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Chronic disease like a troublesome relative is something you can learn to manage

but never quite escape

-Mary Tyler Moore

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1 Introduction

In autumn of 2018 a colleague of mine approached me. He informed me that the FDA[1] was requesting comments to a new draft guidance on developing hemophilia gene therapy products. He was collecting feedback with the intent to send it to the FDA on behalf of Shire, a pharmaceutical company and our employer. At the time, we were both heading different teams that worked on drug development, his focus being animal testing, while mine was human clinical trials. I remember my surprise when reading through the new guidance. It was so… slim. There was not much to comment on since there was not much content to begin with.

Exactly in those months, our company was going through a massive reorganization due to an acquisition by another pharma company, Takeda. Ultimately, my colleague's position was changed and then cancelled, and in the midst of it all the comments he so diligently collected were never sent to the FDA.

The final FDA guidance on gene therapy for hemophilia was made available in January 2020. It was somewhat more logical and comprehensive than the previous draft, but still struck me as superficial. I couldn't help but think: *why bother publishing a vague guidance?*

Having worked for years in rare diseases, focused on hemophilia, experienced with gene therapy, and armed with curiosity, I wanted to find an answer to that question - hence this thesis. I have gone back to that same FDA guidance, multiple press releases, publicly available documents, articles, summaries of meetings with patients, and also relied on my own experience and knowledge in order to contextualize and understand what this guidance is, what it does.

In this study, I've found that above and beyond their purpose as tools to govern objects, guidance documents are instrumental in creating markets and normalizing novel, risky technologies. They have the power to sufficiently do that, and their vagueness supports that purpose. The case of hemophilia gene therapy serves as a prime example of that.

What follows is a breakdown of the steps I took to reach that conclusion.

1.1 Another introduction, or what this thesis is really about

People have illnesses. They become patients. They search for treatment. Companies develop treatments. Governments regulate treatment. In the end, drug developers and governments want patients to be well.

[1] Throughout the document FDA replaces the United States Food and Drug Administration

The equation seems straightforward, but complications arise when trying to apply it empirically. Health is not always an outcome of treatment, nor is health synonymous with wellbeing. Some treatments cure a primary disease and cause the onset of a secondary one. Other therapies only hinder disease progression, and yet are considered good treatment options for chronically ill patients who seek health *stability*, where it is impossible to offer health overall.

What, then, is health? How can successful treatment be quantified?

In hope of promoting and improving health, pharmaceutical and biotech companies (collectively drug developers) embark on complex scientific and technological advances that lead to new innovative treatment modalities harboring promise of better health that may also create unknown health risks. Regulators seek to frame these same innovative therapies in policies that enforce parameters of safety, efficacy, and accessibility. In the end, everyone wants patients to be well. Or healthy. Or at least, *healthier*.

Gene therapy (**GT**) is a small-scale example of such technological efforts. GT is a treatment modality that corrects diseases at the molecular level by introducing new genetic material into the body, a risky feat that is at best a full cure and at worse might cause new diseases such as cancer. Especially in the case of hemophilia GT, questions of how treatment is regulated are one and the same as questions of what treatment is, what treatment does, how to measure treatment success, and is it justifiable to compromise safety in hopes of health.

Policies surrounding GT can be seen as a tool that foregrounds the thought process of regulators. Policies can demonstrate how regulators approach the idea of governing technologies. More specifically, by deconstructing policies that are specific to hemophilia GT, the questions of legitimizing a novel treatment modality and quantifying success criteria can be answered.

The next chapter commences with a literature review of Science & Technology Studies (STS)-specific concepts, especially around rare disease, regulation, and treatment. This is followed by historical and contextual information outlining how hemophilia treatments evolved. The text then introduces the main research question, *how does the FDA hemophilia gene therapy guidance construct gene therapy as a relevant treatment modality*, and thereafter explains the application of biopolitics as a theoretical lens. Clarifications of document analysis as a methodology then follow. Then, empirical findings are described in detail and discussed. The key conclusion presented is that a combination of factors results in a *low threshold attitude* of regulators towards normalizing and commercializing technologies that harbor unknown risks and are only as good as existing alternatives. Hemophilia gene therapy serves as a case example of that finding. The thesis concludes with a summary and final remarks.

2 Current and Relevant Literature

Notions of drug development and healthcare are well established within the STS realm, as are perspectives of policy making, and disease definition. Especially important to this thesis are texts related to drug regulations and drug safety, and how treatment is valued and established. Additional attention is placed on literature related to rare diseases, in line with the case study itself.

Drug development is of the topmost heavily regulated industries. The underlying principle in any medicinal regulation is to make sure that "All medicines must meet three criteria: be of good quality, safe and effective" (Rägo & Santoso, 2008, p.67). Regulations that directly impact drug development cover manufacturing facilities, processes and materials, as well as pre-clinical data, clinical trial design, data collection and analysis, long-term safety requirements, and licensing. Multi-national overarching guidelines harmonize and standardize the acceptable minimal requirements on various topics within drug development (e.g., ICH-GCP or Clinical Trials Directive 2001/20/EC), however each country is ultimately responsible for its own regulatory landscape. Focusing on the regulation associated with drug development in a given location is akin to a window providing a view onto how individual countries balance their role in surveillance of drug development, implement, adopt, or resist global and multi-national standards, and care for (or neglect) the needs of patients.

2.1 Understanding the regulatory environment[2] - safety and speed

The matter of accepting or averting risk through regulation is especially prominent with respect to approving pharmaceutical products. For the most part, processes for safety assessment are independent from processes of approving new therapies, but in some cases, the two intersect.

Abraham & Davis (2020) present a comparative review of such an occurrence. In their research on US and UK drug safety regulations across several decades and shifting political context, they show that processes that intended to protect patients from unsafe drugs fluctuated over time and were generally suboptimal, resulting in drug safety withdrawals (DSW) in the United States (US) and in the United Kingdom (UK). DSWs refers to medicinal products that were approved for use and commercialized, but later removed from the market for safety reasons. Between the 1970s and 1990s the British Medicines Control Agency (MCA) were quick to approve new products, but also suffered many DSWs. In contrast, the US FDA took much longer to approve drugs and imposed more stringent safety requirements resulting in fewer DSWs. The authors look to the 1990s as a watershed moment where regulation changes took place both in the US, and in Europe. On the European side, the European Medicines

[2] In this thesis regulations are not limited to documents which are legally binding legislation, but also policies and guidelines so long as they originate from an official body concerned with drug development (e.g., EMA, FDA, or WHO)

Agency (EMA) was established in Europe in 1995 as a centralized regulatory decision-making body that enforced more rigorous medicinal regulations (based on precautionary approach) and thus somewhat curbed the MCA's leniency in approvals (p.8), so that over time, the MCA continued to have roughly the same amount of DSW, but not more than before. On the American side, the FDA introduced in 1992 the Prescription Drug Users Fee Act (PDUFA) which shifted the cost of drug regulation from taxpayer money to industry payments. These payments were initially spent exclusively on regulatory review, and as such were used to accelerate the drug approval process. US congressional hearings held in the 1990s and early 2000 also enforced the expectation to accelerate new drugs application reviews (p.2)[3]. The result was a clear increase in the FDA's approval speed and DSWs from the 1990s onward as compared to the 1970s, and roughly on par with British DSWs. Abraham & Davis (2020) reviewed potential reasons that can explain the findings, and concluded that "During 1993–2004, FDA became more willing than in 1971–1992 to approve less-safe drugs on to the market and/or leave such drugs on the market, rather than withdraw them, because of a change in its political and institutional culture" (p.8). To clarify, there was both an increase in DSWs, and an increase in unsafe drugs in the market that resulted in adding special surveillance programs for unsafe products. The change in the source of funding prompted FDA regulators to address the industry with increasing importance, while political attention was given to approving products quickly. Of importance, the FDA approved unsafe drugs despite having access to detected or potential safety issues prior to approval. The rational was that accelerated approval to commercializing could be coupled with post-marketing safety evaluation. In 2007 regulations changed again to enable the FDA to transfer PDUFA funds also for post marketing safety surveillance, which led to issuing of safety warnings and limiting of product usage in place of DSWs (p.9). In contrast to the US, industry funding was already quite extensive in the UK in the early 1970s, thus changes in approvals and DSWs in the UK after the 1990s were much humbler, in the sense that the speed of approval and rate of DSW didn't change (p.9). The take home message is that for regulators relying on commercial fee for reviewing marketing applications, approval speed trumps safety risks. The authors dubbed this as *corporate bias*.

Regulations such as the PDUFA are not detached from politics and social expectations. John W. Kingdon's (2010) notion of Multiple Streams Framework (MSF) serves as growingly popular basis to understand how policy makers approach the task of policy making. Originally developed in analysis of American health care and transportation policies in the 1970s, the MSF has since been applied to a multitude of fields, extending also parliamentary systems and European level policies (Zohlnhöfer et al., 2015, p.414). In a nutshell, while each administration has its own political view and pressing needs

[3] As per the FDA (2016), median total approval time for standard marketing application dropped from 27 month in 1993 to 10 months in 2016 following changes in PDUFA.

(i.e., an agenda), the actions that follow are connected to the administration's agenda but not necessarily derived from it. The actions are a result of a time-limited convergence between the problems, policy, and politics often pushed by a dynamic and non-linear action from advocates. Applying these ideas to PDUFA reveals that the PDUFA was the child of growing desperation on behalf of patients - especially around the AIDS epidemic and slow approvals of drug products - commercial companies who were losing revenue due to delays in marketing approval, and the regulators themselves who were discontent with the volume of work piling up against low staffing ("PDUFA", 2022). The political agenda was to accelerate access to new life-saving treatments, the problem was staffing and delayed review timelines, the advocates were both commercial companies and patients, hence, PDUFA is the convergence of politics, policy, and problems.

However, PDUFA was squarely intent on accelerating access to new treatments and reducing marketing request review timelines by regulators ("PDUFA", 2022). PDUFA was not intended to deal with averting risk or accepting risk. The fact that it led to an increase in DSW can be explained through a better understanding of institutional political culture. Citizens and residents in each country expect their lawmakers to define and govern areas of interest that they (i.e., the public) value. What exactly are these areas may differ among publics. Each public has its own culture and expectation, such as innovation, ownership, risk or ethics. Jasanoff (2005) offers insights that explain how such cultural behavior narrates its expectations into institutionalized practices. She coins this as *civic epistemologies* and builds a case that justifies the "divergence between the U.S. insistence on 'risk assessment based on sound science' and the EU nations' concern for 'precautionary' policy" (p.40). More specifically, in the US risk assessment evolved to become a measure of good science. In order to overcome an underlying culturally-driven distrust, expert bodies were typically transparent and pluralistic, or as Jasanoff puts it "This has meant, in the United States, a primary reliance on interested parties -industry, academic researchers, environmentalists – to generate relevant facts and claims" (p.260). In other words, those external to the political system become the credible experts in service of lawmakers, that identify and assess risks, and make recommendations for surveillance.

Tying in the three concepts, and specifically regarding the FDA PDUFA, Abraham & Davis (2020) identified corporate bias to clarify *how* it happened that regulators were inclined to accelerate approval rather than insist on safety – funding schemes changed; Kingdon's MSF (2010) describes *what drove* the PDUFA enactment - accelerate access to products; and Jasanoff's (2005) view of civic epistemologies explains *why* the FDA seemed at ease with deferring safety surveillance to post marketing - risk assessments is a science managed by external experts.

While governance of speed and safety intersect, governance of speed and access have become disconnected. Such is the case for treatments targeted at niche population. Diseases that affect small

populations are called rare diseases, which is a clinical classification based on disease prevalence. Though the prevalence cutoff for defining a rare disease differs between US and EU, both governing bodies (EMA and FDA) have policies addressing development and approvals of treatment through orphan designation, intended to incentivize companies to develop products for a small patient population by providing exclusivity to markets, priority review with regulators, and reduced review timelines for applications. In other words, orphan designation (or orphan disease), are effectively a governance and marketing tool relating to drug development and treatment profitability. From a wider societal perspective, the application of the Orphan Drug Act in the US and Orphan Drug Regulation in the EU have resulted in a significant increase in approvals for products with an orphan designation. At the same time, legislative challenges for orphan medicines (in the US healthcare landscape and in the individual EU countries) result in decoupling between the increase in approvals of products with orphan designations and the sustainable patient access to those very products (Bouwman et al., 2020). Legislative challenges can be related to national pricing and reimbursement regimes. In other words, treatment approval and treatment access do not necessarily cross paths, and accelerating approval to treatments is disconnected from providing access to treatments. On top of this, orphan drug prices are disproportionately high (and tend to increase) to compensate for years of research against a small pool of potential patient-consumers. Hemphill (2009) assesses the phenomenon of extraordinary pricing increase (a price increase of 100% in a single time point, common for products that treat rare diseases) in the US from legal, economic, sociopolitical and ethical perspectives. He concludes that whether extraordinary pricing increase is a socially responsible business behavior of equal access depends on whether patients have options for sustained access to the product. In the US, patients with rare disease who are financially unable to pay for treatment will turn first to assistance programs from private and public healthcare, then to patient assistance programs and disease specific charities, and finally to specialized patient prescription access (which are often subsidized by the developing company itself). However, not all rare diseases have such charities and programs. In case patients do not have these pathways, or these pathways still require patients to cover a substantial amount of the fee as a premium, the extraordinary pricing increase is not socially responsible.

2.2 Connecting disease and treatment

While assuring safety is one parameter of drug regulation, assuring the treatment is efficacious is another.

According to Lakoff (2008) “The regulatory norm that guides pharmaceutical intervention in biomedicine is one of targeted effects: a given drug should work directly on a specific disease.” (p.744). Therefore, an underlying assumption is that a relationship exists between a treatment and an illness definition, or what Lakoff considers *re-codification* of illness. In his words, “on the one hand,

government regulation required that pharmaceuticals be proved to have targeted effects in order to circulate in the biomedical system; on other hand, to demonstrate such effects, researchers had to be able to classify disorders in a standardized way." (p.746). In his research on anti-depressants, Lakoff found that "Drug developers here shift the locus of potentiality in the trial from the drug to the patient. Instead of seeking to test the drug on an established category of patients, they seek to find the right patients for the drug." (p.751). Disease category becomes an identity which is treatable and connects the clinic, insurance funds, and scientific research (p.748).

Levy (2022) approaches this idea from another angle, by looking at the reclassification of Leukemia in the 1960s. In her analysis she identified that drugs with a potential for treating Leukemia showed limited results, but as patients had very little treatment alternatives, oncologists were committed to making the drugs work. At the time, all leukemia patients were lumped together, and treatments were assumed to work equally well (or equally poorly) on patients. However, oncologist noticed that patients react differently to various treatments. Thus, oncologist "created the conditions that enabled them [*the drugs*] to work" (p.3). This was done in two steps. First oncologists became committed to the drugs themselves and the success of drugs, and later they shifted focus from drug testing to assessing what it means for a drug to work (p.7). Levy coined this approach as *adequate trials*. Adequate trials resulted in a reclassification of leukemia into subcategories, such that the new disease categories were aligned with effective treatments and new diagnostic tools differentiating between acute and chronic, age onset, and cancer cell type. Levy (2022) demonstrated through her work that disease definition is intwined with treatment options, echoing Lakoff's (2008) position that patients need to fit the drug.

Hence, an intimate relationship exists between defining what is a treatment and what illness does it treat.

Hand in hand with the process of defining an illness, is the process of discounting aspects that are *beyond* the illness. Alvin (2019) explored this topic by looking at ideas of "added value" to treatment. He compared two treatments for multiple sclerosis[4] that were approved in the EU, where the second treatment to be approved was listed as having no added value relative to the first treatment. The author challenged this notion by showing that the second, newer treatment had added value in the area of patient satisfaction, even though satisfaction was not considered to be relevant enough to warrant measuring it statistically. The newer treatment was easier to administer (oral tablets instead of injections) and therefor created better adherence to long term treatment. Alvin continued to argue that the most important innovation aspect of the newer treatment was not in its therapeutic effect,

[4] Multiple Sclerosis (MS) – a chronic disease of the central nervous system

but in its ease of delivery, commensurate with patient desires. In this regard, he recognized the caretakers and physicians who acknowledge that treatment needs to be more patient centric. He called on regulators to align their valuation processes with what patients need, and to view patient satisfaction not as a nice-to-have but as an integral aspect of treatment.

2.3 Patients as activists, patients as clinical subjects

It is not only physicians and pharmaceutical companies that seek to make adaptations to meet patient needs. Patients also voice their desires through activism, or as participants in clinical trials (i.e., as subjects). Though patients rarely influence *which* products are manufactured, they often wield enough power to obtain research funding and to influence *how* drug products are developed and accessed.

The role of activism was the main theme in a special issue in the journal of BioSocieties dedicated to understanding patient organizations. In the introductory article, Rabeharisoa, Moreira & Akrich (2014) coined the term "evidence-based activism" to describe a multiplicity of knowledge related activities undertaken to raise awareness of public health concerns. If knowledge is a target of activism, then evidence is the bridge between expertise and knowledge. Evidence thus "aims at providing robust knowledge on how patients' and activists' conditions or situations ought to be understood and treated" (p.115). Evidence-based activism calls on patients to mobilize knowledge that is especially relevant to issues of care (or effectiveness of treatment) which may be other than the traditional medical knowledge or point of view (p.118).

One of the most prominent examples of such activism involves the changing landscape of the HIV/AIDS crisis in the 1980s, where patients were frustrated with the speed of treatment development (Epstein, 1996). Potential treatments existed but their testing was slow and bureaucratic whilst patients were dying. Patients formed advocacy and activist groups, gained knowledge and expertise, coordinated among themselves enrollment in clinical trials and sometimes compromised compliance with clinical trial requirements, leading to major changes in how clinical trials were conducted. Ultimately, the HIV/AIDS advocacy groups impacted the ethical and statistical design of clinical studies, and how accessibility to life saving treatments should be handled. Pinch & Collins (1998) use the case of AIDS activism and advocacy to demonstrate the significant and valuable understanding patients have of their illness, so much so that they can learn to harness that knowledge to bend and adapt scientific practice to their benefit.

The coming together of rare disease patients in the 1980s was aimed at generating interest in rare diseases by combating scientific ignorance and indifference, and it culminated in creating power through numbers: "By counting and gathering patients, rare diseases alliances moved towards the mainstreaming of rare conditions, as summed up in their slogan: "Rare diseases are rare, but rare

diseases patients are many" [5]. (Rabeharisoa, Callon, Filipe, et al., 2014, p.197). However, there was some resistance to focus on cumulative numbers of rare disease patients as a source of power, because it marginalized the specific issues associated with each and every rare disease. Rabeharisoa, Callon, Filipe, et al. (2014) demonstrate a shift from *politics of numbers* to *politics of singularization*. The authors begin by describing how in the 1980s patients organized themselves into organizations that actively pursued getting funding and developing a cooperation between patients and experts, shaping rareness around motifs of equity and social justice. However, for some organizations it became apparent that rareness as a virtue is insufficient to address issues associated with "obtaining a rapid and accurate diagnosis, addressing the issue of patients' compounded trajectories and pushing towards the development of adequate treatments" (p.205). Thus, some patient organizations sought to collectively engage in research that profiles their disease's specific condition, contrasting what is common and overlapping from one disease to the other in order to highlight what is unique (p.213). The activities that patient organizations undertook in the name of singularization included participation in registries to gather accurate description of the disease, and also to bring to the fore the aspects of chronic and debilitating rare illness beyond the biology (e.g., depression, fatigue, pregnancy risk). The findings in the article establish a dialogue with this thesis in how the role of patient organizations function as an integral voice involved in research, actively working to shed light on the differences between one rare disease and the other while concentrating on aspects of living that matter to the patients themselves, beyond the biology of the disease.

The effects of such activism in the rare disease arena were shown to influence regulators and market access in a way that is deliberate and specific for the rare condition. For example, Skinner (2008) describes in his review of how the nonprofit organization World Federation of Hemophilia (WFH) is involved with regulators and market access: "Optimum care results are achieved when healthcare professionals, the patient organization, and the Ministry of Health work together via a formal mechanism such as a National Council for Patients with Bleeding Disorders" (p.7). Such National Councils have been set up in multiple countries, whether affluent or developing. In addition, the WHF participates in the World Health Organization (WHO)'s committee on clinical use of blood (ibid).

This aligns nicely with Callon & Rabeharisoa's (2008) idea of "emergent groups" that influence national institutions, innovation, and reconfigure markets. Emergent groups are combined from those who have problematic identities to begin with and who search for clearer identity and common interest (p.235). In the authors' example, the French Muscular Dystrophy Association (AFM) bound together patients and families to construct an identity which could be defended in public space (p.236). AFM turned to scientific collaboration and political advocacy to identify the cause of the illness, and once

[5] Currently the *rare disease alliances* are branded as Rare Diseases International

the genetic composition was found they strategically financed research in areas where patients felt the most progress towards a cure could be made (p.239), and later played an "instrumental part in drafting a law on disabilities" (p.242).

In summary, patient activism offers those affected by an illness not only to create a shared identity that is defendable, but also to influence funding of new research, designing of clinical studies, and legislation that governs access to treatments and support.

2.4 Regulations as normalizing tools

The path from disease definition to treatment goes through regulation and governance. Treatments are commercialized locally only after they obtain governmental approval for marketing.

On this matter, Asdal (2015a) identifies the importance of governance and regulation to normalizing a controversy. For Asdal, rather than viewing regulation and policy as problematizing a phenomenon, the use of governing tools for that issue "may also imply that it is being closed down. Rather than being turned into a controversy, being defined as *Sache* (or issue) can imply that it is becoming transformed into a non-controversy or a non issue." (Asdal 2015a, p.87, emphasis in original). Where new treatment modalities are concerned, regulation and policies can legitimize and provide social acceptance for technoscientific advances in healthcare. For example, in the case of gene therapy (GT), by offering guidance on what would be rendered an acceptable version of GT, the treatment as such is normalized. This leads to question of how any new therapy is valued as a treatment, and how this treatment is normalized and introduced (formally through policies) into the canon of treatments available. The concepts of normalization and legitimization are key to this thesis and will be unpacked and re-evaluated in depth the empirical analysis section.

Above and beyond the ability of regulations to normalize a controversy, they serve as a site of negotiation, that allows for social acceptance and closure of disagreements. For example, discussions relating to governing and regulating embryonic stem cell therapy took place several years ago, at the time that stem cell therapy emerged as a new potential treatment avenue. Salter & Salter (2007) enlist the concept of bioethics to explain how cultural and moral disputes associated with new technologies and their ascribed value come to an end: "The political utility of bioethics to the advance of medical science lies in its ability to normalize the trading of values between conflicting cultural positions so that an ethical solution is produced that can then be translated into legitimate regulatory policy" (p.575). Thus, demarcation and resolution of ethical questions is achieved within the confines of regulation and policies and testifies to the common acceptance of the technology.

Ethical discussions that proceed governing tools draw on values which are influenced by existing cultural norms. Wienroth & Scully (2021) provided a review of GT's sister technology, genome editing,

and the human health discourse in the UK. They touched on the importance of anticipatory discourse and promissory expectations to shaping sociotechnical imaginaries (as are defined by Jasanoff & Kim, 2009). Their findings show a sequential process in which first "associating specific publics and public goods with values and norms, the promissory ethical regime prescribes a role for the technology in the trajectory toward a specific desirable future", then, in a second step these public goods "provide ethical rationales for the suggested promissory (i.e., future) governance of the emerging field of research." (p.795). Wienroth & Scully criticized the limited public engagement in such practices which lead to innovation policies that are deterministic instead of enabling.

Within this thesis, GT is sometimes referred to as "novel", "curative", or "innovative". These powerful adjectives are taken from discourse surrounding GT. Similar to other emerging fields of health and technologies, the discourse around GT is vital to its continued development and subsequent legitimization through policies. Continuing Wienroth & Scully's (2021) thoughts, the point being made is that GT inherits an ethical dimension resulting from its promissory discourse for an imagined public benefiting from the product, and therefore becomes a technology worthy of support and governance.

Finally, one of the outcomes of governing an emerging technology, is that governance mandates funding and costs, which influences drug regulations. Andreoletti & Tiera (2019) assess the financial impact imposed on the FDA when assessing new drug applications (the initial request to gain approval for a new drug product[6]). The gold standard for drug development builds on the RCT-rule (approve a product based on two positive **r**andomized **c**ontrolled **t**rials), which is an inflexible fact (either there are, or there are not, two positive RCTs). The FDA is better off economically by relying on checklists and generalized *rules* of how to approve a clinical study when considering the frequency and volume of applications that the FDA must manage. The alternative would be to set *standards* which are more flexible and comparative in nature, but then would require additional adaptation on a case-by-case basis. An example of such a standard could be not to allow harmful products into the market, but then the understanding of "harmful" would need to be assessed for each product independently (p.1096). The authors demonstrate that rules cost less than standards and are less prone to being distorted. Therefore, they favor the current RCT-rule approach, which may result in some unsafe drugs on the market (refer also back to section 2.1). Though the authors agree that "philosophers of science have argued for increasing safety levels, using methods that would allow regulators to capture adverse events beyond the reach of standard RCTs" (p.1108), they assert that in most drugs overall risk is lower than effectiveness, and perhaps the discussion should shift to understanding what risks patients are willing to take and how patients are treated, instead of discussing better safety assessments.

[6] NDA- New Drug Application, mainly traditional small molecules. Biologics are submitted under a BLA, see section 7.1.

Combining these ideas, and with respect to emerging technologies in the realm of healthcare, regulations can be assumed to display several properties: they normalize controversies by making them non-issues, they close down ethical questions, they assume a given public would benefit from a desired future involving emerging technology, and because they are set in a way that minimizes economic costs to regulators, they reinforce applying rules to the approval processes (as opposed to identifying standards).

3 Hemophilia Gene Therapy - A Case Study

This thesis draws on a specific case study of FDA governance of Hemophilia GT. To present a logical pathway to the main research question, and to make sense of the empirical section, an expanded explanation of hemophilia and gene therapy is offered below.

3.1 Hemophilia disease and treatment

Hemophilia (ORPHAcode ORPHA:448[7]) is a group of rare diseases associated with blood clotting disorders. Hemophilia is an inherited, congenital, recessive, X-linked disease[8], caused by a defective enzyme involved in blood clotting (the coagulation cascade). Congenital diseases present themselves at birth. Diseases that are linked to chromosome X and are recessive almost exclusively affect the male population. By and large, hemophilia can be divided into Hemophilia A and Hemophilia B, and their subcategories depends on a combination of clinical manifestation and genetic profile. Hemophilia A is the more common form, and results from a deficiency in blood clotting Factor VIII (FVIII, pronounced "factor eight"). Hemophilia B is typically a bit milder, and results from a deficiency in blood clotting Factor IX (FIX, pronounced "factor nine'"). The majority of hemophilia patients suffer from the severe form of Hemophilia A. Severe, mild, or moderate subtypes refer to bleeding patterns, and these correlate to the amount of FVIII circulating in the blood. Bleeding can be due to injury (and trauma) or spontaneous; spontaneous bleeding typically happens in joints which are prone to deformation as a result of recurring bleeds. Such damage is usually referred to as hemarthropathy (joint pain and wear). Bleeding can also occur in major organ (such as the brain), or into soft tissue. Severe Hemophilia A patients bleed spontaneously as much as every other week (approximately 25 times per year). Left untreated, these patients die in their first or second decade of life. A bleeding episode can last a few hours, and if left untreated can last days. WFH identified 157,517 patients with Hemophilia A and 31,997 patients with Hemophilia B in a global survey from 115 countries (WFH, 2020, pp.6-7).

Figure 1 summarizes the relationship between the deficient blood clotting factor and the disease phenotype in Hemophilia A. A Similar curve exists for Hemophilia B.

[7] Orphanet is global web-based network dedicated to rare disease, supported by the European Commission.

[8] Within this thesis, ***hemophilia*** **(**ORPHA:448) assumes an X-Linked congenital disease, i.e., Hemophilia A and Hemophilia B, and thus exclude Acquired Hemophilia (AH) and Rosenthal Syndrome (also called Hemophilia C). Inheritance, bleeding patterns, and treatments of AH and Rosenthal Syndrome differ from ***hemophilia***.

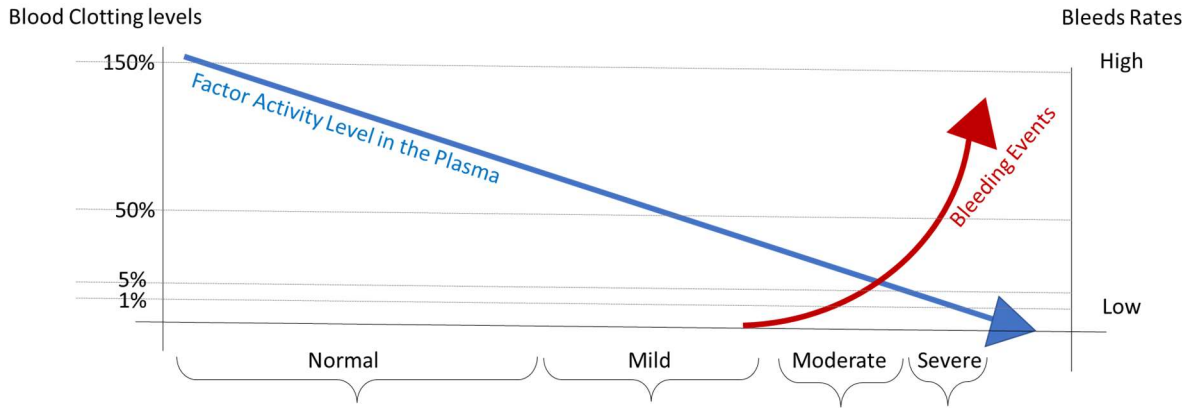

Figure 1. Relationship between blood clotting levels and bleed rates for Hemophilia A patients. Illustrative and not to scale. Factor VIII activity levels relate to disease severity: 50-150% corresponds to healthy population (normal) clotting, 5-40% corresponds to mild disease, 1-5% corresponds to moderate disease, and <1% corresponds to severe disease.

As can be seen from Figure 1, the transition from a "severe patient" to a "moderate patient" requires very little restoration of factor activity and has disproportionate excellent improvement in actual disease expression.

Hemophilia was identified already in biblical times in relation to excessive bleeding post circumcision. Hemophilia treatment products evolved hand in hand with technological advances and scientific innovation. Historically, the treatment paradigm of hemophilia shifted from lifestyle regimes (e.g., abstinence from physical activity and potential injury), to treating each bleeding event, to preventing spontaneous bleedings altogether. GT is the next treatment paradigm, that aims to *cure* the underlying disease, rather than treat or prevent the symptoms.

Over the course of the past decades many products were developed for hemophilia patients. The fact that hemophilia products are entitled to an orphan designation enhances their appeal for drug developers, hence many companies invest in developing therapies for the hemophilia market of treatments, despite the fact that this market is both slim with patients and crowded with treatments. In fact, there are so many products for such a small population, that the plethora of existing hemophilia treatments has been dubbed "an embarrassment of the riches" by Dr. Kenneth Lieuw (2017); about 60 different products are commercialized for Hemophilia A alone (WFH, 2020, pp.80-83).

Table 1 follows a historical approach to summarize key attributes of the various Hemophilia A products and treatments available in the Global North in general. Developing countries and people who live in the Global South do not have access to all types of treatments. Hemophilia B product and product development history is similar and follows the same treatment trajectory in term of treatment targets, technology and innovation progress.

Period	Type of Treatment	Treatment Target, Success, and Risks	Treatment Regime	Impact to Quality of Life	Innovation aspects
Before 1920	Nonspecific treatment, random products (e.g., snake venom)	Survival only. Lifespan is low (death by second decade of life)	Lifestyle changes: avoid an active life and surgical procedures	Extremely low quality of life (considerable pain and physical handicap, joint deformation)	None
1920-1960s	Whole blood donations	Treatment is tailored to avoid death from injury	Intra Venous (IV) infusion in hospital to treat bleeds (on demand treatment)	Still extremely low quality of life; Considerable difficulty to secure treatment access	Treatment of the clinical symptoms and better understanding of the disease
1960-1980s, ongoing today (Global South)	FVIII proteins purified from blood products; a.k.a. concentrated plasma derived (pdFVIII)	Lifespan increases to third decade of life; many patients contract blood-borne diseases HIV and hepatitis through blood donations	on-demand bleed treatment; IV infusions mostly in the hospital	Gradual transition from hospital to home treatment reduces treatment inconvenience and reduces bleed-related sequela	Pathophysiology is understood; blood coagulation factors are purified by cryoprecipitate technology; freeze drying of the purified factor enables home therapy
Mid 1980s, ongoing today (Global South)	Enzyme Replacement Therapy (ERT): treatment with FVIII protein	Increased safety of treatment by removing risk of blood borne diseases (HIV and hepatitis)	Preventative regimes: prophylaxis infusions every other day	Home treatment becomes standardized; quality of life improves significantly	Industrial (synthetic) manufacturing; technology based on new knowledge of genetic and sequencing techniques; removes the need for blood donations
1990s ongoing today (Global North)	Recombinant FVIII (rFVIII) products that display changes in the genetic makeup of the protein (compared to the human FVIII)	Lifespan increases to 7th decade of life; recombinant products are more efficacious than human FVIII; on average, prophylactic patients bleed once to twice a year	Treatment gold standard. IV infusion prophylaxis at home; products require 2-4 dosing per week	Improved the convenience to patients through better infusion delivery device; less frequent infusions	Understanding of protein molecular structure; additional modification to the protein slows down removal from the blood stream; The treatment itself is packaged with designated delivery devices
Starting 2018 ongoing today (Global North)	Non Factor Therapy (NFT), e.g., FVIII Mimetic	Bleeding occurs several times per year (product is inferior in terms of safety to rFVIII). Product targets also inhibitors patients.	Subcutaneous infusion home treatment, once weekly, potentially once monthly	Significant reduction of infusion burden, both in delivery and in frequency	New treatment approach: blocking bleeding instead of accelerating clotting
August 2022 (in Europe only)	Gene Therapy, attempt to cure the patients by forcing the body to generate rFVIII	Potentially a cure; patients may be treated with immunosuppressants to reduce likelihood of rejection of the GT	Single infusion is expected to last for 5-10 years	Quality of life is equivalent to the general population - no need to infuse product at all.	Novel technology: a gene encoding for FVIII is introduced into liver cells through a viral vector, then the liver cells synthesize and secrete the FVIII protein into the blood stream.

Table 1. Hemophilia A products and treatment progress. Resources: BioMarin, 2022; Blair, 2019, p.1704; FDA, 2017; Kingdon & Lundblad, 2002; Lieuw, 2017; Ling & Tuddenham, 2020; Mannucci & Tuddenham, 2001; National Hemophilia Foundation (NHF), n.d.

Prophylaxis, in the context of hemophilia (dubbed "prophy"), is a preventative measure where the body receives sufficient drug product to consistently maintain enough FVIII in the blood stream, thereby avoiding spontaneous bleedings episodes and sustaining enough clotting ability to endure through unexpected minor injury. The current gold standard for a Hemophilia A patient thus requires three to four enzyme replacement therapy (ERT) infusions per week as prophylaxis treatment, contrary to treatment given only once a bleed is identified (Srivastava et al., 2020, p.14). Prophy patients maintain a relatively normal lifestyle, where the extra burden of treatment is incorporated into their daily routine (Ling & Tuddenham, 2020, p.402). By applying prophylaxis, the survival rates for Hemophilia A significantly improve. In the UK, for example, median Hemophilia A survival is 63 years old (Darby et al., 2007). Even for patients who have stable prophylaxis treatment, occasional bleeds will happen (called "breakthrough bleeds"), either due to trauma or spontaneously. These are managed by giving extra factor infusions in addition to the regular prophylaxis regime. In the absence of prophylactic treatment patients revert to treating each bleed after it occurs, called on-demand treatment. In this case each major bleed poses a threat to life, and recurring minor bleeds contribute to irreversible deformation of joints and decreased quality of life (Melchiorre et al., 2017).

A minority of patients develop inhibitors to factor infusions. Consequently, although patients with inhibitors are hemophilia patients, their treatment and prognosis are worse than other hemophilia patients. Once a patient develops inhibitors it becomes especially difficult to control bleedings, although the recent commercialization of non-factor therapies (NFTs) reduces bleeding in inhibitor patients significantly. For the purpose of this thesis, further discussion of inhibitor patients is sidelined as they are currently not the target population for gene therapy. Conversely, *the risk* to develop inhibitors to treatment exists with all therapies, as well as in gene therapy.

Gene therapy is a new treatment, where a one-time infusion will alleviate the burden of thrice-weekly injections, while creating constantly sufficient levels of the clotting factor circulating in the blood. This means that patients will enjoy continuous high level of factor activity, have much better quality of life in terms of burden, and will avoid the prophylaxis treatment profile of peaks and troughs[9]. For both prophylaxis and GT, the actual figure of what is considered "successful" factor level is unclear. Ideal prophylaxis typically revolves around 3-10% factor level – essentially equivalent to moderate or mild hemophilia. GT clinical trials aim for sustained higher factor levels, by constant secretion of factor into

[9] Coagulation factors regularly get cleared from the blood. A peak is a high amount of factor activity following dosing, and a trough is a low amount of factor activity following clearance. Bleeds occur in troughs when there is insufficient blood clotting. Prophylaxis looks like a series of peaks and troughs, where the goal is to find a rhythm in which dosing can happen at intervals that minimize infusions and maximize time above 1% factor activity level.

the blood stream. Figure 2 explains the different profiles between the gold standard, prophylaxis with ERT, and gene therapy.

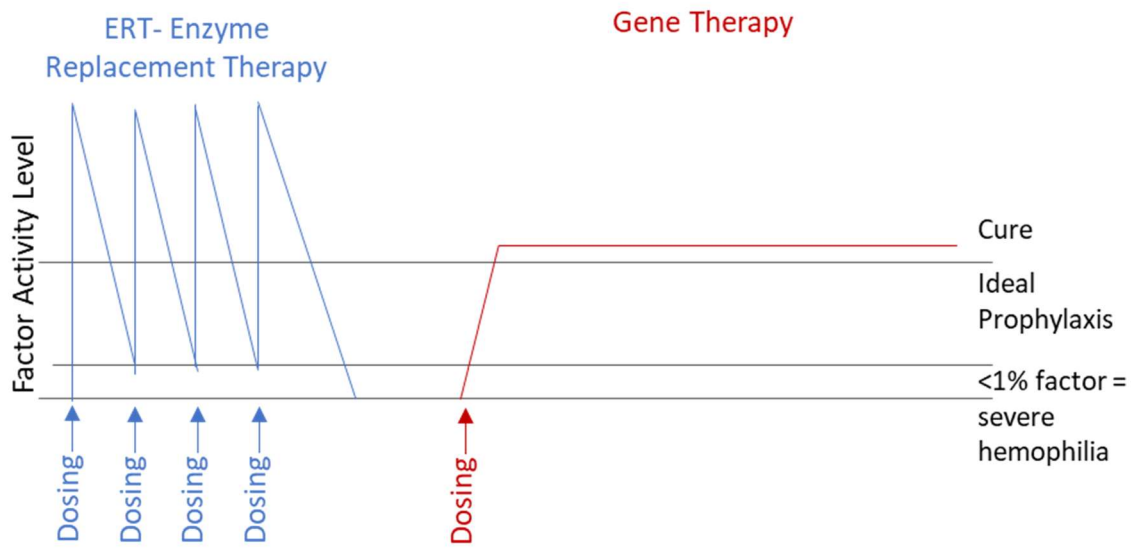

Figure 2. Factor level patterns for ERT prophylaxis vs GT. ERT requires frequent dosing to maintain factor level above a designated threshold; the pattern is full of peaks and troughs. The objective of ideal prophylaxis is to avoid troughs below 1%. GT is expected to sustain high factor level in the body, hence considered to be a cure. This image was inspired by Figure 1 published in Arruda et al., 2017, p.2253.

In the past decades, the hemophilia community (collectively the patient families and treating physicians) have witnessed an evolution in therapies and disease management where neither convenience nor cost were the target for treatment development, but rather efficacy and safety, as is also mirrored in the clinical trial designs and historical policies for product development (Kingdon & Lundblad, 2002).

Konkle et al. (2019) summarized the two main outcome measures that are used to defined treatment success. Since there is a direct and critical relationship between factor activity level, clinical manifestations, and disease severity, the success of the treatment can be measured both at the molecular level by looking at the actual factor activity level, and at the clinical level by looking at the bleeding frequency. In other words, a person that has sufficient factor levels in the blood stream would not bleed. Since the level of factor activity in the blood correlates with the likelihood to bleed spontaneously, factor activity is rendered as a decent surrogate for assessing treatment success. This measurement is not without fault though, as it is hard to quantify factor activity level (especially for recombinant factors) accurately between different labs. Also, different bleeding profiles exist, even among severe hemophilia patients. A second option is instead of measuring factor level as a surrogate

to treatment success, using annual bleed rate (ABR[10]) as a direct measure of clinical benefit. ABR became popular as prophylaxis became more common, and patients had consistently higher levels of factor activity. With prophylaxis, physicians shifted their concern to protecting joints which are the most common targets of bleeding episodes. Because ABR looks at bleeding frequencies it is a better suited to measure prophylaxis. It also allows some space for adapting the treatment to fit the patient's own bleeding pattern. For example, to reach an ABR = 2 (two bleedings per year), one severe patient may require dosing every other day, whereas a different severe patient may require dosing every third day. ABR is not without fault as an outcome measure because it is subjectively based on patient reporting of bleeding sensations (which can be confused with pain) and fails to account for microbleeds which are undetected by patients but cause joint damage in the long run. Konkle et al. (2019, pp.187-188) discuss which outcome measurements would be appropriate for upcoming treatments, among them gene therapy. Their conclusion is that neither ABR nor factor activity level is a suitable methodology to measure benefit for patients who transition to gene therapy from prophylaxis. In patients who do not have preexisting hemarthropathy it would be hard to statistically demonstrate improvement in ABR since prophy patients already have extremely low ABR. For patients with existing joint damage, research has shown that the damage itself triggers bleeds, no matter the factor level, therefor transitioning to gene therapy may not improve their ABR. Machin & Ragni (2018) concur with this notion, and suggest that when calculating the actual factor activity levels "Higher sustained levels possible with gene therapy are leading not only to incremental improvement in activity and sports but also to reduction in fear of bleeds and distress and improvement in well-being, which are increasingly being defined by patients" (p. 84). Machin & Ragni (2018) thus suggest recalibrating the yardstick that could be appropriate to measure success for gene therapy, one that could differentiate and justify GT above ERT.

In line with that concept, van Overbeeke et al. (2021) developed a tool to investigate trade-offs that adult Belgian Hemophilia A and Hemophilia B patients are willing to make when asked to choose between a standard of care and gene therapy (p.2). Their results show that the four top items that guide patients when making their discreet choices on GT were "Annual Bleeding Rate," "chance to stop prophylaxis," "quality of life," and "time that side effects have been studied" (p.8). While these findings are limited to Belgian patients, they reiterate that patients themselves take into considerations matters that go farther than the molecular illness itself when considering treatments.

[10] ABR- annual/annualized bleed rate - is a measure of the bleeds a hemophilic person experiences over the course of a year. ABR can be measured by counting the number of bleeding events divided by the number of months in the reporting time window (typically 6 to 12 months) and multiplied by 12. A patient (on well managed prophylaxis) bleeding twice a year will report ABR=2.

To fully appreciate why wellbeing or quality of life occupy a place of importance, it is prudent to reflect on the reality of disease management beyond the technicalities listed above. ERT prophylaxis treatment can easily reach over $250,000 (USD) annually per patient (Noone et.al, 2020, p.13). Both the cost and the handling of the product (i.e., refrigerated cool-chain and intravenous infusions) make it especially difficult for patients in developing countries to obtain prophylaxis treatment (Ghosh & Ghosh, 2016). This raises societal questions on global access and equity. Moreover, even assuming a patient has access to good healthcare coverage in a developed country, treatment compliance is often an issue, where home infusions three times a week become a burden (Zuiderent-Jerak, 2010), and a negative impact to quality of life: for example, a patient on three-times weekly prophylaxis who wishes to travel for vacation would need to carry sufficient FVIII products in a cooler and stay at a place with access to refrigerators and emergency hospital care. Many patients with excellent ABR values are still sedentary. In a recent multi-country survey, patients identified that major concerns "relate to mobility/movement problems, unexpected bleeding, pain, and uncertainties about daily activities, followed by difficulties with travel, administering medication and other issues" (Banchev et al., 2021, p.872).

3.2 Treating patients with hemophilia

Hemophilia patients practice self-care, where overall treatment is determined and supervised by a clinic, but administration is delegated to the patient (or caretaker). The autonomy of patients in their self-care is well described in Danholt & Langstrup's (2012) account: "It may be that a specific technology or treatment plan prescribes certain behavior, but it is nonetheless *de-scribed* and accommodated to the practices of the patients, in and by the way in which they make use of the treatment." (p.519, emphasis in original). Generally, the treatment plan is adapted by the clinicians to the patient according to the definition of his[11] illness, while the patient himself adjusts and reappropriates the treatment to meet his everyday needs. Thus, though products are scrutinized and have quite careful requirements for dosing, physicians and patients take liberty in applying those instructions. For example, a hemophilia patient who normally infuses twice a week, and intends on playing soccer at a picnic event may choose to infuse additionally several hours before the event to increase factor activity and protection from bleeds. Patients tailor prophylaxis treatment to their lifestyle, and tailor bleed treatment in accordance with the bleed itself (minor bleeds resolve with one extra infusion, whereas major bleeds may require multiple infusions). Thus, at the end of a very stringent regulatory process that dictates dosage and administration lies a very flexible treatment

[11] For simplicity, throughout this thesis, a hemophiliac is assumed to be a male patient

regime. Compliance with treatment regime, and quick action when bleeds occur, is critical for survival, as was described by Zuiderent-Jerak (2010, pp. 685-686):

> During a meeting, a hematologist told me the tragic story of a patient who was recently brought into the hospital in critical condition. He had bumped his head against his garden shed when getting on his bicycle to leave for work that morning. He returned inside and gave himself only about a third of the amount of coagulation factor concentrates that was prescribed in his treatment plan in case of a head-bleed. At work, he became unwell, and by the time he was brought to the hospital, it was too late to save his life. This hematologist also used this example of a preventable and quite clumsy death, to show his medical students that accidents can happen - with drastic consequences - and to stress the weighty task they will face in enhancing compliance.

Danholt & Langstrup (2012) conceptualize medication as *infrastructure of care*, in that products are both infrastructures that manage chronic diseases e.g., by "facilitating communication and interaction between the patient and the healthcare system" (p. 528), but also that products do *infrastructuring:* "Medication initiates the building, structuring and maintenance of arrangements that support the patient in performing self-care by adhering to the treatment plan" (ibid). Of relevance to GT is the fact that it could alleviate the need to uphold a daily treatment routine altogether, thus the relationship between the patient and the treating physician changes, as well as the patient's daily routines associated with handling of the product. Applying Danholt & Langstrup's (2012) concept, one can say that GT strays from the current infrastructure and infrastructuring of hemophilia treatment and frees up resources such as time and storage space, both for patients and for clinics. Furthermore, this kind of change could itself be of importance to defining disease and illness. In other words, is someone who underwent FVIII gene therapy, and who's FVIII levels meet the normal threshold, still considered a severe Hemophilia A patient?

This question has far-reaching consequences. First, disease illness and definition go hand in hand with the guidelines that govern treatment. Second, disease definition is the standard used to assess treatment options and amounts. Hemophilia products are expensive. Product shortages due to scarce medical funding cause anxiety: "Both doctors and patients compared treatment to 'shooting up a Mercedes [Benz] a year' and were well aware of the implications this has for public budgets" (Zuiderent-Jereak, 2010, p.686). In events where patients perform non-compliance with home-treatment plans (too little or too much product infusion as compared to the instructions given by the treating physician), described as *situated (ir)rationalities* by Zuiderent-Jereak (2010), clashes occur between home treatment, cost of treatment, patient's health status and lifestyle, and disease definition. GT has the potential to disrupt each of these items separately; better compliance leads to

reduced clinic checkups, more distanced relationship between patients and physicians, and eventually also relaxing the utilization of public resources (time, budget and clinical staff), so other patients can benefit from them.

3.3 Gene therapy: success, failure, and controversy

To appreciate the conflicting and curious attributes of GT in full, a few words on GT are necessary.

First and foremost, GT is a strange beast. Though it has been around since the early 1990s, GT is still considered a novel and emerging technology. Moreover, despite the therapeutic promise that GT offers, and the huge strides made towards applying it for treatment of sorts, it nevertheless relies on partially understood mechanisms, be they receptors on a cell or technicalities of upscaling of viral particles (Goswami et al, 2019).

In fact, Gene Therapy is not a single technology, but an umbrella term covering a range of therapies that all result in a change of the DNA composition of a treated patient. Of particular importance to this thesis are GT technologies based on virus-mediated introduction of genetic material (typically DNA) to a patient, which results in sustained changes to that patient's ability to synthesize functional versions of a protein that was previously deficient; far beyond a pill that is swallowed and broken down or excreted, the changes that gene therapy causes are at the most fundamental genetic level. Diseases targeted by this type of technology are almost exclusively rare and many of them are congenital, linking GT development to the rare disease arena. Companies that develop such GT strive towards a single-injection cure for a lifelong disease, the caveat being *cure*. This notion of *cure* should be stressed: "GRTs [Gene Replacement Therapy] have the potential to 'cure' diseases. It is important to clarify the meaning of 'cure' in this context. 'Cure' does not necessarily mean that patients will have a normal life, but rather that the underlying pathophysiology will be suppressed." (Aballéa et al., 2020, p.2).

The first GT patient was Ashanti DeSilva in 1990 (Naam, 2005), and her successful treatment and partial cure from SCID[12] disorder sparked enthusiasm, which was severely curtailed with the untimely death of Jesse Gelsinger in 1999 following participation in a GT clinical trial (Lewis, 2021). In the 30 years since GT research began, most clinical trial attempts fail[13]: they do not demonstrate health benefit, or do not meet minimal safety requirements for marketing. As per Ginn et al. (2018) by the end of 2017 there were almost 2600 (!) planned or executed clinical trials using a technology that fits the umbrella description of gene therapy, but by January 2020 the FDA only approved 24 (!) products for marketing

[12] SCID - Severe Combined Immune Deficiency Disorder. A group of rare disorders, resulting from a deficient adenoside deaminase (ADA) protein, affecting the immune system from early childhood. Commonly known as "bubble boy disease".
[13] Most candidate drugs fail during development well before the clinical phase. The rate of failure for GTs is considered especially high as failure continues after commencing clinical trial.

that fall into either gene therapy or its sister technology cell therapy (FDA, n.d.). Globally, there are about 12 products commercialized that met the definition for GT.

GT products that do get commercialized are heralded as "the kind of therapeutic home run scientists have dreamed about for decades" (Knox, 2018), as was said about the GT Luxturna. Luxturna is injected into each eye and claims to restore loss of vision due to a rare hereditary form of blindness. However, when delving into details, Luxturna is shown to have received preferential and flexible reviewing by the FDA, because of its orphan designation and because in instances where no good treatment exists, any treatment that shows improvement accrues benefit. In the case of Luxturna, FDA reviewers approved the drug for commercialization despite identifying "that the drug is not expected to restore normal vision, that only about half of treated patients met the FDA's threshold for minimally meaningful improvement, that improvements might not persist long-term, that the most common measure of visual function was rejected as a primary endpoint after yielding mixed results, and that two patients experienced permanent vision loss." (Darrow, 2019, p.949). Thus, of the few products that do reach the finish line of marketing and commercialization, question of efficacy emerges. This point should be clarified with respect to rules and standards as they were discussed in section 2.4. Regulators will revert to rules where rules can be applied, but for orphan indications, flexibility is encouraged as there is often a shortage of alternative treatments. In addition, orphan indications a-priori allow for reduced patient enrollment into clinical trials. Thus, while the actual drug development process for GT may deviate from acceptable rules, success can be measured against existing standards for treatment. However, questions of what standards apply to measure a cure may still be of relevance.

Luxturna is commercialized at $425,000 (USD) per eye. The fee is set to compensate disproportionally high risk of failure (in the development process) and reflect the orphan designation advantages of pricing. GTs that have been commercialized globally are among the most expensive treatments available, and suffer from lack of long-term financial sustainability, in part due to complexities associated with agreed cost-effectiveness calculations and budget impact (Noone et al, 2020). An example of a colossal commercial failure was Glybera, the first GT approved in the EU in 2012. Glybera was a proven life-saving gene therapy priced at approximately $1 million (USD) for a single dose. Glybera turned out to be too expensive for European health funds, and it quickly lost commercial value for the company producing it. Although hundreds of millions went into its development, Glybera manufacturing was discontinued after it was given to just 31 people worldwide, almost all of them free of charge within a clinical trial setting (Crowe, 2018). Because of the high pricing, GT will remain a product that deepens inequities between those that can afford it and improve quality of life and those that cannot (Noone et.al., 2020).

Nevertheless, developers see GT as a potentially lucrative market. Looking specifically into the hemophilia market in numbers: "The global hemophilia treatment market size was valued at $12.8 billion in 2021 and is projected to reach $26.9 billion by 2031" (Allied Market Research, 2022b). Any company which has a treatment suite[14] in hemophilia will lose their market share if it does not regularly signal its commitment to new hemophilia treatments. Hence investing in GT (whether it is successful or not) will provide evidence towards that commitment, and allow a company to retain patient loyalty, translating to patients staying on existing life-long treatment, while they wait for GT to finally come through. Regarding companies which focus on GT as a proprietary platform that can be adapted for multiple disease, "The global Gene Therapy Market Size was valued at $6.0 billion in 2020 and is projected to reach $46.5 billion by 2030" (Allied Market Research, 2022a)[15].

Two important questions associated with GT are the duration of treatment and chances of treatment rejection. Currently it is unclear how long successful GT treatment lasts, though it is assumed that after five to ten years treatment effect wanes. For chronic patients, such as hemophiliacs, a repeat treatment would be necessary. However, once a patient's body rejects the treatment, that patient is unsuitable for a second attempt at GT. To overcome both problems (avoid initial rejection and enable redosing), many GT products requires concurrent treatment with immunosuppressants at least for several months if not years (Rodríguez-Merchán et al., 2021). It remains to be seen whether products that require continued immunosuppressive therapy are viable from a patient's health perspective, and whether products that require redosing are commercially viable.

A known issue with GT, and especially in the hemophilia sphere, is the level of personalization required for GT treatment to be successful. The right (single) dose for one patient may be inappropriate for another, and patients' immune system differ in their response to GT. For example, in Konkle et al. (2021) the results of Baxter's BAX 335 Hemophilia B gene therapy study are described, where out of 8 patients who received the treatment, all lost factor expression within 11 weeks (i.e., treatment failed), except one patient who went on to have factor activity of about 20% for more than 4 years (thus far). This is attributed to an anomaly in the patient's own immunosuppression system. The other seven patients who lost expression had a strong immunogenic reaction against the treatment (meaning their body rejected the treatment). Overall, the study failed. In other ongoing studies, variability as to treatment success or failure (loss of expression) can be a strange split among treated patients, without a clear understanding why this happens. Spark's SPK-8011 Hemophilia A product showed that 2 out of

[14] Treatment suite refers to a group of products all intended to treat the same disease but targeting different patients or different situations. For example, in hemophilia a suite of treatments could include first generation recombinant Hemophilia A product for developing countries, bypassing products for patients with inhibitors, third generation Hemophilia A products for wealthy countries, third generation Hemophilia B product, etc.

[15] Financials provided in USD. The hemophilia market includes products that are already commercialized globally, whereas the GT market assumes products that will be developed and commercialized across many diseases.

18 patients dosed had lost factor activity within the first year despite heavy treatment with immunosuppressants, while the other 16 patients retained factor expression, and 12 of them retained it for over three years at a level of 12%, resulting in one bleed a year (Figueiredo, 2021).

Finally, GT poses concrete questions of ethics, as stated by the Chief Medical Officer of Bluebird Bio[16]: "I think you have to have humility when you're manipulating the human genome" (quoted in Lewis, 2021, p.5). Here, Rose's (2007) view of vital politics can be applied, as vital politics are not concerned with illness, but rather "with our growing capacities to control, manage, engineer, reshape, and modulate the very vital capacities of human beings as living creatures" (p.3). In this respect, GT offers a discourse which correlates with that of societal discourse on controlling the human body. With vitality anatomized at the molecular level, health can only be obtained through technologies that unlock the genetic elements and separate them from body parts (p.14), as is the case with GT.

At the other end of the ethical spectrum, the dark side of the technology leads to thoughts on superhuman upgrades (Zehr, 2019). GT thus raises ethical questions on manipulation versus enhancement of the physical body and the regulation of such actions. These polarized ideas of using the same technology to augment humans or enable health (whatever *health* may be) are negotiated and agreed upon within the social arena "so that instead of the operation of the global moral economy being guided purely by scientific categories of value it becomes at least partially dependent on cultural categories of value." (Salter & Salter, 2007, p.577). Such GT-specific tensions can be analyzed through the prism of bioethics, demarcating ethical from non-ethical through discursive construction (Pickersgill, 2013, p.38). GT also provokes new ontologies of health, disease, and illness, resonating with Mol's (2003) The Body Multiple on the divide between a patient's view and a physician's view of what exactly is being treated – the patient, the molecular disease, the clinical illness, or the quality of life. Although neither bioethics nor ontologies of illness are the mainstay of this thesis, both converse frequently with biopolitics, which is well suited to research the techno-regulatory landscape and will be expanded on in later sections.

To summarize, gene therapy and gene therapy technology are a fertile land of conflicts: GT is abundant at the clinical trial level, and rarely reaches marketing and commercialization; high pricing strategies reflect the investment in GT development and orphan designation incentives, and align to a high forecast for revenue, but run the risk of turning the GT into a commercial failure and raise societal question of equity and access; GT is marketed as a one-time treatment, though current products may have limited duration and require redosing; GT is seen as a curative therapy, though in marketed products treatment success fluctuates, and in some cases products require long term usage of

[16] Bluebird Bio is a Boston-based biotech focused on Gene Therapy. The company developed Zyntelgo, a GT product for a rare blood disorder, which was approved for marketing in the EU in 2019, priced at $1.8 million (USD) per treatment.

immunosuppressants to avoid rejection of the GT; the technology is simultaneously the key antagonist or protagonist (depending on your point of view) depicted in ideas such as human enhancement and "designer babies"[17] for the wealthy.

[17] Designer Babies - a term denoting the process of selection or altering of the genetic makeup of embryos

4 Research Question

The starting point to this thesis was an FDA guidance on developing hemophilia gene therapy products that raised the question *why bother publishing a vague guidance*. Vague is a subjective term, and here vague denotes limited or incomplete information. The literature presented (i) regulatory approaches towards accelerated approvals to market new products, and subsequent tradeoffs between speed to market and risk to health, (ii) understanding the relationship between health, treatment, and defining what is illness, (iii) the role of patient activism in influencing regulators and study designs, (iv) the role of regulations in normalizing controversies, (v) history of hemophilia treatment and homecare, and (vi) key controversies of gene therapy. Combined, these ideas show that drug products are developed with the intent to provide some form of treatment and restore some form of health to patients, as is expected by patients, and as is governed by regulations. Hemophilia patients look to GT, an emerging technology, to provide a potential cure to an otherwise chronic and disabling disease. Though GT drug development fails more often than succeeds, though there are unknown health risks associated with GT, though plenty of alternative treatments for hemophilia exist, though there is only a tiny pool of patients expected to benefit from hemophilia GT, the FDA nevertheless made a point of publishing a guidance dedicated to governing hemophilia gene therapy development. However, the guidance appears laconic and incomplete. To understand the drivers and processes behind the development of such a guidance, this thesis asks the question:

How does the FDA hemophilia gene therapy guidance construct gene therapy as a relevant treatment modality?

The framing of the research question relies on two foundations: hemophilia as a disease and policies governing treatment development. By unpacking the concept of (i) GT as a treatment and (ii) GT as a governable object, this research endeavors to complement the existing literature with new insights on the relationship between emerging technological treatments and medicinal regulation. In other words, the gap being addressed is how does GT align to treatment conceptualization by regulators, patients, and pharma/biotech, and how does the regulation of GT influence treatment definition.

To close the loop between the starting point (why publish a vague guidance), and the ultimate research question (how GT is constructed in a guidance), a deep view into components of the guidance is managed through two supporting sub questions. Through the combination of questions, the guidance itself can be assessed more objectively: is it indeed vague and laconic or is the content and structure sufficient for its purpose.

Two supporting sub questions are divided into matters of substance and matters of process:

How is hemophilia gene therapy assembled in FDA guidance documents?

How do FDA regulators and stakeholders negotiate success criteria for hemophilia gene therapy?

The first sub question looks into the elements that, when combined, constitute a GT treatment in the policies. Since GT is a broad spectrum of therapies (see also section 3.3) it is important not only to demarcate what exactly is GT in the context of policies, but specifically what is GT in the context of hemophilia – in other words, what elements make up this governable object. The second sub question helps uncover the dynamics that shape what a successful treatment should look like. Documented communication between interested parties (mainly FDA, patients, physicians, and drug developers) can be used to establish how success is defined and institutionalized in the context of a hemophilia GT product. The combination of both sub questions provide answers to how a treatment is perceived and how it becomes governable. Through researching these two ends of the same process, the notion of what forms a treatment is explained, and treatment as such is contextualized.

5 Theories and Concepts

In the case of hemophilia, the treatment itself inhabits the space between disease and patient, and in that regard the medicinal products are front and center. Regulations impose additional interdependencies onto product development, the untangling of which is facilitated by applying the concept of biopolitics, loosely supported by bioeconomics.

5.1 Biopolitics of hemophilia

Simona Rentea opens the Routledge Handbook of Biopolitics (Prozorov & Rentea, 2016) with a discussion about current research in biopolitics. Rentea suggests using Foucault's definition and usage of biopolitics as a starting point, one in which biopolitics represents "a new mode of problematisation, a particular way in which power begins at this time to specify, define and regulate life in its opaque density and challenging complexity" (p.2). She describes Foucault's relationship with biopolitics as one that emerged from an understanding that liberalism and economics are tied to the concept of power and biopolitics: "Biopolitics can thus no longer be separated from an art of government that uses scientific rationalities and knowledge to normalise, optimise and measure the potentialities of life." (p.7). Importantly, Rentea identifies that there is both a deepening in philosophical and theoretical representation and research regarding biopolitics as a concept, and an influx of empirical investigations using biopolitics to explain the management of life. This thesis leans heavily on the empirical capabilities of biopolitics.

Lemke (2011) provides a comprehensive review of biopolitics, from a pragmatic perspective. He starts with Foucault's understanding of biopower and biopolitics and synthesizes unto it various biopolitical applications from the last century, until a single coherent analytical tool intended to bring together different disciplines (e.g., health, politics, society, technology) emerges. The end result of Lemke's suggested analytical usage of biopolitics is rather an open-ended speculative assembly of problems and questions that need to be asked, which stem from the social grounding of processes. "An analytics of biopolitics should investigate the network of relations among power processes, knowledge practices, and modes of subjectivation" (Lemke 2011, p.119). Through this quote, Lemke folds three perspectives into biopolitics (pp.119-120).

The first perspective is that a systemic knowledge of life and life processes are described with an agreed vocabulary and awarded social recognition, or alternatively are marginalized. At a much higher level, biopolitics points to questions of governmentality. Applied to this case, hemophilia patients, scientists, and regulators share basic understandings of the genetic aspect of hemophilia and the science behind it. Nevertheless, gaps exist in what is valued and what is invisible according to the agenda and agency of each actor. With respect to researching hemophilia GT, guiding thoughts are

how regulators decide what aspects of the technology should be governed (development? treatment? accessibility?), how a single patient stands to benefit from GT and what influence this has over society, and should policies intervene with technology intended for a minority of beneficiaries. Answers to these questions differ based on the local social grounding and context.

The second perspective that Lemke (2011) raises is that as power and knowledge enhance each other, structures of inequality become apparent. As such, they lead to questions of economic value, like who stands to gain (financially, politically) and who stands to lose. Within the context of GT, one can question whether a hemophilia GT product that may require long term immunosuppressors is a viable product to develop, who has a right to make that decision, and based on what (scientific) knowledge? Would this be the patients who are "situated" in the disease, the practitioners who balance the needs of the patients with the needs to manage product supply, the regulators who look at safety through medical standards, or the pharma companies who need to sell the product? Reverting back to the research question, the construction of treatment success is not independent of the understanding of what an illness constitutes. On some fronts, patient associations are on par with pharmaceutical companies, insistent on adaptations to clinical study designs and investment in treatment improvement. Thus, new power struggles emerge and redefine what constitutes illness and what is treatable or treatment worthy.

The third and final perspective raised by Lemke (2011), deals with subjectivation, or how individuals actively self-adapt their own bodies through language and practice. An example relevant to this case is how patients go about assessing risk-benefit to participating in a GT clinical trial, or their willingness to be technologically altered (by having DNA inserted into their body) at the cellular level. One layer is the physical aspect of being altered. A second layer is the emotional and epistemic level of being ill versus being treated. Would patients who receive gene therapy claim they are cured? What if gene therapy requires a second dose after five or ten years? Would they define themselves as cured *again*? What is the value of being cured if it is only temporary?

Lakoff (2008) looks at a slightly different practical angle of biopolitics, specifically associated with pharmaceuticals. The starting point is similar to Lemke's assertion on the importance of social processes: "pharmaceutical effects take form in relation to the heterogeneous networks that shape them" (Lakoff, 2008, p.741). Lakoff focuses on problems of access, mainly through analyzing how regulations and standards influence what medicines can go into what bodies. Though his application of biopolitics is narrower than Lemke's, it is still highly relevant for this research, as it asks questions of social agreement on the definition of illness, as well as standards that are set for assessing an effective treatment. As previously mentioned (section 2.2), in his review of antidepressants the accommodation between the illness and intervention is shifted so that the burden of change falls to

the patient. His recommendation was therefore that pharma companies focus on personalized medicine, primarily through genomic studies. Lakoff interprets personalized medicine in a narrow fashion, one that includes only drugs aimed at a specific subgroup of patients or individual person. However, in the pharmaceutical word, personalized often denotes tailoring treatment regimens to patients' illness phenotype and lifestyle – accommodations that are indeed observed in current treatments of hemophilia patients, whether these treatments are given by caretakers according to the prescribed usage of the drug product (per-label), or treatments that are tailored to a patient's illness and lifestyle outside of the prescribed usage of the product (off-label). GT is also considered personalized medicine to the extent that medically it is applicable only to a subset of hemophilia patients who meet predefined physical requirements (don't have inhibitors, don't have pre-existing liver problems, etc.), but also financially personalized towards patients who have access to healthcare insurance and are living in developed countries which have facilities and infrastructure to treat with GT products (technicians, specialized freezers, laminar flows and so forth). Further, GT as a treatment complicates biopolitics and accommodation/adaptation of the drug-patient-disease space even more, as it blurs the line between treatment and cure, illness, and health.

The combination of Lemke's biopolitical analytics framework and Lakoff's conceptualization of biopolitics offers an empirical approach to assess the network of actions that come together in order to identify a treatment and normalize this in society through governance. Lakoff's biopolitics sheds light on the guiding processes in pharmaceuticals, whereas Lemke's biopolitics helps uncover questions of power and neglect. While this description is generalized for any treatment, the novelty here is the review of biopolitics in the purview of GT, which independently already entangles in it questions of nature-culture divide (DNA insertion), emerging and novel technology (genetic engineering), economic questions of financial viability, and more. Overlaying these questions of GT with matters related to rare disease, policies surrounding treatment availability, situatedness and strong patient associations creates a rich system of interactions to explore.

5.2 Bioeconomy of gene therapy

Bioeconomy can be defined as the political economy of life science through markets and social expectations, with an emphasis on shifts and trends in modern capitalism, such as "*asset*-based economic processes (e.g., property, rent, etc.)" that "contrast markedly with *commodity*-based processes (e.g., production, labor, etc.)" (Birch & Tyfield, 2013, p.301, emphasis in original). Translated into hemophilia treatment, pharma companies view GT both as an asset and as a commodity: GT offers fancy modern manufacturing facilities, accumulation of scientific knowledge and subject matter experts (leadership and reputation in the scientific community), potential to change treatment paradigms (leadership in the commercial sector), and a visible commitment to patient communities,

which translates into trust (influential in patient and practitioner choice of treatment). Hence, although hemophilia GT is not a common treatment, and most hemophilia GT treatment products are only assets with future value, the value of GT as an operation is well beyond just selling the product.

The assumption that part of GT's value as an asset is derived from scientific knowledge, aligns with Rabeharisoa & Callon (2004) in their assessment of the co-production of knowledge on a given disease by both patients and scientists. Callon & Rabeharisoa (2008) revisited this topic some years later and conclude that *emergent groups* such as patient associations become stakeholders in the development of economic markets. Following this line of thinking, although pharma may produce GT, and regulators may provide GT marketing approvals, the relevance of GT as a treatment option converges with its value to the end consumer (hemophilia patient).

Finally, Lentacker (2016) wrote of an ensuing concern, where "populations in wealthier parts of the world are consuming drugs from which they might not benefit, even as less privileged populations are denied access to much-needed treatments" (2016, p.141). By introducing the idea of the *symbolic economy of drugs*, he shared his understanding that drug products are assets with separate and concurrent meaning and value, which exist through the brand, patents, clinical trial design, and the drug itself. Together, these features form a system and "are not predefined and unchanging; they are determined instead by their relations with one another in variable local or historical contexts" (ibid, p.154). In this case, beyond GT's status as an asset, it also has its own unique symbolic value.

While biopolitics offers an analytical tool and framework to investigate the interactions and networks that underlay processes in drug regulation and disease definition, the concept of bioeconomy as it is proposed here supports a different question altogether, namely why GT technologies are developed to begin with. Though not directly addressed in this research, this question adds depth and context and provides a foundational layer to understanding GT and its role in disease management.

6 Materials and Methods

Documents are the bedrock of this thesis, and more specifically, FDA generated guidances, press releases and other FDA records. At first glance, these documents seem boring, or technical. They are concise and formal and leave little room for imagination. In truth, getting a document to appear short and simple can be a arduous and complex process, and having laconic and sometimes vague sentences serves a purpose in itself. The method of document analysis looks beyond and within the documents themselves, to piece together the history and lifecycle of these documents, deconstruct the simplified axioms within it, and reconstruct the story from behind the text.

At its core, document analysis draws from document ethnography, or as Lindsey Prior (2007) describes it, documents are "situated products and as such can take on many forms" (p.345). Prior discussed approaches to assess "how documents are produced, how they are used, and how they are exchanged and circulated in various kinds of settings" to demonstrate "manipulation of documents in action." (p.346). While it was not possible to (ethnographically) view how documents were physically negotiated and created at the regulatory office or reviewed by pharma companies, it was possible to thread together what influenced their development as such.

Further on the matter of document analysis, and related to understanding the relationship between policies and their governed objects, Asdal (2015b) in her review of Norway's attempt to create a codfish market, conducted a brilliant methodological practice of following the codfish, not in nature, but in governance documents, in order to uncover how a market is artificially created de novo, and what shifts and changes are imposed on the codfish to enable this market. Asdal uses a two-pronged approach in her review: she traces what happens to the codfish in the document, and she traces what happens to the documents themselves and how they are mobilized. Thus, the documents are not only texts, but become materiality objects in themselves. Similarly, the notion of following the GT itself, not in the lab and not in the clinical trial setting, but in the policy papers could be resourceful here and converge with notions of bioeconomy, governance, and power. Effectively speaking this turns the documentation (mainly policies) into the actual research site – as opposed to labs, the GT manufacturing facility, pharma headquarters, regulatory offices, patient homes or clinics. The policies shape and frame the reality of treatment expectation from GT, by describing development objectives and treatment acceptance criteria.

In the sections below, document analysis as a methodology is broken down, the documents chosen are presented, and the acts involved in document analysis are described in detail.

6.1 Approaching data collection

This thesis looks at the *construction of gene therapy as a relevant treatment modality*. Exciting gene therapy advances are seen all over the globe (for a review see Reiss et al., 2020). The development of GT products is governed differently by each and every regulatory authority, be it a Ministry of Health or a Medicines Agency. Nevertheless, this thesis is regionally and conceptually limited to US FDA policies and does not engage in comparative analysis between different countries. The FDA has a long history of marketing approvals for hemophilia treatments, and a long-standing relationship with major hemophilia advocacy groups.

Choosing to limit the research to the FDA has several advantages to it. First, the FDA is one of the most prominent regulating bodies of medical products, so much so that some smaller countries with less expertise and funding often rely on (and adopt) FDA-issued marketing authorizations, making FDA approvals a tool impacting populations well beyond the United States, thus awarding a biopolitical effect beyond the boundaries of the US. Second, the FDA provides access to both draft and final documents, as well as all public comments submitted to draft guidance. This transparency allows for reconstruction of at least part of the process leading to the final guidance. The FDA also has publicly accessible historical documents relating specifically to GT from the years 1998, 2000, and 2006. Third, the FDA guidance documents relating to GT are relatively recent and up to date with the currently available technology. Fourth, the FDA documents are not only technology specific (gene therapy), but also disease specific to hemophilia, making them more focused and relevant to this case study. Fifth, the FDA documents are all in English, and reduce language-introduced barriers. Finally, the FDA released in July 2018 a package of multiple draft guidance documents aimed to deal specifically with various aspects and types of GT (coined in multiple FDA press releases as the *gene therapy framework,* see also Appendix 1). This was a very focused effort, which raised an even more profound question of what the FDA tried to accomplish around GT with these documents. This importance of the releasing multiple GT guidances as a framework will be investigated in depth in the analysis section.

The full and final list of documents analyzed is available in Appendix 2. Of importance is the fact that all documents analyzed within this thesis were digitally accessed through the FDA's own website. The appendix also lists the internal number assigned to each document and used throughout the analysis. All documents quoted that are part of the document analysis set are referred to by their internal number, as appears in the Appendix 2. For example, the internal number *N1* represents the FDA news release from August 2017 entitled "FDA approval brings first gene therapy to the United States". Often, citations from documents are used without page numbers as many of the documents are not paginated, also the draft and final version of the hemophilia guidance produce the same text on

different pages. Where needed, sections are used as in place of pages to clarify the context of the citation.

At the heart of documents analyzed is the *Human Gene Therapy for Hemophilia; Guidance for Industry*, draft and final versions, in addition to the public comments that were submitted to the FDA following the release of the draft version. Supportive documents include: the FDA notices that the guidances are publicly available; FDA press releases that accompanied the development and release of the guidance; documents associated with the FDA's own procedure for developing a guidance document; two guidances released in the GT guidance framework that were developed concurrently with the hemophilia GT guidance and are relevant to the hemophilia GT guidance itself; FDA generated documents that capture discussions in FDA-initiated events with hemophilia patients, clinicians and caretakers regarding treatment. A total of three events were identified: a workshop, a listening session, and a meeting.

While press releases require a lot of searching and navigating through the FDA's own webpages, the guidance related documents are neatly accessible as dockets that bundle together the FDA notices, draft and final versions of the guidance, as well as all public comments received to the draft version. The FDA-assigned docket number for the hemophilia GT guidance is FDA-2018-D-2238. This docket also includes any reference mentioned in the guidance (for example, if the guidance cites a publication, this publication was uploaded into the docket as a reference). While these references were accessed and read for context purposes, they were treated as background documents, and not subjected to analysis.

As for the documents composing the analysis roster, though analyzed in similar fashion, a distinction should be awarded between them, and especially between FDA guidances and press release, comments to FDA guidance, and FDA reports. Each type of document speaks from a different point of view and towards a different audience. Table 2 offers a rough classification of the documents used in this thesis.

Type of document	Point of View (Originator)	Intended Audience	Type of Content	Internal Number (Appendix 2)
FDA guidance and guidance notice	FDA	Specific stakeholders, i.e., sponsors developing drug product	Formal recommendations and information	O1-O2 H1-H2 H5 H16 H19
FDA press release and statements	FDA	American public	Public announcements, alignment with the US governmental strategy	N1-N8
FDA webpages, factsheets, general reports	FDA	American public	Information on disease or FDA processes	G1-G3 P1
FDA patient reports	FDA and participants	American public	Meeting summary and minutes	P2-P7
Comments to draft guidance	Various (e.g., industry, advocacy)	FDA primarily, but also to the public	Feedback to draft policy	H3-H4, H6-H15, H17-H18

Table 2. Classification of document sample pool analyzed throughout this thesis.

6.2 Data conversions and overlays

For the purpose of analysis, asides from closely reading the documents, engaging with and coding them (as is explained later), some documents underwent additional processing after they were downloaded from the FDA. For this purpose, the draft guidance, final guidance, and comments to the guidance were overlaid one on top of each other. The steps taken for this process are described below

1. Downloaded draft version and final versions of the guidance, and publicly accessible comments.
2. Converted PDF of draft and final guidance into word document and compared the two as a black-line version.
3. Manual quality control to verify that the conversion and comparison did not corrupt the content. The text was well preserved, but footnote numbering was occasionally unreliable, and required manual correction.
4. Information relating to content which was discussed by commentors was copied as a comment into the documents, into its respective section, and assessed if this information was accepted or not by the FDA.

The result was a hybrid document. Figure 3 is a screenshot of the overlay:

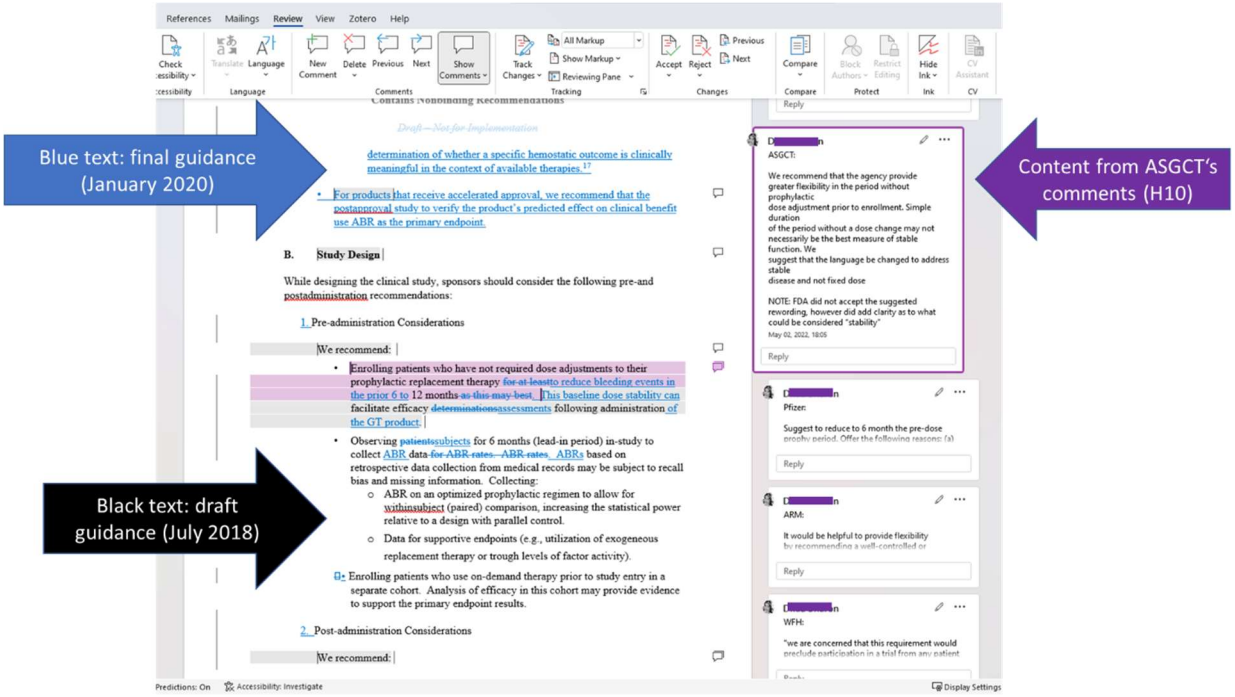

Figure 3. Screenshot of overlay of draft guidance, final guidance, and comments. This screenshot shows a blackline document created by comparing the draft guidance and the final guidance, with blue text denoting the final version, and black text denoting the draft text. On top of this document, information from the commentors was added as comments (typically directly quoted), as well as a "quick and dirty" assessment of how the FDA reacted to the comment within the text.

This role of the hybrid document was to infer which comments the FDA accepted by looking at the changes between the draft and final text. The FDA does not offer replies to commentors.

Regarding the identity of the commentors to the draft guidance, this topic is discussed in detail in the analysis section. Of importance to the methodology is that the commentors are all interested parties, that represent various publics, be they pharmaceutical companies, or patient advocacy groups, consultancy groups, or professional organizations. What this amounts to, is direct access to the thoughts and point of view of the public, and an understanding of who could be impacted by this guidance.

6.3 Learning how to read - Document analysis as a methodology

Having clarified what documents and data was actually collected, the document analysis itself is detailed next.

In their educational book entitled "Doing Document Analysis", Kristen Asdal & Hilde Reinertsen (2022) offer a practical approach to analyzing and learning from documents. Their methodology assumes that "Practice oriented document analysis entails to study documents as forms of material and textual practice" (p.36). They approach documents through six concepts. These are roughly divided to the materiality of the document (format, archiving, circulation, etc.) and textuality of the document

(content, language, etc.). All six concepts were employed throughout the analysis conducted for this thesis - some briefly, others intensively. Following is a summary of these six concepts and their application.

Documents sites- What does site-specific mean for documents? All documents in this thesis were accessed digitally. Allocation of a document within the infrastructure of a website plays a role in that document's own accessibility and distribution. It also helps identify gaps in the process of document generation. For example, draft guidance and final guidance are both visible and accessible, but the revision process between the two versions is invisible. Timing of uploading to a site also impacts the role that documents play. For example, FDA received comments to the draft guidance, and uploaded these in bulk to their website. Had the comments been uploaded as they came in, and not in bulk, would that have made a difference to subsequent actors commenting, who may have been inspired by earlier comments? Here, the FDA's website serves as an archive, or repository, and fosters sharing of information retrospectively.

Document tools- Bureaucracy should not be reduced to document content. The process of making a document involves power structures, financial issues, institutional hierarchies and so forth. Major questions related to this concept have to do with public comments sent to the draft version: who was invited to comment, how many comments were received, who's comments were accepted or ignored; was consensus achieved; what was the overall process from creating a draft to releasing a final guidance; what recommendations does the document carry in its final version and can these be contested at all.

Document work - Documents describe and establish objects. Overall, guidance documents function as a regulatory tool, and in this case the hemophilia gene therapy guidance describes what is needed to meet the minimal requirements for being granted a marketing approval by the FDA. "What is being written down - and what is not? What remains unwritten rules, unspoken expectations, implicit understandings, unexplained routines and untold stories" (Asdal & Reinertsen, 2022, p.78). Through their content, the draft and final guidance documents establish GT as an object and are performative in that sense.

Document texts – Signs that we can interpret. Texts are derived from words, structure, style. They narrate a story and analyzing this story should also consider the history and rhetoric associated with the text. Moreover, a text can have multiple meanings and uses in different situations. Facets addressed here are identification of author (FDA) and audience, the type of language used to include/exclude audiences (e.g., technical language), active voice and passive voice to install a sense

of authority and responsibility, visual layout according to FDA template, and methodological referencing across multiple guidance documents to create credibility.

Document issues – Putting things into context; relationship between documents and issues. The obvious assumption is that documents provide closure. The opposite is also true – documents form issues. In other words, the same guidance document that establishes gene therapy as a treatment modality (closure to the question: Should gene therapy be a treatment modality?), also shapes the development of gene therapy products (generating of a new issue: What kind of treatment can be accepted as a gene therapy?). Document issues thereby connects the material object to the document itself. In some ways document issues is the heart of the thesis, the empirical question behind the research question "*How does the FDA hemophilia gene therapy guidance construct gene therapy as a relevant treatment modality?"*

Document movements - Translation and procedures. Procedures also impact the document and the issues. How the documents travel from inception to completion and circulation is meaningful both to the document (e.g., template, timelines, access, addition of issues), and to the issue or object itself. Documents rely on document chains, such as predecessors, but also subsequent and lateral documents. The final hemophilia guidance therapy guidance was preceded by a draft document and released to the public as a final document within a framework of gene therapy related guidances. Such procedures, of exposing drafts for commenting turn the document into a negotiation site and a democratic tool for engagement with the public. Temporalities associated with these procedures also affect the document and the objects being governed, such as the triggers to publish a draft or release a final version. Lastly, guidance documents are prone to a maintenance lifecycle where versions are superseded with newer revisions, hence attesting to the potential temporary nature of the content.

To summarize the approach suggested by Asdal & Reinertsen (2022) and applied herein, the FDA guidance to hemophilia gene therapy was dissected both in its material and its textual context. This was achieved by looking beyond the scope of the guidance, to the activities and documents proceeding the finalization of the guidance, and at the actual content that was published. On this matter, it is notable that hemophilia GT products were in development well before the draft guidance documents intended to govern their development were published, meaning that the hemophilia guidance governs development of products retrospectively. Unpacking this characteristic of the guidance may foster clarity into how technology pulls regulation to its favor. In this sense, chronology and temporality play a key role in assessing how documents are manipulated, and conversely how documents shape what is a governable object and attach value to that very object.

6.4 Iterative coding as a process for uncovering themes

Imbedded within the document analysis are also matters of assessing the content. Initial coding began with guidance documents. Following Carol Rivas (2018, p.431), coding themes were identified deductively based on the research question. However, codes were adapted and refined as data was being analyzed, thus requiring iterations of coding, to realign findings, adjust themes and standardize coding process through experience and repetition. This process helped uncover issues of relevance (for example the lack of consensus on the definition of gene therapy). The same codes identified for guidances were used as a departing point for the rest of the documents listed in Appendix 2. Coding was done through the MAXQDA software, version 2022.

A key item to be clarified is the handling of FDA generated meeting summaries from patient events that include quotes from patients and caregivers. These documents are a combination of transcripts and quotes and are of a very different nature altogether than guidances or other press releases. Nevertheless, they offer critical insight into understanding how hemophilia and gene therapy are constructed by the patients themselves. The same codes used for guidance documents were applied for patient specific quotes; the codes were wide enough to be inclusive of both kinds of texts, but specific enough to the theme to extract significance and meaning.

The final list of codes appears below.

GT attributes - how is GT defined, how does this definition evolve in regulation.

Policy Setup - why (and why now) the guidance was released, what does the guidance aim to clarify.

Normalization - what aspects are being normalized through the guidance. This includes processes that were informally conducted and are now formally legitimized, and new aspects that are becoming recognized as acceptable or necessary.

Negotiation - what is challenged. Includes texts where commenters to the guidance contest the guidance, or areas where the FDA openly welcomes further discussion. Rarely was this code found alone, typically it was connected to diverging ideas on what the intended treatment should do, what type of drug development and data collection should be presented to the FDA for marketing approval, etc.

Stakeholders - who is invested in GT, and in what capacity. Incorporates the different actors, how they see themselves, how the FDA sees them, and how they view each other and each other's role. Within this code, "patient" was a subcode to highlight when documents refer directly to patients.

Treatment conceptualization - how is hemophilia treatment envisioned to work. This includes both GT and any other treatment- existing, future, or idealized. While this code was established early in the coding process, and stands on its own, for clarity two subcodes were later created and associated with it:

- *treatment risk* - what risks (health or otherwise) are associated with any hemophilia treatment
- *current treatment* - how current treatment is seen by actors (its attributes)

Promissory futures - what is the potential future benefit of GT.

Disease definition - the constructed understanding of hemophilia. Examples include disease manifestation, clinical pathophysiology, and impact to quality of life.

6.5 Limitation of the method

It is worthwhile to contemplate on who and what was neglected in this approach.

Documents forgotten. While all efforts were made to access and obtain the FDA newsroom press release and statements that were relevant for gene therapy, there were some documents that did not meet the requirements for the sample pool for this research. A couple of press releases dealt strictly with non-hemophilia products. Others dealt with a mix of gene therapy, gene editing, and cell therapy, or cell therapy alone. For logistical reasons of time and resource constraints, these press releases were excluded from the final sample pool, as they offered little relevant information (or none at all), most of which was generic or repeated elsewhere. Also, despite the best of efforts, it may be that some press releases were missed within the FDA archive. The final sample pool can be considered as representative, but not exhaustive.

Guidances forgotten. There are historical pre-existing guidances that describe development of special treatments such as gene therapy under a wider understanding of biologics, mostly related to manufacturing or to safety. However, these are outdated, inaccurate, non-compatible with current knowledge of how GT functions, and are not specific to hemophilia. The FDA itself refers to the GT guidance framework as the first dedicated and comprehensive tools to govern GT.

Neglected economics. Along with the earlier discussion on document selection, this analysis is generally blind to the historical context of how commercially driven biotech and pharmaceutical companies began to develop GT as a potential treatment product altogether. Specifically, what drove development of GT in a treatment-crowded market of hemophilia, what does it mean to invest in a healthcare market for rare disease and the wider context of healthcare costs in the general population.

Neglected actors. (i) Documents issued by companies were not part of the intended document sample pool. These could potentially expose the underlying reasons for developing GT and how GT

development is tweaked or adapted according to pressures created through negotiation with regulators, and patients or healthcare funds. Though some information is available in company websites, gaining access to internal documentation is unlikely. While some of the developer's decisions on development could be gleaned out of the guidances and manufacturing regulations, the overall question of *why* commercial actors choose to develop GT is not the main focus here, rather the construction of GT as a treatment. (ii) Downstream to the process of normalizing GT is an understanding of treatment access, and what role payers have in this. Payers are collectively the parties that finance medical treatments, meaning the insurance companies and public healthcare funds. Payers also shape policies, and specifically influence the ability of a product to enter the market. In this research, reduction or marginalization of the payer's role enables a stronger focus on the governmental process. (iii) Finally, in parallel to the development guidances of the FDA, there are also other guidelines and regulatory bodies that shape the development of GT products. A company developing a GT intended for marketing across several regions would need to find a common path to tread between the various requirements. EMA and FDA, for example, are not always aligned on their requirements. Within the US, the American National Institute of Health (NIH) imposes its own guidelines on sponsors choosing to develop GT products with an NIH grant, or to conduct a GT trial in an NIH setting. The point of this thesis is not to compare the impact of various constraints to drug development, but rather to focus on how one dominant and visible regulatory body defines and constructs treatment.

Ethical questions. It is in gene therapy's nature to flirt with ethical questions. For the most part, societies and cultures see gene therapy as a technology that treats illness (hence gene *therapy,* with a positive connotation), and distinguish it from the same technology being used to conduct genetic enhancement, that result in "better" humans or unfairly fit humans (which is often viewed negatively as abuse of the technology and is forbidden in some countries). The ethical aspects associated with (the cultural view of) gene therapy are not the main topic of this thesis, and it is taken at face value that societal matter of culture and ethics contribute to the foregrounding of gene therapy as embodying positive treatment potential. A very different matter altogether is ethical questions about the development of gene therapy through preclinical trials that subject animals to testing, and how the manufacturing process manipulates viruses, which are questionably living organisms. These interesting and important philosophical and ethical questions remain entirely external and separate to this thesis.

Choice of regulatory body. As discussed in detail above, the FDA is one of many regulatory authorities governing development of drug products. Limiting the research to this single body grounds the thesis outcomes in the American politics and context. Though learnings can be applied (or recommended to)

other medicines agencies, they must be taken with a grain of salt as they will never be fully compatible with the cultural behavior of that region or country.

Generalization of treatments. Importantly, the choice of documents does not limit itself to a single hemophilia GT. There are several companies that have ongoing clinical studies for hemophilia with different GT products, and this research does not distinguish between them, just as it does not distinguish between GT for Hemophilia A or Hemophilia B.

Downstream effect and power struggle. By looking at the comments to the guidance, it is also possible to draw somewhat rudimentary conclusion on power struggles (who's comments were accepted and written into the final guidance), but this research does not follow those power struggles to their downstream effect, meaning that it may be that one drug developer benefits from the guidance, whilst the same guidance would work to the detriment of another drug developer. Such situations may lead to differentiated chances of success and market dominance. Similarly, though comments from the hemophilia community (e.g., patient associations, physician societies) at large are reviewed, there isn't a downstream follow up to how the guidance implementation impacts these actors. Finally, all commentors are given an equal voice. For example, BioMarin's comments are treated with the same fervor as are Granzer Regulatory Consulting, though the former is a large biotech that submitted a marketing application for the first hemophilia GT, and the latter is a private consultancy company. This "flattening" of hierarchy hides what may be historical rapport and ongoing communication between commentors and the FDA, but the tradeoff is an ability to acknowledge all commentors, and not only those that the FDA finds it easiest to relate to.

From a research perspective. This research gives voice to a limited set of actors, through predefined documents that were intended for a host of reasons, none of them being this research. There is no voice for the scientists who developed the technology, nor do the documents give much attention to the ensuing competition for "first to market". Those who did not submit public comments are invisible, be they individual people affected by the treatment, groups or organization. For example, patients and their caretakers are lumped into one through advocacy groups, specialized Hemophilia treating centers and physicians are generally ignored altogether (though some may contribute to associations that did comment), ethical review boards within the US, where clinical trials with products would need to be approved, are not heard, and so forth. Thus, though the research aims to provide a well-rounded understanding of concepts such as illness and treatment, it derives this understanding from a partial perspective that, though it is illustrative of a multitude of opinions, it is nonetheless not exhaustive.

7 Analysis

In line with the descriptions in the previous section, intensive document analysis was conducted. The analysis unpacks how a regulatory body of an affluent country approaches governing a novel treatment, in the face of effective existing treatment alternatives, and inconclusive scientific and technological knowledge.

At its worst, the practice of document analysis deconstructs texts that are otherwise rather straightforward, into a menagerie of words and formats. At its best, document analysis gradually recreates a story, much like a detective piecing together clues until a mystery finally resolves.

All stories must begin somewhere, and so does document analysis. The starting point of this analysis is the FDA's report on Good Guidance Practices (GGP) from 2011 (document *G3*), which talks about improving how guidance documents should be developed, issued, and used. Perhaps this isn't the obvious place to begin, hence a clarification may be necessary here. Two strands of analysis complement each-other throughout this thesis: substance level questions and process level questions. One strand follows how is gene therapy ultimately presented in the guidance (substance). The other strand looks at how the guidance gets drafted, finalized, and used (process). To appreciate how treatment is constructed through policies, it is required to understand both the technicalities of creating a formal regulatory guidance and deciding on the actual content within that guidance.

Therefore, the analysis starts with the historical activities leading to drafting the guidance: the FDA's own transparency activities during the Obama presidential era which drove the FDA's report on GGP, followed by the increase in gene therapy trials in the Trump presidential era which drove drafting the gene therapy guidance framework. The analysis then collects the reasons given for creating the hemophilia gene therapy guidance, who the guidance was intended for, how the guidance was used to both solicit input, make a standpoint, and retain regulatory wiggle room for the future. While all these are process-related questions, the second half of the analysis looks at substance, namely what issues are governed by the guidance, how is gene therapy defined and shaped within the guidance, and how the FDA foresees successful treatment with gene therapy.

One final note for ease of reading: each of the analysis subsections that follow relied on quotes from the documents. It is futile to cite in-text all the quotes that support the analysis, as they are plentiful and repetitive. Therefore, quotes used in this analysis, alongside an additional subset of examples supporting the claims, are offered in Appendix 5.

7.1 A small detour - crash course on drug development

Before diving further into the analysis, a brief explanation of drug development in the US is necessary.

Drug developers are those that seek to develop a drug, sponsors are responsible to run clinical trials, and applicants are those that submit a request to market a drug product. For gene therapies, these are often the same entity (i.e., the biotech or pharma company).

The FDA regulates drug products by setting the minimal data requirements to accept a marketing application for review, and by actually approving or rejecting the application, based on the data submitted.

Figure 4 explains the standard development process in a simplified manner. The steps are sequential, though occasional overlap may occur. At first a compound (e.g., naturally occurring molecule or synthetic product) is identified as having potential therapeutic benefit and undergoes testing in a lab setting. This is called the non-clinical phase. Most of this is handled in petri dishes and vials. Once certain aspects have been cleared and demonstrated, the compound is tested on animals, in what is known as the pre-clinical phase. Within this timeframe, drug developers will meet with regulators to align on drug development and request to conduct testing in humans. As animal-testing concludes, the compound, now a drug product, is tested on a small group of healthy volunteers, in the clinical phase, meaning human testing, colloquially known as a clinical study or clinical trial. Human testing is divided in clinical phases, each phase increasingly involving more humans, the first, phase I, being healthy volunteers, phase II being proof of concept, phase III demonstrating efficacy and safety, and phase IV being long term safety surveillance in real world setting. During phase III, one study is designated as the pivotal study, the outcome of this study is a report used as the main data set for a marketing application, alongside data collected during manufacturing, and data from the non-clinical and preclinical phases[18]. The FDA's marketing application request for biologics (such as gene therapy) is called BLA (Biologics License Application) and it intends to show that a product is safe, pure, and potent. The FDA's date at the end of the review period is referred to as the PDUFA date of that product. Approval timelines vary, on average between 8-10 months (FDA, 2016), and in some cases the FDA may request additional information and pause the review period. Once FDA grants marketing approval, the company can commercialize the product. In some cases, the FDA may reject the application and request a resubmission with more (or different) data. In this case the product is not authorized for commercialization.

Rare diseases often have shortcuts to the standard development process since (i) there are very few patients available to test the product, and (ii) there is typically a need to accelerate approval to an underserved population. For many rare disease products, hemophilia products among them, the

[18] The RCT-rule mentioned in section 2.4 refers to the pivotal study and another phase II or phase III study, with the pivotal study being the more clinically important of the two.

healthy volunteer phase is skipped[19] or combined with phase II, phase II and phase III are merged, and marketing approval can be granted after product exposure to as few as 150 patients globally. Pediatric exposure is allowed only after adult exposure is proven as safe, and thus the approval to market for children comes much later than for adults. Most importantly, applicants usually do not have enough data to support a full approval at the time of BLA, and thus the FDA's approval is contingent on additional studies to be carried out. Applicants usually negotiate early in development with the FDA the minimal requirements for BLA, and what contingencies will be requested. This translates to the product still being clinically tested during BLA review and after PDUFA is granted.

Gene therapy poses a new paradigm in drug development. The product can be given to as few as several dozen patients, and the original minimal safety requirements (separate from long term surveillance) can last a couple of years before a marketing application is accepted for review by the FDA. On the other hand, patients dosed before approval continue to be in surveillance for years after the approval has been granted.

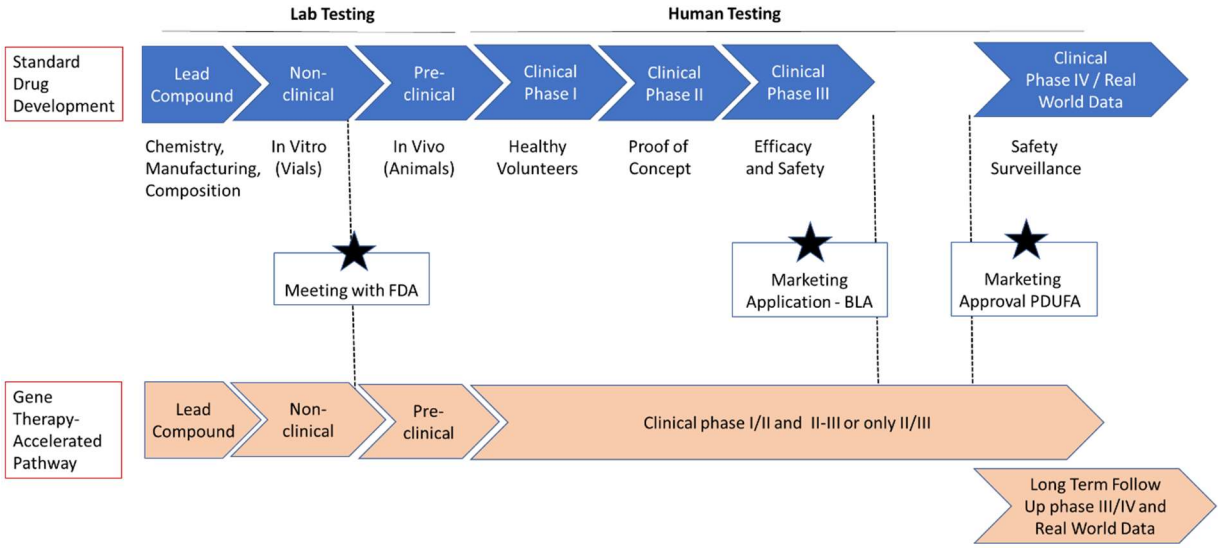

Figure 4. Drug development pathway, simplified. In blue- the standard linear process; In orange – the gene therapy pathway. Some rare diseases will have a similar development pathway. Illustrative only; timelines are not to scale, and non-comparable.

7.2 Setting the stage - why govern GT at all

In order to answer *how* does the FDA construct gene therapy as a treatment, it makes sense to start by asking *why* does the FDA construct gene therapy as a treatment. A key facet of this question is the political ambition and agenda associated with it. The timeline in Figure 5 offers a birds-eye view of

[19] Giving healthy persons additional coagulation factor could result in thrombosis, thus hemophilia treatment is never tested on the healthy population. Initial safety is done as a combined phase I/II in hemophilia patients, followed by a pivotal combined phase II/III study that assesses both safety and efficacy.

major activities in the American hemophilia gene therapy space as well as references for the backdrop of political and policy events.

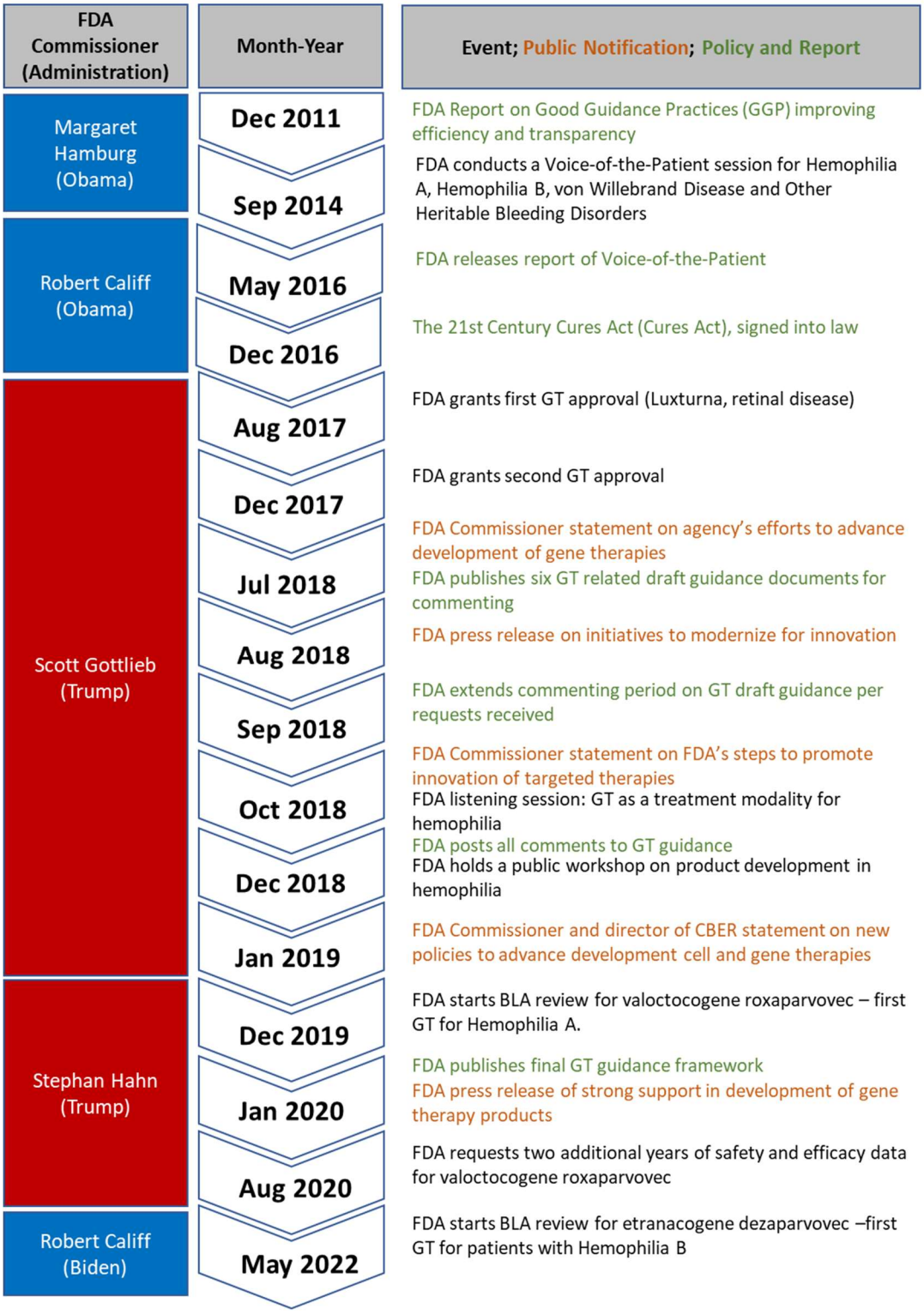

Figure 5. Timeline of key events related to guidance of Hem GT. US administration labeled red for Republican and blue for Democrats. Events labeled black. Guidance labeled green. FDA news/press labeled orange. Timeline is not in linear scale.

The timeline starts with the FDA's GGP report from 2011 (document *G3*). The GGP report itself was part of the Transparency Initiative, launched by the FDA commissioner in response to a memorandum by President Obama on transparency and open government. At that time, the FDA had in place a document which described how to create guidances for more than a decade. The GGP report reviewed the effectiveness of how guidances were created in situ and made recommendations to improve guidance creation in every way possible, be it timelines or public engagement. It is important to explain the role and legal standing of guidance documents: "FDA guidances are documents that explain the agency's interpretation of, or policy on, a regulatory issue" and "Although guidances are not legally binding, they show stakeholders one way to reach their regulatory goal" (fact sheet – *G1*). The GGP report (*G3*) recommends that the FDA "should implement strategies to improve the dialogue with stakeholders regarding the guidance agenda and potential topics for guidance development" (p.7 under Recommendations).

Along those same lines, the FDA also launched in 2012 the Patient-Focused Drug Development initiative (PFDD), to proactively obtain patient perspectives on the diseases and conditions they live with, as well as their approach to treatment. Within this effort, hemophilia patients and caregivers were approached to understand their challenges and worries related to hemophilia in a meeting in 2014 (the meeting report was published in 2016, document *P2*).

Between 2017 and 2020, and within the Trump administration, a flurry of gene therapy events happened. In 2017, the FDA approved for the first time a GT treatment, Luxturna, in the absence of any GT guidance, but at a time when hundreds of GT clinical trials were ongoing. The FDA press release issued with that approval (document *N1*) used language such as "ushering in a new approach" and "committed to helping expedite the development and review of groundbreaking treatments that have the potential to be life-saving." Soon after, the FDA Commissioner Scott Gottlieb released the following statement:

> The culmination of decades of research has resulted in three gene therapy approvals this year for patients with serious and rare diseases. I believe gene therapy will become a mainstay in treating, and maybe curing, many of our most devastating and intractable illnesses…We're at a turning point when it comes to this novel form of therapy and at the FDA, we're focused on establishing the right policy framework to capitalize on this scientific opening. Next year, we'll begin issuing a suite of disease-specific guidance documents on the development of specific gene therapy products to lay out modern and more efficient parameters — including new clinical measures — for the evaluation and review of gene therapy for different high-priority diseases where the platform is being targeted. (press release *N3*)

In July 2018, Dr. Gottlieb released another statement (press release *N4*) explaining that the FDA reached an "inflection point" regarding the technical abilities of GTs, a rather unpretentious admission that there is still much still unknown, coupled with an eye-opening observation that GT challenges do not follow traditional drug review process and will require acceptance of risks, though "When it comes to novel technologies like gene therapy, the FDA is steadfastly committed to a regulatory path that maintains the agency's gold standard for assuring safety and efficacy." The FDA issued concurrently six draft guidance documents to solicit and consider public input in GTs for specific diseases (hemophilia, retinal disorders, and rare diseases in general), manufacturing processes and long term follow up for patients treated with GT (the full list appears in Appendix 1).

Several months later, in Oct 2018 the FDA increased their efforts and dedication to hemophilia-specific GT topic by holding a listening session with hemophilia patients and caregivers on the topic of GT as a treatment modality (document *P3*) and closely followed that with a public workshop for product development in hemophilia, which intended to advance aspects associated with GT products at the patient level (documents *P4-P7*). The workshop was held in Dec 2018.

In January 2020 the FDA issued a press release (*N8*) confirming that all six guidance documents have been finalized. The FDA also opened up about a new guidance being developed to "evaluate differences between gene therapy products when they are intended to treat the same disease" as proof of the surplus of products under development, and the need to differentiate them, not necessarily based on their treatment capabilities, but more on their manufacturing and components[20].

These approvals and guidances were the aftermath of President Obama's 21st Century Cures Act, which intended to accelerate access to new drugs by standardizing and easing requirements from drug companies prior to granting approval. The act focused on the opioid abuse crisis, cancer research, and is mostly known in relation to precision medicine. The act relaxed regulation thus encouraging the commercial sector and was heavily lobbied for by pharmaceutical companies. ("21st Century Cures Act", 2022). It eased the path for breakthrough medical technologies which could be lifesaving, by allowing a quicker approval at the expense of meticulous safety review and enabled drug developers to request approval with the use of data summaries in place of full data sets (Kaplan, 2016). The bill was executed in Obama's last month as president. After the bill was signed in, it was adopted to match President Trump's fiscally conservative republican agenda.

Before delving further into the timeline and the actual policies, it is worthwhile to linger a bit on the role of policy framing and setting an agenda (see also section 2.1). The Obama administration (Democratic) focused on healthcare accessibility through the Affordable Care Act (ACA) as well as the

[20] The guidance on sameness of GT products was finalized in September 2021. See Appendix 1.

Precision Medicine Initiative to understand health and disease[21]. With the switch to the Trump (Republican) administration, two approvals for a gene therapy were granted within a very short timeframe, and multiple companies developing GT were approaching the FDA for guidance on requirements for marketing applications. The bulk of activities in the field of gene therapies were thus held under the Republican administration, who's official targets were to expand healthcare choices for the individual[22], aligned with republican positions of deregulation, a free market and capitalism[23]. As stated by Dr. Scott Gottlieb, FDA commissioner in August 2018 (document *N5*):

> In short, we've had to modernize our overall approach to regulation to effectively advance the kinds of innovations that are becoming available. This includes modernizing how we organize our medical product review programs. These initiatives are part of our comprehensive Medical Innovation Access Plan.
>
> These efforts are strengthened by new authorities and resources made possible by bipartisan legislation like the 21st Century Cures Act, as well as the recent re-authorization of the FDA's user fee agreements. The actions that we're taking have additional support from the President's Fiscal Year 2019 budget.

To summarize this subsection, after decades of research, the biotech industry had matured and gained sufficient experience and data to submit marketing application requests for gene therapy products, the Trump administration was keen on modernizing the drug review processes and opening up options and choices for patients, and patients had already voiced their need for improved treatments through FDA initiated events. The resulting policy framing process for gene therapy is thus a compression of an existing political agenda, availability of reliable expertise, and external pressures.

7.3 Making room - a market full of promises

Within 2017, two sequential GT marketing approvals were granted over a short span, nudging - perhaps downright shoving - the FDA into acknowledging that a market of treatments is de facto being created. This threshold is important because it was preceded by more than two decades of clinical trials that did not mature into marketing approval requests. Ironically, it is the promissory future of treatment that is praised in FDA press releases on GT, but that same promissory future became relevant only once companies transitioned their product from potential treatment (discovery and

[21] See also https://obamawhitehouse.archives.gov/the-record/health-care

[22] See also https://trumpwhitehouse.archives.gov/issues/healthcare/

[23] While it is not the mainstay of this thesis to discuss the Democratic-liberalism and Republican-conservatism agendas, it is worth keeping in mind that the FDA aligns with the white house administration, and the FDA commissioner is appointed by the US President. The work on the guidance documents was done under Trump's Republican agenda; the FDA therefore also positioned the need to govern gene therapy as a "creation of a new market" (as opposed to e.g., a socialist or liberal view of "improving access to healthcare").

development) to actual treatment (marketing). In other words, and as confusing as it may seem, the promissory future of GT became promissory only after it was already established as a reality for at least a couple of diseases. The twin promises praised were (i) potentially treating many rare diseases that have no existing alternative treatment, and (ii) an actual cure to an underlying physiological imbalance (typically a deficit or overproduction of a particular molecular entity).

The main points put forward in statements and press releases from the FDA commissioner at the time, revolve around the reasons to govern GT. In short, with regards to timing, GT should *now* be governed as the FDA had reached a threshold in gene therapy activities, the FDA would like to create a market, develop an innovative field, and "capitalize on this scientific opening" (document *N3*). Furthermore, that market is full of promises for future benefits, cures, and innovation. Some quotes from FDA newsroom that attest to this are (in chronological order):

> "We're at a turning point when it comes to this **novel form of therapy** and at the FDA, we're focused on establishing the right policy framework to capitalize on this scientific opening." (*N3* – on the matter of timing, emphasis added)
>
> "The policy framework we construct for how these products should be developed, reviewed by regulators, and reimbursed, will help set the stage for the continued **advancement of this new market**." (*N4* – on making a market, emphasis added)
>
> "Our new steps are aimed at fostering developments in this **innovative field**" (*N4* – on the nature of gene therapy, emphasis added)
>
> "In the future, we expect this field to continue to expand, with the potential approval of new treatments for many debilitating diseases." (*N4* – on the possibility of future treatment)
>
> "Gene therapy represents one of the most promising opportunities for developing highly effective and even curative treatments for many vexing disorders" (*N4* – on the future curative promise)
>
> "We anticipate that the number of product approvals for cell and gene therapies will grow in the coming years, reflecting significant scientific advancement and the clinical promise of these new innovations." (*N7* – on expectations for a growing market)
>
> "Gene therapy products now have the **potential to cure intractable diseases**, and fundamentally alter the trajectory of many other vexing illnesses." (*N7* – on the curative nature of gene therapies, emphasis added)

Under the Trump administration, the language used in the statements shows that the FDA's role with respect to governing new products is somewhat disconnected to and unconcerned with the welfare of citizens, diagnosis of illness, or access to treatment. Rather it is focused on enabling a market of treatment options or choices. Especially with respect to GT, this market is not disease specific, nor treatment driven, it is technology dependent.

This point, on making a market, is the epicenter of the thesis, and shoulders most of the analysis. It will be shown later that FDA decisions will consistently favor pressing forward with creating a market of treatments than with restraining risky products. Of importance, the market is intended for a novel technology with a potential to cure, making it a legitimate target for treatment. Legitimization is critical in the sense that it justifies moving forward with *this* kind of market. The fact that two GT products were already approved also affirmed the legitimacy of the treatment.

The FDA regarded the six GT guidance documents interchangeably as a "suite of documents" (e.g., press release *N8*) or a "policy framework" (e.g., press release *N3* and statement *N4*). The connecting theme among these documents was their relation to the technology, and not to a particular disease. The power of the guidance documents is in their relatedness. While each of the six guidances is a stand-alone document, their cross referencing and combination delineates the entire pathway to understanding how to develop a gene therapy product. For example, the Human Gene Therapy for Hemophilia (*H19*) refers to the guidance on Long Term Follow-Up after Administration of Human Gene Therapy Products (*O1*), and so does the guidance on Human Gene Therapy for Rare Disease (*O2*). Together, the combined documents are "representative efforts to help advance product development in field of gene therapy" (press release *N8*) and should be viewed in conjunction to benefit from their full effect. They constitute the recommended principles that oversee the access of products into this newly established market of treatments and cures. In other words, by releasing this policy framework the FDA signaled and acknowledged the erection of a gene therapy market. Of note, the guidance framework does not stray to areas that are outside the development remit. In other words, the guidance documents translate the FDA's intent to create a GT market, but do not postulate whether GT products make sense in the wider context of available treatments, nor do the documents handle issues of access or equity within that market.

From a biopolitical perspective this amounts to the FDA seeing its role as an enabler of new treatment modalities, by legitimizing the GT as a treatment worthy of being marketed. This market is non-specific, and can be diverse and far reaching, as can be determined in document the Gene Therapy for Rare Disease Guidance:

> "nearly 7,000 rare diseases affect more than 25 million Americans. Approximately 80% of rare diseases are caused by a single-gene defect, and about half of all rare diseases affect children. Since most rare diseases have no approved therapies, there is a significant unmet need for effective treatments, and many rare diseases are serious or life-threatening conditions" (*O2*, p.2).

As a matter of fact, the FDA opens the door to GT as a desired approach to treating otherwise untreatable diseases. In other words, while GT exists in its own right, the phenomenon of GT as a legitimate therapy, as a market, as a governable object is framed within the guidances that regulate its development. A by-product is that once these guidances are finalized, they enact a reality in which they effectively demarcate what is legitimate gene therapy from what is not.

The commercial failure of Glybera (see section 3.3) was well known to the FDA at the time the framework was released, as the FDA negotiated in 2015 with the company sponsoring the Glybera clinical trials (UniQure) regarding the minimal data required to grant marketing approval, and consequently the sponsor decided not to pursue an FDA marketing approval seeing as the FDA requirements were too laborious (Taylor, 2015). By the time the FDA released the draft versions of the gene therapy guidance framework, Glybera had been withdrawn from the European market. And so, the FDA may have consciously invested in creating a framework that supports a market of treatments that have a high chance to fail commercially. It is one question whether market failures happen because products do not meet the consumer's (physicians and patients, in this case) expectation, and another question altogether if the market fails because of pricing and access – but neither of these are within the remit of the FDA guidance framework, nor do they function as a showstopper for putting out the guidance framework altogether.

This idea of creating a market resonates with the concepts of bioeconomy, and the symbolic economy of drugs (Lentacker, 2016) as was discussed in section 5.2. The FDA assigned a certain type of meaning and value to GT, a financial meaning associated with a market, and concurrently distinguished from the curative or therapeutic potential. By the same token, the FDA legitimized the development of GT by placing it within a tangible and well demarcated reality: a market of treatments, with defined diseases, and explicit product development pathways. This enablement of a market is a political decision, and the success – or failure – of products (or whole markets) is an economic one.

The issuing of documents as a policy framework also serves its purpose to set the stage for increased resources within the FDA, and proper and formal crowning of GT as a field in its own right, with multiple guidances that carve it out of the pre-existing biologics marketing pathway. By issuing six documents at once as a designated framework, the FDA clarifies its support in this field, and the expectation that

GT treatments would only increase in volume- hence anticipated market growth. It also valorizes GT, similar to antibody development:

> "The activity reflects a turning point in the development of these technologies and their application to human health. It's similar to the period marking an acceleration in the development of antibody drugs in the late 1990s, and the mainstreaming of monoclonal antibodies as the backbone of modern treatment regimens." (statement *N7*)

One question that remains unanswered is whether the FDA is opening a market, or whether the FDA is "christening" a de-facto existing market. There are three answers to this question. The first is that the FDA could have reacted to gene therapy marketing requests by continuing to review the data on a case-by-case basis, as they did with the first few products using available guidances on development of biologics that were not specific for GT. This would signal that the gene therapy products are absorbed into existing markets of treatment, be they disease specific, general rare-disease family of treatments, or even into the wide market of biologic treatments. It also implies that the FDA would distance itself from collectively viewing these products as having similarity or shared properties and would not see this as a market in its own right to be regulated. The fact that the FDA chose to create a set of guidances that deals distinctly with GT signals that GT in itself is a governable object, with features that differentiate it from other types of treatments. The second answer derives from a theoretical case in where the FDA would have set a moratorium on gene therapies as a whole, by rejecting any and all future marketing requests, and revoking the ones already granted. But closing down all gene therapies as a class also means that the FDA acknowledges gene therapy is an entity in its own, and thus constitutes a market that should be governed (or in case of a moratorium, a therapeutic modality and market that should be shut down). Finally, the third answer relies on the FDA's investment in this market. Before the guidances were issued, the sponsors-developers of GT products had anyway developed the technology and applied for marketing approvals. The forces compelling developers to continue working on GT products were external to the FDA, be they scientific curiosity, academic leadership, accountability towards patient populations, commercial competition, and so forth. At the time of generating the guidances, none of the companies were requested by the FDA to work on such products, and the FDA did not offer specific awards or encouragement to develop gene therapy. This changed in 2021, when "The National Institutes of Health, U.S. Food and Drug Administration, 10 pharmaceutical companies and five non-profit organizations have partnered to accelerate development of gene therapies for the 30 million Americans who suffer from a rare disease" (NIH, 2021). The FDA's role in this partnership is both funding of early research and to "streamline regulatory requirements and processes for the FDA approval of safe and effective gene therapies". The head of FDA's Center for Biologics Evaluation and Research (CBER, the body that reviews

BLAs/marketing applications) was quoted saying: “FDA is committed to developing a regulatory paradigm that can advance gene therapies to meet the needs of patients with rare diseases.” (NIH, 2021). In other words, FDA indeed sees GT as a treatment modality in its own right, worthy of investment, independent from a specific disease, and independent from other biologic treatments.

To summarize, this section demonstrates two interlinked findings: the FDA thinks that gene therapy is a new, innovative, and potentially curative treatment modality, and the FDA actively chose to create a new market of treatments and expects it to expand. The FDA employed these notions to govern development and marketing of gene therapy products. The combination of the press releases and the decision to publish a GT guidance framework actively legitimizes GT as a treatment modality. Moreover, enacting a market as an official entity with regulation and reasoning is a substantial step in legitimizing the relevance of an emerging technology.

7.4 Identifying stakeholders - who is (not) invited to the process

Having legitimized GT as a treatment modality through press releases and creating a market for it, the FDA identifies the audience for the guidances, and also the experts that could help shape it.

The GT policy framework consists of six individual documents, all of them identified as “Guidance for Industry”. As important distinction is being made here. Though the FDA states in all press releases and statement that it “protects the public health”, the guidance establishes the “industry” as the partner of choice for that action.

Moreover, the FDA specifically states in its notices (documents *H1* and *H16*) that the guidance is developed for “stakeholders developing human gene therapy (GT) products” or “stakeholders developing GT products for the treatment of hemophilia”. In some cases, they are listed as “innovators” (press release *N2*). Rarely are patients listed as interested parties, and in other cases they are well hidden between “product innovators, sponsors, researchers, patients, and other stakeholders” (press release *N8*). The FDA is busy describing to product developers the requirements for entering a new market. The patients, or public, have become innocent bystanders in this equation.

This is exacerbated when looking at the actual draft and final guidance documents for hemophilia gene therapy (*H2* and *H19* respectively). Where the draft opens with the statement: “This guidance is intended to assist ***stakeholders*** developing human gene therapy (GT) products for the treatment of hemophilia” (*H2*, emphasis added), the final guidance opens with “This guidance provides recommendations to ***sponsors*** developing human gene therapy (GT) products for the treatment of hemophilia including…” (*H19*, emphasis added).

Despite the fact that the FDA intends the guidance to be of use for "industry", those commenting on the draft come from a variety of backgrounds. A list of commentors is available in Appendix 3. In total 12 comments were received: 11 comments from 11 different parties, and one comment combined the feedback from two separate entities. Indeed, the industry was well represented with pharma and biotech companies, as well as industry-related advocacy groups, but so were patients with multiple advocacy groups as well as researchers and clinicians through their professional organizations. The commentors have different motives, but all share an interest in either hemophilia or gene therapy or both. This point is important because it establishes that stakeholders in these guidance documents are a much more heterogenic group than simply drug developers or industry (the intended audience for the guidance), that the reach of this guidance is beyond the community of sponsors, and therefore the terms used, and messages conveyed, trickle towards a wider audience.

A worthy mention are the odd cases of World Federation of Hemophilia (WHF), National Hemophilia Foundation (NHF) and Hemophilia Federation of America (HFA). These are three separate non-profit patient advocacy groups, the first being global, and the latter two being focused locally on the US population. NHF and HFA chose to submit their comment together as a single document (document *H17*). WFH also submitted its comments (document *H18*). The two documents are extremely similar in format and in language, and in some sections even identical in content and style - it is clear that the three patient advocacy groups decided to align among themselves before submitting their comments. During the document collection phase of this thesis, it became apparent that these comments were not entered into the Human Gene Therapy for Hemophilia docket (numbered FDA-2018-D-2238) but were misplaced into another docket altogether (Observing Subjects for Delayed Adverse Events Following Administration of Human Gene Therapy Products, docket FDA-2018-D-2173 – the guidance itself is document number *O1*). To be crystal clear, the comments made by WHF, NHF, and HFA specifically and exclusively address the Human Gene Therapy for Hemophilia guidance. It is not known why these comments were placed in the wrong docket, though perhaps this was an honest mistake, as comments were being processed simultaneously for six different draft guidances that made up the policy framework for gene therapy. In reviewing docket FDA-2018-D-2173, additional comments were identified as misplaced, or unnecessarily duplicated. Therefore, although the FDA seeks to demonstrate transparency, and although part of the role of the draft guidance document is to enable discussion, the infrastructure itself creates questions on how effective the communication really is, and the public is left with a major concern: did the FDA consider the patient advocacy group's comments during the review process? Either way, the result may be discerning: at best, these comments were taken into consideration by the FDA and thereafter misplaced in the wrong docket, at worst, these comments were overlooked all together by the FDA precisely because they were misplaced in the wrong docket.

A cautiously optimistic hint that the FDA did consider the patients' comments appears in the shape of one bullet point in the final guidance: "Plans to address inclusion of clinically relevant populations with regard to age, gender, race, and ethnicity should be discussed with the Agency." (*H19*- FDA final guidance p.11 in section VI.C on study population).

The only commentors who directly commented on the composition of patients were the NHF and HFA (document *H17*), where they requested that "Trial design for gene therapy should take efforts to reflect the diversity of the American and global patient populations", and went on to describe racial, socio-economic status and other factors that contribute to that diversity. Hence it is possible that some of the patient-representing comments were not entirely lost.

Notwithstanding, as part of the document analysis phase of this thesis, an email was sent to the FDA on July 07th, 2022 to request the re-allocation of these comments to the right docket, and as no reply was granted, a follow up letter was sent by airmail on July 15th, 2022. As of September 20th, 2022, a reply has not been received.

7.4.1 Patients as stakeholders

Glaringly absent in the guidance documents is any reference to treatment concepts raised by patients in 2014 (*P2*, workshop report released in 2016) and 2018 (*P3*- listening session and *P7*-workshop on hemophilia product development). Both the listening session and the workshop were held after the draft guidance was released and before the final guidance was published, well within the commenting period to the guidance, but in neither meeting were the caretakers, physicians, or patients in the audience asked to provide feedback on aspects of the guidance. In fact, according to the workshop transcript (*P7*), there was only one minor side reference made to the draft guidance ("Maybe there is evidence, and that's actually the question that is represented here, and we described that in our guidance for gene therapy and hemophilia." p. 245).

Neither the guidance documents, nor the notices that informed of them, make any attempt to integrate patients into the process of developing or governing a product. This is in direct opposition to the drug developer's use of the buzz word "patient-centric" (e.g., BioMarin's comments *H11*, under sub header "Importance of Patient Focused Development"), and the FDA's own PFDD (Patient-Focused Drug Development) who's primary goal is "to better incorporate the patient's voice in drug development and evaluation" (document *P1*). From a biopolitics perspective, though it is patient bodies that are being manipulated, though the patients are enabled to provide feedback to the draft guidance, though the developers pride themselves on collaborative patient-centric drug development, the reality is that the patient perspectives are excluded from the existing governing tool.

One may challenge this notion and ask if it would be an effective method to include patients into a technical document. The question should be flipped on its head and asked whether a technical document is sufficient to meet the patient's current needs. Specifically for hemophilia, plenty of alternative products exist, and offer a decent quality of life, even if not ideal. Introducing into the hemophilia GT guidance documents a few minimal barriers that echo the main issues raised by patients would result in products that are likelier to meet the patient's expectations, and thereafter achieve success (however that should be measured). For example, patients refer to disease progression in the form of pain and joint damage as clear issues of existing treatment:

> "Participants with hemophilia spoke about their ongoing struggle with pain and joint deterioration, and the accompanying diseases of aging such as arthritis and gout, which exacerbate their conditions." (PFDD report - *P2,* p.5)

This theme was raised over and over (additional examples provided in *P2*: micro bleeding, joint damage, limited mobility, pain of neuropathy, functional impairment). It is not clear if GT can reduce future joint damage, or if it can reduce pain. Therefore, patients favored correlating the treatment with the symptoms, and not necessarily with factor level activity or bleed rates. They focused on quality of life: "We need better products, and not just different versions of the same treatments" (*P2*, p.16). It is difficult to postulate how the addition of patient outcomes related to quality of life and long term sequala as study endpoints would impact GT development and speed. Some of these outcomes require very long observations to generate statistically meaningful data. Nevertheless, it can be assumed that it is likelier that GT would then be viewed as a more advantageous product by both payers and caretakers. Discussion surrounding disease progression and pain, or quality of life, is not directly regarded in the draft (*H2*) or final guidance (*H19*), with the exception of section VI. F. Patient Experience:

> "Patient experience data may provide important additional information about the clinical benefit of a GT product. FDA encourages sponsors to collect patient experience data during product development, and to submit such data in a BLA".

Sponsors are encouraged to collect such data, and patients indeed fill in designated questionnaires and use patient diaries to account for symptoms, but without incorporating analysis of this data against the treatment itself, and without requiring this data as mandatory for evaluation of treatment success, the added benefit of GT in quality of life is not analyzed and may never be fully established. Asides from this recommendation to collect patient data, the FDA, though soliciting and collecting feedback from patients, chooses to exclude that very feedback from the guidance document, signaling that from the FDA's perspective aspects of a GT that benefits the quality of life of patients might not be part and

parcel of achieving treatment success, and are not limiting factors to entering the newly established treatment market.

The patients are at the receiving end of mutually exclusive messages. The first is that their opinion is sought out by the FDA through meetings and listening sessions. The second is that their opinion as stakeholders and end-consumers is not explicitly relevant for the product development process. The third is that their definitions of what constitutes health and illness (joint disease) differ from those used by the FDA to assess the development of the GT products (factor level and bleedings). Reassessing these messages with the help of Biopolitics offers a gloomy outlook. Biopolitics can be used to untangle the relations and power struggles that ultimately define health, illness, treatment, and cure within the context of gene therapy development, and in that space, patients are rendered almost as an invisible force, sidelined from the main frame. This is not unsimilar to other drug product being developed but is significantly more concerning because unlike other rare disease populations, hemophilia patients already have access to alternative efficacious treatment and have garnered expertise and experience with what works well. Moreover, the physical manipulation induced by gene therapy is at the cellular level- this is not treatment that can be stopped, slowed down, nor turned on or off at will. Adherence or commitment to this treatment is a one-time event with potentially life-long effect.

Removing patients' objectives from the spotlight raises the question: who exactly is being served in this market, and to what end?

7.5 Engaging with a process - documents as barriers, documents as facilitators

Documents have an objective and stated function which is overlaid with their accessibility, materiality, format, and role within a given process. Looking at the materiality of the documents released by the FDA, the following functions are attributed to the documents, above and beyond their content.

7.5.1 Publicizing and detailing a standpoint

Right out of the gate, the documents derive immense power from the authority (institution) issuing them, despite the fact that they are not explicitly legally binding. The guidance documents intend to make transparent the FDA's current standpoint. Guidance documents are formal documents and follow a strict structure that communicates the FDAs standpoint. This structure, or template, has fixed sections such as an introduction, background, and references. These guidances are also released to the public alongside a notice in the federal register which itself has predefined structure and naming conventions. By virtue of the structure, the hemophilia gene therapy guidance presents itself as if it were a legal document, and this perception is further exacerbated by the choice of words, which is adapted for the target audience, clearly described as "sponsors developing human gene therapy (GT)

products for the treatment of hemophilia" (final guidance- *H19*). The end result is format and language that assumes professional expertise and is quite exclusionary for lay people.

Though the document formally represents the FDA's thinking on GT ("This guidance also includes recommendations regarding preclinical considerations to support development of GT products for the treatment of hemophilia", *H19*), in truth it spells out the elements expected by the FDA to be available for review in a GT marketing application, and in between the lines it may be presumed what the FDA thinks about GT or hemophilia or hemophilia treatment. In this regard, the hemophilia GT guidance behaves more as a technical document, and not as a medical protocol or healthcare related advice.

The mere existence of an FDA hemophilia gene therapy guidance that details the requirements for marketing application attests to the regulatory authority's formal embracing of gene therapy. If the preceding press releases legitimized pursuing gene therapy, then the guidance document de-facto normalizes gene therapy, by reducing gene therapy development into items that can be regulated and validated.

7.5.2 Soliciting input

Policies are arguably intended for regulating development, so to some extent it is appropriate to invite patients to give feedback, and address only developers in the final guidance. To that end, asides from the guidance's role to advertise the FDA's standpoint, the guidance document is also part of an infrastructure that brings to life the FDA's intention of communicating with the public ("inviting the public to comments", GGP fact sheet - *G1*). The draft version becomes a baseline expressing the FDA's own objectives, and the comments received to it are meant to help the FDA tweak the content accordingly. The FDA thus solicits feedback from stakeholders, a wide term which hides in it also patients and caretakers. Having incorporated (or ignored) the feedback received from stakeholders, the FDA no longer addresses actors who are not directly involved in developing GT or hemophilia treatment and proceeds to create a guidance fit for sponsors running clinical studies. Of note, the process of soliciting input through draft guidances is not designed specifically for GT, rather it is described in the documents on Good Guidance Practice (GGP docs *G1*-*G3*) as the acceptable process.

The process begins with the FDA uploading the draft guidance and a public notice to the FDA's public website as part of a unique docket. The FDA encourages public engagement with the FDA's "current thinking" and contribution to it through commenting. There are no limitations as to who is allowed to comment or make suggestions to the document. Comments, unless explicitly requested by the commentor, are also made publicly visible. The FDA avoids providing a reply to the comments received (as a matter of process). Subsequently comments that are received by mail or electronically within the commenting period are awarded individual ID numbers and are also uploaded into the same docket.

For the GT draft policy, almost all comments were uploaded on the same day (December 8th, 2018) in bulk. Hence, the draft to final process serves as a communication tool but not for an open, two-way discussion. The process of communicating enabled by the guidance document limits the communication to very rudimentary negotiation and disables a parley between parties. The FDA issued the guidance in July 2018 and offered a 90-day review period (as was written in the notice that accompanied the release of the draft, document *H1*). Following two separate requests (by two advocacy groups Bio and ARM - documents *H3* and *H4* respectively), the commenting period was extended by another 60 days (a formal notice was entered into the FDA register, document *H5*). Nearly all comments were received within the span of a few days (as per the dates on the comments), and near the end of the commenting period (December 2018), and the FDA uploaded the documents in bulk. In this kind of communication pathway, each and every commentor offered feedback blindly and independently to the FDA, gaining access to other actor's comments only after the end of the commenting period. In addition, as the FDA does not reply to any comments received, justification to the final FDA wording is not available, or to the reasons comments were accepted or not. In this case the communication are a one-time event, single direction, and non-reciprocal. This is a very important aspect of the guidance document: while it offers in its draft form the FDA's starting point for normalizing gene therapy, and in the end the FDA's decision on what constitutes a good-enough gene therapy, the in-between is left unknown. In actuality, though the FDA actively assesses external input, there is no bargaining process and the final level of influence on the FDA can't truly be established, because there is no visibility to the discussions held within the FDA after the comments were received.

This type of communication is indicative of the power relations associated with regulatory bodies. The FDA can choose to be receptive and inclusionary by accepting comments and reacting to them, or it can exercise its power and hierarchy to push forward an agenda in spite of the comments that were received.

7.5.3 Offering flexibility

Using guidances to govern a GT market has advantages; though guidances set baseline expectations how to develop products (and meet the entry criteria to the new GT market), they are - unlike rules and acts - flexible in their language, and open to discussion. This flexibility cements into it an important idea, which is the agreement to negotiate the aspects being governed, after-the-fact. What is meant here, is that the FDA is fully aware that GT for hemophilia is far from being a well-understood phenomenon. With this in mind, and with the advances in technology preceding the actual guidelines, the FDA allows itself room for change and growth as the technology and understanding of it improves over time. The potential for change can be quite fundamental, as is seen in two explicit situations stated by the FDA in the final hemophilia gene therapy guidance *H19*:

> "**We may consider revising these recommendations** following the development of reliable evidence on correlates between factor activity and clinical benefit, when such evidence can be generalized to multiple GT products." (p.6 on the FDA's approach to recommending an efficacy endpoint, emphasis added)
>
> "Please be aware that, as additional relevant scientific data becomes available, **FDA may revise its recommendations** for duration of follow-up for adverse events." (p.12, on a safety follow-up period, emphasis added)

Importantly, the concept of flexibility is extended also towards the audience of the guidance. The guidance document header states "contains nonbinding recommendations" (*H19*) and the guidance also defines flexible language ("The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required." - *H19*, p1, emphasis in original). It formally invites product developers to negotiate approaches to gene therapy:

> "It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page." (*H19*-p.1, opening statement)

Within the text itself, and in relation to explicit sections, the FDA exercises this notion of flexibility to allow negotiations surrounding expectations of individual products development:

> "FDA recommends communication with OTAT early in product development, before submission of an investigational new drug application (IND)." (*H19*[24]- p.13, in section VIII. Communicating with the FDA)

In its essence, the hemophilia GT guidance offers multi layered negotiations. Though there is no bargaining process on the guidance draft, once the final guidance is available, there is room to negotiate at the product level. In this case the FDA protects the newly established GT market thrice-over: once by establishing it through publishing the FDA's current thinking that gene therapy is a field that will grow and holds promise; second by acknowledging that there are unknowns and therefor in the future the market will adapt itself; third, by allowing individual negotiations on a product without jeopardizing or putting to question the whole GT market as such. For orientation purposes, sponsors for products other than GT regularly hold meetings with the FDA before and during the development process. Actually, this is common practice for products such as those with an orphan designation, though it is by no means mandatory. The specialty in the GT guidance is that negotiation is a-priori

[24] OTAT - Office of Tissues and Advanced Therapies, within FDA's Center for Biologics, Evaluation and Research (CBER).

incorporated into the GT drug development pathway, changing the status of negotiation from voluntary, to recommended and to some degree even necessary.

To reiterate this point, the FDA took a controversial technique, with a promissory future, legitimized it through press releases and normalized it through policies. The guidance document turns GT into a relevant treatment option for hemophilia and establishes the criteria for entering a market of similar products. However, there is a clear divide between normalizing the idea of a GT market through a guidance and negotiating criteria of individual products that enter that market. While normalization of the GT market is synonymous with the approval of the guidance, bargaining and negotiations become an ongoing activity of refinement required to bridge the gap between what the guidance demands and what sponsors actually develop. The negotiations can therefore only begin *after* the release of the guidance document. Once the guidance is final though, what is considered normalized through policy is entirely limited to how the FDA sees gene therapy and hemophilia treatment. In this sense we can imagine a temporal-divide, where external influence and feedback is welcomed before the guidance is set and disregarded after the guidance is final. The collaborative effort for normalizing the GT and hemophilia treatment takes place after GT is legitimized by the FDA, and before the guidance is final.

This temporal divide has significance, as it is also a symbolic divide between stakeholder types. The FDA describes the guidance audience as "product developers" and "sponsors" but invites "stakeholders" to comment on the draft. So long as stakeholders were commenting the process was not mutual, and the FDA was not negotiating – the FDA was "soliciting feedback" on the guidance. Once the guidance is finalized, the FDA expects to negotiate (physically, in meetings) with sponsors about an actual and specific GT product.

The hemophilia community, and specifically the patient and the treating physician, are welcome to provide feedback which may or may not be accepted by the FDA while the market is being established and normalized- they are stakeholders. However, direct contact and negotiations is limited to companies developing products, those who stand to commercialize (market) their product and make revenue. Figure 6 shows is a visual depiction of the process. On the left-hand side, the FDA develops a guidance based on policy framing (see section 7.2), and input solicited from stakeholders (e.g., through interaction such as *H1*-public notice that the draft is available for comments, *P3*-listening session for GT as a treatment modality or *P7*-product development workshop). The FDA conducts an internal review for an undisclosed timeframe and releases the final guidance. In the right-hand side, this guidance is used as a basis for activities concerning a specific GT product itself. Here, the FDA and sponsor meet regularly to review the product development (as is recommended in the guidance). As technology evolves and more knowledge is acquired, the FDA's development requests are likely to adapt (foreseen in the guidance). The available information will be used in the future to revisit the

guidance content and generate a revised guidance (which may, or may not, be available for stakeholder input). Importantly, no one is invited to question *whether* the market should be established, patients may choose to provide feedback how they think the product entering the market should be governed, and companies developing products are invited to negotiate with the FDA the specifics of how they develop a given product.

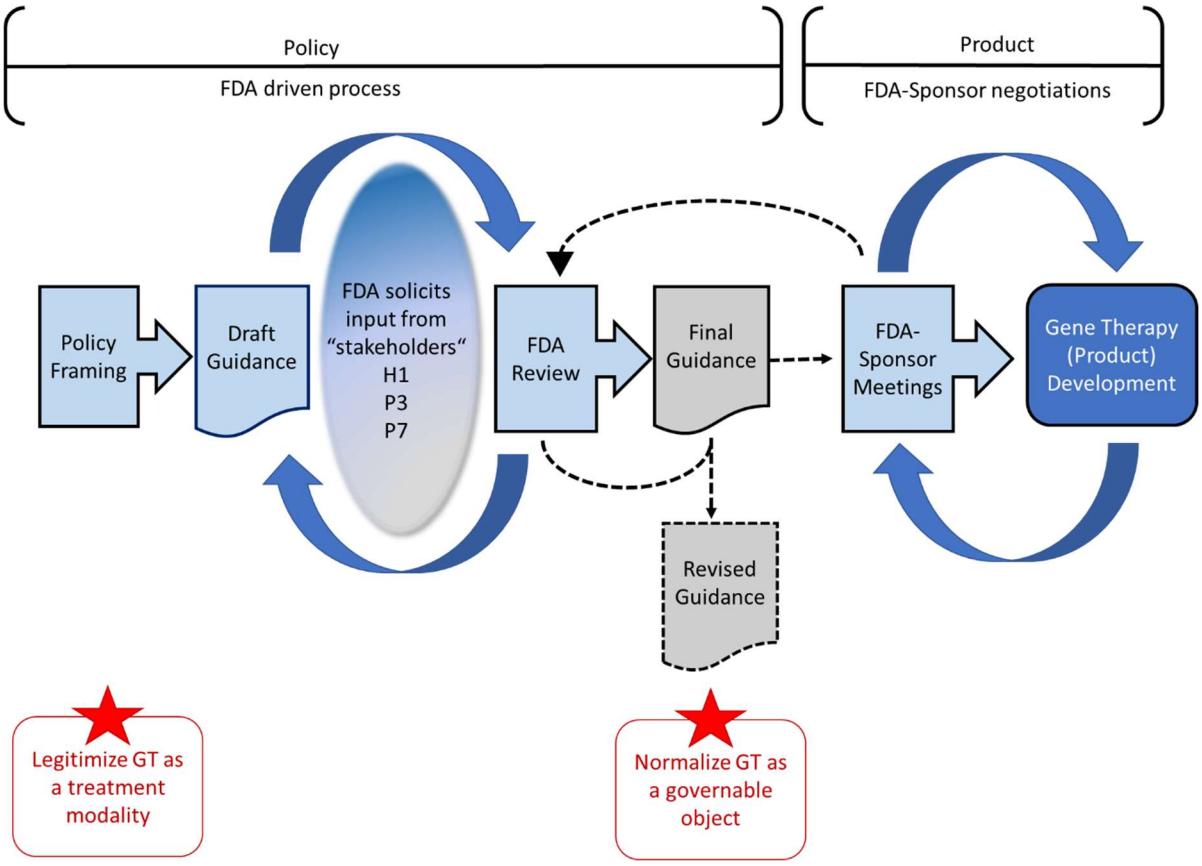

Figure 6. The Policy-Product input process.

To summarize the role of documents, the hemophilia guidance document signals intent and normalize what was previously voiced as legitimate in press releases. The guidance appeals to particular stakeholders, first and foremost to the industry and sponsors, and excludes others through language and style. It explicitly anticipates changes and updates to requirements as the GT field matures and new information becomes available, thereby allowing the FDA flexibility and room for adaptation. By openly embracing negotiation with sponsors on a given product, the FDA tells sponsors that it is ready to adjust their requirements, thereby signaling a favorable and less rigid environment for sponsors. Such a message could, in turn, encourage sponsors to continue developing in GT, and maybe even strengthen the market with more products. In any case, flexibility and adaptations permit the FDA to be committed to the newly established market, without hindering or constraining that very market through regulation. It also hints towards why the guidances are laconic: the final requirements for

products are anyway negotiated on a case-by-case basis. The guidance only needs to provide the starting point for product specific negotiations.

7.6 Drawing boundaries - the issues being governed

Agendas, politics and expertise converged to create policies in the shape of a guidance framework, a market (of promises) has been established, processes were set in motion, and stakeholders identified. What is needed is clarity as to what exactly is being governed within the hemophilia gene therapy guidance.

An axiom of this guidance framework is that by following it, companies that develop gene therapy products will ultimately be able to submit a BLA marketing request (see also section 7.1), and thereafter commercialize the drug product in the US. That is, the policy framework protects the market by defining the minimal requirements for obtaining a license to enter the market. Generally, the guidance documents do not aim to control what happens within the market once products enter it. An exception is the Long Term Follow Up (LTFU) (guidance *O1*, covering long term risk with gene therapies) which is discussed in section 7.6.1, in the context of risk and safety. Nevertheless, in order to enter the market, companies developing GT products adhere to the recommendations set in the guidance framework and commit to collecting LTFU data for many years after the product was granted a license. In other words, the FDA opens a GT market by setting the *minimal standards* to enter it, and what happens within this market will mostly be managed outside of the discretion of the guidance.

These minimal standards are aligned with the FDA's own mission to govern safety and efficacy of treatment, as is evident through their boiler plate language in press releases and formal documents:

> "The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the **safety, effectiveness**, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices." (*N4*, as an example, emphasis added)

The matter of setting *minimal standards* is fundamental to this thesis, in that the products associated with the GT market are not governed by what the end-users want or need (that is, not by what the patients themselves describe as a desired treatment outcome). Product governance is not equity, nor improvement in quality of life. Additional aspects which are not covered are items such as patient satisfaction, treatment access, duration of effectiveness, pricing strategies, product attributes, or alternative treatment options. The guidance also does not intend to resolve existing (general) controversies such as the use of in vitro assessments in place of animal studies during the preclinical phase.

What is left, then, is setting the minimal standards in the following areas, according to the notice in the FDA registry (document *H16*) that accompanied the final hemophilia GT guidance:

> "provides recommendations on the **clinical trial design** and related development of coagulation factor VIII (hemophilia A) and IX (hemophilia B) **activity assays**, including how to address discrepancies in factor VIII and factor IX activity assays. The guidance also includes recommendations regarding **preclinical considerations** to support development of GT products for the treatment of hemophilia" (*H16,* emphasis added)

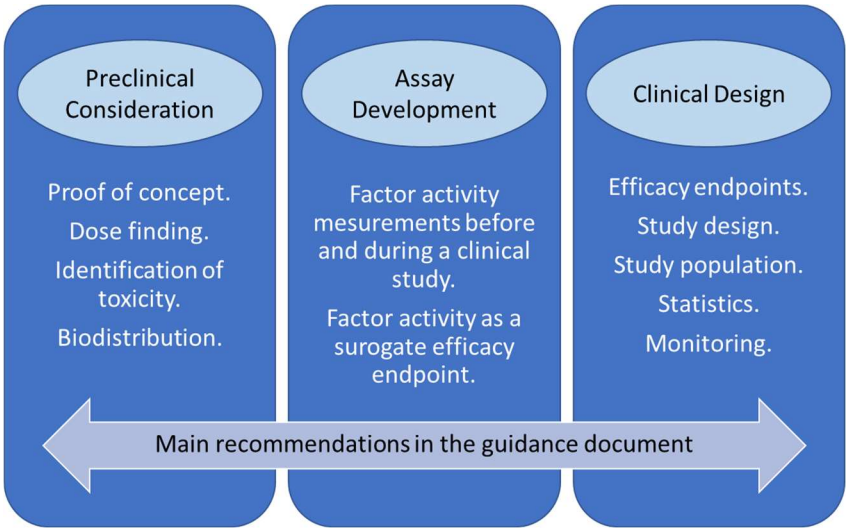

Figure 7. Main elements covered in the guidance document.

Figure 7 summarizes the three elements. Below is an explanation of each element.

Preclinical considerations: lists the types of studies that must be carried out before the product can be administered to humans within the context of a clinical trial. These include proof of concept and toxicology studies that help establish the dose needed and the clearance of the GT vector. Generally, the guidance refers to a separate guidance, issued in 2013, that describes recommendations for preclinical assessments for cell therapy and gene therapies. Ethical questions around the use of model animals are left open, with a very general footnote offering flexibility, and encouraging sponsors to discuss their plan with the FDA (see also section 7.5.3):

> "The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section VIII of this document). We will consider if such an alternative method could be used in place of an animal test method." (final guidance *H19*- footnote 4)

Clinical Trial Design: though the name suggests how to plan a clinical trial, in actuality the guidance covers considerations for trial design, the population which should be enrolled, the efficacy endpoint that success should be measured against, statistical considerations, monitoring objectives, and a recommendation to collect data on patient experience (see section 7.4.1). The statistical hypothesis at the heart of the clinical trial should be a non-inferiority design- in other words, the efficacy of new GT product should not be worse than existing (non-GT) treatment alternatives. A hemophilia GT market is thus a market full of products that have a different mechanism than existing products, but not necessarily better outcome.

Activity assay: An assay is a type of lab testing for biological activity. Successful hemophilia GT should result in the secretion of factor into the blood stream, which could be measured by one of the two existing factor activity assays. There were medical, biological, and technical reasons flagged in comments around the FDA's recommendation on assay development. Section 7.6.3 is dedicated to comments on assays.

Reverting back to the FDA's own objective to develop safe and efficacious products, the overall guidance framework – and especially the hemophilia gene therapy guidance - seems to come up short. The hemophilia gene therapy guidance does not directly discuss safety and efficacy, instead it aims to "provide product developers with meaningful guidance to answer critical questions as they research and design their gene therapy products" (FDA press release - *N8*) and furthermore the FDA would like to make the development and approval process more efficient (but not necessarily the product):

> "We'll continue to work with the product sponsors to help make the development and approval of these innovative gene therapies more efficient, while putting in place the regulatory controls needed to ensure that the resulting therapies are both safe and effective" (*N4*- FDA Commissioner's statement on efforts to advance GT)

This efficacy should be no worse than current treatments ("non-inferior"), nor does it need to measure against GT's promissory future of a cure. Once marketing approval is granted, the products are assumed to have met the minimal requirements of safety and efficacy.

The first issue to arise with this approach is that the FDA must take substantial risks in the approval process if it wants to meet its own goal of advancing this market. In fact, safety cannot be guaranteed as there are unknown future risks associated with introducing foreign DNA into the body. To overcome this matter, the FDA's marketing approval for any GT product is contingent on the sponsor's commitment to develop and adhere to a long term follow up (LTFU) program that monitors the safety

of those who participated in the clinical trial. Putting this into a timeframe: in a theoretical case[25] a clinical study design would enroll and dose 30 patients. A BLA would be submitted based on data collected from two years of follow up of those patients. During the review period, the same patients continue to be intensely followed up, with a commitment to continue infrequent follow up for another 5-10 years. After the commercialization approval is granted, so long as data is being collected and shared with the FDA from the LTFU the commercialization approval stands. The contingency can be as long as 15 years (per LTFU guidance *O1*). In this timeframe, the 30 subjects dosed within the context of a clinical trial are being monitored for safety issues, while new patients are already being dosed commercially.

Interestingly, the duration of monitoring recommended with in the LTFU guidance (document *O1*) is set within a broad range of years, meaning that although the FDA claims its most important objective is safety, this in itself is fluid and negotiable: it's about monitoring risks, more than ascertaining whether or not a GT product is safe.

Put otherwise, GT garnered a right in its own to a market, by virtue of its novelty and promise, and this market accepts a level of risk at the entry point. That being said, the FDA is also acutely aware that this field is still evolving, and what constitutes unknown or acceptable risk at the time of release of the guidance document may be evaluated and scrutinized under more harsh parameters as newer information comes to the fore. Thus, a tradeoff exists between accelerating access to new treatments and claiming safety. Some quotes that support this are:

> "The treatment landscape for hemophilia is evolving. As is the case for other products we review, we intend to evaluate the benefit-risk profile of the investigational product in the context of the treatment landscape at the time of our review of a marketing application." (*H19* p.13 - hemophilia gene therapy final guidance)
>
> "For some of these products, we may need to accept some level of uncertainty around these questions at the time of approval" (*N4* – FDA commissioner's statement)
>
> "In such cases of devastating diseases without available therapies, we've traditionally been willing to accept more uncertainty to facilitate timely access to promising therapies" (*N4* - FDA commissioner's statement, moral justification to accept risk)
>
> "it may not be feasible to conduct pre-market trials that address all these theoretical risks in any reasonably sized study" (*N7* – FDA Commissioner and Director of CBER joint statement, logistical justification to accept risk)

[25] Based on personal experience with setting up GT clinical studies.

The second issue to consider is the one of efficacy. The product should be as good as existing products. This is a confusing item since the FDA clearly sees curative potential for this type of treatment but the barriers that are set forth for marketing are that the products are held to the same standards as existing treatment. Perhaps part of this tension can be explained through the actual ability of GT. If indeed it is a cure, what standard would it be measured against - especially since within the healthy[26] population coagulation factors fluctuate, and so does coagulation ability. On the other hand, while it has been demonstrated in some clinical trials that GT efficacy is of long-lasting nature, more and more evidence show that this so called "curative" treatment is limited in duration, and unpredictable from patient to patient in terms of the ultimate stable level of factor activity. Again, this poses questions of treatment success which are neither commensurate with the GT promise, nor adhere to any standard that can be measured against. Therefore, the minimum that was set for GT is to be measured against existing treatments. The choices for how to measure success are developed further in sections 7.6.6 and 7.6.7.

7.6.1 Carving out safety

Digging a bit deeper into safety leads to a discussion around risks. Safety and risk are not synonymous, in that not every risk will result in a safety issue. For example, waning influence of treatment – reminiscent of reduced efficacy - is a risk, whereas potential bleeding as a result of waning efficacy is a safety issue. The risk of viral shedding (expelling of viral vector to the environment via excreta) could become an environmental safety issue.

Risks foreseen with hemophilia gene therapy include technical issues such as (inappropriate) integration of DNA into the host cell, decreased liver function, antibodies to the viral vector and/or an immune response against the viral vector, inhibitor formation against the secreted factor, and viral shedding. The essence of safety monitoring is early identification of known risks as they emerge, and to identify new unknown risks, for example through adverse reactions associated with the product. In principle, the duration of safety monitoring in a clinical study should be proportionate to the duration that risk prevails. Using this logic, and assuming that gene therapy has a long-lasting effect, the final hemophilia gene therapy guidance differentiates between short term and long term follow up, though both should "monitor the safety and durability of response" (*H19* - section VI.E on study monitoring). "Short term" is a two-year period of following the product, focusing on immediate health risks (e.g., liver problems, inhibitor development) and potential waning influence of the GT. The data collected in this period goes into the final data set served to the FDA for the purpose of marketing approval, but the patient seamlessly continues into a "long term" follow up concurrently and surpassing the BLA review timeframe. Though a few points for hemophilia are specifically written, for the most part the

[26] Healthy here refers to those without hemophilia.

information regarding “long term” is detailed in the separate long term follow up guidance (LTFU document *O1*).

The LTFU specifically intends to monitor patients for risk (not efficacy) after the product is administered for a prolonged period of 5-15 years. Although waning efficacy results in risk by not providing the therapeutic effect that should be, the LTFU looks at risk from a different angle, namely the danger of developing malignancies and immunogenicity reactions, both prominent risk points for AAV vectors commonly used in hemophilia GT. Here, the sustained long-term curative potential of GT is not of interest, but rather any potential long term safety issue resulting from the technology as such.

The matter of risk, as it was presented in the draft guidance, was contested on several fronts by commentors, some questioned the minimal duration of follow up necessary for collecting sufficient data to submit with a marketing application (e.g., Pfizer, who suggested one year in document *H14*), while several questioned how malignancy follow up should be conducted.

The FDA used the listening session (document *P3*) as a place to openly discuss both risk and safety with patients during the review period of the draft guidance. Risk was associated with the patient’s perspective on enrolling into a GT clinical study, within the context of the risk-benefit equation: how much risk would a patient endure to receive sufficient benefit: “While the patient/caregiver perspective varies in openness for enrolling in a gene therapy clinical trial, there was consistent interest in understanding the risks and benefits associated with gene therapy”. Safety was discussed in the context of burden: safety monitoring is a given, the question is how much burden patients would be willing to tolerate within the realm of a clinical trial. Safety monitoring requires patients to both be available to come for clinic visits (implying long travel distances for rural communities) as well as undergoing unpleasant procedures like multiple blood draws over several hours, biopsies, and MRIs. Patients seemed to place less value as to the burden compared to the importance of safety. Without the agreement of patients to participate in clinical trials, data cannot be collected, and a marketing approval cannot be obtained. Setting up minimal requirements that are realistically attainable is mandatory if this new market is to be filled with products. The patients were used to ratify and reify what the FDA was looking for in terms of safety: patients are willing to participate in populating the new market with products and will shoulder the burden associated with participating in complex clinical trials.

The lesson learned is that the risk profile of a hemophilia GT product is the occurrence of adverse events of special interest, such as malignancies and immunological reaction. Bleeding events, captured as ABR, go towards efficacy of the product. The FDA’s position towards both of these is that so long as neither issue occurs in the first two years post administration, the product is declared safe and

effective. How this resonates with GT which should have lifelong effect (or at least, long term effect) is questionable. Once again, the FDA constantly and consistently chooses to prioritize accelerating a new market formation over profound risk averse action, and it normalizes gene therapy as a legitimate treatment based on minimal safety requirements.

An interesting thought experiment is trying to imagine what would come to pass should a product prove to be unsafe, e.g., malignancy causing, after it had received marketing approval. One reaction could be that the FDA revokes the marketing permit or recalls the product. Another could be that the FDA revisits the minimal requirements for future products requesting to enter the market by revising the final guidance. In such a scenario, the element of flexibility comes to the fore, allowing the FDA to adapt its criteria in such a way that raises the bar to enter the GT market without dissolving or deconstructing the GT market as such. It is therefore guaranteed that safety issues with GT in one disease area, or with one type of GT, would not "incriminate" and impact the validity of the entire market. So, while flexibility is retained with respect to criteria for entering the market, the market as such is institutionalized and undisputed, even if one of the products proves unsafe at a later stage.

7.6.2 Targeting the right patient – pediatric population

An area which received much revision, and is conjoined to matters of risk and safety, is the section on patient population, specifically pediatric patients.

The effects of hemophilia are observed as early as in the first year of life. Just like any child, a baby with hemophilia learning to crawl or walk will inevitably bump into furniture, fall down, get his finger caught in a drawer, and a myriad of other bloody events that make up the nightmares of parents.

The process of drug development intends to safeguard children by exposing them to minimal risk. In an ideal world, babies with hemophilia will have access to gene therapy at an early age, well before joint deformation and hemarthropathy develop. That is, a marketed gene therapy product should have permission for treating a pediatric population. To do this, the product must be first tested and approved for use in pediatric populations. The drug development pathway typically integrates the inclusion of pediatric population in the clinical trials with the intent to meet the marketing application requirements for treating this vulnerable population.

Originally, the draft hemophilia guidance (*H2*) had a very lean section on inclusion of pediatric population. Sponsors identified this gap in the guidance and insisted on more comprehensive accords related to pediatrics. The triggers were both consenting (assenting[27]) challenges, considering that

[27] Within the context of clinical studies, *informed consent* is the process by which an adult individual grants permission for participating in a clinical trial. Minors are not legally empowered to make such decisions, and their participation in a clinical

children treated with GT were expected to become adults by the time their long term follow up is complete, as well as when the involvement of pediatrics into clinical trials should begin.

> "We are concerned that this guidance draft does not really engage assent in this special context or provide guidance on re-consent [or consent for the first time] when a child is judged to be capable, or the IRB's role is some form of continuing assessment of when may have matured to the point of being able to give consent." (*H12*- comment by Sangamo)

Parents to children with hemophilia re-iterated this message in the listening session: "If a clinical trial were available for children, the child should be old enough to be involved in the decision and understand the commitment of the trial" (document *P3,* under section Risks and benefits of gene therapy).

The FDA was extremely receptive to this feedback and expanded the section in the final guidance (*H19*) to include more (somewhat generic) information on enrolling practices, and specific guidance as to what is needed for a pediatric study to start. Looking through this information, it is still a very vague set of expectations to be met:

> "To justify enrolling pediatric subjects, you should:
>
> - Submit clinical data from studies in adults to demonstrate sustained and robust steady state factor levels and hemostatic outcomes.
> - Select an appropriate pediatric population that represents a population with an unmet medical need in the context of available therapies.
> - Consider conducting studies in appropriate animal models to support sustained factor expression levels following GT product administration.
> - Consider characterizing the risks of your GT product (e.g., vector integration, insertional mutagenesis) based on available preclinical and clinical data for your product." (*H19*, p.10 section VI.C on study population).

In four sentences, the FDA basically offered guardrails to safeguard pediatric population, but committed to no minimum. It is the responsibility of the sponsor to identify what kind of data is sufficient to establish "sustained and robust steady state factor" (the sponsor dictates the threshold), what concludes an "unmet medical need" (do patients in developing countries have an unmet need? How about patients in a developed country without private healthcare?) What is an appropriate animal model in this case? Most animal models have significantly shorter lives than humans, their maturation

trial hinges on a legal guardian's consent (on the minor's behalf). Minors must independently agree with the situation, at least to the level of their understanding, and this agreement is called *assent*. Assenting in long term studies may need to be repeated as children mature.

duration is incompatible with that of humans. The final bullet point ("characterizing the risk") requires the sponsor to provide further analysis of data from clinical trials (e.g., human adult studies), but no definition is offered as to what are the risks to be characterized, and when these risks should be assessed (after two years? after five years?). Looking carefully, the FDA embraced the need to protect the pediatric population and acknowledged that safeguarding the wellbeing of this vulnerable population should be prioritized. At the same time, the FDA placed this responsibility squarely on the shoulders of the sponsor. It is the sponsor who should suggest what is the acceptable timepoint and the minimal requirements to expose a child to GT. Referring back to the concepts of flexibility, and specifically Figure 6, the FDA is expecting to negotiate with the sponsor at the product level, triggered by whatever the sponsor assumes to be the right starting point for treating children. Vagueness and limited information becomes instrumental in deferring safety.

It becomes evident that while the FDA is busy creating a market, and at the same time proclaiming responsible for safety and efficacy, it does so by offering concepts that need to be adapted on a case-by-case basis by the sponsor. The way that the FDA can control and regulate the market is to effectively force the sponsor to go into negotiations. The boundaries for establishing the minimal safety requirements to include pediatrics are fluid and would be shaped by what the sponsor suggests more than by what the FDA deems to be necessary.

7.6.3 Assays - maintaining the status quo

An area where multiple comments to the draft were received is the factor activity assay development section. Factor activity measures the quantitative amount of factor circulating in the plasma. In some cases, the body produces the missing factor, but in a defective way so that although it circulates in the blood, it is actually dysfunctional. For this reason, any assay developed to assess how a treatment product- whether enzyme replacement therapy (ERT) or gene therapy (GT) - is always specific for the actual product. In a GT, the assay will differentiate between the newly introduced factor (GT product) and any deficient factor that the body might still be producing. In brief, the two types of lab assay methodologies are one stage clotting (OC) and chromogenic substrate (CS). Because the assays are product-specific, each FVIII product must have a specific assay developed, optimized, and validated for use. It is common to have both OC and CS as validated assays to assess FVIII potency in the manufactured lots, as well as actual product circulating/activity in plasma. These two assays differ methodologically and are not interchangeable in the sense that their measurements are not exactly correlated (a little bit like Fahrenheit and Celsius, except there is no formula that can help you convert a result from CS into OC values and vice-versa). A longstanding controversy in the world of hemophilia is which assay is better, as there are discrepancies between the assays, within assays depending on the lab where the assay is administered, and even differences resulting from FVIII origin (i.e., types of

recombinant variants). In the past couple of decades there have been debates amongst the hemophilia community about the value of each assay, and the need to consolidate globally towards one assay, however this controversy has not been resolved. What this means is that the most direct way to measure whether or not the GT actually causes the body to produce the missing factor and secrete it into the blood stream relies on a methodology which is knowingly inconsistent and controversial.

The FDA discusses the need and ways to calibrate and justify whichever assay is to be used by the sponsor developing a GT product. The processes suggested by the FDA include additional animal studies, additional lab studies, and field studies on patient samples as extra efforts to be undertaken that help in justifying the accuracy of assays. Comments received to the draft version questioned the FDA's recommendation to: (a) conduct both animal studies and field studies with patient plasma (b) use both assays in the development process (c) use the assays in preclinical tests (d) use the assays in clinical monitoring of patients.

Ironically, neither clinicians, pharma companies, nor patient advocacy groups find it important to invest time and energy in perfecting these assays with the extra effort that the FDA suggests, and rather assume that fluctuations in assay results can be managed in the context of quality monitoring of patients. Thus, while the FDA insists on establishing precise methodology to have accuracy in FVIII activity numbers before marketing, the commentors to the guidance request to accept variance in methodology to expedite marketing. As the World Federation of Hemophilia (WFH, a patient advocacy group), succinctly stated:

> "Clinicians have had to contend with Factor VIII one-stage/chromogenic assay discrepancies for decades. However, in most clinical practice, the assay discrepancy has not been "resolved" and clinicians have still been able to incorporate these therapies into routine clinical care." (*H18* – under section IV)

From an efficacy perspective, the FDA requested to have accuracy in measuring factor levels. The FDA also expects the product to show non-inferiority to existing products as a sign of being efficacious, but non-inferiority means that GT products should sustain factor levels above 1%[28], which is a very low threshold where most patients will occasionally bleed. These objectives do not resonate with the patients who think that the FDA should instead opt for setting high levels of circulating factor as the efficacy and safety marker - and in these high levels, fluctuations of the assay would anyway be less meaningful.

[28] Severe Hemophilia A is clinically defined both by the manifestation of bleeds and by less than 1% Factor VIII circulating in the blood stream. Thus, above 1% factor means the patient no longer suffers from severe hemophilia, but the patient still has moderate to mild hemophilia. See also Figure 1.

The assay comments demonstrate a distribution of ideas among patients, developers, and regulator. The FDA prefer high measurement precision (to a degree that would require improving existing assays) but accept overall low factor activity that is non-inferior to ERT but could result in occasional bleeding. Patients prefer high factor activity and discount the importance of measurement precision because at high levels of factor protection from bleeds is anyway high thus precision measurement is unimportant. Developers would like to relax the effort of reaching precision in measurement, in part because it has less value clinically and in part because the logistics surrounding the FDA recommendation are questionable, for example, there may be feasibility issues with collecting patient samples for the field testing.

The comments to the assay section, and the fact that the FDA did not fully relax its requirements in the final guidance (compared to the draft), but rather reworded them slightly, shows that although the FDA delegates much responsibility, and power, to the sponsor, the physicians, researchers, and lab experts who deal with the assays on a daily basis have no voice or part to play here. In any case, and similar to other section there is room for the sponsor to later negotiate the per-product assay development.

7.6.4 Shaping the technology - establishing desired GT characteristic

GT is in fact an umbrella for many heterogeneous products that share some commonalities in the technology, and some similarity in mode of action, but overall, it is a mixed bag. The fact that the technology is still being developed is a given. That drives the complexity even higher when trying to describe what exactly is GT. One thing that the guidance framework needed to establish was what kind of products are being governed.

Within the final hemophilia gene therapy guidance, a footnote is used to provide the full definition of what constitutes "gene therapy":

> "Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells. "(*H19*- footnote 1)

This footnote definition was not accepted without comments. Both the pharma company Bayer and the advocacy Alliance for Regenerative Medicine (ARM) questioned whether the definition was

appropriate, as information regarding gene editing is not included in the guidance and the FDA's definition in the draft differs from that in the FDA's own webpage on gene therapy[29]. In defense of the FDA, the webpage is written in lay language, intended for the general public, whereas the guidance is intended for product development experts, thus lingual differences can – and perhaps should- exist between the two, but the questions that remains open is what exactly is being governed here – what is gene therapy? The question is not a semantical one but is derived directly from complex technological methodologies to alter the human genome. Each technology has a different goal, takes place in different bodily organs, and exhibits varied duration of effect. Among the technologies that the FDA included in the draft is gene editing. The most famous method for this kind of correction is by using CRISPR technology. Both gene therapy and gene editing methods use viral vectors to deliver something into the body: gene editing delivers the enzyme that makes a correction of the aberrant DNA sequence at the host's DNA level, and gene therapy delivers a correct genetic sequence itself, external to the host DNA. Would a company developing a gene editing treatment for treating hemophilia be subjected to this guidance as a regulating tool, or not?

At the time of developing the final guidance, a paper was released on gene editing of mice with hemophilia (Chen et al., 2019), and as of Sep 2022 only one such (human) phase III clinical study is ongoing, (Grom, 2022). At the same time, there are dozens of hemophilia gene therapy studies recorded in the clinicaltrials.gov website with gene therapies. Thus, the FDA signals that the market being opened and governed is for both viral vector related treatment modalities, though throughout the guidance the assumption is that gene therapy would be used, and specific gene editing guidance is missing.

Conceptually opening up GT for hemophilia to include gene editing is inconsistent with the FDA's own public stakeholder sessions: (i) In the summary of the listening session on GT as a treatment modality for hemophilia (*P3*) it is not once mentioned or hinted what GT looks like. Rather, the listening session focused on general risks benefits, burden related to participating in a GT clinical trial, and what would be the success criteria for a GT. (ii) In the public workshop on product development in hemophilia (*P7*), gene therapy is referred to, and assumed to be, mediated by a viral vector that delivers external genetic sequence, while gene editing is not mentioned even once. De facto, the FDA is opening up an option for potential treatment wider than what the hemophilia community and developers envision as a relevant treatment, and at the same time acknowledge that "GT products currently in clinical development may use a vector to deliver the coagulation factor gene to the liver" (*H19*-FDA final guidance).

[29] The FDA's webpage on gene therapy: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

Interestingly, the FDA arrived at the understanding that gene editing indeed poses different questions for development and governance, and later released a separate draft guidance on gene editing (see Appendix 1) issued in March 2022. Again, flexibility retained, and the market sustained.

Still, putting aside the question whether or not gene editing is relevant here, understanding what is gene therapy for hemophilia merits a grueling dive into technical terms:

> "It may be important to also recognize that apart from truncating or using hyper active variants, candidate products may also vary in terms of the 'codon optimizing' techniques used which could impact expression." (*H15* – ISTH comments)

> "The question of whether AAV is an integrating or non-integrating vector aside, the fact that this novel therapy involves gene alteration should be justification enough for longer follow-ups." (*H15* – ISTH comments)

> "But there may be some unanticipated effects of codon optimization; altered protein confirmation and stability, altered post-translational modifications, and perhaps even altered protein function in a number of different areas." (*P7* – hemophilia workshop, p. 221, section on replacement therapy vs gene therapy by Dr. Steven Pipe)

> "Specific guidance should be provided as to when existing vector biodistribution data can be used to support clinical trials of vectors that differ only by transgene product" (*H10*- ASGCT comments)

The FDA itself also delves into characteristics of gene therapy in the long term follow up guidance (document *O1*), and gene therapy for rare disease (document *O2*):

> "Are your vector sequences integrated or is the human genome otherwise genetically altered?" (*O1*- p.7, part of a decision tree how to assess delayed risk)

> "However, in some cases there may be unique characteristics of GT products (e.g., a protein that is expressed by a GT product may have different bioactivity than standard enzyme replacement therapy) that warrant additional considerations both pre-approval and post-marketing." (*O2*- p.10 section E. Efficacy Endpoints)

All this is to say that gene therapy is not a single type of product, rather it is an umbrella term that covers underneath it multiple behaviors and different production processes, all aimed to "alter the biological properties of living cells for therapeutic use" (*O2*). Commentors do not dwell on the types of gene therapies per se, but instead point to a vision of what kind of genetic-altering product could offer the benefit of a long-term stable treatment. In other words, GT is multiple products which differ in

structure and anticipated behavior in-vivo, though the outcome of what they will do is expected to be the same.

Just as gene therapy technology is evolving, so is the understanding of what can be called gene therapy for hemophilia. Agreement as to what constitutes gene therapy lies in the lowest common denominator: something that causes genetic modification and results in stable long-term treatment. One can say that gene therapy is defined by its outcome as much as by its impact on genetic material, and not by its innate characteristics, attributes, or mode of action.

One thing that becomes relevant when looking at the other guidances in the framework is that the characteristics of the technology that are laid out are those that have relevance to risk, and much of the long term follow up is linked to the type of product that is being developed. The market allows for this plurality of products to co-exist based on the same entry criteria, and at the same time dictates variable follow up practices related to individual risk levels.

This is especially visible in the ISTH comment above (*H15*) regarding codon optimization, where the comment encompasses differences in product characteristics which may lead to differences in product behavior. ISTH is a non-profit global membership organization of specialists in the field of blood coagulation, and in more ways than one they represent the professional community surrounding hemophilia: sponsors, researchers, and physicians. For ISTH to write this, signals that the hemophilia community has conceptually accepted that GT is not a product, but a class of products which share some similarities, but may have different modes of action and efficiencies. Looking back at policy framing- if the experts agree that an entity of GT exists, and that this entity is a multi-faceted object, then FDA is right in treating this object as a single unit to be governed, and collectively grouping it into one market.

7.6.5 Acceptance criteria - conceptualizing a disease, determining successful treatment

A legitimate treatment would of course need to be efficacious, meaning that improvement in disease status is necessary. One of the reasons that hemophilia is such a popular target for gene therapy is that it is a monogenic disease (only one gene needs to be corrected) and very little change in factor level results in significant improvement in disease status in terms of bleedings (for example in Hemophilia A, a slight increase from no FVIII to some FVIII results in a vastly reduced bleeding pattern).

Initially, the FDA stated that GT products may "provide long-term expression of the *missing or abnormal* coagulation factor *in the patient* at steady levels" (*H2,* draft guidance p.2, section II Background, emphasis added), but following feedback from Bayer (*H9*), the FDA changed the definition to "provide long-term expression of the ~~*missing or abnormal*~~ *deficient* coagulation factor ~~*in the patient at steady levels*~~" (*H19*-final guidance, emphasis added). Ontologically speaking, *abnormal* is a confusing

definition since in the healthy population *normal* amounts anyway vary across a wide range, whereas missing means that absolutely no coagulation takes place. Conversely, *deficient* places the target population of gene therapy to be those who may have severe, mild, or moderate disease, but definitely not within the healthy population range. It is deficiency that is pursued for gene therapy. By refining the language, treatment success is derived and shaped. What remains to be contested is how much expression is sufficient to overcome deficiency, and how long does steady state last. The FDA does not pose thresholds for neither of these, but so long as a sponsor can negotiate the values of deficiency and steady state with the FDA, the product will meet the requirements for marketing application.

7.6.6 Efficacy endpoints - measuring success

Treatment success is measured in clinical trials through a target that is assessed statistically. These targets are called endpoints and can refer to efficacy or safety. Endpoints are measured against the desired outcome. The FDA require that clinical studies meet the designated efficacy and safety endpoints in order to grant marketing approval for a drug product. Historically, studies for prophylaxis with enzyme replacement therapy were expected to meet an ABR efficacy endpoint of less than 2 bleeds per year.

Figure 8 below describes the two potential efficacy endpoints for GT: factor activity level and ABR. Of note, patient quality of life outcomes are left outside of this equation, because they are not the primary role of GT, which is to stop bleeds. Quality of life could serve as a differentiator between optimized prophylaxis and GT and would be useful as a secondary outcome.

Of the two primary outcomes, factor activity measurements is the direct method to quantify that the GT is actually working, and factor is secreted into the blood stream. Factor activity is an indirect measurement of clinical benefit to the patient (in other words, there is an assumed correlation between factor activity level and actual bleeds). The problem with factor activity is that assays to measure factor activity are not very accurate (see also section 7.6.3). The second outcome uses ABR as an endpoint, which is the clinical representation of the disease. The target of hemophilia treatment, GT included, is that patients will not bleed, and this is the most direct way to assess it.

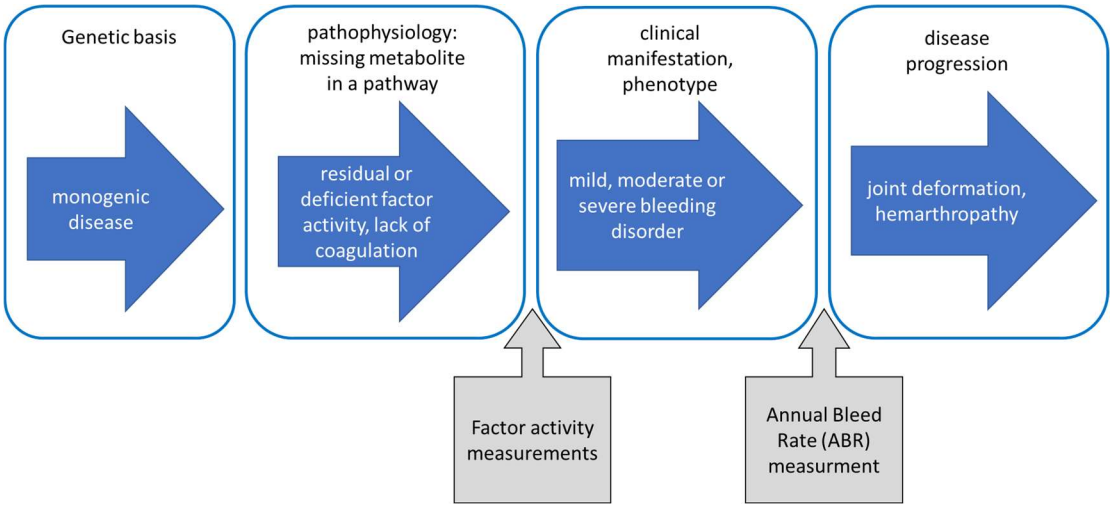

Figure 8. Possible measurements for treatment success. Normally, disease severity is correlated with factor activity. ABR is the most relevant clinical representation of the disease, and indirectly a sign of factor circulating in the plasma.

Especially with respect to gene therapy, using ABR as an endpoint to assess success of treatment harbors complications that should be emphasized here. The difficulty with assessing the bleed is that it is often based on pain, and thus subjective. On the one hand, bleeding, and especially bleeding into joints, is a harmful process that causes joint deformation in the long run, which may further cause pain that is unrelated to bleeding (hemarthropathy). Some patients experience pain well after a bleed is resolved and have a hard time differentiating an unresolved bleeding event from hemarthropathy. On the other hand, there are also microbleeds, and subclinical bleedings, which normally go undetected, but may also result in abnormalities in joint structure. Bleeds can be seen in ultrasounds, but it is not normal practice (nor a practical effort) to conduct an ultrasound for every bleed. Patients treat for bleeds at home as soon as they sense pain associated with bleed onset. Bleeding is therefore a subjective form of pain. Assessing treatment success by bleeds is thus a problematic issue, and not specific to gene therapy; even the FDA acknowledges that "Although ABR is a direct assessment of clinical benefit, ABR has limitations in that it is a relatively infrequent event in patients on prophylactic factor regimens and the decision by a patient to treat a possible bleeding episode is usually somewhat subjective" (*H19, p.7,* section on traditional approval).

Historically, products were approved for marketing if they reduced bleeds, measured as annualized bleed rate (ABR), because:

- factor levels were difficult to assess since they incur a burdensome blood sampling strategy to evaluate the peak-and-trough cycles of treatment.
- with enzyme replacement therapy, the objective was to reduce bleeds, but not to sustain factor level

Gene therapy, though, is not expected to go through a peak and trough cycle, rather it is expected to create a steady state of treatment (see also Figure 2). This steady state is the objective of the treatment, as opposed to the measurements of bleeds. To clarify the point: enzyme replacement therapy went from saving lives during a bleed to minimizing bleeds, and always focused on the most prominent feature of hemophilia which was the bleeds, and treatment of bleeds. GT's narrative is different, as it aspires to be a cure, and thus focused not on the bleed but rather on the molecular cause which is factor activity at steady state. By targeting the factor activity, the bleeds – and also other (secondary) manifestations of the disease, such as joint damage, microbleeds, and hemarthropathy - should be alleviated. Measuring GT's efficacy through ABR, then, makes little sense.

Looking through the FDA guidance, by and large the sections that underwent the greatest number of changes from the draft to the final are the ones that deal with efficacy endpoints, and the statistical considerations for assessing them.

The FDA designated ABR as the efficacy endpoint for approval, mostly because it is clear that measuring factor activity levels relies on assays which are controversial or inaccurate. However, this approach garnered mostly negative feedback from patients and physicians, as was made evident by WFH, HFA and NHF, ISTH:

> "We would strongly advocate against the use of annual / annualized bleeding rate (ABR) as the primary efficacy end-point for the 'traditional' or 'accelerated' approval of a GT product. It should be included only as a secondary endpoint. The primary endpoint in GT should be based on plasma clotting factor levels directly reflecting function of the transferred gene." (*H15*- ISTH comments)
>
> "It is important to appreciate ABR has a major subjective component, lead to both false positive and false negative rates of joint bleeding due to the underlying arthropathy and inflammation. A patient's current joint disease status is largely based on his treatment history and has a large influence on occurrence and reporting of ABR." (*H18* – WFH comment)
>
> "ABR has a subjective component, which would require complicating the study design to handle false positive and false negative rates in the adjudication of joint bleeding. Also, the current joint disease status of a patient is largely based on his treatment history and has a large influence on occurrence and reporting of ABR. Moreover, ABR only captures clinically-recognized bleeding events; it does not capture subclinical bleeds that regularly occur when factor activity level drops below a therapeutic level." (*H17* - HFA and NHF).

Alternatives for using ABR as an endpoint are to focus on activity levels, despite the lack of consistency with factor assays. HFA and NHF (*H17*) list the following reasons: (i) clinical trials built on ABR as an

endpoint might not be powered enough to show a statistical difference between optimized prophylaxis to gene therapy. Measurement of ABR should be retained as legacy secondary outcome to allow comparison with other types of treatment in development (e.g., non-factor therapy, see also Table 1) (ii) patients are at a lower risk of bleeding as factor levels rise. Considering that microbleeds go undetected, a patient with an ABR of zero (no bleeds) might still have underdiagnosed microbleeds, but the likelihood of microbleeds goes down as factor activity levels rise (refer also to Figure 1). Factor levels could help assess the actual success of gene therapy, which is expected to avoid the peak-trough cycle and rest on constant and consistent level of factor activity (see also Figure 2). The plot thickens with this expectation, since achieving a higher factor activity level requires using higher dosing regimens, which could exacerbate negative consequences in liver function, and require more vigorous and focused risk monitoring for patients. A relevant sidenote here, is that the tradeoff between higher dose and more risk is not discussed or assessed in the guidance. (iii) if optimized prophylaxis results in an ABR of less than 3 (meaning less than 3 bleeds per year), it is unclear what kind of ABR would be adequate for GT as a success measure.

As ISTH summarized: “Products which range in creating sustained plasma factor levels of 5-100% or higher may all look the same in terms of ABR while it is quite obvious that their clinical impact is likely to be clearly quite different.” (H15).

In the final guidance, the FDA acknowledged that ABR is less than optimal, but insisted that it will be the primary efficacy measurement until factor activity levels can be suggested as the primary endpoint by sponsors, of course presuming that sponsors can meet the FDA’s extensive requirements for assay development.

The FDA could have chosen to introduce the quality of life of patients as a secondary endpoint, for example by measuring secondary sequela (like joint pain and immobility). This would have supported and strengthened the primary outcome. Unfortunately, a holistic approach towards quality of life is not accounted for in the guidance documents associated with GT. It is also demarcated from the FDA’s formal language and incentives for developing and regulating GT, as those focus on novel treatments (novel, not better) and life-saving cures.

There are advantages to staying with ABR and factor activity assays, the FDA’s chosen endpoints, as they are established and well known. They are standard practice, quantifiable, and comparable. They can be evaluated in high quality and accuracy after as little as 6 months of continued treatment of prophylaxis (where the patient is re-dosed regularly, and each single administration has a short duration of therapeutic benefit). Choosing these endpoints for GT means sponsors can reach the end of the clinical study much quicker than if they have to follow the patients for the duration that the GT

lasts. Alternatively, looking at quality of life would require longer monitoring, as some of the endpoints could be statistically significant only after long durations (for example, assessing joint pain against joint damage would require MRIs over a period of several years to see if damage occurs). Providing two years of data instead of five or ten is a real benefit in terms of cost and time to market. It potentially gives patients a shorter waiting time until GT becomes commercially available. This makes the "fast to market" concept twice as compelling: it appeals both to sponsors who want to commercialize and patients who are eagerly waiting for several decades for new tidings (in the shape of GT) to be brought. For sponsors, it also means sticking to what is known, rather than developing new measures. Some tools for quality of life are available and commonly used in the form of questionnaires and diaries, however they are rather rudimentary and non-comprehensive. Turning that information to measurable, quantifiable, and significant data that could be used to demonstrate a product's superiority in quality of life is a heavy undertaking. Sponsors are not eager to tread that path if it is unnecessary. The FDA would equally need to learn how to assess such measures. On this regard both patients are aware that existing quality of life measures may be complex, hence the NHF and HFA comments (document *H17*) and the WFH comments (document *H18*) referred to the need to use better tools to document quality of life and patient outcomes. Both explicitly stated that alternatives exist in the form of the "National Hemophilia Foundation-McMaster treatment guidelines on care models for hemophilia specifically reviewed outcomes important to assessing care", as well as an ongoing attempt by a multi-stakeholder project (CoreHEM) to develop a new set of core outcomes for clinical trials. Patients are helping, guiding, and insisting that sponsors engage with a wider set of outcome measures. This is akin to a mini rebellion. The FDA allows a market to thrive with products that are approved based on non-inferiority, but patients have made allies with caretakers and physicians, and are pushing sponsors to aim higher if they expect to gain the trust of patient to consume these products. In some ways, patients are laying the ground for recreating what matters within the market. If the FDA won't change the tolerance for entering the market, then patients are creating a new tolerance for what they choose to be treated with. In other words, patients want quick access to products, but are also suggesting new types of outcomes.

One item that may still be confusing is why some sponsors also suggest complicating or slowing down the development process by using quality of life parameters which take longer to assess. The reason could be that the data is anyway collected (even if not analyzed), and patients will anyway stay very long under clinical supervision. Also, if patients choose products according to their anticipated improvement in quality of life, it makes sense to make quality of life a clear objective in the development of a commercially viable product.

The discussions around ABR, and the thorough justification that the FDA added to the final guidance about their choice of endpoints, are fundamental for this thesis. They speak directly to how treatment success is measured by those in power, and by inference what a relevant treatment should aspire to do. Here lays the greatest irony: the FDA, by its own press releases, is intent on creating a market for a curative treatment, and by its own disclaimers is responsible for safeguarding the wellbeing of patients through ensuring safety and effectiveness of products. These abstract objectives are made tangible within the guidance. A market is created by assuring that the FDA will review marketing applications for GT products that meet some requirements. Safety requirements are expected to evolve as data becomes available, which may take years after the product entered the market. Efficacy is ensured so long as products are assessed in a way that the FDA can measure, where the FDA prioritized measuring ABR– a superficial measurement that addresses only some of the disease issues and compares GT with existing treatments. The oddity is that GT is not at all *just another treatment*, it's a whole new modality with much higher clinical aspirations than existing treatments, but these aspirations are not considered by the FDA, though they are the main thing that patients are looking forward to. One is left to ponder - is the FDA truly creating a new market here, or is the FDA expanding the existing market for hemophilia treatment by allowing GT to compete in the same arena? Is this restricted to new technologies as such, or for any new treatment modality? What does this mean for future treatment paradigms: so long as a product is not worse than existing treatments, it shall be relevant? What is the role then of the promissory future, the cure? And of course, how much can patients rebel against the FDA's decisions.

7.6.7 Measuring the added value of gene therapy

Though the guidance offers some information about safety and efficacy, what is left unspoken is what do the patients expect of the treatment. A patient who receives proper prophylaxis is a patient who does not spontaneously bleed. Would this patient be a candidate for GT? If the treatment is only measured according to parameters of ABR, and is required to be non-inferior to existing marketed treatment, then what value does GT offer to patients? In the FDA's summary of the session on Gene Therapy Treatment Modalities, *P3,* in the section regarding risk/benefit of gene therapy it is stated that "Patient/caregiver's interest in new therapy is partly dependent on the success of their current treatment modality", and also "Some patients/caregivers are less likely to enroll themselves or their child in a clinical trial if their current prophylaxis treatment is working and manageable." In other words, they would not risk transitioning to GT if their current treatment is good enough. So long as there is no differentiation between gene therapy and prophylaxis, it is unclear why patients would opt to treat themselves with gene therapy.

However, value can be derived in many ways: (i) products might be non-inferior but much cheaper than existing products, so that their added value is their accessibility, especially in chronic diseases. Gene therapy pricing, however, is currently questioned and contested as it is very high (as explained in section 3.3), thus this is not a relevant point for gene therapy consumers. If anything, it shrinks the potential consumer pool, and complicates accessibility. Accordingly, the FDA does not regulate pricing of a product within development guidances, rather the focus is on attributes necessary to meet marketing requirements, not market rates. (ii) Some products may have a special niche of patients; however, GT seems to compete for the same hemophilia patients targeted by prophylaxis, except GT upfront has a smaller patient pool potential – similar to existing enzyme replacement therapy, GT excludes patients with existing inhibitors to the factor, but it also excludes patients who have inhibitors to the vector, and excludes patients with problematic liver functions (e.g., patients with comorbidities of HIV or hepatitis). (iii) Finally, value can be derived in what the product does to the patient outside of the molecular parameters. Here, gene therapy has the most leverage: it's promise for a cure and the promise of better quality of life. On this account, the pharmaceutical company Bayer expressed their frustration at the FDA's suggestion to have ABR as the primary efficacy point, boldly stating that ABR may not be a relevant point of reference for the patient:

> "There is more discussion needed regarding the expected value of gene therapy to the patient. The current guidance strongly suggests a comparative benefit to patients based on either 1) non-inferiority in ABR to a well-managed prophylaxis regimen, or 2) potential superiority to on-demand (which is no longer an acceptable standard). This needs to be reconsidered, as ABR does not provide a full picture of clinical outcomes that could be evaluated.
>
> We recommend emphasizing the many important outcomes of gene therapy, as well as the impact on quality of life, ongoing healthcare utilization, and other important patient determined outcomes. For example, a patient currently on regular and frequent infusions may only have an ABR of ~2 (which is the average) and still require occasional additional treatments in response to injury or surgery. However, this same patient is sedentary, restricted in the ability to travel due to the need to always carry the treatment product, and frequently requires healthcare support – potentially related to difficulties related to infusion. After gene therapy, the patient is no longer sedentary or restricted and will rarely need replacement factor (which is usually a subjective decision). The ABR might be reported as higher as the patient may infuse replacement factor occasionally for fear of possible bleeds rather than actual events." (*H9*-Bayer, on choosing ABR as the efficacy endpoint)

Bayer list out concerns that were raised by other commentors, above and beyond the problematic choice of primary efficacy endpoint: the fact that the patient's quality of life, comorbidities, and

disease progression are of no interest to the FDA from an approval perspective, but ironically are the main reason that patients are so interested in GT and are willing to enroll in clinical studies and engage with the technology despite the unknown risks.

The biotech BioMarin went one step further and commented on the "importance of patient focused development", and directly encouraged the FDA to use learnings from the PFDD as well as learning from patients and advocates to understand the patient perspectives, the need for gene therapy, as "These learnings collectively formulate patient experience data that will inform FDA's regulatory decision-making." (*H11*). This resonates with section 7.4.1, which praised the FDA's attempts to engage with patients, but was disappointed with the FDA's failure to integrate those findings into the guidance.

By normalizing GT, and establishing the efficacy endpoints as the FDA did, what was also normalized is the fact that hemophilia should be treated only at the molecular level, and not holistically. In the process of normalizing GT for hemophilia the secondary disease aspects of joint pain and deformation, as well as quality of life, are relegated outside of the realm of what formally constitutes a treatable aspect of the disease. Thus, the guidance also normalizes illness as molecular issue, and not as a progressing holistic condition, and treatment expectation is normalized along those lines.

With this information, we can now compliment Figure 7, and add to it areas which are excluded from the guidance, as shown in Figure 9 below. The fact that patient experience and alternative measures of treatment success/risk are not covered in the guidance does not imply that they are unimportant, nor does it suggest that sponsor are not actively pursuing them. On the contrary. Sponsors are all too concerned with future marketing needs for their product, driving the sponsors to embark on collecting marketing-supportive data from as early as possible. Within this market of treatments, differentiating gene therapy from prophylaxis is only the first step. More importantly, if the promissory future of gene therapy comes to fruition, then sponsors will need to differentiate one GT product *from another* in the future. Non-inferiority to prophylaxis will simply not be enough.

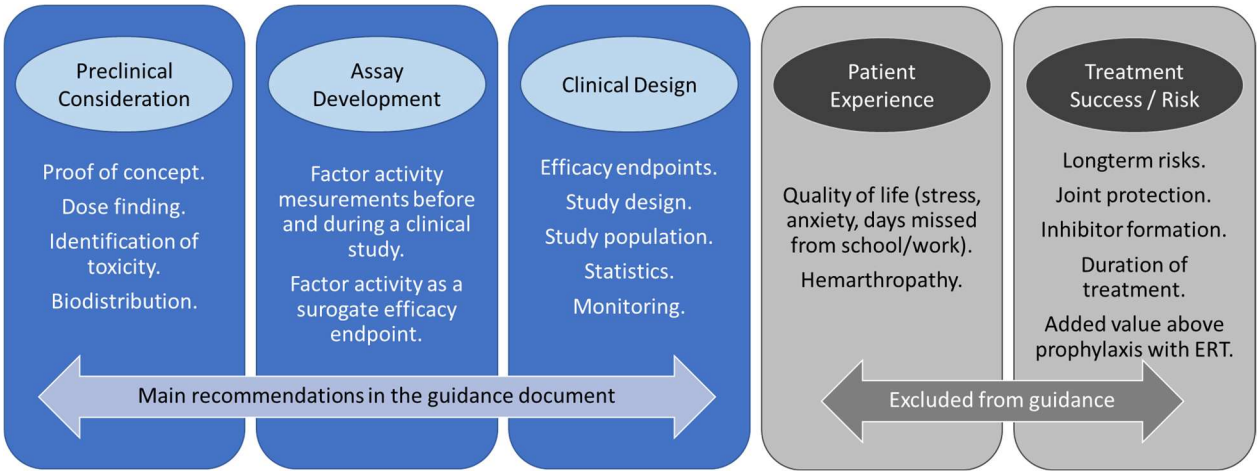

Figure 9. The gap between the technical properties governed (blue boxes) and stakeholder expectations from a novel treatment (grey boxes).

8 Discussion

The predecessor section was devoted to analyzing hemophilia GT related FDA documents. These documents, and guidances in particular, are the result of the FDA's reaction to a growing number of marketing request applications, a political agenda towards opening up more treatment choices, and a will to capitalize on a promissory novel technology.

In short, the documents animate two major notions. The first is the inclusion or acceptance of a new treatment modality. The documents collectively erect a new market for treatments of this technology, in sync with the FDA's own language and press release. This new market becomes a governable object, and to be allowed in this market, the products within must comply with a predefined set of requirements and definitions. More importantly, the market signals the end of a long process of normalization of a new technology, from legitimizing a concept (of a new way to treat diseases) to regulating the development of a gene therapy product.

The second relates to defining what is valued as treatment success. Through the guidance document, as well the entire drafting-finalizing process, the FDA construct what effective therapy encompasses, heavily reliant on pre-existing quantifiable and comparable short term clinical criteria, and in blatant disregard to gene therapy's long-term potential, promissory future, anticipated benefit to quality of life, and inherent unknown risks.

At first glance, it may seem that the former is a general outcome relating to any GT technology, while the latter is mostly relevant in the context of hemophilia. However, after deeper consideration both can be seen as general outcomes. This is especially clear when trying to assess what kind of endpoints the FDA would accept for other GTs for any rare disease, as is listed in the guidance for human gene therapy for rare disease (document *O2*) where, under section E. Efficacy Endpoints, the FDA begins by stating: "Demonstration of clinical benefit of a GT product follows the same principles as for any other product." The guidance *O2* then continues to explain that efficacy endpoints should consider the different bioactivity of gene therapy relative to existing treatments, and in case there are no treatments should design an endpoint meaningful from a pathophysiology (surrogate biomarker) and natural disease progression (clinical) perspective: simply put, measurable and quantifiable parameters. The same section also suggests exploring new measures of *clinically* meaningful aspects. Thus, the act of sidelining or minimizing the two hallmark promises of gene therapy, i.e., a patient's quality of life and the potential for long term relief from disease, is not a unique occurrence to hemophilia, but actually an exemplar of the overall definition the FDA sets for treatment success of gene therapy. Efficacy is dictated by short term disease-specific isolated outcomes, and not by a holistic view of the patient's disease burden, or quality of life, though these qualities are front and center in patient

feedback. This also means that in particular for hemophilia treatment sponsors need to make less of an effort to meet the minimal criteria: on the one hand, pivotal clinical trials are short in comparison to the treatment duration, and on the other hand it is much more complex to quantify quality of life, and also difficult to statistically prove it. Of note, while holistic endpoints might not be in the sponsor's interest for hemophilia, the case may be different for sponsors of other diseases (for example in cases where the pathophysiology of the disease is not fully understood), and in that case the FDA's approach of pathophysiological endpoints is to their detriment.

Overall, the twin-effect of legitimizing and normalizing through regulation while enabling simplified and flexible barriers for market entry is indicative of a ***low threshold attitude*** towards gradual acceptance of new or emerging technologies.

Why should the FDA engage with a low threshold attitude, and is this governance behavior unique for gene therapy?

8.1 Bringing the pieces together, or what does this all mean

The process of legitimizing gene therapy as a cure through press releases was coupled by normalizing gene therapy as a treatment via publishing guidances for development of GT products, thereby creating a market. This is reminiscent of Asdal's (2015a) view on regulation as a tool to close down controversies, and again as per Asdal's (2015b) review of how the Norway codfish market was artificially created by the government. In the case of GT, the FDA represented an empowered governmental agency that was keen on catching two birds with one stone, the birds being streamlining of drug development and accelerating the time to market, the stone being the 21st Century Cures Act, which intended to create more treatment options for patients by allowing to accept higher safety risks along with shorter development timelines. The FDA actively pursued a low threshold attitude because that attitude echoed the political agenda set forth.

Furthermore, the guidance document was shown to: keep open some controversies and acknowledge their inconsistency in the scientific world, such as factor assay development, without diminishing the relevance and viability of GT itself; facilitate, simplify, and increase the likelihood of marketing application review by providing insight to the minimal requirements necessary for that application to be accepted by the FDA; maintain flexibility at the expense of clarity by keeping guidelines vague while negotiating actual requirements at the product level with sponsors; ingrain and cement a hierarchy or structures of power and inequality in drug development - the regulator, developer and product are at the center of the document, but not the patient nor the disease; apply ideals of efficacy that fit transient recurring treatment (prophylaxis) to a steady state single shot treatment plan, thereby ignore both the potential and more importantly the risk in a new treatment modality.

All of these issues combined lead the FDA to actively cast responsibility onto the drug developer directly, and in an indirect, discreet fashion also onto the patient. The sponsors are expected to negotiate with the FDA their plan of a clinical trial which minimizes risk to the patient as per the sponsor's mapping of risks, and patients are expected to embody those risks as enrolled subjects in said clinical trial. In the end, the FDA does not offer neither concrete safety nor an ideal efficacy, what it offers is a chance for patients to experiment and take it upon their shoulders to decide if the product is safe *enough* or efficacious *enough* for them to try it out. Borrowing from Lakoff's (2008) assertion that patients need to fit the product rather than the product needs to fit the patient, one can say that GT patients quite literally embody the product in this case, along with the risks and unknown safety issues. Unlike other treatments that have well defined risks (probability, possibility, duration, and temporal association to the drug), in GT the risks are a-priori expected to be both high and unknown – there are no standards. For the patients, this is quiet an undertaking: once a treatment is administered it cannot be undone, and it lasts forever (or maybe less than five years. No one knows).

When viewed through the idea of low threshold attitude, it becomes clear that delegating responsibility is the result of the FDA's own need to somehow bridge the gap between the political agenda on one hand, and their own mandate to oversee safe and efficacious drug development on the other hand. In other words, the FDA needs to generate new treatment alternatives by encouraging drug developers through lenient regulation, and at the same time maintain some sort of facade as if the FDA is actively pursuing safety and efficacy. In light of GT's optimistic potential, the risks associated with GT are assumed to be acceptable, although many of them are unknown. By wavering or deferring more stringent risk assessments, both the GT is normalized as a treatment, and so are the risk associated with it. Normalizing GT therefore generates flexibility, or compromises, in the FDA's own raison d'etre of safeguarding patients, which can only be acceptable if there is mutual agreement that safety is negotiated and resolved by the sponsor, and efficacy is deemed good enough to warrant marketing to the patient. To make a point clear: with a low threshold attitude, the FDA delegates responsibility to sponsors for identifying and negotiating measures to monitor risk independently for each and every product, while at the same time leaving it to the patients to deal with the fallout both for safety and for efficacy.

Low threshold attitude and delegation of risk:

It is arguable that in any case of clinical studies, patients take upon themselves risks, so it is worth detailing why the concept of low threshold attitude is unique and limited to novel or emerging technologies, GT being prominent among them. There are multiple contributary factors.

To understand the first, Callon & Rabeharisoa's (2008) concept of "emergent groups" should be reexamined. Hemophilia's multiple patient associations are well connected (i.e., with international bodies such as the WHO, or national regulating bodies), have gained expertise over many years of activity, and have the support of professional associations (such as ISTH). Patients and caretakers have been vocal in presenting their clear interest in novel therapies and have been waiting for years for the GT technology to come to fruition, expressing their will to join clinical studies in the hope of a treatment that will take the next step forward in the evolution of care from treating a bleed to a bleed-free world. Hemophilia patients aren't being coerced to join just *any* clinical trial; they are advocating for *these* trials to take place.

The second factor is the complexity of GT and level of personalization. Some GTs, unlike hemophilia GT, are so unique, they literally can only be applied to a single patient. Some types of such GTs call on harvesting cells from sick patients, genetically modifying those cells, and reintroducing them to the same patients who becomes an experiment of one. Though hemophilia GT is not the same technology, it is similar in the sense that once a product is administered what happens at the patient's body differs vastly from patient to patient. Preliminary results from ongoing clinical trials with hemophilia products show a variance of complete success and complete failure within the same study, which are attributed mostly to unique properties of the patients themselves. This is reminiscent of Lakoff's (2008) application of biopolitics, that speaks to illness and health and the gap between how governments define these items and how patients experience them. A product may be deemed appropriate, fitting, and curative as per the FDA, but for the single patient it may offer the same level of treatment albeit with higher risk than existing alternatives; such is the case for a patient on prophylaxis who is sedentary and limited by frequent infusions, but bleeds only once a year, against that same patient being administered a GT that could improve mobility and infusion burden, will not result in the same amount of bleeding events, and may cause liver damage. Nevertheless, the FDA in its attempt to open a GT market normalizes this risk and leaves it to the patient to decide if the treatment is worth it. Patients entering clinical trials of novel technologies, and especially those with lifelong effects, take on a different risk than, e.g., those joining a study for a cardiovascular stent, or a generic version of pain killer tablets.

Low threshold attitude and sponsor incentives:

The next contributing factor is that sponsors continuously choose to engage with GT development either because they are market leaders (or wish to be) in that space of disease, or because they are dedicated to GT development, and own proprietary material for their GT platform (e.g., the viral vector that is used in the GT). Both reasons have financial incentives associated with them which drives the motivation of commercial companies. What would happen should the FDA, or payers, insist on better

outcomes for patients? What would happen if pharmaceutical companies were paid in a prorated fashion according to the duration of treatment success, or according to improved quality of life? This could be an interesting bioeconomic twist where the symbolic economy (Lentacker, 2016) of GT, which is the promissory life-long cure, is actually pinned against the product's monetary value. Years of health equate with years of revenue. This extraordinary idea is not fictional, but actually being assessed for certain GTs in European countries such as France, Germany, and the UK, but also for the US, for example by introducing outcomes-based payment or payments in installations linked to success for GT (Jørgensen & Kefalas, 2021). In any case, at present, the primary incentive to develop GT is financial. Regulatory incentives may increase the appeal of GT but are insufficient in their own to drive GT development.

Under the umbrella idea of finance and markets, competition also plays a role in low threshold attitude. Everything written to this point is amplified when considering that the European Union (EU) already approved the first ever GT product *before* the FDA. The EU has a large pool of documents that deal with GT (guidelines, reflection papers, and Q&A documents). If the FDA wants to open up markets of treatments for patients and modernize its processes, it can't afford to lag behind the EU. The FDA thus accepts to normalizes the technology, along with its risks, and leaves it to the downstream stakeholders to deal with the most important aspects.

Tying all these factors together, the FDA engages in low threshold attitude towards novel technologies, when the climate is favorable: meaning that patients are willing to take on risk for a potential cure, sponsors are anyway investing in the technology, safety and efficacy are too complex to fully understand and prove in the context of a clinical trial, and liable to be different from patient to patient. Low threshold attitude means that the FDA: (i) is listening to the patients, and acknowledging their will for new products; (ii) is listening to the sponsors and acknowledging that they will anyway invest in this technology (if not for the American market, then for European and others markets); (iii) and is looking realistically at what can be done, which is to retroactively accept that the train has already left the station – it is better to hop onboard rather than to stay behind: GTs are already out there.

Low threshold attitude and markets:

One of the important ideas to consider here, is how low threshold attitude is reliant on the concept of a market. Implicit in the low setting of safety and efficacy standards is the concept of a market that can, and will, regulate itself. Who would be the parties managing (influencing? controlling?) this market? From a patient's perspective, if a GT is too risky, or insufficiently curative, it will have little value, and therefore unlikely to become a chosen treatment. Irrespective of the FDA's lenient efficacy criteria, if the products aren't good enough for patients, the market will either diminish or the products

have to improve over time. In other words, the concept of market resonates with what the FDA does not concerns itself with and avoids regulating - namely patient satisfaction. From the GT developer's point of view, they have limited capacity to make product changes, as these are entrenched in the proprietary components of the GT platform that is owned by them. Their hope is that the FDA sets the bar for the lowest acceptable criteria threshold possible because they have difficulties to commit to changes. One way to overcome this challenge is to allow further manipulation of the body in order to increase chances of success, for example by dosing with immunosuppressants to reduce the body's reaction against the GT and decrease chance of GT rejection (whether a product that requires one year, or two years, or lifelong immunosuppressants can still be called a commercially viable product has yet to be demonstrated). By adding physical manipulation to increase the chances of success, the drug developers hope to sustain relevance in the market, resonating with Lakoff (2008) ideas of patients being made to fit the product. Alternatively, drug developers are already planning to re-dose patients that lose vector expression over time. The FDA agrees to this: "If the transgene expression and consequent treatment effect decrease over time, consideration may be given to repeat administration of the GT product" (*O2*- rare disease guidance). It is not enough that the body is manipulated to increase chances of success, within the market, success duration is redefined, and normalized as temporary. The promissory future of a cure is normalized to be temporary within the market. Finally, payers are expected to dish out up to $2,000,000 USD per treatment (Antrobus, 2021). This is not an equitable product. Most patients (and some payers) simply can't afford this fee. To be clear – this treatment is so expensive, that only wealthy patients in wealthy countries with wealthy insurance groups can even afford it, it will not matter for poor people or for developing countries (where on-demand treatment prevails, i.e., treating of bleeds, and not prophylaxis). The FDA ended up opening an exclusive market, so from a population and statistics perspective, the risk being taken is actually quite small – only a very few subsets of a patients will ever be exposed to risk from these products. Within the American approach of neoliberal healthcare and markets in general, if one day the products prove to be amazing, and technological changes will allow easier manufacturing, and costs will go down (similar to mobile phones, or genomic sequencing), then this market will grow significantly. But until then, the market is full of promise, physical manipulation, and risk only for very few people. There is one consolation in this type of market – it is so small, it is unlikely to lead to the dismissal of existing treatments, which are also extremely expensive, but still more accessible and equitable than GT. This is the final idea behind low threshold attitude: the new GT market will not negatively influence current existing treatments; GTs will augment them.

Low threshold attitude as a model of regulation:

To summarize, a low threshold attitude can be advantageous when an existing political agenda aimed to enable more choice to the population is met with enthusiasm from commercial actors ready to develop the products, and consumers willing to try the products. The low threshold attitude manifests as lenient regulation in safety and efficacy in order to accelerate opening a market for products that are already in development, where standardization of minimal requirements is too complex to define (due to existing controversies, or lack of tools to quantify more holistic aspects rather than explicit singled out criteria). Products are too expensive to be ubiquitous, and thus are anyway intended for a small portion of the potential population. Success can be redefined within the market to be more limited or require additional manipulations (e.g., immunosuppressants) than what was initially envisioned. Since unknown safety risk is high in such a market, the final condition to apply a low threshold attitude is to verify that risk is mitigated by the fact that the product will only be accessible to very few end-users and will not impact existing alternatives. Consumers that have the ability to afford these products will pay in non-traditional pathways to guarantee and assign monetary relation to some level of success. Ultimately, these very few will go on to either prove the relevance of the product (and increase the market, provide new data, and allow recalibrating of requirements from products), or diminish the market altogether. In any case, existing treatments will continue to be commercialized as planned.

Finally, the FDA's application of a low threshold attitude for GT aligns well with the biopolitical notion of governing: the grounding of opening a new market of treatments assumes that at least some patients are willing to take on risks which the government has no intention of assessing at this point. If in the long run these risks are proven to be either minimal or affordable, then the market will grow to the credit of the FDA, and the benefit of commercial actors, and perhaps also to the wider population of patients.

Figure 10 summarizes the main factors that lead to a low threshold attitude from a governance perspective, and the result of that attitude.

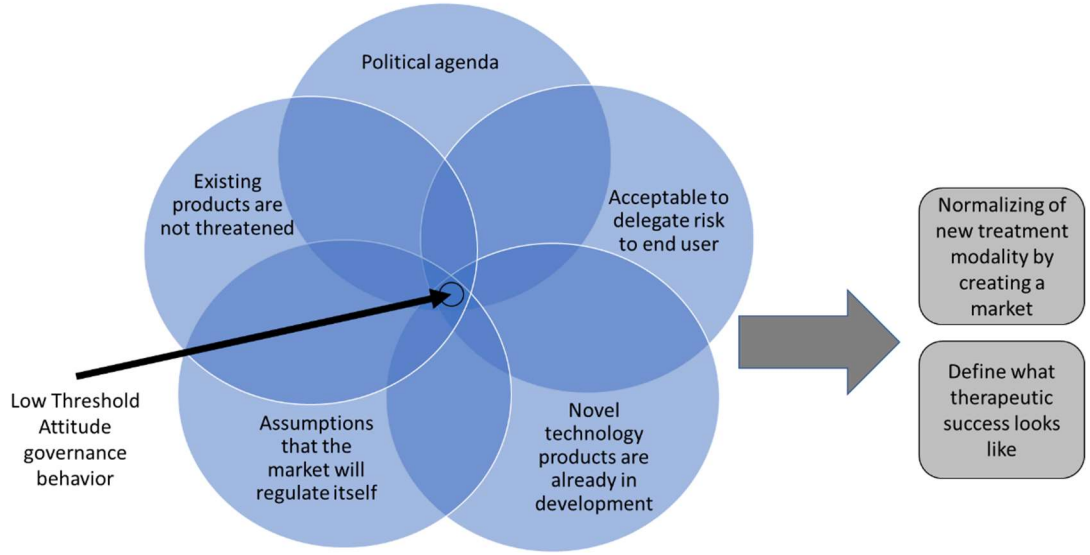

Figure 10. Low threshold attitude. The political agenda calls to open up new treatment choices. Risks are unknown, assessing them will take years, and they may be very different from patient to patient, thus risks are delegated to the patient, while the required level of product-specific safety parameters is negotiated between the sponsor and FDA. Products are developed by commercial actors and their arrival is anticipated by the patients, or already approved in other regions. The market will prove itself over time, either by expanding to include new and more products or by failing commercially and ceasing to exist. Existing products do not become redundant, patients still have the same available treatment options so there is no negative consequence to existing treatment alternatives. Once parameters converge, the regulator can normalize a treatment by turning It into a governable object within a market, while at the same time (re)define therapeutic success for the new products based on existing products knowledge, and not based on the promissory potential of the new product.

8.2 Normalizing new therapies - hemophilia GT as a swallow

Swallows are migratory birds, and the arrival of a gulp of swallows (to Europe) is a measure of the changing seasons, from the gloomy, cold winter into the hopeful, sunny summer. It is the observant Greek philosopher and scientist, Aristotle, who is credited with the saying "one swallow does not a summer make", meaning that a single (optimistic) event does not necessarily indicate a trend. The first three gene therapy products approved by the FDA in 2017-2018 were swallows, on whose wings a new, hopeful age was expected to dawn. Four years later, in 2022 not much has changed with a total of nine US FDA approved gene therapy products[30]. In the statements and press releases that accompany the FDA's GT policy framework there is a sense of urgency, but also a sense of the dawning of a new age. Still, as of September 2022, not a single hemophilia GT has made it through the BLA process, though a market has been established de facto. Is it too early to establish that GT is not quite

[30] An independent list of FDA-approved GTs is not available; GTs are lumped together with cell therapies. A cell therapy guidance framework was released several months prior to GT guidances. The technology, emergent and novel, is inherently different from GT. All cell and gene therapy approved products are identified at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.

there yet, or will a little more patience prove that the GT era is just around the corner? Has the market already failed, or should we wait a little longer before offering it condolences?

What remains clear for the next years is that GT is not expected to revolutionize or overtake the hemophilia market. It will be one of many products out there. Historically, recombinant products were viewed as the greatest game changer for hemophilia patients. They prolonged life and improved life's quality, while maintaining safety. A GT product is envisioned to be the next phase – not a treatment, but a cure. A very expensive cure. The dawning of a new age happens to a select few. What difference do migratory birds in Europe make for the average South American? What difference does hemophilia gene therapy in the US make for the Indian hemophilia patient, struggling to get on demand care with stone old plasma derived products, let alone prophylaxis with recombinant factor?

Normalizing a treatment based on a novel technology is not synonymous with normalizing its abundance, distribution, accessibility. GT may very well become the new way forward as a treatment, but it will take years of refining until it will be ubiquitous, and a first-choice treatment. Also, normalizing hemophilia GT fixes the efficacy measurements of GT to be on par with enzyme replacement therapy. With the onset of enzyme replacement therapy, the definition of a well-managed disease was reduced to bleeding events. The normalization of GT through guidance documents takes that definition and normalizes it as well. These swallows arriving on the heels of warm, promissory front and being guided by the magnetic fields of technological advances may bring on a new era of treatments, but not necessarily a new era of health.

9 Summary and Final Remarks

Throughout this thesis, an answer was sought to the question "*How does the FDA hemophilia gene therapy guidance construct gene therapy as a relevant treatment modality?"*. Literature in the fields of patients and treatment, gene therapy, hemophilia treatment, promissory futures, and governance were presented. Ideas of biopolitics and bioeconomy guided the analysis.

The result of a comprehensive document analysis was that several factors had to intersect so that the FDA would favor governing with a low threshold attitude, meaning that they would favor normalizing a high risk technology by legitimizing the technology in press releases, actively create a market for it by generating guidance documents that dictate the minimal requirements to enter this market, establish lenient success criteria to facilitate opening the market, negotiate with sponsors the safety issues to be considered, and delegate any safety risk onto the patients themselves. Once the FDA erected a market for GT, it signaled that GT is a relevant and governable treatment option.

The research sub questions dealt with how success criteria for treatment are negotiated and how GT is assembled in the guidances. In the process of reviewing the documents, gene therapy was identified to be a mix bag of many products. It is not so much what gene therapy *is*, as what gene therapy *does* (replacing, inactivating, or modifying defective genes with healthy ones) and *how* gene therapy does (transferred genetic material). More importantly, gene therapy was legitimized publicly as offering a cure, but normalized in documents as having unknown safety issues, and limited success capabilities. The FDA stubbornly stuck to existing success criteria instead of fashioning new success criteria as was desired by patients, supported by professional associations, and suggested by at least some of the pharmaceutical companies developing the product.

To make a long story short, GT is endorsed as a treatment modality through the act of normalizing it and creating a market for it. The FDA normalizes GT because it favors a low threshold attitude towards governing this specific technology, and it fulfills normalization by legitimizing GT publicly, and then turning it into a governable commodity in official documents, with predefined attributes and characteristics, inherent (and acceptable) unknown risks, potential (promissory and undefined) long term benefits, and at a minimum at least as much therapeutic benefit as existing products. Although hemophilia was used as a case study, it was shown that the act of constructing GT as a treatment modality is independent of the disease impacted.

9.1 The bigger picture

Is a low threshold attitude a unique occurrence, relevant only to gene therapy?

Are other novel technologies normalized differently?

In a two-part podcast about self-driving cars the host Jack Stilgoe asks several questions about the relationship between novel and emerging technology, regulation and society (Stilgoe, 2022 June and 2022 July). Understanding that technology proceeds governance, Stilgoe lists the adaptations that automated cars implore, namely that commercial developers need to adapt the technology to new risks (considering that city and rural driving conditions differ), that the community and neighborhood need to accept self-driving cars as an intricate part of their daily life and surroundings with the inherent benefit and risks that they bring, and that the existing infrastructure used by cars needs to be redesigned in areas so that it accommodates self-driving car needs. All of these are fenced in by regulation at various levels (Stilgoe specifically discussed US and UK regulation), but the technology is always based on company proprietary information and available expertise, and thus designing the cars is limited by commercial capabilities. The technology drives the vision (pun intended), rather than the other way around. If historically self-driving cars were expected to be safer than human-driven cars, nowadays current knowledge expects that self-driving cars can only be as good as their algorithms and are unfortunately not error-proof.

Taking a slight mental leap between industries, many parallels can be drawn between self-driving cars, a novel new technology that has been seriously discussed since the mid 1990s and is being introduced as an upgrade to existing mobility alternatives, and gene therapy, also a novel technology that has been seriously discussed since the mid 1990s and is being introduced as an upgrade to existing treatment alternatives. Commercial developers need to adapt GT technology platforms to new diseases, though they are limited by their own proprietary materials. The community of patients and physicians need to accept gene therapy as a treatment alternative, with its inherent hope and hazard, and so do healthcare funds and insurance companies. Existing infrastructure needs to be accommodated to allow for uptake of gene therapy to be successful, which is done by supplementing hospital facilities with equipment compatible with the needs of gene therapy administration. Of course, as with self-driving cars, the most interesting parallel is that the GT technology precedes the vision.

But does low threshold attitude, and normalization as was demonstrated here, also fit with self-driving cars? In a very brief view: yes, it fits because the factors that lead to a low threshold attitude intersect for self-driving cars just as they do for GT: Self driving cars promise to be safe, or at least s*afer*; politically, governments wish to reduce automobile accidents[31] without impacting mobility of people; those who choose self-driving cars still need to apply steering and assume responsibility for risk as the

[31] per the WHO (2022) “Road traffic injuries are the leading cause of death for children and young adults aged 5-29 years.” and “the United Nations General Assembly has set an ambitious target of halving the global number of deaths and injuries from road traffic crashes by 2030”.

technology is not fully validated yet; cars are anyway already being developed and tested by automobile companies; companies such as Uber are eager to use these cars, and are advocating for them, along with tech-enthusiasts, and strong lobbying forces; and existing cars will continue to be manufactured, at least until self-driving cars prove themselves as better.

As Stilgoe (2022) appropriately summarized regarding the availability of self-driving cars: it is not a question of when, but where and for who. In a climate that favors low threshold attitude, governance of novel technologies becomes easier, and a market that normalizes self-driving cars through regulation is being established both in the US and in UK.

Another example for normalization as a result of low threshold governance can be mRNA based COVID vaccines. Similar to self-driving cars and GT, mRNA vaccine technology had been around since the 1990s, and by the time the COVID pandemic started there were results from clinical trials with mRNA vaccines (Dolgin, 2021). The mRNA COVID vaccines were a new technology, approved with testing schemes commensurate with traditional vaccines and targets (e.g., preventing infection and reducing hospitalization), but ignorant of the unknown long-term risks of mRNA vaccines, especially mRNA multiple dosing. Risk was delegated onto the vaccinated person, in some countries with repercussions for those refusing to vaccinate. The political agenda served was slowing down the COVID-19 disease spread. Other vaccines are still being manufactured in the traditional form and are unlikely to change (e.g., measles vaccine); even for COVID-19 some vaccines manufacturers still use traditional vaccine technology. Once proof came about that mRNA vaccines reduce mortality, the concept of mRNA garnered more legitimacy as an acceptable new mechanism to be developed for vaccinating against other infectious diseases- the market is growing and regulating itself.

It is tempting to try and apply low threshold attitude and normalizing of any novel technology, be it alternative energy (small nuclear reactors), environment related regulation (circular economy), digital database usage, application of machine learning and artificial intelligence tools, and so on. This, however, would be inappropriate. Key factors within the concept of low threshold attitude are that products already exist and are being independently developed by commercial drivers for an enthusiastic audience, and thus can be easily commodified and governable, and that the inherent risks can be delegated onto the end user, a single person who is fully aware and consents to this. In cases where the governing body retains responsibility of the risk, or where the technology has not yet matured to be tangible, a low-threshold attitude is unlikely to drive regulatory decisions. Normalization of such technologies exists, but the pathways that lead to it embark on a different logic and context.

9.2 Recommendations and reflection

On the matter of recommendations:

This thesis explored several facets of regulation. The outcome showed that the FDA was keen on creating a market and on delegating safety to the end user. Considering the political culture in the US, it seems unrealistic to recommend that the FDA not make a market and instead move towards more socialistic and equitable treatment regulation. It is equally unrealistic to expect that the FDA does not delegate safety to the end user. What can be recommended is how to introduce small and practical changes that could improve regulation itself in both substance and process. To begin with, the thesis shows that regulators minimize the importance of patient needs when regulating GT for hemophilia. One way to improve this is quite directly by adding mandatory analysis of at least some of the items deemed important by patients. This is not such a large leap as it may seem. In the past decade electronic diaries have simplified collection of patient data, and nowadays, eDiaries and phone apps are a normative part in participating in clinical trials for hemophilia, where sponsors regularly collect data on joints that have recurring bleeds, and patients are accustomed to entering data for parameters such as days missed off work. Sponsors use this data for marketing purposes, and to support negotiations with payers on pricing schemes. Though the FDA encourages sharing that information as part of the data submitted for a BLA, it does not mandate analysis of that data. Were the FDA to insist that at least one or two items should be analyzed as an outcome (even if not the primary outcome), it would signal that (i) there are anticipated benefits beyond bleeding prevention, and that (ii) patient preferences are taken into consideration when approving new treatments. To make sure that the FDA really is choosing aspects that matter to patients, the FDA should choose items that correlate to those identified through multi-stakeholder projects such as CoreHEM (developed by NHF, a patient association). Adding such outcomes would not change the delegation of safety to the end user and would not impact the creation of a GT market. The only thing it would do is recalibrate what treatment success may look like for this treatment modality, and not necessarily in comparison to other treatments. Alternatively, the FDA could mandate analysis of the quality of life data as a post-marketing commitment to be completed within the long term follow up. While this would not change acceptance criteria, it would signal a gradual shift in FDA mindset to the importance of quality of life, and encourage the industry to develop this field better, so that in the future it would become an expectation also for initial marketing approvals. This recommendation is specific for *substance* or content. However, there is also a recommendation that would be more appropriate for the *process* of regulating emerging or novel technologies. The FDA refuses to reply to comments received from stakeholders on draft versions. This is understandable as it may be a laborious effort for the FDA with little benefit. However, similar to the listening session held with patients, it would be beneficial for the

FDA to hold a workshop or listening session with the commentors after all comments were received, and all parties have a chance to read each other's comments online. In this session, the FDA could verify why some parts of a guidance receive such strong resistance, and work with commentors to identify concrete alternatives, acceptable by all parties. For example, in hemophilia both the assays development and ABR as an endpoint were criticized. The FDA could have reached an agreement with commentors that successful GT results in sustained factor activity levels above 10% in at least 50% of the participants for at least 1 year. This would mean that ABR is not the primary endpoint, and that assays do not have to be developed in the rigorous fashion that the FDA insisted on, because they can afford a much higher level of inaccuracy. These threshold items are anyway negotiated between the FDA and sponsors on a case-by-case basis later. By holding a listening session with commentors, the FDA would frontload some of the negotiation into the feedback soliciting part, where also patients could have a say. Again, this would not change the delegation of responsibility to patients, not impact opening a market as such. It would however reduce and simplify the required negotiation later on, and shift the acceptance criteria to mirror the expectations from this treatment modality.

On the matter of reflection:

There are some loose ends that require clarification.

This thesis focused on FDA regulation and refrained from comparing to other regulators. To be fair, although the FDA decides what products would be approved under their jurisdiction, in reality many smaller countries have agreements with the FDA, so that whatever is approved by the FDA receives technical approvals in their own country as well, thus the reach of such guidance and of FDA approval processes is much wider than just the US. Moreover, drug developers must abide with FDA requirements no matter where they are located if they want to ultimately market a product in the US. As the same drug developers may target commercializing their products in other regions, the geographical footprint of the FDA's biopolitics is potentially very wide.

Another point to bring forth is the choice of documents. This thesis is deliberately not symmetrical. The analysis hinges on a single document authored by the FDA. All other documents analyzed come to clarify this one guidance, be they press releases, comments, reports from patient meetings, or other guidances. There is less of a focus on patients, the hemophilia community, the healthcare system, and drug developers. Originally, the thesis intended to pit patients against regulators, and identify who contributes what to the process of normalizing a controversial therapy, and how the process redefines matters such as illness and health. In the course of collecting documents, it became clear that the historical developments of hemophilia treatment and the abundance of regulatory documents that were available were complex to navigate even without additional documentation. It also became clear

that the focus of interest was not redefining the illness but governing the technology, where treatment success became a derivative of that. Choosing to look into documents presented in professional conferences, dedicated pages on patient advocacy websites, or pharmaceutical news releases may have added understanding to the way developers and consumers see gene therapy but would have added little benefit to understanding how regulators view the technology. Nevertheless, the picture painted is one-sided, and offers the point of view of how the FDA embarks on biopolitics, but not how patients experience this type of biopolitics.

A good reflection must be honest about how robust and complete the work is. An assumption that was taken for granted is that regulation indeed normalizes an object by making it governable. Findings were pulled together to demonstrate that a low threshold attitude is the predecessor for normalizing GT. Could the factors enlisted in creating a low threshold attitude be assembled differently? Should they be seen as sequential, independent events, that do not compose a temporally associated situation, but rather a fluid context of random events? Neither the baseline assumption, nor the compilation of factors are uncontested, but at least for now, they both seem to have value in explaining the end result, which is a guidance document that puts the onus on patients to take therapeutic and health risk and sets (outdated) definitions for what constitutes treatment success.

There are many ways to expand on this thesis. One interesting possibility is to test the idea if low threshold attitude can also explain the other regulatory body's approach towards approving the use of GT products. Another direction would be to develop the findings further towards the patients, to gain an understanding of how the authorization of gene therapy impacts (or doesn't impact) their view of treatment options and understanding of health. In addition, regulation and genetic modification are both mutually evolving fields (not unsimilar to an arms race). As the FDA recently released a gene editing draft guidance it would be interesting to see how that guidance reshapes the FDA's own understanding of what constitutes gene therapy, what is a governable genetic manipulation, what are the risks, and so forth.

Lastly, there are two questions that should be settled: Has a GT product for hemophilia been approved for use (as of Sep 2022) anywhere, and what happened to the two hemophilia products submitted to the FDA. The first answer is that on August 24, 2022, The European Medicines Agency (EMA) approved valoctocogene roxaparvovec, the first ever GT for Hemophilia A (BioMarin, 2022). That same product was submitted also to the FDA in December 2019, and after the FDA requested two additional years of data, a resubmission of data has been postponed to late 2022 (NHF, 2022). The second hemophilia product submitted to the FDA for approval, etranacogene dezaparvovec, is under priority review with a tentative PDUFA date planned for November 2022 (CSL Behring, 2022).

In place of a closing statement, a quote:

> "*Take health as the end. One man is always healthy, another becomes healthy by slimming down, another by running and slimming down … while another cannot attain health, though he can attain running or slimming down. There are different ends for these different men. For while it is certainly best for all to attain the end; yet, if that is not possible, it is always better, the closer one is to the best*"
>
> - The philosopher Aristotle, on the matter of attaining health. Extract taken from *de Caelo* II 12 (as is cited in Baker, 2020, p. 20).

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11 Appendices

Appendix 1 - FDA original framework of policies for gene therapy

Appendix 2 - List of documents analyzed

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11.1 Appendix 1 - FDA original framework of policies for gene therapy

Guidance for Industry - Title	Docket number
Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)	2008-D-0205
Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up	FDA-1999-D-0081
Long Term Follow-up After Administration of Human Gene Therapy Products	FDA-2018-D-2173
Human Gene Therapy for Hemophilia	FDA 2018-D-2238
Human Gene Therapy for Retinal Disorders	FDA-2018-D-2236
Human Gene Therapy for Rare Diseases	FDA-2018-D-2258

Additional guidance policies were later added to the GT policy framework:

(i) *Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*, docket FDA-2019-D-5392, introduced as draft in January 2020, finalized in September 2021

(ii) *Human Gene Therapy Products Incorporating Human Genome Editing*, docket FDA-2021-D-0398, introduced as draft in March 2022

11.2 Appendix 2 - List of documents analyzed

Internal Number	Type of document	Docket ID / URL	Document name	Date of issue	Identifier
G1	Fact Sheet	https://www.fda.gov/media/82791/download	Fact Sheet: FDA Good Guidance Practices	NA	NA
G2	Final Rule	99N–4783	Administrative Practices and Procedures; Good Guidance Practices	Sep-00	00-23887
G3	Report	https://www.fda.gov/media/82644/download	Food and Drug Administration Report on Good Guidance Practices Improving Efficiency and Transparency	Dec-11	NA
H1	Notice	FDA-2018-D-2238	Human Gene Therapy for Hemophilia; Draft Guidance for Industry; Availability	Jul-18	FDA-2018-D-2238-0001
H2	Guidance for Industry	FDA-2018-D-2238	Human Gene Therapy for Hemophilia Draft Guidance for Industry (Renamed: 2018-125 Guidance GT for Hemophilia_7-09-2018 -508 Compliant)	Jul-18	FDA-2018-D-2238-0002
H3	Comments	FDA-2018-D-2238	Request for Extension from Biotechnology Innovation Organization (BIO)	Aug-18	FDA-2018-D-2238-0021
H4	Comments	FDA-2018-D-2238	Request for Extension from Alliance for Regenerative Medicine (ARM)	Aug-18	FDA-2018-D-2238-0022
H5	Notice	FDA-2018-D-2238	Draft Guidances Relating to the Development of Human Gene Therapy Products; Availability; Extension of Comment Period	Sep-18	FDA-2018-D-2238-0023
H6	Comments	FDA-2018-D-2238	Comment from Biotechnology Innovation Organization (BIO)	Dec-18	FDA-2018-D-2238-0024
H7	Comments	FDA-2018-D-2238	Comment from Granzer Regulatory Consulting	Dec-18	FDA-2018-D-2238-0025
H8	Comments	FDA-2018-D-2238	Comment from Oxford BioMedica	Dec-18	FDA-2018-D-2238-0026
H9	Comments	FDA-2018-D-2238	Comment from Bayer	Dec-18	FDA-2018-D-2238-0027
H10	Comments	FDA-2018-D-2238	Comment from American Society of Gene & Cell Therapy	Dec-18	FDA-2018-D-2238-0028
H11	Comments	FDA-2018-D-2238	Comment from BioMarin Pharmaceutical Inc.	Dec-18	FDA-2018-D-2238-0029
H12	Comments	FDA-2018-D-2238	Comment from Sangamo Therapeutics	Dec-18	FDA-2018-D-2238-0030
H13	Comments	FDA-2018-D-2238	Comment from Alliance for Regenerative Medicine	Dec-18	FDA-2018-D-2238-0031

Internal Number	Type of document	Docket ID / URL	Document name	Date of issue	Identifier
H14	Comments	FDA-2018-D-2238	Comment from Pfizer, Inc.	Dec-18	FDA-2018-D-2238-0032
H15	Comments	FDA-2018-D-2238	Comment from International Society on Thrombosis and Hemostasis (ISTH)	Dec-18	FDA-2018-D-2238-0033
H16	Notice	FDA-2018-D-2238	Human Gene Therapy for Hemophilia; Guidance for Industry; Availability	Jan-20	FDA-2018-D-2238-0034
H17	Comments	FDA-2018-D-2173	Comments from NHF and HFA	Dec-18	FDA-2018-D-2173-0051
H18	Comments	FDA-2018-D-2173	Comments from WFH	Dec-18	FDA-2018-D-2173-0052
H19	Guidance for Industry	FDA-2018-D-2238	Human Gene Therapy for Hemophilia; Guidance for Industry	Jan-20	FDA-2018-D-2238-0035
N1	FDA News Release	https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states	FDA approval brings first gene therapy to the United States	Aug-17	NA
N2	FDA News Release	https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework	FDA announces comprehensive regenerative medicine policy framework	Nov-17	NA
N3	FDA News Release	https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss	FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss	Dec-17	NA

Internal Number	Type of document	Docket ID / URL	Document name	Date of issue	Identifier
N4	FDA Statement	https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-efforts-advance-development-gene-therapies	Statement from FDA Commissioner Scott Gottlieb, M.D. on agency's efforts to advance development of gene therapies	Jul-18	NA
N5	FDA News Release	https://www.fda.gov/news-events/fda-voices/fdas-comprehensive-effort-advance-new-innovations-initiatives-modernize-innovation	FDA's Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation	Aug-18	NA
N6	FDA Statement	https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-new-steps-modernize-drug-development-improve	Statement by FDA Commissioner Scott Gottlieb, M.D., on FDA's new steps to modernize drug development, improve efficiency and promote innovation of targeted therapies	Oct-18	NA
N7	FDA Statement	https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics	Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies	Jan-19	NA
N8	FDA News Release	https://www.fda.gov/news-events/press-announcements/fda-continues-strong-support-innovation-development-gene-therapy-products	FDA Continues Strong Support of Innovation in Development of Gene Therapy Products	Jan-20	NA

Internal Number	Type of document	Docket ID / URL	Document name	Date of issue	Identifier
O1	Guidance for Industry	FDA-2018-D-2173	Observing Subjects for Delayed Adverse Events Following Administration of Human Gene Therapy Products (previously entitled Long Term Follow-up After Administration of Human Gene Therapy Products)	Jan-20	FDA-2018-D-2173-0063
O2	Guidance for Industry	FDA-2018-D-2258	Human Gene Therapy for Rare Diseases	Jan-20	FDA-2018-D-2258-0027
P1	Webpage	https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development	CDER Patient-Focused Drug Development	NA	NA
P2	Report	https://www.fda.gov/media/99237/download	The Voice of the Patient - Hemophilia A, Hemophilia B, von Willebrand Disease and Other Heritable Bleeding Disorders	May-16	NA
P3	Summary	https://www.fda.gov/media/124436/download	Listening Session: Gene Therapy as a Treatment Modality for Hemophilia	Oct-18	NA
P4	Notice	FDA–2018–N–3693	Product Development in Hemophilia; Public Workshop	Nov-18	NA
P5	Meeting (speakers)	https://www.fda.gov/media/124995/download	Product Development in Hemophilia Workshop Speakers-Panelists Biographical Information	Dec-18	NA
P6	Meeting (agenda)	https://www.fda.gov/media/124994/download	Product Development in Hemophilia Public Workshop - Agenda	Dec-18	NA
P7	Transcript	https://www.fda.gov/media/124993/download	Product Development in Hemophilia Public Workshop - Full Transcript	Dec-18	NA

Legend:

N- **N**ewsroom. Includes statements or press releases. Ordered according to date

H- **H**emophilia guidance docket FDA-2018-D-2238. Ordered according to docket identifier, except *H17* and *H18* which are wrongly allocated in the FDA website.

O – **O**ther guidance within the GT framework. Ordered according to docket number.

P – **P**atient related. Ordered according to date

G – **G**ood Guidance Practices. Ordered according to date

11.3 Appendix 3 - List of commentors

Sources for the table:

Commentors "Type" and "Description" are based off the commentor's dedicated website, either quoted in full or shortened for simplification. Supplementary information was also used in cases where commentors provided a short summary of themselves as part of their submitted comments (documents *H3-H4* and *H6-H18*). Where necessary, missing information was completed using the commentor's respective Wikipedia page.

Commentors are listed in alphabetical order, with acronyms serving as the name source.

Commentor and Website Source	Type	Description
ARM - Alliance for Regenerative Medicine https://alliancerm.org/	International advocacy for regenerative medicines and advanced therapies	ARM is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 300 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community.
ASGCT - American Society of Gene & Cell Therapy https://asgct.org/about/mission-vision	Largest global professional organization for medical and scientific application of gene and cell therapy	ASGCT is a professional membership organization for gene and cell therapy with over 3,000 members. Membership consists primarily of scientific researchers, physicians, other professionals, and students in training. The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease.
Bayer Bayer US: https://www.bayer.com /en/us/our-values Bayer AG Global: https://www.bayer.com /en/strategy/profile-and-organization	US-based division of Bayer AG, which is one of the world's top 10 pharma companies by revenue and employees	The Bayer Group is managed as a life science company with three divisions – Pharmaceuticals, Consumer Health, and Crop Science. The Pharmaceuticals division focuses on prescription products, especially for cardiology and women's healthcare, and on specialty therapeutics in the areas of oncology, hematology, and ophthalmology.
BIO - Biotechnology Innovation Organization https://www.bio.org/about	Global advocacy for the biotech industry	BIO is the largest advocacy association representing member companies, state biotechnology groups, academic and research institutions, and related organizations across the United States and in 30+ countries. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

Commentor and Website Source	Type	Description
BioMarin https://www.biomarin.com/our-company/about-us/	US-headquartered biotech for rare genetic diseases. *Submitted the first BLA for hemophilia GT*	BioMarin's focus is on developing therapeutics that provide advances to patients who live with serious and life-threatening rare genetic diseases. Focused on enzyme replacement therapies.
Granzer Regulatory Consulting http://www.granzer.biz/index.html	Private consultancy company for the pharma industry, focused on EU and US regulation	Granzer Regulatory Consulting & Services, provides clients support with European and US regulatory requirements, and offer guidance to optimize the time to market for their client's products.
HFA - Hemophilia Federation of America **NHF** - National Hemophilia Foundation (*submitted together) HFA - https://www.hemophiliafed.org/home/our-role-and-programs/what-is-hfa/about-hfa/ NHF – https://www.hemophilia.org/who-we-are/our-story/mission-history	US-based nonprofit organizations, patient advocacy for hemophilia and related bleeding disorders	NHF and HFA are national non-profit organizations that represent individuals with bleeding disorders across the United States. Their missions are to ensure that individuals affected by hemophilia and other inherited bleeding disorders have timely access to quality medical care, therapies, and services, regardless of financial circumstances or place of residence. NHF - dedicated to finding cures for inheritable blood disorders and to addressing and preventing the complications of these disorders through research, education, and advocacy enabling people and families to thrive. HFA - Community based organization for patient education service and advocacy exclusively focused on bleeding disorders patient and caregiver community.
ISTH - International Society on Thrombosis and Hemostasis https://www.isth.org/page/Mission	Not-for-profit global membership organization of specialists in the field of blood coagulation and its disorders. Publishes the peer reviewed journals: "Journal of Thrombosis and Haemostasis" and "Research and Practice in Thrombosis and Haemostasis"	ISTH advances the understanding, prevention, diagnosis, and treatment of conditions related to thrombosis and hemostasis. The Society is dedicated to transformative scientific discoveries and clinical practices, the development of young professionals and the education of physicians, scientists and allied health professionals wherever they may live.
Oxford Biomedica https://www.oxb.com/about	Originally a spinoff from the University of Oxford, currently a public company for gene and cell therapy	Oxford Biomedica is a viral vector specialist focused on cell and gene therapy. The viral vector platform is at the heart of the business.

Commentor and Website Source	Type	Description
Pfizer Inc. https://www.pfizer.com/about	US pharma and biotech company. One of the world's top 10 pharma companies by revenue and employees	Pfizer is in pursuit of breakthroughs that change patients' lives.
Sangamo Therapeutics https://www.sangamo.com /about/	US-based genomic biotech company	Sangamo is a genomic medicine company with a strategic focus on serious conditions with high unmet need, and partnerships with leading global pharmaceutical companies.
WHF - World Federation of Hemophilia https://wfh.org/about-wfh/	International not-for-profit global advocacy organization for hemophilia and related blood disorders	WFH is working to ensure that individuals affected by hemophilia and related inherited bleeding disorders have access to high quality medical care and services. WHF works in partnership with healthcare providers, governments, and a global network of national member organizations in 147 countries to provide the knowledge and tools they need to identify, support and treat people living with bleeding disorders in their communities, while promoting global advocacy and collaboration to achieve our common goals.

11.4 Appendix 4 - Glossary of technical terms

Terms are explained as they are used in this thesis. For the purpose of coherence some definitions were simplified. For the purpose of comprehension definitions were explained in lay man terms.

Term	Acronym or shortened version	Definition as was used and relevant for this thesis
Annual Bleed Rate	ABR	A measure of the bleeds a hemophilic person experiences over the course of a year, measured by counting the number of bleeding events divided by the number of months in the reporting time window (typically 6 to 12 months) and multiplied by 12. Historically used as the endpoint for hemophilia treatments that aim to reduce bleeding events
assay		A lab test for presence of biological substance and activity
assent		An agreement of a minor to participate in a clinical study. The assent language and format are adapted to the age of the child (e.g., pictograms for a 6-year-old, short sentences for a 10-year-old), and in studies that last long periods must be re-obtained as the child matures. An assent is obtained in addition to parental consent.
Biologics License Application	BLA	A formal request made to the FDA where an applicant would like to receive approval for marketing or commercializing a biological product.
bleeding episodes		A common occurrence for hemophilia patients, due to their deficient coagulation. Bleeding episodes can be spontaneous and frequently occur in joints. Some bleeding episodes happen in soft tissue like muscles. Without treatment bleeding episodes can last days.
breakthrough bleeds		A bleeding episode that happens to a hemophilia patient on prophylaxis treatment. A severe hemophilia patient with well managed prophylaxis will bleed less than 3 times per year. A breakthrough bleed is treated with an emergency dose of coagulation factor.
clinical phase		Within the drug development pathway, the clinical phase is the collection of studies conducted on humans. The clinical phase is further divided into phase I, phase II, phase III, and phase IV. In each phase increasing amounts of people are exposed to the drug product, and different type of information is collected.
clinical study / clinical trial		Research performed in people to evaluate an intervention. In this thesis refers to a medical therapeutic intervention.
coagulation cascade		A series of steps employed by the body to stop a bleed. The process involves multiple enzymes, knows as clotting factors.
congenital		A trait or disease present at birth.
cryoprecipitate	cryo	Frozen blood plasma that is especially rich in clotting factors.
designer babies		Babies that underwent embryonic genetic alteration or pre-selection for a desired genetic makeup.
delivery device		A tool intended to reduce the inconvenience of preparing and administering treatment while increase sterility and accuracy in dosing. Can be, for example, a combination of specially designed syringes and vials.
Drug Safety Withdrawal	DSW	Commercialized drugs that are removed from the market due to safety findings.
efficacy		The desired therapeutic effect from a drug, measured under (ideal) circumstances within a planned and controlled clinical trial setting.

Term	Acronym or shortened version	Definition as was used and relevant for this thesis
endpoint		An outcome analyzed within a clinical trial. Primary and secondary endpoints typically deal with issues of efficacy and safety. Exploratory endpoints are typically used to validate ideas the clinical trial is not powered to statistically verify.
Enzyme Replacement Therapy	ERT	A treatment to replace or replenish a deficient or absent enzyme by supplying that enzyme from an external source. ERTs were the first treatments that targeted hemophilia at the molecular level.
factor activity level		A qualitative measurement of clotting factor in the blood.
Factor VIII	FVIII	An enzyme in the coagulation pathway that is deficient or absent in Hemophilia A patients
gene therapy	GT	The introduction of genetic material in order to correct genetic disorders for therapeutic reasons. GT works by introducing a missing or modified gene or by introducing genetic material that inactivates a disease-causing gene.
genome editing		The manipulation of genetic material that results in the deletion, modification or replacement of genetic material in the host genome.
hemarthrosis		Bleeding into a joint
hemarthropathy		Pain, typically in joints, as a result of an ongoing bleed or deformation of joints from hemarthrosis
Hemophilia A		A rare inherited bleeding disorder where clotting Factor VIII is deficient or missing
Hemophilia B		A rare inherited bleeding disorder where clotting Factor IX is deficient or missing
Intra Venous treatment	IV	Rapid delivery of treatment to the blood stream by an infusion through veins.
Long Term Follow Up	LTFU	Extended assessments that continue some of the scheduled observations of a clinical trial past the active follow-up period, and are an integral portion of the study of some investigational GT products (definition as per document *O1* - The FDA LTFU guidance)
non-clinical phase		Experiments of candidate therapies under lab conditions in e.g., vials, petri dishes. In some cases, the non-clinical phase proceeds the preclinical phase, and in other cases they overlap. Occasionally, the non-clinical phase is considered to include within it also the pre-clinical phase.
off-label		Drug treatment administered in discord with its designated usage, or marketing approval. Can be relative to dose, frequency, administration route, indication, and target population. In hemophilia ERT this is usually in speed of infusion, dosage (too high or too low), and frequency (too often, not frequent enough). Contrast with "per-label"
on demand		Treating per occurrence. In hemophilia: treating a bleed once it occurred.
orphan designation / orphan disease		A regulatory status awarded to certain drug products. Advantages include financial incentives, market exclusivity, and regulatory assistance in developing clinical studies. The exact drug products that fall into its category differ by EU and US definition.
ORPHAcode		Orphanet is an online source for information on rare diseases, with the intent of improving knowledge and diagnosis. It is a global initiative supported by European grants. ORPHAcode is the nomenclature maintained by Orphanet to distinguish rare diseases and rare disease families.

Term	Acronym or shortened version	Definition as was used and relevant for this thesis
Patient-Focused Drug Development	PFDD	An FDA initiative intended to better incorporate the patient's voice in drug development decision making process. This is done via e.g., designated FDA-held meetings with patients.
payers		The body that finances the user fees associated with medical treatment. Typically, it is insurer companies (private or publicly traded) and public health funds.
peaks and troughs		An indication of the level of drug product circulating in the body. In hemophilia, a peak-and-trough profile is typical for prophylaxis with ERT, where peaks occur immediately after dosing, and as the product gets cleared from the body the trough shows (the lowest amount of product in the body). Bleedings occur in troughs.
per-label		Drug treatment administered as per its approved usage with respect to dose, frequency, administration route, indication, and target population. Contrast with "off-label".
pivotal study		The main clinical study for collecting data that will support a marketing application. Typically, a clinical phase III study for demonstrating safety and efficacy.
post marketing		Effort undertaken to collect data related to drug safety. For post-marketing commitment a full clinical study is involved. For post-marketing surveillance real-world data safety is collected.
pre-clinical phase		Studies conducted in animals before drugs can be tested a clinical setting with humans. Typically includes testing the drug is several animals (ranges from small mammals such as mice to big primates such as chimps).
Prescription Drug Users Fee Act	PDUFA	PDUFA is a US law to collect fees from drug manufacturers as part of the application request. The fees are designated for funding FDA review processes. The PFUDA date represents the marketing approval date for a BLA.
prevalence		How common is a disease (at a given time). Usually, represented as a fraction of the population.
prophylaxis	prophy	Routine treatment that is intended to prevent disease.
rare disease		An illness that affects fewer than 200,000 people in the United States, or less than 1/2000 in the EU.
Subcutaneous treatment	SC	Delivery of treatment through an injection under the skin.
treatment compliance		Conformance to medical instructions and advice in terms of treatment and lifestyle (taking treatment as prescribed, avoiding certain activities, etc).
upscaling		The process of increasing manufacturing capacity, without impacting quality of product produced.
viral particles		Usually refers to proteins from the outer coat of a virus.
viral shedding		Expelling of viral vector to the environment via excreta.

11.5 Appendix 5 - Supportive quotes

Documents are named in accordance with Appendix 2.

Within each section, quotes are ordered according to the Document column.

Quotes are listed according to the section where they were cited. Some quotes listed were used for the purpose of analysis but were not cited in text for logistical reasons. Some quotes may be duplicated, as they served multiple sections.

Full sentences were quoted, also for cases where the in-text citation was partial.

Doc.	Quote
7.2 Setting the stage - why govern GT at all	
G1	Industry, consumers and other stakeholders play a significant role in the agency's guidance development processes. FDA welcomes individuals' and stakeholders' suggestions of topics for guidances, and in certain instances solicits draft proposals. Draft proposals can help the agency better understand stakeholder positions, particularly if the subject involved deals with novel scientific issues.
G1	FDA guidances are documents that explain the agency's interpretation of, or policy on, a regulatory issue. The FDA prepares guidances primarily for industry, but also for other stakeholders and its own staff, and uses them to address such matters as the design, manufacturing, and testing of regulated products; scientific issues; content and evaluation of applications for product approvals; and inspection and enforcement policies.
G1	Although guidances are not legally binding, they show stakeholders one way to reach their regulatory goal. However, stakeholders are free to use other approaches that satisfy the relevant law and regulations. Recently, FDA published a report on how to improve the processes that make these important documents available.
G3	Guidance documents are documents prepared for FDA staff and/or Agency stakeholders that describe the Agency's interpretation of, or policy on, a regulatory issue. Guidance documents include documents that relate to: (1) the design, production, labeling, promotion, manufacturing, and testing of regulated products, (2) the processing, content, and evaluation or approval of submissions, and (3) inspection and enforcement policies. Unlike statutes and regulations, guidance documents themselves cannot generally create legally binding requirements.
G3	FDA is issuing this report to the public to make its decision-making processes regarding guidance more transparent. The Agency looks forward to engaging with its stakeholders as it continues to seek opportunities to improve the efficiency and transparency of the guidance life-cycle.
G3	Stakeholders often informally identify issues that would benefit from guidance at advisory committee meetings, industry meetings, roundtables, and listening sessions. Stakeholders also submit citizen petitions to identify policy issues that the Agency may decide to address by issuing guidance.
G3	Submitting *draft guidance*, rather than guidance topics, enables the Center/Office to approach a guidance topic with a better understanding of the issues that interest the stakeholder. This may expedite the guidance development process, particularly if the topic involves novel scientific issues.
G3	FDA, as a whole, as well as the individual Centers/Offices, should implement strategies to improve the dialogue with stakeholders regarding the guidance agenda and potential topics for guidance development.
G3	As mentioned, FDA generally solicits public input on a Level 1 guidance prior to implementation, and in preparing the final guidance, the Agency reviews and considers the comments that it has received.
N1	The U.S. Food and Drug Administration issued a historic action today making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.
N1	At the FDA, we're committed to helping expedite the development and review of groundbreaking treatments that have the potential to be life saving.

Doc.	Quote
N3	Today's approval marks another first in the field of gene therapy — both in how the therapy works and in expanding the use of gene therapy beyond the treatment of cancer to the treatment of vision loss — and this milestone reinforces the potential of this breakthrough approach in treating a wide-range of challenging diseases. The culmination of decades of research has resulted in three gene therapy approvals this year for patients with serious and rare diseases. I believe gene therapy will become a mainstay in treating, and maybe curing, many of our most devastating and intractable illnesses
N3	We're at a turning point when it comes to this novel form of therapy and at the FDA, we're focused on establishing the right policy framework to capitalize on this scientific opening. Next year, we'll begin issuing a suite of disease-specific guidance documents on the development of specific gene therapy products to lay out modern and more efficient parameters — including new clinical measures — for the evaluation and review of gene therapy for different high-priority diseases where the platform is being targeted.
N4	We look forward to working with the academic and research communities to make safe and effective products a reality for more patients
N4	As we develop this evidence-based framework, we're going to have to modernize how we approach certain aspects of these products in order to make sure our approach is tailored to the unique challenges created by these new platforms.
N4	The agency is issuing a suite of six scientific guidance documents intended to serve as the building blocks of a modern, comprehensive framework for how we'll help advance the field of gene therapy while making sure new products meet the FDA's gold standard for safety and effectiveness.
N4	We're committed to working with stakeholders to bring novel treatments to the market while ensuring the safety of patients.
N4	An inflection point was reached with the development of vectors that could reliably deliver gene cassettes in vivo, into cells and human tissue.
N4	When it comes to novel technologies like gene therapy, the FDA is steadfastly committed to a regulatory path that maintains the agency's gold standard for assuring safety and efficacy.
N5	In short, we've had to modernize our overall approach to regulation to effectively advance the kinds of innovations that are becoming available. This includes modernizing how we organize our medical product review programs. These initiatives are part of our comprehensive Medical Innovation Access Plan. These efforts are strengthened by new authorities and resources made possible by bipartisan legislation like the 21st Century Cures Act, as well as the recent re-authorization of the FDA's user fee agreements. The actions that we're taking have additional support from the President's Fiscal Year 2019 budget. Together, these efforts will enable the FDA to fund the creation of a cross-cutting data enterprise
N8	The draft guidance on interpreting sameness of gene therapy products under the orphan drug regulations provides the FDA's proposed current thinking on an interpretation of sameness between gene therapy products for the purposes of obtaining orphan-drug designation and eligibility for orphan-drug exclusivity. The draft guidance focuses on how the FDA will evaluate differences between gene therapy products when they are intended to treat the same disease.
P1	The primary goal of patient-focused drug development is to better incorporate the patient's voice in drug development and evaluation, including but not limited to: • Facilitating and advancing use of systematic approaches to collecting and utilizing robust and meaningful patient and caregiver input to more consistently inform drug development and regulatory decision-making. • Encouraging identification and use of approaches and best practices to facilitate patient enrollment and minimizing the burden of patient participation in clinical trials • Enhancing understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes • Identifying the information that is most important to patients related to treatment benefits, risks, and burden, and how to best communicate the information to support their decision making.
7.3 Making room - a market full of promises	
N3	We're at a turning point when it comes to this novel form of therapy and at the FDA, we're focused on establishing the right policy framework to capitalize on this scientific opening.

Doc.	Quote
N4	Once just a theory, gene therapies are now a therapeutic reality for some patients. These platforms may have the potential to treat and cure some of our most intractable and vexing diseases.
N4	The policy framework we construct for how these products should be developed, reviewed by regulators, and reimbursed, will help set the stage for the continued advancement of this new market.
N4	Today, we're unveiling a complementary framework for the development, review and approval of gene therapies.
N4	In the future, we expect this field to continue to expand, with the potential approval of new treatments for many debilitating diseases. These therapies hold great promise. Our new steps are aimed at fostering developments in this innovative field
N4	The field of gene therapy has progressed rapidly since these guidances were first issued. Therefore, the FDA is updating these guidances to provide sponsors with the agency's most up-to-date thinking
N4	Some of these products are almost certainly going to change the contours of medical practice, and the destiny of patients with some debilitating diseases
N4	Our goal is to help these innovations advance in a framework that assures the safety and effectiveness of these resulting treatments, and continues to build peoples' confidence in this novel area of medicine.
N4	Gene therapy represents one of the most promising opportunities for developing highly effective and even curative treatments for many vexing disorders. Some of these products are almost certainly going to change the contours of medical practice, and the destiny of patients with some debilitating diseases.
N7	The activity reflects a turning point in the development of these technologies and their application to human health. It's similar to the period marking an acceleration in the development of antibody drugs in the late 1990s, and the mainstreaming of monoclonal antibodies as the backbone of modern treatment regimens. In the case of antibodies, it was a product innovation that sparked an inflection point in the advance of those products, after which antibody drugs became a mainstay of medical care.
N7	Based on this activity, we anticipate that the number of product approvals for cell and gene therapies will grow in the coming years, reflecting significant scientific advancement and the clinical promise of these new innovations.
N7	In the case of gene therapy, it's similarly a product innovation that has marked an inflection point in the development of these therapies, and a surge in new product activity. In this case, it was the advent of safe and effective vectors for the delivery of gene therapy products, such as the adoption of adeno-associated virus (AAV) vectors.
N7	Gene therapy products now have the potential to cure intractable diseases, and fundamentally alter the trajectory of many other vexing illnesses.
N7	We believe that for gene therapy products that are offering meaningful therapeutic advantage over available therapies for a serious or life-threatening disease or condition, the accelerated approval pathway offers some unique opportunities.
N7	Taken together, these guidance documents, along with other policies that we plan to issue in 2019, are aimed at helping advance the field of cell and gene therapy.
N7	We believe these cell-based and gene therapy technologies hold tremendous promise for addressing some of the most intractable diseases
N8	The agency is issuing this suite of documents to help advance the field of gene therapy while providing recommendations to help ensure that these innovative products meet the FDA's standards for safety and effectiveness.
N8	In sum, these policy documents are representative of efforts to help advance product development in the field of gene therapy.
O2	The National Institutes of Health (NIH) reports that nearly 7,000 rare diseases affect more than 25 million Americans. Approximately 80% of rare diseases are caused by a single-gene defect, and about half of all rare diseases affect children. Since most rare diseases have no approved therapies, there is a significant unmet need for effective treatments, and many rare diseases are serious or life-threatening conditions.
7.4 Identifying Stakeholders - who is (not) invited to the process	
H1	The draft guidance document provides recommendations to stakeholders developing human gene therapy (GT) products for the treatment of hemophilia.

Doc.	Quote
H2	This guidance is intended to assist stakeholders developing human gene therapy (GT) products for the treatment of hemophilia.
H16	The guidance document provides recommendations to stakeholders developing human gene therapy (GT) products for the treatment of hemophilia.
H17	In addition to the foregoing concerns, we note that hemophilia affects individuals of all racial/ethnic categories and socio-economic levels. And yet some of these population segments are too often under-represented in clinical trials, leading to gaps in knowledge and compounding health disparities.
H17	Trial design for gene therapy should take efforts to reflect the diversity of the American and global patient populations.
H17	Consideration of the socioeconomic diversity of the hemophilia patient population should be integrated into clinical trial design as well as in the development of strategies to reduce enrollment barriers and patient burden of trial participation (e.g., outreach strategies to recruit trial participants, timing and location of clinical / laboratory appointments).
H19	This guidance provides recommendations to sponsors developing human gene therapy (GT) products for the treatment of hemophilia including clinical trial design and related development of coagulation factor VIII (hemophilia A) and IX (hemophilia B) activity assays, including how to address discrepancies in factor VIII and factor IX activity assays.
H19	Plans to address inclusion of clinically relevant populations with regard to age, gender, race, and ethnicity should be discussed with the Agency
N2	This modern framework is intended to balance the agency's commitment to safety with mechanisms to drive further advances in regenerative medicine so innovators can bring new, effective therapies to patients as quickly and safely as possible. The policy also delivers on important provisions of the 21st Century Cures Act.
N7	At the same time, we are committed to continue to develop efficient pathways by which sponsors can come into regulatory compliance while working toward approval of a new Biologics License Application (BLA) for their products.
N7	We already have consortiums of academic investigators who are in active discussions with the FDA about this proposed new approach.
N8	We will continue to work with product innovators, sponsors, researchers, patients, and other stakeholders to help make the development and review of these products more efficient, while putting in place the regulatory controls needed to ensure that the resulting therapies are both safe and effective.
7.4.1 Patients as stakeholders	
H11	We are especially encouraged by FDA's recognition of the importance of the patient voice in drug t. As a patient-centric company, we support the Agency's recommendation that patient experience data be collected and submitted, as it can provide additional information on patient tolerance for risk, perspective on clinical benefit, and can inform overall benefit-risk evaluations.
H19	FDA encourages sponsors to collect patient experience data during product development, and to submit such data in a BLA.
P1	The primary goal of patient-focused drug development is to better incorporate the patient's voice in drug development and evaluation, including but not limited to:
P2	Participants with hemophilia spoke about their ongoing struggle with pain and joint deterioration, and the accompanying diseases of aging such as arthritis and gout, which exacerbate their conditions. They described their limited mobility, easy bruising, and unpredictable bleeding into joints, soft tissue, muscles, and the brain.
P2	Participants, including those with bleeding disorders other than hemophilia, discussed the challenges of decreased school attendance, constrained social interactions, disrupted family life, and limitations in career choices
P2	When queried on the impact of their disease symptoms, two thirds of responding participants (Appendix 3, question 7) cited joint damage and/or pain as having the most significant impact on their or their loved one's daily life. One participant told of having "six joint replacements – both knees, both elbows, one ankle, and one hip."

Doc.	Quote
P2	As one mother said, "one of the most difficult symptoms to deal with is the joint pain during bleeding episodes. When my four-year-old son has bleeding into his knees or ankles, he is unable to walk. It is always a challenge to watch…"
P2	"I have a lot of micro bleeds in my head…I've had blood clots, subdural hematomas. Spent months and months in the hospital, almost died…so micro bleeding is a big thing."
P2	Participants discussed other symptomatic comorbidities associated with aging including the pain of neuropathy that has worsened bleeding pain, longer recovery times, and the need to infuse more coagulation factor products more frequently
P2	We need better products, and not just different versions of the same treatments
P2	Many participants commented on their desire for treatments that can enhance their, or their loved ones' daily quality of life.
P2	We need to shift our clinical focus and to build the outcome around outcomes that are important to patients, not just relevant clinical endpoints, so that I don't have to make decisions about my life goals related to the disease.
P2	A number of participants commented that a patient should be treated according to the patient's symptoms rather than just on the level of factor when assigning the patient to a severe, mild, or moderate category.
P2	The study identified "pain and functional impairment as well as the impact on work and relationships as current issues for our young adults (ages 18-30) highlighting that more ought to be done beyond just encouraging prophylaxis for children with hemophilia.
P7	Maybe there is evidence, and that's actually the question that is represented here, and we described that in our guidance for gene therapy and hemophilia. But the issue is the kind of evidence that is available to us to say that this is enough.
7.5.1 Publicizing and detailing a standpoint	
H19	This guidance provides recommendations to sponsors developing human gene therapy (GT) products for the treatment of hemophilia including clinical trial design and related development of coagulation factor VIII (hemophilia A) and IX (hemophilia B) activity assays, including how to address discrepancies in factor VIII and factor IX activity assays
H19	This guidance also includes recommendations regarding preclinical considerations to support development of GT products for the treatment of hemophilia
7.5.2 Soliciting input	
G1	The agency also invites the public to comment on its draft Level 1 guidances and reviews and considers the submitted comments in preparing the final documents. In some instances, FDA may hold public meetings or workshops on draft Level 1 guidance to solicit additional comments, or it may present draft Level 1 guidance to an advisory committee for review.
H1	Submit either electronic or written comments on the draft guidance by October 10, 2018 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.
H19	Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.
H5	The Food and Drug Administration (FDA or the Agency) is extending the comment period for the notices of availability for six draft guidance documents relating to the development of human gene therapy products that appeared in the Federal Register of July 12, 2018. The Agency is taking this action in response to requests for an extension to allow interested persons additional time to submit comments and any new information.
H5	FDA is extending the comment period on the six documents that published on July 12, 2018 (see SUPPLEMENTARY INFORMATION). Submit either electronic or written comments by December 10, 2018, to ensure that the Agency considers your comment on these draft guidances before it begins work on the final version of the guidances.
H3	Given the breadth and depth of the input requested across all six guidances published simultaneously, BIO requests a 60-day extension of the comment period so that we may be able to provide the Agency with comprehensive comments.

Doc.	Quote
H4	However, due to the number of draft guidances issues, as well as the complexity and importance of the subject matter to the sector, ARM requests that the Agency extend the deadline for comments by 60 days. This will allow us, as well as other stakeholders, the opportunity to fully evaluate the guidances and respond in a detailed and specific manner.
7.5.3 Offering flexibility	
H19	This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.
H19	To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page
H19	Contains Nonbinding Recommendations
H19	We may consider revising these recommendations following the development of reliable evidence on correlates between factor activity and clinical benefit, when such evidence can be generalized to multiple GT products.
H19	Plans to enroll pediatric subjects should be discussed with the Agency in the context of the anticipated benefit-risk profile of the product.
H19	Please be aware that, as additional relevant scientific data becomes available, FDA may revise its recommendations for duration of follow-up for adverse events.
H19	FDA recommends communication with OTAT early in product development, before submission of an investigational new drug application (IND).
H19	Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA's guidances means that something is suggested or recommended, but not required.
7.6 Drawing boundaries – the issue being governed	
H16	The guidance provides recommendations on the clinical trial design and related development of coagulation factor VIII (hemophilia A) and IX (hemophilia B) activity assays, including how to address discrepancies in factor VIII and factor IX activity assays. The guidance also includes recommendations regarding preclinical considerations to support development of GT products for the treatment of hemophilia.
H19	The treatment landscape for hemophilia is evolving. As is the case for other products we review, we intend to evaluate the benefit-risk profile of the investigational product in the context of the treatment landscape at the time of our review of a marketing application.
H19	The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section VIII of this document). We will consider if such an alternative method could be used in place of an animal test method.
N4	For some of these products, we may need to accept some level of uncertainty around these questions at the time of approval. For example, in some cases the long-term durability of the effect won't be fully understood at the time of approval.
N4	In such cases of devastating diseases without available therapies, we've traditionally been willing to accept more uncertainty to facilitate timely access to promising therapies.
N4	We'll continue to work with the product sponsors to help make the development and approval of these innovative gene therapies more efficient, while putting in place the regulatory controls needed to ensure that the resulting therapies are both safe and effective.
N4	The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Doc.	Quote
N7	Since many of the risks associated with gene therapy products relate to questions about the product's durability and potential for rare instances of off-target effects, it may not be feasible to conduct pre-market trials that address all these theoretical risks in any reasonably sized study.
N8	One of the most important steps the FDA can take to support safe innovation in this field is to create policies that provide product developers with meaningful guidance to answer critical questions as they research and design their gene therapy products.
O1	In addition, the recommended LTFU (e.g., 15-year period) will often not elapse for all subjects who received an investigational GT product in the pre-marketing program before the product is licensed.
7.6.1 Carving out safety	
H13	As written, it is not clear whether active or passive monitoring for malignancies is recommended. An expectation for active monitoring for malignancies would be challenging. Passive monitoring for malignancies would be acceptable and should be specified.
H14	The document is silent on whether passive or active monitoring, e.g., for hepatic malignancy, is necessary. We feel that passive monitoring is sufficient as long as there is follow up if specific events are identified. We recommend that the agency identify where passive monitoring is appropriate.
H14	We recommend that greater discussion be provided about the amount of follow up that will be needed for BLA submission purposes. For, example, 1 year of follow-up may appropriate for primary efficacy analysis for BLA submission purposes.
H19	The goal of the follow-up is to monitor the safety and durability of response.
H19	Short-Term Monitoring (first 2 years following GT product administration)
H19	Long-Term Monitoring (≥2 years following GT product administration): Please refer to the FDA guidance on *Long Term Follow-Up After Administration of Human Gene Therapy Products* for recommendations on duration and design of long-term follow up
N4	Even when there may be uncertainty about some questions, we need to make certain we assure patient safety and adequately characterize the potential risks and demonstrated benefits of these products.
N4	Our goal is to help promote safe and effective product development in this field.
P3	Some patients/caregivers are interested in gene therapy but feel there is still too much unknown information about the treatment, including inconsistency about the achieved coagulation factor level and its persistence, and the unknown long-term safety.
P3	The requirement for long-term follow up procedures once a year are generally not considered burdensome. This may include invasive procedures such as a liver biopsy and non-invasive procedures such as an MRI.
P3	Some patients/caregivers are less likely to enroll themselves or their child in a clinical trial if their current prophylaxis treatment is working and manageable.
P3	While the patient/caregiver perspective varies in openness for enrolling in a gene therapy clinical trial, there was consistent interest in understanding the risks and benefits associated with gene therapy:
P3	While patients/caregivers acknowledge that aspects of enrolling in clinical trials can be burdensome, the frequency of safety monitoring was not seen as a high priority when deciding whether to enroll in a clinical trial:
7.6.2 Targeting the right patient - pediatric population	
H10	This statement and the subsequent paragraph provides principles for pediatric studies. While the guidance provides broad, standard ethical principles for conducting pediatric studies, it does not provide recommendations with regard to evaluating gene therapy products in pediatric patients. It would be helpful for the Agency to include additional recommendations for development in this special population, including the appropriate time to start pediatric studies.
H12	Sangamo's specific development focus on hemophilia involves trials that have and will continue to include children and adolescents after appropriate efficacy and safety information has been collected in adults. Given the lifelong impact of our gene therapies, and the years of long-term follow-up involved as discussed elsewhere in the guidance, we recognize that a child in today's trial may well be an adult by the time a clinical trial follow-up period is concluded

Doc.	Quote
H12	We are concerned that this guidance draft does not really engage assent in this special context, or provide guidance on -re-consent [or consent for the first time] when a child is judged to be capable, or the lRB's role is some form of continuing assessment of when may have matured to the point of being able to give consent.
H12	We find the referral to 50.52 and 50.55 helpful, but do not see that either is responsive to the unique aspects of gene therapy clinical trials in the sense above. We are also concerned about the exemptions from assent in 50.55 9 (c) 'The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines..." as above. We urge FDA to reflect further on this area and develop more focused guidance aligned to the specific gene therapy context overall.
H14	We understand the concern about investigations in children. However, we would appreciate more discussion on when it is appropriate to start pediatric studies.
H19	Plans to enroll pediatric subjects should be discussed with the Agency in the context of the anticipated benefit-risk profile of the product. Benefit-risk calculations for GT trials in pediatric patients with hemophilia should consider durability of expression, potential insertional mutagenesis, episomal dilution during liver growth, and the effect of transgene expression. To justify enrolling pediatric subjects, you should: • Submit clinical data from studies in adults to demonstrate sustained and robust steady state factor levels and hemostatic outcomes. • Select an appropriate pediatric population that represents a population with an unmet medical need in the context of available therapies. • Consider conducting studies in appropriate animal models to support sustained factor expression levels following GT product administration. • Consider characterizing the risks of your GT product (e.g., vector integration, insertional mutagenesis) based on available preclinical and clinical data for your product.
P3	Patients/caregivers indicated that the decision to enroll in a clinical trial affects many people beyond the patient. This could include their spouse, children, parents/siblings, and other dependents, all of whom should be involved in the decision to enroll. If a clinical trial were available for children, the child should be old enough to be involved in the decision and understand the commitment of the trial.
7.6.3 Assays – maintaining the status quo	
H6	However, preclinical models have limitations which should be recognized in the Draft Guidances. These include limited utility when informing assays for human use and practical as well as biological limitations in the collection of samples from animal models. Therefore, Sponsors should have the flexibility to use different clinical laboratory assays, where feasible, assays intended for human use, as well as discretionary use collection and use of samples.
H9	Based on several studies it is widely acknowledged that FVIII activity discrepancies between these two assay formats can exist, depending on the type of recombinant FVIII and reagents used for the OC assay. However, these discrepancies rather reflect (technical) limitations and the different set-up of the OC assay than differences in the intrinsic activity of rFVIII variants, including BDD-rFVIII compared to endogenous FVIII as such. FVIII activity levels based on the CS assay are considered predictive of the in vivo efficacy in preclinical models, as well as clinical outcome, and qualify as a valid surrogate endpoint.
H9	It is unclear why a comparative field study recommended, as this is not standard practice for validation of assays in routine clinical practice.
H9	For example, studies in wild type nonhuman primates (no factor deficiency) would not enable the accurate measurement and translatability of hFVIII activity to clinical efficacy based upon an aPTT assay ex vivo. Due to the endogenous animal FVIII there would be hardly any additional assay "window" (further reduction of clotting time) to probe for additional hFVIII activity.
H10	Because sponsors may not have sufficient patient plasma to conduct a traditional large-scale field study, ASGCT recommends that sponsors propose to FDA performing a study that indicates that assays are providing comparable data.

Doc.	Quote
H15	The important point to note though is that despite these problems of assays discrepancies, multiple new CFC products have been licensed by several regulators during these years and have been safely used in all clinical circumstances achieving clinically safe levels of clotting factor activity deemed appropriate for hemostasis in those situations
H15	This matter though while being addressed should not become a reason for delayed registration of these products if they are otherwise safe and effective.
H15	Therefore, we think that it is unlikely that data from early phase clinical studies will be adequate to make these conclusions or clinically relevant decisions at the time of their market authorization given the small numbers of patients recruited during these clinical trials. Yet, as long as significant levels of FVIII or FIX activity can be demonstrated with both these assays, certainly above 5% and preferably above 10%, levels which have been associated with major modification of clinical bleeding profile among these patients, as explained below, those products should qualify for consideration for approval provided all other requirements are met.
H15	We must recognize that this community has a good understanding of the factor levels required to achieve clinically safe hemostasis and those levels will be achieved through additional CFC supplements, as required, beyond what is shown by OC or CS assays of the GT product related clotting factor levels ensuring that patient safety is maintained at all times.
H17	Assay discrepancies matter most for clinicians and patients when they occur either at the low end of factor activity levels and when they occur at a clinical decision point. In some cases, these discrepancies may be overcome through product-specific standards or changes to labeled potency.
H17	The Agency encourages sponsors to "resolve" these discrepancies, particularly if they seek to use factor activity level as a surrogate endpoint. While we are aware of and strongly encourage industry scientists to pursue studies to better understand the biologic bases of this discrepancy, we are concerned that "resolving" this question will delay the clinical trial process and approval of gene therapy products for hemophilia.
H18	Clinicians have had to contend with Factor VIII one-stage/chromogenic assay discrepancies for decades.
H18	However, in most clinical practice, the assay discrepancy has not been "resolved" and clinicians have still been able to incorporate these therapies into routine clinical care. Beyond a threshold of ~15%, differences in the two assays do not affect clinical management.
7.6.4 Shaping the technology – establishing desired GT characteristics	
H9	FDA's definition of gene therapy includes gene editing (footnote 1 on page one), however, this draft guidance does not specifically address gene editing. It would be important to clarify whether any of the components or the combinations of the different components of gene editing, such as gRNA, Cas9, AAV, lipid nanoparticles, etc., would need to be tested in vitro or in nonclinical studies.
H10	Specific guidance should be provided as to when existing vector biodistribution data can be used to support clinical trials of vectors that differ only by transgene product.
H13	ARM encourages the FDA to select a definition for gene therapy, such as the one listed on FDA's website, and to use this definition consistently throughout the guidance documents.
H15	It may be important to also recognize that apart from truncating or using hyper active variants, candidate products may also vary in terms of the 'codon optimizing' techniques used which could impact expression.
H15	The question of whether AAV is an integrating or non-integrating vector aside, the fact that this novel therapy involves gene alteration should be justification enough for longer follow-ups.
H19	GT products currently in clinical development may use a vector to deliver the coagulation factor gene to the liver
H19	Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells.
O1	Are your vector sequences integrated or is the human genome otherwise genetically altered?

Doc.	Quote
O2	Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use
O2	However, in some cases there may be unique characteristics of GT products (e.g., a protein that is expressed by a GT product may have different bioactivity than standard enzyme replacement therapy) that warrant additional considerations both pre-approval and post-marketing.
P7	But there may be some unanticipated effects of codon optimization; altered protein confirmation and stability, altered post-translational modifications, and perhaps even altered protein function in a number of different areas.
7.6.5 Acceptance criteria – conceptualizing a disease, determining successful treatment	
H2	GT products for the treatment of hemophilia are being developed as single-dose treatments that may provide long-term expression of the missing or abnormal coagulation factor in the patient at steady levels to reduce or eliminate the need for exogenous factor replacement.
H9	Change “missing or abnormal” to “very low, missing or unfunctional”.
H19	GT products for the treatment of hemophilia are being developed as single-dose treatments that may provide long-term expression of the deficient coagulation factor at steady levels to reduce or eliminate the need for exogenous factor replacement.
7.6.6 Efficacy endpoints – measuring success	
H15	We would strongly advocate against the use of annual / annualized bleeding rate (ABR) as the primary efficacy end-point for the ‘traditional’ or ‘accelerated’ approval of a GT product. It should be included only as a secondary endpoint. The primary endpoint in GT should be based on plasma clotting factor levels directly reflecting function of the transferred gene.
H15	While ABR has been a good surrogate marker of outcome in hemophilia, its clinical definition has been a challenge leading to major discrepancies in reporting rates. This is because of several reasons including differences in understanding of what should be called a bleed not only among patients but also health care professionals. Anything from a mild discomfort (‘aura’) to a very clinically obvious bleed have all been reported as bleeds
H15	It is also well recognized that among older patients with significant joint disease, many of whom are the subjects of these GT trials, it can be extremely difficult to differentiate pain of chronic arthritis and inflammation from that of an acute bleed.
H15	Products which range in creating sustained plasma factor levels of 5-100% or higher may all look the same in terms of ABR while it is quite obvious that their clinical impact is likely to be clearly quite different.
H17	As mentioned above, NHF has been pleased to sponsor CoreHEM, an international multi-stakeholder project to develop a core outcome set for clinical trials of gene therapy in hemophilia. This core set will ensure that patient perspectives on critical outcomes are included in pivotal trials, allow fair comparisons between alternative treatments, and allow more accurate assessments of the value of these therapies.
H17	Very good results are achieved in terms of ABR with current hemophilia treatments, and clinical trials built on this clinical end-point might not be powered enough to show a statistical difference, even non-inferiority, of gene therapy
H17	Bleeding will be expected to be low for gene therapy, and it is already low for optimized prophylaxis treatment.
H17	ABR has a subjective component, which would require complicating the study design to handle false positive and false negative rates in the adjudication of joint bleeding. Also, the current joint disease status of a patient is largely based on his treatment history and has a large influence on occurrence and reporting of ABR.
H17	Moreover, ABR only captures clinically-recognized bleeding events; it does not capture subclinical bleeds that regularly occur when factor activity level drops below a therapeutic level.
H17	Importantly, since more vector may be required to achieve higher factor levels, this has implications for vector dose, resultant immune responses and transient hepatotoxic effects of the treatment if a level of 50-150 IU/dL becomes the target level.

Doc.	Quote
H18	Unfortunately, morbidity and mortality related to bleeding do continue despite these advancements. For instance, prophylactics delays but do not entirely eliminate progressive joint disease due to the need for compliance with frequent repeated intravenous treatment and aiming for trough levels of 1%, which are inadequate to prevent all bleeding
H18	However, there are no troughs to measure in gene therapy, thus factor levels make sense as a primary endpoint, followed by ABR as one of several secondary endpoints.
H18	Correlating factor activity and bleeding rates will be complex, since it requires understanding what else may have changed in a person's life (such as more or less physical activity, career changes, comorbidities that could increase a person's likelihood for bleeding) that could confound the analysis.
H18	People with hemophilia who receive gene therapy may be more active or take more "risks" than previously, perhaps prematurely before their joints/muscles have time to rehabilitate and strengthen.
H18	It is important to appreciate ABR has a major subjective component, lead to both false positive and false negative rates of joint bleeding due to the underlying arthropathy and inflammation. A patient's current joint disease status is largely based on his treatment history and has a large influence on occurrence and reporting of ABR.
H18	In addition, the National Hemophilia Foundation-McMaster treatment guidelines on care models for hemophilia specifically reviewed outcomes important to assessing care. Outcomes such as bleeding and bleeding rate were considered important but judged not important enough to be included in the final list of patient-important outcomes.
H19	Although ABR is a direct assessment of clinical benefit, ABR has limitations in that it is a relatively infrequent event in patients on prophylactic factor regimens and the decision by a patient to treat a possible bleeding episode is usually somewhat subjective. For these reasons, more objective endpoints, such as factor activity levels, are desirable.
H19	In the drug development process, validated surrogate endpoints may be used to obtain traditional approval for products. However, as noted above, at the present time factor activity levels have limitations that make it difficult for them to be used as a validated surrogate endpoint.
H19	For products that receive accelerated approval, we recommend that the post-approval study to verify the product's predicted effect on clinical benefit use ABR as the primary endpoint
H19	FDA is optimistic that factor activity levels could potentially serve as a validated surrogate endpoint. Pending the availability of such data and reliable calibration methods, we recommend ABR as a primary endpoint to demonstrate clinical benefit
7.6.7 Measuring the added value of gene therapy	
H9	There is more discussion needed regarding the expected value of gene therapy to the patient. The current guidance strongly suggests a comparative benefit to patients based on either 1) non-inferiority in ABR to a well-managed prophylaxis regimen, or 2) potential superiority to on-demand (which is no longer an acceptable standard). This needs to be reconsidered, as ABR does not provide a full picture of clinical outcomes that could be evaluated.
H9	We recommend emphasizing the many important outcomes of gene therapy, as well as the impact on quality of life, ongoing healthcare utilization, and other important patient determined outcomes.
H9	For example, a patient currently on regular and frequent infusions may only have an ABR of ~2 (which is the average) and still require occasional additional treatments in response to injury or surgery. However, this same patient is sedentary, restricted in the ability to travel due to the need to always carry the treatment product, and frequently requires healthcare support – potentially related to difficulties related to infusion. After gene therapy, the patient is no longer sedentary or restricted and will rarely need replacement factor (which is usually a subjective decision.
H11	While patient experience data is informative, we encourage FDA to continue to utilize learnings obtained from the FDA Public Meeting on Patient-Focused Drug Development for Hemophilia A, Hemophilia B, von Willebrand Disease, and Other Heritable Bleeding Disorders held on September 22, 2014, and other patient-focused meetings, as well as learnings obtained directly from patients and advocates who can provide added perspective on the burden of hemophilia, the need for gene therapy treatment options, and acceptable risks.
H11	These learnings collectively formulate patient experience data that will inform FDA's regulatory decision-making.
P3	Some patients/caregivers are less likely to enroll themselves or their child in a clinical trial if their current prophylaxis treatment is working and manageable.

Doc.	Quote
P3	Patient/caregiver's interest in new therapy is partly dependent on the success of their current treatment modality
P3	Some of the benefits considered when thinking about enrolling in a clinical trial include not having to do infusions, the ability to be more active, the prevention of additional pain and joint deterioration, and helping the next generation of hemophilia patients.
	8 Discussion
O2	Sponsors should understand the pathophysiology and natural history of a disease as fully as possible at the outset of product development. Full understanding of mechanism of product action is not required for marketing approval; however, understanding of disease pathophysiology is important in designing clinical trials, including selection of endpoints.
O2	Demonstration of clinical benefit of a GT product follows the same principles as for any other product. However, in some cases there may be unique characteristics of GT products (e.g., a protein that is expressed by a GT product may have different bioactivity than standard enzyme replacement therapy) that warrant additional considerations both pre-approval and post-marketing.
	8.1 Bringing the pieces together, or what does this all mean
O2	If the transgene expression and consequent treatment effect decrease over time, consideration may be given to repeat administration of the GT product.

11.6 Appendix 6 - Abstract in English and German

Hemophilia is a rare disease where the body's ability for blood clotting is compromised. Current treatment guidelines consist of multiple weekly infusions that manage the disease and adjust survival rate to close to normal. Hemophilia is a candidate disease for gene therapy (GT) - a single dose technology to cure the disease or suppress it for several years. GT and hemophilia drug development are both regulated by the FDA. This study draws on publicly available documentation authored by regulators, and endeavors to untangle the dynamics between governance and treatment, by following the process of constructing gene therapy as a relevant treatment modality in FDA guidance documents. Using biopolitics as an analytical tool, this research offers the explanation of a *low threshold attitude* that enables creating a market for novel technologies, thereby normalizing a treatment while deferring its safety risks on to the end user. The research adds to the body of knowledge surrounding the tension between societal expectation of healthcare, the fragile risk-benefit ratio of new treatments, and governmental regulation of novel or emerging technologies.

Hämophilie ist eine seltene Krankheit, bei der die Fähigkeit des Körpers zur Blutgerinnung beeinträchtigt ist. Die aktuellen Behandlungsrichtlinien bestehen aus mehreren wöchentlichen Infusionen, die die Krankheit behandeln und die Überlebensrate auf einen nahezu normalen Wert bringen. Hämophilie ist ein Krankheitskandidat für die Gentherapie (GT) – eine Einzeldosis-Technologie, um die Krankheit zu heilen oder für mehrere Jahre zu unterdrücken. Die Entwicklung von GT- und Hämophilie-Medikamenten wird von der FDA reguliert. Diese Studie stützt sich auf öffentlich zugängliche von Aufsichtsbehörden verfassten Dokumentation, und versucht, die Dynamik zwischen Governance und Behandlung zu entwirren, indem sie den Prozess der Konstruktion der Gentherapie als relevante Behandlungsmodalität in FDA-Leitliniendokumenten verfolgt. Unter Verwendung von Biopolitik als analytisches Werkzeug, bietet diese Forschung die Erklärung einer niederschwelligen Haltung, die es ermöglicht, einen Markt für neuartige Technologien zu schaffen und dadurch eine Behandlung zu normalisieren, während ihre Sicherheitsrisiken auf den Endverbraucher verschoben werden. Die Forschung ergänzt das Wissen um die Spannung zwischen den gesellschaftlichen Erwartungen an die Gesundheitsversorgung, dem fragilen Risiko-Nutzen- Verhältnis neuer Behandlungen und der staatlichen Regulierung neuartiger oder aufkommender Technologien.