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HONG KONG DOCTORS UNION
香港西醫工會

Our ref.: HKDU/105/2010

25th May 2010

By fax & mail

Dr. Lam Ping Yan
Director
Department of Health
17/F, Wu Chung House
213 Queen's Road East
Wanchai, Hong Kong

Dear Dr. Lam,

Re: Concerns on the "Avastin in HA" Clinical Trials with Off-label Use of Avastin (bevacizumab)

On behalf of the Hong Kong Doctors Union and The Practising Pharmacists of Hong Kong, we would like to express our concerns regarding the Hospital Authority's plan to conduct an "Avastin in HA" clinical trial with the use of repackaged Avastin to be used in an off-label indication to treat Acute Macular Degeneration (AMD).

According to our understanding, Avastin is packaged and labelled in a 4 and 16 ml single-use glass vials. The labelled precautions include "discard any unused portion left in a vial, for intravenous use to treat colo-rectal cancer". For the off-label use to treat Age-related Macular Degeneration (AMD) disease, Avastin needs to be repackaged into smaller containers or syringes injection for intravitreal use. Due to a recent news report by the Society of Ophthalmology, six patients in Portugal have been blinded after compounding errors while repackaging Avastin for the off-label use to treat Age-related Macular Degeneration (AMD).

In view of the latest drug safety and quality information concerning repackaged Avastin, we are concerned with the high levels of risks being imposed on patients in the proposed trial. After having researched on the practices of overseas health authorities (i.e. US FDA), we have shared our concerns and findings with the HA Institutional Review Board as in the attached document. [Attach IRB document]

From our understanding of the current situation in the USA, the off-label use of Avastin to treat AMD is an area of high concern to the health authorities and is being monitored closely by the US FDA, particularly in regards to the quality issues pertaining to the repackaged Avastin products. In 2006, the US FDA had issued a warning letter to individuals and organizations, engaged in the repackaging of Avastin products for intravitreal use, and advised the need for applying of a manufacturing license and to be subjected to regulatory oversight by the US FDA, to ensure the repackaging process is of acceptable standards to guarantee the quality of the final product to be safe for use on patients. The US FDA highlights the fact that Avastin is "packaged and labelled in 4 and 16 ml single-use glass vials. The labelled precautions include discard any unused portion left in a vial..." Each step in the manufacture and processing of a new drug or antibiotic, from handling of raw ingredients to final packaging, must be approved by FDA, whether carried out by the original manufacturer or by some subsequent handler or repacker of the product.

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Pharmacists are not exempt from these statutory requirements. Generally, the agency regards mixing, packaging, and other manipulations of approved drugs by licensed pharmacists, consistent with the approved labelling of the product, as an approved use of the product if conducted within the practice of pharmacy, i.e., filling prescriptions for identified patients.

However, processing and repacking (including repackaging) of approved drugs is beyond the practice of pharmacy and is thus subject to the Act's premarket approval requirements. FDA is particularly concerned about the manipulation of sterile products when a sterile container is opened or otherwise entered to conduct manipulations. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies supporting the standard are compromised and are no longer valid. We are especially concerned with the potential microbial contamination associated with splitting Avastin - a single-use, preservative-free, vial -- into multiple doses. When used intravitrealy, microbes could cause endophthalmitis, which has a high probability for significant vision loss. The absence of control over storage, and delays before use after repackaging, only exacerbate these concerns." [US FDA Warning Letter]

With reference to the above information, we are concerned with a number of important quality issues that have been reported with repackaged Avastin products.

Important Quality Issues Include:

1. Microbial Contamination - Once the preservative-free, single use vial of Avastin is opened, microorganisms may contaminate the product. Since the repackaged product is intended for use as an intravitreal injection, the facilities and repackaging process must meet GMP requirements for manufacturing of sterile intravitreal use products. [Attach microbial contamination paper]

2. Impurities Contamination - Once the preservative-free, single use vial of Avastin is opened, harmful impurities may contaminate the product. Since the repackaged product is intended for use as an intravitreal injection, the facilities and repackaging process must meet GMP requirements for manufacturing of sterile intravitreal use products.

3. Appearance of Large Particulate Matter - Once the preservative-free, single use vial of Avastin is opened and repackaged into different primary container, it has been reported that exposure to sunlight or left unused for a period of time, large particulate matters have appeared in the product.[attach Hawaii Eye report]

4. Stability of Active Ingredients - Once the preservative-free single use vial of Avastin is opened, the active and inactive ingredients may become unstable due to variations in storage containers and storage conditions.

5. Chemical reactions from rubber stoppers in new container-closure systems - Once the preservative-free single use vial of Avastin is opened and repackaged into a syringe, it has been reported that chemical reactions occur between the product and the rubber stopper to induce the appearance of new and potentially harmful particulate matters. [Hawaii Eye Report]

According to our understanding of the requirements of the Pharmacy and Poisons Ordinance, any form of clinical trial on human beings need to obtain a Clinical Trial Certificate (CTC) from the Department of Health to ensure that the drugs used are manufactured according to Good Manufacturing Practice (GMP) standards.

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It has been brought to our attention that the HA hospitals (United Christian Hospital and Tuen Mun Hospital) have been conducting clinical trials on patients with the use of repackaged Avastin for the past two years. We would like to confirm whether the HA has obtained approval from the Department of Health for those particular trials or any other trials involving the off-label use of repackaged Avastin and how quality of the repackaged Avastin product had been assured.

With reference to the above-mentioned concerns on the quality and safety of repackaged Avastin being offered for use by patients, we are of the view that the repackaging of Avastin for intravitreal use should only be performed by licensed GMP certified entities and be subjected to be regulated by the HK Department of Health in order to ensure for the safety and quality of the final repackaged products, provided for use of patients participating in clinical trials or seeking treatment in the private or public health care sector.

We hope the Department of Health will imminently investigate into the matter and take the appropriate actions to ensure that off-label medicines being used on patients in clinical trials and in other health care organizations are of acceptable quality as to safeguard the health of the innocent patients being offered treatment of experimental off-label drugs.

Thank you for your kind attention to this important matter and we look forward to your kind reply.

Yours faithfully,

Dr. Yeung Chiu-Fat
President
Hong Kong Doctors Union

Iris Chang
President
The Practising Pharmacists Association of Hong Kong

cc:
Members of the Legislative Council Panel on Health Services
Dr. Chow Yat Ngok, York, Secretary for Food and Health, Food and Health Bureau
Mr. Shane Solomon, Chief Executive, Hospital Authority
Mr. K.P. Tsang, Chairman, Retina Hong Kong
Ms. Connie Lau, Consumer Council
Mr. Christopher Hickey, Country Director, US FDA