

Contamination of Heparin

- Update in Japan -

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Indications and Administration for Heparin Products in Japan

- Heparin Products

- <Indication>

- For the treatment of Disseminated Intravascular Coagulation (DIC)
 - As an anticoagulant in extracorporeal circulation and dialysis procedure
 - As an anticoagulant in blood transfusions and in blood samples for laboratory purposes
 - For the prevention of clotting in arterial and cardiac surgery
 - For the prophylaxis and treatment of pulmonary, peripheral arterial embolism, and atrial fibrillation with embolization, etc.

- <Administration>

- intravenous infusion, intermittent intravenous, subcutaneous injection, intramuscular route of administration, and extracorporeal circulation

Heparin Test Results

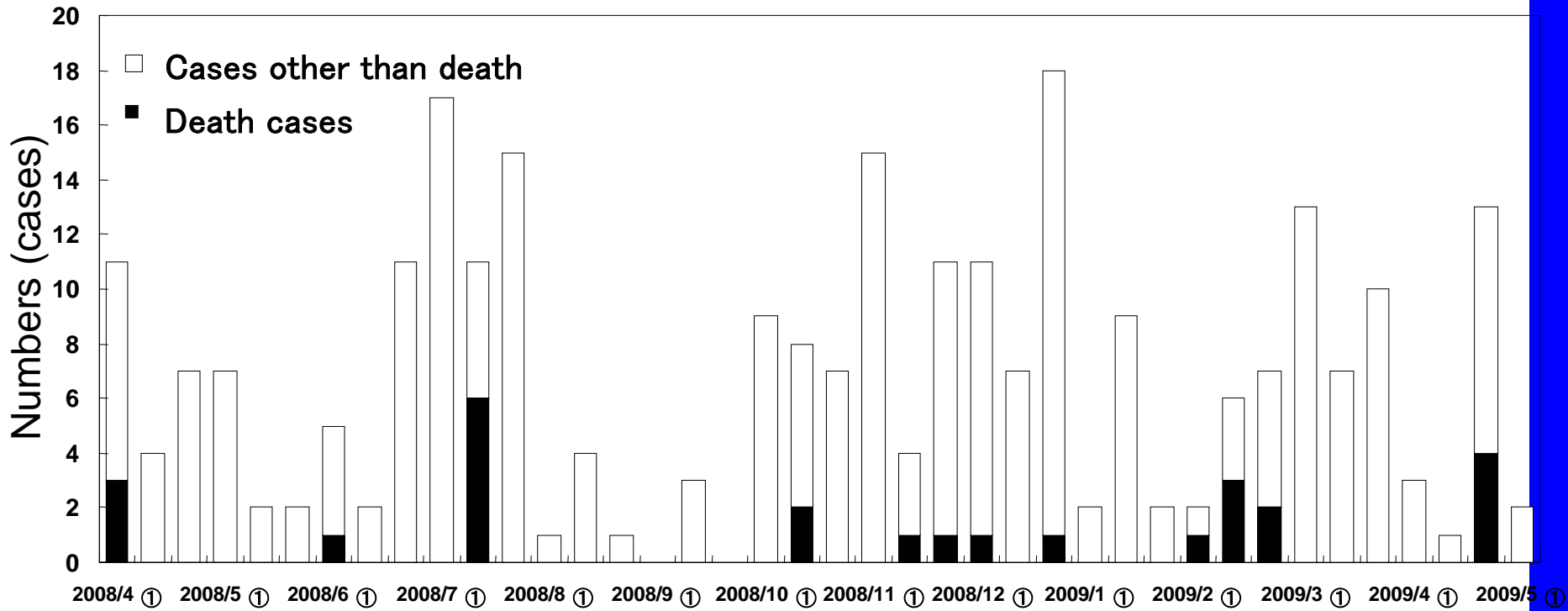
- MHLW instructed companies with Heparin products; i.e., heparin sodium, heparin calcium and low molecular mass heparins, including dalteparin sodium, parnaparin sodium, reviparin sodium and enoxaparin sodium, along with device companies with heparin to analyze their heparin API according to the FDA recommended two screening methods, $^1\text{H-NMR}$ and CE last year.
- There were some products to have contaminants and to be recalled.

Adverse Events

- In Japan, MHLW has not received any spiked adverse events associated with all the Heparin products; i.e., heparin sodium, heparin calcium and low molecular mass heparins, including dalteparin sodium, parnaparin sodium, reviparin sodium and enoxaparin sodium, along with medical devices with heparin as the following slides:

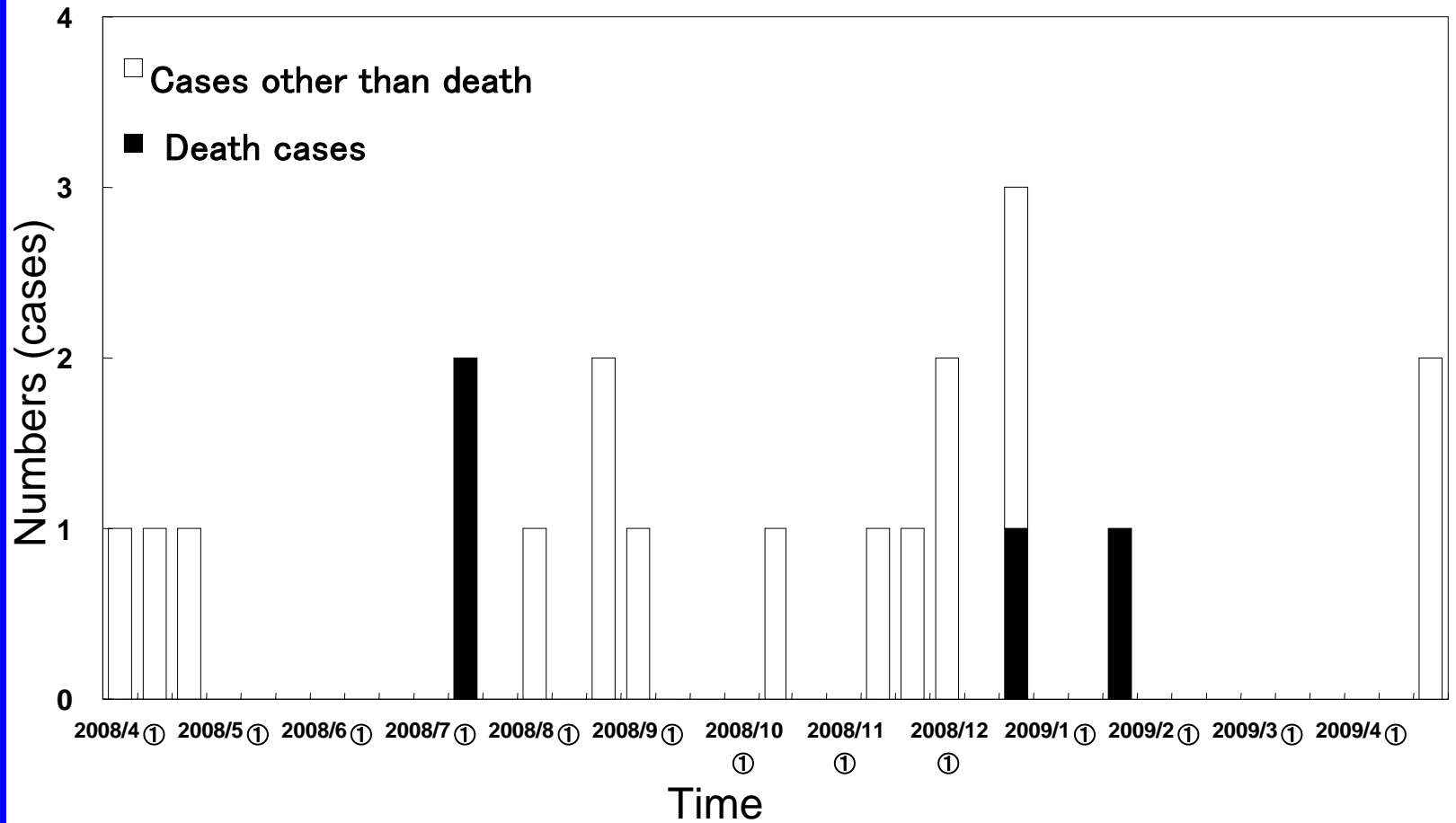
Heparin sodium

(副作用)

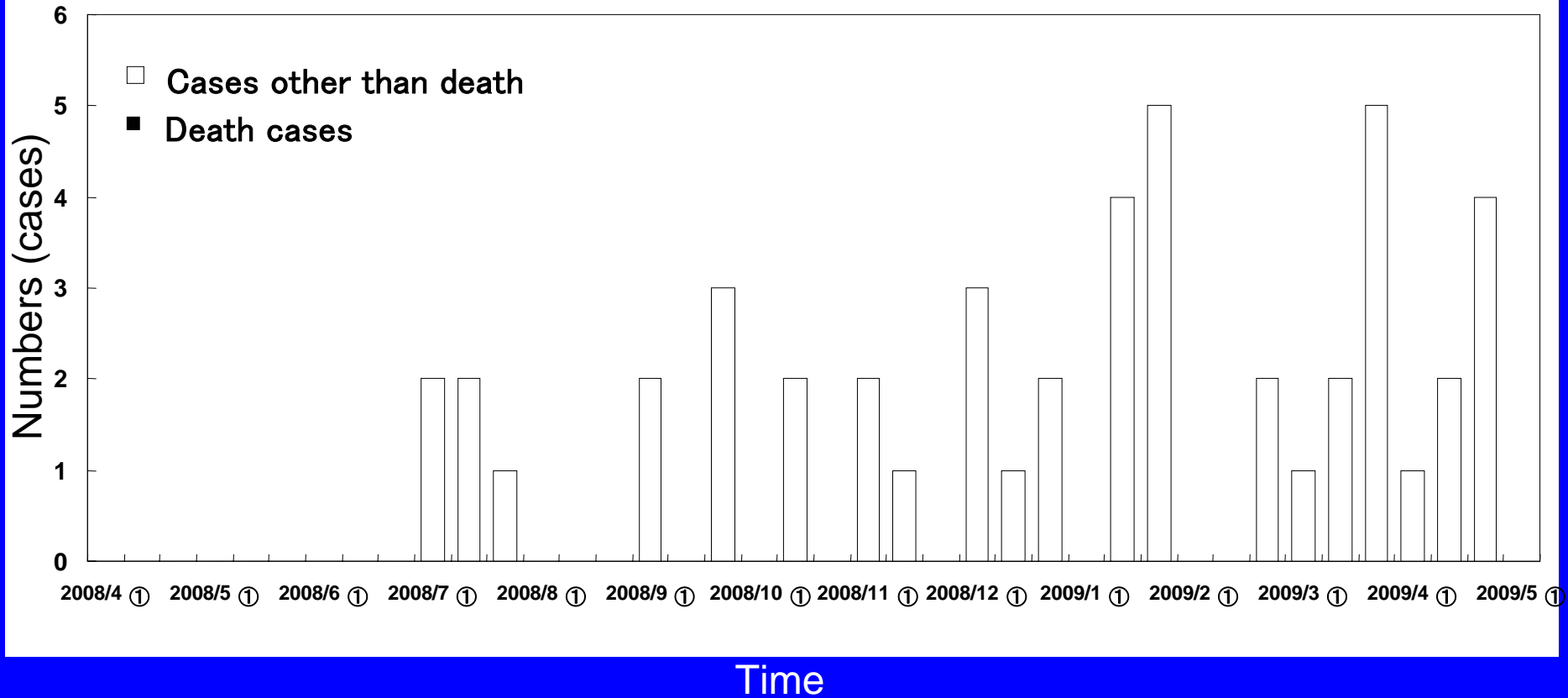


Time

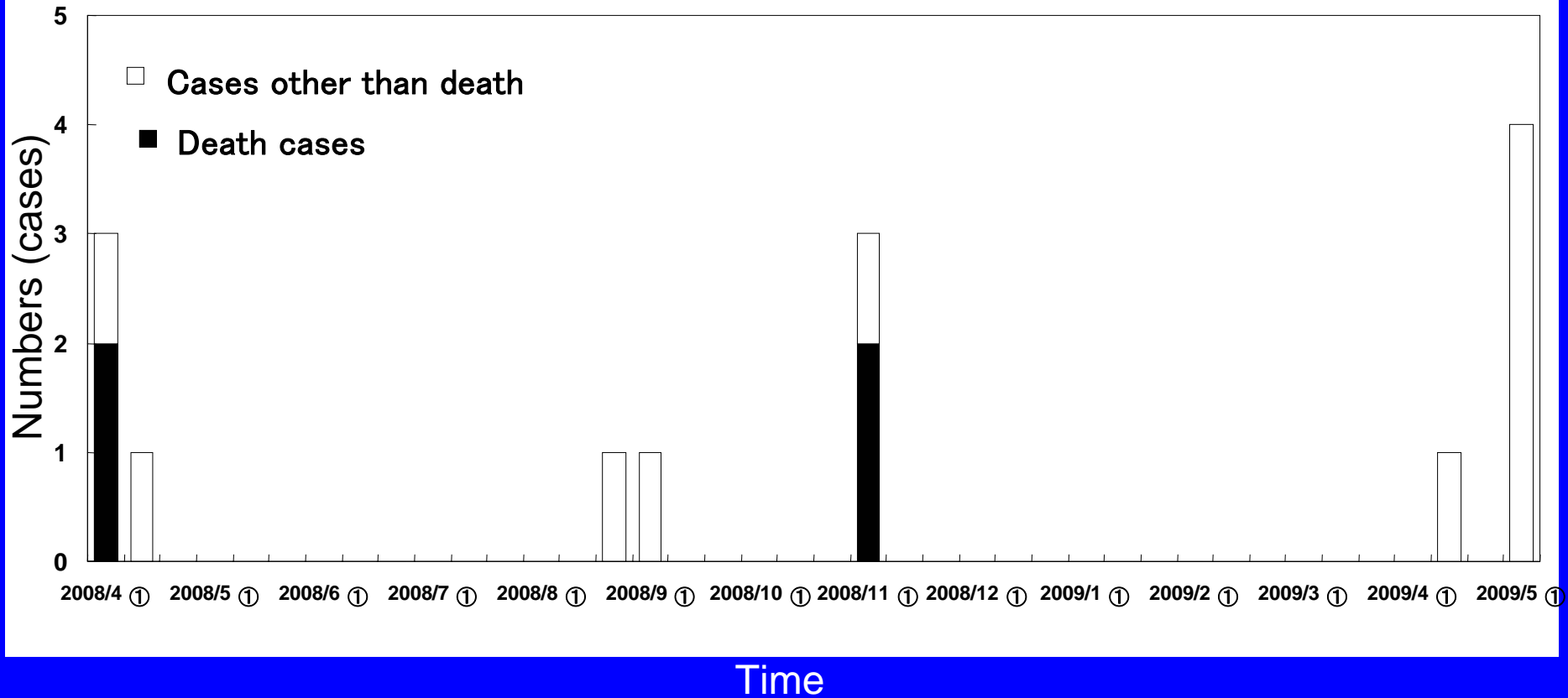
Heparin Calcium



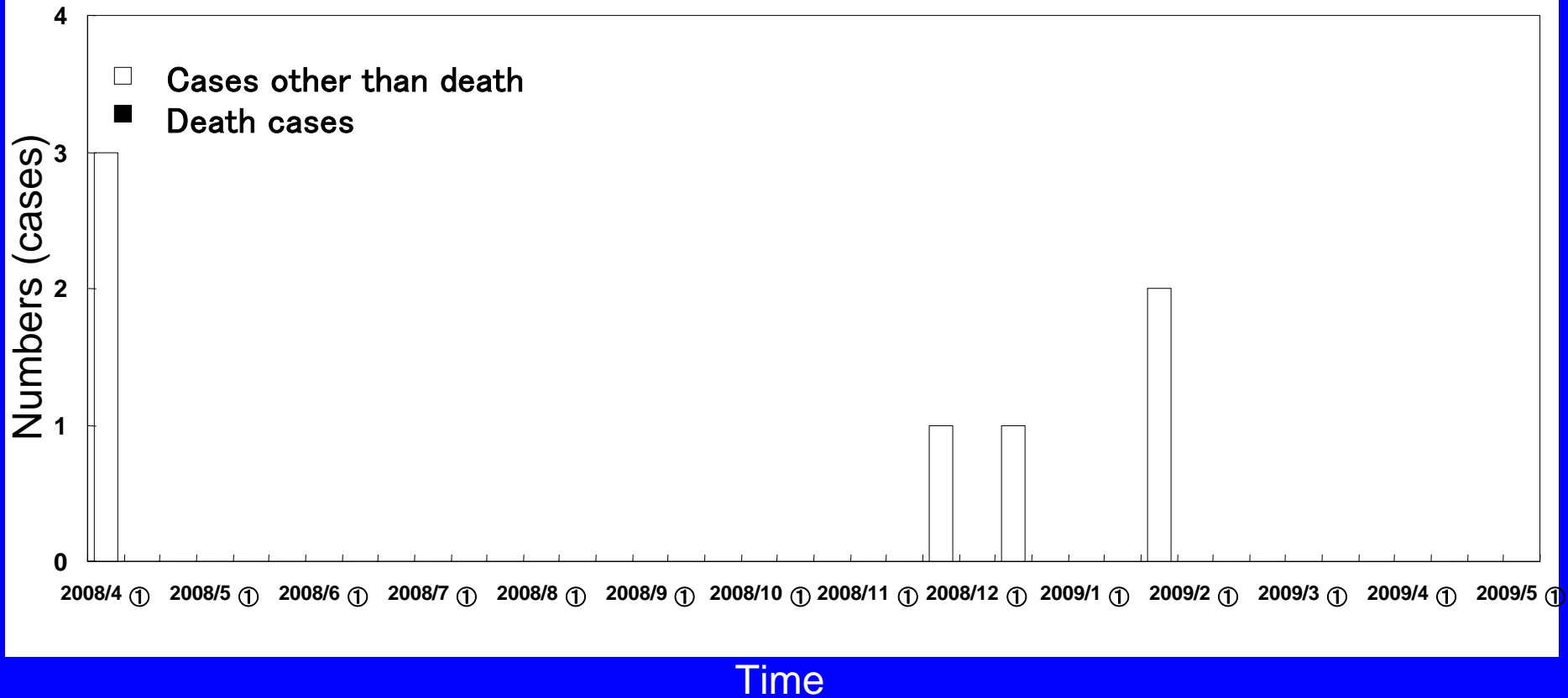
Enoxaparin Sodium



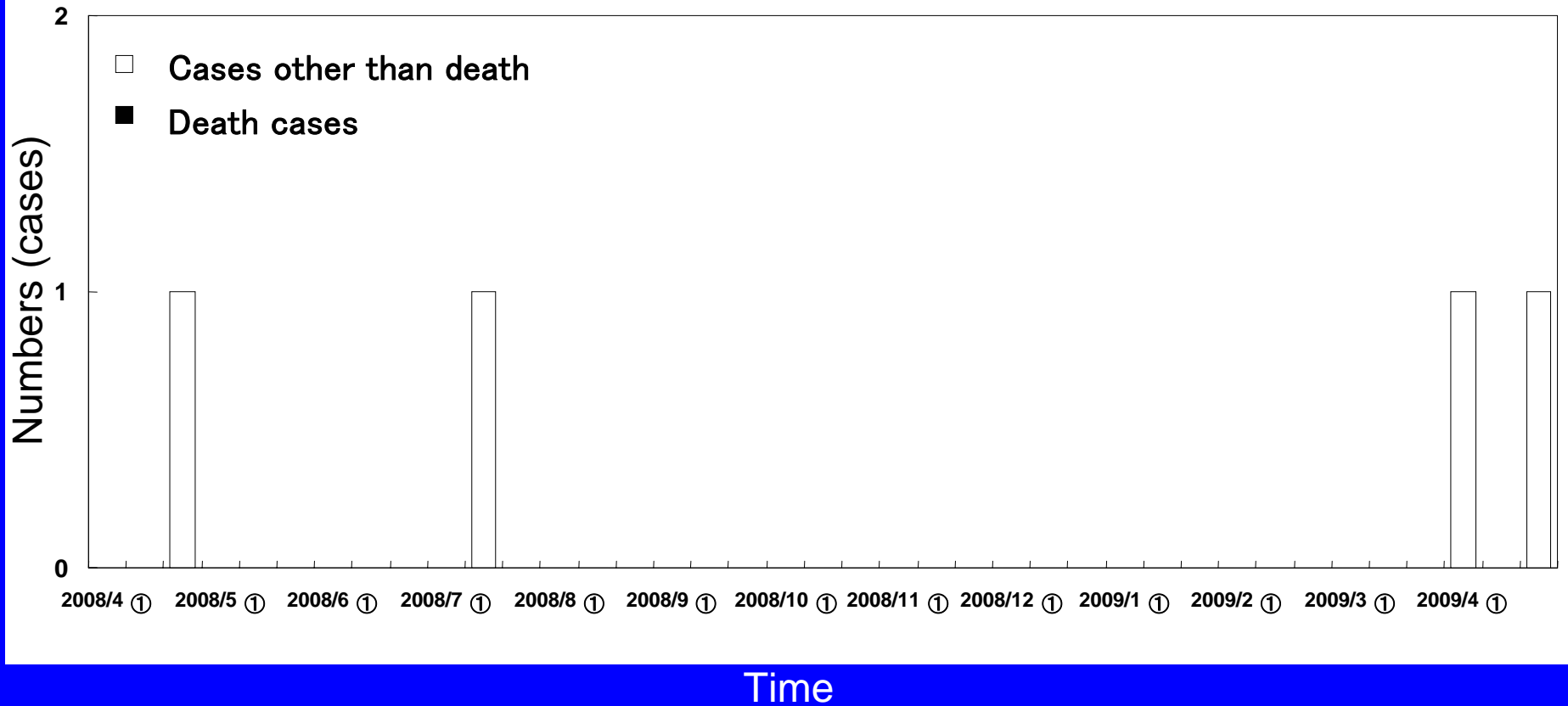
Dalteparin Sodium



Reviparin Sodium



Parnaparin Sodium



Measurement for OSCS

MHLW introduced a new regulation for OSCS in the Purity Test, July 31 2008.

Over-sulfated chondroitin sulfate – Dissolve 20 mg of Heparin Sodium in 0.60 mL of a solution of sodium 3-trimethylsilylpropionate- d_4 for nuclear magnetic resonance spectroscopy in heavy water for nuclear magnetic resonance spectroscopy (1 in 10000), and use this solution as the sample solution. Determine the spectrum of the sample solution as directed under Nuclear Magnetic Resonance Spectroscopy <2.21> (1H) in accordance with the following conditions, using sodium 3-trimethylsilylpropionate- d_4 for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits no signal corresponding to N -acetyl proton of over-sulfated chondroitin sulfate at δ 2.13 – 2.17 ppm.

Control on impurities derived from manufacturing process (1)

1. Barium: Dissolve 0.03g of Heparin Sodium in 3.0mL of water, and use this solution as the sample solution. To 1.0mL of the sample solution add 3 drops of dilute sulfuric acid, and allow to stand for 10minutes: no turbidity is produced.
2. Total nitrogen: Weigh accurately about 0.1g of Heparin sodium, previously dried at 60°C for 3 hours under reduced pressure, and perform the test as directed under Nitrogen Determination: the amount of nitrogen is not more than 3.0%.
3. Protein: To 1.0mL of the sample solution obtained in 1. add 5 drops of a solution of trichloroacetic acid (1 in 5): neither a precipitate nor turbidity is produced.

Control on impurities derived from manufacturing process (2)

- At present, there are no regulations on Dermatan Sulfate, Nucleic Acid and residual solvents in Japan.
- NIHS and related companies developed the quantitative test method for Dermatan Sulfate.
- MHLW plans to introduce a new regulation for Dermatan Sulfate early next year.
- MHLW/PMDA continue to consider the development of regulation for nucleic acid and protein.

Responsibility of MAH under PAL

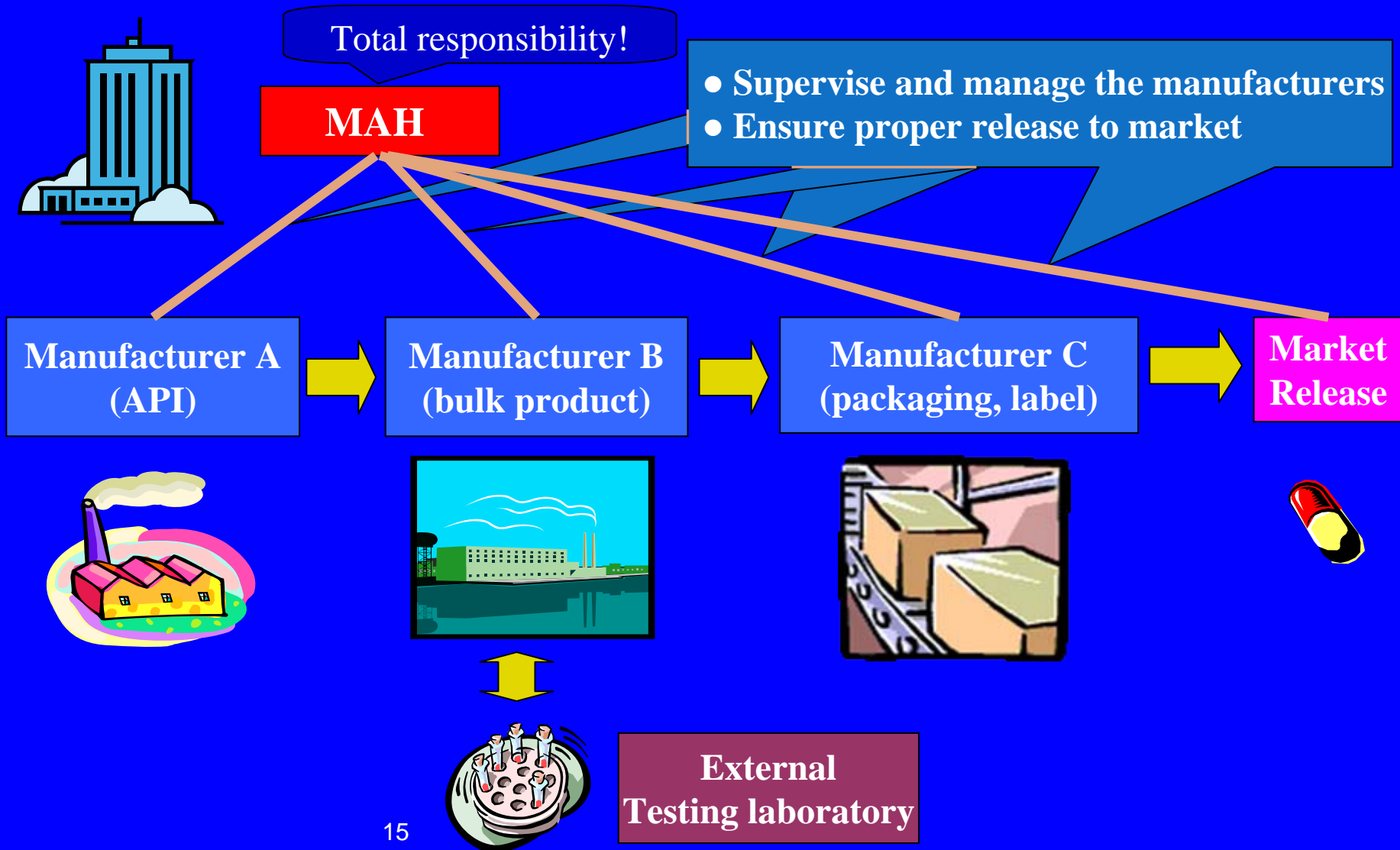
- as prerequisites for license of MAH -

- MAH must comply with **GQP** for its License.
 - *GQP: Good Quality Practice
Rules for quality assurance operations
- MAH must comply with GVP for its License.
 - *GVP: Good Vigilance Practice
Rules for post-marketing safety management

Tentative English translation of GQP, GMP ordinances are posted at
<http://www.pmda.go.jp/english/services/reviews/ordinance.html>

MAH: Marketing Authorization Holders

Responsibility of MAH based on GQP



Control on raw materials

- MHLW has instructed marketing authorization holders (MAHs) with Heparin products to:
 - validate heparin products and their raw materials in terms of quality control and GMP immediately
 - verify the purity of refined heparin as raw materials in each lot based on the FDA's published test method

Instructions for medical institutions through MAHs

- MHLW has also requested MAHs to provide relevant information of rational use of heparin products for medical institutions as follows:
 - caution against adverse drug reactions such as shock
 - close monitoring of patients for anaphylactic symptoms such as decreased blood pressure or decreased consciousness during and after treatment
 - careful administration of heparin products in terms of dose and infusion rate



Thank you