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HONG KONG DOCTORS UNION
香港西醫工會

Our ref.: HKDU/117/2010

11th June 2010

By fax and mail

Mr. Shane Solomon
Chief Executive
Hospital Authority
Hospital Authority Building
147 Argyle Street
Kowloon

Dear Mr. Solomon,

Re: Request for Clarification on Hospital Authority (HA)'s Views on Avastin (Bevacizumab) as Safe and Efficacious Treatment for Wet AMD

On behalf of the Drug Safety Consortium, comprising of member associations of the Hong Kong Doctors Union, The Practising Pharmacists Association of Hong Kong, Retina Hong Kong, and Alliance for Patients Mutual Help Organizations, we would like to seek further clarification on the views made by the Hospital Authority in the letter dated 23 May 2010 to The Practising Pharmacists Association of Hong Kong in response to our concerns on the risks to patient safety with the use of unlicensed drugs by the HA [1].

Firstly, it had been stated in the HA's reply letter that "International studies have also shown that Bevacizumab is safe and efficacious in treating wet AMD". We are of the view that this statement may be inaccurate in view of the internationally recognized and acceptable standards required for pharmaceutical products to claim product safety and effectiveness for the use on the general public.

To enable better mutual understanding of our concerns, we would like to submityou the rationale for our above-mentioned view for your kind information. According to our knowledge of the current situation, there has been no clinically significant scientific evidence generated from randomized controlled trials (RCT) to show that Avastin is safe and effective to treat wet AMD. From our understanding of the current situation, that is the very reason why some randomized controlled trials are being conducted in the USA (i.e. CATT study) and in Europe (i.e. IVAN study) but the results have yet to be published in the coming few years to have an indication on the actual safety and effectiveness profiles of Avastin to treat wet AMD.

Since a drug's safety and effectiveness are two distinct features and with safety being the more important and fundamental factor, we would first like to clarify the HA's views on claiming that international studies have also shown that Avastin (Bevacizumab) is safe for the treatment of wet AMD.

Standardized Drug Safety Evaluation Procedures

Due to the fact that the safety of medicinal drugs is of paramount importance to protect the health of the general public, it is a standardized practice, in all developed countries, to conduct the safety assessment of any particular drug product through internationally recognized and standardized procedures in a fair and objective manner by trained drug safety evaluation experts before the drug product can claim to be safe for the use by the public.

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The HA should understand that to make a public statement to claim the safety of a pharmaceutical product, when used in an unlicensed manner, to treat any disease condition is a serious and important statement which may involve legal and professional responsibility. Since the claim that Avastin is safe for use to treat wet AMD has not been supported by any drug regulatory authority in Hong Kong or overseas, in the interests of public safety, we would need the HA to provide the relevant clinically significant scientific evidence based on internationally recognized and properly conducted randomized controlled trials from which HA's statement to claim Avastin's safety to treat wet AMD has been derived, for our reference and further professional evaluation.

Since the primary assessment of a drug product's safety profile is a highly specialized function which can-not be casually performed by front-line health care professionals such as doctors, pharmacists, pharmacologists, and other health care professionals that have not received the proper training to perform this specialized role, you should require a team of highly qualified, trained, and experienced drug evaluation experts, to perform this specialized function in the capacity of a government drug regulatory authority. We would need to request for the HA to provide the specific names of the drug safety evaluation experts, with information regarding their relevant qualifications, training, and experience in performing formal drug safety evaluations, that provided the opinion to support the HA's claim that Avastin is safe to be used to treat wet AMD, for our reference. In addition, we would need the HA to provide information about the nature of the internationally recognized, standardized, and objective safety evaluation systems and procedures, if any, that have been applied by the drug safety evaluation experts to derive the conclusions for the HA's claim that Avastin is safe to be used to treat wet AMD.

Differentiation between Avastin in the original package and "Repackaged Avastin" products

Secondly, we would like to highlight the fact that Avastin is only approved to be used as a single-use sterile product, with specific labeled instructions to "Discard any unused product after opening" and is only intended to be safely used as an intravenous infusion (infused into the veins) to treat cancer. For the off-label treatment for wet AMD, the original vial of Avastin needs to be further repackaged into another form of product for intravitreal use (injection into the eyeball). Therefore, for the purpose of our discussion, we will need to make a differentiation between Avastin in its original packaged form and the repackaged form of Avastin, which we will refer to as "HA Repackaged Avastin". In fact, the product of our particular concern is the "HA Repackaged Avastin" which is being proposed to be used on HA patients for treatment of wet AMD rather than Avastin in its original packaged form.

According to the US FDA Warning Letter on Repackaging of Avastin issued in 2006 [2] highlighting concerns about the manipulation of sterile products, FDA states that as soon as the moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and thus previous studies supporting the standard are compromised and are no longer valid.

Since the quality standards of the sterile Avastin product is destroyed when opened for the purpose of repackaging for use to treat wet AMD and previous studies supporting the standards are no longer valid, we would need the HA to provide the new product specifications together with the stability test data for the "HA Repackaged Avastin" products, as evidence to support the quality standards of the repackaged products intended to be used to treat wet AMD, for our reference and further evaluation.

Unsafe and Improper Use of "Repackaged Avastin" Products

Thirdly, we would like to clarify with the HA on your reference to current medical practices made in your reply letter stating that "The off-label use of Bevacizumab (Avastin) is common in various overseas countries and the local private market."

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In order to clarify our concerns on the possibility of unsafe and improper medical practices to treat wet AMD in Hong Kong and across the world, we would need for the HA to provide evidence to show that the above-mentioned off-label use of Avastin, in overseas countries and the in local private market, is provided with "Repackaged Avastin" products that are of the required levels of quality to provide for patient safety.

Therefore, we would need the HA to provide the relevant information regarding the standards of drug quality of the "Overseas Repackaged Avastin" and of the "Local Private Market Repackaged Avastin" as evidence to show that the specific "Repackaged Avastin" products being used on patients have been duly evaluated according to internationally recognized, standardized, and objective quality assurance methods to ensure that the products are of the required quality to provide for patient safety, for our reference and further professional evaluation.
From our understanding of the current practice in the USA, the quality standards of "US Repackaged Avastin" is highly regulated by the US FDA in that the repackaging of Avastin is not allowed to be performed by doctors, pharmacists, and dispensers as a routine dispensing activity and any individual performing such activity, as a dispensing function, contravenes the law. The US FDA currently requires any repacker of Avastin to apply for licensing and be subjected to regulatory oversight by the US FDA to ensure that the "US Repackaged Avastin" products are of the required quality standards to provide for patient safety.

We would like to bring to your kind attention that the repackaging of Avastin products for the use in the previously mentioned on-going CATT clinical trial in the USA is not being performed by pharmacists working in the pharmacy department of the research institution and is being performed by a US FDA licensed repackaging company named Formatech Ltd. This is to ensure the benefit and safety of the human subjects involved in clinical trials using off-label "Repackaged Avastin" products.

Since Hong Kong, at this moment in time, has no regulatory supervision by the Department of Health on the quality standards of any kind of "Locally Repackaged Avastin" products to provide for patient safety, we are of the view that any form of "Locally Repackaged Avastin" may be of questionable quality and may impose high risks on patient safety when used by health care professionals as treatment for wet AMD. We are currently seeking the advice of the Department of Health on the patient safety implications of unregulated "Locally Repackaged Avastin" products being offered to patients in the local market.

Unless the HA can provide the required level of clinically significant scientific evidence to show that the quality of "Locally Repackaged Avastin" products have been properly evaluated through internationally recognized, standardized, and objective processes, to be safe for patient use, we are of the view that the use of any kind of "Locally Repackaged Avastin" products to treat wet AMD should not be considered by the HA as safe and proper practice.

We are also of the strong view that the HA should not take ready reference and/or follow the examples of what may be improper, unsafe, and unethical practices of the local private market in using drugs of questionable safety and quality for treatment of Hong Kong citizens but rather the HA should continue to uphold its primary responsibility as a public health care institution to provide standard levels of quality care in an ethical and proper manner to the public.

We look forward to your kind reply and to your providing the requested information for our reference at your earliest convenience on or before 30 Jun 2010. We shall seek further professional advice from experienced and credible drug safety evaluation experts. The information that the HA provides for us may be shared with overseas drug regulatory authorities (e.g.: US FDA) to seek their expert opinion evidence-based to support HA's claim that Avastin has been shown to be safe for the use to treat wet AMD.

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Thank you for your kind attention to this urgent and important matter regarding the safe use of medicines on HA patients.

Yours faithfully,

Dr. Yeung Chiu-Fat
President
Hong Kong Doctors Union

Ms. Iris Chang
President
The Practising Pharmacists Association of Hong Kong

Mr. K.P. Tsang
Chairman
Retina Hong Kong cum Alliance for Patients Mutual Help Organizations

cc: Legislative Council Members
Ms. Connie Lau, Chief Executive, Consumer Council
Dr. Chow Yat Ngok, York, Secretary for Food and Health, Food and Health Bureau
Prof. Gabriel M Leung, Under Secretary for Food and Health, Food and Health Bureau
Dr. Lam Ping Yan, Director of Health, Department of Health
Mr. Anthony T.Y. Wu, Chairman, Hospital Authority
Institutional Review Board of Queen Mary Hospital; Tuen Mun Hospital; United Christian Hospital
Mr. Christopher Hickey, Country Director, US Food and Drug Administration

References:

1. Letter to The Practising Pharmacists Association of Hong Kong
2. US FDA Warning Letter

23 May 2010

Ms Iris CHANG
President
Practising Pharmacists Association of Hong Kong
4/F., Duke of Windsor Social Welfare Building
15 Hennessy Road
Wanchai, Hong Kong

Dear Ms CHANG,

Concerns on the Risks to Patient Safety
by the Use of Unlicensed Drugs by the Hospital Authority

I refer to your letter of 1 March 2010 on the captioned matter. Thank you for bringing your Association's concerns over the treatment of wet age-related macular degeneration (AMD) to our attention.

As discussed and expressly indicated in our meeting on 10 February 2010, drug safety and patient benefits are the Hospital Authority (HA)'s primary concerns in providing healthcare services for the community.

The off-label use of Bevacizumab (Avastin) is common in various overseas countries and the local private market. International studies have also shown that Bevacizumab is safe and efficacious in treating wet AMD. The HA is open to different treatment options and would consider the safety, efficacy and cost-effectiveness of different drugs with reference to published scientific evidence, expert advice as well as international practice in the safe use of drugs. We will also keep abreast of international studies that are currently underway and strive to enhance the safety and benefits for our patients.

Thank you for your attention.

Yours sincerely,

(SIGNED)

(Dr W L CHEUNG)
Director (Cluster Services)
for Chief Executive
Hospital Authority

c.c. Secretary for Food and Health
Director of Health
Chief Pharmacist, Department of Health
Chairman, Legislative Council Panel on Health Services
Chairperson, Consumer Council
President, Alliance for Patients Mutual Help Organizations
Professor Dennis LAM, The Chinese University of Hong Kong
Professor David WONG, The University of Hong Kong
Chief of Service (Ophthalmology), Tuen Mun Hospital
Chief Pharmacist, Hospital Authority

Extract from US FDA Warning Letters 2006

http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074385.htm
CPG Sec. 446.100 Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076196.htm

3. Repackaging;
Additionally, we are in receipt of a complaint alleging that you are repackaging the approved injectable drug, Avastin, into syringes for subsequent promotion and sale to health professionals . Avastin is unpreserved and is packaged and labeled in 4 and 16 ml single-use glass vials. The labeled 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. 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 labeling 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.
The agency has an established policy, articulated in Compliance Policy Guide Sec. 446.100, Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations (CPG 7132c.06) (copy enclosed), concerning the manipulation of approved sterile drug products outside the scope of the FDA-approval. 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 intravitreally, 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.***

Avastin is approved for use in the treatment of colorectal cancers. The text of your alleged promotional material offers this drug to ophthalmologists . Avastin has no approved indications for use in the eye. As such, your firm is distributing an unapproved new drug in violation of section 505 of the FDCA. Because the product lacks adequate labeling for its intended use (see 21 CFR § 201.128) your firm is also distributing a misbranded drug in violation of section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)). Also, please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited.
