Gene Therapy for Blood Disorders
March 3-5, 2020 | Boston, MA

Gaining Insights into a Successful Hemophilia Gene Therapy Trial

March 5, 2020

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Meet the Presenter

- 15+ years strategic leadership of clinical trials in hemophilia, metabolic disease, and other areas
- Prior Sr Manager of Clinical Operations for GE Healthcare, and Director of Strategic Development of Quintiles/IQVIA
- ASGCT Government Relations Board Member
- ARM EU and US Regulatory Committee Member
- Author of 2017 GCP, and 2019 Gene & Cell Therapy chapters in Best-selling RAPS regulatory strategy textbooks

Agencies Wrote the Regulations.
We Wrote the Book.

Fundamentals of US Regulatory Affairs, 10th Edition

History of Hemophilia Care & Research

1800s

The Royal Disease

Bleeding observed in 19th & 20th century, found in Britain and passed to various royal houses in Spain, Germany, and Russia

1920s

Whole blood transfusion; experimentation with natural coagulants

Whole Blood

1950-60s

First Cryoprecipitates

Characterization of rare factor deficiencies, (FVII, X, XI and XII first recognized; FXIII in 1960)

1970s

Plasma-Derived Factor Concentrates (1st Home Therapy)

1973 Hemophilia Care Act

Federal funding for comprehensive hemophilia treatment centers

1980s

Bad Blood Scare

Early 1980s

FVIII & FIX genes and cloning

1990s

1992 — **1st Gen rFVIII** (animal derived)

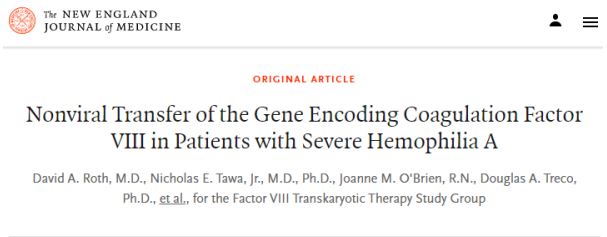
1994 — **2nd Gen FIX** (human derived)

Recombinant Factor Therapy (decreased immunogenicity & longer half-lives)

Early gene therapy (not hemophilia)

First non-viral gene therapy

Non-viral somatic cell gene therapy using autologous fibroblasts transfected with plasmid containing the cDNA for BDD-FVIII


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nonviral Transfer of the Gene Encoding Coagulation Factor VIII in Patients with Severe Hemophilia A

David A. Roth, M.D., Nicholas E. Tawa, Jr., M.D., Ph.D., Joanne M. O'Brien, R.N., Douglas A. Treco, Ph.D., et al., for the Factor VIII Transkaryotic Therapy Study Group

2000s

2000 — **2nd Gen rFVIII**

2003-2008 — **3rd Gen rFVIII & rFVIX** (no animal or human protein in production)

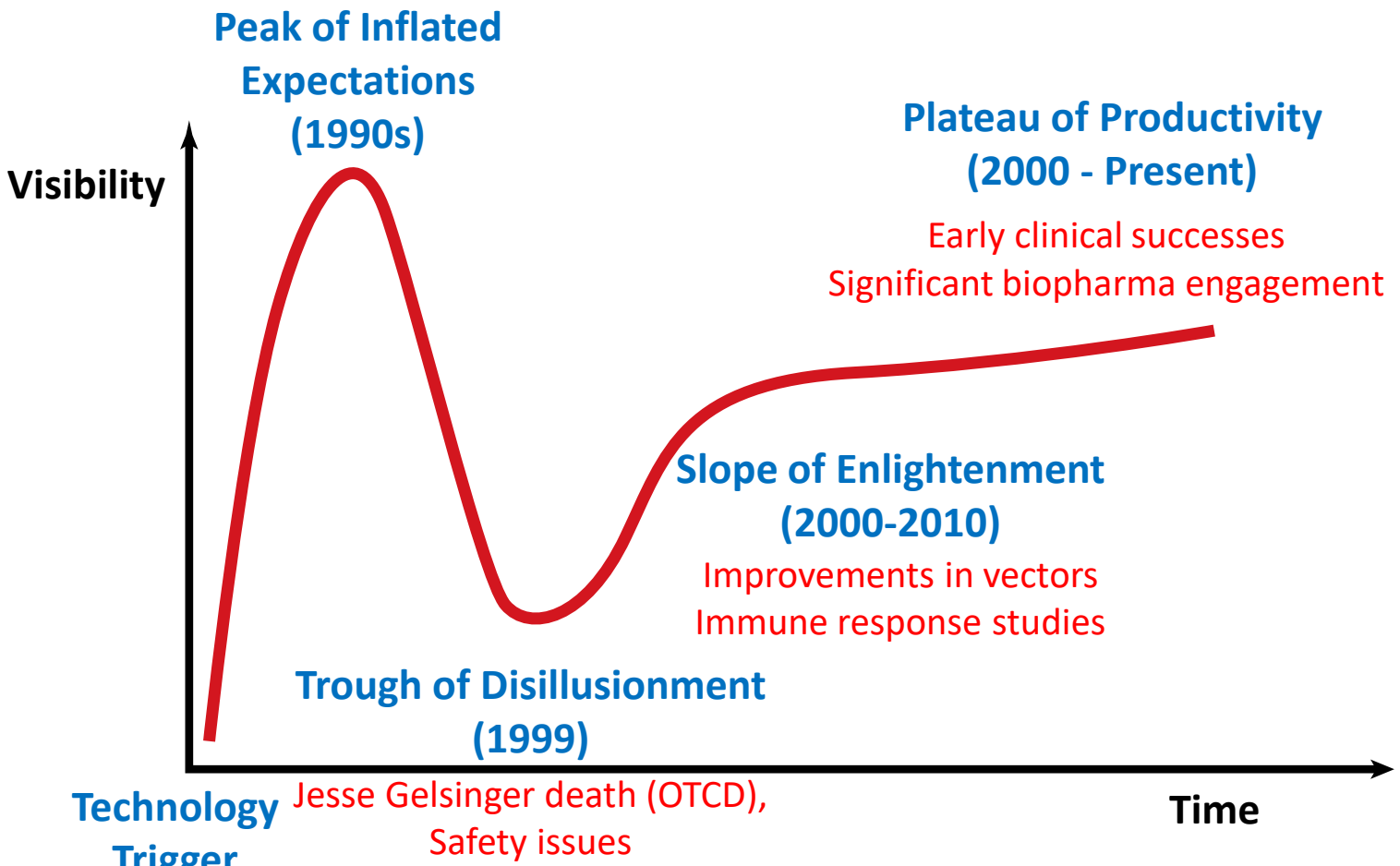
Viral Vector Gene Therapy

First gene therapy trial for hemophilia B using AAV-mediated FIX gene transfer to skeletal muscle by direct injection

2010s

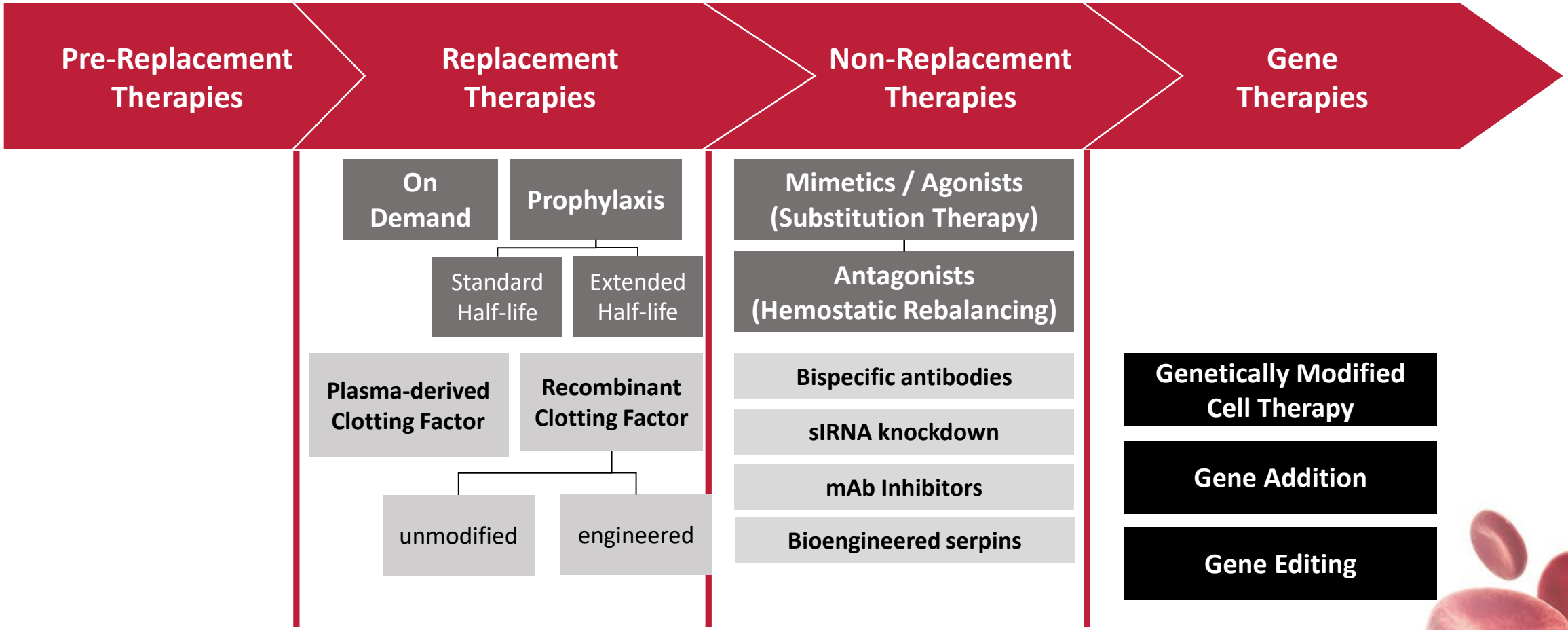
2014-2016 — **4th Gen rFVIII**

The “Hype Cycle” for Gene Therapy



See Rinde (2019). The Death of Jesse Gelsinger, 20 Years Later: Gene editing promises to revolutionize medicine. But how safe is safe enough for the patients testing these therapies? Science History Institute.

Current & Future Hemophilia Care Landscape

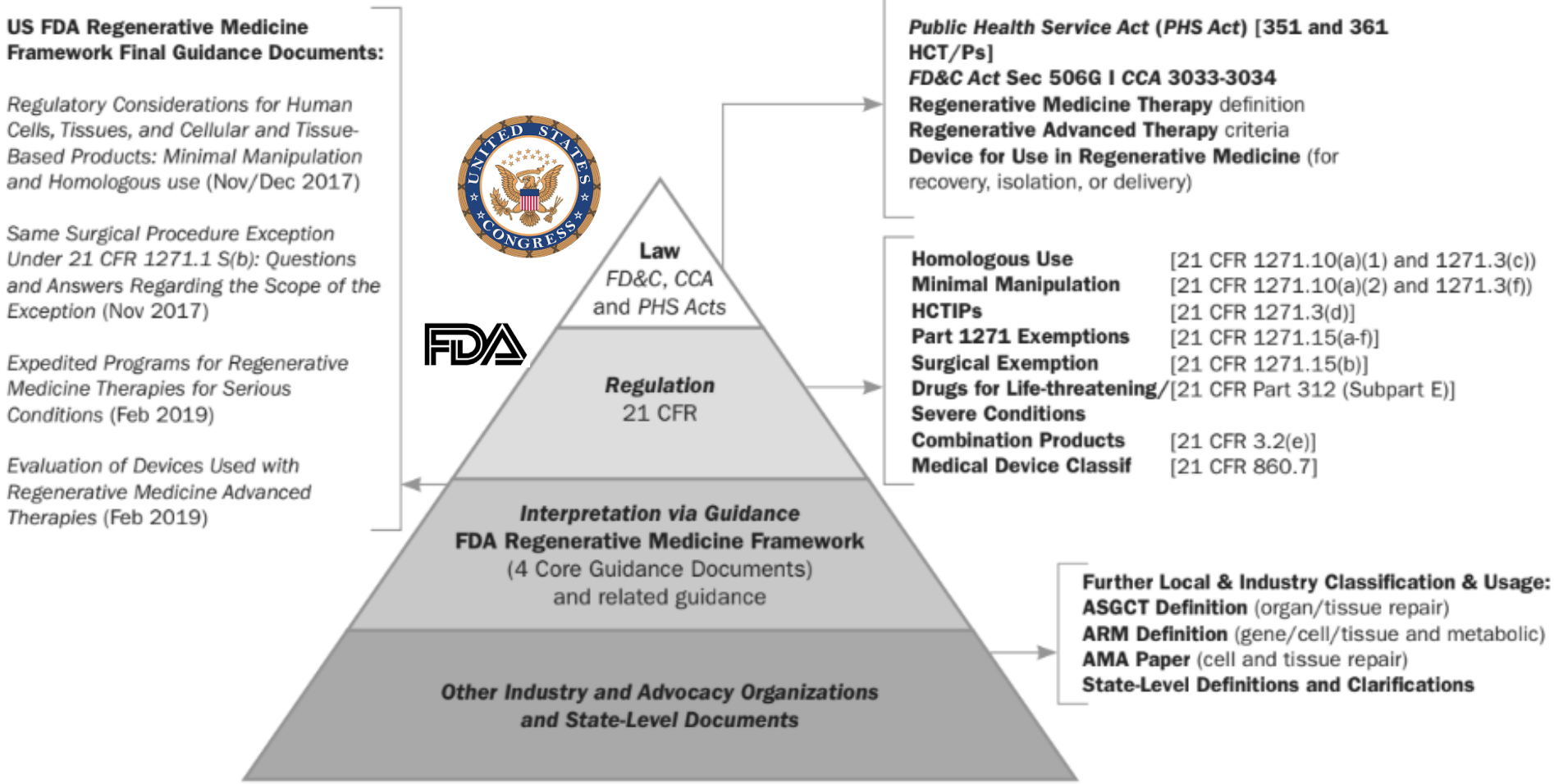


Adapted from Pipe SW. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):650-656

Select Ongoing Hemophilia Gene Therapy Clinical Trials

Manufacturer	Type of Program	Hemophilia A	Hemophilia B
BIOMARIN	AAV	BMN-270 **BLA Feb/20/2020** (valoctocogene roxaparvovec)	N/A
Pfizer Spark Therapeutics	AAV	SPK 8001 (Phase 3 lead in)	SPK 9001 (Phase 1/2)
Pfizer Sangamo Therapeutics	AAV	SB-525 (Phase 3 lead in)	SBIX (Phase 1/2)
FREELINE Therapeutics	AAV	FLT180a (Phase 1/2)	FLT-180 (Phase 1/2)
Takeda	AAV	BAX888/SHP654/TAK-754 (Phase 1/2)	SHP648
Bayer Dimension Therapeutics	AAV	BAY 2599023/DTX201 (Phase 1/2)	N/A
Bioverativ A Sanofi Company	LV	LV-FVIII	LV-FIX
uniQure	AAV	N/A	AMT-061 (Phase IIb)
sigilon therapeutics	GT Cell Therapy	SIG-001 (IND enabling 1H2020)	SIG-003 (preclinical)

FDA Regulatory Framework for Gene Therapy



Used with author permission from Johnson, A.N. (2019) "Regulating Cell and Gene Therapies, Genetically Modified Cells and Devices in Regenerative Medicine." *US Regulatory Affairs Fundamentals*. Regulatory Affairs Professional Association (RAPS): Rockville, MD, USA.

FDA Finalizes Gene Therapy Framework

On **January 28th 2020**, FDA announced finalization of several guidance documents of the 27 gene and cell therapy relevant in its framework:

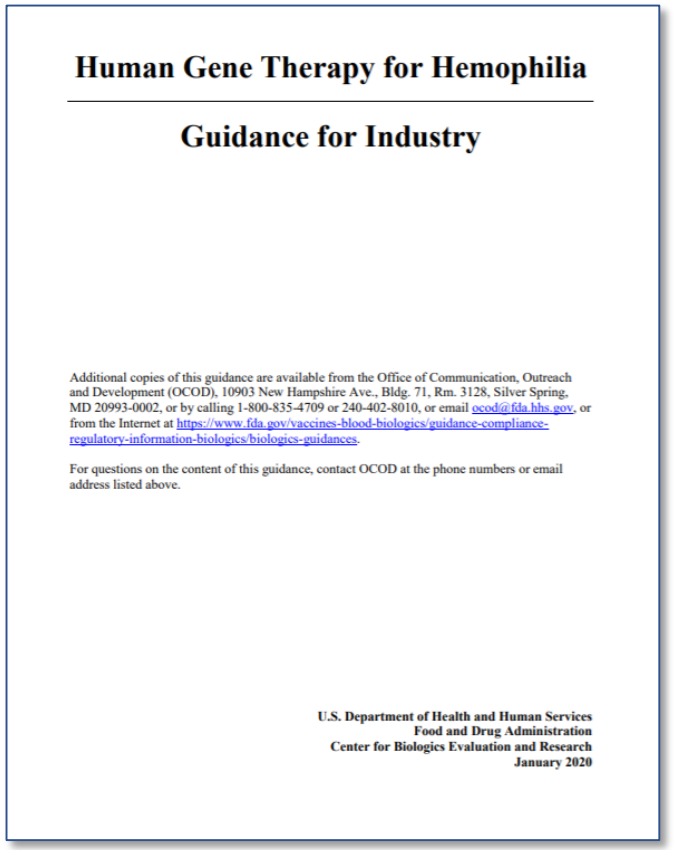
- Final Guidance: Human Gene Therapy for Hemophilia
- Final Guidance: Human Gene Therapy for Rare Diseases
- Final Guidance: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- Final Guidance: Long Term Follow-Up After Administration of Human Gene Therapy Products
- Draft Guidance: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations

Hemophilia Trial Design

The Jan 2020 guidance finalizes the recommendations for hemophilia trial design first published in draft in Jul 2018.

Key changes from 2018-2020:

- Clarification on ABR vs factor level as efficacy measures
- Specifications for traditional and accelerated approval
- Discussion of assay selection, limitation, and validation



Human Gene Therapy for Hemophilia

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

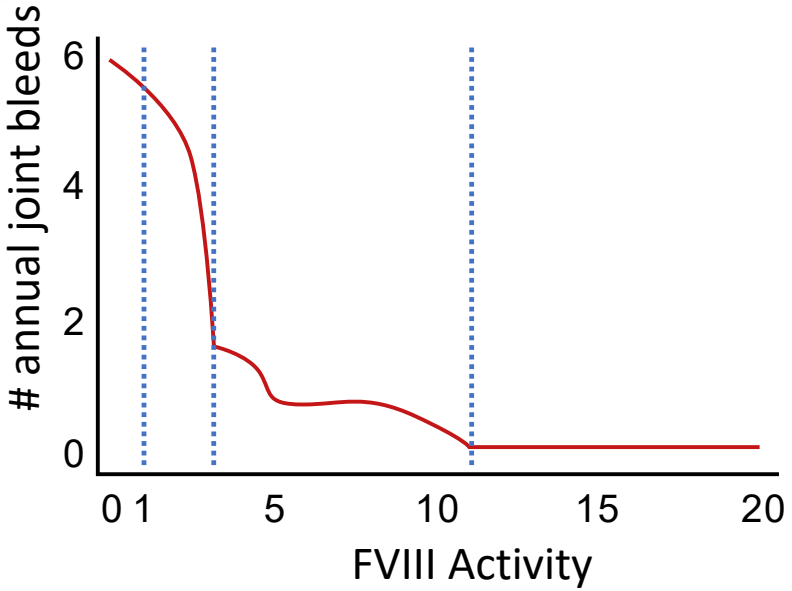
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

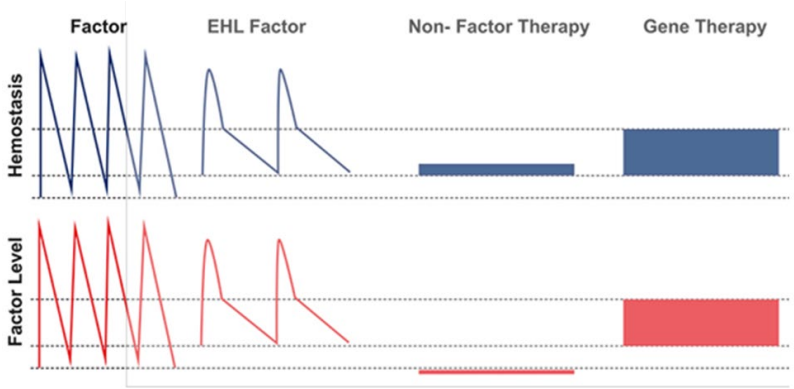
Essential Concepts in Modern Trials

- Hemophilia treatment has advanced dramatically, with more treatment options and improved safety
- Standard outcome measures of factor activity and Annualized Bleeding Rate (ABR) have strengths and limitations
- Studies of therapies that provide sustained hemostasis require reassessment of outcome measures.
- Patient important outcomes (PIOs) and patient reported outcomes (PROs) are critical for meaningful studies.

See Konkle et al. (2019) Hemophilia trials in the twenty-first century: Defining patient important outcomes. Res Pract Thromb Haemost. 2019 Apr; 3(2): 184–192.

Hemophilia Severity & Access





- FVIII levels 1-3% significantly moderates symptoms
- Around 10-15% risk of joint bleeds start to disappear
- Typical treatment entails frequent intravenous infusions of missing coagulation protein, which is costly, burdensome, and factor levels stull flux.
- **Despite improvements, only ~25-30% of patient have access worldwide to replacement factor**

Gene Therapy for Blood Disorders

Adapted from Den Uijl IE. Hemophilia. 2011; 17(6):849-853

Factor Level as Surrogate Measure of Efficacy

Factor activity level was historically used as a primary endpoint.

Plasma-derived & recombinant factor surrogate endpoint

- **Primary Efficacy:** factor activity level
- **Secondary Efficacy:** cessation of bleeding, surgical hemostasis, neutralizing antibody (NAb) / inhibitor formation
- **Safety**: Viral safety, etc.

Limitations of Factor Level Surrogate

- Variation of up to 15% based on lab used
- Younger generations receiving recombinant factor since childhood evidence less progressive joint injury
- Not a 'patient relevant' outcome,

  e.g. lifestyle factors may influence actual bleeding issues with same factor level
- One-stage vs. chromogenic assays produce different values for recombinant factor

See Konkle et al. (2019) Hemophilia trials in the twenty-first century: Defining patient important outcomes. Res Pract Thromb Haemost. 2019 Apr; 3(2): 184–192.

ABR Measure of Efficacy

Currently, annualized bleeding rate (ABR) is widely recommended as a primary efficacy measure, including in FDA guidance.

Gene Therapy ABR Efficacy Endpoints

- **Primary Efficacy:** ABR
- **Secondary Efficacy:** bleeding events, factor consumption, annualized number of infusions (AIR), joint specific ABR
- **Safety**: SAEs

Benefits of ABR Efficacy Measure

- Demonstrates more than simple bioequivalence
- Is a 'patient relevant' outcome

Limitations of ABR Efficacy Measure

- May be influenced by trauma or physical activity, reporting of precipitating events critical
- Differentiating between all bleeds and significant joint bleeds needed
- Joint function scales (e.g. hemophilia joint health score, HJHS) more reliable but much longer follow-up

See Konkle et al. (2019) Hemophilia trials in the twenty-first century: Defining patient important outcomes. Res Pract Thromb Haemost. 2019 Apr; 3(2): 184–192.

FDA Traditional vs. Accelerated Approval

Traditional Approval

Primary Efficacy: Annualize Bleeding Rate (ABR)

Phase 1/2 | Phase 1/2 Follow-up (5 -15 yr)

Phase 3 | Phase 3 Long-term Follow-up (5 -15 yr)

▲ Market Authorization Submitted (BLA/MAA)

Accelerated Approval (uses surrogate endpoint representative of clinical benefit)

Primary Efficacy (Surrogate): Factor Level

Phase 1/2 | Phase 1/2 Follow-up (5 -15 yr)

Phase 3 | Phase 3 Long-term Follow-up, includes ABR (5 -15 yr)

▲ Market Authorization Submitted (BLA/MAA) with interim/surrogate

Factor Level Assay Discrepancies

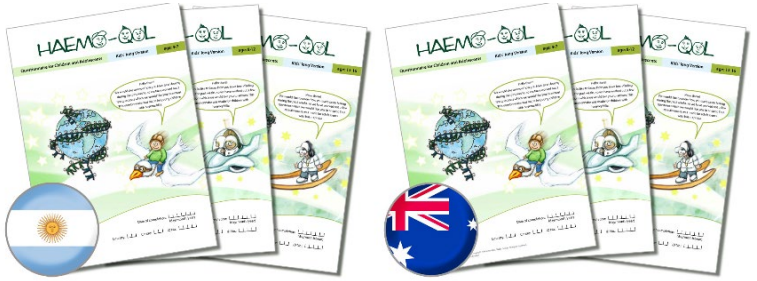
Discrepancies pose particular challenges for early phase and accelerated approval. FDA indicates validation needed.

One stage clotting (OC) assay		Chromogenic substrate (CS) assay
• Most widely used • Risk of false negatives/false positives • may be influenced by nonspecific inhibition • Gene therapy BDD-FVIII transgene patients show higher levels vs CS	**VS.**	• More recently developed • Two-staged test (purified coagulation factors and FXa-specific chromogenic substrate) • rBDD-FVIII treated patients show higher levels than in OC

Capturing Patient Experience

FDA guidance emphasizes **patient experience assessments**, and while not explicit on specific tools literature shows an array of options:

- **Haemo-QoL-A** is a hemophilia-specific, health-related quality of life questionnaire for adults, validated in many languages
- **Patient Diaries & e-Patient Reported Outcome** (ePRO), for survival, function, and QoL
- **Patient Participation in Research design**
- **Real World Data (RWE)** & Social science research methods (e.g. ethnography, social media research)



Protected: Argentina | Spanish

Protected: Australia | English

Protected: Belgium | French

Protected: Brazil | Portuguese

Strategies & Heuristics for Patient Experience

Tier 1: Health Status Achieved or Retained

Survival	Degree of health or recovery	
Life Expectancy	Functional/activity	Bleeding
		Pain
	Serious bleeds	HRQoL
Overall Survival	Musculoskeletal complications	Cure/Recurrence

Tier 2: Process of Recovery

Time to Recovery / Normal Activity	Disutility of Care / Treatment Process
Time to diagnosis (birth, later, etc.)	Inhibitor development
Time to treatment onset	Pathogen transmission (e.g. blood-born disease)
Time to recover from bleeding	Orthopedic intervention (e.g. joint surgery)
Time missed at school / work	Infection (local infection, e.g. at port site)
	Long-term venous access

Tier 3: Sustainability

Sustainability, Recovery, Recurrences		Long-Term Consequence
Bleed Frequency	Joint preservation	Short and Long term disability
Lifelong productivity	Sustained activity	Age-relate comorbidities & complications

Adapted from O'Mahony B, Dolan G, Nugent D, Goodman C. Patient-centred value framework for haemophilia. Haemophilia. 2018;24:873–192.

FDA Recommended Lead-ins

- 6-12 months without change in prophylaxis recommended
- Observational (rather than chart review) ABR and factor use lead-in, establishing baseline and increasing statistical powering
- Enrolling on-demand therapy patients in separate cohort

Pre- & Post-Administration Considerations

FDA Jan 2020 guidance makes recommendations:

Pre-Administration

- 6 -12 month lead-in period to establish baseline (no change in prophylaxis or inhibitor status)
- Lead-in should be observational, where possible
- On-demand therapy patients in separate cohort

Post-Administration

- Plan for rFVIII intervention for bleeding
- Pre-specify target factor activity level and time of discontinuing current therapy
- Specify start of ABR rates and durability of response is to begin (e.g., 3 weeks after steady state levels are reached)
- Plan for initiation/dosing/tapering of corticosteroids treatment/prophylaxis) for immune-mediated liver dysfunction.

Statistical Design & Monitoring

- To support a BLA for traditional approval, FDA recommends a **non-inferiority (NI) clinical trial design** with ABR as the primary efficacy endpoint, using within-subject comparison
- 1-2x weekly monitoring liver function and activity levels to steady state; factor activity thereafter at least every 6 months for 5 years
- Periodic monitoring for
  - levels of vector-related antibodies
  - inhibitor antibodies to factor VIII or factor IX
  - emergence of new clinical conditions, e.g. new malignancies and incidence or exacerbation of pre-existing neurologic, rheumatologic, or autoimmune disease
  - factor activity at least once every 6 months for 5 years.

Population Selection

- Consider if pre-existing antibodies are an issue; FDA encourages companion product development where applicable

  e.g. For example, Biomarin AAV5 total antibody assay, submitted as a PMA alongside the BLA. Other IVDs may be useful in patient selection
- Include washout period following exogenous factor replacement
- Measure inhibitor levels, generally patients with existing inhibitors to replacement factor are ineligible

Current Limitations to Patient Eligibility

Current Populations:

- Adult males
- Moderate severe/severe hemophilia
- AAV vector serotype negative (except UniQure Hem B trial)

Future target populations

- Current or past inhibitors (in early phase)
- Pre-existing anti-AAV antibodies
- Females with hemophilia
- Pediatrics and Adolescents (AAV modifications may be lost in growing liver)
- History of failed gene therapy / redosing

FDA Long-Term Follow-up Recommendations

FDA recommends Long-Term Follow-up based on product type, as follows:

- 15 years for integrating vectors such as gammaretroviral and lentiviral vectors and transposon elements.
- Up to 15 years for herpes virus vectors (or oncolytics) that are capable of establishing latency.
- Up to 15 years for microbial vectors that are known to establish persistent infection.
- Up to 15 years for genome editing products.
- Up to 5 years for AAV vectors.

*15 years includes 5 years annual observation, 10 years follow-up by questionnaire/etc.

Future Issues in Trial Design

- **Shrinking Patient Pool**: From a pragmatic standpoint, there may be an insufficient number of hemophilia subjects for future trials, if conducted according to the current American and European regulatory requirements
- **Limitations of Redosing**: This is particularly a consideration for therapies that cannot currently safely redose. Particularly in younger patients, formation of neutralizing antibodies to AAV can mediate vector clearance and inhibit efficacy.
- **Genetically modified cell therapies** may offer an attractive alternative for redosing and patients ineligible for AAV

Summary

- AAV-mediated gene therapy has been successful in increasing FVIII and FIX levels, potential to decrease factor usage and bleeding
- More long-term safety and efficacy data is needed, and FDA/EMA currently recommends relatively long Long-Term Follow-up (up to 15 years)
- The regulatory framework continues to develop for gene therapies and tissue-engineered products

Thank You

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