



**Generic Anticoagulant,
Antithrombotic and Thrombolytic
Agents. Are There Any Specific
Guidelines?**

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Anticoagulant and Antithrombotic Drugs

Thrombin and Xa Inhibitor



TFPI



HEPARIN

Platelet Inhibitors



Cyclic Peptides



Ticlopidine, Clopidogrel

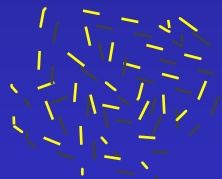
Recombinant agents

Peptidomimetics

Fibrinolytic modulators



HIRUDIN



LMWH



Peptidomimetics

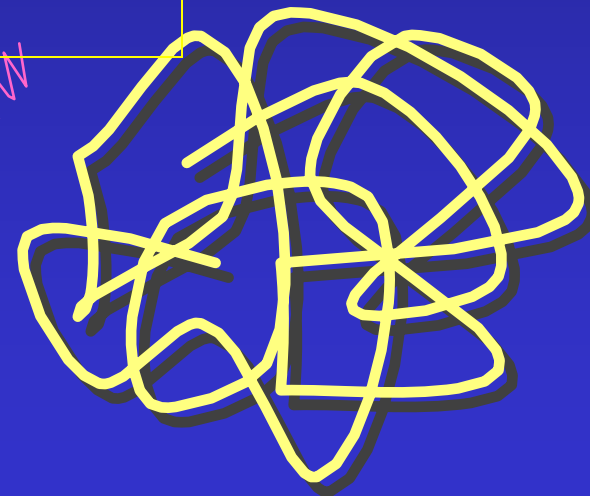


Oligopeptides

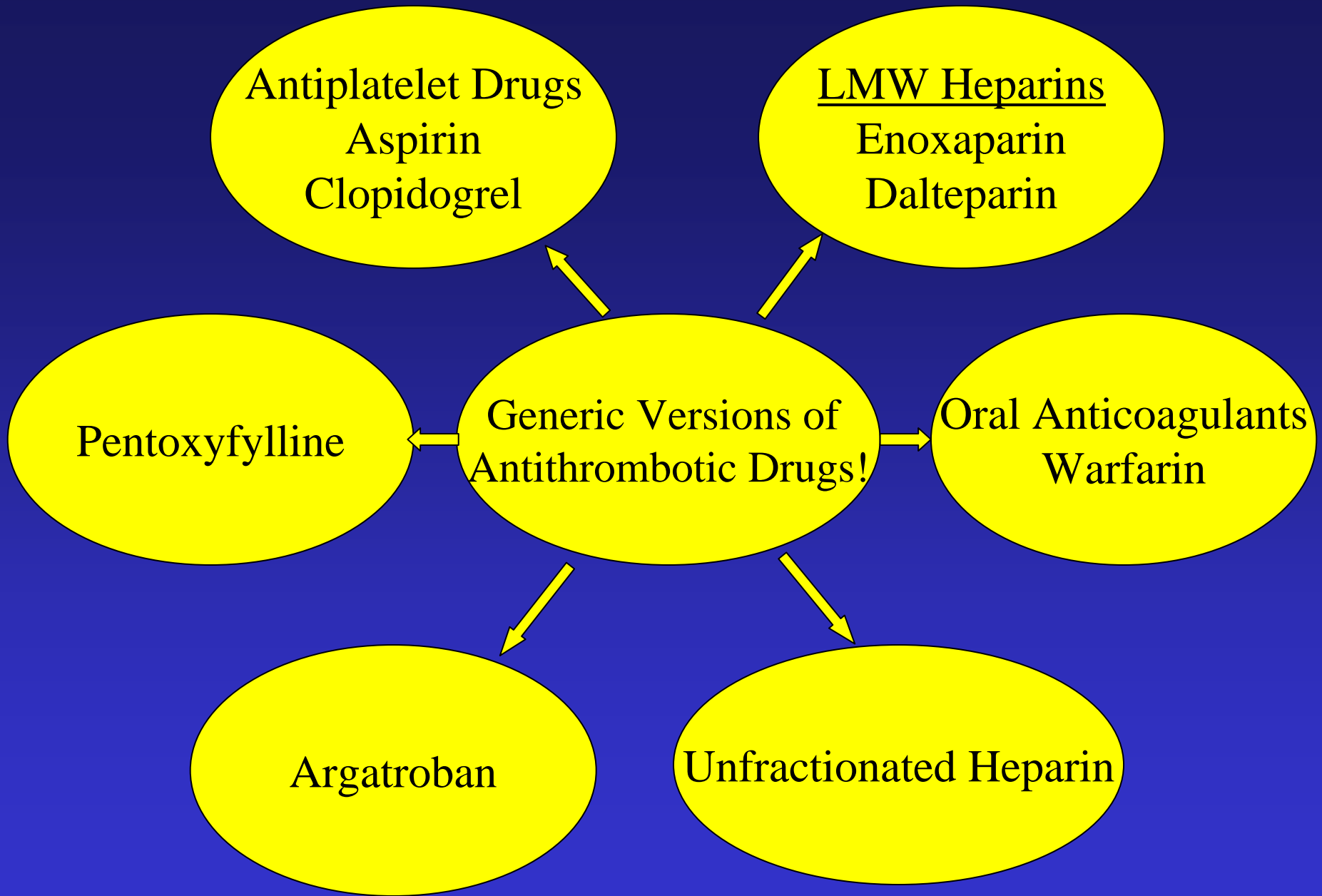
TAFI
PAI-1 inhibitor
Factor XIIIa inhibitor

Di-, tripeptides and peptidomimetics

HIRULOG



ReoPro and YM 337



Generic Conversion of Branded Antithrombotic Drugs

- **No clear cut guidelines from the regulatory bodies.**
- **Complex drugs/compositional variations may occur leading to safety/efficacy compromise.**
- **Minimal requirements from regulatory bodies which can be easily fulfilled.**
- **Newer guidelines from peer groups and regulatory bodies are needed to validate the generic antithrombotic drugs.**

Generic Versions of Antithrombin Drugs. Reported Issues

- **Molecular profile and AXa activity adjusted agents. Generic enoxaparin produced by other processes have been introduced/withdrawn**
- **Some aspirin preparations contain high free salicylic acid and active acid content**
- **D&L ratios of MTTPA in clopidogrel vary. Higher dosage are needed to achieve similar effects**
- **Ratio of distereoisomers (R&S forms) vary in different preparations**

Generic Conversion of Branded Antithrombotic Drugs

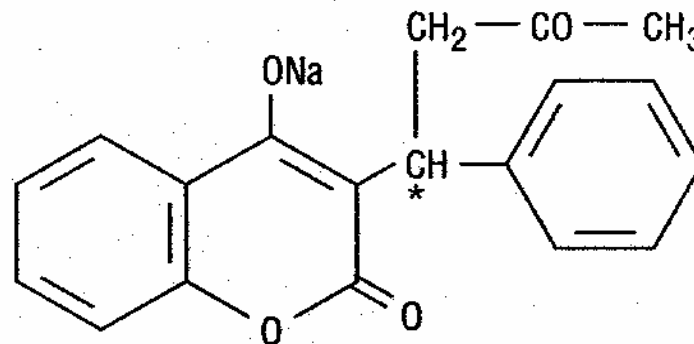
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Oral Anticoagulants

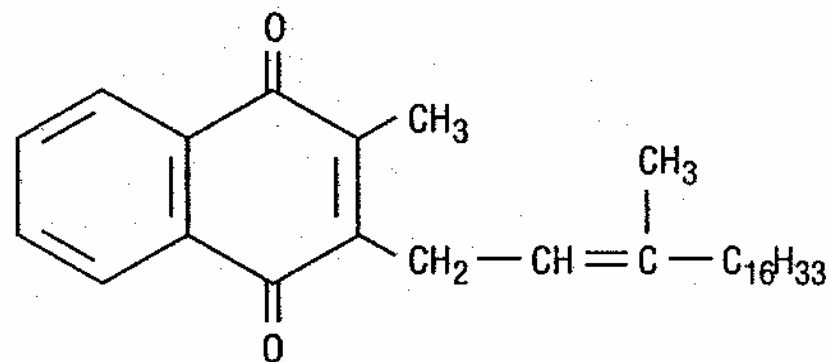
- Warfarin (Coumadin®) and its derivatives [phenprocoumon (Sintrom®); acenocoumarol (Marcumar®)] have been used for over 50 years.
 - Prophylactic use: Prevention of thrombotic disorders
 - Therapeutic use: Treatment of established thrombus

The Structure of Warfarin

Warfarin is an Analogue of Vitamin K



Warfarin sodium



Phytonadione (vitamin K₁)

Precautions with the Use of Warfarin

- A narrow therapeutic index (range between effective and toxic doses)
- Non-linear pharmacokinetics
- Small changes in dose can result in considerable changes in the anticoagulant response

Control of Warfarin Dose

- Response can vary greatly
- Many factors affect the dose of warfarin:
 - Patient age
 - Nutrition
 - Dietary vitamin K
 - Alcohol use
 - Concomitant disease state
 - Anemia
 - Liver disease
 - Biliary obstruction
 - Concomitant drug use
 - Compliance

Drug Interactions with Warfarin

- Drugs potentiate warfarin:
 - By causing vitamin K deficiency
 - by displacing warfarin from protein binding sites
 - by decreasing clotting factor synthesis
 - by suppressing or competing for microsomal enzymes
 - by having antiplatelet aggregating properties
- Drugs inhibit warfarin:
 - by decreasing warfarin absorption
 - by enhancing warfarin metabolism

Generic Oral Anticoagulants

- Generics warfarins available since 1997
- 6 generic warfarins FDA rated bioequivalent to warfarin:
 - Barr Laboratories
 - Apothecon
 - Genpharm
 - Sandoz
 - USL Pharm
 - Taro Pharmaceuticals

FDA Approval of Generics

- FDA standards for generic approval:
 - Mean difference in bioavailability cannot differ by more than – 20% to + 25 % from innovator product.
 - A drug approved as bioequivalent is *assumed* to be a therapeutic equivalent (same clinical effect and safety profile).
 - Clinical studies are NOT required.

Are these standards sufficient to prove therapeutic equivalency for a drug with variable pharmacodynamic responses and wide inter-patient variability?

Concerns with Generic OACs

- Bioequivalence to the innovator product
- Consistency that product contains the same amount of active drug
- Consistency of bioavailability of drug between batches

Clinical Perception of Generic OACs

- Use of generic warfarin in clinical practice:
 - 2/3 of physicians prefer the innovator product
 - 40% of these had concerns over potential differences in bioavailability, INR, manufacturing quality control standards
 - 40% reported variations in INR associated with generic substitution
 - Increased clinic visits
 - Increased frequency of INR fluctuations
 - Rare published reports of clinical complications
 - Spontaneous nose bleeding
 - Drug interactions altering protein binding or hepatic metabolism of warfarin
 - Could result in increased morbidity and healthcare costs.

Bongiorno RA, et al. *Seminars Thromb Hemost* 2004;30(6).

PK Comparison of 3 Brands of Warfarin

[n=12 normal volunteers]

	<u>Time to Peak (hrs)</u>	<u>AUC</u>	<u>Absorption Rate Constant</u>	<u>Half Absorption Time</u>
<u>Coumadin</u> (Endo)	2.3	67.1	2.19	19.0
<u>Athrombin K</u> (Purdue Frederick)	3.6	72.7	1.06	39.2
<u>Panwarfarin</u> (Abbott)	4.1	72.7	0.05	78.3

Clinical Studies of Generic OAC

- 2 small randomized, cross-over, observer-blinded studies
- Atrial fibrillation on stable Coumadin
 - Stated that generic and brand name formulations were equivalent for anticoagulant activity and side-effects, but
 - Small populations (n= 55 and 57)
 - Excluded patients requiring dose change
 - Pooled data

Neutel JM, *et al.* Cardiovasc Rev Rp 1998;19:49-59.
Handler J, *et al.* Prev Cardiol 1998;4:13-20.

Clinical Studies of Generic OAC

1. Observational study (n=210)
 - No difference in INR when patients converted from innovator to generic product
2. Multi-center, prescriber-blinded, randomized, crossover trial (n=113)
 - No difference in INR or hemorrhagic event rates between groups
3. Prospective, observational study (n=182)
 - No difference in INR, frequency of INR monitoring, number of dose changes, rate of thrombotic or hemorrhagic events

Swenson CN, *et al.* Am J Health Syst Pharm 2000;57:452-455.
Weibert RT, *et al.* Ann Pharmacother 2000;34:981-988.
Milligan PE, *et al.* Ann Pharmacother 2002;36:764-768.

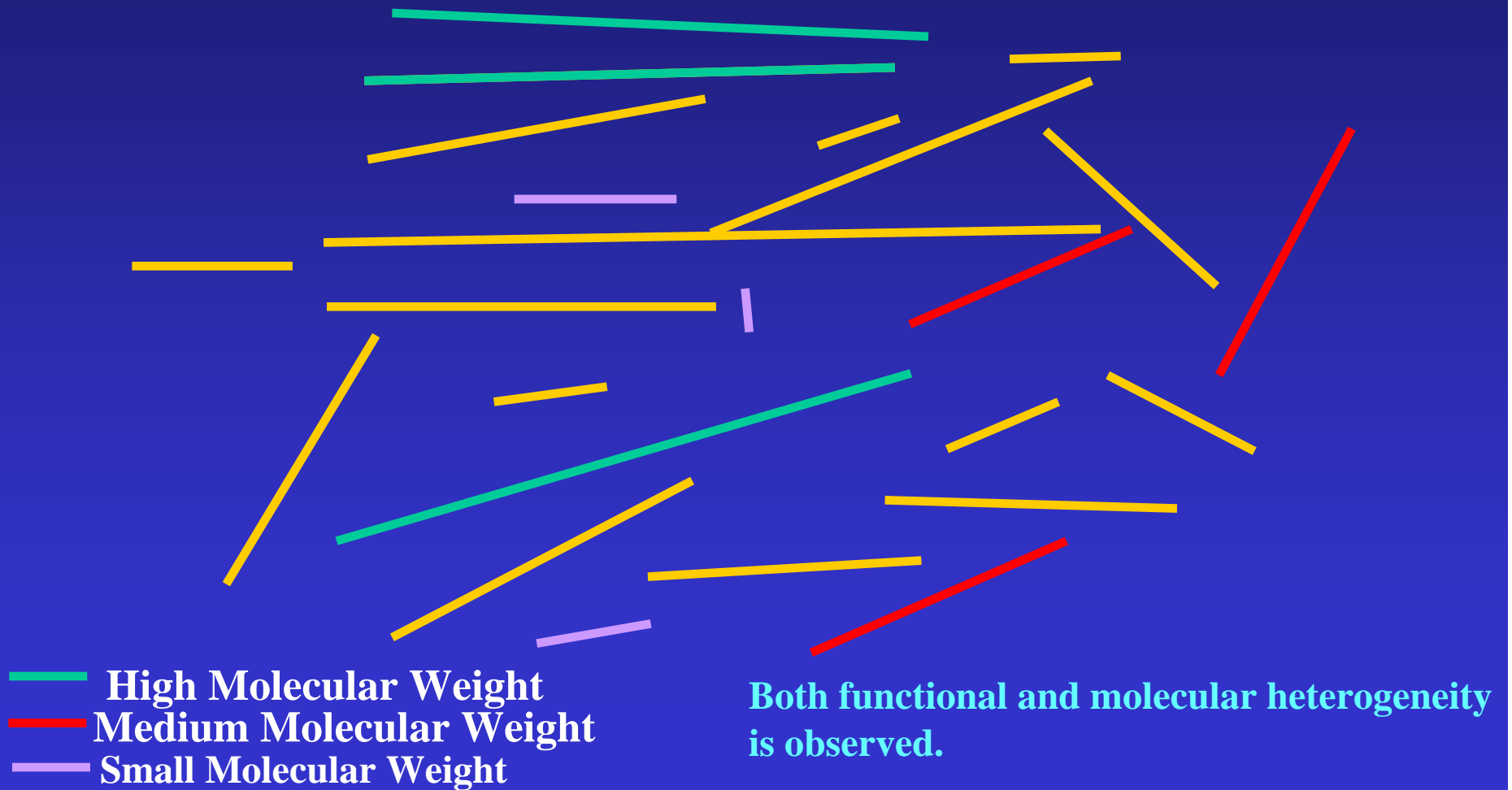
Clinical Studies of Generic OAC

4. Largest trial to date (n=2299)
 - Significant difference in INRs within the therapeutic range before and after the switch to generic (66 vs 63%, $p=0.0002$)
 - Not considered clinically significant
 - Most patients successfully switched from brand to generic warfarin
 - But suggest supplemental INR monitoring to detect those patients who experience significant changes in anticoagulant responses.

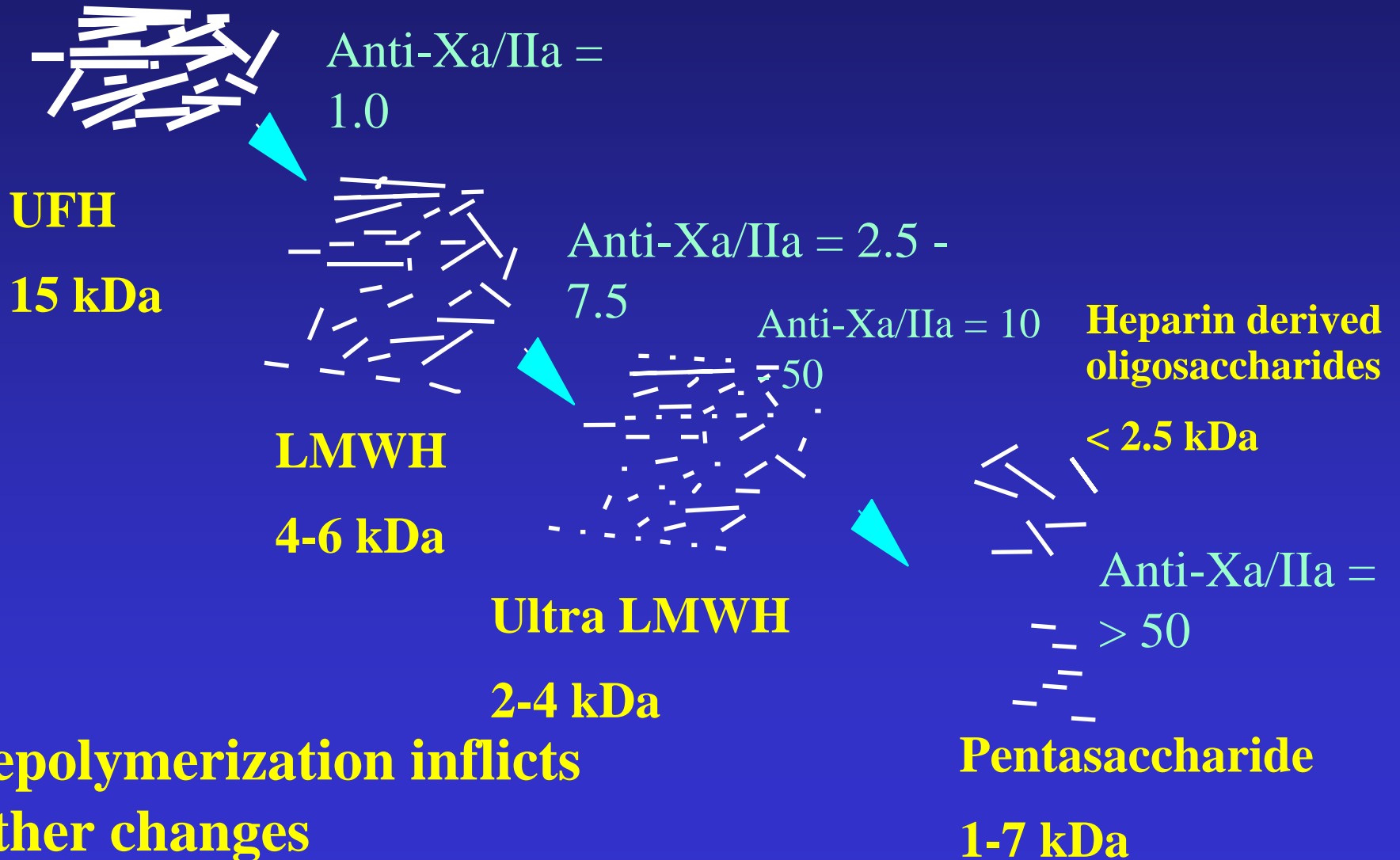
Conclusions on Generic OAC

- Warfarin has a narrow therapeutic index and a varying pharmacodynamic response.
- Close monitoring is needed when patients are switched from brand name to generic product, or *vice versa*, or from one generic to another generic to avoid under-dosing or over-dosing.
- The generic interchange of warfarin should be avoided in elderly patients, and patients with liver disease and gastric resection.
- All anticoagulants are critical drugs. In the case of warfarin, small changes can result in large pharmacodynamic variations.

Molecular Heterogeneity of Heparin



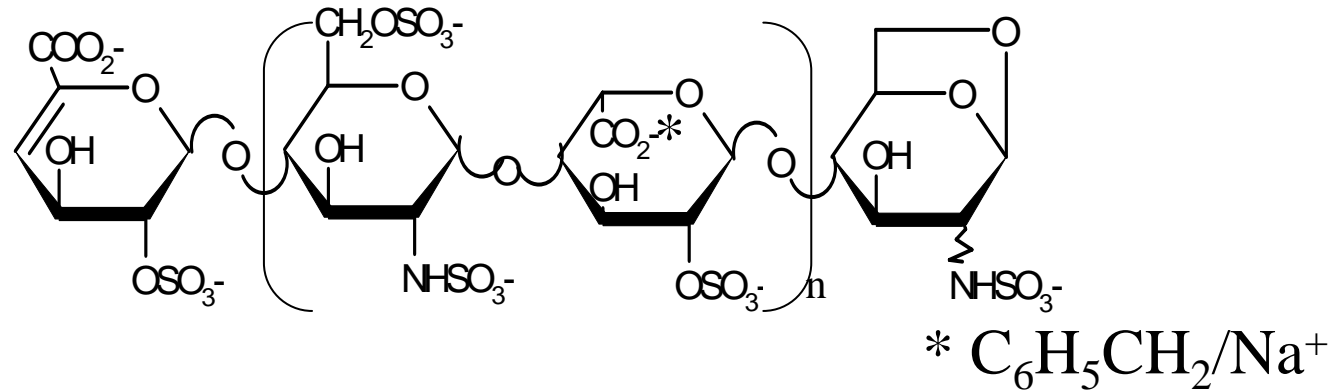
Manufacturing Process for Low Molecular Weight Heparin and Lower Low Molecular Weight Heparin



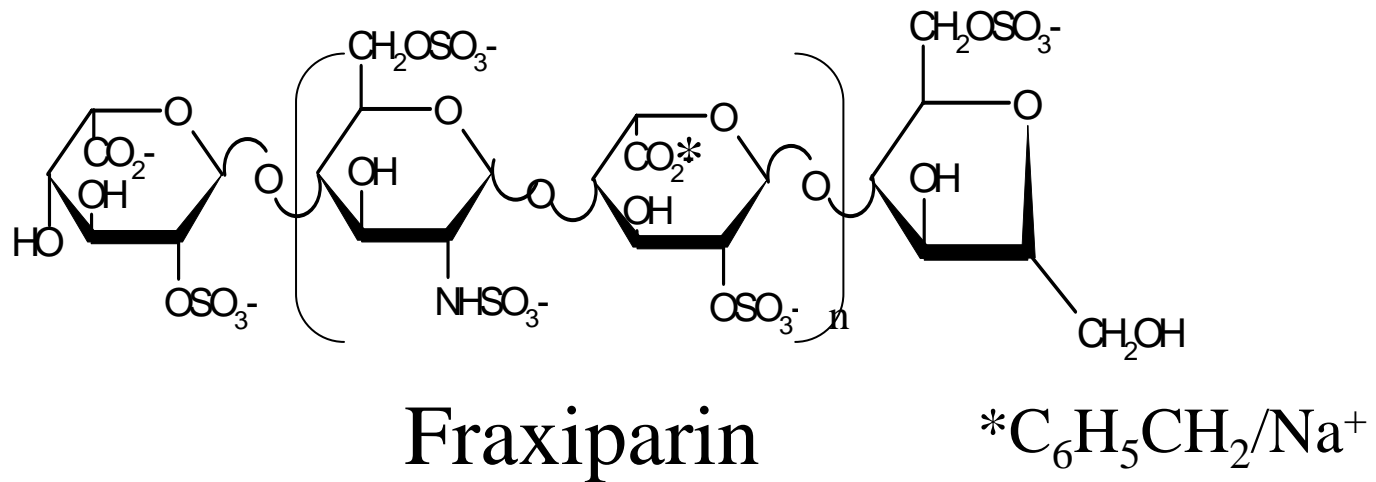
Currently Developed Generic LMWHs

1. **Enoxaparin**
(Aventis, France)
2. **Dalteparin**
(Pfizer, USA)
3. **Tinzaparin**
(Leo, Denmark)
4. **Parnaparin**
(Opocrin, Italy)

Specific Structural Features in LMWHs



Enoxaparin



Fraxiparin

$* C_6H_5CH_2/Na^+$

Any generic product must exhibit similar structural features.

Molecular and Structural Profiling of Various Batches of Commercial Enoxaparin

<u>Parameter</u>	<u>Mean + SD of 12 batches</u> <u>1987-2004</u>
1,6 Anhydro Manno	14.9 _± 5.1
1,6 Anhydro Gluco	21.8 _± 8.1
Benzyl Moieties	0.72 _± 0.26

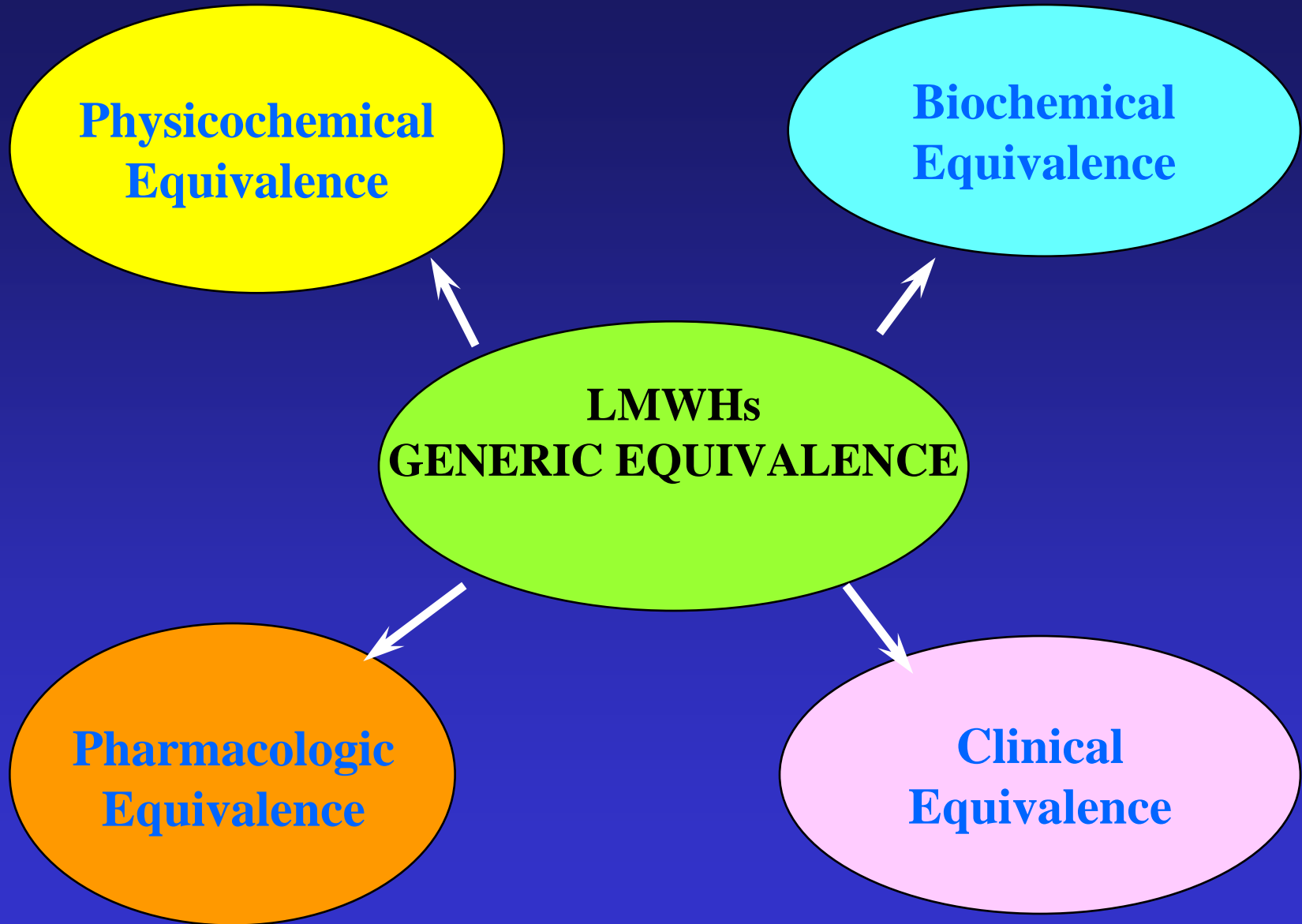
**Physicochemical
Equivalence**

**Biochemical
Equivalence**

**LMWHs
GENERIC EQUIVALENCE**

**Pharmacologic
Equivalence**

**Clinical
Equivalence**



Generic Enoxaparin

Enoxaparin is made by using benzylation followed by alkaline depolymerization of porcine mucosal heparin. One of the patents covering this drug has already expired where as the second patent will expire in December 2004. Knowing this several manufacturers of LMWHs have produced generic versions of enoxaparin with claimed equivalence in accordance to the available specifications. **While the generic products may have similar molecular weight and anti-Xa potency but their biochemical and pharmacologic behavior may not be the same and require further characterization.**

LOW MOLECULAR WEIGHT HEPARIN

0.2 ml in a PFS

Dalteparin Sodium Injection

Daltehep* 5000 IU (anti - Xa)

INJEKTA....PFS A PRE-FILLED SYRINGE UNIT

FOR SUBCUTANEOUS USE

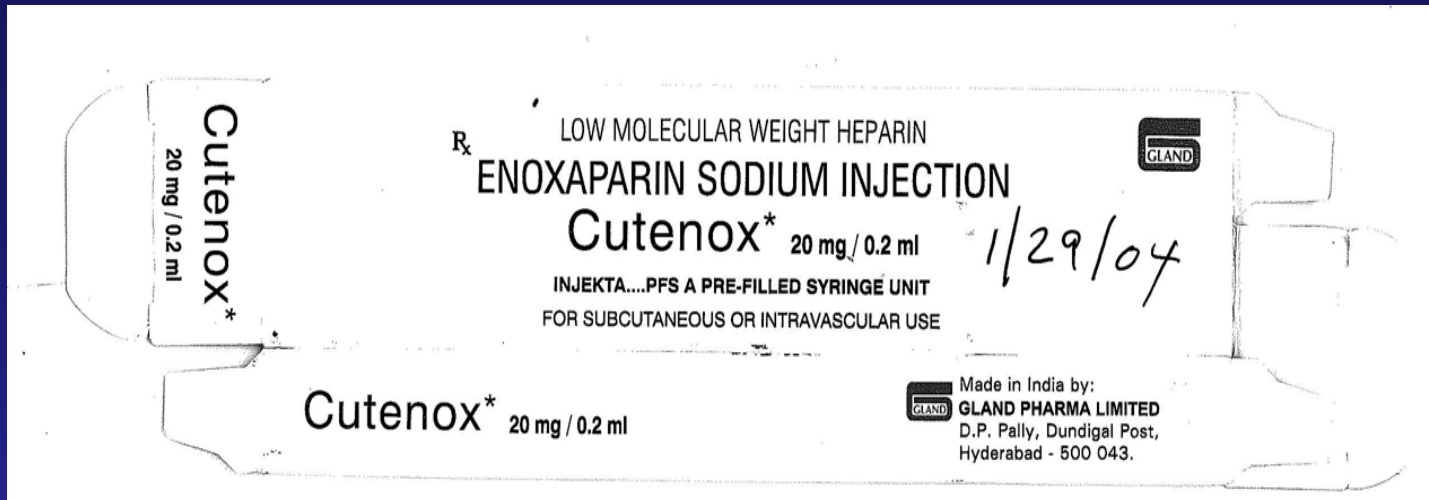
CONTROL SAMPLE
NOT FOR SALE



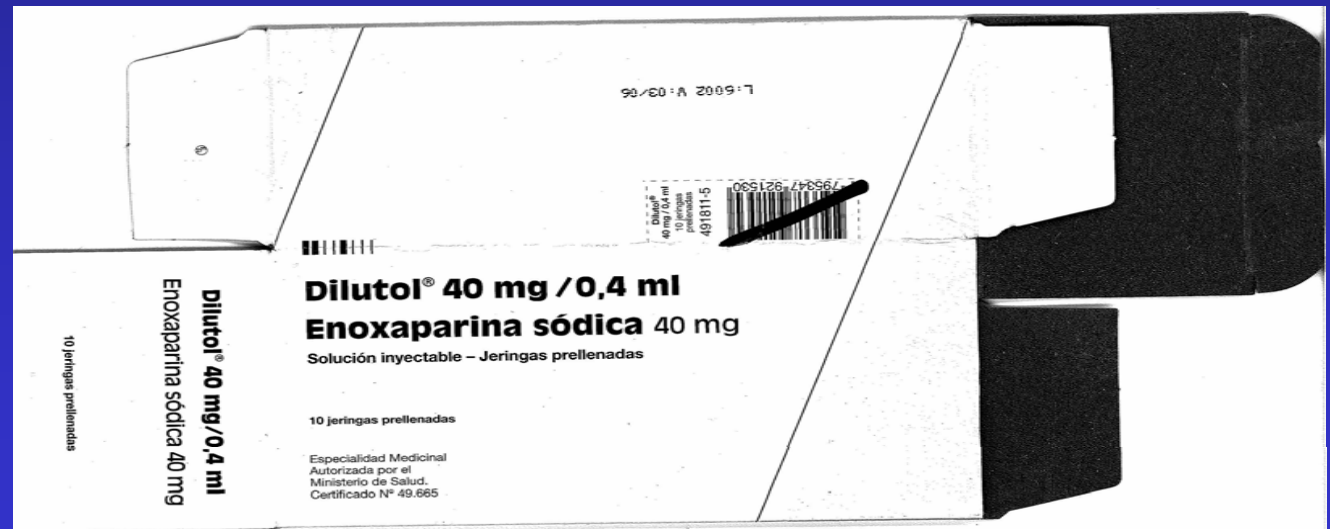
Daltehep* 5000 IU (anti - Xa)



Made in India by:
GLAND PHARMA LIMITED
D.P. Pally, Dundigal Post,
Hyderabad - 500 043.

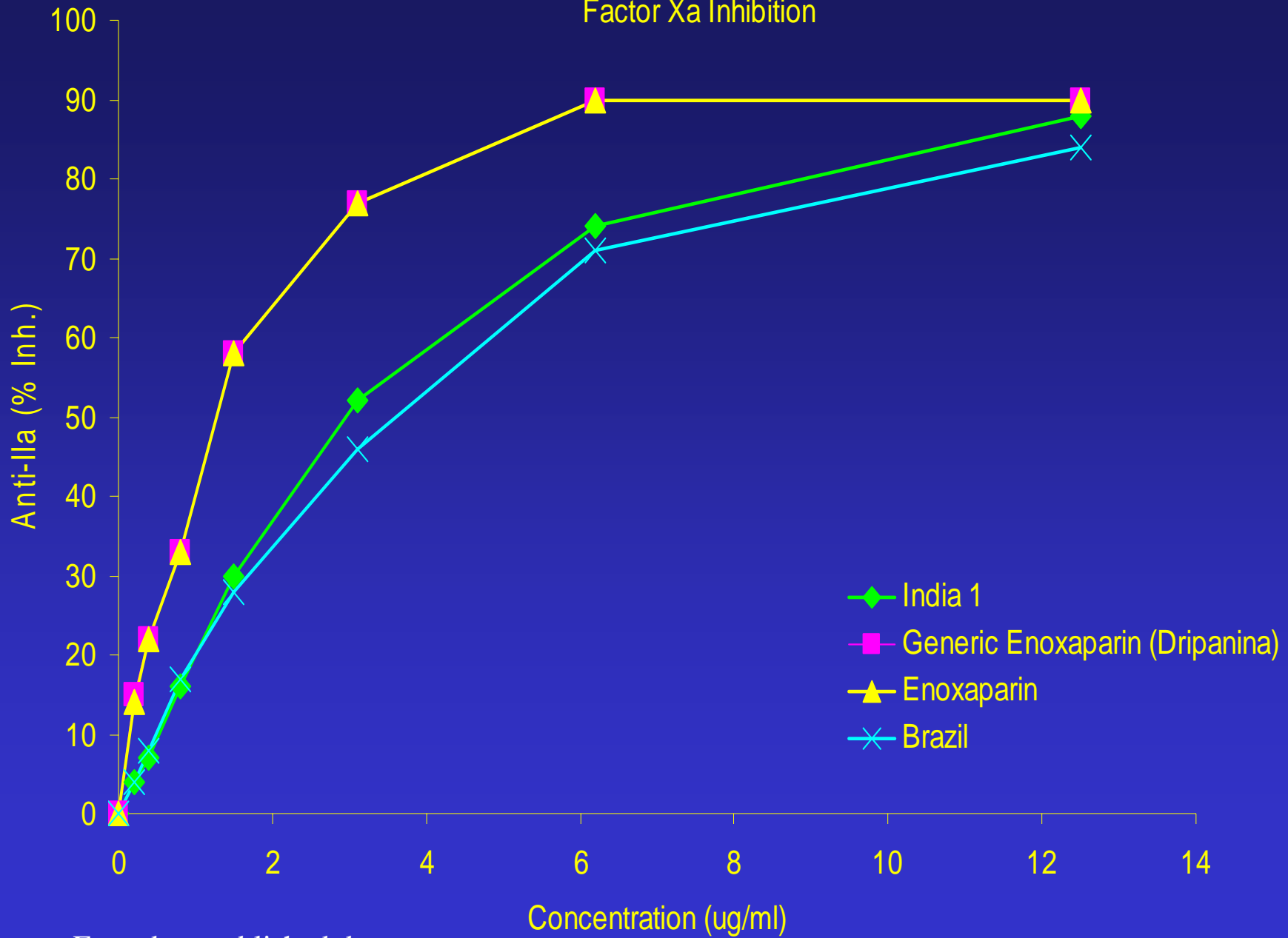


Gland Pharma From India



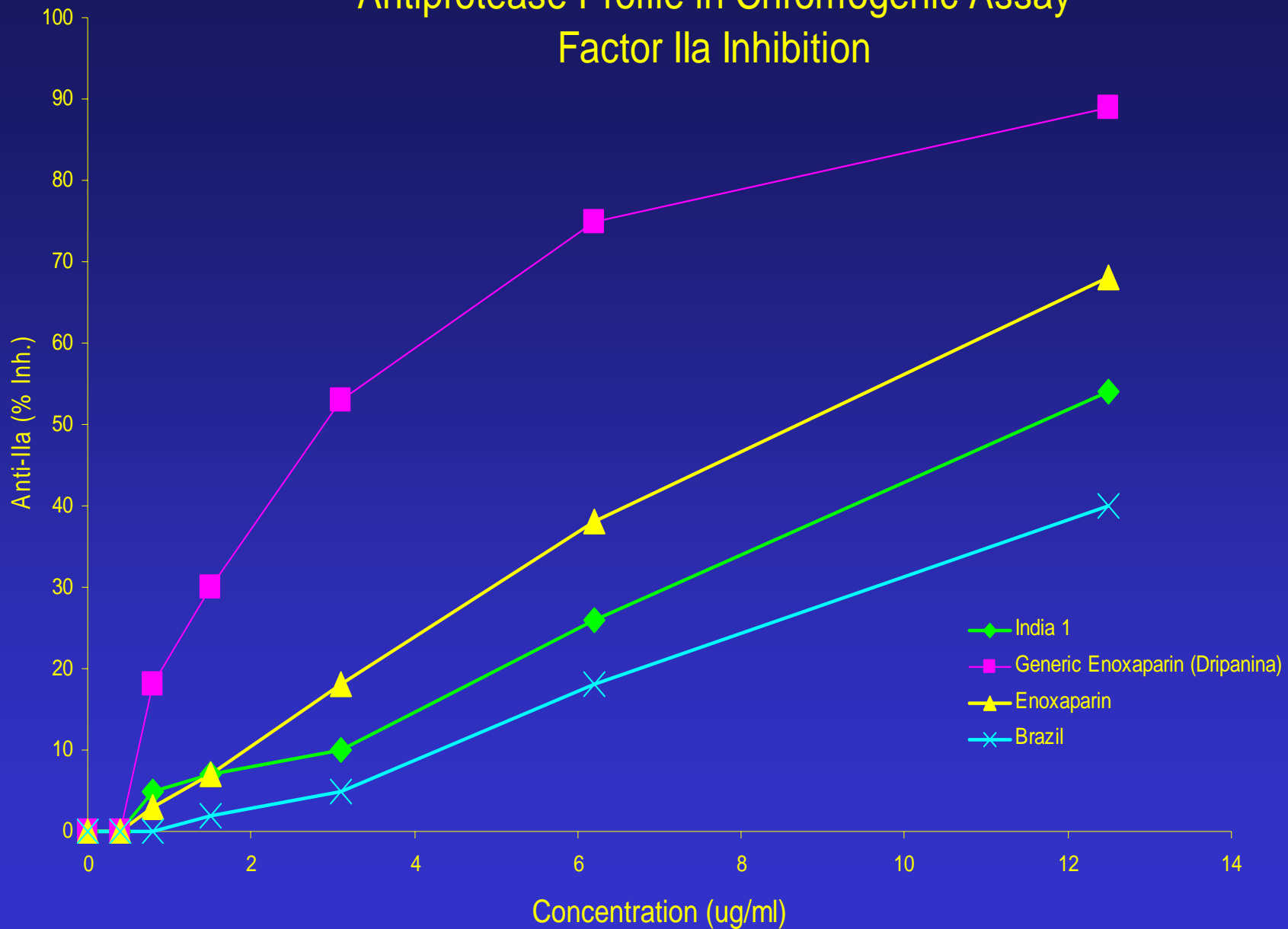
Argentina

Antiprotease Profile in Chromogenic Assay Factor Xa Inhibition



Fareed, unpublished data.

Antiprotease Profile in Chromogenic Assay Factor IIa Inhibition



Fareed, unpublished data.

**GENERIC VERSION OF BRAND
LMW HEPARINS: ARE THE
CURRENT REGULATORY
GUIDELINES ADEQUATE?**

No. Because of the complex nature of these agents requiring both the biologic and chemical expertise, there are no specific guidelines at this time.

CLINICAL IMPLICATIONS

- 1. Enoxaparin represents a low molecular weight heparin with wide clinical indications including arterial, venous and cardiovascular use.**
- 2. The dosage range varies widely for different indications. Minor compositional differences may therefore impact pharmacokinetics/pharmacodynamics of these agents.**
- 3. The generic versions of enoxaparin must exhibit all physicochemical and biological attributes to mimic the clinical performance of the innovator product.**

CURRENT PERSPECTIVE ON GENERIC LMWHS

- The regulatory bodies, US FDA and EMEA, may allow the generic versions of LMWHs and apply the same guidelines as for other biologicals.
- Additional requirements to provide supplementary chemical and biological data to support the filing may be needed. Some stipulations from the Citizens Petition may be considered.
- Clinical trials may or may not be required for specific products for approved indications depending upon the filing material review.

Requirements for the Acceptability for Generic Version of LMWHs

1. Manufacturing compliance to the pharmacopial descriptions.
2. Physioco-chemical and biologic characterization.
3. PK/PD studies
4. Clinical trials?

Is Chemical Characterization of Branded LMWHs Sufficient to Satisfy Assure Pharmacodynamics Equivalence?

No. Because LMWHs are hybrid products of biologic origin with chemical modifications. Moreover the starting material is more important to characterize for product consistency.

Minimal Requirements For the Considerations For A Generic LMW Product

- 1. Comparable Pharmacopoeial Monographs**
- 2. Pharmacological and biochemical
characterization**
- 3. Pharmacokinetic/Pharmacodynamic studies
(AUC)**

Unresolved Issues in the Development of Generic Low Molecular Weight Heparins.

- 1. Current guidelines for generic drugs are not valid.**
- 2. Complex multicomponent drugs requiring specifications.**
- 3. Chemically modified complex natural glycosaminoglycans.**
- 4. Bioassay specifications only require partial characterization.**
- 5. Xa and AIIa only represent partial pharmacological activities.**
- 6. No requirements for raw material specifications.**

Clinically Used Thrombolytics

- Urokinase
- Streptokinase
- **Recombinant tissue plasminogen activator**
- **TNK-tissue plasminogen activator (longer half-life)**

Urokinase is no longer available in the US.

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New Anticoagulant Drugs

Developmental Issues

Agent

- | | |
|--------------------------------|--|
| 1. Pentasaccharides | Bleeding, limited indications, no antagonists |
| 2. Direct Antithrombins | Monotherapeutic, no antagonist, inhibits regulatory functions of thrombin |
| 3. Direct Xa Inhibitors | Monotherapeutic, no antagonist, does not inhibit thrombin |

None of the newer agents release TFPI.

Newer Concepts in Anticoagulant Therapy

1. Synthetic organomimetics with multiple targets.
 - a. Multiple antiprotease targeting agents
 - b. Dual antiprotease and antiplatelet actions
2. Oral antithrombin and anti-Xa agents
3. Combination therapy
4. Heparinomimetics-single and multiple targets
5. Biotechnology derived antithrombotic agents

Antithrombotic therapy

