During the past decade a large number of new anticoagulant and antithrombotic drugs have been developed. As shown in Fig. 1, these agents represent a wide variety of substances which are derived utilizing natural sources, biotechnology based methods and synthetic approaches. Because of the structural and molecular characteristics, these agents exhibit both physicochemical and functional diversities. Thus, each of these classes of drugs control thrombogenesis via distinct mechanisms.

The main classes of these new drugs include peptides, peptidomimetics, heparinomimetics and recombinant proteins. In addition there are several antiplatelet drugs such as the GP IIb/IIIa inhibitors.
and ADP receptor antagonists which have played a major role in the management of cardiovascular disorders. Despite these significant developments heparin and heparin derived drugs have continued to play a major role in the management of thrombotic and cardiovascular disorders.

There remain several unanswered important issues related to the current practices of anticoagulant therapy as many of the newer drugs are monotherapeutic. The widely acclaimed notion that these new drugs will eventually replace conventional anticoagulants such as coumadin, and heparin require objective validation. Drugs such as the Pentasaccharide (Arixtra®) and antithrombin agents (Hirudin, Angiomax) target only one site whereas the conventional anticoagulants are polytherapeutic. It is therefore difficult to perceive that a monotherapeutic agent will produce all of the polytherapeutic effects of conventional drugs without the potential toxicity associated with their use.

Unfractionated heparin has remained the anticoagulant of choice for interventional and surgical indications despite the development of newer agents. Several newer low molecular weight heparins (LMWHs) are now routinely used for specific indications in both the arterial and venous indications. It is important to note that each LMWH is a distinct drug and that the different LMWHs can not be interchanged for specific indications. Not until, parallel clinical trials have been done to show equivalence can these drugs be interchanged. However, each of these products will have its own specific dosage for a given indication. LMWHs have gradually replaced heparin for prophylaxis and treatment of DVT, the role of these agents as surgical and interventional anticoagulants is not clearly established. Although LMWHs are widely used for various other indications, there are still several unresolved questions related to the development of these drugs.

1. Are different low molecular weight heparins distinct drugs?
2. Can we interchange various LMWHs for specific indications?
3. Will low molecular weight heparins replace unfractionated heparins for anticoagulation indications?
4. Will antithrombin drugs and anti-Xa agents eventually replace LMWHs in anticoagulation indications?
5. What is the feasibility of oral LMWHs for specific indications?
6. What is the possibility of the introduction of the generic version of LMWHs? Are there any adequate guidelines to compare these drugs with the branded products?

Currently, several newer agents are being investigated as possible substitutes for heparin. These new agents include antithrombin, anti-Xa, anti-TF, heparinoids, oral formulations of heparin, glycosaminoglycans mixtures, activated protein C and biotechnology derived SERPINS such as the recombinant AT and HC II. All of the agents are currently developed for indications in both arterial and venous thrombosis. Each of these agents may be used for a specific and relatively narrow range of indications and may not have a broad clinical spectrum as observed with the heparins.

Both the unfractionated heparin and LMWHs are chemically and functionally heterogeneous in nature. Figure 2 describes the depolymerization of heparin resulting in a low molecular weight heparin product (MW 4-8 kDa). The resulting LMWHs also exhibit differences in both molecular and functional properties due to significant differences in the procedures used to prepare each LMWH. Initial attempts to standardize LMWHs based on their biologic and physiochemical properties have failed. Each LMWH has distinct properties which are largely dependent on the molecular composition. Each LMWH differs in its biochemical, physicochemical, clinical and pharmacological profile and thus these products are not equivalent. Each product is therefore individually developed for a given indication and the data from one product to the other is not interchangeable.

The depolymerization of heparin to prepare LMWHs can be accomplished by chemical, enzymatic, physical and radiochemical methods. The resulting LMWHs exhibit marked differences in their chemical and biological activities. This may be due to the procedure-induced structural differences and molecular
Low Molecular Weight Heparins: Basic and Applied Considerations

Different LMWHs show distinct chemical groups which make these agents distinguishable. As listed in Table 1, nadroparin, dalteparin, certoparin and reviparin all have a 2,5-anhydro-D-mannose at the reducing terminus whereas Enoxaparin and Tinzaparin have a 4,5-unsaturated uronic acid at the non-reducing end. These differences contribute to the uniqueness of each product. Additional structural differences in each product can also be found. However, such investigations may require knowledge of carbohydrate chemistry and advanced instrumentation.

Table 2 lists the currently available LMWHs along with the trade name and the manufacturer. Most of these LMWHs are sodium salts of depolymerized porcine mucosal heparin with the exception of, nadroparin which is a calcium salt. Each of LMWHs is designated by an international non-formulary name (INN) and a trade name. However, additional commercial names are also given to different LMWHs by various companies in different countries.

The LMWHs are usually characterized by their anti-Xa and anti-IIa potencies.

A comparison in the molecular weight, anti-Xa and anti-IIa potency and the ratio of Xa/IIa in the different LMWHs is shown in Table 3. Dalteparin has the highest median molecular weight and the highest anti-IIa activity whereas, clivarine has the lowest molecular weight and the lowest anti-IIa activity. The other LMWHs values are in between dalteparin and clivarine. While the anti-Xa and anti-IIa actions of LMWHs are usually designated for pharmaceutical characterization, this also reflects on the functional diversity in each LMWH.

The USP assay is usually employed for the potency evaluation of unfractionated heparins, however...
at high concentrations (>10 μg/ml) the LMWHs also show anticoagulant actions in the USP assay. The USP potency of several LMWH preparations compared to unfractionated heparin is shown in Figure 3. The USP activity is measured using a standard US Pharmacopeial coagulant method. As can be seen the USP activity of most LMWHs is lower than the unfractionated heparin, however each of these LMWHs exhibit a distinct USP potency which is largely dependent by the components (oligosaccharides). The molecular and structural features also contribute to the in vivo pharmacodynamic effects. Since the LMWHs are expected to be used in the surgical and interventional indications it is therefore recommended that these drugs should also be characterized in terms of their USP U/mg.

As LMWHs are usually administered in repeated dosages there is a possibility of these drugs to accumulate. The accumulation profile of each drug may also be product dependent. The effect of repeated administration of the various LMWHs on the AUC as measured by the anti-Xa and anti-IIa activity as shown on Figure 4. The AUC of the different LMWHs also varies. When the anti-Xa method is used, AUC is higher for Tinzaparin 5.4 on day 5, compared to the other LMWHs (range 3.0-4.6). If the anti-II method is used similar results are obtained for the AUC with the different LMWHs (Range 1.0-1.9). The bioavailability of each of these LMWHs is largely determined by the type of test used to quantitate the pharmacodynamic effects. Therefore the accumulation profile for each of these drugs may be different in the type of assay used. The bioavailability of each of these drugs also varies regardless of their in vitro potency.

To show the relative peak concentrations of different LMWHs, rats were administered with different LMWHs and heparin at a 1 mg/kg SC dosage. The LMWH concentration in terms of anti-Xa was measured. As shown in Figure 5 the different LMWHs showed different peak concentrations. In addition, the enoxaparin peaked at a later time point in comparison to the other LMWHs. Thus the pharmacokinetic and pharmacodynamic profile of each of the individual LMWHs differs widely and will translate into the clinical effects in specific indications.
It has been widely accepted that endogenous protein binding modulates the pharmacologic actions of unfractionated heparin. The variations in clinical response are attributed to the differential protein binding. Several pre-clinical and clinical studies have demonstrated the differences in the protein binding profile of heparin and LMWHs. However, Young and colleagues⁴ did not show any differences...
Fig. 5: Differential bioavailability of subcutaneously administered low molecular weight heparin and heparin. After a 1mg/kg subcutaneous dosage each of the low molecular weight heparin study exhibited better bioavailability than heparin. However there are significant differences in the relative bioavailability of each drug.

Fig. 6: Influence of protein binding on the anti-Xa activity of various low molecular weight heparins in normal and sick individuals. The binding is measured in terms of its influence on the anti-Xa activity. No difference are observed between the sick and normal individuals however different products bind differentially to plasma protein.


in the protein binding profile of heparin and different LMWHs in normal and sick patients. Fig. 6 describes the effect of plasma protein binding. Both at prophylactic and therapeutic dosages of different LMWHS, no effect was observed on the concentrations obtained by the anti-Xa method in plasma from normal versus sick patients.
In a study performed by Houbouyan the ED 80 for thrombin inhibition was calculated in terms of anti Xa and anti-IIa activities using chromogenic methods. The ED 80 for the different LMWHs ranged from 0.48 - 1.26 IU/ml for anti-Xa and 0.19-0.35 for the anti-IIa. Enoxaparin and nadroparin showed similar Xa/IIa ratios and dalteparin and tinzaparin showed similar ratios. This demonstrated the point that the different LMWHs are distinct drugs.

LMWHs are also capable of producing endogenous release of various substances such as tissue factor pathway inhibitor (TFPI) and von Willebrand Factor (vWF). It is expected that various LMWHs will produce differential release of these factors. The effects of various LMWHs on von Willebrand factor release in patients with unstable angina are shown in Figure 7. This data reported by Montalescot, demonstrates that enoxaparin releases less vWF in comparison to dalteparin or UFH, resulting in reduced platelet aggregation. Thus, each of the LMWHs produces somewhat different effects in terms of their effects on vascular function. The release of such substances has an impact on the overall effects of these agents. This is particularity true for LMWHs use in surgical and interventional indications.

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LMWHs have been previously reported to produce fibrinolytic effects. However, mechanism of this action is not known. It has been suggested that LMWHs may produce this effect by modulating the fibrinolytic process. Thrombin activatable fibrinolytic inhibitor (TAFI) is a carboxypeptidase U which produces a molecular change in fibrin. This modified fibrin is resistant to the lytic actions of plasmin. Fig. 8 depicts the activation of TAFI to TAFI a by the thrombin/thrombomodulin complex. LMWHs are capable of inhibiting thrombin and its generation. Accordingly, these agents can modulate the action of TAFI. The different LMWHs produce different effects on the activation of TAFI. It has also been demonstrated that agents with a high anti Xa/anti IIa ratio produce weaker inhibition in comparison to agents with a lower anti Xa/anti IIa ratio. This inhibition may play a role in the safety/efficacy of these drugs. Different LMWHs have different anti-Xa/IIa ratios. These agents are expected to modulate the thrombin mediated activation of TAFI at a different rate. Fig. 9 shows the effects of different LMWHs on the functional levels of TAFI expressed as the IC 50. Different LMWHs produce different effects of the activation of TAFI. Thus, the relative antithrombin activity of each of these LMWHs may be proportional to the inhibitory actions on TAFI activation. The profibrinolytic effects produced by different LWMHs may be determined by the composition of these agents. Thus, the bleeding
Complications and antithrombotic efficacy of these agents may be related to the modulation of TAFI. More recently LMWHs have undergone clinical trials in patients undergoing angioplasty. Marmur and colleagues have recently published on the successful ACT guided use of dalteparin in interventional cardiology. In this study dalteparin produced a significant increase in the ACT with a small degree of variance as compared to UFH. At 80 IU/kg dalteparin increased the ACT from 125 seconds to 195 seconds. Similarly, the APTT, Heptest time, anti-IIa activity and TFPI concentration were also increased. These authors concluded that the ACT and APTT are sensitive to intravenous dalteparin at clinically relevant doses. These data suggest that the ACT may be useful in monitoring the anticoagulant effect.
of intravenously administered dalteparin during PCI. Because of the different anti-Xa and anti-IIa actions, it should be emphasized that each LMWH will have its own specific dosage in the interventional cardiovascular indications. Enoxaparin and dalteparin have been used at various dosages in PCI. The comparative anticoagulant effects of various LMWHs as measured by the ACT in patients undergoing PCI is shown in Figure 10. At a comparative dosage of 100 U/kg IV of various LMWHs different levels of prolongation of the ACT were measured. Heparin exhibited the strongest prolongation in the ACT followed by dalteparin, certoparin and enoxaparin. Thus, the dosing of LMWHs in PCI can be guided by monitoring the ACT.

The effect of dalteparin on the APTT at two different dosages is depicted in Figure 11. Dalteparin was administered to patients undergoing PCI at a dosage of either 60 or 80 IU/kg IV. Blood samples were drawn at baseline, 5 min and 20 minutes post administration of dalteparin. This figure shows the prolongation of the APTT obtained in these patients. A dose response was observed in the APTT. This study suggested that the APTT can be used to monitor the anticoagulant effects of dalteparin at these dosages. This data also suggests the view that LMWHs can also be monitored by using the APTT test. In the same study the ACT was measured. As shown in Figure 12 the ACT increased from 125 seconds at baseline to >180 seconds after the administration of 80 IU/kg dalteparin. At the lower dosage the ACT was prolonged to 170 seconds. Thus, a dose response in the anticoagulant effects of these agents is demonstratable.

The comparative effects of heparin and enoxaparin in PCI as measured by the ACT is shown in Figure 13. As mentioned before, the prolongation of ACT was more pronounced in the heparin (10,000-12,500 U IV) treated patients in comparison to the enoxaparin (1 mg/kg IV) treated patients. However, there was a slight prolongation in the enoxaparin treated patients which increased to 190
Fig. 11: Comparative anticoagulant effects of dalteparin as measured by APTT in PCI. Patients were administered 60 and 80 units per kg of dalteparin. A dose dependent of the effect is evident.

Fig. 12: Comparative anticoagulant effects of dalteparin as measured by ACT in PCI. A dose dependent for the 60 units per kg and 80 units per kg is observed.

seconds. The patients treated with enoxaparin remained anticoagulated throughout the procedure. While the initial anticoagulant effects of a drug may be stronger, it is likely that the duration of this action may be shorter.

In the same study the APTT was measured in the plasma of these patients. As shown in the Figure 14 heparin treated patients showed a greater prolongation in the APTT in comparison to the enoxaparin treated patients. The APTT value five minutes post administration of enoxaparin was > 100 seconds. As seen in the previous study using dalteparin the APTT can be used at these dosages to monitor the effects of LMWHs. This data suggests that the duration of effects is also dependent on the assay
Fig. 13: Comparative anticoagulant effects of unfractionated heparin and enoxaparin in PCI as measured by ACT. Heparin produced a much stronger effect than enoxaparin.

Fig. 14: Comparative anticoagulant effect of heparin and enoxaparin in percutaneous intervention as measured by APTT. The relative anticoagulant effect of heparin in this test is much stronger than enoxaparin.

The pharmacokinetics of various LMWHs in terms of biologic T1/2 as measured by employing the anti-Xa and anti-IIa methods during PCI is depicted in Figure 15. The half-life of the different LMWHs ranged from 2.3-3.4 depending on the LMWH and the method used to determine half life. Enoxaparin has the longest high life in comparison to certoparin and dalteparin. Once again the half-life of this agent is largely dependent on the type of test used.

Besides the half-life, other pharmacokinetic parameters are also equally modulated by individual LMWHs. Each of the LMWHs produces distinct effects and may therefore exhibit different profiles. As seen in the Figure 16 the different LMWHs gave different clearance rates. Enoxaparin had the highest clearance rate followed by dalteparin and certoparin. Therefore, the dosing of various LMWHs in interventional cardiology will require individual optimization studies.
One of the drawbacks in the use of LMWHs is that there is no effective antidote to neutralize their effects. Protamine sulfate is only partially effective in the neutralization of LMWHs. More recently, it has been reported that heparinase-1 can neutralize the effects of LMWHs. The digestion of tinzaparin by heparinase-I is depicted in the Figure 17. Heparinase is an enzyme produced by Flavobacterium heparinum. It has been used in several clinical trials. It is capable of digesting tinzaparin to form lower molecular weight components with a molecular weight in the range of 2200 daltons. Heparinase is capable of digesting various LMWHs and reducing their anticoagulant actions. This depolymerization is product dependent and the results show marked variations from one compound to the next. The biologic activities of the resulting products are also different.

This data also points out that different LMWHs are differentially digested by heparinase-1.

Figure 18 shows the heparinase digestion of sodium unfractionated heparin (UFH-Na). Heparinase digests UFH and converts it into small molecular weight oligosaccharides. Note the fingerprinting of the digested material. In contrast to heparin, the relative digestion of various LMWHs to heparinase exhibits different profiles. The heparinase digestion of tinzaparin is shown in Figure 19. In comparison to UFH, the fingerprinting of the oligosaccharide profile is quite different. This clearly suggests that endogenously different LMWHs give rise to different oligosaccharide components. Thus, each LMWH may be digested differentially by endogenous heparinases. Therefore, the overall pharmacologic action...
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The effect of heparinase-I on the interventional dosage of dalteparin as measured by the Heptest is described in Figure 20. Patients undergoing PCI were treated with 40, 60 or 80 U/kg of dalteparin after heparinase administration the dalteparin activity as measured by heptest is completely abolished. This suggests that heparinase is capable of digesting dalteparin. The relative effect of this digestion by heparinase on bleeding and the adverse reaction require clinical validation.

While heparinase may be a useful neutralizing agent for the heparins, several safety issues have been raised in clinical trials. More recently, a phase III clinical trial in Switzerland was stopped due to bleeding and other complications. Earlier studies in cardiopulmonary bypass surgery have also resulted in similar concerns. This may be a dosing problem. Therefore, a dose finding study prior to the clinical trial of LMWHs may be dependent on endogenous liver catabolism by heparinase like enzymes.

Interventional and surgical dosages of LMWHs can also be neutralized by heparinase-1. The effect of heparinase-I on the interventional dosage of dalteparin as measured by the Heptest is described in Figure 20. Patients undergoing PCI were treated with 40, 60 or 80 U/kg of dalteparin after heparinase administration the dalteparin activity as measured by heptest is completely abolished. This suggests that heparinase is capable of digesting dalteparin. The relative effect of this digestion by heparinase on bleeding and the adverse reaction require clinical validation.

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Although heparin is still the drug of choice for parental anticoagulant therapy, the current data indicates that the LMWHs are also capable of producing adequate anticoagulation and antithrombotic effects. Several clinical trials have been completed. At the higher dosages these drugs can be used for interventional purposes however, major differences in different products are noted. The following are the current perspectives in parenteral anticoagulant therapy.

- LMWHs are currently evaluated for surgical and interventional indications.
- Antithrombin drugs are being developed for surgical and interventional use. However unlike...
heparin there is no antidote for their neutralization.

- Anti-Xa drugs are being developed for various parental indications. Similar to antithrombin drugs there is no antidote for the neutralization of these agents
- Major differences in the anticoagulant effects are observed among different LMWHs. Therefore each drug may produce differential dosing and neutralization approaches.

Based on the published data on the differential behavior of currently available LMWHs it is clear that each of these drugs is distinct.\(^5\)-\(^13\) Upon reviewing the pre-clinical and clinical data, several regulatory and professional agencies have classified these agents as distinct drugs. The American College of Chest Physicians clearly recommended that LMWHs are different and should not be interchanged. According to ACCP guidelines, the results of the clinical trials on LMWHs conducted cannot be generalized to other LMWHs. Thus, the current data on the use of enoxaparin in cardiology is product specific and should only pertain to enoxaparin. The International Cardiology Forum also has the same opinion and in conclusion the ICF has clearly stated that these compounds should be considered as distinct therapeutic agents. Similarly, the American College of Cardiology and American Heart Association have recommended that each drug must be considered individually rather than as members of the interchangeable compounds.

Several other National and International regulatory agencies along with professional societies have clearly classified LMWHs as distinct drugs. The US FDA has clearly mandated that individual LMWHs cannot be used as interchangeably with one another.\(^14\) According to FDA guidelines LMWHs cannot be used interchangeably, unit for unit, with heparin, nor can one individual LMWH be used interchangeably with another.

The clinical differentiation of LMWHs has been demonstrated in the DVT prophylaxis and treatment for acute coronary syndromes.\(^15\)-\(^17\) For example the dosage of enoxaparin and dalteparin are different for the Acute Coronary Syndrome.\(^18\),\(^19\) Additional data on the clinical differentiation of each of these individual LMWHs are continuously becoming available.

At a higher dosage such as in the surgical use, percutaneous intervention and cancer studies, the LMWHs exhibit wide variations in their anticoagulant profile. Similarly, thrombotic stroke and combination treatment protocols have shown the individual effects of LMWHs. It should therefore be emphasized that these drugs cannot be interchanged. In the event interchange is carried out, safety and efficacy compromise may be observed risking patients’ welfare.

As shown in Figure 21, using the depolymerization process LMWH, ultra-LMWH, heparin-derived oligosaccharides such as pentasaccharides can be prepared. These agents show a progressive change in the anti-Xa and anti-IIa ratio. Therefore, at equivalent anti-Xa activities these agents exhibit marked differences. It is therefore recommended that these agents should not be considered similar regardless of potency adjustment. Since most of the commercially available LMWHs are produced by patented manufacturing processes, the resulting products exhibit individual characterization unique to a particular brand of the LMWH. Thus, utilizing patented processes, specific LMWHs can be produced within regulatory guidelines. In addition, generic versions of branded LMWHs can be produced after the expiration of patents. It is important that these generic versions exhibit the same biologic and clinical characterizations.

While some of the questions on the differentiation of LMWHs have been adequately answered. There may be specific differences, which remain unclear at this time. Regardless of this we know the sites of actions of these drugs which contribute to their anticoagulant and antithrombotic actions. However, the mechanisms for the additional actions such as the anti-inflammatory effects, anti-cancer effects and other regulatory actions remain unclear at this time. Some of these issues have been currently debated in reference to the uniqueness of the commercial product and the claim that the generic version of LMWHs are not the same as the innovative product.
If a generic version of a branded product is made it should use exactly the same process patent and must exhibit physical, chemical, biological and clinical equivalence. Therefore, it is very important to make sure a generic product has similar profile as the branded product. More importantly with out regulatory approval a generic product should not be considered for clinical usage.

A recent, communication by Drs. Leong and Hoppensteadt has addressed several important issues on the possible introduction of generic forms of low molecular weight heparins (LMWHs). The authors have convincingly argued in favor of the development of the generic version of LMWHs and have cited certain examples in the light of current guidelines by the US FDA. The authors have focused on the equivalence criteria by which the potential manufacturers of generic versions of LMWHs are required to adhere to demonstrate clinical and biologic equivalence of the generic products. They have also commented on the non-requirement for clinical trials of the generic product as the regulatory agency stipulates that a generic drug produced by exactly the same patent/manufacturing conditions is expected to behave similarly as the branded drug. While this may be true for synthetic drugs such as warfarin and clopidogrel, it will require additional review and discussions in the case of complex mucopolysaccharide derived agents such as the LMWHs.

Considering the current awareness of the escalating cost of medications, it is more than likely that the generic versions of LMWHs will eventually become available for clinical use in the western countries. Recently two companies have already filed an Abbreviated New Drug Application (ANDA) for generic versions of enoxaparin. Several other companies are in the process of filing for approval from the regulatory agencies to allow marketing of generic versions of LMWHs. On June 26th the US FDA accepted the application for a generic version of Aventis’ enoxaparin (Lovenox®) from Amphastar, Inc. (USA) who filed a certification against one of two patents for enoxaparin. However, the US FDA cannot approve the generic version before the drug’s second patent expires December 24, 2004. Teva Pharmaceutical (USA), submitted an ANDA against the same enoxaparin patent on June 30, 2003. Gland Pharma (India) introduced the Cutenox brand of generic enoxaparin in India. The same generic version of enoxaparin is also available in Brazil. Several other companies throughout the world are

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**Fig. 21:** A diagrammatic illustration of the manufacturing processes for low molecular weight heparins and their derivatives. Both the chemical and enzymatic depolymerization result in a progress depolymerization of heparins eventually leading to heparin derived oligosaccharides. If the depolymerization is exhaustive it may result in the degeneration heparin derived di-saccharides the tri-saccharides.
considering the development of generic versions of the branded LMWHs. It is, therefore, important to have specific guidelines for the acceptance of generic LMWHs.

Because of the complex nature of LMWHs, one should question the adequacy of the current requirements for acceptance of these drugs, be it an original or a generic, by the regulatory agencies. To demonstrate the similarities and differences among various LMWH products, several systematic approaches have been developed. We recommend, that in the case of generic LMWHs, the regulatory bodies have to reconsider their criteria for accepting a generic equivalent. The following lists some of the basic requirements for characterizing a LMWH, which should be employed in determining approval of a product as a true generic:

1. Physicochemical equivalence
2. Biological equivalence
3. Pharmacologic and toxicologic equivalence
4. Dosage (for both clinical safety and efficacy) equivalence

Besides the physicochemical and biologic equivalence, a generic equivalent of a branded drug should also exhibit pharmacologic and toxicologic equivalence at the dosage stipulated in Phase I or equivalent clinical trials. All studies should be carried out over a dosage range where the branded drug will be used.

Various regulatory agencies such as the FDA, EMEA and WHO consider each of the LMWHs to be a distinct drug. However, these agencies only consider molecular weight profile and anti-Xa/anti-IIa potency which may not be adequate for the demonstration of generic product equivalence to the branded product. The branded LMWHs are only partially characterized if these limited specifications are used. A generic version of a brand named LMWH must be manufactured by exactly the same process as the original drug, but must, in addition, exhibit physical, chemical, biological and clinical equivalence.

It is well known that each of the branded LMWHs exhibits product specific pharmacodynamic and pharmacokinetic differences. Such data as the molecular weight distribution of the components, structural characteristics, interactions with endogenous proteins, biologic actions such as the anti-Xa and anti-IIa, and other specific actions should also be identical. Physicochemical methods such as NMR, as well as oligosaccharide profiling such as the structural distribution of various components and heparinase digestion signature profile can be used to prove the identity of a generic drug.

Current regulatory requirements do not consider all of these specifications, making it very likely that a generic product would not behave in a similar fashion as the original drug if the required characterization is not undertaken. Generic versions of each branded product can be manufactured utilizing methodology described in each of the individual patents of the branded products. However, certain specific differences may still exist which can only be demonstrated in biologic assays and dosage optimization study in clinical trials.

Initially wide lot to lot variations were observed between batches of the same branded product. It is expected that the generic equivalent agents may also exhibit similar variations. The impact of these batch variations on each product should be documented on the clinical outcome. Some regulatory stipulations on the batch to batch variations should also be addressed.

At the present time, there are no specific guidelines for the assessment of generic equivalent LMWHs. The existing guidelines from the Bureau of Generic Drugs may not be adequate for generic LMWHs. Because LMWHs represent a hybrid drug product between biologic and chemical entities, there is a need for developing specific guidelines for the acceptance of individual generic versions of branded LMWHs.

The regulatory bodies eventually may allow the generic versions of LMWHs and apply the same or
expanded guidelines as for other biologicals. This may result in generic products which will meet these specifications, but in fact they may not be the same, and may therefore behave differently in clinical settings. It is important, therefore, to have additional requirements to provide supplementary chemical and biological data to support the filing of a generic version of a branded drug. Clinical trials may or may not be required for specific products for approved indications depending upon the filing process to evaluate data for the FDA review.

The generic pharmaceutical industry has played a key role in providing cheaper equivalents of original branded drugs for patients which would not have been otherwise accessible to a large group of patients. Thus, the generic drugs have a major public health importance. Recognizing this, President Bush has already announced the expansion of the Office of Generic Drugs. Thus, at a Federal Government level there is endorsement of the development of generic drugs and to have them accessible to all patients.

On August 30th in a landmark decision the World Trade Organization agreed to let impoverished nations import cheap copies of patented medicines needed to fight killer diseases. While the idea for allowing the African countries to import generic versions of anti-Aid medication was approved, the World Trade Organization board debated over an accompanying statement meant to address some pharmaceutical companies concerns on the exploitation of their patents. The proponents of this move issued a joint statement indicating that the non-availability of these drugs has continued to add to the unnecessary fatalities in excess of 10,000 deaths.

Thus, there is a global pressure to make innovative drugs generic versions at a reduced cost. However, some regulatory guidelines should be implanted to adjust the operational cost and compensation to the companies in the event a generic version of a branded product is introduced due to the expiration of the patent.

In the case of generic versions of the LMWHs, it is clear that the manufacturers of the generic versions may not have adequate expertise to compare these different LMWHs in refined methods to assure clinical, biologic and pharmacologic equivalence. Such studies should be carried out by independent research groups following establishment of specific guidelines.

It is now widely agreed that the introduction of generic versions of LMWHs will be approved in the near future. However, it is important that the generic products should be manufactured in strict compliance with the manufacturing specification of the branded product. Furthermore, regulatory agencies should require additional data on the chemical biological, pharmacologic/toxicologic and dose response relationship in specific settings.

The heparins not only differ substantially in their pharmacodynamics but also in pharmacokinetics. The difficulty in assaying heparins poses another problem, since the assays aimed at assessing the pharmacokinetics of UFH or LMWH are based on pharmacodynamic effects such as anti-Xa or anti-IIa activity, rather than direct detection of the molecular species involved. The anti-Xa and anti-IIa activities of UFH correlate well with the concentrations of UFH molecules. However, with enoxaparin the anti-Xa activity persis for longer than the enoxaparin molecules are detectable. In one study the anti-Xa activity of enoxaparin persisted for days after discontinuation of subcutaneous enoxaparin administered at a dose of 40mg/day when compared to the very weak anti-IIa activity during the seven day treatment period. Enoxaparin is linearly absorbed after subcutaneous administration, with peak activity (Amax) occurring at 2.5-4 hours (tmax). A close relationship has also been shown to exist between the dose of enoxaparin administered subcutaneously and anti-Xa Amax as measured in plasma using a standardised amidolytic anti-Xa method. LMWHs are easily absorbed from subcutaneous tissue and have a lower tendency to bind to endothelial cells. Following the administration of enoxaparin at a dose of 40 mg, more than twice as many heparin molecules of sufficiently high molecular weight to inhibit thrombin were bioavailable than after UFH 5000IU,
despite the presence of more than twice the amount of such heparin molecules in the UFH injection. Several studies have shown LMWHs to have greater bioavailability when compared to unfractionated heparin. However, there are significant differences observed among LMWHs following subcutaneous administration. The bioavailability of anti-Xa activity varies from 87% with dalteparin to 98% for nadroparin. Bioavailabilities of other LMWHs range from 90% to 98% (90% for tinzaparin, >90% for parnaparin and ardeparin). For anti-Xa activity, enoxaparin (40mg (4000IU) has an area under the concentration time curve (AUC) of about 3.5 IU •h/ml, compared with 3.2 IU •h/ml for dalteparin 5000 IU, 1.35 IU •h/ml for tinzaparin 50 IU/kg and 1.33 IU •h/ml for UFH 5000IU. Although the clinical significance is not known, the AUC values for anti-Xa activity are greater than those for anti-II activity. Although laboratory monitoring is required due to high variability in effect following UFH administration, the variability with enoxaparin is lower than UFH. The absorption rate of different LMWHs differs in terms of maximal concentration (Cmax) and may or may not be related to bioavailability which is measurable in terms of AUC. Wide variations in the absorption rate and bioavailability profile are observed with UFH; however with a given LMWH such as enoxaparin both the absorption rate and bioavailability patterns are consistent and predictable.

The apparent volume of distribution (Vd) of the anti-Xa activity of enoxaparin and other LMWHs following subcutaneous injection is close to plasma or blood volume. The Vd of enoxaparin (5.3L) has been shown to be significantly lower than those of dalteparin (7.7 L) and nadroparin (6.8L). Significant differences have also been reported for mean residence times (MRTs). Both enoxaparin and nadroparin exhibit significantly longer MRTs (mean 7 hours) than dalteparin (mean about 5.3 hours).

UFH and LMWHs are metabolized by depolymerization and desulfation. After getting degraded by the liver they are eliminated by the kidneys in forms retaining their biological activity. The clearance of enoxaparin and other LMWHs does not change as a function of administered dose, unlike that of UFH, which is dose dependent. This may be attributed to the lower cellular uptake of LMWHs when compared to UFH. The average apparent total body clearance of enoxaparin has been shown to be lower than that of UFH and further differences have also been observed between enoxaparin, dalteparin and nadroparin. In a comparative study between enoxaparin 20mg and 40mg (equivalent to 2000IU and 4000IU of anti-Xa activity), dalteparin 2500IU (equivalent to 2500IU and anti-Xa activity) and nadroparin 7500ICU (equivalent to 3075IU anti-Xa activity) injected subcutaneously, the average apparent total body clearance of enoxaparin was 1.56 ml/min which was significantly lower than that of dalteparin (33ml/min) and nadroparin (21.4 ml/min). Dalteparin is therefore cleared from the body more rapidly than nadroparin and enoxaparin.

The use of LMWHs has been studied in young and old patients. Its safety has been investigated in a group of very elderly patients (over 80 years, mean age 84) with unstable coronary artery disease. Ninety-eight such patients were randomized to treatment with enoxaparin (1.0 mg/kg SC twice daily) or UFH (1000 IU/h as a continuous IV infusion) for 7 days. There were no significant differences between the groups in the rate of bleeding, cardiac death, angina pectoris, or changes in electrocardiogram. This study shows that no obvious adverse events were observed in the elderly patients recruited in this study. An open study in children receiving enoxaparin for a variety of indications showed that a therapeutic anti-Xa activity could generally be obtained after a SC dose of 1.0 mg/kg twice daily. However, newborn infants (under 2 months old) required a mean dose of 1.6 mg/kg twice daily. The open design of the trial made it difficult to assess the safety of enoxaparin precisely in this population, but no obvious limitations on the safety of enoxaparin were observed. Interestingly, a study in 19 children (aged 18 days to 19 years) showed that a starting dose of 1.0 mg/kg SC enoxaparin twice daily achieved the adult therapeutic target anti-Xa activities. These results, however, should be confirmed owing to the small number of patients in the study population.
Major randomized controlled trials support the use of LMWH as an alternative to UFH in the management of Non-ST-segment elevation myocardial infarction. The FRIC (Fragmin in Unstable Coronary Artery Disease, dalteparin) and FRAXIS (Fraxiparin Versus Unfractionated Heparin in Acute Coronary Syndrome, nadroparin) trial results showed equivalence of LMWH with UFH. The ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) study and the TIMI 11B (Thrombolysis in Myocardial Infarction) study showed a significant reduction in the composite end points of death, myocardial infarction and recurrent angina leading to revascularization in patients with unstable angina or non-Q-wave-MI with enoxaparin versus UFH. The Global registry of Acute Coronary Events (GRACE) is a large prospective study of patients hospitalized with ACS. The GRACE study has been launched to improve the quality of care of patients with ACS by providing information about differences or relationships between patient characteristics, treatment practices and hospital outcomes. In the current GRACE report, the use of LMWH and UFH was analyzed in 13,231 ACS patients. The results reveal that younger patients (<60 years) receiving antiplatelet therapy, beta-blockers, ACE inhibitors, patients admitted to hospitals with PCI facilities and patients undergoing invasive procedures received UFH or both UFH and LMWH than LMWH alone (80.1% enoxaparin, 19.9% other LMWH). After adjusting for covariables, the use of LMWH was associated with a 37% lower risk of mortality (p=0.009) and 55% lower bleeding rates (P<0.0001) across all ACS categories and similar results were found in STEMI and UA/NSTEMI subgroups. One of the limitations of the current study is that 80% of patients received enoxaparin and it is cautioned that the results may not be generalized to all LMWHs.

This caution is perhaps due to the fact that LMWHs are different entities. Predictable pharmacodynamic effects after dosing with LMWHs are encouraging and clinical experience has been promising. Two recent trials of enoxaparin in acute coronary syndromes have shown that the theoretical advantages of enoxaparin are indeed realized in terms of important clinical outcomes. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial compared enoxaparin with UFH in 3171 patients with angina at rest or non-Q-wave myocardial infarction. The risk of death, myocardial infarction or recurrent angina was significantly lower in the enoxaparin group at 14 days (16.6 vs 19.8%, p = 0.019) and at 30 days (19.8 vs 23.3%, p = 0.016), an effect which was maintained until 1 year after initial treatment. The Thrombolysis In Myocardial Infarction (TIMI) 11B trial included 3910 patients with unstable angina or non-Q-wave myocardial infarction, who were treated with either UFH or enoxaparin. The primary endpoint was death, myocardial infarction or urgent revascularization in the first 8 days of treatment, which was significantly more common in the UFH group than in the enoxaparin group (14.5 vs 12.4%, p = 0.048). Other LMWHs (nadroparin and dalteparin) have also been compared to UFH in unstable angina patients. The results of the major clinical trials have shown that nadroparin and dalteparin are equivalent in terms of efficacy to UFH. Although there are no trials between enoxaparin, nadroparin and dalteparin, the encouraging findings of the ESSENCE and TIMI 11B trials support the use of enoxaparin in unstable angina patients. These findings are further supported by a recent head-to-head trial between enoxaparin and tinzaparin in 438 patients with unstable angina or non-Q-wave myocardial infarction, which showed that antithrombotic treatment with enoxaparin for 7 days was more effective than tinzaparin at reducing the incidence of recurrent angina in the early phase, and significantly reduced the need for revascularization at 30 days.

Some recent trials in patients undergoing percutaneous coronary interventions have confirmed that enoxaparin is effective. The ENoxaparin and TICLopidine after Elective Stenting (ENTICES) trial compared a combination of enoxaparin, aspirin and ticlopidine with UFH, dipyridamole and warfarin in patients who had undergone coronary stenting. The composite endpoint of death, myocardial infarction, stent thrombosis, coronary artery bypass graft and repeat percutaneous transluminal coronary angioplasty at 30 days was significantly lower in the enoxaparin group (4 of 79 patients) than
in the UFH group (9 of 44 patients). The National Investigators Collaborating on Enoxaparin 1 and 4 (NICE-1 and NICE-4) trials treated patients undergoing percutaneous coronary interventions with enoxaparin alone (NICE-1) or in combination with abciximab (NICE-4). Both trials were open label. The incidence of major non-coronary artery bypass graft-related bleeding was 0.5% of 828 patients in the NICE-1 trial, and was only 0.2% of 818 patients in the NICE-4 trial. There seemed to be a synergistic effect of enoxaparin and abciximab, the combination being more effective than either drug alone.

As an illustration of the differences that can occur between LMWHs, enoxaparin 40 mg once daily has been compared with UFH 5000 IU three times a day as prophylaxis against venous thrombosis in patients undergoing hip surgery. The incidence of deep-vein thrombosis was 25% in a group of 113 patients receiving UFH, and 12.5% in a group of 124 patients receiving enoxaparin (p = 0.03). This is an important benefit for enoxaparin, particularly in view of the more convenient dosing regimen. In contrast, a trial with a similar design that compared nadroparin with UFH found very similar rates of deep-vein thrombosis in both treatment groups (33% of 137 nadroparin patients vs 34% of 136 UFH patients). This clearly cannot be regarded as a direct comparison of enoxaparin with nadroparin in this indication, but it does appear that LMWHs have the advantage over UFH of reducing the incidence of deep-vein thrombosis, while nadroparin does not.

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