sanofi

Review and Q&A Checkpoints:

Checkpoint 1

- *Overview of Hemophilia A and B Module*
- *Management of Hemophilia A and B Module*

Facilitator Guide

Introduction

This Facilitator Guide is designed to help you follow a process that will ensure representatives under your leadership are well-prepared with the foundational knowledge that is critical to their careers at Sanofi.

Why Checkpoints?

As a facilitator, you have an opportunity to share your hard-earned experience in a meaningful way: through guidance and coaching. Through these series of Checkpoints, you will give learners opportunities to:

- Ask questions
- Review key content
- Verbalize complex concepts
- Prepare for success in the field

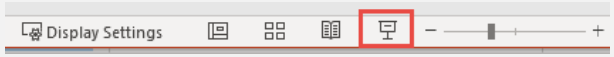
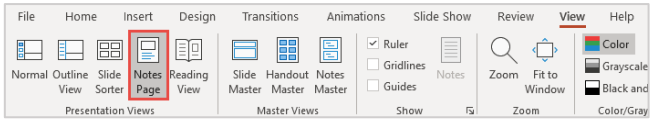
> “Leadership is about making others better as a result of your presence and making sure that impact lasts in your absence.”
>
> Sheryl Sandberg

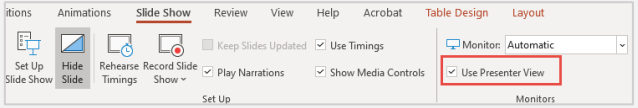
A great coach:

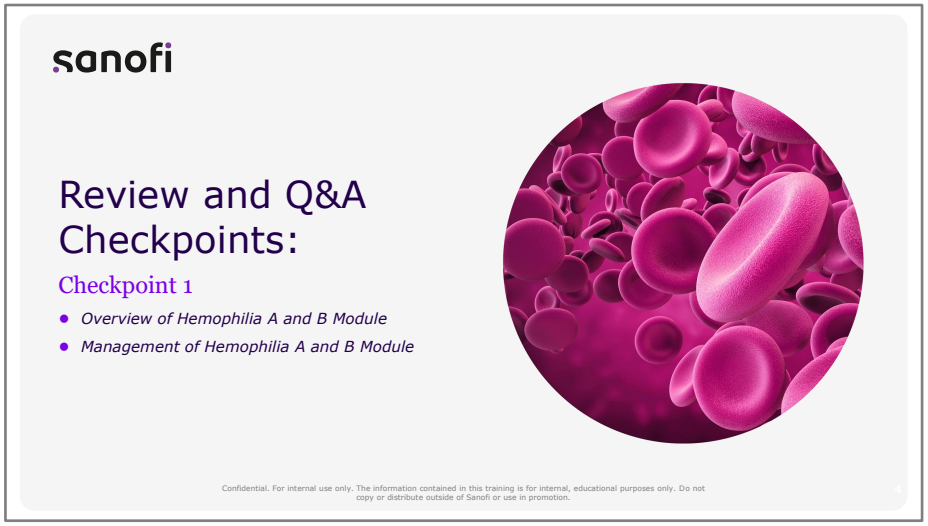
- Listens more than speaks
- Asks great questions
- Clarifies when needed
- Avoids “telling”
- Doesn’t judge
- Helps others commit to specific actions

How to Use This Guide

This workshop is developed in PowerPoint (PPT) to function as both a Facilitator Guide and presentation slides. Prior to the workshop, review this page to familiarize yourself with how to navigate the PPT seamlessly during the session.

View	Primary Audience	Primary Audience Sees	How to Access This View
Slideshow	Participants	• Full-screen slides • Share this view with participants on the big screen (in person) or on screenshare (virtual)	• Click the **slideshow icon** in the *Display Settings* on the right side of the bottom bar  • OR, click **Slide Show** on the top menu bar and select **From the Beginning** or **From Current Slide**
Facilitation Notes	Facilitator(s)	• Slide thumbnail • Facilitator directions for that slide	• Click **View** on the top menu bar • Select **Notes Page** (not Notes Master)  *Note: This same view appears in your PDF Facilitator Guide for printing and mark-up prior to the workshop.*

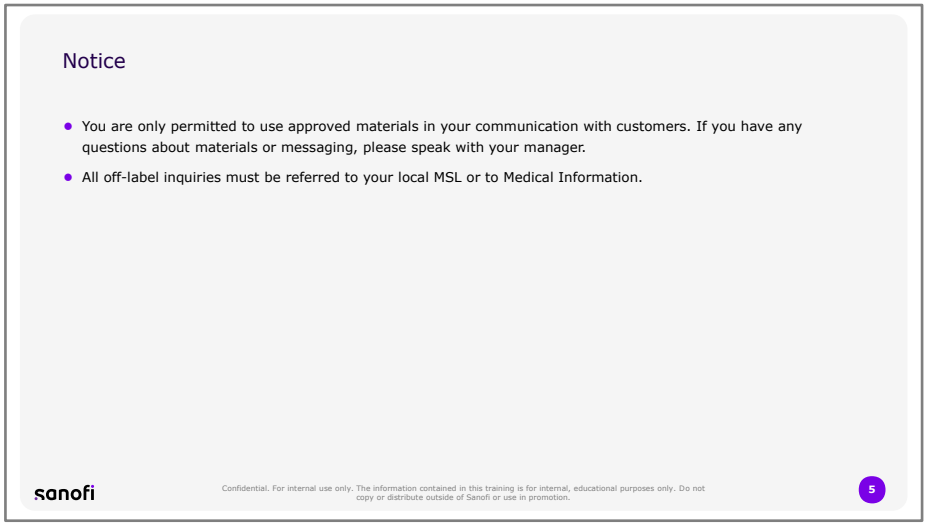
Presenter View (with multiple screens)	Facilitator(s)	**On presenting screen:**
		• Full-screen slides for participants to view
		
		On 2nd screen:
		• On left:
		  • Current slide
		• On right:
		  • Next slide thumbnail
		  • Facilitator directions for current slide (under next slide thumbnail)
			• Click **Slide Show** on the top menu bar
			• Click to select **Use Presenter View** checkbox if you would like it to show on a different screen while the audience views your projecting/shared screen
			 
			*Note: Hidden slides (eg, Workshop At-A-Glance on the previous page) will not show in Presenter View, so make sure to print those pages prior to facilitating. To determine hidden slides, click **View** on the top menu bar and select **Normal**. Hidden slides are dimmed in color and the slide number is crossed off.*



Key Concepts

- **Display** this slide on-screen as participants arrive.
- **Welcome** participants to *Checkpoint 1*.
- **Introduce** yourself and any other facilitators.

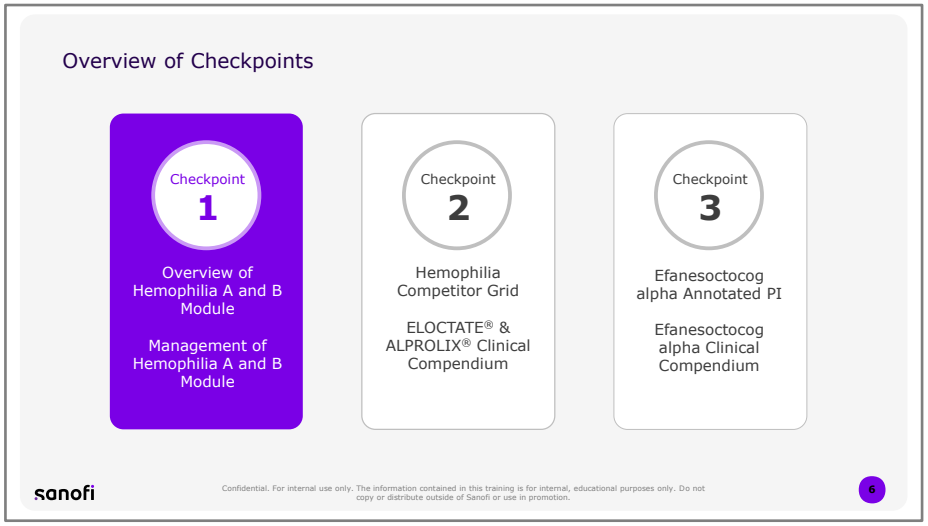
Facilitator Notes



Key Concepts

- **Review** on-screen content.

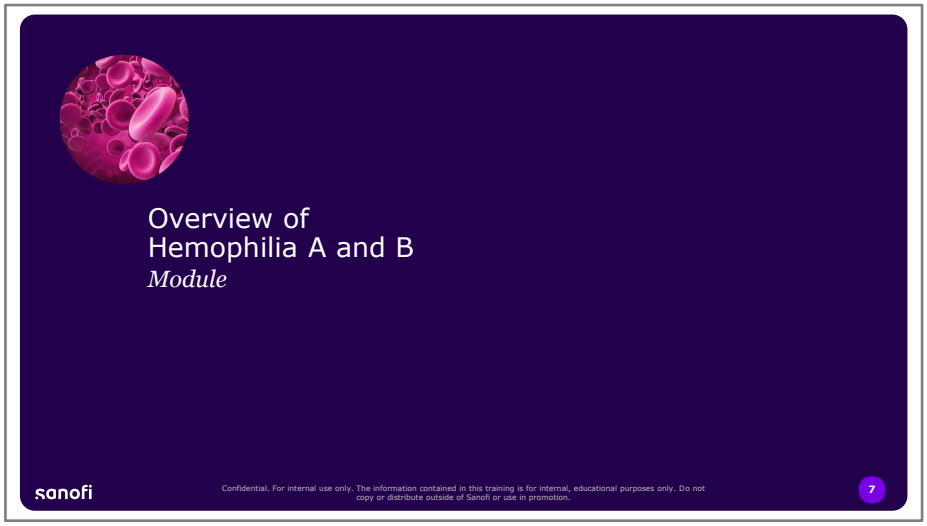
Facilitator Notes



Facilitator Notes

Key Concepts

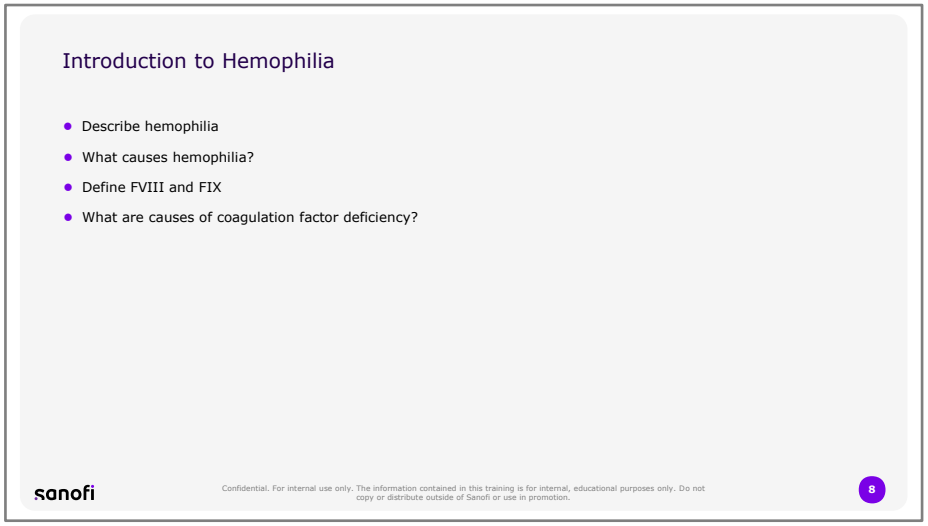
- **Provide** an overview of the three checkpoints that will be held during foundational training:
- **Say**: *Checkpoints are structured group sessions designed to provide you with an opportunity to review complex content. With my coaching and guidance at each session, you will:*
  - *Review applicable content*
  - *Ask questions in a safe environment*
  - *Practice verbalizing key concepts and information from the content you have studied at home*
  - *Get feedback on your verbalization skills*
- Checkpoints will cover the material from the deliverables seen on screen.
  - **Review** each checkpoint and its corresponding topic.



Key Concepts

- **Introduce** the first module for review during Checkpoint 1, Overview of Hemophilia A and B.

Facilitator Notes



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

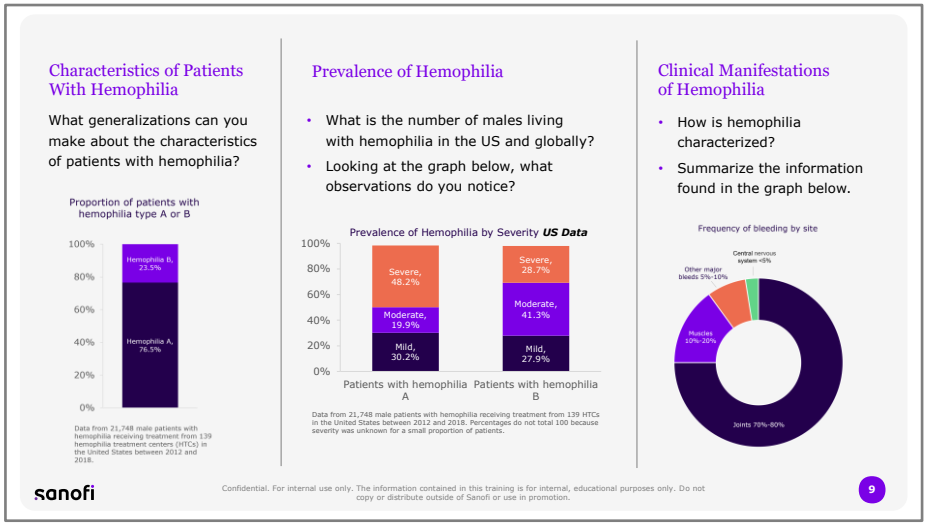
Key Concepts

Disease description:

- Hemophilia is a bleeding disorder resulting from the partial or complete lack of coagulation factor VIII (hemophilia A) or IX (hemophilia B).
- Hemophilia is characterized by excessive bleeding due to an impaired ability to form a blood clot.
- Bleeding can happen with or without a challenge to hemostasis, such as trauma or surgery.

Characteristics of hemophilia:

- Caused by the deficiency of a functional coagulation factor (aka, clotting factor) in the blood.
  - Hemophilia A: factor VIII (FVIII) deficiency
  - Hemophilia B: factor IX (FIX) deficiency
- Disease severity correlates with the degree of coagulation factor deficiency.
- FVIII:
  - Protein produced mainly in the liver.
  - Circulates in inactive form in the blood, largely bound to another clotting protein, von Willebrand factor (vWF), which protects it from breakdown and clearance, thus increasing the half-life of FVIII.
    - Half-life of vWF-bound FVIII: 12 hours
    - Half-life of free FVIII: 2 hours
  - During coagulation, FVIII separates from vWF when activated by thrombin; it then acts as a cofactor with activated FIX.
- FIX:
  - Protein produced in the liver.
  - Circulates in the blood in inactive form, with a half-life of 18-24 hours.
  - During coagulation, activated FXI activates FIX, which then activates factor X (FX) in the presence of its cofactor FVIIIa.
- The factor deficiency is caused by a mutation in the gene encoding the deficient factor.
  - The genetic mutation is usually inherited, with two-thirds of affected patients having a family history of hemophilia. About one-third of cases have no family history and are thought to result from spontaneous genetic mutations.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

Characteristics of Patients With Hemophilia:

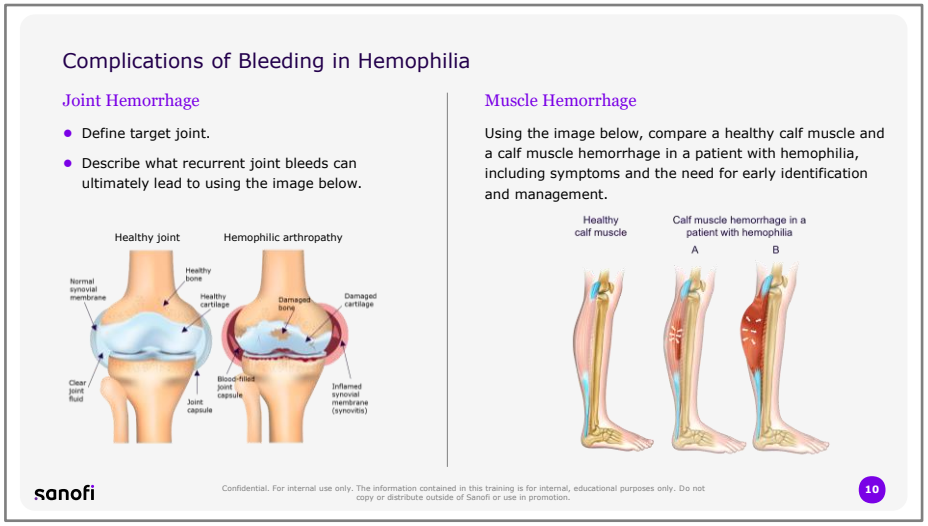
- Congenital disorder generally affecting males.
- Hemophilia A is the most common form, affecting approximately 80% of patients with hemophilia.

Prevalence of Hemophilia:

- Estimated prevalence of males living with hemophilia:
  - US: ~30,000 to 33,000
  - Globally: ~1,125,000
- The largest proportion of patients with hemophilia A have severe disease.
- In those with hemophilia B, the largest proportion have moderate disease.

Clinical Manifestations of Hemophilia:

- Hemophilia is characterized by prolonged and excessive bleeding. The severity of bleeding correlates with the degree of coagulation factor deficiency.
- Hemophilia causes excessive, prolonged bleeding after injury or surgery, or sometimes for no obvious reason.
- Bleeding can happen anywhere in the body, but is most common in joints, which account for roughly 70%-80% of bleeds.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

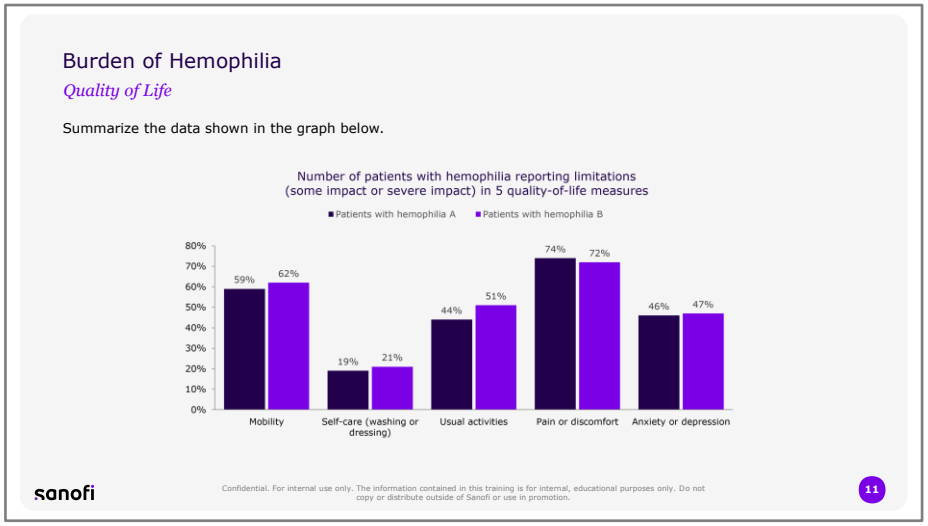
Key Concepts

Joint Hemorrhage:

- A target joint is defined by the World Federation of Hemophilia as a single joint in which 3 or more spontaneous bleeds have occurred within a consecutive 3-6-month period.
- The accumulation of blood in a joint cavity causes synovitis.
- Recurrent joint bleeds lead to chronic synovitis and progressive joint damage as the chronically inflamed synovial membrane becomes enlarged and prone to further bleeds, ultimately resulting in irreversible damage to the cartilage and bone.
- As arthropathy worsens, there can be progressive fibrosis of the synovium and joint capsule and the joint may become ankylosed.
- Thus, hemophilic arthropathy is both inflammatory and degenerative.
- Chronic hemophilic arthropathy often manifests in young individuals, during the second decade of life, especially without preventative treatment.
- It is associated with substantial burden to patients, including chronic pain, disability, and the potential need for joint replacement.

Muscle Hemorrhage:

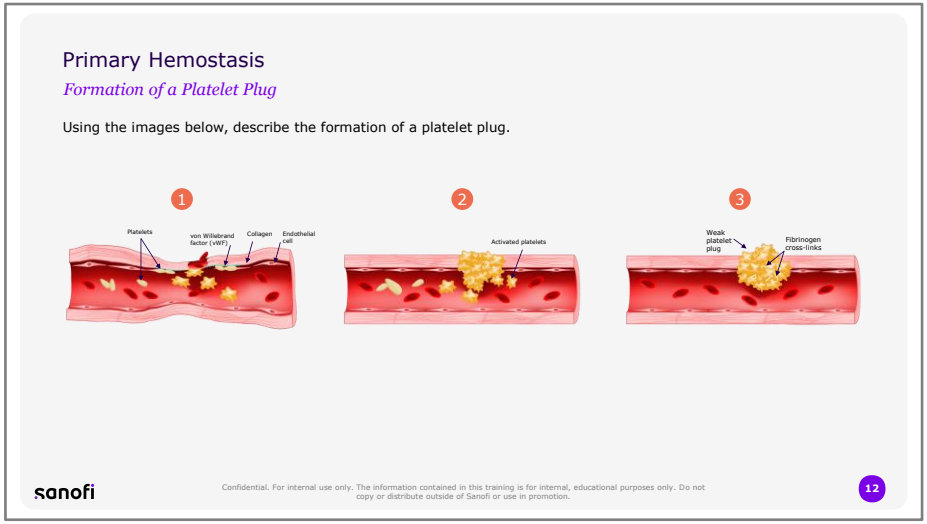
- In patients with hemophilia, bleeds can occur in any muscle as a result of trauma, sudden stretching, or even spontaneously in patients with more severe disease.
- Muscle bleeds are most problematic when they occur in the body's deep muscle compartments, such as in the iliopsoas, calf, or forearm.
- Bleeds in these locations can compromise associated nerves and blood vessels, and therefore require immediate medical attention to prevent permanent damage and loss of function.
- Muscle bleed symptoms include pain, swelling, and functional impairment of the affected muscle.
- Early identification and management are necessary to prevent rebleeding, permanent muscle contracture, and the formation of pseudotumors.



Key Concepts

- Collectively, the bleeding manifestations of hemophilia impose substantial quality-of-life burdens, including chronic pain and impaired mobility, in affected patients.

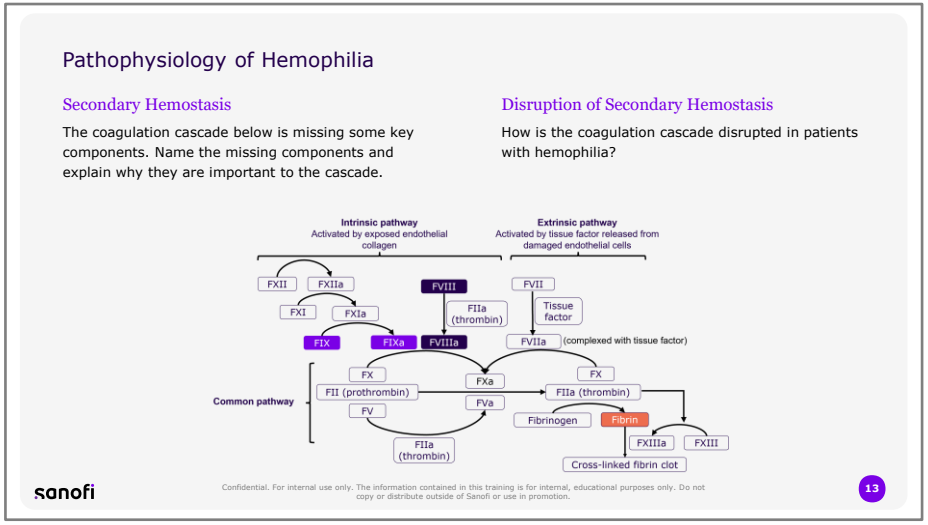
Facilitator Notes



Facilitator Notes

Key Concepts

1. **Platelet adhesion**
   - The damaged endothelium exposes collagen and vWF below its surface.
   - Inflammatory mediators cause platelets to attach to the exposed (subendothelial) vWF and collagen.
2. **Platelet activation**
   - Thrombin activates vWF-bound platelets to secrete mediators for platelet aggregation.
   - Platelets change in shape to a pseudopodal, or spiky, form that increases their surface area and promotes aggregation.
3. **Platelet aggregation**
   - Activated, vWF-bound platelets adhere to fibrinogen in the blood. Fibrinogen is a plasma protein that is later converted to fibrin by the action of thrombin.
   - The fibrinogen interconnects the platelets to form a weak plug.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

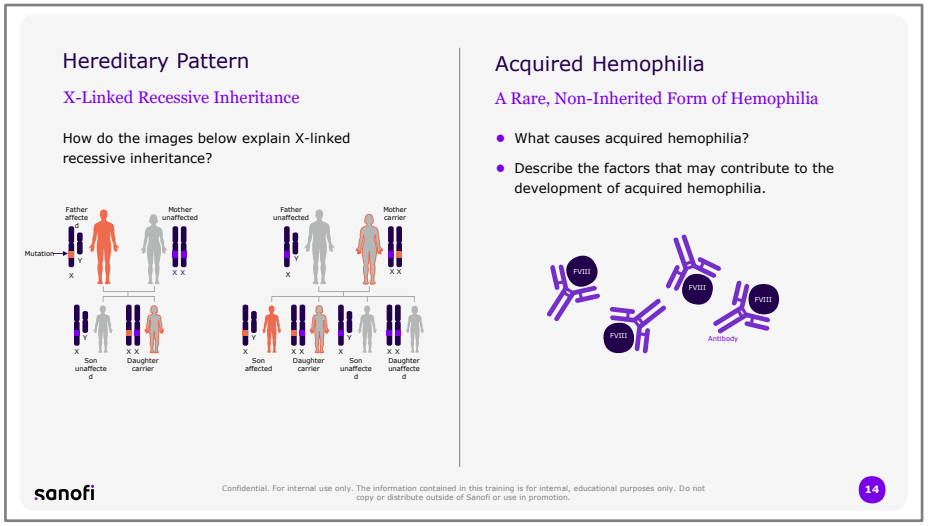
Key Concepts

Secondary Hemostasis:

- The coagulation cascade:
  - Secondary hemostasis involves the activation of coagulation factors in a cascade to ultimately stabilize the weak platelet plug (formed in primary hemostasis) with fibrin mesh. It involves intrinsic and extrinsic pathways, which begin separately but meet to form the common pathway. The goal of the common pathway is to activate fibrinogen into fibrin, which forms strands that bind platelets together, thereby stabilizing the platelet plug. FVIII and FIX are both part of the intrinsic pathway.
  - When thrombin, a key player in coagulation, is generated in the common pathway, it cleaves fibrinogen to fibrin and also reinforces the cascade by activating certain factors, including FV, FVIII, and FXIII. It also plays a role in platelet activation in primary hemostasis.
  - Arrows represent the activation of a clotting factor by the factor(s) directly above, below, or to the side of it. The "a" in a factor name indicates the activated form. The factors deficient in hemophilia A and B, FVIII and FIX, respectively, are highlighted, as is the goal of the cascade, fibrin.

Disruption of Secondary Hemostasis

- The enzyme FIXa activates FX in the presence of cofactor FVIIIa.
- In patients with hemophilia, the absent or dysfunctional FVIII or FIX results in insufficient generation of FXa, with consequent insufficient generation of thrombin and fibrin.
- Ultimately, without the necessary fibrin, blood clots do not form properly in response to tissue injury.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

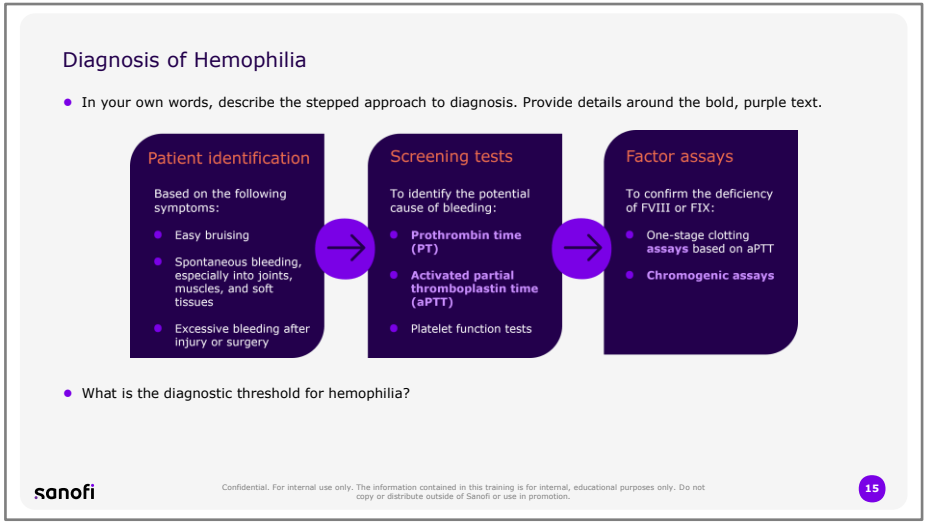
- The F8 gene contains the genetic code needed to produce FVIII; mutations, or variants, in this gene cause hemophilia A.
- The F9 gene contains the code needed to produce FIX; variants in this gene cause hemophilia B.

Hereditary Pattern:

- In X-linked recessive inheritance, males carrying a disease-causing mutation will be affected with the disease because they have only one X chromosome.
- Females carrying the mutation on one X chromosome, with a normal gene on the other, are generally unaffected (called carriers).
- Affected fathers cannot pass the trait of hemophilia to their male children, but will produce daughters who are carriers of the variant on one of their X chromosomes.
- A male child with hemophilia is born from a mother who carries the F8 or F9 variant on one of her X chromosomes and then passes that affected chromosome to him.
- In rare cases, females can have both X chromosomes affected, or one affected and the other inactive, and may therefore show signs of hemophilia.

Acquired Hemophilia A:

- It is caused by the development of autoantibodies against factor VIII (these antibodies are called inhibitors).
- Acquired hemophilia occurs with similar frequency in males and females, and incidence greatly increases with age, with a median age at onset of 75 to 78 years.
- Individuals may be predisposed by factors such as other autoimmune disorders, infections, pregnancy, cancer, and medications. The cause of acquired hemophilia is undetermined in about half of cases.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

Patient identification:

- Patients suspected of having hemophilia are identified based on symptoms of bleeding, including easy bruising, bleeding with no apparent cause, or excessive bleeding as a result of trauma or surgery.
- The bleeding history for these patients should be obtained, as well as any family history of abnormal bleeding to assess the potential of inherited disease.

Screening tests:

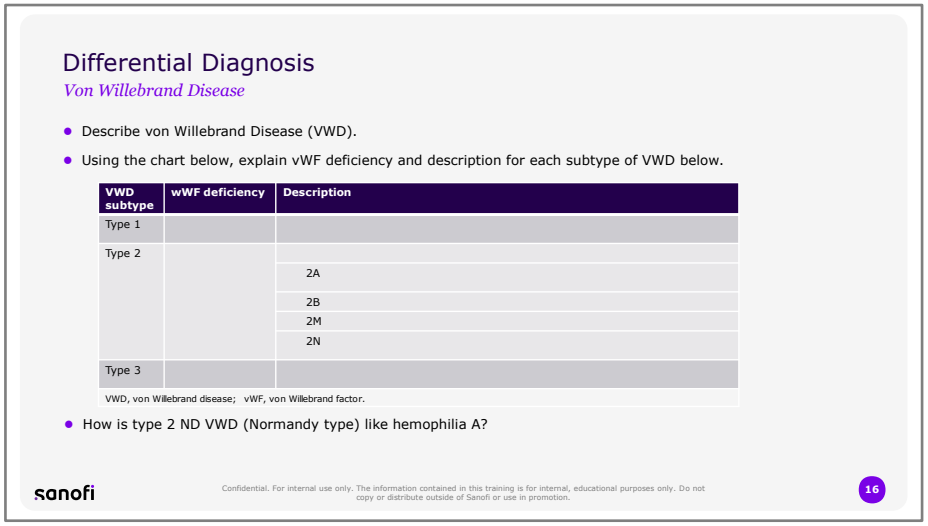
- Once identified, screening tests are used to help determine the potential cause of bleeding.
- The prothrombin time (PT) is used to measure the time needed for clotting via the extrinsic pathway, whereas the activated partial thromboplastin time (aPTT) reflects the time needed for clotting via the intrinsic pathway.
- Thus, in patients with hemophilia, the PT is expected to be normal and the aPTT prolonged.
- However, a prolonged aPTT can also occur in other clotting disorders (eg, deficiencies of FXI or FXII). Thus, aPTT is not a definitive test for hemophilia.

Factor assays:

- After other causes are ruled out and hemophilia is suspected, factor assays confirming reduced or missing FVIII or FIX activity are necessary for a definitive diagnosis of hemophilia.
- One-stage clotting assay: the most common assay used in labs
  - Based on the aPTT, this test reflects the functionality (time needed for clot formation) of the intrinsic and common pathways.
  - Specifically, it measures the ability of a patient's plasma sample to correct (shorten) the prolonged coagulation time (aPTT) of FVIII- or FIX-deficient reagent plasma.
- Chromogenic assay: Guideline recommended for the diagnosis of hemophilia A only; current evidence is insufficient to support its use in diagnosis of hemophilia B
  - This two-stage assay measures the amount of functional clotting factor in a patient's plasma sample according to its ability to generate FXa.

Diagnostic Threshold:

- Hemophilia is diagnosed in individuals with coagulation factor levels (FVIII or FIX) less than 40 IU/dL, or less than 40% of normal.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

- VWD is an inherited bleeding disorder that affects up to 1% of the population in the United States.
- VWD is caused either by abnormal (dysfunctional) vWF or an insufficient amount of normal vWF and is thus divided into subclasses depending on whether the vWF deficiency is qualitative or quantitative.

vWF Deficiency:

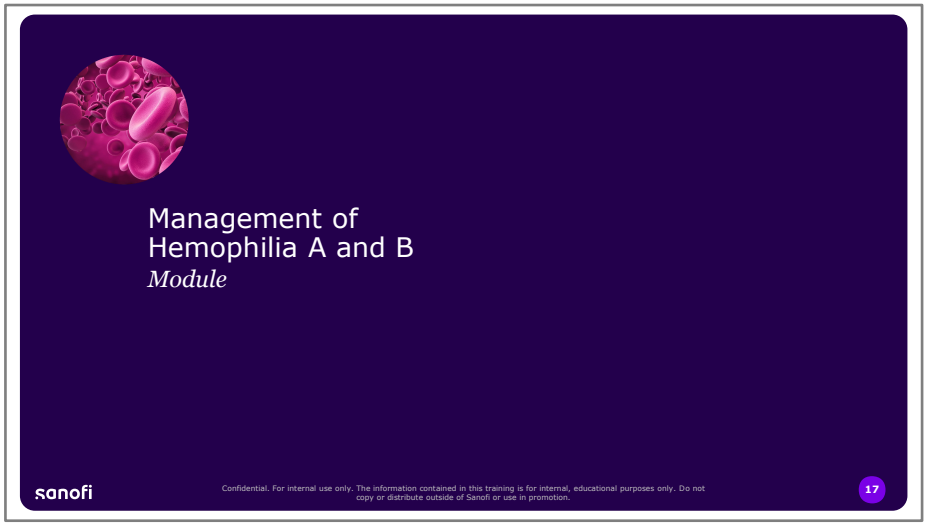
- Type 1: Quantitative, partial absence
- Type 2: Qualitative
- Type 3: Quantitative, complete absence

Description:

- Type 1: Patients have reduced levels of normal vWF (mildest and most common form of VWD)
- Type 2: Patients have a normal amount of vWF, but it is dysfunctional
- Type 2A: reduced or absent high-molecular-weight vWF; results in decreased vWF binding to platelets
- Type 2B: vWF has increased affinity for platelets; can result in thrombocytopenia
- Type 2M: vWF has reduced binding to platelets or collagen
- Type 2N: vWF has reduced binding to FVIII, resulting in premature clearance of FVIII and low FVIII levels
- Type 3: Patients have virtually absent vWF and an associated FVIII deficiency (most severe and rarest form of VWD)

Type 2 ND VWD & Hemophilia A:

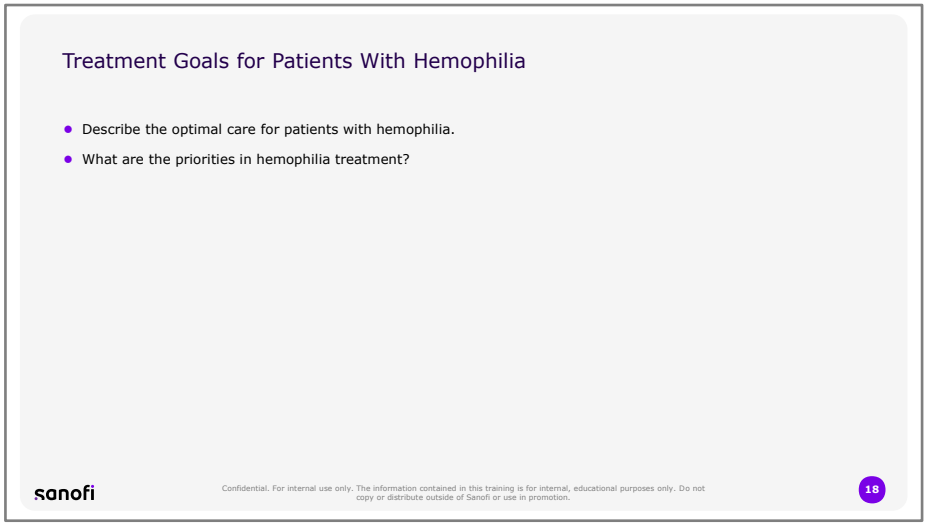
- Like hemophilia A, type 2N VWD (Normandy type) is characterized by normal vWF levels and low FVIII levels.
- Thus, hemophilia management guidelines recommend that all patients with reduced FVIII activity and a possible diagnosis of hemophilia should have a full laboratory assessment to rule out VWD, with particular emphasis on distinguishing type 2N VWD from mild hemophilia A.



Key Concepts

- **Introduce** the second module for review during Checkpoint 1, Management of Hemophilia A and B.

Facilitator Notes



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

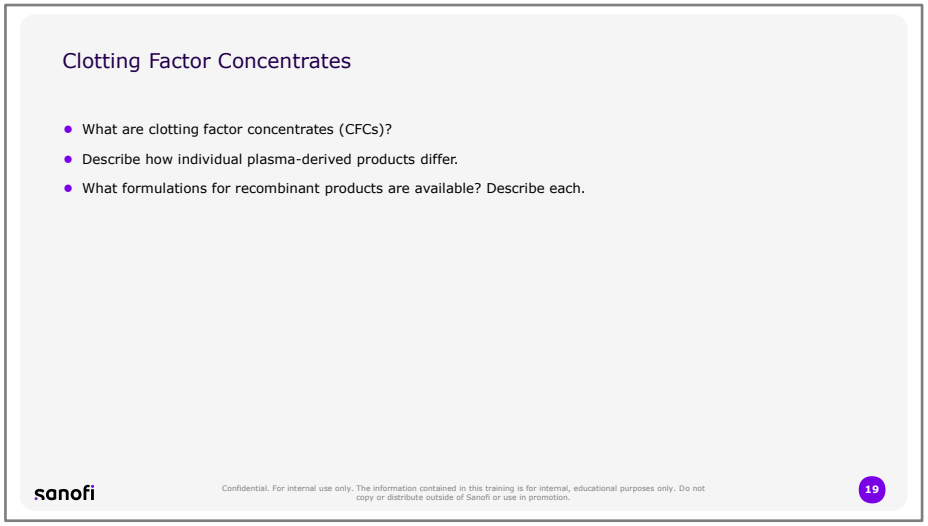
Key Concepts

Comprehensive, multidisciplinary care:

- Care for patients with hemophilia should be comprehensive and involve multidisciplinary medical services, such as those provided by hemophilia treatment centers (HTCs), to ensure proper management of the disease and its complications.
- Optimal care is complex and involves much more than management of acute bleeding.
- Ideal care for patients with hemophilia promotes physical health, psychosocial well-being, and quality of life while reducing morbidity and mortality.

Priorities in hemophilia treatment:

- Prevention of bleeding and joint damage
- Prompt management of bleeding episodes, including physical therapy and rehabilitation after joint bleeds
- Pain management
- Management of musculoskeletal complications
- Management of inhibitors
- Management of comorbidities
- Dental care
- Quality-of-life assessments and psychosocial support
- Genetic counseling and diagnosis
- Ongoing education and support for patients and caregivers



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

What are CFCs?

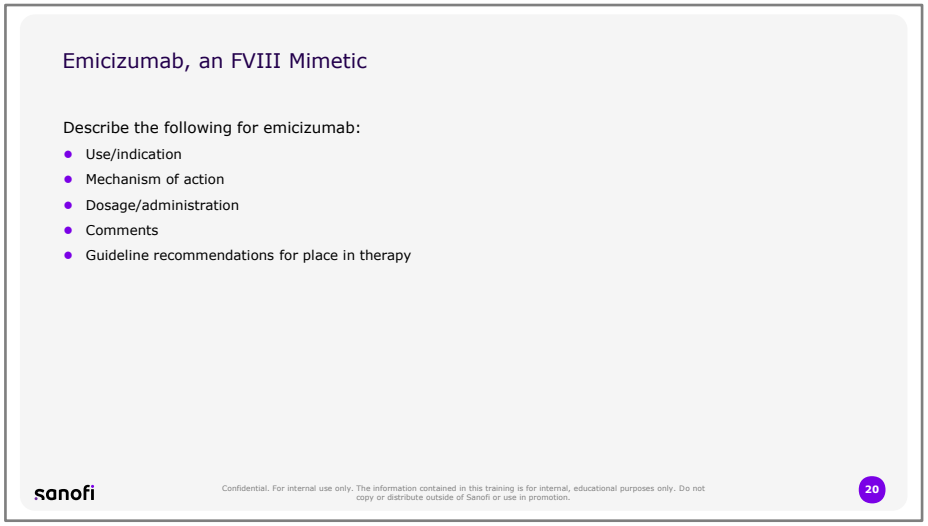
- CFCs replace missing or dysfunctional clotting factor VIII (FVIII) or IX (FIX) and are first-line therapy because they are safe and effective for treating and preventing bleeds.

Plasma-derived products: Made from donated human blood plasma

- Individual plasma-derived products differ by purity and viral inactivation methods used in manufacturing.
  - Purity is the percentage of the desired factor (FVIII or FIX) relative to the other ingredients; it has no relation to viral safety. There is no standard for purity, and the purity of available products varies.
  - Virus inactivation and removal processes are key contributors to product safety. Two methods of virus inactivation are generally used in the manufacturing process to minimize risk, as not all viruses are susceptible to all methods. Available methods include the following: heat treatment (dry heat, pasteurization, or vapor/steam), solvent/detergent treatment, and ultrafiltration

Recombinant products: Made using genetically engineered cells and recombinant technology

- Recombinant CFCs (denoted rFVIII or rFIX) are classified according to the manufacturing process used and their biologic half-life.
  - Manufacturing process classification: first-generation products, second-generation products, and third-generation products
  - Half-life classification:
    - Standard half-life (SHL) products
      - FVIII: ~12 hours
      - FIX: ~18-24 hours
    - Extended half-life (EHL) products
      - FVIII: 1.4-fold to 1.6-fold increase in half-life compared with SHL products
      - FIX: 3-fold to >5-fold increase in half-life compared with SHL products



Facilitator Notes

Key Concepts

Use/indication:

- For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with or without inhibitors.

Mechanism of action:

- Emicizumab is a bispecific antibody; it has 2 separate antigen-binding sites that are each specific for a given target: activated FIX (FIXa) and FX. It mimics the action of FVIII by bridging FIXa and FX, thus restoring the function of missing FVIII needed for hemostasis.

Dosage/administration:

- Subcutaneous (SC) loading dose: 3 mg/kg once weekly for 4 weeks, followed by a subcutaneous maintenance regimen (one of the following options): 1.5 mg/kg once weekly, 3 mg/kg once every 2 weeks, or 6 mg/kg once every 4 weeks. Prophylactic use of bypassing agents (to be discussed later) should be discontinued before starting emicizumab.

Comments:

- Combination use with activated prothrombin complex concentrates (aPCC) may lead to thrombosis.
- Because emicizumab acts as a substitute for FVIII, it is only for use in patients with hemophilia A.
- Benefits of emicizumab are its SC route of administration and long half-life, which allows for infrequent administration.
- It is only indicated for prevention of bleeds, not treatment of bleeding episodes. When used for routine prophylaxis, the long-term impact on joint health is not known.

Guideline recommendations for place in therapy:

- Emicizumab is the only non–factor-replacement therapy available and is a useful option for bleeding prophylaxis in patients with hemophilia A.
- It is used only for prevention, not treatment, of bleeds.
- Breakthrough bleeding while on emicizumab must be treated with FVIII or bypassing agents (discussed later).

Facilitator Notes

Key Concepts

Use/indication:

- Treatment of mild to moderate hemophilia A in patients who can achieve therapeutic FVIII levels with its use.
- Treatment and prevention of bleeding in hemophilia A carriers.

Mechanism of action:

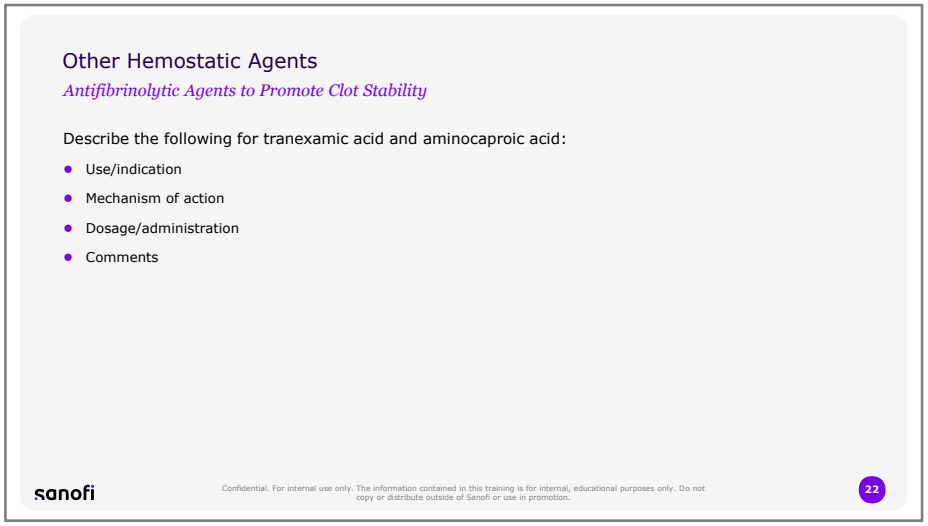
- A synthetic analogue of vasopressin that increases plasma levels of FVIII and vWF.

Dosage/administration:

- Intravenous (IV) or SC: a single dose of 0.3 µg/kg body weight boosts FVIII level 3- to 6-fold; peak response occurs within 60 minutes.
- Intranasal: a single, metered spray (1.5 mg/mL) in both nostrils for adults ≥40 kg or in 1 nostril for adults <40 kg.
- Administer once daily for no more than 3 days in children >2 years old and adults (in adults, may be administered twice in a single day, but subsequent dosing should be limited to once daily). Continued use beyond 3 days is associated with increased complication risk and tachyphylaxis. Use in children <2 years old is contraindicated.

Comments:

- Use should be tested prior to therapy, as patient response is variable. Response to intranasal DDAVP is more variable than SC or IV response.
- Has no effect on FIX levels; should not be used to treat hemophilia B.



Facilitator Notes

Key Concepts

Use/indication:

- Tranexamic acid: To treat superficial soft tissue and mucosal bleeds (oral, nasal, gastrointestinal, or excessive menstrual bleeding) in patients with hemophilia A or B.
- Aminocaproic acid: Similar to tranexamic acid, but not widely used because of lower potency, shorter half-life, and greater toxicity.

Mechanism of action:

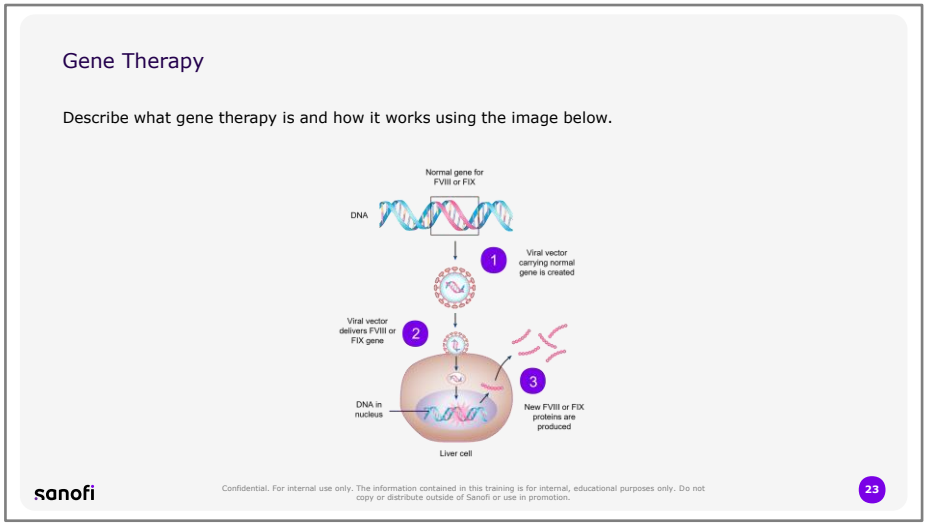
- Tranexamic acid and aminocaproic acid: Promotes clot stability by preventing fibrinolysis; works by inhibiting the activation of plasminogen to plasmin, which degrades fibrin.

Dosage/administration:

- Tranexamic acid:
  - Oral tablet: 25 mg/kg/dose, 3-4 times daily
  - IV infusion: 10 mg/kg/dose, 2-3 times daily
  - May be used as an oral rinse
- Aminocaproic acid:
  - Oral: 100 mg/kg/dose up to 2 g/dose
  - IV: 100 mg/kg/dose up to 4 g/dose
  - Doses may be given every 4-6 hours, up to 24 g/day

Comments:

- Tranexamic acid:
  - May be used alone or as adjuvant therapy with standard doses of CFCs.
  - Contraindicated in patients with hemophilia B receiving prothrombin complex concentrates (PCCs) because of increased risk for thromboembolism.
- Aminocaproic acid: Can be associated with myopathy, especially with administration of high doses for several weeks; myopathy resolves after stopping treatment.



Facilitator Notes

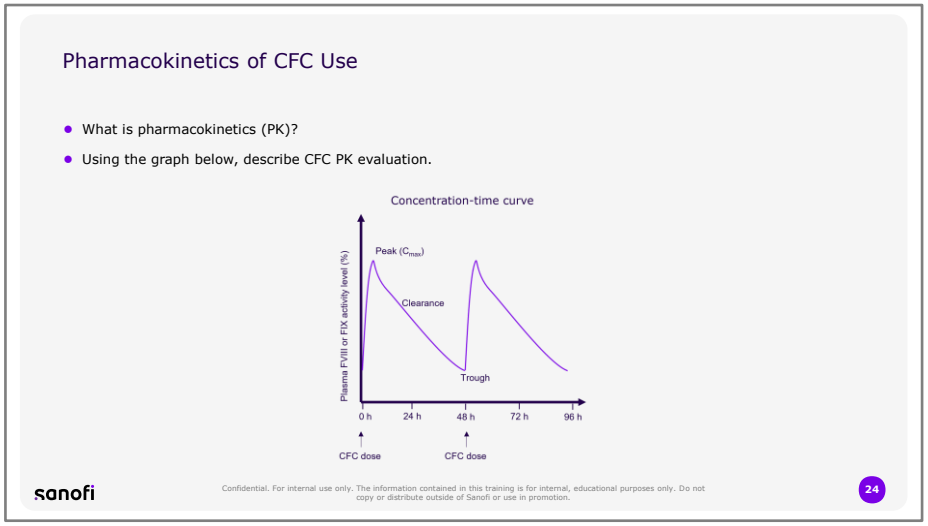
Key Concepts

What gene therapy is:

- Gene therapy is used to treat or prevent a disease by correcting the underlying genetic problem.
- The goal is to recover the function of critical proteins, which are encoded by genes.
- One technique is to insert a normal gene to replace a defective one, thus restoring normal function (protein production).

How gene therapy works:

- In hemophilia, a normal gene for FVIII (hemophilia A) or FIX (hemophilia B) is transferred to a patient to replace the defective version.
    1. A carrier, or vector, is engineered to deliver the normal gene. Viruses, modified so they cannot cause human disease, are often used as vectors to deliver the gene by infecting the cell. In gene therapy for hemophilia, the vectors used are recombinant adeno-associated virus (AAV) vectors.
    2. The vector is introduced into a patient (eg, intravenously), taken up by certain target cells (usually the liver), and deposits the normal gene into the nucleus of the cell.
    3. The cell's machinery uses the new gene's instructions to make a functioning protein.
- There are currently no gene therapies for hemophilia approved in the United States.



Facilitator Notes

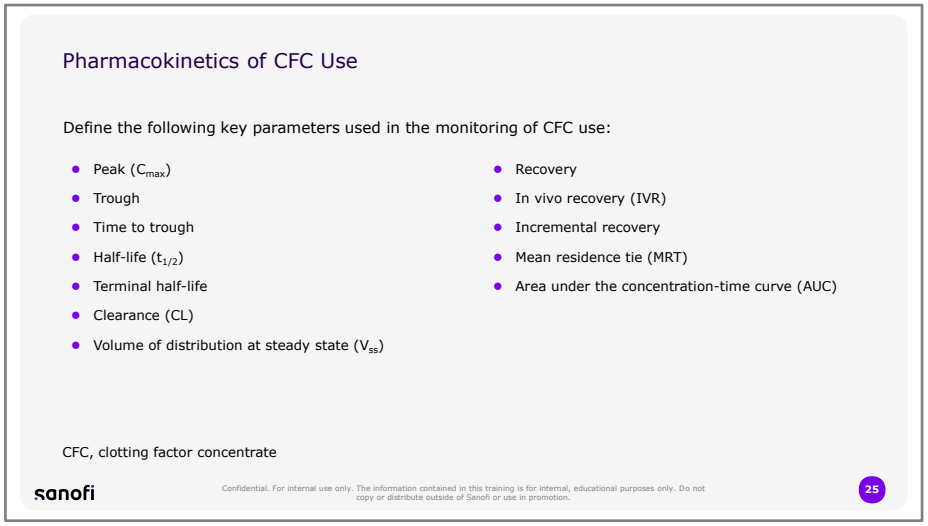
Key Concepts

What is PK?

- Pharmacokinetics (PK) describes the fate of administered drugs in the body.
- More specifically, it describes the time course of an administered drug's concentration in plasma, and generally comprises drug absorption (into the circulation), distribution (between the circulation and body tissues), metabolism (breakdown), and elimination (clearance from the body).

Concentration-time curve

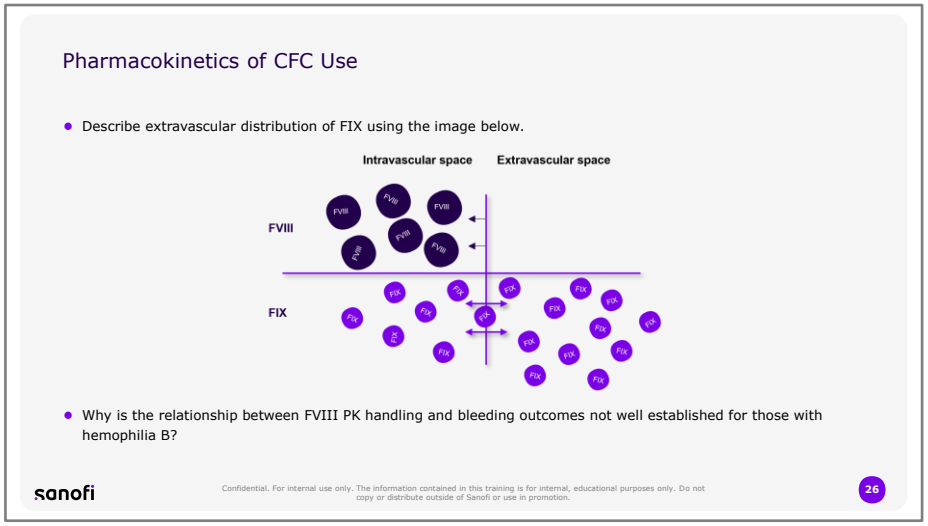
- In hemophilia, CFC PK evaluation is based on plasma CFC activity level (also referred to as concentration), which is measured either as a percentage of normal or as international units per deciliter (IU/dL).
- A factor level of 1% is equal to 1 IU/dL or 0.01 IU/mL.
- After administration, CFC plasma levels can be measured serially and plotted as a function of time.
- This is called a concentration-time curve and gives a visual representation of a patient's PK handling of CFC. (An example of plasma sampling times would be pre-dose and then post-dose at 30 minutes and 1, 3, 6, 12, 24, and 48 hours).
- For all CFCs, this curve follows the same general pattern: a rapid increase in measured plasma level, described as a "peak" of factor activity, and then a gradual decline of CFC from the blood, known as "clearance."
- The lowest plasma CFC concentration reached after an infusion and before the next dose is the "trough."



Facilitator Notes

Key Concepts

- **Peak (C_{max}):** maximum plasma concentration of factor after infusion.
- **Trough**: minimum plasma concentration of factor reached after infusion and before the next dose.
- **Time to trough:** amount of time plasma factor activity is above a minimum threshold (trough); a 1% threshold is commonly used. This is a key metric of treatment efficacy.
- **Half-life ($t_{1/2}$):** time for plasma concentration of factor to decrease by half. **Terminal half-life** is specified for drugs that have an initial distribution phase followed by an elimination phase and is the concentration halving time during the elimination phase.
- **Clearance (CL):** volume of plasma cleared of CFC per unit time.
- **Volume of distribution at steady state (V_{ss}):** volume of plasma and tissues in which CFC is distributed after infusion, when the concentrations in plasma and tissues are in equilibrium. Higher values reflect greater distribution to tissues.
- **Recovery:** ability of CFC to increase circulating factor level after infusion.
- **In vivo recovery (IVR):** peak factor activity after infusion divided by expected peak of activity.
- **Incremental recovery:** peak factor level in the first hour of infusion.
- **Mean residence time (MRT):** average time in hours that a single molecule of CFC remains in the body.
- **Area under the concentration-time curve (AUC):** the integral of the concentration-time curve; reflects total exposure of the body to CFC over time.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

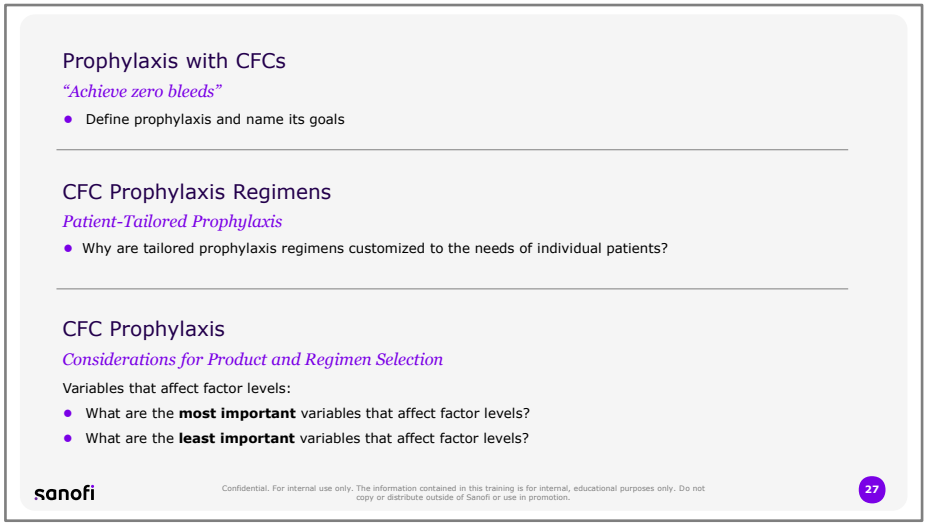
Key Concepts

Extravascular distribution of FIX:

- Given its relatively large size, FVIII is predominantly restricted to the intravascular space, rather than moving into surrounding tissues; in the circulation, FVIII exists in a stable complex with vWF.
- In contrast, FIX has a much smaller size and does not circulate in complex with other proteins.
- It is able to move into the extravascular space, and some data suggest that high concentrations of FIX may be stored there, bound to collagen IV in extravascular endothelial cells.
- It appears that FIX spends nearly half (44%) of its mean residence time (MRT) in the extravascular space, rapidly diffusing there after infusion.
- Thus, its elimination half-life is longer than that of FVIII as it must first return, or redistribute, from the extravascular space to the plasma.
- Animal studies suggest that this extravascular FIX has a role in coagulation, offering protection from bleeding even when plasma levels are <1%.

PK vs clinical outcomes in hemophilia B:

- Reliance on trough values as a reflection of bleed protection does not consider the large extravascular distribution of FIX (which is not reflected in trough levels) and the possible role of these extravascular pools in hemostasis.
- This reinforces the importance of considering patient outcomes (frequency and severity of bleeds) in addition to PK parameters when monitoring patients with hemophilia B.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

Define prophylaxis:

- Prophylaxis with CFCs (aka, regular replacement therapy) refers to regular, proactive treatment to prevent bleeds, especially in joints, thus preventing long-term adverse outcomes (eg, arthropathy and disability).
- This is recommended over episodic, or on-demand, therapy in which CFCs are administered reactively, at the time of bleeding.
- Although episodic therapy is necessary to achieve hemostasis during bleeding episodes, it does not change the natural course of hemophilia ultimately leading to musculoskeletal and other complications.

Goals of prophylaxis:

- The ultimate aim of all approaches to prophylaxis is the same: to have no spontaneous bleeding.
- Historical goal: maintain factor trough levels above 1% (1 IU/dL) to convert a patient with severe hemophilia to the bleeding profile of moderate or mild hemophilia in order to avoid spontaneous bleeds and preserve joint function

Patient-tailored prophylaxis:

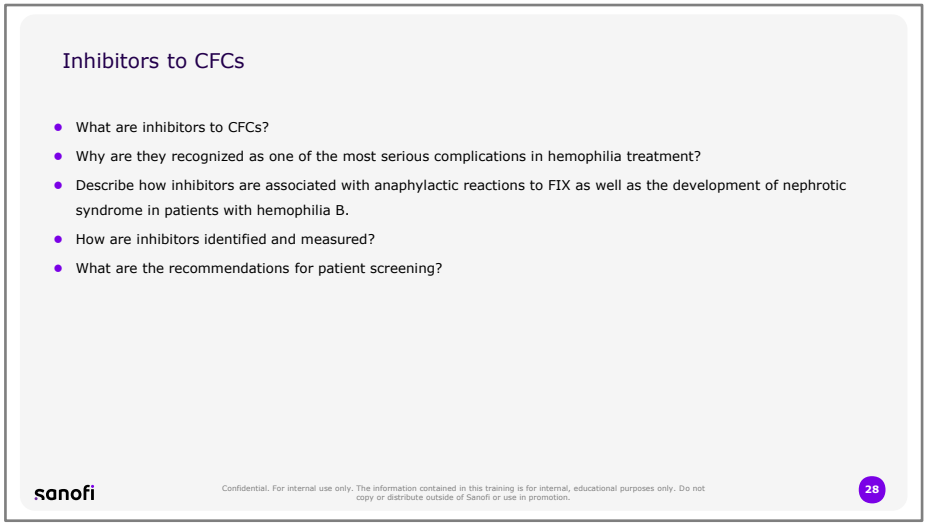
- The goal is to supply the right amount of replacement factor according to a patient's needs—no more, and no less.
- This approach is based on the recognition that important differences exist between patients in PK handling of CFCs and bleeding characteristics.
- Regimens can be tailored according to an individual's PK handling of CFCs and clinical factors such as bleeding phenotype and physical activity patterns.

Most important:

- Frequency of dosing
- Half-life/clearance

Least important:

- Dose
- Factor recovery



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

Definition, frequency, and complications:

- Inhibitors are antibodies that develop against exogenous FVIII or FIX (ie, after exposure to CFCs).
- The immune system in an affected patient identifies the CFC as foreign and develops antibodies against it.
- Inhibitors are a serious complication because they neutralize the activity of administered CFCs, rendering them ineffective.
- PK evaluations in affected patients show that inhibitors reduce both factor recovery and half-life.
- Thus, bleed control is much more difficult in patients with inhibitors.
- Inhibitors can occur in patients with either hemophilia A or B, but are more common in those with hemophilia A.
- Inhibitors are more common in patients with severe hemophilia compared with those with mild or moderate disease. (For hemophilia B, inhibitors occur almost exclusively in patients with severe disease.)

Anaphylaxis and nephrotic syndrome (hemophilia B)

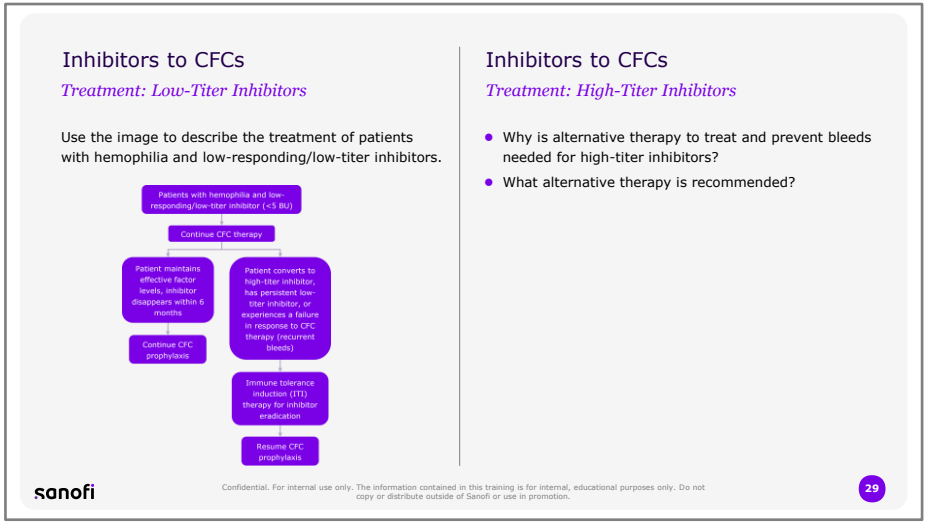
- Anaphylaxis and nephrotic syndrome can occur in conjunction with inhibitor development in patients with hemophilia B.
- In one registry of 94 patients with hemophilia B and inhibitors, 56 patients (60%) had anaphylaxis after exposure to FIX (anaphylaxis was defined as an allergic reaction with respiratory or cardiovascular compromise).
- Of the patients undergoing immune tolerance induction (ITI) therapy (a treatment for inhibitors), one-third developed nephrotic syndrome, almost all of whom had a history of anaphylaxis to FIX. (ITI to be reviewed in more detail in an upcoming slide.)

Identity and measurement:

- Inhibitors are identified and measured by the Nijmegen-modified Bethesda assay, which reports results in Bethesda units (BU). The greater the number of BU, the more inhibitors are present.
- Assay value thresholds differentiate high-titer from low-titer inhibitors as follows:
  - High-titer inhibitor: ≥5 BU
  - Low-titer inhibitor: <5 BU

Recommendations for patient screening:

- An exposure (previously known as "exposure day") is a 24-hour period in which a CFC product is given.
- In general, inhibitor development is most common during the first 20 exposures, and nearly all occur within 75 exposures.
- Routine screening is recommended during this period of initial exposure and is responsible for identifying half of inhibitor cases.
- Other cases are usually identified when patients fail to respond to adequate CFC treatment.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

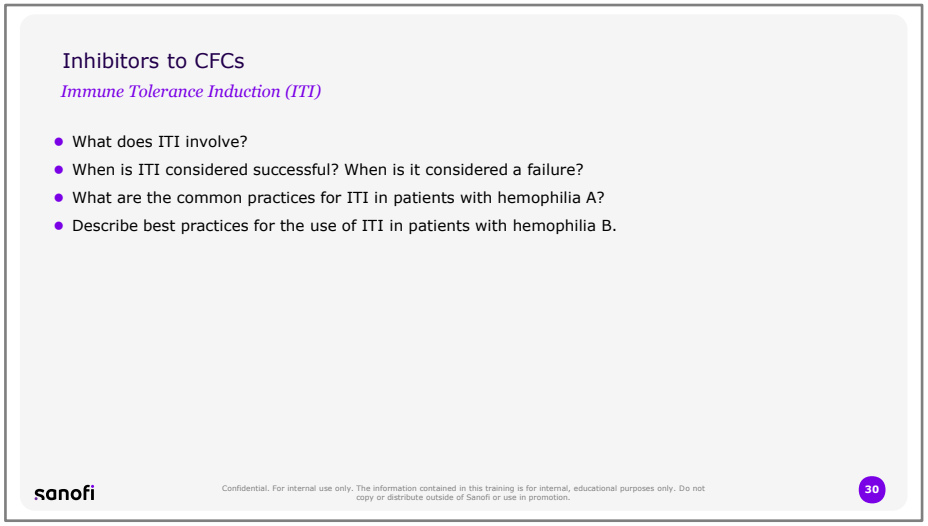
Key Concepts

Low-Titer Inhibitors

- Low-titer inhibitors are often transient, resolving after 6 months despite consistent CFC treatment.
- For these patients, maintaining CFC replacement therapy is recommended if measurable factor levels can be achieved (with close monitoring in patients with hemophilia B because of the high risk of anaphylaxis).
- Higher doses of CFCs may be required to neutralize antibodies.
- Patients should be monitored every 2 to 4 weeks to ensure the inhibitor hasn't become high titer via an anamnestic response.
- If monitoring demonstrates a high-titer inhibitor or a persistent low-titer inhibitor, or the patient has recurrent bleeding, a more aggressive approach with ITI may be needed.

High-Titer Inhibitors

- Because high-titer inhibitors tend to be persistent (rather than transient) and they render CFC ineffective, alternative therapy to treat and prevent bleeds is needed.
- For these patients, bypassing agents are recommended:
  - Recombinant, activated factor VII (rFVIIa)
  - Activated prothrombin complex concentrate (aPCC)
- Emicizumab may also be used to prevent (not treat) bleeding in patients with hemophilia A and inhibitors.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

ITI involves:

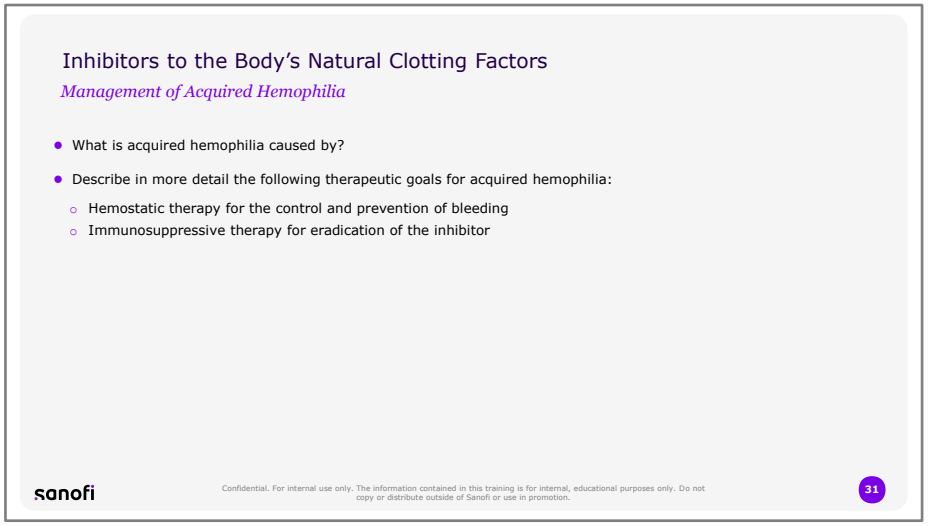
- ITI involves regular treatment (daily or several times weekly) with CFCs over months or years in an effort to achieve immune tolerance to FVIII or FIX (cessation of antibody production upon factor exposure).

ITI success and failure:

- ITI is considered successful if the patient achieves a persistently negative Bethesda titer and normal CFC PK, including recovery and half-life.

Common practices in patients with hemophilia A & B:

- The optimal protocol for ITI (product or dosage) is not established.
- Patients with poor prognostic factors should receive high-dose regimens.
- As for product choice, none is proven superior. ITI is often started with the patient's usual CFC product, which may be switched to another product type (eg, plasma-derived or recombinant) if no response is observed.
- In patients with breakthrough bleeding on ITI, initiation of prophylaxis with bypassing agents or emicizumab is recommended.
- In patients with hemophilia A, emicizumab is preferred over bypassing agents for prophylaxis.
- After successful ITI, prophylactic CFC therapy should be resumed, with close monitoring of clinical response.
- Best practices for the use ITI in patients with hemophilia B are not well established.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

Causation:

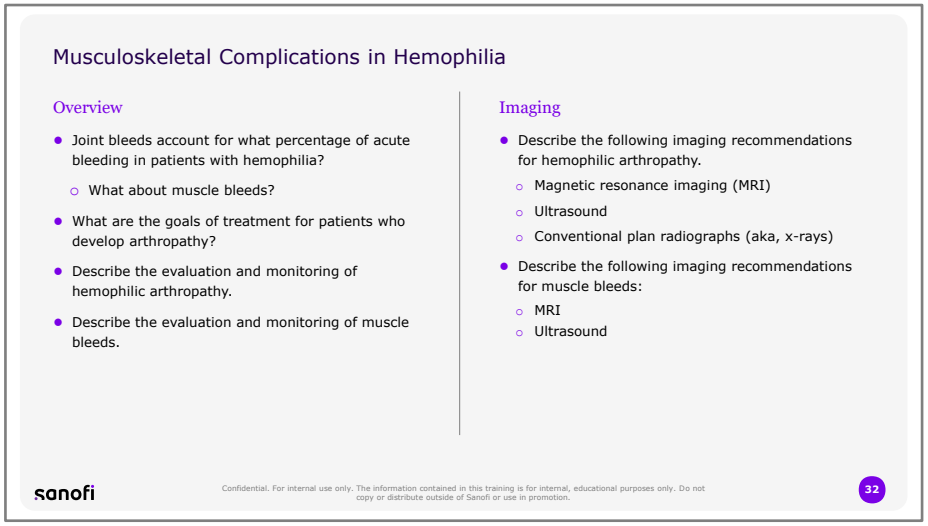
- Unlike congenital hemophilia (the classic form of hemophilia), acquired hemophilia is caused by the development of autoantibodies (also called inhibitors) against endogenous clotting factors (usually FVIII).

Hemostatic therapy:

- rFVIIa or recombinant porcine factor VIII (rpFVIII) are recommended for treatment of clinically relevant bleeding regardless of FVIII activity or inhibitor titers.

Immunosuppressive therapy:

- Immunosuppressive treatment is recommended in all patients with acquired hemophilia and is successful in eliminating the inhibitor in 60% to 80% of patients.



Facilitator Notes

- **This is a build slide. Advancing the slide will allow additional content to appear on-screen.**
- **As you discuss on-screen content, ensure participants understand the key concepts at right.**

Key Concepts

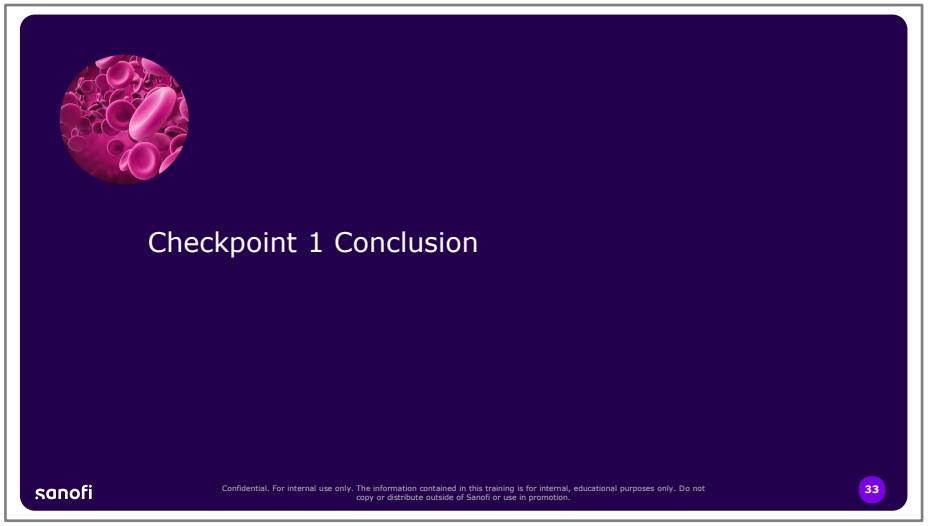
Overview:
- Joint bleeds account for 70% to 80% of acute bleeding in patients with hemophilia, with substantial long-term consequences, including hemophilic arthropathy and associated disability.
- Muscle bleeds, which make up 10% to 20% of acute bleeding, can also impose serious long-term consequences and functional impairment.

Hemophilic arthropathy – evaluation and monitoring:
- Regular evaluation of synovial condition is recommended after every bleed.
- In patients with synovitis, routine assessment is required until the joint and synovial condition are recovered, with no evidence of residual blood or swelling.

Muscle bleeds – evaluation and monitoring:
- Muscle bleeds should be suspected in patients complaining of muscle pain (especially with contraction or stretching), tension, tenderness to touch, swelling, and functional impairment.
- Patients with identified muscle bleeds should be monitored for symptoms of compartment syndrome.

Imaging recommendations for hemophilia arthropathy:
- MRI:
  - Able to assess all stages (early and late) of joint disease
  - Early changes, including effusions and hemarthrosis are easily identified
  - Can also show synovial hypertrophy and inflammation, and subchondral cysts
  - Can show later changes, including cartilage loss
- Ultrasound:
  - Useful to identify soft tissue and cartilage changes in early joint disease
  - Less expensive and more accessible than MRI but, unlike MRI, it has limited ability to image subchondral bone
  - Can identify hemarthroses and synovial inflammation
- X-rays:
  - Are not sensitive to early changes in joint health and thus are not recommended to diagnose early disease
  - Are useful to assess later stages of arthropathy, such as joint space loss (indicating cartilage destruction), and subchondral cyst formation and bone damage

Imaging recommendations for muscle bleeds:
- Ultrasound:
  - Can quickly and easily assess muscle bleeds and differentiate muscle bleeds from other regional causes of pain
  - Echogenicity varies with timing of the bleed
  - Ultrasound may be negative in the first 24 hours of a muscle bleed, so repeat ultrasound or MRI may be necessary
- MRI:
  - Can also be used for imaging of muscle bleeds
  - Like ultrasound, MRI images vary with timing of the bleed, based on signal differences of various hemoglobin breakdown products



Key Concepts

- **Address** outstanding questions/concerns.
- **Thank** participants for attending Checkpoint 1.
- **Conclude** the session.

Facilitator Notes