Revolutionizing Gene Therapy for Hemophilia B

Kaushik D Save:

Statistical Data Sciences Lead,
Pfizer Healthcare India Pvt Ltd

Profile highlights

- Statistical Programming and Data Management (>13 years)
- SDTM, ADaM and TFLs datasets and outputs
- CDISC Standards for Data Acquisition, SDTM and ADaM
- **Data Management**: Study Start-up, Conduct and Close-out activities
- Leading studies and projects across statistical programming and data management
- Study management and documentation

PharmaSUG SDE HYDERABAD, INDIA APRIL 12, 2025

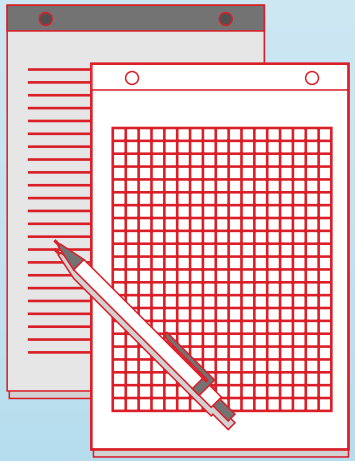
Revolutionizing Gene Therapy for Hemophilia B

Ushering in a New Era for Hemophilia B Gene Therapy

HYDERABAD, INDIA
PharmaSUG SDE
APRIL 12, 2025

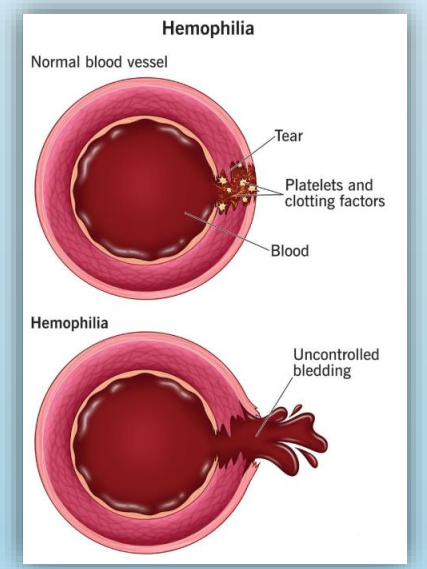
Presentation Overview

- Hemophilia B
- Blood Clotting Pathway
- Conventional Therapy
- Gene Therapy and Advantages
- Gene Therapy – Mode of Action
- Current Study, Study Outcomes
- Regulatory Outlook for Gene Therapy (US, EU, Japan)



Hemophilia B

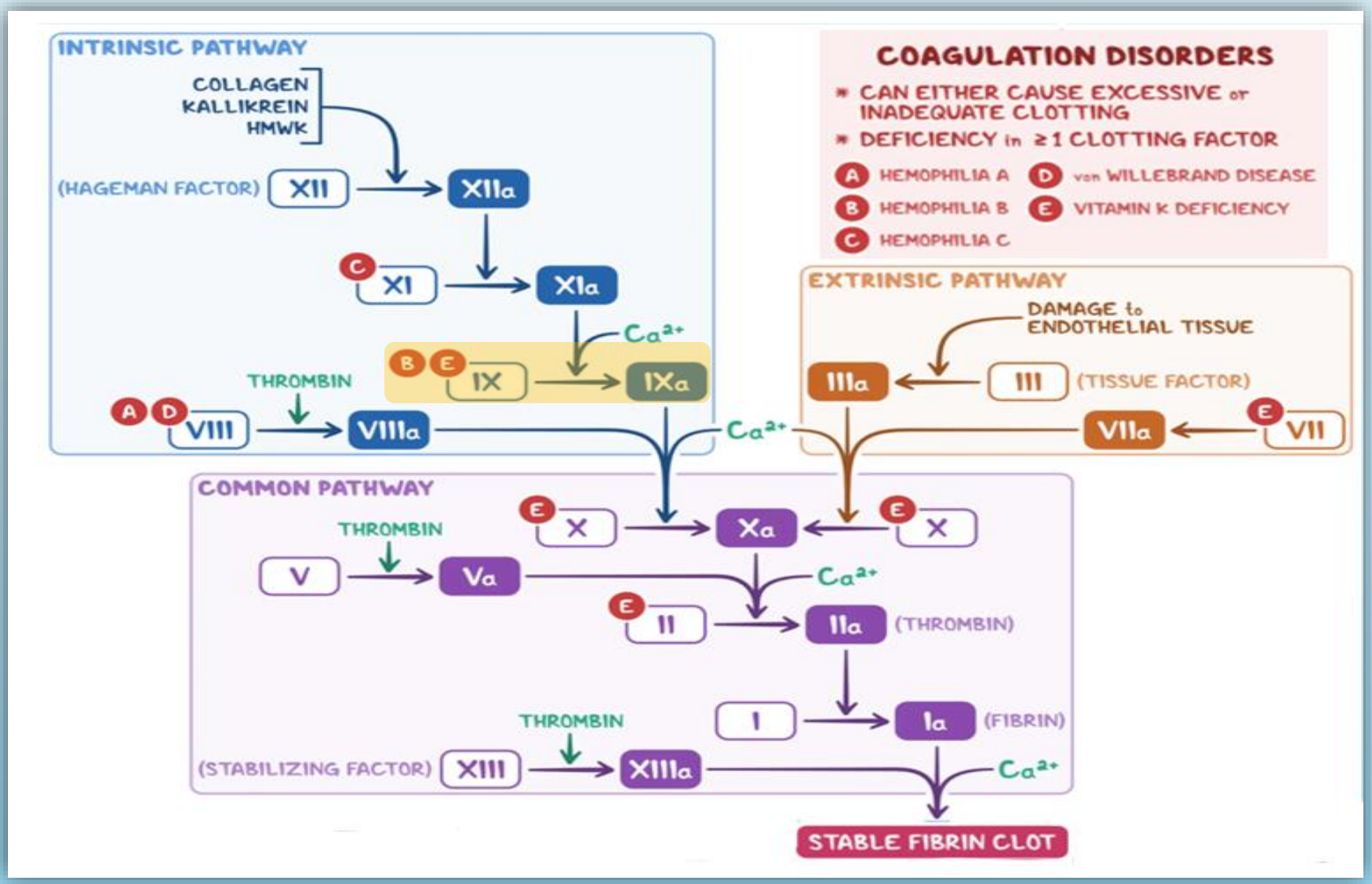
- Rare Genetic Bleeding Disorder
- Deficiency in coagulation factor IX (FIX)
- **38,000** affected worldwide
- **X-linked disorder**, mainly impacts males (1 in 30,000 male births)
- Severity ranges from increased bleeding post-injury to spontaneous hemorrhages



Hemophilia B Severity

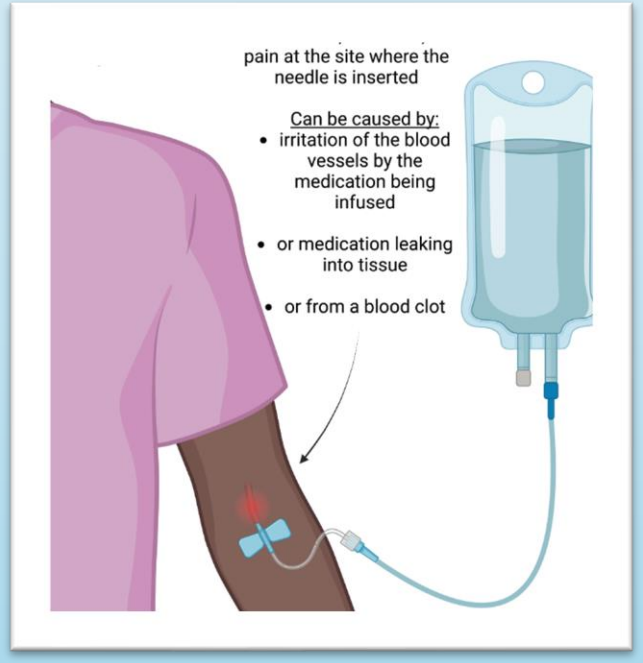
Severity Criteria (Normal FIX value 3–5 mg/mL)	Severe	Moderate	Mild
	< 1% of normal factor IX activity	1% to 5% of normal factor IX activity	5% to 40% of normal factor IX activity
	Spontaneous bleeding episodes (Joints Muscles, etc.)	Bleeding usually occurs after minor injuries or surgeries. Spontaneous bleeding is less common	Bleeding typically happens only after significant injuries, surgeries, or dental procedures

Blood Clotting Pathway and FIX

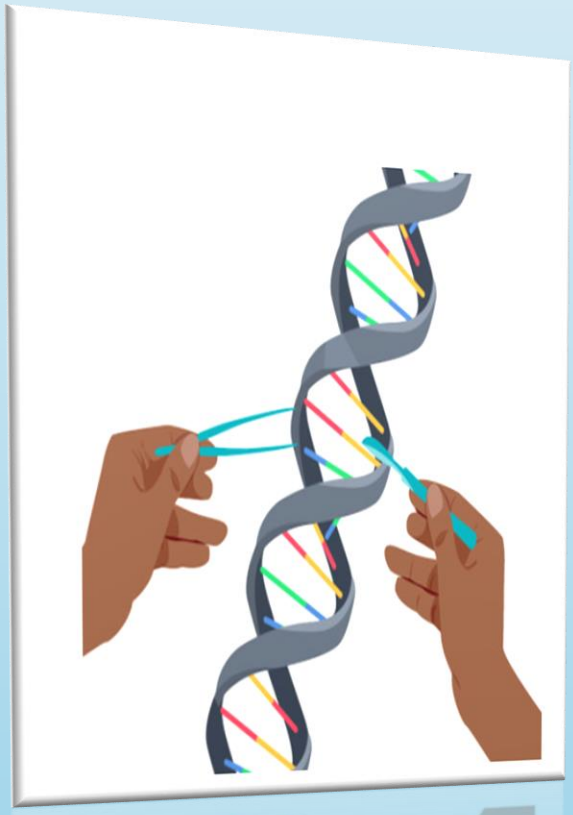


Conventional Therapy

- **Prophylactic Factor Replacement Therapy**
  - IV injection Factor IX concentrates
  - Aim to raise FIX activity above detectable levels (>1%)
  - **Requires frequent infusions** (3x/week for Hemophilia A, 2x/week for Hemophilia B)
- Complications
  - **Inhibitory antibodies** against the coagulation factors



Gene Therapy and its Advantages



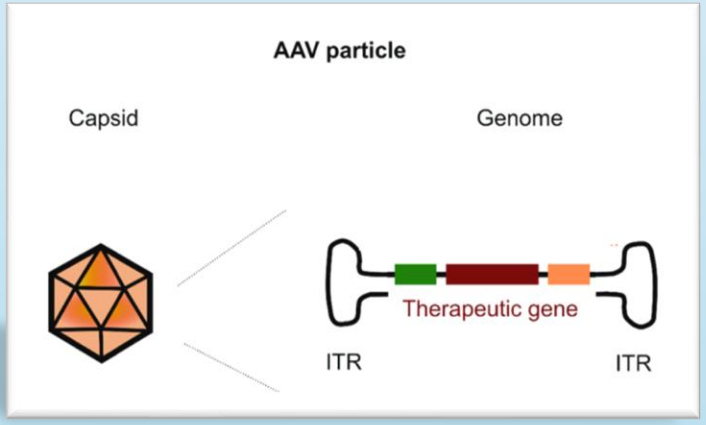
- **Fidanacogene Elaparvovec (BEQVEZ) – a Gene Therapy Product**
  - **One-time** treatment
  - Enables production of FIX **internally**
  - Reduces need for regular infusions
  - Sustained bleed protection, potentially avoids years of prophylaxis

Gene Therapy – Mode of Action

Fidanacogene Elaparvovec (BEQVEZ)

1. Capsid Process (Delivery Phase)

- Bioengineered **AAV** Capsid
- Strong **hepatotropic profile** (affinity or specificity for the liver).
- Increases resistance to circulating nAbs to AAV



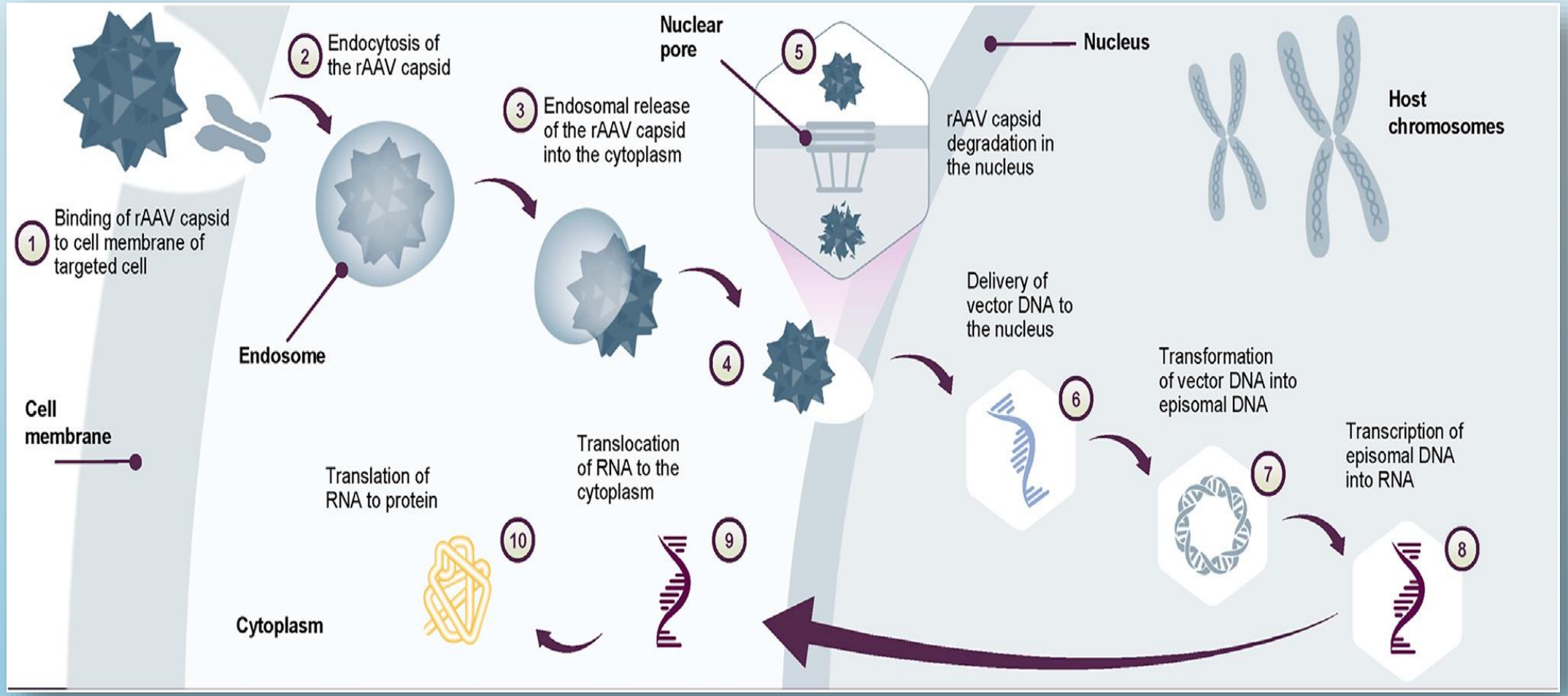
2. Cassette Process (Expression Phase):

- Encodes a naturally occurring FIX variant
- Functional copies of a high activity FIX gene into **hepatocytes**

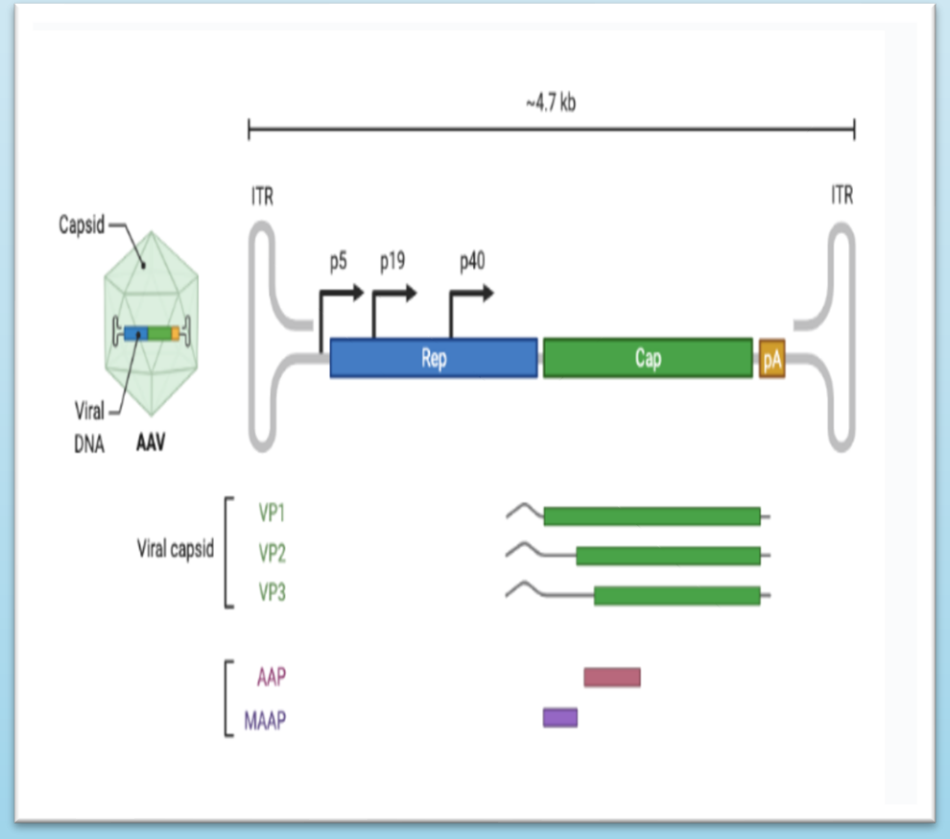
(Naturally F-IX is synthesized in the liver and is vitamin K-dependent)

- FIX expression

Gene Therapy – Mode of Action



Adeno-Associated Virus (AAV) Vectors



AAV, Structure and Function

- Icosahedral capsid composed of 60 protein subunits (VP1, VP2, VP3).
- Contains single-stranded DNA (~4.7 kb).
- Contains Inverted Terminal Repeats (ITRs) critical for replication and packaging

Recombinant AAV, Structure and Function

- **Remove rep & cap genes** from natural AAV genome
- Insert **therapeutic gene** between ITRs.
- Use helper plasmids providing rep, cap, and adenovirus helper functions
- Serotypes specific **cell receptors specificity**

Adeno-Associated Virus (AAV) Vectors

Why AAV/rAAV?

- **Non Pathogenic Virus**: Doesn't Cause Disease
- **Long Term Expression**: Especially in Non Dividing cells
- **Low Immune Response**: Compared to other viruses
- **Tropism Versatility**: Serotypes can target specific tissues (Brain, Liver Muscle) due to **cell receptors specificity**

Serotype	Tropism	Key Features & Applications
AAV1	Muscle, heart, CNS	High efficiency in muscle gene delivery, used in muscle disorders
AAV2	Liver, muscle, CNS, retina	One of the first studied, well-characterized; used in eye gene therapy (e.g., Luxturna)
AAV3	Liver	Less commonly used, has potential for liver-targeted therapies
AAV4	CNS	Central nervous system
AAV5	Lung, retina, CNS	Useful in lung and eye gene delivery
AAV6	Muscle, lung, heart	good for muscle and lung tissues
AAV7	**Liver, muscle**	**Strong liver tropism, Less use in clinical setting**
AAV8	Liver, muscle, heart	**Highly efficient liver transduction**, widely used in liver-targeted gene therapies
AAV9	CNS, heart, muscle, liver	Can cross the BBB; used in therapies for neurological diseases
AAVrh10	lung, muscle	Good CNS penetration; alternative to AAV9

Clinical Study and Outcomes

Clinical Study – General Information

- Pivotal Phase 3, open-label, single-arm study
- 45 Adult male participants (age 18-65) with moderately severe to severe hemophilia B
- Approved in USFDA, EMA, Taiwan
- Comparing pre and post treatment parameters

Efficacy Parameters

- Annualized bleeding rate (ABR)
- Annualized infusion rate (AIR) of exogenous FIX
- Vector-derived FIX:C (Circulating FIX level)
- Annualized FIX consumption
- Annualized number of bleeding events
- Frequency of target joint bleeds
- Changes in HJHS, QoLs, HAL.

Safety Parameters

- Hypersensitivity reactions
- Clinical thrombotic events
- FIX inhibitors
- Hepatic malignancies
- Drug related elevated hepatic transaminases
- Immunogenicity

Clinical Study and Outcomes

Outcomes

- **ABR (Annualized Bleeding Rate)** vs. prophylaxis regimen (**44% decrease**).
  Mean ABR: 2.5 post-treatment vs. 4.5 pre-treatment (2/4.5=44%)
  Median ABR of 0 (range: 0–19) Vs prophylaxis regimen median ABR 1.3 (range: 0–53.9).

- Bleeds eliminated in **60% of patients** (ZERO bleeds during the efficacy evaluation period 27 out of 45)

- **87%** of participants **prophylaxis free** (39 out of 45 participants)

- No deaths, SAEs related to treatment or associated with infusion reactions, thrombotic events, or FIX inhibitors were reported.

Clinical Study and Outcomes

Parameter	Stats	FIX Prophylaxis	Gene Therapy	Type of Statistical Test	Test of Hypothesis Pvalue	Method	Estimation Parameter	Estimated Value	(2-Sided) 95% CI
ABR Total Bleeds	Mean (95% CI)	4.43 (1.81 to 7.05)	1.30 (0.59 to 2.02)	Non-Inferiority	0.0081	GLM	Mean Difference	-3.13	-5.44 to -0.81
ABR Treated Bleeds	Mean (95% CI)	3.35 (1.71 to 4.98)	0.73 (0.25 to 1.21)	Non-Inferiority	0.0019	GLM	Mean Difference	-2.62	-4.27 to -0.96
ABR Spontaneous Bleeds	Mean (95% CI)	3.24 (0.92 to 5.56)	0.69 (0.19 to 1.20)	Non-Inferiority	0.0191	GLM	Mean Difference	-2.55	-4.67 to -0.42
ABR Traumatic Bleeds	Mean (95% CI)	1.16 (0.34 to 1.98)	0.59 (0.26 to 0.92)	Non-Inferiority	0.1528	GLM	Mean Difference	-0.57	-1.35 to 0.21
ABR Untreated Bleeds	Mean (95% CI)	1.07 (-0.32 to 2.47)	0.57 (0.14 to 1.00)	Non-Inferiority	0.3738	GLM	Mean Difference	-0.51	-1.63 to 0.61
AIR of Exogenous FIX	Mean (SD)	58.83 (29.056)	4.46 (10.028)	Superiority	<0.0001	Paired t-test	Mean Difference	-54.37	-63.64 to -45.10
Annualized Factor Consumption	Mean (SD)	3170.74 (1634.753)	235.04 (538.977)	Superiority	<0.0001	Paired t-test	Mean Difference	-2935.7	-3403.10 to -2468.30

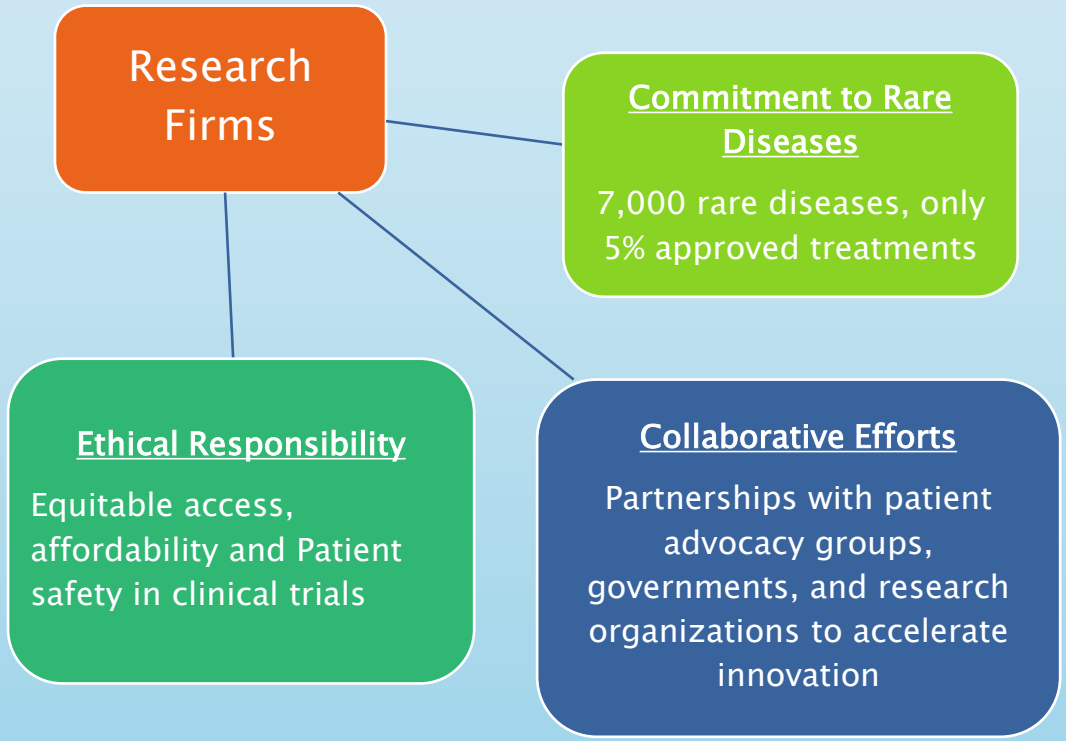
Clinical Study and Outcomes

Parameter	Stats	FIX Prophylaxis	Gene Therapy	Type of Statistical Test	Test of Hypothesis Pvalue	Method
Steady State Circulating FIX (FIX:C)	Mean (SD)	NA	12.62 (8.92)	Other	<0.0001	One-sided t-test
Number of Target Joint Bleeds	Mean (SD)	2.9 (7.81)	0.3 (1.02)	NA	NA	NA
Participants Without Treated Bleeds	%	NA	73.3	NA	NA	NA
Participants Without Untreated Bleeds	%	NA	64.4	NA	NA	NA
Change from Baseline HJHS	Mean (95% CI)	NA	-2.6 (-4.7 to -0.6)	Other	0.0117	Paired t-test
Change from Baseline Haem A QoL	Mean (95% CI)	NA	-7.70 (-12.95 to -2.45)	Other	0.0052	Paired t-test
Change from Baseline HAL	Mean (95% CI)	NA	7.59 (1.07 to 14.11)	Other	0.0237	Paired t-test

Patients' Journey with the Therapy

Having faced years of challenges with Hemophilia B, patients who participated in a clinical trial for this innovative treatment shared their experiences with physicians and research professionals. They expressed transformative changes that greatly enhanced their ***quality of life*** *and restored their ability to enjoy daily activities; urging them to continue research efforts to make this life-changing therapy available to broader population in need.*

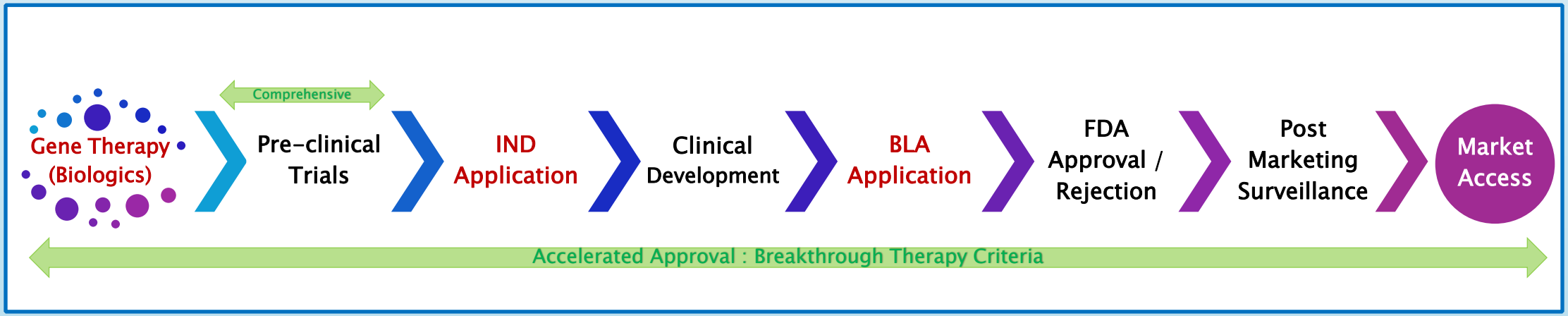
Research Firms Responsibility in Rare Disease



Examples of Approved Gene Therapy

- Transthyretin amyloidosis
  - **(Vyndaqel/Vyndamax – Pfizer).**
- Hemophilia B
  - **(Beqvez, Hympavzi – Pfizer)**
- Spinal Muscular Atrophy (SMA)
  - **(Zolgensma – Novartis).**
- Hemophilia B
  - **(Hemgenix - uniQure Inc. / CSL Behring LLC)**

Regulatory Considerations – US



351 Products

- Gene Therapies
- Vaccines
- Blood products
- Recombinant Therapeutic Proteins
- *products meet stringent standards compared to 361 products*

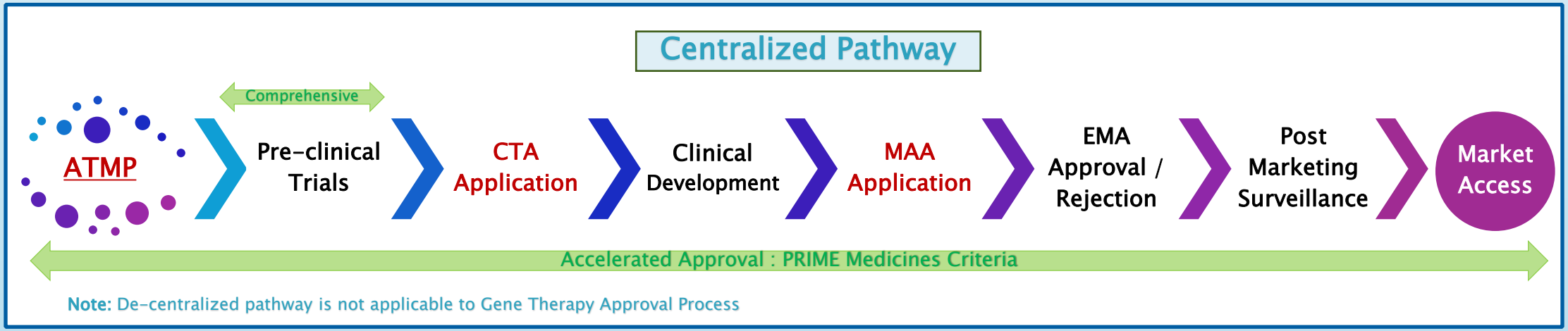
Regulatory Law/Guidelines

- **PHS** (Public Health Services) Act
- Guidance for Human Somatic Cell Therapy and Gene Therapy

Regulatory Components

- **FDA** (Food & Drug Administration)
- **CBER** (Centre For Biologics Evaluation and Research)
- **OTP** (Office of Therapeutic Products)
  - Office of Gene Therapy CMC
- **IRB** (Institutional Review Board)

Regulatory Considerations – EU



Advanced Therapy Medicinal Products (ATMP)

- Gene Therapy Medicinal Products (GTMP)
- Somatic Cell Therapy Medicinal Products (CTMP)
- Tissue Engineered Products (TEP)
- Combined ATMPs

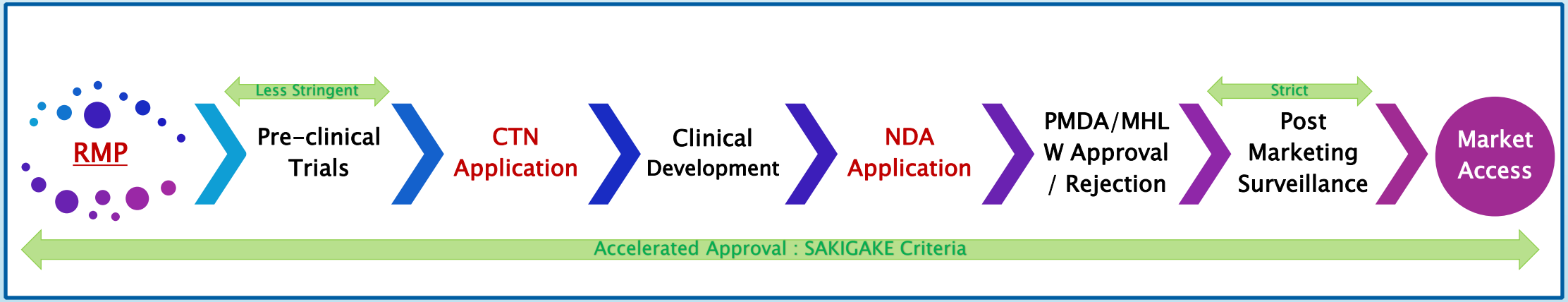
Regulatory Law/Guidelines

- Directive 2001/83/EC, Annex I, Part IV, as amended in Directive 107 2009/120/EC)

Regulatory Components

- **EMA** (European Medicines Agency)
- **CHMP** (Committee for Medicinal Products for Human Use)
- **CAT** (Committee for Advanced Therapeutics)
- **EC** (Ethics Committee)

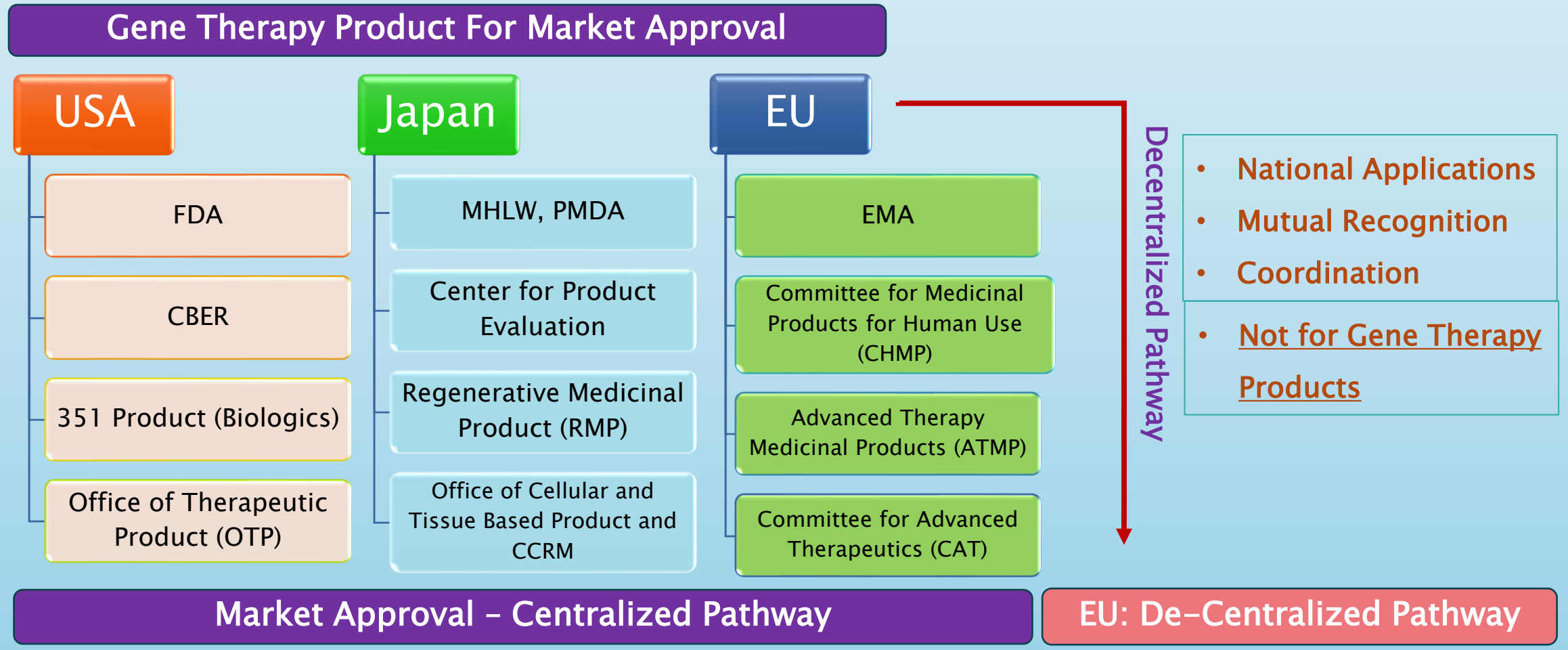
Regulatory Considerations – Japan



Regenerative Medicine Product (RMP)	Regulatory Law/Guidelines	Regulatory Components

• Gene Therapy Products
  • Gene Modified Cell Therapy
  • Nucleic Acid Based Gene Therapy
• Cellular and Tissue-based Products
	• Act on Pharmaceutical and Medical Devices, Chapter 1 Article 2-9 **(PMD Act – RMP)**
	• The Act on the Safety of Regenerative Medicine **(Safety Act)**
		• **MHLW** (Ministry of Health, Labor and Welfare)
		• **PMDA** (Pharmaceuticals and Medical Devices Agency)
		• **CCRM** (Certified Committee for Regenerative Medicine)
		• **IRB** (Institutional Review Board)

Regulatory Considerations – US, EU and Japan



Conclusion

Innovative Gene Therapy

- Revolutionizing gene therapy for Hemophilia B
- Sustained bleed protection, improved quality of life
- Ongoing trials to monitor long-term safety and efficacy with promising outcomes

Regulatory considerations

- Differences in EU, Japan, US regulatory agencies for Gene Therapy
- Gene therapies classifications
- Premarketing and Post Marketing considerations

References

- https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-beqveztm-fidanacogene-elaparvovec
- https://beqvez.pfizerpro.com/efficacy/results
- https://pmc.ncbi.nlm.nih.gov/articles/PMC5733859/
- https://labpedia.net/blood-coagulation-factors-and-their-interpretations/
- https://www.pmda.go.jp/english/review-services/reviews/0003.html
- https://clinicaltrials.gov/study/NCT03861273?cond=Hemophilia%20B&term=Hemophilia%20B&intr=fidanacogene%20elaparvovec&rank=1&tab=results

Thank You ..!

Name: Kaushik Dinanath Save
Organization: Pfizer Healthcare India Pvt Ltd
Address: The Capital, 1802, 19th Floor, Plot No C70, G-Block, Bandra Kurla Complex
City, State ZIP: Mumbai, India - 400051
Work Phone: NA
Fax: NA
E-mail: kaushikdinanath.save@pfizer.com
Web: NA
Twitter: NA