# GUIDE TO NATIONAL TENDERS FOR THE PURCHASE OF CLOTTING FACTOR CONCENTRATES

2nd edition

Brian O'Mahony

WFH
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# INTRODUCTION

**Clotting factor concentrates (CFCs)** for the treatment of people with **hemophilia** and other inherited **bleeding disorders** are essential, life-saving medicines that are relatively expensive in comparison with other medications. Setting up a **national tender system** or even multinational system for the purchase of clotting factor concentrates can help ensure that the best products at the best price are selected.

National **procurement** of factor concentrates can help to ensure that people with hemophilia, **von Willebrand disease (VWD)**, and other inherited bleeding disorders have access to treatment that is not only sufficient in quantity, but also meets the required standards in relation to safety, **efficacy**, and quality. In the absence of a national tender system, individual clinicians, hospitals, insurance companies, or health officials may choose products without having the appropriate level of expertise and knowledge available to them. As a result, products may be chosen on the basis of limited hospital budgets or insurance reimbursement schemes.

This guide explains what a national procurement system is, how to set up such a system, and the steps involved in carrying out a tender. In addition, it provides an overview of the current tender and procurement systems in some 50 countries around the world in 2014 and 2015, and sets out the advantages and disadvantages of national tenders. The guide also speculates on potential methods to evaluate extended or **prolonged half-life factor concentrates** which may well require novel approaches to procurement evaluation.

# WHAT IS A NATIONAL TENDER SYSTEM?

A national tender system, or unified procurement system, is a cost-effective system for the purchase of products or services. Instead of each organization purchasing its own supply of a particular product or service, the government purchases what is needed for the entire country or population. A national tender can bring together the key experts in a country and lead to a more rigorous and effective analysis of the criteria used to decide on which products should be purchased. This system can achieve cost savings by buying large volumes and soliciting competitive bids called tenders from suppliers, with the contract awarded for a period of time to the bidder or bidders who best meet those criteria.

An increasing number of countries are using national tenders for the purchase of clotting factor concentrates for their bleeding disorders population. Since the quantity of factor concentrates needed in a particular country in any given year can be predicted within defined margins, it is possible to purchase the entire supply for a population and period of time at once. However, there are many variables that affect the safety and efficacy of a product. Therefore, it is key to ensure that the clinicians, hemophilia organizations, and regulatory authorities with expertise in this area are directly involved in the tender process and that decisions are not made solely by officials or procurement officers with inadequate knowledge of the products.

Examples of countries that do not use a national tender system currently, such as the United States and Germany, are presented in the case studies section of this guide. There are also systems where groups of countries collaborate to procure regionally, such as the tender system in the Middle East led by Saudi Arabia and including the Gulf States, and the Central American system which includes eight countries. Tenders for the purchase of factor concentrates can also be conducted by a **consortium** of hospitals, health insurance companies, or in some cases by individual hospitals aiming to optimize the effectiveness of their purchasing system. In addition, some countries—including Canada and Brazil—use a tender system to select a company to fractionate their nationally collected plasma under a contract **fractionation** arrangement. This type of arrangement will typically supply **albumin**, and **intravenous immunoglobulin (IVIG)**, and may be used to supply **plasma-derived factor IX (FIX) concentrate** and some of the national requirement for **factor VIII (FVIII) concentrate**.

To work effectively, a national tender system should be open, objective, and transparent. To ensure that tenders are carried out properly, certain rules and principles, outlined in this guide, should be observed.

## Advantages of a national tender system

National tender systems for the purchase of factor concentrates have a number of distinct advantages:

- Hemophilia is a relatively high-cost condition to treat. In many countries, factor concentrates and **bypassing agents** for the treatment of **inhibitors** are among the top 10 most expensive medicinal products purchased. This has led to an increased interest in hemophilia by government health economists and an increased tendency to evaluate hemophilia therapies using **health technology assessment (HTA)** or other economic evaluation methodologies. National tenders can be cost effective as large quantities of products are purchased relative to the amount purchased by individual hospitals or areas of the country. Countries such as Ireland, the United Kingdom, and Australia, which have well established national tender systems for factor concentrates have benefitted greatly by virtue of lower cost of factor concentrates and a corresponding ability to increase per capita factor use, thereby moving toward optimal treatment. The survey of tender and procurement systems in 38 European countries, carried out on behalf of the European Haemophilia Consortium (EHC) in 2015 and published in *Haemophilia*, clearly demonstrated that tender systems with a legal framework and appropriate clinician and patient organization involvement are more cost effective [1]. The demonstrated **cost effectiveness** of national

tender processes with rigorous selection criteria argues for the replacement of HTA or other assessments in countries with well developed tender systems. Furthermore, an adequate tender process may increase the probability of access to newer products and newer generations of products.

- The national tender process can lead to a more uniform, higher standard of care nationally as the safest and most efficacious products can be purchased for the use of all people with hemophilia or other inherited bleeding disorders. It can help to prevent the situation where some people with hemophilia in some regions of a country get substandard treatment, due to inadequate health budgets for their local hospital or health authority. This can be greatly assisted by concurrently ensuring that a good system for distribution and utilization of products is developed and implemented nationally.
- Involvement of clinicians, hemophilia organizations, and regulatory authorities in the tender process brings an appropriate range of expertise together. The collective wisdom of the constituents will usually lead to better award criteria; better analysis of the various safety, efficacy, and supply considerations; and better decision making than that which would normally be made by individuals, clinicians, hospitals, or health insurance companies operating on their own.
- The process can lead to an improved assessment of the products, based on collection of comparative data and meetings with the pharmaceutical companies over the defined time period allocated for the tender process. The process does not rely on marketing or advertising materials for the various products, or on meetings with companies. The individual views of the experts on the **tender commission**, when taken together utilizing a clear and unambiguous set of selection criteria, will usually lead to a better, more rigorous, and more representative decision.
- National tenders can lead to an increased use of factor replacement therapy, up to the point where treatment is optimized. For example, in Ireland, where the current tender system was established in 2002, FVIII usage increased from 3.7 to 8.2 **international units (IU)** per capita between 2002 and 2014 despite an economic downturn from 2008 to 2012. In Brazil, FVIII usage has increased from 1.0 to 3.3 IU per capita between 2004 and 2014. It is highly unlikely that these very significant increases would have occurred without a national tender system as patients would have had to rely on the provision of treatment and tendering by individual hospitals or health board areas. These increases occurred independently of the general economic development in the country. In the last 10 years, the Brazilian economy has grown significantly, and in the last five years the Irish economy and health budget have contracted. The major reasons for the increased per capita factor usage were movement to more optimized treatment protocols driven by the presence on the tender commission of key clinicians who understand hemophilia, as well as more competitive prices for the products driven by a competitive tender process.
- A national tender system allows for prediction of national demand and use, and allows planning for a national budget for the provision of factor replacement therapy. A national budget brings clarity to the total cost of factor concentrates and prevents individual hospitals from subjecting people with hemophilia to a lower standard of care than available elsewhere in a country in an effort to restrict their own hospital expenditure.
- The involvement of clinicians and national hemophilia patient organizations in the process can lead to a more cost effective process. The EHC survey of tender and procurement systems for factor concentrates demonstrated a clear link between clinician and patient organization involvement and the achievement of lower prices.
- A variation in the amount to be supplied can be built into the contract so that it allows for contingency planning in case the actual requirement is more or less than that planned for.

- In the event of a product shortage, having a contract to purchase significant quantities of factor concentrates from specified companies may be an advantage towards ensuring supply of product. The existence of a national database and stock monitoring and distribution system can also help minimize the impact of a shortage.
- National tenders can increase the range and choice of products available to clinicians and patients in a particular country. In developing and emerging countries where hospital, social security systems, or insurance providers purchase relatively small quantities of factor concentrate, it has often been noted that very few companies register their products and compete for the market. This is partially due to the fact that the amounts being purchased are not deemed significant by the companies. If these disparate purchases are combined into a national tender (or even into a multinational tender such as those in Central America or the Gulf States), then the quantity purchased increases significantly and it becomes more attractive for companies to register their products in those countries and submit bids for the tender.

## Disadvantages of a national tender system

There are a few potential disadvantages with national tenders for the purchase of factor concentrates:

- A national tender might limit the availability of different products. However, the tender can specify that more than one factor concentrate will be chosen, thereby giving some availability and access to different products.
- National tenders have the potential to limit clinical freedom. However, clinicians are not generally restricted to using only the products purchased through the national tender. In Canada, any factor concentrate that is licensed by Health Canada can be prescribed by a clinician, and indeed 5-10% of the factor concentrates used are not necessarily provided through the national tender. In Ireland, clinicians may use a product that has not been purchased through the national tender, although they have to justify the need based on clinical grounds. Restrictions to clinical freedom can also be avoided if the leading clinicians with expertise on these products are directly involved in the selection process.
- A company that is unsuccessful in bidding for a tender may decide not to continue operating in a particular country and may not bid for future tenders, thereby decreasing the future availability and choice of products. This situation is more likely to occur where the volume of product being purchased or the financial value of the tender is low.
- If a national tender results in lower total cost of factor concentrates for a country on repeated occasions, the health authorities may recalibrate their fiscal expectations of the cost of hemophilia care and may always expect a downward trend in cost. This has the potential to limit access to new and possibly more expensive generations of products. Lower costs may also result in reduced funding being available from pharmaceutical companies for the additional supports required by **hemophilia treatment centres (HTCs)** and patient organizations.
- The standard tender model may be more difficult to apply if the country is assessing prolonged half-life recombinant factor concentrates or if they are comparing prolonged to normal half-life recombinant factor concentrates. This requires some new potential approaches and this is dealt with in a later section of this guide.

These potential disadvantages are largely theoretical and rather minor, and as the following discussion demonstrates, any downside they present can usually be ameliorated.

It is more common for the number of products available in a country to be limited by regulation if some products are not licensed in that country. Arguably, clinical freedom can be overstated as a requirement.

Ideally, products for a country should be chosen by a tender or procurement body which includes the country's leading clinical experts in hemophilia care and a representative of the national hemophilia patient organization. These would generally be directors or leading clinicians at comprehensive care centres. There is no apparent disadvantage to limiting the selection to expert clinicians who treat many people with hemophilia on a frequent basis, rather than allowing individual physicians who may treat a very small number of patients with hemophilia or who may only treat sporadically to select the products. In the latter case, they may not have the necessary time or inclination to develop a full and detailed knowledge of the more than 40 FVIII concentrates, or the more than 20 FIX concentrates, on the market.

The issue of tenders requiring a change of product for individual patients, possibly frequently as part of a tender process, is among the concerns about tenders that have been expressed in the past [2, 3, 4, 5]. Several studies have demonstrated no link between product switching and inhibitor risk following a tender resulting in a switch of products for the majority of patients. The duration of tenders should not be so short as to require very frequent switching. Some tender systems allow for several products to be purchased thereby facilitating no requirement to switch products in defined cases such as patients with a previous history of inhibitors.

Companies will not abandon potential markets that purchase a significant amount of factor concentrates. There may be occasions when they temporarily close their distribution network or operations but they will usually resubmit a bid for the next tender unless their product has no real possibility of gaining all or part of the tender on safety, efficacy, or quality grounds. A much more common situation is that companies do not register their products in a country or do not actively seek to enter the market because the amount being purchased is relatively insignificant. This is much more likely where there are no national tenders, and consequently individual hospitals or regions seek to purchase smaller quantities of factor concentrates. They may have to purchase products from a very limited choice of factor products or companies as the amount being purchased is not sufficient to generate tenders.

Managing the fiscal expectations of health authorities depends on dialogue and a well developed understanding by the authorities of the comprehensive care model for the treatment of hemophilia and other inherited bleeding disorders. This requires the participation of expert clinicians and the national patient organization in the tender process. If the process excludes these key **stakeholders**, then this can become a real problem and the health authorities could seek lower and lower prices on each tender, possibly to the detriment of standards of treatment and care and with no appreciation of the requirement for the purchase of the safest and most efficacious products. In addition, a proportion of any savings made on a tender for factor concentrates should arguably be made available for strengthening comprehensive care provided by HTCs as well as services offered by the patient organization. This would make up any shortfall from possibly decreased funding from the pharmaceutical industry.

## Figure 1: Establishing a national tender process

### DEFINE THE CONTRACTING AUTHORITY

**Contracting authority:** Holds legal responsibility for national tenders; issues and receives the tender documents, signs legal contracts, and approves payments, schedules, and logistics. The contracting authority can be any of the following:

- ☐ Ministry of Health
- ☐ Government agency
- ☐ Government department
- ☐ Blood transfusion service
- ☐ Hospital
- ☐ Government-appointed commission or board
- ☐ National hemophilia organization

### ESTABLISH A TENDER COMMISSION

**Tender commission:** Decides on the evaluation and award criteria, evaluates tenders, and makes the decisions on the award of the tender.

☐ **Two-tier system**

- Scientific advisory group made up of clinicians, patient organization representatives, and regulatory authority officials; evaluates products by scientific criteria and recommends products for tender to the commission.
- Tender commission comprised of government officials, accountants, lawyers, and other professionals; seeks technical advice from the advisory group and makes the decisions on tenders.

☐ **Integrated single-tier system**

- Single integrated tender commission with officials with procurement expertise, clinicians, patient organization representatives, regulatory authorities, and health ministry officials.

**Composition**

- ☐ Clinicians
- ☐ Patient organization representatives
- ☐ Regulators
- ☐ Health officials
- ☐ Virologists

**Definition of terms of reference**

- ☐ Mandate
- ☐ Product requirements
- ☐ Membership
- ☐ Liability issues
- ☐ Reporting relationships
- ☐ Administrative procedures
- ☐ Conflict of interest
- ☐ Commission work between tenders

### DEFINE THE TENDERING PROCEDURES

**Guidelines:** Procedures should include principles and guidelines on the tendering process.

- ☐ Threshold or minimum value of tender contract
- ☐ Principles of product selection and selection criteria
- ☐ Types of tender (open tender, restricted tender, competitive dialogue, negotiated tender)
- ☐ Selection criteria
- ☐ Electronic auction
- ☐ Call for tender
- ☐ Receipt and review of tenders
- ☐ Award of tender contract

# ESTABLISHING A NATIONAL TENDER PROCESS

Before a request for tenders can be issued, the system for processing and evaluating bids must be established. This includes:

- defining the contracting authority;
- establishing a tender commission; and
- defining the tendering procedures.

## Define the contracting authority

The contract holder or **contracting authority** is the organization that has the legal responsibility for the contract, and actually issues and receives the tender documents. It is usually the Ministry of Health or a government health agency, but can also be a government department, government agency, health agency, blood transfusion service, hospital, government-appointed commission or board, or even the national hemophilia patient organization. For example, in Argentina the contracting authority is the national hemophilia patient organization.

The contracting authority must have the ability to sign legal contracts and approve payments, delivery schedules, and other logistical requirements. They will require expertise in contract management and may need to have significant storage capacity for factor concentrates in a manner that will maintain the required **cold chain** processes.

## Establish a tender commission

A tender commission or committee is the group that decides on criteria for awarding contracts, evaluates tenders, and makes the decisions about the award of the tender. Wheras the final contract is signed by the contracting authority, the tender commission is responsible for evaluating and advising on the selection of products. The role of the commission should be set out in clear, well defined **terms of reference**.

The composition of this group is absolutely vital to the success of the tender process. It is in fact, the single most important step. Making the best decisions relies on having the correct people in the room. It is important that in an effort to control the cost of hemophilia treatment products, safety and efficacy as well as patient and clinician choice, are not compromised. The best way to ensure that decision making is representative is by establishing a permanent tender commission for hemophilia including clinicians, patient representatives, and other experts such as regulators, virologists, and health officials. In Ireland, the commission includes three key clinicians who treat the majority of persons with hemophilia and other bleeding disorders. It also includes two representatives of the Irish Haemophilia Society and an external advisor who is nominated by the Society.

With a representative commission of knowledgeable stakeholders and experts, products can then be evaluated on the basis of criteria relating to safety and efficacy, recovery, risk of inhibitors, supply/availability, scientific support, and other value added services offered by pharmaceutical companies. Decisions made by the tender commission will be based on the criteria that are most important to the stakeholders and therefore are more likely to be fully supported by the stakeholders.

By defining the selection criteria and their relative importance in advance, the tender commission is able to control procurement and greatly increase the probability of purchasing products that meet a country or region's requirements and budget, as opposed to reacting to bids received from companies without prior thought about the requirements.

## Tender commission models

In general there are two models for tender commissions: the two-tier system and the integrated single-tier system.

### Two-tier system

The two-tier system has two separate groups with clearly defined functions:

- The technical or scientific advisory group is made up of clinicians, representatives of the hemophilia organization, and representatives from the national regulatory authority. The advisory group examines the various scientific criteria relating to the products and makes recommendations to the tender commission on products appropriate for tender.
- The tender commission seeks technical advice from the advisory group and makes a decision on the tender. The tender commission is usually comprised of government officials or accountants, notaries, lawyers, and other professionals.

There are several disadvantages to this model which may outweigh the advantages. There is potential for miscommuication or disconnection between those who choose the products (government officials) and those who use the products (clinicians and patient representatives from hemophilia organizations). As a consequence, the technical advice and specifications forwarded by the advisory group may not be followed by the tender commission and there may be a lack of assurance that all of the products tendered for comply with the technical requirements. Also, in this model, price can be the overriding consideration, and the tender could be awarded based solely on the lowest price, without due consideration being given to product safety, efficacy, and quality aspects.

To avoid such critical drawbacks, there needs to be a very clear overlap between the advisory group and the tender commission to ensure that the technical **product specifications** and important criteria such as safety and efficacy are fully taken into consideration in the decision making process.

The two-tier system is used in a number of countries including in South America and Europe. In Brazil, the Workgroup on Coagulopathies, appointed by the National Coordinator of Blood and Hemoderivatives, decides on technical specifications in relation to the products and provides their advice to the tender commission. There was originally no overlap between the workgroup and the tender commission in Brazil but following specific input and assistance from the World Federation of Hemophilia (WFH), Brazil has now developed a more robust and inclusive system for the purchase of factor concentrates. They have examined an integrated selection criteria which would alter the terms of their tenders and increase the number of preferred suppliers, and built in a degree of flexibility in the amount for which they tender.

In Uruguay, a similar system is used. The technical advisors are the director of the National Hemophilia Program and the director of the National Blood Transfusion Service. The technical advisors examine all of the scientific criteria and the proposed prices for the tenders, and recommend the products that should be purchased. Their technical advice is transmitted to the technical commission of the Ministry of Health. However, there is overlap and communication between the technical advisors and the Ministry of Health Tender Committee, providing a mechanism of checks and balances in the system.

In Europe, a two-tier system operates in several countries including Romania, Poland, Bosnia and Herzegovina, and Moldova, in which the hemophilia clinicians are only consulted on the scientific and technical aspects. In these countries, the clinicians or patient organizations, respectively, are not party to the final decision.

**Integrated single-tier system**

In the single-tier system, there is a single integrated tender commission which incorporates the officials with procurement expertise, clinicians, hemophilia organization representatives, regulatory authorities, and health ministry officials in one group.

This system has a number of advantages. There is no disconnect between the users of the products and those who choose the products. All relevant factors are taken into consideration and discussed by one group. This group also decides on the award criteria for the tender. The presence of appropriate clinicians and hemophilia organization representatives ensures that the decision making process also includes quality and safety criteria, in addition to price considerations. The likelihood of inadequate or unsafe products being chosen solely on the basis of price is decreased. In addition, the diverse but necessary stakeholders gain a greater understanding of the viewpoints of other stakeholders and very effective working dynamics can develop by having an ongoing and structured inclusive dialogue.

This system is used in countries such as Ireland, Canada, and Serbia. The Canadian Selection Advisory Committee is comprised of two **hematologists**, two representatives from patient groups (Canadian Hemophilia Society and Canadian Immunodeficiencies Patient Organization), and five to six representatives from the government blood services (Canadian Blood Services and Héma-Québec).

## Requirements for hemophilia organization representatives on tender commissions

The presence of representatives of the hemophilia community on the tender commission is vital in ensuring that products purchased are not only sufficient in quantity but also meet the required safety and efficacy standards. If patient representatives and leading hemophilia clinicians are not members of the commission, the views and knowledge of the **end users** and key prescribers of the products will not be heard. Decisions could potentially be made solely on the lowest price without any consideration of quality or safety criteria.

Equally, if representatives of a national hemophilia patient organization sit on the tender commission, their input should not be merely symbolic. The patient organization should ensure that their representatives have the necessary knowledge and resources so that they can gain the required expertise for this vital task. Volunteers should commit to this task and responsibility for the medium to long term. The organization should appoint specific representatives to this task for a number of years and ensure that they have the interest, support, and resources required to carry out their roles. This is not an area where a different representative can be assigned each year since they would not likely have the expertise to provide valuable input.

In Ireland, members of the tender commission are appointed for a five year term, which is renewable. Therefore, the commitment of a volunteer in this area must be for at least five years. Organizations must actively search for suitable representatives and help them gain the knowledge they will require to represent the community on the commission. This will include access to scientific journals and publications, attendance at key conferences, and training opportunities.

## Terms of reference

The mandate of the tender commission must be clearly set out and agreed upon. This may be done by setting out agreed terms of reference, rules and procedures, or even a specific law, as in Ireland (see Appendix 1: Terms of reference – HPSMAB Ireland and Appendix 2: Irish legislation on change of contract holder for national tenders, 2012). The terms of reference should include a definition of the commission's mandate (which defines the categories of products that fall under its remit), functions, membership, reporting relationships, and procedures for meetings and decision making. They should also set out the broad product

selection principles that apply (these may be based on the laws or regulations of a country or a region such as the European Union), and the procurement and contract administration procedures. They should also clearly define the role of commission members and outline procedures to deal with conflicts of interest and liability issues.

### Definition of mandate

The terms of reference should clearly state which categories of products will be chosen by the commission; for example, FVIII and FIX concentrates, all clotting factor concentrates, all blood products or plasma components, or solely recombinant products. The mandate may include products for the treatment of inhibitors to FVIII or FIX. It may also include products for the treatment of von Willebrand disease and for rarer bleeding disorders such as deficiencies in factors V, VII, X, and XIII.

### Product requirements

The tender commission must look at which products are required based on historical use, estimates of future use, and budgets available. The commission should specify which types of products are required (e.g., recombinant or plasma-derived factor concentrates). It should also specify by which regulatory agency or agencies the products should be licensed and, in some cases, the number of suppliers required to ensure continuity of supply.

### Membership

It is important that the composition of the commission include the specific expertise required to choose the products within its remit and be chosen with due care and knowledge. It may be possible for additional experts to be added to the commission or attend specific meetings of the commission to participate in its deliberations on specific products or issues.

### Liability issues

The issue of liability of commission members should be clearly set out and **indemnity** offered by the government or contract holder if required.

### Reporting relationships

The body or persons to whom the commission reports should be clearly defined. This will usually be a government department or agency.

### Administrative procedures

The terms of reference should clearly define procedures for conducting the business of the commission. This includes procedures for meetings such as the frequency of meetings and the definition of a **quorum**. Procedures for resolving conflicts of opinion within the commission should also be clarified in the terms of reference. Should a serious conflict of opinion occur, this will not be the ideal time to define mechanisms for resolving these questions—these procedures should be carefully considered and specified in advance.

### Conflict of interest

There should be a clear **conflict of interest** policy that deals with potential or actual conflicts of interest and disclosure to the commission in case any member has any direct or indirect beneficial interest in any company that submits a tender. General ethical rules governing the award of tenders in a country will probably also apply to the commission. In Ireland, for example, the members of the Haemophilia Product Selection and Monitoring Advisory Board (HPSMAB) must comply with the provisions of the Ethics in Public Office Acts of 1995 and 2001. Contact between members of a tender commission and companies

that tender should be regulated during the tender process. Commission members should not discuss the tender with companies without the permission of the commission.

**Commission work between tenders**

Ideally, the commission would meet regularly between tenders to receive reports on product use, **adverse events**, new information on products, international trends, and published scientific and clinical data. This ensures that the commission members are optimally prepared when the next tender process starts. In Ireland, the tender commission proactively organized meetings with all the companies that are currently developing prolonged half-life factor concentrates a full year prior to the possible licensing of these products in Europe.

## Define the tendering procedures

Having clear procedures for tendering ensures that tenders are carried out in an open, objective, and transparent manner to achieve best value for expenditure. Tendering procedures should protect the essential principles of non-discrimination, equal treatment, transparency, and mutual recognition. Procedures regarding tendering may be governed by procurement rules in some countries. The European Union (EU), for example, has procurement rules with which all tenders over a certain value must comply.

If there are no national procurement procedures in place, the tender commission should develop its own tendering procedures that outline the principles and the process in clear, logical steps with defined timelines. The EU procurement rules, outlined in the next section, may serve as a model. Tendering procedures should be agreed upon as soon as possible following the identification of the contracting authority and the establishment of the tender commission.

The tendering procedures should include guidelines on:

- threshold, or minimum value of contracts that must go to tender;
- principles of product selection and selection criteria;
- types of tender;
- invitation, receipt, and review of tenders; and
- award of the contract.

## The European Union Procurement Directive

The EU public procurement rules are a pertinent model as they now apply to 28 countries in the European Community [6]. This robust process has been developed over time by many stakeholders with the goals of transparency and accountability. This framework was designed for the procurement of a wide variety of goods and services by government. Compliance with EU procurement rules ensures compliance with the Government Procurement Agreement (GPA) of the World Trade Organization (WTO). Suppliers in the 12 countries covered by the GPA have the same rights as those based in the EU. Tenders must comply with different national procurement procedures, and in the case of countries in the European Community must comply with specific European Directives.

A new EU Procurement Directive for public sector bodies was published in April 2014 and must be transposed into national law in the 28 EU countries no later than April 17, 2016, which is coincidentally World Hemophilia Day. This new directive, 2014/24/EU (see Further reading section), is currently being transposed into national law in EU member states and will replace the currently applicable directive (Directive 2004/18/EC) in this area. The new directive is discussed in more detail in the next section of this guide. In general within the European Union, a tender system for procurement must be used by government

departments or agencies such as health authorities and state bodies that rely on government departments for more than 50% of their funding.

### Threshold, or minimum value of contracts

In the EU, tenders must be used where the estimated value of the contract is over a specified threshold level. These threshold limits are updated every two years. Currently, for government departments the threshold is EUR 137,000 and for health agencies it is EUR 211,000 (both net of value added tax).

### Types of tender

The existing EU public procurement directive (Directive 2004/18/EC) specifies four types of tender and the rules for applying them.

*Open tender*

This is the most common tender. In an open tender procedure, companies are invited by public advertisement to tender for the supply of goods or services. Any company may apply for a copy of the tender documents and submit a tender.

*Restricted tender*

This type of tender applies when particular companies are invited to tender where there is a specific element of design or intellectual input required and where it is evident that a limited number of companies could satisfactorily provide the goods or services. This is a two-stage process. In stage one, the requirements are set out and expressions of interest are sought. In stage two, tender documents are sent to companies that possess the necessary professional and technical capacity and expertise.

*Competitive dialogue tender*

Competitive dialogue tenders may be applied where only certain companies or products would be able to meet the tender criteria. The contracting authority advertises the requirements and enters a dialogue with interested parties who pre-qualify, as with the restricted tender procedure. In the EU, at least three companies must be asked to submit tenders and the **most economically advantageous tender (MEAT)** is selected.

*Negotiated tender*

This type of procedure must be used in exceptional circumstances only, when there are compelling reasons for its use. Generally, it can be used if the nature of the goods or services to be provided are such that only one company is capable of carrying out the contract. It may also be used if no tenders have been submitted following an open or restricted tender procedure or where there have been irregular tenders submitted.

Where a single possible supplier exists, open or restricted tender procedures may result in an exceptionally high price being quoted given the fact that no subsequent negotiation with the company may take place. Competition between companies generally results in more competitive prices. Where a single possible supplier exists, better value for expenditure may be obtained with a negotiated tender.

Tenders for factor concentrates in the EU are generally open tenders unless there is only one possible supplier, in which case they are best carried out as negotiated tenders. The time requirements that apply to the various types of tenders are clearly specified in the directive.

In some cases, minimum times for responses can be reduced by up to 12 days if all documentation is transmitted electronically. A reduction of seven days can be obtained if communication with suppliers on contract notices is electronic. If tender submissions can be submitted electronically, an additional five-day reduction can be granted.

### Selection criteria

Contracts are awarded on the basis of price or the most economically advantageous tender (MEAT), in which additional criteria as well as price are specified. When a tender is awarded on the basis of MEAT, the tender documents must state all the criteria being applied in the award process and provide the relative weighting or score available for each criterion. If it is not possible to indicate the criteria, weighting, or scores in advance, the reason why it is not possible to do so must be specified and the criteria must be listed in descending order of importance. New or amended criteria must not be introduced later in the process. Companies must know at the outset the conditions under which they are required to provide goods or services under a tender.

### Electronic auction

The EU directive makes provision for tenders to be conducted by electronic auction (e-auction) where prices can be revised downwards following a full initial evaluation of the tenders using MEAT criteria. In this case, all companies whose products fulfill the MEAT criteria listed would be invited to bid electronically in a process with a specified start time and end point (either a specified time after the e-auction begins or after a specified period of time has elapsed since the last bid was submitted). This system, which has been used in the United Kingdom, is similar to the Pregão system used in Brazil. With this system, there is a strong probability that companies will not submit their best price initially but will wait until the e-auction begins. There are concerns about this system as it can lead to the decision being made solely on price to the exclusion of safety, efficacy, and quality criteria. It is perfectly valid to make a decision based on price once the differences in safety, efficacy, and quality have been accounted for; but these differences, however small, should not be discounted when selecting products. To ensure a sound decision, it would not be difficult to include and carry forward differences in non-price criteria and only apply the e-auction to that portion of the overall score based on price.

### Calls for tender

Calls for tender must be published in the *Official Journal of the European Union* (*OJEU*). This is now done via the Tenders Electronic Daily (TED) website, which is the online version of the Supplement to the OJEU dedicated to European public procurement. An additional notice is often published in national newspapers at the same time. The award criteria must be either stated in the notice of advertisement or alternatively listed in the tender documents. If award criteria are listed in the tender documents, the advertisement notice should state, under the award method heading: "Most economically advantageous tender based on criteria more particularly described in the tender documents." Price must be one of the award criteria under "most economically advantageous tender." Companies are given a specific period of time to submit tenders (Table 1) after the publication of the advertisement. Tenders are not accepted after the deadline and errors in the tendered documents will not be corrected. If there is any extension of the deadline in order to receive further information, clarification, or amendment, then this opportunity must be given to all companies that submit tenders.

### Table 1: Types and features of tenders in the European Union

| TYPE OF TENDER | Time Limit for Receipt of Expressions of Interest | | Time Limit for Receipt of Tenders** | |
|---|---|---|---|---|
| | NORMAL | URGENT | NORMAL | URGENT |
| **Open procedures** | | | Not less than 52 days | Not less than 10 days |
| **Restricted and competitive dialogue procedures** | Not less than 37 days | Not less than 15 days | Not less than 40 days | Not less than 10 days |
| **Negotiated procedures** | Not less than 37 days | Not less than 15 days | Agreed between parties | |
| **PIN* published—open, restricted or competitive dialogue** | | | 36 days | Not less than 22 days |

* A prior information notice (PIN) may be published in the *Official Journal of the European Union* stating the intent to tender and the quantity of product required. This should be done where the value of the tender is likely to exceed EUR 750,000.

** Changes to these values as stated in the new EU directive 2014/24/EU are described in the following section.

## Receipt of tenders and award of contract

Tender documents must be submitted to the stipulated location on or before the deadline stated, and an appointed receiver should date and time stamp the outside of the envelope. All tenders should be stored together in a secure place until the time for opening.

Tenders must not be opened in advance of the stipulated time and date, and no tender information should be given to any other parties. The tenders should be opened together as soon as possible after the time and date set for receipt for tenders. In case there is any dispute over the award of the contract, it is important that there is a formal record of receipt of tenders.

If MEAT criteria are being used, the price information should be submitted in a separate sealed envelope and not scored until the non-price criteria have been evaluated. This will protect against unintentional bias where individuals or a tender commission may be inclined to score a product more generously on non-price criteria if they know it is available at a lower price than the competitors.

Tenders received must be evaluated objectively and transparently against the published weighted criteria. The best way is to use a scoring system that includes a comparative assessment of the tenders received. Examples of such score sheets are included in Appendix 3: Tender score sheet for recombinant FVIII (Ireland, 2012), Appendix 4: Tender score sheet for plasma-derived FVIII (Ireland, 2012), and Appendix 5: Tender score sheet for prothrombin complex concentrate for treatment of FX deficiency (Ireland, 2015).

Contracting authorities may seek additional information or clarification following submission of tenders. This opportunity, if offered to one company, should be offered to all who have tendered bids. Substantive alterations to the bids received are not allowed under the open or restricted tender procedures.

When the decision has been made, unsuccessful applicants should be informed and an award notice must be placed in the *OJEU* within 48 days of the contract being awarded. There is typically a cooling off period of 14 days following notification of award of the tender before contracts are signed to allow for any challenge to the validity of the awards. Ideally, **debriefing** should be offered to unsuccessful applicants for tenders.

## New EU Directive 2014/24/EU

A new EU procurement directive has been agreed and must be transposed into national law in each of the 28 member states of the European Community no later than April 17, 2016. EU Directive 2014/24/EU seeks to make procurement simpler and more efficient.

The new EU directive is broadly similar to the existing EU Directive 2004/18/EC but there are several crucial differences:

- Tenders will be allowed to be fully electronic by October 2018 with no requirement for tendering companies to submit paper copies of their bids or supporting documentation.
- There will be decreased minimum deadlines for submission of tenders from the current 52 days to 35 days for open tenders, with an accelerated time limit of 15 days where there is a duly substantiated state of urgency.
- Current contracts can be awarded based on most economically advantageous tender (MEAT) or price. In the new directive, contracts shall continue to be awarded on the basis of MEAT using a cost effectiveness approach but criteria may be broadened to more holistic criteria including life cycle costs and best price/quality ratio. Contracts awarded based solely on price will remain an option but their use may be restricted. This could mean, for example, that a tender could be held for the purchase of a specified amount of factor concentrates plus the provision of some healthcare elements (e.g., information and communication technology systems, nursing or clinical posts, provision of defined and quantifiable support in various clinical or research areas). The new directive seeks to discourage selection on the sole basis of price, instead using MEAT or price/quality ratio, which should include qualitative measures linked to the tender (e.g., delivery time, specified support).
- Cross-border procurement involving contracting authorities from several member states will be permitted although, in practice, this may be difficult to agree upon and achieve as well as legally complex.
- The introduction of a competitive dialogue within the negotiated tender procedure may be of particular interest when tendering for different classes of product; for example new prolonged and normal half-life products together. The scope will be broader than allowed under the current negotiated tender procedure. In this new process, a minimum of three companies must be invited to negotiate. The procedure may take place in successive stages but must be fair and transparent, and ensure equal treatment for all bidders. The minimum requirements and award criteria are non-negotiable.

This new directive is meant to ensure that the evaluation criteria should be selected based on the interests of patients, clinicians, payers, and economic operators (i.e., pharmaceutical companies in the area of hemophilia). Preliminary market consultations will be allowed and the MEAT process is meant to become more holistic with costing of the entire life cycle. Before launching a procurement procedure, the contracting authority may conduct market consultations in order to inform pharmaceutical companies and distributors of their plans and requirements and seek advice from independent experts or market participants. The consultation must not preclude competition or infringe on the principles of nondiscrimination and transparency. This may assist in the preparation of optimized selection criteria in light of the current market situation and may therefore assist in the realization of an improved price/quality ratio as the tender commission specifies the criteria that are of importance to reflect, ideally, the interests of patients and clinicians in addition to payers.

The competitive dialogue tender procedure with negotiation is designed to foster comprehensive understanding of different offerings. The process is designed to ensure sustainable results with improved price/quality ratios and improved value and effectiveness of healthcare spending.

It is to be hoped that the aspiration to ensure that the interests of patients are met results in ensuring the formal involvement of national hemophilia patient organizations in the tender process in each EU member state. The real impact of this new directive on actual tender practices will start to become evident beginning in 2016.

## STEPS IN CONDUCTING A TENDER

Steps in the tender process include:

1. Ensure that the tender falls within the remit of the commission
2. Determine the product requirements
3. Determine the award criteria
4. Specify the type of tender
5. Specify the number of suppliers
6. Specify the quantity to be purchased and term of the tender
7. Produce score sheets based on award criteria
8. Prepare the tender documents and publish the call for tender
9. Receive the tenders
10. Review the tenders
11. Make a decision on the successful tender
12. Communicate the results to tenderers
13. Debrief tenderers
14. Publish results of the tender

### Ensure that the tender falls within the remit of the commission

Before beginning a tender, the commission must determine:

- Is the product required one which the commission has the remit to choose?
- Is the quantity required sufficient to warrant a tender?

Individual countries may have rules governing the value of contracts that must be put to tender. For smaller contracts, a tender is unnecessary and in any event may not be an optimum use of time, expertise, and resources.

### Determine the product requirements

The commission must define the products to be included:

- Is the tender for factor VIII, factor IX, **prothrombin complex concentrates (PCCs)** for the treatment of factor II, VII, IX or X deficiency, factor VII, concentrate for the treatment of VWD, or products for the treatment of factor VIII or factor IX inhibitors?
- Is the tender for a single product or a combination of different products?
- Does the tender specify the category of product required? For example, is the tender for plasma-derived or recombinant products, or can both product types be considered? Is the product required of intermediate or high **purity**?
- Are prolonged half-life recombinant factor concentrates also being considered? If so, the call should specify if the tender is for normal or prolonged half-life factor products, or if both will be considered together in the same tender process.
- Is the tender for products that must be licensed by a specified regulatory agency, for example, the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), or the national authority in the country?

## Determine the award criteria

The tender commission determines the specific criteria for awarding the tenders. Tenders can be awarded based on the lowest price or the most economically advantageous tender. MEAT, balancing various criteria, is the usual method for the purchase of factor concentrates. Lowest price tenders are seldom used and are more likely to be used in cases where the tender commission is not representative of the stakeholders and does not comprehend or properly analyze the appropriate and vital non-price criteria. In this situation, the key hematologists and the patient community who are excluded from the process can be justifiably concerned about the decision making process.

When using MEAT, tenders are evaluated and scored against pre-stated award criteria. For factor concentrates, the award criteria will typically include criteria such as safety and quality profile, clinical efficacy, supply considerations, technical and medical support, and price. The call for tender and tender documents must include the criteria and the relative weightings and score applied to each. If it is not technically possible to indicate criteria scores in advance, the criteria must be listed in descending order of importance.

## Specify the type of tender

The tender commission must determine the appropriate type of tender, according to the governing procurement procedures. Open tenders are the most common tender. However, if only one company can supply the product, it would be beneficial to use a negotiated tender. Examples of where this may apply would be the purchase of recombinant activated factor VII (rFVIIa) in Europe, excluding Russia, where there is currently only one supplier for this product. As competitive products come on the market, this should shift to an open tender process.

## Specify the number of suppliers

A tender can seek products from more than one supplier but it must be specified in the tender documents. This is especially relevant where there may be concerns about continued availability of supply in the future or where access to different types of products is being sought (e.g., both plasma-derived and recombinant concentrates).

In Ireland, tender documents for the purchase of recombinant factor VIII (rFVIII) specify at least one supplier but the contract may be awarded to more than one company. In England, clinical freedom mandated that treatment centres could choose the products they required from a list and at the prices agreed upon during the tender process. The tender process effectively sets the price for several products and the relative amounts of each product that the country commits to purchasing. Individual treatment centres can then select a specific product or products within the overall supply constraints and at the specified price for each product. In Hungary, a tender for plasma-derived concentrates specified the purchase of products in different purity categories. There is an often misplaced concern that a national tender will totally remove clinician and patient choice and lead to only one product being available. This is not necessarily the case unless the tender commission wants this outcome and intentionally recommends or selects just one product for each tender.

## Specify the quantity to be purchased and the term of the tender

The tender must specify the quantity of factor concentrates required and the period of time over which they are required. The quantity should be based on projections of clinical need over the time period of the tender. The presence of clinicians on the commission, the availability of a national **registry** of people with bleeding disorders, and an agreed system for collecting data among clinicians and hospitals are very useful in this regard[1].

The tender should allow for a variance in the supply of products required. It may state, for example, that 10 million IU FVIII will be purchased but that the contract may require 10% more or less to be supplied at the same price during the term of the contract. For example, Ireland typically allows for a variation of up to 20% during the course of the tender.

Predicting the quantity of product required for the treatment of inhibitors can be more difficult as this can vary enormously according to individual cases and circumstances that cannot be foreseen. Tenders for these products may require a greater degree of flexibility in relation to the quantity to be purchased, with a minimum quantity specified but a clear commitment on supply and cost for additional product.

The term of tenders can vary from three months to three years. In 2004, Brazil was, at one point, issuing a call for tender every three months. This made the decision making process continuous and did not allow much time for due consideration of selection criteria, international developments, and publications relating to the products. In Ireland, tenders tend to be for a two year period. This is a good timeframe as it is long enough for due consideration. A one year timeframe is also reasonable, particularly if the government or funding agency is not willing to commit a budget for more than one year. Canada has used a three year tender. This provides stability and allows for proper consideration and review between tenders. However, three years may be viewed as too long as it may commit the country to one product for a period during which an improved or more efficacious product becomes available.

The tender process should take place well before the product is needed to ensure that the successful company or companies can deliver the required product in the requested **potencies** (e.g., a company may require more lead time to deliver a large quantity of 250 IU vials). In general, a tender should be awarded at least three months before the product is required.

It is also possible to build in an option for contract renewal at the same terms for an additional period of time. In Ireland, the commission usually reserves the right to renew a two year tender, to extend the contract in individual increments of one year for up to a further two year period.

## Produce score sheets based on award criteria

The ideal method for evaluating tenders is to prepare a score sheet using the award criteria and assigning weightings or specific scores to each criterion and sub-criterion. For factor concentrates, these criteria typically include safety, efficacy, availability of supply, and price. For plasma-derived concentrates, they may include sub-criteria such as plasma source, pool size, **quarantine**, **nucleic acid testing (NAT)**, and **viral inactivation** (see Appendices 3, 4, and 5).

The scores assigned to each criterion and sub-criterion should ideally be included in the tender documents. If this is not possible, they must at the very least be ranked in order of decreasing importance with the criterion with the highest score listed first.

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1 The *WFH Guide to Developing a National Patient Registry* is a practical resource on how to set up and maintain an effective registry, and use the valuable data to track diagnosis and disease prevalence, identify treatment needs and healthcare priorities, and determine what quantities of treatment products should be purchased.

Score sheets greatly assist the discussion and decision process by a tender commission in addition to providing a permanent record of the decision rationale. For each criterion or sub-criterion, the rationale for assigning a product a specific score is discussed and agreed upon by consensus. A record should be kept of the rationale for each score. This system is invaluable in reaching a decision and also ensures openness and transparency.

## Prepare the tender documents and publish the call for tender

The tender documents should clearly set out:

- products required;
- quantity required;
- term of the tender;
- award criteria (in as much detail as possible);
- date and time deadline for submission of tenders;
- time interval between date of receipt of tenders and awarding of contract; and
- contact person in the contracting authority.

A call for tender, specifying these parameters, should be published in newspapers or other publications according to the tender procedures. A reasonable amount of time must be allowed for companies to prepare tender documents. In the EU, for example, this is currently 36 days when a prior information notice (PIN), also called a prior indicative notice, has been published. The same information should be sought from all companies submitting tenders.

Companies that are known to supply the factor concentrates being sought could be separately informed by the commission that a tender will take place. If this step is being contemplated, the contracting authorities should take care to ensure that all companies known to the commission that manufacture or supply these products are notified to ensure fairness and transparency. This can also be done using a PIN.

## Receive the tenders

Care must be taken to ensure that the proper tender procedures are followed to ensure fairness and transparency. Each tender submission received should be stamped with the time and date of receipt and held by the designated contact person within the contracting authority until the final deadline for receipt of tenders.

If any clarification or additional or technical information is required and a time extension granted, the same time extension should be given to all companies and the same information circulated to all.

The tenders should be opened as soon as possible after the deadline for receipt.

The contracting authority should ensure that proper procedures are in place for opening tenders in order to prevent abuse or impropriety at this stage. These procedures should require that the opening of tenders take place in the presence of at least two officials of the contracting authority. The procedure adopted should ensure that, in the case of any dispute, there is a clear and verifiable record of the tenders received.

## Review the tenders

As soon as possible after the deadline closes for receipt of tenders and the opening of the tenders, the commission should meet to review the tenders received. The number of valid tenders should be confirmed.

If any further information or clarification is required, it should be sought from the companies and a time extension agreed upon for the provision of this information. If this opportunity is offered to one tendering company, it should be offered to all. Information requested should be limited to clarification of data received or further data required based on the existing published award criteria. It is not acceptable at this stage for the commission to ask for information based on new criteria.

Following receipt of clarification, if required, the commission can make its decision. Alternatively, the companies tendering may be asked to make a presentation to the commission for the purposes of elaboration and clarification. In this event, the presentations should be based solely on the award criteria and the information contained in the tender bid. Any dialogue with tenderers that could be construed as "post-tender negotiation" on price, or result in significant changes to tender criteria or specifications, is to be avoided. The companies should be given the same amount of time for their presentations.

## Make a decision on the successful tender

The commission should score each product according to the agreed criteria. Each product is assigned a score for each category. The total of the scores for each category is the final score for that product. The rationale for each score given should be noted and recorded. This may be important if later there is a challenge to the award of the contract by an unsuccessful tenderer.

There are two ways to score:

- Score each product for all categories including price – The product (or products if the tender specifies that more than one supplier may or will be chosen) with the highest score is awarded the tender.
- Score each product for all categories excluding price – Then, products that have not achieved a pre-defined minimum score indicating they broadly satisfy important criteria such as safety and efficacy are eliminated. The products that have met the minimum score required are then assessed on price, and a decision is made. This method helps ensure that safety and efficacy criteria are paramount in the deliberations. Price should be the deciding factor only when the commission is satisfied that the products meet the necessary standards for safety and efficacy and other important criteria. This is the approach used when making decisions based on MEAT. Differences in scores for the different qualifying products should be carried forward when looking at price and not excluded.

## Communicate the results to tenderers

All tenderers should be informed of the tender results without delay. Unsuccessful tenderers should be informed promptly of the outcome and contracts should not be formally awarded before a specific time interval has elapsed (the EU recommends 14 days) during which an unsuccessful tenderer can seek a review of the decision if they feel that the process was unfair or unlawful. The contracting authority should inform the successful tenderer as soon as possible following this interval and proceed to negotiate contracts in relation to delivery schedules and other logistics.

## Debrief tenderers

It is good practice to offer all the companies that tendered a post-tender debriefing meeting. They should be told how their product scored for each category and subcategory. They should not be given the individual scores for their competitors' products. Here, the advantage of having a record of the rationale for each score awarded becomes clear. Tenderers should be given the range of prices (but not the individual prices for each company's product) submitted by tenderers. The debriefing meeting should result in the unsuccessful tenderers knowing the areas where their product was seen as deficient and where concerns were raised.

In the EU, unsuccessful tenderers who request the information must be informed of the reasons for rejection of their bid within 15 days. They must also be advised of the name of the successful tenderer.

## Publish the results of the tender

In some countries, results of the tender must be published. Publication of the results helps ensure a transparent process and should be considered even when it is not required by law.

Proposals in a tendering process are normally submitted on a confidential basis. In order to preserve the integrity of the process and respect the commercial and competitive positions of tenderers, details of tenders must be kept confidential at least until the evaluation process is concluded. If tenderers are imparting commercially sensitive information to the commission, this should not be disclosed. Commission members, in some cases, are required to sign confidentiality agreements.

It should also be borne in mind that the more information that can be made available to interested parties and the public, the greater the confidence will be in the process. The requirements of national freedom of information legislation in a country must also be considered.

## Figure 2: Steps in conducting a tender

**ENSURE THAT TENDER IS WITHIN THE REMIT OF THE COMMISSION**

- ☐ Commission has the remit to choose product required and quantity required warrants a tender

**DETERMINE THE PRODUCT REQUIREMENTS**

- ☐ Type of products (e.g., factor concentrates, prothrombin complex concentrates, inhibitor products)
- ☐ Category of products (e.g., plasma-derived, recombinant, prolonged half-life factor concentrates)

**DETERMINE THE AWARD CRITERIA**

- ☐ Lowest price
- ☐ Most economically advantageous tender (MEAT) based on various criteria (safety, quality, efficacy, supply, technical/medical support, price)

**SPECIFY THE TYPE OF TENDER**

- ☐ **Open tender** – Invite companies by public advertisement to tender; any company can apply for tender documents and submit a tender.
- ☐ **Restricted tender** – Invite particular companies to tender where it is evident that a limited number can provide the goods or services.
- ☐ **Competitive dialogue tender** – Apply where only certain companies or products are able to meet the tender criteria.
- ☐ **Negotiated tender** – For exceptional circumstances only, when only one company is capable of providing the goods or services sought.

**SPECIFY THE NUMBER OF SUPPLIERS**

- ☐ One supplier
- ☐ Multiple suppliers

**SPECIFY THE QUANTITY TO BE PURCHASED AND TERM OF THE TENDER**

- ☐ Quantity of factor products
- ☐ Period of time required

**PRODUCE SCORE SHEETS BASED ON AWARD CRITERIA**

- ☐ Assign weightings or specific scores to each criterion and sub-criterion (e.g., safety, efficacy, availability of supply, and price).

*continued on next page*

**Figure 2: Steps in conducting a tender** ***(continued from previous page)***

**PREPARE THE TENDER DOCUMENTS AND PUBLISH THE CALL FOR TENDER**

**Open tender**

- ☐ Set out products and quantity required; term of the tender; award criteria and relative weightings and score; submission deadline; time interval until awarding of contract; and contact person. Publish call for tender.

**Restricted tender**

- ☐ Set out the requirements and seek expressions of interest.
- ☐ Send tender documents to companies with the necessary professional and technical capacity and expertise. Publish call for tender.

**Competitive dialogue tender**

- ☐ Advertise the requirements and enter a dialogue with interested companies that pre-qualify. Publish call for tender.

**Negotiated tender**

- ☐ Negotiate tender with single company capable of carrying out the contract to provide the goods or services being sought.

**RECEIVE THE TENDERS**

- ☐ Stamp each tender submission received with the time and date of receipt and hold until the final deadline for receipt of tenders.

**REVIEW THE TENDERS**

- ☐ Review the tenders received and confirm number of valid tenders.
- ☐ If required, seek further information or clarification from the companies and grant time extension for the provision of this information.
- ☐ If required, invite tendering companies to make a presentation for the purposes of elaboration and clarification.

**DEBRIEF TENDERERS**

- ☐ Offer all companies that tendered a post-tender debriefing meeting on how their product scored for each category and subcategory.

**PUBLISH RESULTS OF THE TENDER**

- ☐ Publication of the results helps ensure a transparent process and should be considered even when it is not required by law. The requirements of national freedom of information legislation in a country must also be considered.

## TRAINING AND INVOLVEMENT IN TENDER PROCESSES

It is vital to ensure that hemophilia patient organizations and clinicians are involved in their national tender or procurement processes for factor concentrates. The clinicians will ideally be those who are working full time in comprehensive hemophilia centres and who have the knowledge and experience required to contribute to the process. The selection of patient organization representatives requires more thought and consideration. National hemophilia patient organizations must carefully and proactively select their representatives on tender boards. This can be an intimidating prospect for many patients, the majority of patients do not have a scientific background. National organizations should work to find volunteers who are interested in this area of work, or who have the ability to become involved and the willingness to give the time commitment necessary to learn. When looking for potential representatives, organizations could look at their current and past leadership. They could look at their young members who have completed college and consider those taking degree courses in science or medicine.

A scientific background is useful but not essential. Some of the most knowledgeable and effective hemophilia patient advocates in this area, globally, had no scientific background when they started their work for their hemophilia organizations. Commitment and hard work are equally or more important. Volunteers should realize that this area of work is a medium- to long-term commitment (usually several years). They should be given access to journals, publications, and conference attendance, as well as access to their peers and experts from other hemophilia organizations.

Ideally, training should be provided to all tender board members. The author of this guide has been involved in, and witnessed the great benefit of, training courses for hemophilia patient organization leaders, clinicians, and Ministry of Health officials from many countries including: the United Kingdom, France, Germany, Ireland, Italy, New Zealand, Lebanon, Honduras, Brazil, Peru, and Colombia. Training courses ideally consist of two separate three-day workshops separated by one year, with study of a defined reading list between the initial and follow-up course. Courses typically include lectures on tender methodology, basic concepts, safety concepts, economics, and licensing and regulation. It is also important to use the knowledge gained in a practical setting, such as a series of simulated tender processes where the actual characteristics of real products are altered to make a decision process more interesting and often more difficult.

It is very beneficial for the entire tender board to also undergo training together, typically for a two- to three-day workshop. This builds collaboration and clearly demonstrates, through the simulated tender processes, the absolute importance of having hemophilia clinicians and patient leaders in the room in addition to payers and health authority or hospital representatives.

# MANAGING CHANGE: TENDERING FOR LONGER-ACTING FACTOR CONCENTRATES

Tender and procurement criteria for factor concentrates will require rethinking now that prolonged half-life factor concentrates are licensed and available. Comparisons will no longer be of like with like, as 1 IU of a prolonged half-life factor will not be equivalent to 1 IU of normal half-life products. The number of units of factor to be purchased will differ between prolonged half-life factor and the normal half-life concentrates. Countries may also look at the differences in half-life, trough level, or treatment protocols for the different products using **prophylaxis** or **on-demand** regimes.

In the United States, the published average wholesale unit prices for the first licensed prolonged half-life recombinant FVIII and recombinant FIX were increased almost in line with the reported extension in half-life. However, hospitals or payers in the U.S. very often secure discounts on these prices, therefore the actual prices paid are not clear. Indeed a network of treatment centres in the U.S. benefits from a price discount in excess of 17% on published prices. New or novel methods of pricing and value comparisons may be required. Outcome based pricing based on defined annual bleed rates, total cost of all the factor concentrate requirements for a country, or average annual cost per patient with severe hemophilia are all possible mechanisms. The new EU Directive 2014/24/EU will assist in this process for EU countries as it includes provision for increased discussion under the competitive procedure, with negotiation and evaluation of life cycle costs such as estimating total factor consumption differences between products, which can be carried out as part of a tender process.

The well defined selection criteria which have been used for several years in countries such as Ireland (Appendices 3, 4, and 5) will require substantial alteration if prolonged half-life factors are being procured as part of an inclusive approach or tender with normal half-life products. In Québec, Canada, in 2015, the tender board applied a weighting factor linked to the increase in half-life. Countries may decide to carry out separate tenders for prolonged half-life and normal half-life recombinant products. If separate, they will have to decide on the amounts to be purchased. This will depend on their prior decision as to which patients or categories of patients will be treated with which generation of product. In addition, they will have to decide which products to use for on-demand therapy, prophylaxis, or surgery, where a decision might be made between bolus injection with prolonged half-life factor and continuous infusion with normal half-life products.

If the products are all to be assessed in a single tender, tender boards will have to apply criteria to differentiate between them. What would be the projected quantity of prolonged half-life product required compared to normal half-life product? Will they apply a weighting factor to account for the difference in half-life? And how would such a weighting factor be determined? They may also look at their total requirements for all patients and ask companies to tender to provide for all their requirements for a specified cost. They may look at average annual cost per person with severe hemophilia and seek to have all the factor requirements for each individual met within a specified budget.

In many countries, the decision may initially be taken by health technology assessment (HTA) agencies that will look at the incremental cost per quality-adjusted life year of any change in product or the additional benefit that a new generation of product would possibly provide. It is possible that HTA agencies will not approve reimbursement of new products at the prices submitted by the pharmaceutical companies, especially if the incremental cost or the total budget increases significantly. It is also probable that the manufacturers of the normal half-life products will decrease their unit cost or make more innovative offers to tender boards to maintain market share; for example, a company may offer to provide an unlimited quantity of factor for a specified total budget or may lower the unit cost to a level where the prolonged half-life factor concentrates would struggle to compete, even with the difference in half-life.

The key element is to continue to ensure that hemophilia clinicians and patient organizations are fully and formally involved in the tender process and to ensure that the process is not taken over by HTA agencies. The optimum outcome is most likely to occur in countries where the involvement of clinicians and patient organizations have, to date, resulted in a well defined and cost effective procurement process. It is less likely to occur in countries where the government or authorities are concerned about the current procurement system and the potential for large increases in cost and consequent budget impact. A successful inclusive national tender process may offer a degree of protection to the hemophilia community and a greater possibility of access to new and innovative products.

# CONCLUSION

National tenders can be a cost effective way to purchase large quantities of treatment products for bleeding disorders. A good tender process can lead to a more uniform and higher standard of care nationally. It helps to prevent the situation where some people with hemophilia in some regions of a country get substandard treatment, due to inadequate health budgets for their local hospital or health authority. A good tender process can lead to an increased use of factor replacement therapy, up to the point where treatment is optimized. It allows for prediction of national demand and use, and allows planning for a national budget for the provision of factor replacement therapy.

To work effectively, a national tender system should be open, objective, and transparent. It is essential that key clinicians, the hemophilia patient organization, and regulatory authorities be directly involved in the tender process, and that decisions not be made solely on price by officials with inadequate knowledge of the products. Price is a good final selection criterion to use provided that the products that are assessed at that stage satisfy the criteria for safety, efficacy, quality, and supply.

# CASE STUDIES

## CASE STUDY: TENDERS AND PROCUREMENT FOR FACTOR CONCENTRATES IN EUROPE

Availability of **clotting factor concentrates (CFCs)** in Europe varies enormously with reported use of **clotting factor VIII (FVIII)** per capita in 2012 varying from 0.1 **international units (IU)** per capita in Armenia to 8.56 IU per capita in Sweden, and reported use of **clotting factor IX (FIX)** per capita varying from 0 IU per capita in Armenia to 2.66 IU per capita in Ireland [7]. Among the member states of the European Union (EU), which come under the auspices of the specific EU Procurement Directive 2004/18/EC [8], there was also great variation in reported factor use, with factor VIII per capita in Romania at 0.51 IU compared to Sweden at 8.56 IU per capita.

Clearly, the levels of economic resources available and gross domestic product (GDP) per capita vary among countries as do the healthcare systems and the priority afforded to hemophilia treatment and care. In 2014, on behalf of the European Haemophilia Consortium (EHC) and together with two colleagues from Ireland, EHC President Brian O'Mahony set out to examine the different tender and **procurement** systems used in Europe for factor products. A survey was sent in late 2014 to 45 national hemophilia patient organizations that are members of the EHC and national member organizations (NMOs) of the World Federation of Hemophilia (WFH). The EHC survey asked the patient organizations to complete detailed information on their national system for procurement and separately asked for information from countries that use a **national tender process** or an alternative procurement process.

Responses were received from 38 countries; 7 did not respond. From the survey results, 19 countries use a tender, 17 use an alternative procurement process, and 2 use a combination of tender and alternative procurement methods. (Table 2)

### Table 2: Tender and alternative procurement processes in 38 European countries

| TENDER | ALTERNATIVE | COMBINATION |
|---|---|---|
| Albania | Austria | Bulgaria |
| Azerbaijan | Belgium | Lithuania |
| Belarus | Croatia | |
| Bosnia & Herzegovina | Estonia | |
| Czech Republic | Finland | |
| Denmark | France | |
| Hungary | Germany | |
| Ireland | Greece | |
| Moldova | Italy | |
| Montenegro | Kyrgyzstan | |
| Poland | Latvia | |
| Portugal | Netherlands | |
| Romania | Norway | |
| Russia | Spain | |
| Serbia | Sweden | |
| Slovak Republic | Switzerland | |
| Slovenia | Turkey | |
| Ukraine | | |

## Tender process

All of the 19 countries that use a tender process have a legal framework or law that governs the tender process. Nine are EU member states and therefore come under the jurisdiction of the EU procurement directive. Fifteen countries have a national tender, two countries (Romania, Czech Republic) have hospital-based tenders, and one country (Portugal) has a combination of national and hospital-based tenders. Bosnia and Herzegovina have a variation on a national tender in which the majority of the country is covered by one tender and an individual district is covered by a separate tender. Table 3 shows the key representative bodies that have formal involvement in the **tender commissions** or boards. The vast majority of EHC countries surveyed have a tender committee or board for hemophilia products and only three countries do not (Azerbaijan, Hungary, Poland).

### Committees and framework

Of the countries with a tender process, clinicians or hemophilia centres are formally involved in five countries (Ireland, Denmark, Montenegro, Serbia, U.K.); only involved in the scientific and technical aspects of the tender in four other countries (Bosnia and Herzegovina, Moldova, Portugal, Romania); informally involved in the process in another five countries (Azerbaijan, Hungary, Czech Republic, Romania, Ukraine); and clinicians are not involved in two countries (Poland, Russia).

The patient organization is formally involved in two countries (Ireland, Serbia); only involved in the scientific and technical aspects in three countries (Portugal, Slovenia, U.K.); and informally involved or has observer status in six countries (Hungary, Slovak Republic, Bosnia and Herzegovina, Ukraine, Moldova, U.K.). Nine countries have no patient organization involvement in the tender process. Other members of tender committees formally involved in different countries include: a virologist, procurement agency, blood safety expert, regulator, and clinician involved in the national **registry**.

**Table 3: Organizations involved in the tender process in 19 European countries**

**INVOLVED IN ALL ASPECTS OF THE TENDER PROCESS**

| HEALTH INSURANCE FUNDS | MEDICINES AGENCIES OR PHARMACIES | HOSPITALS OR BLOOD CENTRES |
|---|---|---|
| Bosnia & Herzegovina | Denmark | Albania |
| Hungary | United Kingdom | Czech Republic |
| Montenegro | Azerbaijan | Ireland |
| Serbia | Romania | Portugal |
| Slovak Republic | Belarus | Romania |

| MINISTRIES OF HEALTH | CLINICIANS OR HEMOPHILIA CENTRES | PATIENT ORGANIZATION |
|---|---|---|
| Albania | Ireland | Ireland |
| Azerbaijan | Denmark | Serbia |
| Belarus | Montenegro | |
| Ireland | Serbia | |
| Russia | United Kingdom | |

**SCIENTIFIC AND TECHNICAL ASPECTS ONLY**

| CLINICIANS OR HEMOPHILIA CENTRES | PATIENT ORGANIZATION |
|---|---|
| Bosnia & Herzegovina | Portugal |
| Moldova | Slovenia |
| Portugal | United Kingdom |
| Romania | |

The mean term of office for members of the tender commissions is four years, with the minimum being two months prior to the tender in the Slovak Republic and the maximum being six years in Russia. In Portugal, there are no term limits. Ten countries have written **terms of reference** for the tender commission, seven have no written terms of reference, while two countries did not respond to this question.

### Tender details

Of the countries that use a tender process, all tendered for **plasma-derived factor VIII** (pdFVIII) and **factor IX concentrates** (pdFIX), 16 countries tendered for **recombinant factor VIII** (rFVIII), 8 countries tendered for **recombinant factor IX** (rFIX) and 12 countries tendered for plasma-derived factor VIII containing **von Willebrand factor** (pdFVIII/VWF). The survey did not specify if these were tenders for products used to treat hemophilia A, **von Willebrand disease (VWD)**, or for use in immune tolerance therapy. Ten countries carried out a tender process for **prothrombin complex concentrates (PCCs)**, 11 countries carried out tenders for **bypassing agents** and 6 countries carried out tenders for products for rare **bleeding disorders**.

Only 6 countries reported that patients can stay on their current product (U.K., Denmark, Slovak Republic, Slovenia, Czech Republic, Ukraine) if the outcome of the tender results in the selection of a different product than they are currently using. Of the 19 countries that use a tender process, 16 countries publish a call for tender and 15 countries publish selection criteria with the call for tender. Under the provisions of the EU Procurement Directive 2014/18/EU, public tenders are obligatory for procurement by public authorities and bodies funded mainly by government if the value of the contract is expected to exceed a defined national threshold; public contracts valued below the applicable national threshold are not required to follow the prescribed procurement process. This threshold varies but is approximately EUR 250,000. In some cases, countries can use variations on tenders or purchase smaller amounts on a frequent basis for individual hospitals in order to keep the value of any specific contract below the defined thresholds.

In relation to the criteria used, countries were asked to respond if they used any of the following criteria: safety, quality, **efficacy**, convenience, security of supply, price, or other criteria. Eighteen countries use price as a criterion (exception is Slovenia), 14 countries use safety, 12 countries use quality, 12 countries use efficacy, 8 countries use convenience, and 10 countries use security of supply. When asked if price was the main criterion used, 14 countries responded that it was the main criterion and 4 countries responded it was not (Ireland, Slovenia, Serbia, Slovak Republic). The countries were also asked to rank the criteria based on the order of importance in the tender process. The most important criterion reported by the countries was safety followed by price, efficacy, other, quality, security of supply, and then convenience. Eight countries cited other criteria, such as country of origin, technical and scientific support, dosage, **inhibitor** risk, and continuity of product for an individual.

## Alternative procurement process

Seventeen countries reported using an alternative procurement process that is not a tender, all of which were highly varied. In Latvia, products are purchased nationally if they are included in a reimbursement list. There are several lists and the majority of factor concentrates are included in List A, where the government pays for the least expensive therapy and a patient who wishes to use a different product has to pay the difference in cost. The decisions are made by individual hospital boards in the Netherlands, and by state agencies involved in procurement in Spain, Turkey, Switzerland, and Kyrgyzstan. In Sweden, purchasing is overseen by the Dental and Pharmaceutical Benefits Agency (TLV) and in France by hospitals. In France and Belgium, all products that are licensed must be made available and this mitigates against using a tender system. In Finland, companies apply to the national health authority for inclusion of their products for reimbursement. In Croatia, factor concentrates are made available under the Expensive Drugs Budget. In

Germany, **hemophilia treatment centre (HTC)** hospitals and clinicians decide which products should be used and these are then reimbursed by health insurance. In Estonia, purchase of factor concentrates in two hospitals is linked by the hospitals to the sale of donor plasma. Bulgaria and Lithuania use a combination of both tender and alternative procurement processes.

### Committees and framework

Of the 17 countries with an alternative procurement process, 13 countries have a legal framework or law that governs the procurement process (Austria, Estonia, Kyrgyzstan, Belgium, Italy, Switzerland, Turkey, Finland, Spain, France, Croatia, Sweden, Latvia), and 3 countries reported no legal framework governing the procurement of products for hemophilia (Netherlands, Greece, Germany).

A number of different organizations or authorities are responsible for the procurement of products for hemophilia. Hospitals are responsible in six countries (Greece, Germany, Spain, Estonia, Netherlands, France), Ministries of Health or regional government in four countries (Turkey, Finland, Italy, Latvia), specific medicines agencies or pharmacies in three countries (Sweden, Belgium, Austria), and health insurance funds in two countries (Croatia, Kyrgyzstan). Nine of the 17 countries have a procurement committee or board involved in the process (Italy, Estonia, Croatia, Kyrgyzstan, Finland, Turkey, France, Sweden, Belgium) and 7 countries reported that they do not (Austria, Greece, Switzerland, Germany, Latvia, Netherlands, Spain).

Table 4 shows the key representative bodies that have formal involvement on the tender committee or boards for the selection of hemophilia products. Unlike the countries using a tender system, 47% of countries using an alternative process have a committee or board for the selection of hemophilia products. In other countries, other additional members are involved in the board including a procurement agency, a social security institution, or the Ministry of Finance.

#### Table 4: Organizations involved in alternative procurement processes in 17 European countries

**INVOLVED IN ALL ASPECTS OF THE ALTERNATIVE PROCUREMENT PROCESS**

| HEALTH INSURANCE FUNDS | MEDICINES AGENCIES OR PHARMACIES | HOSPITALS OR BLOOD CENTRES |
|---|---|---|
| Kyrgyzstan<br>Croatia | France<br>Belgium<br>Kyrgyzstan<br>Switzerland<br>Spain | Germany |
| **MINISTRIES OF HEALTH** | **CLINICIANS OR HEMOPHILIA CENTRES** | **PATIENT ORGANIZATION** |
| Kyrgyzstan | Germany | Kyrgyzstan |

**INVOLVED IN SCIENTIFIC AND TECHNICAL ASPECTS ONLY**

| CLINICIANS OR HEMOPHILIA CENTRES | PATIENT ORGANIZATION |
|---|---|
| Turkey | France<br>Kyrgyzstan<br>Estonia<br>Norway |

Clinicians are informally involved in the procurement process but not on procurement boards in five countries (Austria, Italy, Estonia, Greece, Sweden) and in seven countries there is no involvement of clinicians (Finland, Belgium, Croatia, Turkey, Switzerland, Netherlands, Latvia) in the procurement process.

In three countries (Croatia, France, Italy), the patient organization has informal involvement or observer status. Five countries have no patient organization involvement (Turkey, Sweden, Estonia, Finland, Belgium) and seven countries have no patient organization involvement in any element of the procurement process or choice of product (Austria, Germany, Greece, Latvia, the Netherlands, Norway, Switzerland). In Spain, the patient organization can make recommendations on products used to treat previously untreated patients.

The mean term of office on a procurement board is 1.4 years with the minimum being three months prior to the tender in Italy and the maximum being three years in Finland. Four countries (Finland, Estonia, Croatia, Italy) have written terms of reference for the procurement committee, and eight do not have written terms of reference.

**Procurement details**

All 17 countries use a procurement process to purchase plasma-derived FVIII and plasma-derived FIX, 16 purchase recombinant FVIII (exception is Estonia), and 14 purchase recombinant FIX. In addition, 14 countries purchase prothrombin complex concentrates, 16 countries purchase bypassing agents (exception is Kyrgyzstan) and 14 countries purchase products for rare bleeding disorders**.** In relation to the criteria used, 12 countries reported using price as a criterion. Nine countries use safety, eight countries use quality, ten countries use efficacy, three countries use convenience of use, and six countries use security of supply. Estonia uses other criteria based on plasma sale contracts. When asked if price was the main criteria, six countries responded it was the main criterion and seven countries responded it was not. The countries were also asked to rank the criteria based on the importance in the tender process. The most important criteria reported by countries was safety followed by efficacy, price, other, security of supply, convenience, and finally quality.

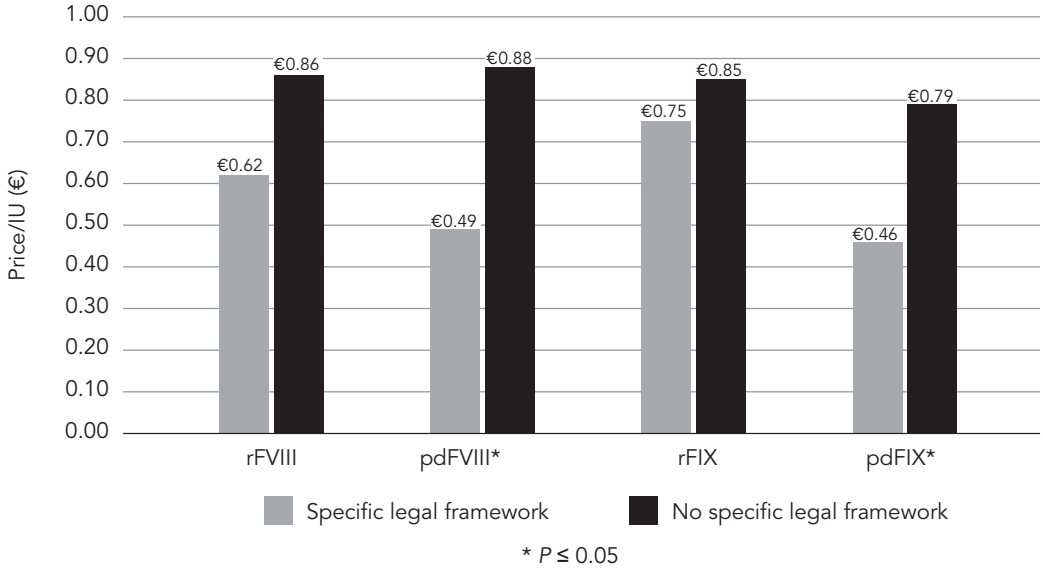
## Patient organization and clinician involvement and cost of factor concentrates

The importance of the involvement of key clinicians and patient organizations in any tender or procurement process has been strongly emphasized in previous sections of this guide. In order to objectively assess the impact of this involvement, price was compared against the involvement of clinicians and patients both for the tender and alternative procurement processes surveyed above. In tender processes, 15 of 19 countries reported clinician involvement and 8 of 19 countries reported patient organization involvement. For alternative procurement processes, 9 of 17 countries reported clinician involvement and 4 countries reported patient organization involvement. In Bulgaria and Lithuania, which use a mixture of both systems, clinicians are involved in the alternative procurement process in both countries and in the tender process in Lithuania. The patient organization is not involved in either country.

For every category of product, patient organization involvement resulted in lower prices being paid for factor concentrates with a statistically significant difference in the price of recombinant FVIII. A similar, though less marked, impact is observed for the involvement of clinicians.

Countries were asked if there was a specific legal framework or law that governs the tender or procurement process (Figure 3). There was a trend of reduced price per IU across all factor concentrates if there was a legal framework.

**Figure 3: Mean price per IU of factor concentrate with specific legal framework**

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The mean duration of a contract is longer with alternative procurement processes, 1.9 years compared to 1.4 years for tender processes. In countries using a tender system, 83% use a registry to predict the supply required, with the majority using national registries and two countries using hospital registries. This is different compared to the countries using an alternative procurement process, with only 33% using a registry to predict supply of product required.

In terms of contracts awarded, in countries with national tenders, 7 countries reported that one company was awarded the tender and 12 countries reported that tender contracts were awarded to multiple companies. When assessed against price, there were no statistical differences or trends between awarding contracts to one company or multiple companies.

For countries using a tender system, if the outcome of the tender results in the choice of a different product from that currently used by patients, 6 countries stated that patients have the right to stay on their current product, while in 13 countries, patients must switch to the new product. There were some caveats based on clinical requirements in some of the 13 countries that allowed individual patients to stay on their current product in specified clinical situations, such as previous history of an inhibitor or allergic reactions to the new product.

## Discussion of EHC survey results

In many countries, the high cost of hemophilia treatment can act as a barrier to government commitment to adequate access to treatment. Effective purchasing of factor concentrates on a cost-sustainable basis can greatly improve access to treatment. The arguments in favour of national tenders have been outlined in previous sections of this guide and include better evaluation and selection criteria being used when agreed upon by all the key **stakeholders**, collective decision-making by all the key stakeholders, better prediction of national supply and demand, and lower prices based on higher volume purchased amounts. It has been argued that competitive tender systems lead to lower prices for factor concentrates [9]. This point is clearly borne out by the results of the EHC survey. In countries using a tender system when compared to an alternative system, the mean price of recombinant FVIII products, plasma-derived FVIII products and

plasma-derived FIX products were lower. There was no appreciable difference in the mean price of recombinant FIX but this is due to the fact that there was only one recombinant FIX product licensed in Europe at the time of the survey.

An open tender process, carried out under the framework of the EU Procurement Directive 2004/18/EC, would not be expected to result in cost reductions where there is only one suitable product; in this case, a negotiated procedure can and should be used. The essence of a tender system is real competition and in the case of a monopoly supplier, a negotiated tender is preferred to an open tender. A similar situation prevails with some products for the treatment of rare bleeding disorders and to a lesser extent with bypassing agents.

Where tenders are used, a greater proportion of the purchasing is carried out under a specific legal framework. All countries that use tenders reported doing so under a legal framework, whereas only 12 of the 17 countries that use an alternative procedure do so under a specific legal framework.

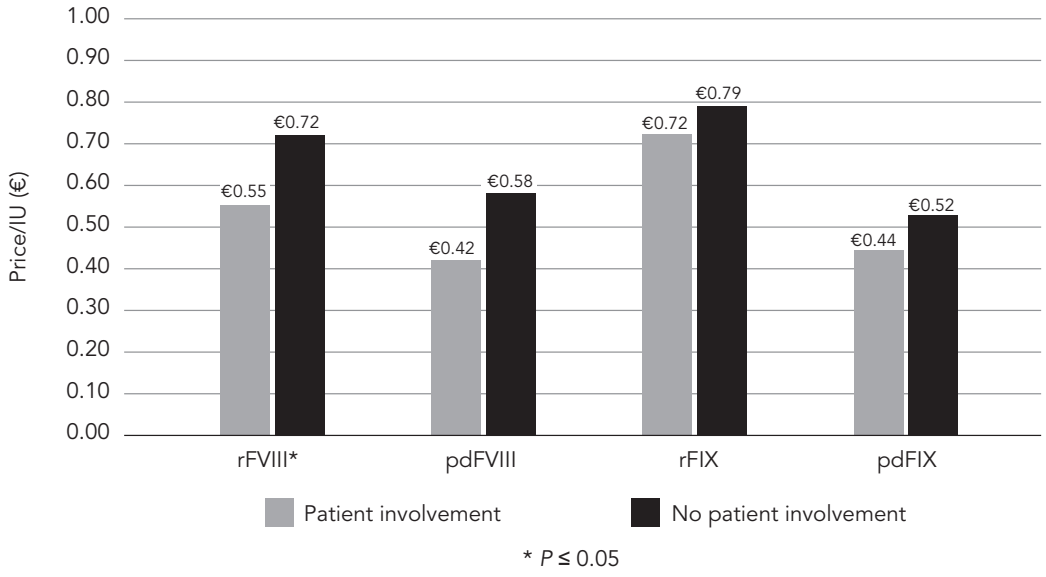
The EHC survey demonstrates that in the absence of a legal framework, prices paid for factor concentrates tend to be higher. The overriding legal framework for ten of the countries surveyed that use tenders and are member states of the EU is Procurement Directive 2004/18/EC. This directive provides a clear framework for every step in the tender process and allows for a transparent and consistent system. This directive will be replaced by a new EU directive 2014/24/EU [10], which has to be transposed into national law no later than April 17, 2016. This new directive will make tender systems more attractive by shortening the time period for submissions, mandating a move to full electronic submission of tenders, and allowing for a greater degree of competitive dialogue as part of an open tender process.

Another feature of the tender system is the difference in the group of people making the decision. In countries using tenders, 16 of the 19 countries use a tender commission or procurement board compared to 9 of the 17 countries using alternative procurement processes. Looking at the composition of these boards, the striking differences are the degree of involvement by hemophilia clinicians and patient organizations. In tender countries, clinicians are involved in 15 of the 19 countries (79%), compared to in 9 of the 17 countries (53%) using alternative procurement processes. The presence of clinicians on tender commissions or within other procurement processes results in lower mean prices for most categories of products.

The involvement of patient organizations has an even greater impact on mean prices for products (see Figure 4). In 8 of the 19 countries (42%) that use a tender process, patient organizations are involved, compared to 4 of 17 countries (24%) using another procurement method. Patient organization involvement results in lower prices for all categories of products to a greater extent than seen solely with clinician involvement. This difference is statistically significant in the case of recombinant FVIII, with a mean reduction in price of 23% in countries with patient organization involvement in tenders. This is not surprising. Clinicians on a national tender commission tend to be among the leading hemophilia clinicians in their country and experts in hemophilia. Patient organization representatives tend to be knowledgeable and committed to the best standards of hemophilia treatment.

Where patient organizations are involved, clinicians are also involved. It is clear that the involvement of both clinicians and patient organizations greatly improves the outcome of a tender or procurement process. The knowledge and judgment that clinicians and patient organizations can bring to the process usually means better selection criteria being adopted and a better, more knowledge-based analysis of these criteria when compared to countries where they are not included. They may also have comparative information available from their clinical and other hemophilia organization colleagues and thus be able to make better judgments about the respective products. Including clinicians and patient organizations demonstrates a commitment to an open, transparent, and optimal procurement process. The formal involvement of clinicians in a tender process and the informal involvement of the patient organization in the United Kingdom has previously been reported and led to an almost 50% reduction in unit cost over a six year period [9].

**Figure 4: Impact of patient organization involvement on mean prices of factor products**

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Only two countries, Ireland and Serbia, have full formal participation by the patient organization in their national tender process.

In Ireland, from 2004 to 2014, the formal involvement of clinicians and the patient organization contributed to a 60% reduction in the unit cost of recombinant FVIII over that time period and a 70% reduction in total cost, when handling fees and associated charges were removed. This has led to a stabilization of the hemophilia budget during a time when the FVIII per capita consumption increased from 3.2 to 8.2 IU, and the country experienced a major economic downturn and very significant decrease (22%) in the national health budget [11]. This reduction in cost contrasts with ten European countries in this survey for which there is comparable price data for 2004, and for which there was no decrease in the mean price between 2004 and 2014. Price reductions were more modest with recombinant FIX due to the necessity to carry out a negotiated tender as there was only one supplier.

Patient organization involvement demands a serious commitment and well trained and knowledgeable patient organization representatives. The authors of the 2014 EHC survey have been involved in training patient organization representatives and indeed clinicians and health ministry officials from several countries for participation in tender processes [12]. In their view, any tender or procurement process that excludes or does not specifically include key hemophilia clinicians and patient organization representatives is deficient. In these cases, the decision can be taken by individuals with little or no knowledge of hemophilia and whose sole motivation is lower price, to the detriment of any real evaluation of safety, efficacy, quality, or other relevant criteria. This situation has been the subject of representations by the EHC to the governments of two EU member states where the tender commission has not included the clinical and lay expertise to properly evaluate the products, leading to strong dissatisfaction by both the patients and clinicians.

In countries using tender processes, 18 of the 19 countries reported that price is one of the criteria. Under the provisions of the EU directive, price must be one of the criteria—either as sole criterion or as part of a most economically advantageous tender. Countries ranked safety as the most important criterion but 14 of the 19 countries listed price as the main criterion. The selection criteria often used include safety,

efficacy, quality, security of supply, and price. When examining products, it may be the case that tender commissions find small differences between several products in the same class (e.g., recombinant FVIII or plasma-derived FVIII); and even though safety may be the most important criterion, the deciding criterion may ultimately be price as this is where there can be significant differences between products. In the United Kingdom's recombinant FVIII tender for 2010-2014, unit price constituted 75% of the total scored criteria; in Ireland's recombinant factor VIII tender for 2012-2014, price constituted 30% of the total. However, in both cases, price was the most significant criterion in the final decision as the differences between the products based on other criteria were minimal, albeit important. There is no contradiction in stating that safety and efficacy are the most important criteria as this does allow a tender commission or procurement board to decide not to purchase products that do not meet their standards for safety and efficacy when compared to the other products being considered.

## Germany

Germany does not use a national tender system but its pricing model has implications not only for procurement in Germany but may also have an impact in other areas in Europe. Pricing and procurement in the German healthcare market has changed since the Act on the Reform of the Market for Medicinal Products (AMNOG) entered into force on January 1, 2011. In the past, high costs have been incurred, in particular with the market launch of new medicinal products, especially since Germany is considered a "reference price country" in the pharmaceutical industry. It was not necessary to demonstrate an additional therapeutic benefit, therefore, the pharmaceutical companies could set the price for their medicinal products as they saw fit—whether appropriate or not. It was then left to the discretion of the health insurance funds or clinicians, within the framework of clinical freedom, to assess whether the product provided any added benefit or not.

However, this changed with the Act in 2011, which regulates the pricing of newly authorized medicinal products and thus their eligibility for reimbursement by the publicly funded Statutory Health Insurance. The pharmaceutical company must demonstrate proof of an added benefit over a comparator therapy for all new medicinal products. The Federal Joint Committee (G-BA), a centralized body, decides on the extent of the medicine's added benefit and therefore on its eligibility for reimbursement. In order to reach a decision on the benefits of pharmaceuticals that is as scientifically substantiated as possible, the Federal Joint Committee commissions **health technology assessments (HTAs)**. The Institute for Quality and Efficiency in Health Care (IQWiG) is one of the bodies entrusted with HTAs in Germany.

For orphan drugs for rare diseases, the Federal Joint Committee decides on the extent of the added benefit without a prior benefit assessment from the Institute for Quality and Efficiency in Health Care. This means that the extent of the added benefit of orphan drugs has implications for their rebate negotiations as well.

If the medicinal product is not assigned any added benefit by the Federal Joint Committee, it is classified in the corresponding reference price group. This reference price then represents the maximum amount for reimbursement by Statutory Health Insurance. If it is not possible to classify the medicinal product in a reference price group, negotiations take place between the pharmaceutical company and the national authority, the Central Federal Association of Statutory Health Insurance Funds (GKV-Spitzenverband). Here, agreement is reached on the reimbursed amount, which does not lead to higher annual treatment costs than the appropriate comparator therapy.

If it is confirmed that the medicinal product has an added benefit, negotiations are held between the pharmaceutical company and the national authority. If an agreement is reached, a rebate on the manufacturer's price is set 12 months following the market launch. If the pharmaceutical company and the national authority cannot agree on a rebate, an arbitration board is brought in. Thus an arbitration award is carried out by a neutral officer who mediates between the two parties. The rebate adopted is set no later than 15 months after the market launch of the product and applies retroactively to the original price 12 months following the market launch.

By participating in the Federal Joint Committee, selected patient representatives (who are not necessarily representatives of the NMO) are involved in both the determination of the appropriate comparator therapy as well as the decision on the added benefit. However, the patient representatives simply have a right to consultation, with only an indirect influence as their votes are recorded but not counted.

Only one factor concentrate has undergone and completed the early benefit assessment in Germany so far, with a second in progress. In the case of the first product, the Institute for Quality and Efficiency in Health Care has not assigned an added benefit. Furthermore, the Federal Joint Committee did not confirm an

added benefit for the second product in comparison over a comparator therapy. Therefore, the new price must be lower than the annual treatment costs of the appropriate comparator therapy. These two products were not prolonged half-life factor concentrates.

Even though the process of pricing is considered to be transparent, further rebate negotiations and agreements between the health insurance funds, physicians, and care centres are neither clear nor open to the public.

## United States

### 340B Drug Pricing Program and hemophilia

All prescription drugs licensed by the U.S. Food and Drug Administration (FDA) are eligible for coverage and reimbursement subject to the rules and limitations of different health insurance plans. Health insurance providers within the United States (public or private) typically contract, or have in-house, pharmacy benefit managers who administer their prescription drug program. Pharmacy benefit managers are responsible for processing and paying for prescription drug claims, and often develop and maintain the formulary of prescription drugs covered by the health plan.

There is no single price or drug formulary for the purchase of factor concentrates in the U.S. The lack of a centralized tendering mechanism has allowed pharmaceutical companies to establish market-based pricing strategies. The relatively higher U.S. price points have encouraged significant investment in research and development in new and innovative products.

The U.S. Congress established the 340B Drug Pricing Program [13] in 1992 to enable certain healthcare providers to stretch scarce federal dollars and to better serve low-income and other medically vulnerable populations. The 340B Program requires pharmaceutical companies to provide outpatient drugs to "covered entities" at significantly discounted prices. Only nonprofit healthcare organizations that have certain federal designations or receive funding from specific federal programs are eligible (covered entities) to purchase discounted drugs through the 340B Program. These include federally qualified health centres, Ryan White HIV/AIDS Program grantees, and certain types of hospitals and specialized clinics such as HTCs. Currently, 340B pricing provides a 17.1% discount off the average manufacturer's price[2]. Covered entities may negotiate deeper discounts and rebates with pharmaceutical companies. The 340B programs typically offer discounted pricing in excess of the prices offered by other commercial pharmacy vendors despite the commercial vendor's significant group purchasing power.

Health insurance providers, or their pharmacy benefit managers, contract with a 340B pharmacy provider (typically integrated with an HTC) to deliver factor concentrates and supplies, hemophilia education materials and programs, as well as emergency telephone support. Within the U.S., the majority of comprehensive HTCs (currently 105 out of 135 centres) participate in or operate 340B programs to enhance cost containment for outpatient use (e.g., home treatment) of factor concentrates. Factor products accessed through a 340B program are not eligible for use in an in-patient setting.

While a treatment centre provides clinical care to 100% of the patients who come to their clinics, only about 20% receive their factor concentrate and other medically necessary supplies from a 340B provider. 340B providers are an important component of the U.S. comprehensive hemophilia care system. As federal grantees, HTCs are required by the terms of their grant to reinvest their program income (e.g., 340B program income) in maintaining and expanding services for patients with bleeding disorders (e.g., providing funding, salary, and other support for members of the HTC clinical care team).

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2 The Veterans Health Care Act of 1992 mandated that manufacturers who wished to have their drugs reimbursed by Medicaid sign a participation agreement that mandated they pay rebates for commercial products bought and sold to Medicaid beneficiaries. The per unit rebate for factor concentrates is 17.1%.

# CASE STUDIES: NATIONAL TENDERS FOR PROCUREMENT OF FACTOR CONCENTRATES

## Ireland

In Ireland, a Haemophilia Product Selection and Monitoring Advisory Board (HPSMAB) was formally established in 2002 to advise on the national tender for the purchase of factor concentrates and operates under detailed terms of reference (Appendix 1: Terms of Reference – HPSMAB Ireland). The contract holder for the purchase of factor concentrates was the Irish Blood Transfusion Service until 2011, when the contract holder was changed to St. James Hospital, the largest hospital in Dublin and location of the national hemophilia centre for adults. This change in contract holder required specific legislation (Appendix 2: Irish legislation on change of contract holder for national tenders, 2012). The contract holder issues the call to tender and receives the tender documents.

The mandate of the HPSMAB is to advise on the selection and monitoring of all plasma-derived and recombinant products used in the treatment of hemophilia, von Willebrand disease (VWD), and other inherited deficiencies of factors I, II, V, VII, X, XI, and XIII, and products used for treatment of inhibitors to factors VIII and IX. The HPSMAB decides on the amounts of product to be purchased and the award criteria to be used in the evaluation of tenders. Following receipt of the tenders, the board meets and evaluates the tenders based on the specified award criteria, and then recommends which products to purchase. The board also advises on monitoring the product used, on delivery, tracing, and **recall** procedures. The membership of the HPSMAB consists of the national hemophilia director, two additional consultant **hematologists**, two representatives from the Irish Haemophilia Society, a representative from the contract holder, a transfusion medicine expert, a representative from the Irish Medicines Regulatory Authority (the national licensing authority), a representative from the Department of Health, and a virologist with expertise in blood-borne infectious diseases. HPSMAB also includes an external advisor to the Irish Haemophilia Society nominated by the society. The board is appointed by the Minister of Health for a renewable term of five years and members are granted legal **indemnity** by the Department of Health.

Tenders follow the EU procurement rules and are in line with the terms of reference of the HPSMAB. Prior to the call for tender, the award criteria are decided by the HPSMAB and these criteria are listed in the tender documents. A call for tenders is issued in the *Official Journal of the European Community*. The tender contract is normally for a period of two years, with the HPSMAB retaining the option to extend the contract at the same price for an additional two years in one year increments. To date the HPSMAB has carried out five tenders for recombinant FVIII, four tenders for plasma-derived FVIII for the treatment of VWD, three tenders for FX deficiency products, and negotiated tenders for recombinant FIX and recombinant activated FVII (for which there was only one possible supplier at the time).

The HPSMAB devises selection criteria for each tender, which are published as part of the call for tender. Products are selected based on the criteria of most economically advantageous tender (MEAT). These criteria always include safety, efficacy, quality, supply/availability, and cost. To date, the single most important criterion has always been safety. Between 15% and 30% of the total score are allocated to cost. In the most recent tender for recombinant FVIII, (see Appendix 3: Tender score sheet for recombinant FVIII Ireland, 2012), the products were scored with a total available score of 200 points as follows: safety 37%, efficacy 15%, quality 10%, supply/availability 5%, scientific and technical support 3%, and cost 30%. In the most recent tender for plasma-derived FVIII, (see Appendix 4: Tender score sheet for plasma-derived FVIII Ireland, 2012), the products were scored with a total available score of 245 points as follows: safety 41%, efficacy 16%, quality 14%, supply/availability 7%, scientific and technical support 3%, and cost 18%. The most recent selection criteria for prothrombin complex concentrate for treatment of FX deficiency

are shown in Appendix 5: Tender score sheet for prothrombin complex concentrate for treatment of FX deficiency (Ireland, 2015).

Products must be licensed for marketing or distribution in Ireland or, in the case of a new product, the successful tenderer must register the product for licensing as soon as the tender is awarded and in advance of the start of supply. (This illustrates one of the reasons it is important to ensure that tenders are carried out in a timely basis with a sufficient interval before product is to be delivered.) Presentations from tendering companies are not usually required but have been allowed during some tenders. Following the award of the tender, a notice is published in the *Official Journal of the European Community* and the unsuccessful companies are notified as quickly as possible. All companies that tender are offered a **debriefing** meeting where they are given the scores for their product.

If a tender process results in a product change, meetings are organized by the Irish Haemophilia Society in the major cities in Ireland, where people with hemophilia, other inherited factor deficiencies, or FVIII or FIX inhibitors, are informed of the results of the tender process and given information on the new products including familiarization with the new home treatment kits. The HPSMAB meets a minimum of six times per year to monitor developments in this area, and to conduct the ongoing tender processes.

The broad based nature of the HPSMAB and the range of expertise available to the board have made procurement of factor products a very inclusive process.

The results of the HPSMAB's work have been very beneficial for hemophilia care in Ireland over the past 12 years. The product which, in the opinion of the HPSMAB, is the safest and most efficacious product at the time of procurement has always been awarded the tender. The presence of the leading clinicians and the patient organization has resulted in an increased emphasis on optimal treatment regimes. This, together with widespread use of **prophylaxis** in children and adults and with net immigration into the country, has resulted in the per capita use of FVIII increasing from 3.7 IU per capita in 2003 to 8.2 IU per capita in 2014, and an increase in FIX per capita use from 1.4 to 2.2 IU per capita in the same time period. The clinicians and patient community are very satisfied with the outcome of the process. The patient community takes great reassurance from the fact that the clinicians and the patient organization are both formally involved in the process. The Ministry of Health is also very pleased with the process as it has resulted in very significant savings.

Prior to the formation of the HPSMAB in 2002, Ireland was paying 26% more than the EU average price for recombinant FVIII. Successive tender processes have made the purchasing system more and more economical and by 2014 the price for recombinant FVIII was just 50% of the average EU price. This has resulted from a combination of greater competition, a rigorous approach to appraisal of the products, and economies of scale due to the purchase of larger amounts of factor using two year contracts. The typical FVIII tender would now be for 50-60 million IU over a two year period. Additional savings were also made by changing the contract holder, thereby eliminating additional handling fees. The tender process has allowed hemophilia treatment in Ireland to flourish, increase optimal care, and expand prophylaxis to all adults who require it without any significant increase in overall budget impact. This has been particularly important since 2008 when the overall health budget was cut by approximately 27% in the midst of an economic crisis.

## Brazil

Brazil has had a tender process for the purchase of factor concentrates for more than a decade, and indeed the use of factor concentrates in Brazil has increased dramatically over the past 10 years to 3-4 IU per capita. The tender is under the control of the Ministry of Health. Products to be purchased during the tender must be licensed by the regulatory authority, the Brazilian Health Surveillance Agency (ANVISA), which is the

national authority for product regulation and inspection, as well as by the FDA, the European Medicines Agency (EMA), or another European regulatory agency.

Brazil has a two-tier tender process:

- The National Coordinator of Blood and Hemoderivatives defines the specifications. Historically, the technical specifications of products to be purchased have been proposed by a workgroup on coagulopathies appointed by the National Coordinator of Blood and Hemoderivatives. The workgroup consists of 12 clinicians (6 voters and 6 alternates) and 2 representatives (1 voter and 1 alternate) of the national hemophilia organization, Federação Brasileira de Hemofilia. Previously, specifications remained largely unchanged over several years; however, more recently the workgroup has revised the specifications in light of new products being available, and they maintain the right to make further changes. It can recommend the type and amounts of of factor concentrates to be purchased, and can also specify criteria in relation to safety, efficacy, and **purity**. These technical specifications are sent by the National Coordinator of Blood and Hemoderivatives to the tender commission.
- The tender commission then advertises the tender in the official government paper, specifying the deadline for receipt of tenders and the documentation required. Detailed tenders are submitted to the tender commission, which makes the decision, and the decision is published by the government, including the prices paid.

The major weakness of this system is that the decision is mainly based on price—a requirement by Brazilian law that must be followed for all tenders in the public sector. While obliged to follow the law, the Ministry of Health has been successful at providing the country with high-quality blood products in the last several years. However, as an attempt to provide even better quality products and to overcome the weakness imposed by the law, in recent years, the required specifications have been revised in order to include criteria related to quality, which improved the quality of some acquisitions.

Since 2003, following complaints of corruption and interference with the tender process, the government switched to an auction system known as a Pregão. Following publication of the tender, the bids received are processed publicly, in the presence of the tender commission, the tendering companies, and members of the public. This change to the purchasing process has dramatically reduced prices [14] from about US$0.45 to less than US$0.20 per IU of plasma-derived FVIII and FIX. This price has remained stable since 2003, reflecting the impact of the change to a public bidding process. Today, tenders are held electronically and broadcast live on the internet.

Until 2012, treatment for hemophilia A in Brazil consisted exclusively of plasma-derived FVIII. In 2012, Brazil signed a **transfer of technology** agreement with a recombinant manufacturer for the provision of recombinant FVIII and the development of local manufacturing capacity. The transfer of technology and expertise on the production of recombinant FVIII is taking place over ten years, with production of the drug in Brazil anticipated within five years, by 2017. The product first became available in Brazil in 2013 and the supply of recombinant FVIII from the company concerned soon reached 70% of total FVIII use in Brazil, with plasma-derived FVIII accounting for the remaining 30% since then.

Currently, Brazil purchases plasma-derived FVIII and FIX, recombinant FVIII, plasma-derived FVIII with von Willebrand factor (VWF), prothrombin complex concentrates, FXIII and fibrinogen concentrates, bypassing agents (recombinant activated FVII and activated prothrombin complex concentrates), tranexamic acid, and desmopressin acetate (low and high concentration) through their tender system.

## Canada

Canada has two tenders for the purchase of factor concentrates, one for the province of Québec and one for the other nine provinces and three territories. Currently Canada purchases annually approximately 200 million IUs of recombinant FVIII, 48 million IUs of recombinant FIX, and 55 million IUs of plasma-derived FVIII-VWF.

### Canada (except Québec)

In the nine provinces and three territories, the tender is held under the auspices of a Selection Advisory Committee appointed by the Canadian Blood Services (CBS) Board of Directors. In order to be eligible for the tender, the product must be licensed by Health Canada. Demand is estimated based on historical trends. The FVIII contracts have historically been for five to seven year periods.

The contract holder is Canadian Blood Services. It issues the request for proposals (RFP), manages the information, communicates with bidders, and seeks supplementary information when required. The Selection Advisory Committee advises the contract holder, who ultimately makes the tender decision. The committee considers criteria including safety, efficacy, range of products, consumer and physician preference, mix of products, value added in research and development, fiscal health and reliability of the potential supplier, and price. Initial bids are received in writing. This is followed by meetings with the tenderers, usually on several occasions. Additional information may be sought in writing by Canadian Blood Services between meetings. Score sheets are used for each product and, where possible, at least two suppliers are chosen for major products.

Interestingly, licensed products that are not chosen for the tender can still be prescribed by physicians as long as the company registers the product in Canada. The tender tends to provide 95% of the national FVIII concentrate requirement, the additional 5% comprises products that are licensed by Health Canada but not purchased under the tender process.

### Québec

Québec operates its own blood supply system separately. Its National Advisory Committee on Transfusion Medicine (Comité consultatif national de médecine transfusionnelle) makes recommendations on the list of blood products, including which products to add or remove. The blood agency, Héma-Québec, is responsible for supplying blood products in the province.

In 2015, Québec carried out a tender process to procure recombinant factor concentrates for a two to three year period. This tender is of note as it is the first known occasion where a tender compared normal **half-life** to new **prolonged half-life recombinant factor concentrates**. The tender covered the period of 2015 to 2018.

The RFP was communicated to all companies in the Canadian market in early November 2014, following prior notice in the summer that it was imminent. Bidders' products were required to be licensed by Health Canada, recommended by Québec's National Advisory Committee on Transfusion Medicine, and approved for reimbursement by Québec's Ministry of Health and Social Services. Companies were given three weeks to submit their bids.

The RFP communicated strict and detailed requirements for the bids and some guiding principles. To promote security of supply, two products would be selected in each category. In the event that the price of a prolonged half-life recombinant factor product resulted in higher costs, Héma-Québec could enter into an agreement with the supplier without any volume commitment or purchase obligation, and put in place control measures to restrict distribution based on published guidelines. All proposals would be analyzed to determine the products that offered the best quality/price ratio.

Following an analysis of the product development pipeline in Canada, Héma-Québec requested recombinant FVIII bids for two and three years, and recombinant FIX bids for two years. Companies were required to submit their price proposals separately from all other bid documents. Prices were requested for the full range of expected demand for recombinant FVIII and FIX. Submissions for seven recombinant FVIII and two recombinant FIX products were received.

The selection committee was made up of two very experienced clinicians representing Québec's HTCs, two patients with extensive knowledge of coagulation products representing the patient organization, and several senior scientists and managers at Héma-Québec. The committee met for a total of 12 hours in December to conduct a preliminary bid evaluation. Questions were prepared and submitted to the companies, which then each had 90 minutes in January to appear, in person, before the committee. The committee then scored the bids according to pre-determined criteria. These included a 50% allocation for product quality and 50% for other factors.

The 50% allotted to product quality included the following criteria, each with an assigned score:

- half-life
- **shelf life** and storage temperature
- inhibitor rates
- current approved indications and anticipated indications
- quality of clinical data
- adverse reactions
- potential for the product to be withdrawn from the market in the next five to seven years
- conformity with GS1 barcoding standards
- range of vial formats supplied
- quality of administration device
- product history of recall, **withdrawal,** or **quarantine**

The 50% allotted to other factors included:

- 5% for the company's profile including anticipated manufacturing enhancements, products in the pipeline, its presence in other markets and how this presence affects its ability to respect its commitments, its involvement in research, and its support of the community and of HTCs in any introduction of new products;
- 15% for the company's quality assurance systems including quality assurance manual and policies, management of changes in production methods and quality assurance procedures, and official procedures in the event of a withdrawal or recall;
- 10% for the company's infrastructure to handle medical information requests and complaints, support for customers, procedures to handle conflicts with Héma-Québec, and respect for drug product advertising codes;
- 20% for the company's supply and logistics capability including its ability to adjust deliveries to fluctuations in demand, contingency plans in case of an unexpected emergency or disruption, and its ability to maintain eight weeks of supply in the country.

Unanimous agreement between committee members was required to assign a score for each criterion. For a product to move forward in the selection process, it had to score at least 70% in the product quality category and at least 70% overall, all criteria considered.

Only after all scores were compiled did the members of the selection committee open the price bid envelopes. At this point, the score for each product was calculated based on allotting 70% to product and company quality and 30% to price.

One other important calculation was required. Prolonged half-life products were considered in both the recombinant FVIII and recombinant FIX categories. As total utilization of a prolonged half-life product is expected to be less than that of normal half-life factor concentrate, a correction factor was developed, corresponding to an estimate of the expected decrease in units required.

The selection committee made its decision in late January, which for all intents and purposes was final. Only a failure to have followed the pre-set rules for the tender process could have been considered just cause for Héma-Québec's Board of Directors or Québec's Ministry of Health to nullify the result. Héma-Québec then proceeded to inform the bidders and, in February and March, negotiated the final contracts with the winners.

The clinician and patient representatives on the selection committee concluded that the process had been well defined, rigorous, and fair. Héma-Québec was appreciative of the expertise and knowledge contributed by the clinicians and patients, and reassured that the final result, which will bring significant changes to the hemophilia product landscape in Québec, will be well accepted by the community.

## United Kingdom

Factor concentrates have been purchased centrally by tender in the United Kingdom since 2005, underpinned by consensus across the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Recombinant FVIII and FIX are widely used in the U.K. and are the products of choice. The UKHCDO's objective has been to drive down price. They view the standard recombinant FVIII products as essentially generic products and their price based approach assumes therapeutic equivalence among these products. The tender process is carried out under the auspices of the Commercial Medicines Unit of the Department of Health. The tender board members are selected by the Department of Health, the Commercial Medicines Unit, and the UKHCDO.

The UK Haemophilia Society is not formally involved in the tender process although they have been consulted on occasion especially on scientific and technical aspects. Contracts are generally awarded for a two year period with the possibility of extension for a further two years. A national registry is used to predict demand and the tender is awarded to more than one company. Price is the main criteria but safety, efficacy, quality, convenience, and security of supply are also examined. The amounts purchased are high at approximately 400 million IU per year.

Prior to 2012, tenders were carried out in a number of segments at different times meant to ensure diversity of supply and good economic outcome. Electronic auctions were utilized to maximize price savings. Tenders were also carried out separately for different parts of the U.K. In 2012, a single unified tender for the U.K. was carried out for 475 million IU recombinant FVIII. The only selection criterion used was price, and closed bids were used in preference to an e-auction. This resulted in a lower price but also a decreased number of suppliers. Following the awarding of the tender contracts, which are generally awarded to several companies which must supply specified quantities , individual centres may choose the products they wish to use from the list of tender suppliers. They pay the appropriate price per unit based on the tender price. The aggregate amount utilized by all the centres must correspond to the contracted amount of each product purchased under the tender contract. In this way, a measure of clinical freedom is maintained.

The U.K. is one of the first EU member states to have ratified the new EU Procurement Directive into national law. For future tenders, it plans to use closed bids under the open tender process and not revert to the use of e-auctions. They may tender separately for prolonged half-life factor concentrates. The U.K.

tender system has resulted in real savings to the national budget and allowed them to increase FVIII use from just under 300 million IU in 2005 to just under 500 million IU in 2014. However, apart from the increased factor use (which may to a large extent have resulted, in any event, from demographics and increased use for prophylaxis), none of the savings have been rolled back into hemophilia care. No additional resources have been made available for comprehensive care centres and the patient organization receives no funding from government. There is a concern that the sole focus on price may diminish patients' capacity to access new prolonged half-life factor concentrates. It is a further concern that the national patient organization is not formally involved in all aspects of the process.

## Portugal

In Portugal, currently, the procurement of treatment for hemophilia is organized by the hospitals that have HTCs, i.e., on a hospital to hospital basis. Tender boards must include at least one immunohemotherapist or hematologist, who should issue a technical and scientific opinion, as well as the support and the opinion of the national hemophilia patient organization, the Associação Portuguesa de Hemofilia (APH). The involvement of these two parties has been mandatory by law since 2008.

Accordingly, the patient organization should provide formal and written advice in any type of procurement process that involves factor concentrates, whether plasma-derived or recombinant. This is currently under discussion as the APH is now only involved in the tender process for plasma-derived factor concentrates but not for recombinant factor concentrates. Nothing in the law limits their opinion only to plasma-derived products. The APH is actively working to ensure the patient organization's participation in both plasma-derived and recombinant tenders in future.

The role of the APH has been to ensure that the **effectiveness**, quality, and safety of products chosen are beyond doubt and that price is not the only criterion for awarding tenders. In October 2013, a government bill declared that price would be the only criterion. Even though there could be some interpretation of law issues surrounding this bill, the major hospitals in Portugal have adopted this single criterion. Some minor hospitals continue to operate with price as only one of the criteria. The APH continues to fight to ensure that safety, efficacy, and quality criteria are considered together with price. The Portuguese Ministry of Health Shared Services (SPMS) is currently working on a new procurement law, presumably based on the new EU Procurement Directive.

## South Africa

South Africa uses a national tender process [15] under the auspices of the Department of Health. The tender board members are selected by the provinces, and hemophilia clinicians and the patient organization are not involved. Contracts are generally for a two year term and only plasma-derived factor concentrates are purchased. In 2012, the guideline tender amount was for 40 million IU FVIII. The state may purchase higher or lower amounts than stated in the call for tender, which is published in a government publication. A registry is not used to predict the quantities required and the tender is typically awarded to more than one company. Products must be registered with the licensing authority, the Medicines Control Council (MCC), and the main criteria used are security of supply and price.

## China

China does not use a tender process, but rather an alternative procurement process. Each hospital buys product from local commercial distributors which have relationships with local authorities. One distributor is used for all products for a region or province. The procurement board is selected by the central government and there is no involvement of hemophilia clinicians or the patient organization. The central

government sets the prices nationally following discussion with pharmaceutical companies. Individual clinicians indicate how much product they need and obtain it from the distributor; prices are relatively high given the GDP. Information on the selection criteria, duration of contracts, and procured amounts are not readily available.

Companies also have to bid each year for the market in each province. Prices should be lower or equal to the central price. Individual clinicians can usually choose the products, while people with hemophilia can decide, as co-payers, if they want plasma-derived or recombinant treatment. The co-payment amount depends on the individual's health insurance coverage and typically would be 15-30 per cent of the price.

People with hemophilia can also get some free product from pharmaceutical companies or charity funds. Some companies have a cap program which provides some factor free of charge if the patient purchases a certain quantity. Licensed recombinant FVIII and FIX products from abroad, and several plasma-derived products manufactured in China, are available.

## Mauritius

In Mauritius, a national tender process is used. The tender board includes the Ministry of Health and a physician and a pediatrician who are hemophilia treaters. The national patient organization is not formally involved. Contracts are typically for one year and only plasma-derived products are purchased. A registry is used to predict demand and the contract is normally awarded to one company. The main selection criterion used is price.

## Thailand

Thailand does not use a tender process; an alternative procurement process is used. A budget is allocated for each person with hemophilia depending on the severity of their disorder (different amounts are allocated for **mild, moderate,** and **severe hemophilia**). That amount is given to the treating hospital by the National Health Security Office (NHSO). Each hospital then carries out procurement under the auspices of the hospital pharmaceutical committee. Clinicians are involved in the evaluation of scientific and technical aspects of the process, and typically a pharmacist, hospital director, and administrator then also contribute to the decisions, based on price. The national patient organization is not involved. Contracts are generally for one year and products purchased are mainly plasma-derived, with some recombinant. A registry is used to predict demand and the contract is typically (but not always) given to one company. Thailand is currently building a manufacturing facility with technology transfer from a pharmaceutical company to manufacture plasma-derived products. Capacity is expected to be in the region of 500,000 litres of plasma annually which is expected to yield 100–150 million IU FVIII per year. They plan to use this to supplement the quantity of treatment currently being used.

## Honduras

Honduras carries out a national tender but the main hospital and social security system also carry out separate tenders. Honduras is also party to the Council of Ministers of Health of Central America (COMISCA), a coordinating body that addresses regional health issues (see section on Central America purchasing system [COMISCA], below). The tender committee members are selected by the Ministry of Health, which is involved in all aspects of the process. Hematologists are consulted on the scientific and technical aspects and civil society groups (such as Transparency International) are invited as observers on some occasions. The national patient organization is not involved. Contracts are typically awarded for one year and only plasma-derived products are purchased. The tenders are for relatively small amounts (less than 1 million IU) and therefore the advantages of collaboration on a regional procurement process through COMISCA

are obvious. Selection criteria used include safety, efficacy, quality, experience with the product, licensing, and potency—but price is the main criterion. The main hospital carries out a separate tender involving a hematologist, pharmacist, lawyer, and administration personnel. Again, the patient organization is not involved. A national registry is used to predict demand. The social security system also purchases factor concentrates through COMISCA.

## Centralized multinational purchasing systems

There are currently two systems where countries join together to tender for the purchase of factor concentrates, in Saudi Arabia and the Gulf States, and in Central America. This concept makes sense where small countries would potentially benefit greatly from combining their purchase of factor concentrates. This should result in volume discounts as much larger quantities would be purchased. It would also, if correctly established, give the countries access to greater expertise if the leading hemophilia clinicians and patient experts from the relevant countries are formally involved.

The multinational purchasing system would also benefit other groups of contiguous countries. For example, the Baltic countries of Latvia, Lithuania, and Estonia would potentially greatly benefit from such a system and efforts are being made to encourage this. Currently, all three countries purchase factor concentrates separately. In Estonia, factor products are purchased through several mechanisms giving no economy of scale. In addition, the current tender board does not have the clinical and patient input to assist with proper assessment of the products. The patient organization in Latvia also has strong and ongoing concerns about the quality of the decision making by the national tender commission, where again there is no formal role for the patient organization or leading hemophilia clinicians. A more efficient, inclusive, economic, and ethical system would, it can be argued, require formal roles for both the patient organizations and the hemophilia clinicians, ideally in a combined Baltic regional procurement process which would yield economies of scale and a better use of the resources available for hemophilia treatment.

### Central America purchasing system (COMISCA)

In Central America, the Council of Ministers of Health of Central America (COMISCA) has established a mechanism for purchasing drugs and high cost medications such as factor concentrates. COMISCA is made up of eight member countries: Belize, El Salvador, Honduras, Panama, Costa Rica, Nicaragua, Guatemala, and the Dominican Republic. COMISCA purchases FVIII, FIX, albumin, IVIG, some cancer drugs, and other high cost medications.

The purchasing process is carried out by three separate committees: legal, administrative/technical, and negotiation. The committees are composed of officials nominated by each of the member countries in accordance with their national regulations. The committee members are usually officials from the national health ministries, social security organizations, and legal representatives. All committee members are trained by COMISCA.

COMISCA carries out a procurement process for factor concentrates for a two year contract every two years. Each country indicates the amount of factor concentrates they seek to purchase and their budgeted funds. Funds are held by one bank which ensures that payment is made.

Initially, COMISCA posts on its website the technical specifications for the products they wish to purchase and the volume to be purchased over the two year period. This includes information on potency requirements, labelling, diluent volumes, **viral inactivation** requirements, and licensing requirements. Companies then express their interest and go through a pre-qualification process. In this process, COMISCA looks at the company documents, verifies legal requirements, evaluates the specific product characteristics, and decides if the product meets its requirements. This process is carried out by the legal and administrative/

technical committees. The product must be licensed or currently used in one of the countries in order to be eligible for the tender. In the case of a new product, it must be licensed in at least one of the member countries. There is a centralized list of medicines which currently meet these requirements and COMISCA also consults this list.

Companies whose products meet these requirements are then invited to meet COMISCA and submit written bids. Upon receipt of the bids, negotiation takes place with the companies separately on a specified day until a price is agreed upon. This process is carried out by the negotiation committee and is similar to the Brazilian Pregão system (with the difference being that negotiations with the companies occur individually and not collectively in the same room). The tender is awarded on the basis of price and awarded to one company. COMISCA refers to regional reference pricing when carrying out these negotiations.

Effectively, this process results in COMISCA awarding the tender contract to one company at the negotiated price and setting the price to be charged for the product. Each country then enters into a contract with the pharmaceutical company for their national supply, for the pre-indicated volume of factor concentrate at the agreed price. Each country may also, during the course of the two year contract, purchase more than the pre-indicated amount at the agreed price.

This is a logical system for a region where the availability of replacement factor therapy for hemophilia is very low. The amount purchased by each individual country annually would be relatively low and unlikely to attract the interest of many of the pharmaceutical companies. For example, Honduras has, until recently, purchased through three different mechanisms with purchases being made by the health ministry, the social security system, and the main hospital treating people with hemophilia in the capital city. A better outcome would be achieved by combining these three separate purchases into one national tender, but an even better outcome could be anticipated by purchasing together with the other participating countries via COMISCA. The tender via COMISCA, given that it is for a two year term, is for a much larger quantity than any one of the countries would purchase individually. This should result not just in lower prices through economy of scale, but also an increased number of companies bidding, which increases choice. The final choice is made on the basis of price once products have satisfied the minimum requirements of pre-qualification, which does include some reference to safety and quality.

### Saudi Arabia and the Gulf States

A joint tender is carried out by Saudi Arabia, Qatar, Bahrain, Oman, the United Arab Emirates, and Kuwait. Some 70-80% of the product is used by Saudi Arabia. The tender is typically for 28 million IU and an additional 10 million IU is usually purchased outside the tender process. The tender is organized by the Saudi Ministry of Health and includes their purchase of factor concentrates. Other entities in Saudi Arabia such as social security, the police force, armed forces, and private hospitals purchase separately outside the tender. Tenders are typically for a three to five year term with no options to extend. Tenders are advertised in the newspapers by the Ministry of Health and a specific amount is tendered for with an option to purchase 10-20% more or less than the tendered amount. Products must be licensed in the country prior to application for the tender. The selection criteria include price and viral inactivation. Products must be also licensed in one of two reference countries (typically the U.S. or the U.K.). The tender board consists of officials from the ministries of health and pharmacists. It does not include hemophilia clinicians or representatives from the national patient organizations. The committee receives the tenders, and meets to make recommendations on the products to be purchased. They can then meet with companies, clarify information, and negotiate further on price.

If they wish to choose a product which is not that which tendered at the lowest price, they can negotiate with the individual company and purchase their preferred product if the company matches the lowest price or gives an even lower price. The tender is always awarded to only one company. The clinicians are informed

of the outcome but are not involved in the purchasing process. Clinicians are free to use a different product for individual patients.

Separate tenders are organized for plasma-derived and recombinant factor concentrates. Unsuccessful bidders can make use of an appeal mechanism available through the court system.

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# FURTHER READING

## EU directives

Directive 93/36/ECC (Supplies Directive)
Directive 2004/18/EC (Public Procurement Directive)
Directive 2014/24/EU (Public Procurement Directive repealing Directive 2004/18/EC)

## Journal publications

*Haemophilia*, official journal of the WFH, published by Blackwell
*Transfusion Today*, published by the International Society of Blood Transfusion
*International Blood Plasma News*, published by Patrick Robert & Marketing Research Bureau
*The Source*, published by the Plasma Protein Therapeutics Association
*Blood*, published by the American Society of Hematology

## WFH publications

*Treatment of Hemophilia* monographs
*Registry of Clotting Factor Concentrates*
*Report on the Annual WFH Global Survey*
*Guide for the Assessment of Clotting Factor Concentrates for the Treatment of Hemophilia*
*Proceedings of the WFH Global Forum on the Safety and Supply of Treatment for Bleeding Disorders*
*WFH Guide to Developing a National Patient Registry*
WFH publications are available at **www.wfh.org**

## Websites

**Regulatory authorities**
European Medicines Agency (EMA): www.ema.eu
U.S. Food & Drugs Administration (FDA): www.fda.gov
Paul Ehrlich Institute (PEI): www.pei.de

**Government agencies**
*Canada*
Biologics and Genetic Therapies Directorate: found at www.hc-sc.gc.ca
Canadian Blood Services: www.bloodservices.ca

*Europe*
EU Public Procurement website: http://simap.europa.eu/index_en.htm
General EU website: http://europa.eu/index_en.htm
World Trade Organization site on the 1994 Government Procurement Agreement: found at www.wto.org

*United States*
Department of Health and Human Services, Blood Safety Advisory Committee:
http://www.hhs.gov/ash/bloodsafety/advisorycommittee
Centers for Disease Control, Atlanta (CDC): www.cdc.gov

**Hemophilia organizations**

World Federation of Hemophilia (WFH): www.wfh.org
Canadian Hemophilia Society (CHS): www.hemophilia.ca
National Hemophilia Foundation, USA (NHF): www.hemophilia.org
European Haemophilia Consortium (EHC): www.ehc.eu
Irish Haemophilia Society (IHS): www.haemophilia.ie

**Industry and not-for-profit sector**

Plasma Protein Therapeutics Association (PPTA): www.pptaglobal.com
American Association of Blood Banks (AABB): www.aabb.org
International Plasma Fractionation Association (IPFA): www.ipfa.nl

**Meetings and conferences**

International Congress of the World Federation of Hemophilia (WFH): www.wfh.org
WFH Global Forum on the Safety and Supply of Treatment for Bleeding Disorders: www.wfh.org
European Haemophilia Consortium (EHC) Annual Conference: www.ehc.eu
International Society on Thrombosis and Haemostasis (ISTH) Congress: www.isth.org
International Plasma Protein Congress (IPPC): www.ppta.org
International Plasma Fractionation Association (IPFA): www.ipfa.nl
Plasma Protein Therapeutics Association (PPTA) Plasma Protein Forum (USA): www.pptaglobal.com
U.S. National Hemophilia Foundation (NHF) Annual Meeting: www.hemophilia.org
International Society of Blood Transfusion (ISBT) Congress: www.isbt-web.org

# APPENDIX 1: TERMS OF REFERENCE – HPSMAB IRELAND

## Terms of Reference and Procedures

**Haemophilia Product Selection and Monitoring Advisory Board on Clotting Factor Concentrates for Persons with Haemophilia and Other Bleeding Disorders**

### 1. MISSION STATEMENT

The mission of the Haemophilia Product Selection and Monitoring Advisory Board is to help ensure the selection of an adequate and ongoing supply of clotting factor concentrates that meet the highest standards of safety and efficacy. The process by which this is achieved will involve consumers, service providers and administrators acting in partnership and having due regard to emerging national and international developments and standards.

### 1.1 Definitions

References to the Board or to the HPSMAB in this document will be taken to mean the Haemophilia Product Selection and Monitoring Advisory Board to be established by Statutory Instrument.

The "Contract Holder" means the legal contracting entity for purchase and supply of clotting factor concentrates. Until further notice, the legal contracting entity will be the Irish Blood Transfusion Service.

### 1.2 Framework

The Board will define and advise on how clotting factor concentrates can most effectively be selected and usage monitored on a national basis.

The Board will advise the Contract Holder in relation to:

- product selection, procurement and supply;
- monitoring of safety, efficacy and supply;
- delivery, tracing and recall.

### 1.3 Scope

The mandate of the Board will include advising on the selection and monitoring of all plasma-derived and recombinant products used in treatment of the following conditions:

- inhibitors to factors VIII and IX;
- inherited deficiencies of factors I, II, V, VII, VIII, IX, X, XI, XIII;
- Von Willebrands disease.

The Board will advise the Contract Holder on how best to ensure that products supplied adhere to the highest standards of quality, safety and efficacy.

The Board will also assist the Contract Holder in determining adequate supplies of products and will give guidance and support in relation to delivery and tracing and any subsequent recall of products.

Nothing in the terms of reference of the Board shall impede the contract holder in discharging its responsibilities in law, including responsibilities relating to product safety, public procurement and licensing.

### 1.4 Functions

The purpose of the Board will be to advise the Minister, the Contract Holder and the Health Services Executive on any matter relating to products, on its own initiative or at the request of the Minister, the Contract Holder or the Health Services Executive.

The Board may perform the following functions:

(a) two shall be nominated by the Irish Haemophilia Society;
(b) one shall be the National Haemophilia Director;
(c) one shall be a consultant haematologist with an interest in paediatric haemophilia;
(d) one shall be a consultant haematologist who treats persons with haemophilia (PWH);
(e) one shall be nominated by the Contract Holder;
(f) one shall be a transfusion medicine expert, nominated by the Irish Blood Transfusion Service Board;
(g) one shall be an officer nominated by the Irish Medicines Board, and shall be an officer with responsibility for liaising with the EMEA on blood products;
(h) one shall be a person working in a management capacity within the health services, nominated by the Health Services Executive;
(i) one shall be a virologist with expertise in blood borne diseases;
(j) one shall be the external reviewer of the National Centre for Hereditary Coagulation Disorders;
(k) up to two other members may be appointed by the Minister.

The Board may perform these functions as a body, or may delegate one or more members to carry out specific tasks or give specialist advice.

### 1.5 Membership

The membership of the Board will consist of:

1) The Board shall consist of not more than 13 members appointed by the Minister, of whom –
(a) two shall be nominated by the Irish Haemophilia Society;
(b) one shall be the National Haemophilia Director;
(c) one shall be a consultant haematologist with an interest in paediatric haemophilia;
(d) one shall be a consultant haematologist who treats persons with haemophilia (PWH);
(e) one shall be nominated by the Contract Holder;
(f) one shall be a transfusion medicine expert, nominated by the Irish Blood Transfusion Service Board;
(g) one shall be an officer nominated by the Irish Medicines Board, and shall be an officer with responsibility for liaising with the EMEA on blood products;
(h) one shall be a person working in a management capacity within the health services, nominated by the Health Services Executive;
(i) one shall be a virologist with expertise in blood borne diseases;
(j) one shall be the external reviewer of the National Centre for Hereditary Coagulation Disorders;
(k) up to two other members may be appointed by the Minister.

2)
(a) The Irish Haemophilia Society will be entitled to nominate an external expert adviser to attend
(b) and participate in all meetings of the Board on an ex-officio basis;
(c) The Board may invite other expert advisers to attend and participate in meetings of the Board on an ex-officio basis as and when required;
(d) Persons who attend and participate in Board meetings on an ex-officio basis will not be entitled to have a vote on any matter coming before the Board, and will not be counted as part of the quorum for a meeting.

The Secretariat for the Board will be provided initially by the Department of Health and Children, and thereafter by the secretariat of the National Haemophilia Council.

The Chair of the HPSMAB will be appointed by the Minister for Health and Children for a term of five years. The HPSMAB will initially be chaired by the National Haemophilia Director.

Members will be appointed by the Minister for Health and Children for a term of five years. Where possible, members should be available for re-appointment to the Board after their initial term, to ensure continuity.

### 1.6 Conflict of Interest Disclosure

Members of the Board will be covered by the Ethics in Public Office Acts, 1995 and 2001. The Ethics in Public Office Acts provide for "the disclosure of interests of holders of certain public offices..." Under the Acts, a designated person is required to furnish a statement, in writing, of the interests which could materially influence the person in the performance of his/her official functions by reason of the fact that such performance could confer (or withhold) a substantial benefit on the person, or his/her spouse or child.

Under the legislation, a Statement of Interests must be completed each year where the office holder has something to disclose, and a Nil Statement is recommended where no such interests exist. Completed statements will be made available to the chairman, members of the Board and the secretariat. In addition, while not required by the legislation, members will be expected to declare potential as well as actual conflicts of interests.

A member of the Board, or any relevant employee of the agency appointed as Contract Holder, who is either directly or indirectly interested in any company or concern with which the Contract Holder proposes to make any contract, will also be required to disclose or cause to be disclosed to the Board the act and nature of such interest at the meeting of the Board at which the question of entering into such a contract is first considered or, if he or she has no such interest at that time, as soon as may be after he or she has acquired such interest.

During the tendering process, members of the Board will not enter into discussions with suppliers relating to the tenders under consideration.

### 1.7 Meetings and Procedures

The Board will meet as often as necessary, and not less than 3 times per annum.

The quorum for a meeting of the Board will be 5, which must include at least one member who was appointed by the Minister on the nomination of the Irish Haemophilia Society and a member who is a consultant haematologist. A member who participates in a meeting by means of teleconference facilities will be deemed to be in attendance at the meeting, for the purpose of the quorum.

The Board may regulate by Standing Orders or otherwise, its procedures and business.

The proceedings of the Board will not be invalidated by any vacancy or vacancies among its members, or by any problem with the appointment of the Board or any of its members.

All acts of the Board and all questions coming or arising before the Board in relation to product procurement may be done and decided by a two thirds majority of such members of the Board as are present and vote at a meeting of the Board. All other acts and questions may be done and decided by a simple majority of such members of the Board as are present and vote at a meeting of the Board.

In the case of equality of votes on any question requiring a simple majority arising at a meeting of the Board, the person chairing the meeting shall have a second, or casting vote.

A memorandum signed by all the members of the Board shall be effective for all purposes as if it was a resolution of the Board passed at a meeting duly convened, held and constituted.

All deliberations, decisions and advice of the Board will be recorded in writing and will be circulated to Board members. Consideration will be given to establishing a website and placing on it as much documentation as possible, except commercially sensitive information and personal details.

### 1.8 Reporting Relationship

The Board will present an annual report to the Minister for Health & Children by 30th June each year. The Board will also submit to the Minister any further information regarding the performance of its functions as the Minister may from time to time request, other than commercially sensitive information.

## 2. PRODUCT SELECTION PRINCIPLES

Purchase of products for persons with haemophilia (PWH) and other inherited bleeding disorders must comply with national and international regulatory requirements in relation to product safety. Government EU purchasing requirements and licensing requirements (when suitable products are licenced) must also be met.

Products selected for purchase must meet agreed criteria, including: quality, safety, efficacy, availability, delivery and scientific and technical support. The national/international regulatory criteria which must be met by the products is a product authorisation. The Board will advise on the relevant safety criteria and standards for recombinant and plasma derived products taking into consideration the national/international regulatory criteria which must be met by the products. When all these factors have been taken into account, cost effectiveness will be considered by the Board.

Provision will be made by the Board for low volume use essential products which do not have a Product Authorisation.

The Board will also advise the Contract Holder on the assessment of product supply issues. To help ensure security of supply, where possible products should be sourced from more than one supplier. Every effort must be made to ensure that sufficient quantities of product are purchased by the Contract Holder to ensure that individuals have access to a continuing supply of relevant products.

The Board will advise on products for purchase and distribution. Products may also be recommended for all relevant conditions which come within the Board's ambit.

The Board will advise the Contract Holder on the contingency plans which should be put in place. The purpose of a contingency plan will be to help ensure availability of alternative products in case of emergencies. The Board will operate on the basis of the integrity of the licensing process and will not seek to duplicate the role of the IMB and the European Medicines Evaluation Agency (EMEA).

Suitability of products for home use will be taken into consideration when products are being evaluated. The Board will advise on mechanisms to be developed to monitor usage of the products selected.

## 3. ADVISORY PROCESS

The list of products recommended will form the basis of a National Recommended Product List. Individual treating consultants may apply to the Board to have other products added to the recommended list under special circumstances.

Treating consultants will be requested to notify the Board of prescriptions for products not recommended by the Board.

Note – the Board is of the view that the position regarding legislation for unauthorized products in general needs to be clarified.

The product consumer will be represented on the Board by the nominees of the Irish Haemophilia Society.

## 4. INDEMNITY AND LIABILITY

### 4.1 Indemnity for HPSMAB

Government has indemnified all members of the Haemophilia Product Selection and Monitoring Advisory Board in respect of all advices, decisions and activities which they undertake in the discharge of their functions, and any consequences arising from the discharge of these functions, except any consequences arising because of willful neglect.

The contract holder will to the greatest extent possible obtain indemnities from suppliers in respect of product liability and will liaise with the Department of Health & Children to obtain confirmation from the government that it will be indemnified in respect of any liability for the supply of clotting factor concentrates in any event.

The position regarding product liability for all parts of the supply chain needs to be clarified. The Board is of the view that the preferred position is that indemnity in respect of product liability is provided to the whole supply chain, once appropriate conditions are met.

### 4.2 Product liability & safety

The Contract Holder is responsible for ensuring that the selected products meet the necessary safety criteria for distribution in the market place. In this respect the Contract Holder is obliged to comply with its common law duties and with relevant Irish and European legislation, including the Liability for Defective Products Act, 1991, the Product Liability Directive (Directive 85/374 amended by Directive 95/34), the General Product Safety Directive (Directive 92/59) and the revised General Product Safety Directive (2001/95/EEC). This legal responsibility exists notwithstanding the fact that the Board will advise and recommend to the contract holder on the evaluation criteria for selection of products. Nothing in the Terms of Reference of the Board will relieve the Contract Holder of its legal responsibilities in respect of product safety, or impede it in discharging such responsibilities.

## 5. PROCUREMENT AND CONTRACT ADMINISTRATION PROCEDURES

### 5.1 Procurement Process

#### *5.1.1 Tender Specification*

The tender specification will advise on effective stock-holding levels and stock-holding policies and procedures. The Board will advise on stock requirements for the Contract Holder.

International developments with regard to product development and replacement therapy will be monitored on an ongoing basis, together with issues of safety, efficacy and supply.

Before each contract expires, all options regarding the provision of factor replacement therapy will be reviewed. Future requirements for factor replacement therapy for the next tender period will be identified.

Following this review, the specification for the required products and the quantities necessary will be discussed and the Contract Holder advised accordingly.

### *5.1.2 National and E.U. Public Procurement requirements*

Tenders will be invited in accordance with national and EU public procurement requirements. EU Directives in the field of public procurement have the force of law in Member States and must be strictly adhered to (violations can give rise to serious legal/financial sanctions).

The Directive which covers procurement of supplies is: 93/36/EEC. (OJ L 199/1 of 9.7.1993) consolidating Directives 88/295/EEC, 80/767/EEC and 77/62/EEC. Regard must also be had to Directive 2004/18/EEC, which consolidates the earlier Directives and the Directives on the procurement of works and services: this Directive will soon be transposed into Irish law. The Contract Holder will have legal responsibility for ensuring that all relevant requirements are met.

### *5.1.3 Tender Documents*

The Contract Holder will seek all relevant information from potential suppliers, including safety and efficacy, purity, availability of supply, manufacture, potency, delivery arrangements and cost. In respect of all products manufactured with or containing human or animal components, full information will be required on the source of such products. In relation to human-derived plasma components, including albumin, full information will be required on donor recruitment, selection and testing procedures and policies. The availability of current product authorizations, where they exist, will either be included as part of the tender specification or as one of the tender evaluation criteria. If specified as one of the tender evaluation criteria, it will be specified under a separate heading and not as a subset of quality. Copies of product licences, where they exist, will be provided to the Contract Holder.

Members of the Board will receive any documentation they require from the Contract Holder, provided that this does not conflict with the legal requirements of the Contract Holder. Documentation will be made available to members of the Board as soon as available, and in advance of any decisions taken by the Contract Holder.

The Contract Holder may, in turn, request further documentation from potential suppliers in relation to requests for tender, contracts and any other relevant information, provided this request does not conflict with national and EU procurement guidelines.

### *5.1.4 Technical Specifications*

Individual members of the Board may decide not to receive detailed technical documentation and may indicate accordingly to the Contract Holder. In such instances, the Contract Holder will hold the documents and make them available should the member wish to inspect them at any time.

Members will remain responsible for the Board's advice whether they choose to receive full technical documentation or not.

### *5.1.5 Tender Evaluation*

Tenders may only be evaluated in accordance with the selection criteria as defined in the tender documents. Selection criteria must be related to the product or a company's ability to fulfill the contract.

In accordance with EU procurement guidelines in either open or restricted procedures, all negotiations with tenderers on fundamental aspects of contracts, and in particular on prices, is ruled out; however, discussions with candidates or tenderers may be held, but solely for the purpose of clarifying or supplementing the content of their tenders or the requirements of the Contract Holder and provided this does not involve discrimination. In relation to the tender process all written and verbal communications with tenderers in relation to the tender process, including discussions and supplier presentations, will be directed through the Contract Holder.

*5.1.6 Freedom of Information Requirements*

Members will agree to maintain the confidentiality of commercially sensitive information, and will be subject to the requirements of Data Protection legislation. When the Board is established under SI it will be added to the schedule of bodies listed under the Freedom of Information Act.

*5.1.7 Award of Contract*

Tenders will be assessed by the Board. The Contract Holder will be advised of the Board's recommendations according to the agreed product selection principles defined above. Subject to any concerns and reservations of the contract holder, contracts will then be awarded by the Contract Holder.

In the event of a disagreement between the Board and the Contract Holder in relation to a decision on product selection, both parties will present the reasons for their conclusions to a joint meeting. Discussions will be held and all reasonable efforts made to reach a consensus. If this does not result in agreement, the contracts will not be signed and the matter will be referred by the Board to the Minister for Health and Children with recommendations for resolution.

Under no circumstances will the Contract Holder be obliged or requested to breach its legal responsibilities or obligations.

### 5.2 Contract Holder

The Minister for Health and Children will designate the legal contracting entity for clotting factor concentrates. Until further notice, the legal contracting entity will be the Irish Blood Transfusion Service.

The Minister may, at his own discretion, or on the recommendation of the National Haemophilia Council, decide to appoint an alternative Contract Holder, having due regard to the legal position regarding any contracts currently in place.

The role and responsibilities of the Contract Holder in the context of this Board will be as follows:

- to consult with and provide technical and medical information to the treating consultants, and to the Board;
- to execute the tendering process in accordance with national and EU public procurement guidelines;
- to provide all relevant documentation to the Board;
- to contract and purchase product from suppliers based on the criteria, specifications and volumes advised by the Board;
- to provide adequate and proper storage of the product;
- to ship and deliver product in accordance with distribution requirements;
- to maintain procedures which allow proper tracing and recall of product in a timely manner from point of delivery.

The Contract Holder will inform the Board of financial arrangements employed in relation to any relevant product it purchases and distributes.

The Contract Holder may engage third parties to perform some of these functions on its behalf. The Contract Holder will ensure all relevant national and international product licences are available for the products purchased through the agreed tender process. In the case of unlicensed products required on a named basis, the contract holder will comply with the provisions of the relevant law.

Responsibility for product tracing and recall procedures rests with the contract holder and relevant hospitals.

It is essential that the Contract Holder has in place effective quality management systems, audited/inspected by the competent national authority (Irish Medicines Board), to fulfill its responsibilities.

The contract holder should hold a current Wholesaler's Licence in accordance with the Medical Preparations (Wholesale Licences) Regulations 1993-1996. Any sub-contractor involved in wholesale/ distribution activities should be similarly licenced.

Any company involved in importing any medicinal product from a non-EEA country may also be required to hold a manufacturer's licence in accordance with the Medical Preparations (Licencing of Manufacture) Regulations 1993-1996.

### 5.3 Product delivery and distribution

Important benefits have been identified from a centralized product delivery and distribution process. The Board will advise on the criteria for this process and will also advise an appropriate body for management of the process.

### 5.4 Contract monitoring and review arrangements

The Board will receive reports from the Contract Holder on contract monitoring and review. It will also advise on contingency arrangements to be put in place in case of emergencies.

# APPENDIX 2: IRISH LEGISLATION ON CHANGE OF CONTRACT HOLDER FOR NATIONAL TENDERS, 2012

*Number* 8 *of* 2012

**CLOTTING FACTOR CONCENTRATES AND OTHER BIOLOGICAL PRODUCTS ACT 2012**

ARRANGEMENT OF SECTIONS

Section



1

*Number* 8 *of* 2012

# CLOTTING FACTOR CONCENTRATES AND OTHER BIOLOGICAL PRODUCTS ACT 2012

AN ACT TO PROVIDE FOR THE PROCUREMENT AND MAKING AVAILABLE OF CLOTTING FACTOR CONCENTRATES AND OTHER BIOLOGICAL MEDICINAL PRODUCTS, INCLUDING RECOMBINANT PROTEIN PREPARATIONS, FOR THE PURPOSE OF TREATING COAGULATION AND OTHER DISORDERS AND TO PROVIDE FOR RELATED MATTERS.

[27*th March*, 2012]

BE IT ENACTED BY THE OIREACHTAS AS FOLLOWS:

St. James's Hospital Board to procure and make available clotting factor concentrates and other biological products.

**1.**—(1) The St. James's Hospital Board shall procure and make available clotting factor concentrates and other biological medicinal products, including recombinant protein preparations, for the purpose of treating coagulation disorders and other congenital or acquired disorders that are characterised by diminished levels of, or dysfunctional forms of, plasma proteins.

(2) Nothing in this section affects the functions of the St. James's Hospital Board under Article 4(3) of the St. James's Hospital Board (Establishment) Order 1971 (S.I. No. 187 of 1971).

Preservation of certain contracts and adaption of references to Irish Blood Transfusion Service.

**2.**—Every contract, relating to the products referred to in *section 1*, made between the Irish Blood Transfusion Service or any trustee or agent thereof acting on its behalf, and any other person, which is in force immediately before the commencement of this section, shall continue in force and shall be construed and have effect as if the St. James's Hospital Board were substituted therein for the Irish Blood Transfusion Service or, as the case may be, its trustee or agent acting on its behalf, and shall be enforceable by or against the St. James's Hospital Board.

Revocation.

**3.**—Paragraph *(l)* (inserted by Article 2 of the Blood Transfusion Service Board (Establishment) Order 1965 (Amendment) Order 2003 (S.I. No. 268 of 2003)) of Article 4 of the Blood Transfusion Service Board (Establishment) Order 1965 (S.I. No. 78 of 1965) is revoked.

# APPENDIX 3: TENDER SCORE SHEET FOR RECOMBINANT FVIII (IRELAND, 2012)

| Scoring Criteria | | Maximum Score | |
|---|---|---|---|
| **PHASE 1** | | | |
| Safety | Human albumin in culture medium | 15 | |
| | Additional human or animal protein (eg monoclonal **antibodies**) | 5 | |
| | Viral inactivation | 10 | |
| | Inhibitors | 30 | |
| | **Prion** removal | 5 | |
| | Others | 10 | |
| | **Total for Safety** | **75** | |
| Efficacy | Recovery/Half-life (adult/paediatric) | 12 | |
| | Clinical response (adult/paediatric) | 18 | |
| | **Total for Efficacy** | **30** | |
| Quality | Stability | 5 | |
| | Volume of administration | 3 | |
| | Instructions for use and handling | 3 | |
| | Ease of administration | 3 | |
| | Application of unique bar code | 5 | |
| | **Total for Quality** | **19** | |
| Security of Supply/ Availability | Number of manufacturing plants | 4 | |
| | Security of supply | 6 | |
| | **Total for Supply/Availability** | **10** | |
| Scientific Support | Clinical opinion | 2 | |
| | Consumer opinion | 2 | |
| | Tender | 2 | |
| | **Total for Scientific Support** | **6** | |
| **Total Scores Awarded: Phase 1** | | **140** | |
| **PHASE 2** | | | |
| **Cost** | **Total for Cost** | **60** | |
| **Total Scores Awarded: Phase 2** | | **200** | |

# APPENDIX 4: TENDER SCORE SHEET FOR PLASMA-DERIVED FVIII (IRELAND, 2012)

| | | Maximum Score | |
|---|---|---|---|
| Safety | Plasma source | 10 | |
| | Donor test and NAT testing of donors | 10 | |
| | Quarantine | 5 | |
| | **Mini pool** NAT | 5 | |
| | Inhibitors | 10 | |
| | Prion removal | 10 | |
| | Dual viral inactivation using complementary methods | 40 | |
| | Adverse reports covering other safety issues | 10 | |
| | **Total for Safety** | **100** | |
| Quality | Product authorisation | 13 | |
| | Stability | 4 | |
| | Volume of adminstration | 5 | |
| | Instructions for use and handling | 3 | |
| | Ease of administration | 3 | |
| | Application of unique bar code | 6 | |
| | **Total for Quality** | **34** | |
| Efficacy | Recovery | 20 | |
| | Clinical response | 20 | |
| | **Total for Efficacy** | **40** | |
| Supply/Availability | Number of manufacturing plants | 6 | |
| | Security of supply | 12 | |
| | **Total for Supply/Availability** | **18** | |
| Technical Support | Clinical opinion | 3 | |
| | Consumer opinion | 3 | |
| | Tender | 2 | |
| | **Total for Technical Support** | **8** | |
| | | **200** | |
| | Tender price | 45 | |
| **Cost** | **Total for Cost** | **45** | |
| **Total Score** | | **245** | |

# APPENDIX 5: TENDER SCORE SHEET FOR PROTHROMBIN COMPLEX CONCENTRATE FOR TREATMENT OF FX DEFICIENCY (IRELAND, 2015)

| | | Maximum Score | |
|---|---|---|---|
| Safety | Plasma source | 10 | |
| | Donor test and NAT testing of donors | 12 | |
| | Quarantine | 5 | |
| | Mini pool NAT | 5 | |
| | Inhibitors | 10 | |
| | Prion removal | 20 | |
| | Dual viral inactivation using complementary methods | 40 | |
| | Adverse reports covering other safety issues | 10 | |
| | Reported incidence of thrombosis | 10 | |
| | Measurement of activation | 5 | |
| | **Total for Safety** | **127** | |
| Quality | Product authorisation | 13 | |
| | Qualitative composition | 10 | |
| | Quantitative composition | 20 | |
| | Stability | 5 | |
| | Volume of adminstration | 10 | |
| | Instructions for use and handling | 3 | |
| | Ease of administration | 3 | |
| | Application of unique bar code | 3 | |
| | **Total for Quality** | **67** | |
| Efficacy | Recovery | 20 | |
| | Clinical response | 20 | |
| | **Total for Efficacy** | **40** | |
| Supply/Availability | Number of manufacturing plants | 6 | |
| | Security of supply | 12 | |
| | **Total for Supply/Availability** | **18** | |
| Scientific Support | Clinical opinion | 6 | |
| | Consumer opinion | 6 | |
| | Tender | 3 | |
| | **Total for Scientific Support** | **15** | |
| **Cost** | **Total for Cost** | **30** | |
| **Total Score** | | **297** | |

# APPENDIX 6: NON-EXHAUSTIVE LIST OF POSSIBLE SELECTION CRITERIA FOR TENDERS

## Plasma-derived factor concentrates

### SAFETY

#### Plasma source

- Paid or unpaid donors
- Prevalence of BSE in the countries of collection
- Cases of vCJD in donors
- Donor deferral measures
- Recovered or pheresis plasma
- Proportion of repeat donors

#### Pool size

- Viruses
- Prions

#### Donor testing

- Universal individual donor serologic tests (Syphilis, **HIV** 1-2, HBsAg, **HCV** Ab)
- Optional (p24 Ag, HTLV-1, ALT, B19)
- Mini pool donor NAT testing
- Mini pool size
- Mandatory (HCV)
- Optional (HIV, **HAV**, B19, **HBV**)

#### Quarantine or inventory hold

- Number of days
- Plasma released for use only following subsequent donation

#### Inhibitors

- Published data
- Clinical trial data
- Anecdotal reports

#### Viral inactivation/removal

- Effective step against lipid-enveloped viruses
- Effective step against non-lipid-enveloped viruses
- Dual inactivation using complementary methods
- **Nanofiltration**

#### Prion removal

- Impact of manufacturing process
- Data from spiking experiments
- Impact of pool size

#### Postmarketing surveillance

- Experience with product internationally
- Published data or studies
- Adverse event reports
- Defined postmarketing surveillance studies

## EFFICACY

### Recovery

- Published data
- Adults and children
- Ratio of VWF/ristocetin co-factor to FVIII activity
- Clinical response

### Clinical trials

- Published peer reviewed data
- Experience
- Anecdotal reports

## QUALITY

### Licensing

- Licensed by EMA, FDA, PEI or well recognized regulatory authorities
- Licensed for use in FVIII deficiency
- Licensed for use in VWD

### Stability

- At room temperature
- At 2–8°C

### Infusing factor

- Volume in ml per vial and per infusion
- Suitability of home treatment pack and contents
- Portability
- Practical ease of administration
- Instructions for use and handling
- Range of potencies available

### Traceability

- Bar codes on boxes
- Bar codes on vials
- Serialized bar codes on vials

## COST

- Scores for other criteria carried over when examining cost
- Products which fail to meet minimum standards under other criteria not considered when cost being examined
- Products which meet minimum standards considered in a second stage with cost as the only criteria
- Discretion to select only product with highest overall score or select more than one product
- Scoring system for cost
- Scoring system with different product volumes
- E-auction
- Availability of supply
- Number of sites of manufacture
- Capacity to manufacture
- Number of plasma collection facilities
- Storage facilities in country
- Guaranteed minimum supply levels
- Ability to vary amount purchased by agreed percenta

### SCIENTIFIC AND TECHNICAL SUPPORT

- Company office or distributor
- Clinical experience with company or distributor
- Consumer experience with company or distributor
- Specified from tender documents
- Scientific and medical expertise available in country
- Arrangements for scientific and technical expertise available in emergency

### DIVERSITY OF SUPPLY (MAINTAIN DIVERSITY IN MARKET*)

- Avoid a monopoly supply from 1 company
- Ability to cope with shortages or plant shutdowns
- Maintain presence of all companies in national market
- Maintain level of company support for treatment centres, clinicians and patient organizations
- Past experience with the product
- Past experience with the company

## Recombinant Factor Concentrates

### SAFETY

#### Presence of human or animal proteins

- Albumin as a stabilizer
- Human albumin in the culture medium
- Murine monoclonal antibody
- Other human or animal proteins

#### Inhibitors

- Published data
- Clinical trial data
- Anecdotal reports

#### Viral inactivation/removal

- Effective step against lipid-enveloped viruses
- Effective step against non-lipid-enveloped viruses
- Nanofiltration

#### Prion removal

- Impact of manufacturing process
- Data from spiking experiments

#### Postmarketing surveillance

- Experience with product internationally
- Published data or studies
- Adverse event reports
- Defined postmarketing surveillance studies

### EFFICACY

#### Recovery

- Published data
- Adults and children

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* Not consistent with EU Procurement Directive

### Clinical response

- Clinical trials
- Published peer reviewed data
- Experience
- Anecdotal reports

## QUALITY

### Licensing

- Licensed by EMA or FDA
- Specific conditions on licensed use (adult/pediatric)

### Stability

- At room temperature
- At 2–8°C

### Infusing factor

- Volume in ml per vial and per infusion
- Suitability of home treatment pack and contents
- Portability
- Practical ease of administration
- Instructions for use and handling
- Range of potencies available

### Traceability

- Bar codes on boxes
- Bar codes on vials
- Serialized bar codes on vials

## COST

- Scores for other criteria carried over when examining cost
- Products which fail to meet minimum standards under other criteria not considered when cost being examined
- Products which meet minimum standards considered in a second stage with cost the only criteria
- Discretion to select only product with highest overall score or select more than one product
- Scoring system of cost
- Scoring system with different product volumes
- E-auction

## AVAILABILITY OF SUPPLY

- Number of sites of manufacture
- Capacity to manufacture
- Storage facilities in country
- Guaranteed minimum supply levels
- Ability to vary amount purchased by agreed percentage

## SCIENTIFIC AND TECHNICAL SUPPORT

- Company office or distributor
- Clinical experience with company or distributor
- Consumer experience with company or distributor
- Specified information from tender documents
- Scientific and medical expertise available in country
- Arrangements for scientific and technical expertise available in emergency

### DIVERSITY OF SUPPLY (MAINTAIN DIVERSITY IN MARKET*)

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- Past experience with product
- Past experience with company

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* Not consistent with EU Procurement Directive

# LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AMNOG | Act on the Reform of the Market for Medicinal Products, Germany |
| ANVISA | Brazilian Health Surveillance Agency |
| APH | Associação Portuguesa de Hemofilia |
| CBS | Canadian Blood Services |
| CFC | Clotting factor concentrate |
| CHS | Canadian Hemophilia Society |
| COMISCA | Council of Ministers of Health of Central America |
| EHC | European Haemophilia Consortium |
| EMA | European Medicines Agency, previously known as the EMEA |
| EU | European Union |
| FDA | U.S. Food and Drug Administration |
| FIX | Clotting factor IX (concentrate) |
| FVIII | Clotting factor VIII (concentrate) |
| G-BA | Federal Joint Committee, Germany |
| GDP | Gross domestic product |
| GPA | Government Procurement Agreement of the World Trade Organization |
| HPSMAB | Haemophilia Product Selection and Monitoring Advisory Board, Ireland |
| HTA | Health technology assessment |
| HTC | Hemophila treatment centre |
| IQWiG | Institute for Quality and Efficiency in Health Care, Germany |
| IVIG | Intravenous immune globulin |
| IU | International unit |
| MCC | Medicines Control Council, South Africa |
| MEAT | Most economically advantageous tender |
| NAT | Nucleic acid testing |
| NHSO | National Health Security Office, Thailand |
| NMO | National member organization |
| OJEU | Official Journal of the European Union |
| PCC | Prothrombin complex concentrate |
| pdFIX | Plasma-derived factor IX concentrate |
| pdFVIII | Plasma-derived factor VIII concentrate |
| pdFVIII/VWF | Plasma-derived factor VIII concentrate containing von Willebrand factor |
| PIN | Prior information notice |
| rFIX | Recombinant factor IX concentrate |
| RFP | Request for proposals |
| rFVIIa | Recombinant activated factor VII concentrate |
| rFVIII | Recombinant factor VIII concentrate |
| TED | Tenders Electronic Daily |
| SPMS | Portuguese Ministry of Health Shared Services |
| UKHCDO | United Kingdom Haemophilia Centre Doctors' Organisation |
| VWD | von Willebrand disease |
| VWF | von Willebrand factor |
| WFH | World Federation of Hemophilia |
| WTO | World Trade Organization |

# GLOSSARY

**Adverse event**: An incident in which harm resulted to a person receiving medical care.

**Albumin**: A protein found in human plasma that is used as a stabilizer in factor VIII and factor IX products including recombinant factor concentrates. Some new concentrates now use sucrose instead of albumin as a stabilizer.

**Antibodies:** Proteins made by the body's immune system to fight off substances it perceives as foreign. Antibodies that occur in people with hemophilia are called inhibitors. See "inhibitors."

**Bleeding disorders**: Diseases in which the blood does not clot as quickly or as effectively as normal. Untreated, these diseases usually result in prolonged bleeding. These disorders include hemophilia A, hemophilia B, von Willebrand disease, platelet function disorders, and a variety of other rarer factor deficiencies.

**Bypassing agent:** A special clotting factor used in patients with antibodies (inhibitors) to their usual factor, to overcome the blockage or cessation in the clotting system.

**Clotting factor concentrates (CFCs)**: Preparations of clotting proteins that are used to prevent and/or treat bleeds in people with bleeding disorders. Concentrates exist to treat deficiencies in factors I, II, VII, VIII, IX, X, XI, XIII, and von Willebrand factor. The concentrates can be manufactured from human plasma or by recombinant technology. They are purified and treated to destroy any potential viruses or diseases, then freeze-dried, and stored in sterile vials. Before an infusion, sterile water is added to the clotting proteins for reconstitution. Also referred to as coagulation factor concentrates.

**Clotting factor:** Any of the factors in blood plasma that work together to form a clot to help stop bleeding. Also referred to as coagulation factor.

**Cold chain**: Clotting factor concentrates are sensitive biological substances that will lose their potency with time. In order to maintain their quality, clotting factors must be continuously stored at the appropriate temperature from the time they are manufactured up until the moment of use. The system used for keeping and distributing clotting factors at the appropriate temperature is called the cold chain.

**Conflict of interest**: A conflict between the private interests and the official or professional responsibilities of a person in a position of trust.

**Consortium**: A cooperative arrangement among groups or institutions.

**Contracting authority:** The organization that has the legal responsibility for a tender contract, and issues and receives the tender documents. It is usually the Ministry of Health or a government health agency but can also be a government department, government agency, health agency, blood transfusion service, hospital, government-appointed commission or board, or the national hemophilia organization.

**Cost effectiveness:** Description applied to an intervention (treatment, diagnostic test, etc.) for which the costs are considered to be justified by the benefits provided.

**Debrief**: To report after an event.

**Effectiveness:** The effect of a treatment as measured in the usual clinical environment.

**Efficacy:** The effect of treatment as measured in the controlled environment of a clinical trial.

**End user**: The ultimate consumer of a product, especially the one for whom the product has been designed, manufactured, or procured.

**Factor VIII (FVIII):** A clotting factor manufactured in the liver. Deficiency or absence of factor VIII clotting activity results in hemophilia A.

**Factor IX (FIX):** A clotting factor manufactured in the liver. Deficiency or absence of factor IX clotting activity results in hemophilia B.

**Factor concentrates:** See "clotting factor concentrates."

**Fractionation:** The process of separating and processing human blood plasma into a range of products for therapeutic use. The plasma is separated into its component parts, such as clotting factors, albumin, and immunoglobulin, and then purified.

**Half-life:** The time is takes for infused factor to lose half of its potency. Factor VIII has a half-life of 8 to 12 hours. After the first infusion, the half-life of factor IX increases to 18 to 24 hours for subsequent infusions.

**Health technology assessment (HTA):** A review of the evidence (usually a systematic review) on the impact of a healthcare intervention (or "technology"), often including economic evaluation evidence.

**Hepatitis A (HAV)**: Hepatitis A virus, which causes inflammation of the liver. HAV is usually transmitted through food or drink that has been handled by an infected person.

**Hepatitis B (HBV)**: Hepatitis B virus, which causes inflammation of the liver. HBV can be transmitted by needle sticks, body piercing and tattooing using non-sterilized instruments, dialysis, sexual contact, child-birth, and, in very rare cases, by fresh blood components.

**Hepatitis C (HCV)**: Hepatitis C virus, which causes inflammation of the liver. HCV is usually spread through contaminated blood transfusions, hemodialysis, and needle sticks.

**Hematologist**: A doctor who specializes in blood disorders.

**Hemophilia**: A hereditary bleeding disorder in which bleeding lasts longer than normal. Hemophilia is characterized by frequent bleeding into joints, muscles, and tissues. It is caused by a defect in a protein required for blood clotting. This defect results in a deficiency or absence of a clotting factor, usually factor VIII or IX.

**Hemophilia treatment centre (HTC)**: A comprehensive care centre that has medical professionals from several areas of medicine with expertise in hemophilia. They care for people with hemophilia and their families.

**Human immunodeficiency virus (HIV):** A retrovirus that causes acquired immunodeficiency syndrome/ AIDS.

**Indemnity**: Security against financial or legal responsibility.

**Inhibitors:** Antibodies to infused factor VIII or factor IX produced by the immune system that attack and destroy the factor VIII or IX proteins in factor concentrates, making treatment ineffective.

**International unit (IU)**: A standardized unit of measure that determines the potency of the product by measuring the activity of a substance.

**Intravenous immunoglobulin (IVIG):** An intravenous blood product made from pooled human plasma which contains immunoglobulin G (IgG) immunoglobulins and is used in the treatment of a range of medical conditions including immunodeficiencies, autoimmune disorders, rare bleeding disorders, and factor inhibitors including acquired hemophilia, acquired von Willebrand syndrome, inhibitors to factor VIII in hemophilia A, and inhibitors to factor IX in hemophilia B.

**Mild hemophilia:** Condition resulting from a level of factor VIII or factor IX clotting activity between 5 to 40% of normal activity in the bloodstream.

**Mini-pools:** Plasma samples pooled from several donations, and then tested for viral markers.

**Moderate hemophilia:** Condition resulting from a level of factor VIII or factor IX clotting activity between 1-5% of normal activity in the bloodstream.

**Most economically advantageous tender (MEAT):** European Union tender selection criteria which include considerations of price, but also more holistic criteria including life cycle costs, best price/quality ratio, and technical and sustainability aspects.

**Nanofiltration**: A method of removing certain viruses and impurities from a protein solution. The solution passes through a small pore filter that removes viruses but allows therapeutic proteins to pass through.

**National tender system (or process):** A cost-effective system for the purchase of products or services such as clotting factor concentrates. Instead of each organization or hospital purchasing its own supply, the government purchases what is needed for the entire country. This system achieves cost savings by buying large volumes and asking for competitive bids from manufacturers. Suppliers are invited to submit a bid, or tender, then these bids are evaluated based on certain defined criteria (such as safety, efficacy, and cost), and the contract is awarded to the bidder who best meets those criteria.

**Nucleic acid testing (NAT):** Testing used to detect viruses by looking for viral nucleic acid. NAT allows for the detection of viruses before the development of immunological markers of infection.

**On-demand therapy:** An infusion of factor concentrate as soon as the person with hemophilia is aware of a bleed. The goal is to promptly stop the bleed.

**Plasma-derived factor concentrates:** Factor concentrates that contain factor I (fibrinogen), factor VIII, factor IX, von Willebrand factor, factor XI, factor XIII, or prothrombin complex concentrate that have been fractionated from human blood.

**Potency**: The measurable biological activity related to a product's actual therapeutic effect.

**Prion**: A tiny protein particle that is similar to a virus but does not contain any genetic material. It is thought that **variant Creutzfeldt-Jakob disease (vCJD)** is caused by a misfolded prion.

**Procurement**: The purchasing of something usually for a company, government, or other organization.

**Product specification**: The properties of a product which can be measured in a laboratory, allowing a manufacturer to assess and demonstrate fitness of purpose.

**Prolonged half-life factor concentrates:** A new generation of recombinant factor concentrates based on new strategies such as pegylation, fusion technologies, and amino acid sequence modification, which extend their half-life.

**Prophylaxis**: The scheduled infusion of clotting factors, usually two to three times a week, in order to prevent future bleeds. The goal is to keep factor levels in the plasma high enough to prevent bleeding episodes.

**Prothrombin complex concentrate (PCC):** A combination of blood clotting factors II, VII, IX and X, as well as proteins C and S, prepared from fresh-frozen human blood plasma.

**Purity**: In factor concentrates, the proportion of a desired substance, such as factor VIII, relative to the other ingredients that are present.

**Quarantine:** The holding back of a blood product or other drug for a short period of time because of a possible problem with its quality.

**Quorum**: The minimum number of members of an organization or committee necessary to conduct business and make decisions.

**Recall**: The removal of a product from the market because either the manufacturer, a regulatory agency, or both think that a product is not safe for use.

**Recombinant clotting factor concentrate**: A preparation of factor proteins manufactured without using human plasma. Like plasma-derived concentrate, recombinant clotting factor concentrate is dissolved in sterile water for infusion.

**Registry:** A database or record of identified people with hemophilia or inherited bleeding disorders. A registry includes information on personal details, diagnosis, treatment, and complications.

**Severe hemophilia:** Condition resulting from a level of factor VIII or factor IX clotting activity of less than 1 % in the bloodstream.

**Shelf life**: The period of time a product can be stored under normal conditions and retain its characteristics.

**Stakeholder**: Any person or organization with an interest in a topic.

**Tender commission**: A committee or group that decides on criteria for awarding contracts, evaluates tenders, and makes the decisions about the award of the tender.

**Terms of reference:** A document specifying the scope and details of the activity to which it refers and any conditions relating to the appointment of persons to undertake the activity.

**Transfer of technology:** The transfer of any process together with its documentation and professional expertise between development and manufacturing or between manufacturing sites. It is a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and/or commercialization to an appropriate, responsible and authorized party.

**Variant Creutzfeldt-Jakob disease (vCJD):** A fatal brain disease thought be the result of eating contaminated beef products. vCJD is the human form of bovine spongiform encephalopathy (BSE) and is believed to be caused by an infection with a mutant protein called a prion.

**Viral inactivation**: The process of making certain viruses non-infectious, without necessarily removing them from the product.

**von Willebrand disease (VWD)**: An inherited blood clotting disorder caused by a defect in the von Willebrand/factor VIII molecule. The results are prolonged bleeding and poor blood coagulation. This disorder can affect both men and women.

**Withdrawal**: The removal of a product from the market because the manufacturer believes that the product does not meet with manufacturing standards. This does not automatically mean that the manufacturer believes that the product is unsafe.

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