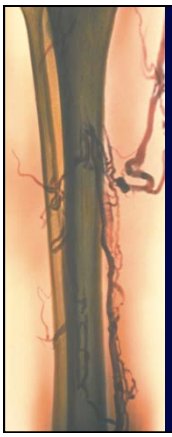


Thromboprophylaxis - where do we stand?

Dr. Badri Paudel
GMC

Objectives

- Rationale for thromboprophylaxis
- Lessons from surgical patients
- Realizing the benefits of thromboprophylaxis for medical patients
- Impact of thromboprophylaxis on outcome

Rationale for Thromboprophylaxis

Natural history of VTE → Fatal disease

↓

Characteristics of risk population

↓

Incidence sufficient to warrant routine thromboprophylaxis

↓

Thromboprophylaxis effective in major clinical outcomes

Why is prophylaxis under-used?

- Clinicians are unaware of the level of VTE risk
- Heterogeneous population
- Perceived difficulties in risk assessment
- Few studies of prophylaxis
  - **poorly defined patient populations**
  - **different methods of DVT diagnosis/outcome definition**

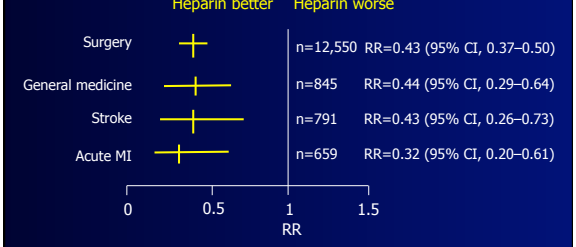
Risk of DVT in the Absence of Thromboprophylaxis

Patients	% at risk
General medical[1,2]	10–26
Stroke[3]	11–75
Myocardial infarction[3]	17–34
Spinal cord injury[3]	6–100
Congestive heart failure[4]	20–40
Medical intensive care[1,5,6]	29–44

[1]Cade JF. *Crit Care Med* 1982;10:448–50; [2]Belch JJ et al. *Scott Med J* 1981;26:115–7
[3]*Int Angiol* 1997;16:3–38; [4]Anderson DR et al. *Am Heart J* 1950;39:697–702
[5]Dekker A et al. *Thromb Haemost* 1991;65:1348 [abstract]; [6]Hirsch DR et al. *JAMA* 1995;274:335–7

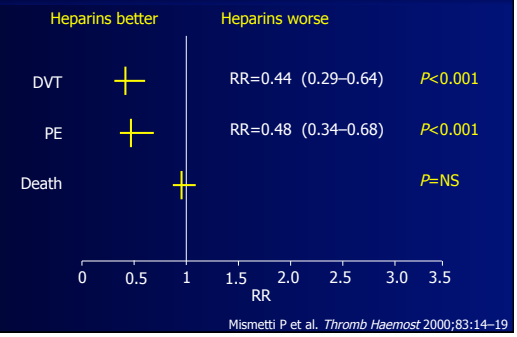
Prophylaxis of VTE in Medical Patients

RR of DVT in studies comparing heparins with no treatment



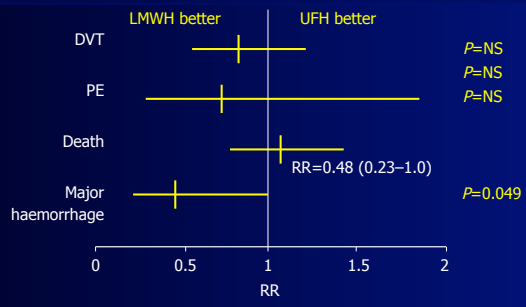
CI, confidence interval; MI, myocardial infarction

Thromboprophylaxis in Medical Patients: Heparins (UFH and LMWH) versus Control

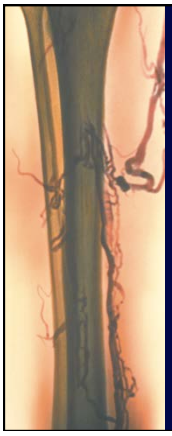


Mismetti P et al. *Thromb Haemost* 2000;83:14–19

Thromboprophylaxis in Medical Patients: LMWH versus UFH



Mismetti P et al. *Thromb Haemost* 2000;83:14–19



Is VTE rare in Asian Patients?

VTE Incidence in Asia Autopsy studies

The incidence of fatal and non-fatal PE found at autopsy is close to that observed in Western countries

There is an increasing rate of PE over time in Asian countries

Incidence of VTE in Indian Patients

- Autopsy data at PGIMER,Chandigarh to establish the incidence of Pulmonary Thromboembolism (PTE).*
- Retrospective data at Sri Ramachandra Medical College and Research Institute, Chennai.
- PROVE : Prospective Registry on Venous Thromboembolism

Autopsy Data, PGIMER, Chandigarh

Aim

- To evaluate incidence of PTE in Adult autopsy cases at PGIMER, Chandigarh, India

Method

- 1000 consecutive Adult Autopsy Cases between years 1997-2002 were studied
- Mean age – 37.8 years (14-72 years)
- Male preponderance in the ratio of 1.82 : 1

Autopsy Data, PGIMER, Chandigarh

The underlying risk factors in patients who died of PTE (14.4%) were analyzed and recorded.

Most common underlying conditions	%
Sepsis	40.28
Respiratory Illness	10.42
Cardiovascular disorders	6.94
Malignancies	9.72
Renal disease	8.33
Hepatobiliary disease	7.46
GIT Disease	3.47
Vasculitis	2.78
Miscellaneous	10.42

Data yet to be published

Autopsy Data, PGIMER, Chandigarh

Key Findings of the study

- 14.4% of hospital death showed evidence of PTE at Autopsy
- Clinical suspicion was present in only 29.7% of cases
- Fatal PE formed 14.58 % of all PTE (i.e. 1.45% of all hospital deaths)
- Almost all cases were Medical patients

Data yet to be published

Retrospective Clinical Data: SRMC, Chennai

Method

- The case records of all patients who had diagnosis of DVT during last 18 months were studied.
- DVT was suspected on history, clinical examination and Doppler study findings in all patients.
- Diagnosis was confirmed by Ascending venogram or colour duplex scan.

Indian Journal of Surgery, Vol.63. No.2,2001

Retrospective Clinical Data: SRMC, Chennai

The study recorded the common underlying risk factors for DVT for all the confirmed cases of DVT.

Associated Risk Factors for DVT

- Immobilization : 32.5%
- Post.Operative : 20.9%
- Varicose Veins : 20.9%
- Trauma : 11.6%
- Others : 35.6%

Most common associated risk factor was Immobilization, followed by post –operative period and varicose veins.

Indian Journal of Surgery, Vol.63. No.2,2001

Retrospective Clinical Data: SRMC, Chennai

Results

- No. of Surgical OPD Patients (In 18 Months) : 23,962
- Confirmed DVT : 43
- Overall Incidence : 1.79 per 1000
- Incidence in western world : 2 - 5 per 1000*

The Overall Incidence of DVT in Indian patients was found to be comparable to that in Western world.

Indian Journal of Surgery, Vol.63. No.2,2001
Bergquist et al,BJS,1985; 72

The SMART Study

Surgical Multinational Asian Registry in Thrombosis

SMART

Prospective, international, multicenter, observational study of a cohort of consecutive Asian patients undergoing major lower limb orthopedic surgery

*The first large prospective international multicenter observational study on the rate of **symptomatic VTE** in a large cohort of Asian patients undergoing major orthopedic surgery **without thromboprophylaxis***

SMART Study Design

- Observational study of a cohort of 2,400 consecutive Asian patients undergoing major orthopedic surgery.
- 11 participating countries: ***Bangladesh, Hong Kong, India, Indonesia, Korea, Malaysia, Pakistan, Philippines, Singapore, Taiwan and Thailand,***
- 39 centers
- Recruitment period: 15 months
- Follow-up: 1 month after surgery

Incidence of Symptomatic VTE at Discharge (or End of Prophylaxis)

	VTE	DVT	PE	Fatal PE
SMART Investigators (n=2432)	1.9%	1.8%	0.3%	0.4%
Samama 1997 (n=85, THR, no prophylaxis)	1.2%	1.2%	0	0
Douketis 2002 (n=6089, short-term prophylaxis, THR/TKR)	1.1%	?	?	0.04%
Turpie 2002 (n=7211, short-term prophylaxis, THR/TKR/HFS)	0.5%	0.3%	0.2%	0.1%

Samama CM et al. Br J Anaesth 1997;78:660-5
Douketis JD et al. Arch Intern Med 2002;162:1465-71
Turpie AGG et al. Arch Intern Med 2002;162:1833-40

VTE Rates at One-month Follow-up

A rate of symptomatic VTE at one-month follow-up consistent with that observed in the West

Incidence of Symptomatic VTE at Follow-up

	VTE All
SMART CEC (n=2432, THR/TKR/HFS, 1 month)	1.5%
SMART Investigators (n=2432, THR/TKR/HFS, 1 month)	2.8%
Mohr 1992 (n=173, THR/TKR, no prophylaxis, 3 months)	2.3%
Warwick 1995 (n=1162, THR, no prophylaxis, 6 months)	3.4%
Eikelboom 2001 (n=1744, THR/TKR, short-term prophylaxis, 1 month)	3.3%

Mohr DN et al. Mayo Clin Proc 1992;67:861-70
Warwick D et al. J Bone Joint Surg Br 1995;77-B:6-10
Eikelboom JW et al. Lancet 2001;358:9-15

Risk Factors for VTE in SMART Consistent with those found in Western Patients

Potential predictive factors	Odds Ratio	95% CI	p
History of VTE	26.9	2.9 – 250.7	0.004
Chronic heart failure	5.1	1.5 – 17.9	0.011
Varicose veins	3.6	1.2 – 10.6	0.024

The following factors were entered into the model: age, personal or familial history of VTE, history of cancer or currently active cancer, varicose veins, and chronic heart failure

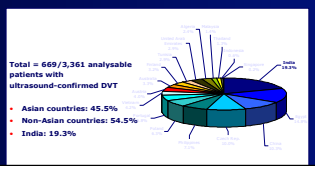
VTE Rates in SMART

The rate of symptomatic VTE at discharge (CEC or Investigators) is similar to that observed in the West

PROVE
Prospective Registry On Venous thrombotic Events

PROVE REGISTRY

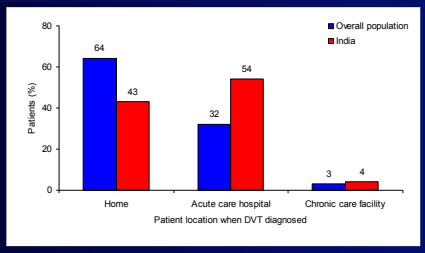
- A Multi-national, multicentre observational study involving 254 centers in 19 countries.
- Consecutive patients with ultrasound confirmed DVT were enrolled.
- Data from patients in INDIA was compared with the overall PROVE population.
- Of the 3526 patients enrolled in the registry, 667 (19%) were from INDIA.



PROVE RESULTS

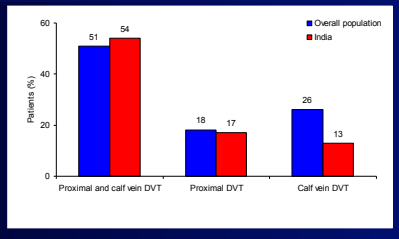
Presented at ISTH, 2005
Sydney , Australia

Patient status when DVT was diagnosed



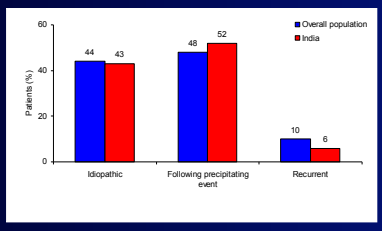
Majority of overall population was at home when they developed DVT, while most of the INDIAN patients were in Acute Care facility.

Location of DVT



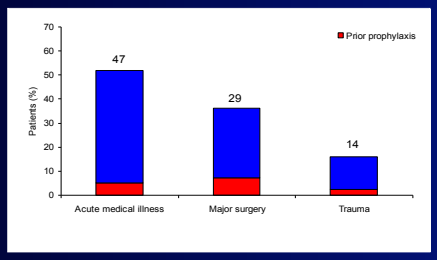
Fewer patients in INDIA were diagnosed with a Calf vein thrombosis alone compared with the overall population.

Type of DVT



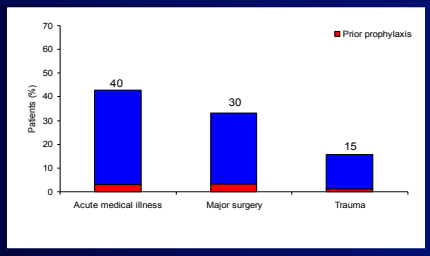
Similar proportions of patients in INDIA and overall population were diagnosed with Idiopathic DVT, DVT following a precipitating event, or recurrent DVT

Precipitating Events for DVT and Prior Prophylaxis (OVERALL PROVE POPULATION)



19% of the overall population received prior Prophylaxis

Precipitating Events for DVT and Prior Prophylaxis (INDIA)



Only 7% of Indian patients received Prior Prophylaxis

Is VTE rare in Asian Patients?

- About 1 in 1000 individuals are affected with VTE in US.
- >2 lakhs new cases of VTE/year in US The incidence of VTE is not low in India
- The trends shows an increase over time
- The use of prophylaxis should therefore be considered in all high risk patients.
- Incidence of DVT in Indian populations varies7.8-28%.

DVT : Suspecting the Diagnosis...

...are risk factors present?

The presence of risk factors is a clue that VTE may develop or that it may *already* be present

VTE Risk Stratification

Patient Factors: Clinical

- Previous VTE
- Malignancy
- Advancing age
- Obesity
- Prolonged immobility
- Trauma
- Surgery
- Pregnancy/ postpartum
- Indwelling central venous catheter
- Medical illness
  - stroke
  - MI
  - CHF
  - pneumonia
  - COPD
  - infections
  - nephrotic syndrome
  - inflammatory bowel disease
- Oral contraceptives
- Varicose veins

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction

Geerts WH et al. *Chest* 2001;119;132S–75S.

VTE Risk Stratification
Patient Factors: Molecular

Inherited

- Deficiency of antithrombin III, protein C, protein S, heparin cofactor II
- Activated protein C resistance (factor V Leiden)
- Prothrombin G20210A mutation
- Hyperhomocysteinemia
- Other

Acquired

- Myeloproliferative disease
- Hyperhomocysteinemia
- Antiphospholipid antibodies
  - lupus anticoagulant
  - anticardiolipin
- Elevated levels of factor XI, factor VIII

Geerts WH et al.
Chest 2001;119;132S–75S.

Facts

- 50% of the of the DVT patients are asymptomatic.
- Absence of known genetic factors, a familial histry or personal DVT---- s/o hereditary thrombotic disorder--- factor V leiden allele is associated with VTE.
- Approx. 10-20% of idiopathic DVT have or develop clinically overt cancer.
- Cancer patients undergoing surgery have atleast twice risk of postoperative DVT then noncancer

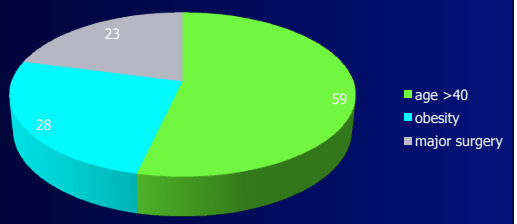
Facts

- Risk of DVT increases with age; >60 years – becomes more evident.
- CHF is independently associated with DVT and is a significant cause of mortality and morbidity.
- Incidences upto 29% for DVT in pts undergoing rehab.
- Injuries of face, chest, abdomen, and major head injuries have high frequency of DVT. Lower limb factures has a strong influence.
- 23% of DVT rate in mechanically ventilated patients

Facts

- Extend of risk of DVT depends on types of surgery--- orthopedics, vascular, and neurosurgery are at high risk.
- 70% of patients undergoing total hip/knee arthoplasties are at risk of developing DVT.
- DVT common in a patients with respi/urinary infections.
- Hospital acquired DVT: 10-40% among medical/ surgical;upto 40-60% in pts undergoing major orhtopedic surgery.

Major risk factors of DVT in hospitalized pateints



Myth Vs reality

- Disease of west vs Asia
- Occurs in hospitalized pt vs out patients
- Occurs in critically ill (ICU PT) Vs other wards
- Occurs in surgical/post operative pt only Vs in medical patients
- Risk of VTE is high during hospitalization Vs becomes zero once the patient is ambulant/ discharged
- Older pts are at high risk Vs younger Pt

Myth Vs reality

- Better to treat VTE than prophylaxis
- Difficult to indentify pt at risk : older age, smoking, obesity, immobilization, acute medical illness, cancer, and major surgeries.
- Mechanical thrombo-prophylaxis vs pharmacological.
- Heparins are associated with high risk of bleeding Vs

Facts

- UFH is as good as LMWH Vs LMWH have few more advantages- single dosing, less heparin induced thrombocytopenia, no aPTT monitoring cost
- All LMWH are same?

What' s the difference

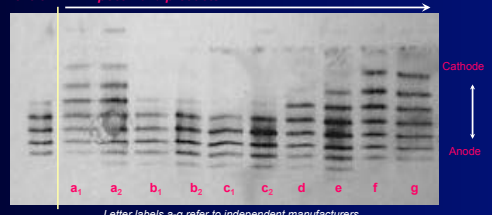
CONVENTIONAL DRUG BIOLOGICAL DRUG

Conventional Drugs vs Biological Products

	Conventional Drugs	Biological Drugs
Size	Small	Large
Structure	Simple	Complex
Manufacturing	▸ Predictable chemical process ▸ Identical copy can be made	▸ Unique line of living cells ▸ Impossible to ensure identical copy
Characterization	Easy to characterize fully Generic : Physicochemical tests Bioequivalence	Difficult to characterize fully due to a mixture of related molecules Fingerprints Biosimilar : ???

Biological Products are heterogeneous

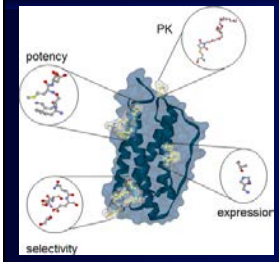
Different epoetins from around the world – Isoelectric focusing



Letter labels a-g refer to independent manufacturers
Numbers refer to batches from same manufacturer

Adapted from Schellekens, H. (2004) Eur J Hosp Pharm 3:43-47

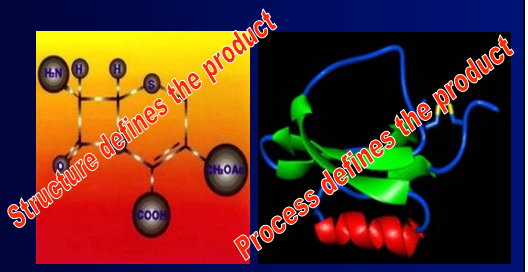
"The Process is part of the Product"



Any minor change in process may have an impact on

- **Potency (i.e. Biological activity)**
- **Selectivity**
- **Pharmacokinetics**
- **Immunogenicity**

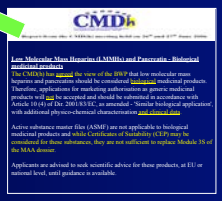
Structure vs Process



CONVENTIONAL DRUG BIOLOGICAL DRUG

LMWHs are Biological Products - EMEA

- LMWHs are BIOLOGICAL PRODUCTS obtained from heparin by depolymerization
- No generic applications are accepted
- CEP (Certificate of Suitability) is not enough to replace Clinical Data


CMDh

Low Molecular Mass Heparins (LMWHs) and Pancreatin - Biological medicinal products

The CMDh has agreed the view of the BWP that low molecular mass heparins and pancreatins should be considered biological medicinal products. Therefore, applications for marketing authorisation as generic medicinal products will not be accepted and should be submitted in accordance with Article 10 (4) of Dir. 2001/83/EC, as amended - 'Similar biological application', with additional physico-chemical characterisation and clinical data.

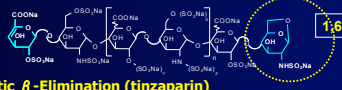
Active substance master files (ASMF) are not applicable to biological medicinal products and whilst Certificates of Suitability (CEP) may be considered for these substances, they are not sufficient to replace Module 3S of the MAA dossier.

Applicants are advised to seek scientific advice for these products, at EU or national level, until guidance is available.

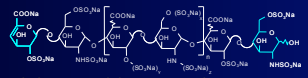
http://heads.medagencies.org/index.html

Manufacturing Process Triggers Specific Modifications at the Cleavage Point So Called "Fingerprints"

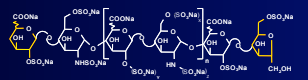
- **Chemical β-Elimination (enoxaparin, bemiparin)**



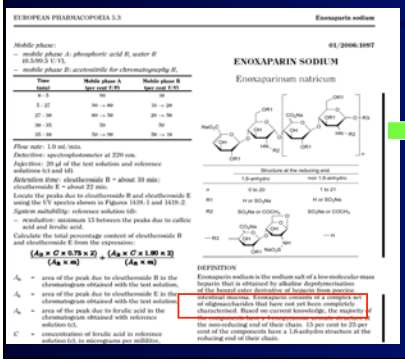
- **Enzymatic β-Elimination (tinzaparin)**



- Nitrous acid cleavage: dalteparin, nadroparin



Enoxaparin is yet not Fully Characterized


EUROPEAN PHARMACOPOEIA 5.3 — Enoxaparin sodium

01/2006:1097

ENOXAPARIN SODIUM

Enoxaparinum natricum

DEFINITION

Enoxaparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin consists of a complex set of oligosaccharides that have not yet been completely characterised. Based on current knowledge, the majority of the non-reducing end of their chains. 15 per cent to 25 per cent of the components have a 1,6-anhydro structure at the reducing end of their chain.

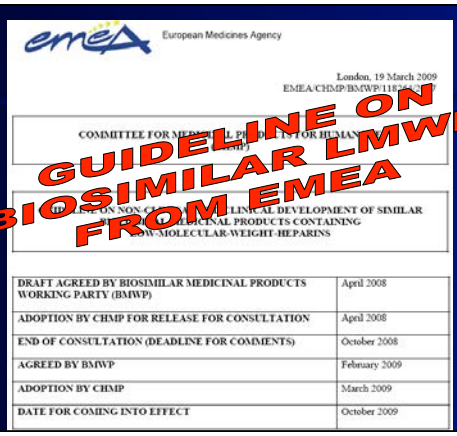
- Complex mixture of sugars
- 70-80% characterized
- 20-30% unknown

As a summary

Technological Limits	Product Characterizable	Specifications
Oligoaccharides < 13 sugars	70% of our compound	Monograph Finger prints 1, 6 anhydro ring CATIII B S

Oligosaccharides > 13 sugars	30% of our compound	Unidentified & Unknown fingerprint

GUIDELINE ON BIOSIMILAR LMWH FROM EMEA


European Medicines Agency

London, 19 March 2009

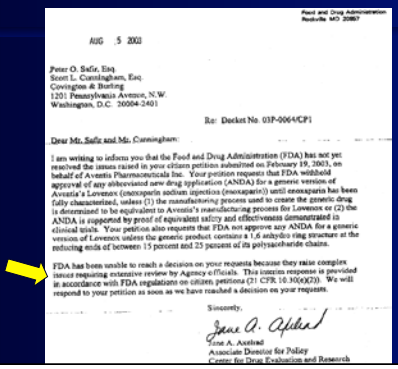
EMEA/CHMP/BMWP/118264/...

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING LOW-MOLECULAR-WEIGHT-HEPARINS

DRAFT AGREED BY BIOSIMILAR MEDICINAL PRODUCTS WORKING PARTY (BMWP)	April 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	April 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	October 2008
AGREED BY BMWP	February 2009
ADOPTION BY CHMP	March 2009
DATE FOR COMING INTO EFFECT	October 2009

FDA Unable to Reach Decision on Approval of Biosimilar LMWH



Food and Drug Administration
Rockville MD 20857

AUG 5 2003

Peter O. Safir, Esq.
Scott L. Cunningham, Esq.
Covington & Burling
1201 Pennsylvania Avenue, N.W.
Washington, D.C. 20004-2401

Re: Docket No. 03P-0064/CP1

Dear Mr. Safir and Mr. Cunningham:

I am writing to inform you that the Food and Drug Administration (FDA) has not yet resolved the issues raised in your citizen petition submitted on February 19, 2003, on behalf of Aventis Pharmaceuticals Inc. Your petition requests that FDA withhold approval of any abbreviated new drug application (ANDA) for a generic version of Aventis's Lovenox (enoxaparin sodium injection (enoxaparin)) until enoxaparin has been fully characterized, unless (1) the manufacturing process used to create the generic drug is determined to be equivalent to Aventis's manufacturing process for Lovenox or (2) the ANDA is supported by proof of equivalent safety and effectiveness demonstrated in clinical trials. Your petition also requests that FDA not approve any ANDA for a generic version of Lovenox unless the generic product contains a 1,6 anhydro ring structure at the reducing ends of between 15 percent and 25 percent of its polysaccharide chains.

FDA has been unable to reach a decision on your requests because they raise complex issues requiring extensive review by Agency officials. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your requests.

Sincerely,

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

No Generic Approvals in US, Europe, Canada and Brazil

- US : 1st generic application submitted in April 2003
  ⇒ Non approval letter issued in November 2007
- EU : Numerous applications pending since 2003
- Canada : Approval granted to a Generic enoxaparin in February 05
  ⇒ Cancelled by Health Canada on January 06
- Brazil : ANVISA refused the renewal of the registration for the follow-on enoxaparin product Dripanina in Oct 07

As Consequences

- **LMWHs are biological compounds (EMEA, WHO) not fully characterized**
- **Process determines the product. Process creates unique finger prints which determine the pharmacological and clinical profile**
- **Immunogenicity is an important safety issue**
- **Clinical trials and pharmacovigilance help guard against immunogenicity**
- **Biosimilars must provide relevant quality, pre-clinical and clinical data for marketing authorisation. No automatic extrapolation of data.**
- **EU has a new guideline for approval of similar LMWHs – asks for comparability and preclinical / clinical data, US has not yet provided any guideline**
- **India has a biological guideline but it is not retrospective**

Individual risk assessment in non-surgical patients

Conclusions

- VTE is a major clinical problem
- Knowledge of the benefits of thromboprophylaxis in medical patients is not being used effectively
- Need for practicing risk stratification to identify the " At-risk" patients of DVT.
- Thromboprophylaxis with LMWH is effective and safe,
- Opportunity to further improve patient outcomes

Thromboprophylaxis: Future Challenges

- How long are patients at risk?
  → Duration of thromboprophylaxis
- Are certain patient populations at greater risk of a poor outcome after DVT?
- Extending benefits of current thromboprophylactic regimens to medical patients
  → Save more lives

Similar is not Same

Thank you