 (describing DNDi as a “non-profit drug development organisation [*sic*],” Mundo Sano as a “non-profit foundation,” and Chemo Group as a “pharmaceutical company” that is a “corporate responsibility partner” with Mundo Sano, and stating that the trio “are entering into a formal collaboration to boost affordable access to benznidazole”).

In June 2106, Drugs for Neglected Diseases initiative (DNDi), Mundo Sano, and Chemo Group entered into formal agreements to provide benznidazole to the 300,000 Chagas disease patients in the United States.¹⁹² The team also hoped to increase the worldwide availability of benznidazole while maintaining the drug's attainable cost.¹⁹³ Chemo Group sought to gain FDA approval for benznidazole in 2013— before the FDA added Chagas disease treatments to the list of PRV eligible drugs.¹⁹⁴ In the agreement with Mundo Sano, DNDi committed to providing research data and support.¹⁹⁵ Additionally, Chemo Group would give Mundo Sano half of “any PRV-related financing” if Chemo Group secured a PRV.¹⁹⁶ The agreement then stipulated that “DNDi and Mundo Sano would manage jointly those funds” to support non-profit activities benefitting Chagas disease patients.¹⁹⁷ Moreover, Chemo Group agreed to provide benznidazole “on an affordable basis.”¹⁹⁸

¹⁹² DNDi, Mundo Sano, and Chemo, *supra* note 190; (calling the group's effort a “bid to overturn a situation where less than 1% of people with Chagas disease have access to treatment”); Eric Sagonowsky, *FDA Blesses Nonprofit-Backed Chagas Drug, Thwarting Ex-Shkrei Biotech's Bid for Rival Launch*, FIERCE PHARMA (Aug. 20, 2017) (“Chemo Group is a Spanish multinational pharma that sells generics and branded drugs, and it runs an Argentina-based nonprofit foundation, Mundo Sano.”); *see* Press Release, FDA Approves, *supra* note 4 (stating that “recent estimates are that there may be approximately 300,000 persons in the United States with Chagas disease”).

¹⁹³ DNDi, Mundo Sano, and Chemo, *supra* note 190 (stating that Chemo Group was “commit[ted] to ensuring [benznidazole] is available to the public sector in Chagas-endemic areas on an affordable basis”).

¹⁹⁴ BAROFSKY & SCHNEIDER, *supra* note 176 at 11; Hernández, *supra* note 176 (“The pharmaceutical company Chemo Group had been trying to register the drug with the FDA before the disease was even tied to the voucher.”).

¹⁹⁵ Hernández, *supra* note 176; see BAROFSKY & SCHNEIDER, *supra* note 176 at 11 (“DNDi provided technical expertise, including data from two DNDi-led clinical trials of benznidazole that were used in the FDA application.”).

¹⁹⁶ DNDi, Mundo Sano, and Chemo, *supra* note 190.

¹⁹⁷ *Id.* (stating that the funds would “be dedicated to actions that benefit patients and encourage access, by supporting not-for-profit programs to scale up diagnosis and treatment for Chagas disease”); Sagonowsky, *supra* note 192 (stating that fifty percent of the revenue from a PRV sale would fund a ‘far-reaching’ access program to ensure supply in the U.S. and other countries); see also BAROFSKY & SCHNEIDER, *supra* note 176 at 11 (noting that in addition to providing research data for benznidazole, DNDi is searching for new pharmaceutical treatments for Chagas disease); *U.S. FDA Approves Chemo Group’s Benznidazole to Treat Children with Chagas Disease*, DNDi (Aug. 31, 2017), [https://www.dndi.org/2Press Release, FDA, FDA Approves First Treatment for Chagas Disease017/media-centre/press-releases/fda-approves-benznidazole-chagas-children/](https://www.dndi.org/2Press%20Release,%20FDA,%20FDA%20Approves%20First%20Treatment%20for%20Chagas%20Disease017/media-centre/press-releases/fda-approves-benznidazole-chagas-children/) (“DNDi is also involved in early-stage research for entirely new drugs for Chagas Disease.”).

¹⁹⁸ DNDi, Mundo Sano, and Chemo, *supra* note 190 (explaining that an “affordable basis” would involve “a price that covers manufacturing and distribution costs plus a reasonable margin”); cf. Hernández, *supra* note 176 (stating that in its agreement with DNDi Chemo Group would “provide benznidazole on a “no profit no loss” basis”).

Despite its early setback with Shkreli, KaloBios continued its pursuit of FDA approval of benznidazole throughout 2016 and into the first half of 2017.¹⁹⁹ In December 2016, KaloBios completed a face-to-face meeting with the FDA and in January 2017, the FDA gave KaloBios positive guidance on benznidazole.²⁰⁰ In May 2017, the FDA accepted KaloBios's Investigational New Drug application for benznidazole.²⁰¹ In July 2017, the FDA granted KaloBios's sponsorship request to designate benznidazole as an orphan drug.²⁰²

¹⁹⁹ See *BRIEF*, *supra* note 186 (stating on December 5, 2016, that KaloBios “expect[ed] to have an FDA meeting to confirm regulatory pathway for benznidazole in treatment of Chagas disease”); *Mole*, *supra* note 186 (stating in February 2016 that KaloBios “may now be poised for a comeback” and that KaloBios had “renewed [its] plan to buy the worldwide regulatory rights to benznidazole from Savant”).

²⁰⁰ JGR CAPITAL PARTNERS, KALOBIOUS PHARMACEUTICALS, INC., 1 (2017), <https://www.jgrcap.com/wp-content/uploads/2017/05/KBIO-May-2-2017-RE.pdf> (stating that the “FDA accepted [KaloBios’s] intention to use existing safety and efficacy data from previous studies”); Press Release, KaloBios Pharmaceuticals, Inc., KaloBios Announces Positive Guidance from FDA for Benznidazole (Jan. 5, 2017), <https://ir.humanigen.com/press-releases/detail/88/kalobios-announces-positive-guidance-from-fda-for> (“This guidance makes it clear that we are on the right track with our development of benznidazole, and we expect we will progress expeditiously toward a submission”); *KaloBios Pharma (KBIO) Completes Face-to-Face Meeting with FDA for Benznidazole*, STREET INSIDER (Dec. 12, 2016), <https://www.streetinsider.com/Corporate+News/KaloBios+Pharma+%28KBIO%29+Completes+Face-to-Face+Meeting+with+FDA+for+Benznidazole/12332118.html>; see Ciara Linnane, *KaloBios Stock Jumps on News of Positive Guidance from Rare Disease Drug*, MARKET WATCH (Jan. 5, 2017), <https://www.marketwatch.com/story/kalobios-stock-jumps-on-news-of-positive-guidance-from-fda-on-rare-disease-drug-2017-01-05>

²⁰¹ Press Release, KaloBios Pharmaceuticals, Inc., Benznidazole IND for Chagas Disease Receives Clearance by FDA (June 27, 2017), <https://ir.humanigen.com/press-releases/detail/107> .

²⁰² *KaloBios Recieves Orphan Drug Designation for Benznidazole in the treatment of Chagas Disease*, NASDAQ GLOBENEWSWIRE (July 11, 2017), <https://globenewswire.com/news-release/2017/07/11/1042699/0/en/KaloBios-Receives-Orphan-Drug-Designation-for-Benznidazole-in-the-Treatment-of-Chagas-Disease.html>; *Search Orphan Drug Designations and Approvals (Benznidazole)*, U.S. FOOD & DRUG ADMIN. (last visited Dec. 25, 2017), <https://www.accessdata.fda.gov/scripts/opdlisting/oodp/listResult.cfm> (hereinafter *Search Orphan Drug*] (listing a “designated” but not approved status for KaloBios’s sponsorship of benznidazole).

However, the FDA had granted Chemo Group orphan drug status for benznidazole back in 2014.²⁰³ Although Kalo Bios “outlined an approach to pricing benznidazole fairly,”²⁰⁴ Chemo Group persisted in its efforts to gain FDA approval.²⁰⁵ Chemo Group submitted an NDA with the FDA on December 29, 2016.²⁰⁶

²⁰³ *Search Orphan Drug*, *supra* note 202 (listing an April 14, 2014 “designated/approved” date for Chemo Group’s sponsorship of benznidazole); see Jeff Antos, *Common Misconceptions About the Orphan Drug Designation*, PHARM. COM. (Mar. 3, 2014), <http://pharmaceuticalcommerce.com/opinion/common-misconceptions-about-the-orphan-drug-designation/> (explaining that “more than one sponsor can receive an orphan designation for the same drug/indication”).

²⁰⁴ U.S. SEC & EXCH. COMMI’N, FORM 10-K, KALOBIO PHARMACEUTICALS 4 (2017), <https://ir.humanigen.com/all-sec-filings/content/0001214659-17-001799/0001214659-17-001799.pdf> (“Upon regulatory approval of any of our products, we intend to apply our Reasonable Pricing Model, which focuses on affordability for patients and payers, transparency for all stakeholders, and delivery of a reasonable return in recognition of the risks we are taking in our development efforts.”).

²⁰⁵ See Alpern, *supra* note 136 (noting that Chemo Group’s efforts afforded patients and the medical community “reasons for cautious optimism for affordable and dependable access to benznidazole” and that “[w]e are left watching and waiting to see who obtains FDA approval” for benznidazole).

²⁰⁶ SUMMARY REVIEW, *supra* note 143 at 9.

B. The FDA Approval of Benznidazole for Chagas Disease

Finally, on August 29, 2017, the FDA approved Chemo Group's NDA for benznidazole for the treatment of Chagas disease in children ages 2 to 12.²⁰⁷ Additionally, the FDA granted Chemo Group a PRV.²⁰⁸

²⁰⁷ SUMMARY REVIEW, *supra* note 143 at 1; Press Release, FDA Approves, *supra* note 4 (“The U.S. Food and Drug Administration today granted accelerated approval to benznidazole for use in children ages 2 to 12 years with Chagas disease.”); *see* Hernández, *supra* note 176 (noting that “doctors will still be able to prescribe [benznidazole] off-label for adults”); Sagonowsky, *supra* note 192 (adding that Chemo Group, Mundo Sano, and DNDi “picked up seven years of orphan drug exclusivity for benznidazole; *see also* Jaime Altcheh et al., *Population Pharmacokinetic Study of Benznidazole in Pediatric Chagas Disease Suggests Efficacy Despite Lower Plasma Concentrations Than in Adults*, 8 PLOS NEGLECTED TROPICAL DISEASES 2 (2014), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031103/pdf/pntd.0002907.pdf> (stating in the author summary that although “the elimination of [benznidazole] is significantly faster in children than in adults, leading to lower plasma concentrations . . . unlike adults, all children in the study responded well and had few adverse reactions to the drug”); Mario J. Olivera et al., *Risk Factors for Treatment Interruption and Severe Adverse Effects to Benznidazole in Adult Patients with Chagas Disease*, PLOS ONE 2 (2017), <http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0185033&type=printable> (stating that [i]n some adult [Chagas disease] populations the incidence of [adverse drug effects] has reached up to 100%”).

²⁰⁸ Press Release, FDA Approves, *supra* note 4 (stating that “[w]ith this approval, benznidazole’s manufacturer, Chemo Research, S.L., is awarded a Tropical Disease Priority Review Voucher in accordance with a provision included in the Food and Drug Administration Amendment Act of 2007”).

Chemo Group's pharmaceutical division, Exeltis, will distribute benznidazole in the United States.²⁰⁹ Although the FDA approval was a victory for the Chemo/Mundo Sano/DNDi group, the trio still has challenges to face.²¹⁰ For example, Chemo Group's ability to affordably provide benznidazole to Chagas patients may not be a simple task.²¹¹ Because the CDC has treated many U.S. Chagas patients for free, some concern exists over these patients' ability to afford and access the drug.²¹² Additional variables may arise, such as providing access to benznidazole through local pharmacies and "reach[ing] patients who might not even know they are infected."²¹³ However, the FDA approval of benznidazole represents a crucial step in Chagas disease treatment worldwide.²¹⁴

²⁰⁹ *Exeltis US Will Distribute Benznidazole for the Treatment of Chagas Disease in Patients 2–12 Years Old*, EXELTIS (Aug. 31, 2017), <http://www.exeltis.com/exeltis-us-will-distribute-benznidazole-treatment-chagas-disease-patients-aged-2-12-years-old> ("Exeltis will use its operational and technical platform to support the availability of benznidazole in the United States in support of Mundo Sano—to help minimize cost and ensure compliance with FDA regulations").

²¹⁰ Press Release DNDi, *supra* note 187 (stating that "Chemo Group will continue working . . . to overcome barriers to treatment of Chagas disease" and that "Mundo Sano and DNDi will pursue efforts to boost access and increase patient awareness").

²¹¹ Columbus, *supra* note 176 (stating that a concern exists that "many Chagas patients will need financial help" and that for some patients "almost any price would be too high").

²¹² *Id.* (noting that "having the CDC supply of the drug has been crucial").

²¹³ Hernández, *supra* note 176.

²¹⁴ Press Release DNDi, *supra* note 187 (“ ‘I am thrilled that we are taking a giant step forward in our journey to overcome to many barriers to Chagas treatment,’ said Dr. Silvia Gold, President of Mundo Sano.”); *Drug to Treat Chagas Disease to Become Available in the U.S.*, MÉDECINS SANS FRONTIÈRES (Aug. 31, 2017), <http://www.doctorswithoutborders.org/article/drug-treat-chagas-disease-become-available-us> [hereinafter *MSF Drug to Treat*] (stating that the “registration and availability of this medicine in the United States is a positive step for children with Chagas in the U.S.” and that “[w]ithout treatment, many Chagas patients are at risk of dying from complications, and few patients in the U.S. currently diagnosed and treated for this disease”).

IV. CONCLUSION

The PRV program played a critical role in helping to bring benznidazole to Chagas disease patients in the United States.²¹⁵ Although benznidazole had been available to treat Chagas disease since 1971,²¹⁶ the U.S. pharmaceutical industry ignored the drug until the FDA provided the PRV incentive for a Chagas disease treatment.²¹⁷ The time from the FDA's addition of Chagas disease to the list of NTDs to the FDA's approval of benznidazole for Chagas disease was two years and nine days.²¹⁸ The PRV incentive brought two pharmaceutical companies into fierce competition with one another to obtain FDA approval for a drug that had existed for more than forty years.²¹⁹ Thus, in the FDA approval of benznidazole, the PRV program appears to have succeeded in its original goal to "encourage the development of new drug and biological products for the prevention and treatment of certain tropical diseases affecting millions of people throughout the world."²²⁰

²¹⁵ *Supra* text accompanying note 176; see Press Release, FDA Approves, *supra* note 4 ("The FDA granted benznidazole priority review . . . because Chagas disease is a rare disease and until now, there were no approved drugs for Chagas disease in the United States.").

²¹⁶ *Supra* text accompanying note 143.

²¹⁷ MSF *Drug to Treat*, *supra* note 214 ("The FDA also announced that Chemo will receive a lucrative Priority Review Voucher (PRV) for registering benznidazole even though the drug has been used to treat Chagas disease in adults in Latin America for more than 40 years.").

²¹⁸ See 21 C.F.R. § 317 (stating that on August 20, 2017, the FDA added Chagas disease to the list of NTDs—the treatment for which the FDA would award a PRV upon FDA approval); Press Release, FDA Approves, *supra* note 4 (announcing the FDA approval of benznidazole and the FDA's PRV award to Chemo Group on August 29, 2017).

²¹⁹ MSF *Drug to Treat*, *supra* note 214 (stating that Chemo Group, Mundo Sano, and DNDi “beat” KaloBios in the bid for FDA approval for benznidazole).

²²⁰ TDPRV GUIDANCE, *supra* note 68 at 1.

Yet, the original authors of the PRV concept had a more expansive goal of “achieving better population health.”²²¹ Ridley et al. included two criteria in their paper that Congress did not include in the PRV legislation.²²² First, the PRV concept’s authors proposed that the FDA award PRVs for therapies that are “clinically superior to existing treatments.”²²³ Second, the winner of the PRV should “forgo patent rights” for the drug.²²⁴ The authors included these criteria to further the goal of “help[ing] people suffering from neglected diseases who are in need of new medicines that are affordable and available regardless of where they live.”²²⁵ Including these requirements in future legislation would increase the PRV program’s ability to truly “develop drugs for developing nations.”²²⁶

²²¹ See Ridley, *Developing Drugs*, *supra* note 20 at 313 (proposing a PRV incentive program that “could benefit consumers in both developing and developed countries” by “speed[ing] access to highly valued treatments”).

²²² Compare Ridley, *Developing Drugs*, *supra* note 20 at 315 (“To receive a voucher, a therapy must . . . (3) be clinically superior to existing treatments, (4) forgo patent rights”) with 21 U.S.C. § 360n (lacking provisions contained in the original proposal paper by Ridley et al.).

²²³ Ridley, *Developing Drugs*, *supra* note 20 at 315.

²²⁴ *Id.*

²²⁵ David Ridley & Jeffery Moe, *An FDA Drug Voucher Program Needs a Reboot*, THE HILL (June 30, 2017), <http://thehill.com/blogs/pundits-blog/healthcare/339913-fdas-neglected-disease-incentives-need-teeth-to-ensure-patient>

²²⁶ *Id.* (explaining that “limit[ing] vouchers to rewarding only new drugs and vaccines . . . will reduce the supply of vouchers and increase their price” and that requiring “voucher winners [to] forgo their patent rights” would hold drug companies “publically accountable to make their treatments available to where it is most needed”).

While the benznidazole approval appears to validate the PRV program, Chagas patients may have narrowly dodged a bullet.²²⁷ Although legislation enacted in August 2017 that expanded the PRV program requirements, additional concerns remain.²²⁸ U.S. lawmakers should continue refining the PRV program to meet the needs of neglected disease patients everywhere.²²⁹

²²⁷ Hernández, *supra* note 176 (stating that the “unique agreement” between Chemo Group, Mundo Sano, and DNDi “fills in some gaps that scholars who created the priority review voucher program 10 years ago have said they now want to incorporate”); *see* MSF *Drugs to Treat*, *supra* note 214 (noting that while it is “good news that Chemo has made a commitment to promote access to the drug . . . other companies have abused the PRV program for neglected diseases without any benefit to the patient”); *see infra* note 170 and accompanying text.

²²⁸ FDA Reauthorization Act of 2017, Pub. L. No. 115-52, 131 Stat. 1005, <https://www.congress.gov/bill/115th-congress/house-bill/2430>; *FDA User Fee Reauthorization Legislation Enacted by Congress*, ROPES & GRAY (Aug. 7, 2017), <https://www.ropesgray.com/newsroom/alerts/2017/08/FDA-User-Fee-Reauthorization-Legislation-Enacted-by-Congress.aspx> (explaining that the FDA Reauthorization Act tropical disease PRV provision requires “applicants to demonstrate they conducted or sponsored at least one clinical investigation essential to the application”); *FDA Reauthorization Act Passes U.S. House and Senate Without Fixes to Deliver Urgently Needed New Drugs, Vaccines for Neglected Diseases*, MÉDECINS SANS FRONTIÈRES (Aug. 2, 2107), <http://www.doctorswithoutborders.org/article/fda-reauthorization-act-passes-us-house-and-senate-without-fixes-deliver-urgently-needed-new> (“Both chambers of U.S. Congress missed another opportunity to help people living with neglected diseases by passing the FDA Reauthorization Act (FDAFA) of 2017 today without fixing the [FDA’s PRV] program for neglected diseases.”); *see* Ridley & Moe, *supra* note 225 (“Unfortunately, the fix as written to the *FDA Reauthorization Act* does too little to help the millions of people at risk for these diseases.”).

²²⁹ MSF *Drugs to Treat*, *supra* note 214 (“Before a company can receive this prize, U.S. Congress should mandate that only new medicines receive a PRV and that companies ensure access and affordability for all patients.”); Ridley & Moe, *supra* note 225 (explaining that Congress should enact “[t]ighter eligibility [that] would bolster the value of vouchers by reducing the supply”).

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