For information on
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Legislative Council Panel on Health Services

Regulation and Control of Pharmaceutical Products in Hong Kong

PURPOSE

This paper briefs Members on the measures to be taken by the Administration to review and enhance the existing regime for the regulation and control of pharmaceutical products in Hong Kong, in the light of the recent incidents concerning pharmaceutical products. The Hospital Authority will also strengthen procurement procedures for drugs.

EXISTING REGULATORY REGIME

Registered Pharmaceutical Products in Hong Kong

2. To date, some 19 500 pharmaceutical products are registered in Hong Kong. Around 70% are imported while the rest are manufactured locally. The imported pharmaceutical products are either patented drugs or off-patent generics. Local manufacturers only produce off-patent generics. Of the 13 000 imported drugs, about 11 000 are off-patent drugs. There are about 6 500 locally manufactured off-patent generics.

Regulation of Drugs in Hong Kong

3. Regulation of drugs is essentially provided for by the Pharmacy and Poisons Ordinance (Cap. 138) ("the Ordinance") and implemented through a dual target multi-pronged system at various levels involving (a) control of the trade; and (b) control of the drugs. Section 3 of the Ordinance provides for the establishment of a Pharmacy and Poisons Board ("the Board") for enforcement of the Ordinance. Section 4A of the Ordinance further allows the Board to establish executive committees to register drugs and license medicine dealers.

Control of the Trade

4. There are four levels of players in the drug supply chain, viz. manufacturers, importers, wholesalers of poisons, retailers of poisons (including the pharmacists overseeing the operations of the retailers). At present, there are 25 manufacturers, 240 importers/exporters, 860 wholesalers for poisons and 3 800 retailers in the Hong Kong. They are all subject to licensing control under the Ordinance.

Manufacturers

5. All pharmaceutical manufacturers must first obtain a licence from the Manufacturing Licensing Committee of the Board. The licensing requirements to be met in approving the manufacturer's licence and during licence renewal include –

(a) the manufacturing process be under the supervision of registered pharmacist;

(b) proper labeling of drugs manufactured;

(c) adequate hygiene control of personnel and premises to avoid contamination of drugs; and

(d) quality assurance of raw materials and finished products with retention of control sample and all the related record control of these different processes.

Since 2002, compliance with the Good Manufacturing Practice (GMP) (see paragraphs 18 – 20 below) has become an additional important licensing condition. Under the existing Ordinance, except for the compliance with GMP licensing requirement, noncompliance of licensing requirements are an offence and are subject to a maximum penalty of $100,000 and 2 year's imprisonment.

6. Licensed pharmaceutical premises of manufacturers are regulated by the Ordinance and monitored by means of GMP inspections conducted by two inspectors of Department of Health (DH) once or twice a year, each inspection lasting one or two days. These inspections aim at ensuring the continuing compliance with the GMP requirements.

During inspections, all different GMP aspects will be audited for compliance and checked against a checklist and samples of drugs will be selected for analysis to ensure quality. If there is minor noncompliance with any licensing conditions, the manufacturer is instructed to remedy the situation and verbally reprimanded. For other serious noncompliance, the Manufacturing Licensing Committee may revoke the licence or suspend it for such period as it thinks fit.

7. In addition, warehouses of poison wholesalers, pharmacies of authorized sellers of poisons, and medicine companies of listed sellers of poisons are also regulated by the Ordinance because the nature of poisons may cause risk to the public if handled improperly. DH regularly inspects these premises to ensure the premises comply with the requirement of the law. The inspections on these premises of the traders are unannounced. Additional ad hoc inspection would be carried out when the premises are involved in complaints or investigation of drug incidents.

Importers/Exporters and Wholesalers

8. There are around 1 100 traders licensed to deal with imports/exports and wholesale of pharmaceutical products. Depending on the nature of the drugs being handled, different types of licences are required. For company importing or exporting drugs not classified as poisons under the Ordinance into or out of Hong Kong, a Certificate of registration as an Importer and Exporters (IE) is required. For company handling import and export, and / or wholesaling in drugs classified as poisons under the Ordinance, a Wholesale Poisons Licence (WPL) is required. There are about 860 WPL and about 240 IE certificates issued. These licences/certificates are issued by the Wholesale Licences and Registration of Importers & Exporters Committee of the Board. No licence is required for company trading in drugs of non-poisons inside Hong Kong, provided the drug is registered.

9. General licensing conditions for the wholesalers and importers/exporters include the suitability of the premises and the adequate knowledge of the person-in-charge in the pharmaceutical trade.

10. Additional licensing requirements for dealers holding WPL include proper record keeping of all transactions and restriction of sales

of poisons to authorized persons only. Failure to comply with the licensing requirements is an offence and is subject a maximum penalty of $100,000 fine and 2 years' imprisonment. The Wholesale Licences and Registration of Importers & Exporters Committee of the Board may revoke or suspend the licence for such period as it thinks fit if the licensee has failed to comply with licensing conditions or has been convicted of an offence.

11. These dealers are monitored by means of unannounced inspections. During inspections, transaction records with the relevant supporting documents, storage conditions of the premises, and the labeling of the pharmaceutical products are audited. For minor irregularities, the dealers will be instructed to rectify the situation. For noncompliance with the law, prosecution will be instigated.

Retailers

12. A total of around 3 800 retailers (around 500 authorized sellers of poisons and 3 300 listed sellers of poisons) are now licensed to deal with retail business of drugs.

Authorized seller of poisons

13. Authorized seller of poisons (ASP), commonly known as pharmacies, is authorized to sell drugs including those classified as poisons. The Board will issue an ASP licence if it is satisfied that the applicant is a fit and proper person and the premises is suitable to conduct the retail sale of poisons. Licensing requirements also include proper supervision of sale of poisons by registered pharmacist. The name, pharmacist's certificate of registration and notice of pharmacist's working hours must be displayed in a conspicuous location inside the ASP. Other requirements include full adherence to the Code of Practice for ASP in respect of procurement, storage, sale and supply, and record keeping for transactions of medicines and poisons.

14. Regular unannounced inspections to ASP are conducted on average twice a year. During the inspections, records of sales, storage and physical stock of drugs will be checked for law compliance. Professional advice on the standard of pharmacy practice will also be given. For noncompliance with the law, prosecution will be instigated. The maximum penalty upon conviction is a fine of $100,000 and 2 years'

imprisonment. After conviction, the ASP may be subjected to inquiry by Disciplinary Committees appointed by the Board. Disciplinary sanctions ranging from written warning to disqualification from being an ASP for a specified period of time may be directed. The Board may also reject the renewal application of an ASP whom it considers not being fit and proper for business. For minor infringement, the Board may direct an interview and verbal caution to the proprietor/director and pharmacist concerned.

Listed seller of poisons

15. Listed seller of poisons (LSP) licence is required for company conducting the retail sale of drugs classified as Part II poisons. They are commonly known as medicine companies. The Listed Seller of Poisons Committee of the Board issues licence to LSP on the basis of the suitability of the premises and knowledge of the person-in-charge of the trade.

16. Like the ASP, LSP is also inspected on average twice a year as unannounced visit. Inspection for law compliance regulating to the sale, storage and proper labeling of drugs will be conducted. For noncompliance with the law, prosecution will be instigated. The maximum penalty upon conviction is a fine of $100,000 and 2 years' imprisonment. The Board may remove the name of an LSP from the list of LSP if it considers him not a fit and proper person to continue the retail business of Part II poison upon any convictions. For minor infringement, the Board may issue a written warning.

Control of Drugs

17. As for drugs, it is stipulated in the Ordinance that all drugs in Hong Kong must be registered with the Board before sale. In line with international practice, only products which are safe, efficacious and of good quality will be registered. Drug safety and efficacy are mainly demonstrated through clinical trial results. As regards assurance of product quality, it is through the licensing requirement for local pharmaceutical manufacturers to have the status of GMP. There is also a similar mandatory requirement for imported drugs, though certification of GMP for imported products is performed by the corresponding overseas authorities.

Good Manufacturing Practice

18. GMP is a quality assurance approach used by the drug manufacturing industry worldwide to ensure that products are consistently produced and controlled according to quality standards appropriate to the products' intended use. Most countries have adopted the GMP guidelines promulgated by the World Health Organization (WHO), although countries such as USA, EU and Australia have drawn up their national GMP guidelines which are recognized to be of a standard higher than the WHO guidelines. There is consensus among leading world regulatory authorities that the purpose of the GMP is to diminish risks inherent in any pharmaceutical production. The spirit of the GMP emphasizes that the assessment of "good quality" should be based on scrutiny of the manufacturing process and not by testing of the pharmaceutical goods produced.

19. A GMP manufacturer should have adequate premises, spaces, laboratories, personnel, suitable storage and transport. The personnel should be appropriately qualified and trained. All the manufacturing processes must be validated and clearly defined, systematically reviewed and shown to be capable of consistently manufacturing pharmaceutical products of the required quality and comply with their specifications. Instructions and procedures are required to be written in clear and unambiguous language, specifically applicable to the facilities provided. Records must be made during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations must be fully recorded and investigated. In addition, appropriate materials, containers and labels must be used.

20. It is internationally accepted that in response to commercial practice and its own capacities, a manufacturer may only carry out a particular step, certain steps, or all steps in the manufacturing process. Whatever manufacturing steps the company carries out, those steps must be GMP certified. Of the 25 licensed manufacturers in Hong Kong, 24 are GMP certified to perform the manufacturing of various kinds of medicines as the case may be. The remaining one is GMP certified to perform the packaging of pharmaceutical products, which is regarded as part of a manufacturing process by leading regulatory authorities.

Two-tier Monitoring and Control System

21. To ensure proper control of the safety, efficacy and quality of drugs, Hong Kong has a two-tier monitoring and control system that is very similar to those in many other overseas authorities, comprising pre-market and post-market control.

Pre-market Control

22. Pre-market control refers to the assessment of safety, efficacy and quality of pharmaceutical products, which are products containing new chemical entities, generic versions of drugs, or products that required re-registration before they are released to market. When there are changes in product name, dose form and/or name and quantity of all its active ingredients of a product, the products need to be re-registered under the Pharmacy and Poisons Regulations.

23. An application for registration has to include information on the product's formulation, specification, analysis results, stability data, label and insert, plus a sample. Evidence that the product is available for sale in the country at where the product is manufactured must also be in the submission. Specifically for quality assurance, GMP certificate issued by the relevant competent authority is required.

24. When a product's safety, efficacy and quality has been proved to the satisfaction of the Registration Committee of the Board, and its packaging, insert and labelling have also been found to meet the legal requirements, the product can be registered. To this end, a registration certificate bearing the name of the drug as well as the registration number will be issued. The certificate is valid for five years and renewable on expiration.

25. For public health protection, any change in a drug's registered particulars, including the pack size and manufacturer, requires the approval of the Registration Committee.

Post-market Control

26. To complement licensing of the trade and inspections of licensed premises described above, DH also has in place the following programme to monitor the safety, efficacy and quality of marketed drugs –

(a) **A drug surveillance programme**. Registered drugs are subject to a mixture of random and risk-based sampling for chemical, microbiological (for sterile products only) and stability testing and checks for packaging, insert and labelling compliance.

(b) **An adverse drug reaction reporting programme.** Healthcare professionals are encouraged to report signs and symptoms which are uncommon under normal pharmacological dose.

(c) **A toxicovigilance programme**. It is a collaborative programme between DH and the Hospital Authority (HA). When HA encounters patients suspected to have been affected by the consumption of harmful products (e.g. Traditional Chinese Medicine or health products adulterated with western drug ingredients, herbal tea made with harmful ingredients, or ingredients of the wrong identity), it refers to DH for follow-up investigation. Reports which have public health implications will be announced to healthcare professionals, members of the general public and overseas health authorities when necessary.

27. Besides, manufacturers and wholesalers are required by law to devise and maintain a recall mechanism so as to ensure comprehensive and speedy recall of their products at various levels whenever required. The recall mechanism is a key area for consideration when relevant licences are renewed. To facilitate manufacturers and wholesalers, DH has issued a set of recall guidelines since 2000. As regards retailers, they are expected to cooperate with the manufacturers and wholesalers when the latter initiates a recall, by immediately removing the products concerned from display shelves and returning them to the manufacturer or wholesaler concerned.

DRUG PROCURMENT ARRANGEMENT OF HA

28. As the provider of public health services, HA prescribes a wide spectrum of pharmaceutical products for patients in its hospitals and institutions, Specialist Outpatient Clinics and General Outpatient Clinics. HA has established a mechanism in its procurement arrangement of pharmaceutical products to safeguard the safety of its patients. In

compliance with the requirements of World Trade Organization, items of high volume and value with market alternatives are purchased through open tenders. All bids from suppliers for drug items must comply with the mandatory quality requirements as specified in paragraph 29 below before their price offer will be considered. In other words, price only comes into consideration after quality. There are about 3 200 in use drug items in HA, approximately 50% are of off-patent products. Of the off-patent drugs items, 430 items are purchased through tender with award to single-supplier whilst the remaining off-patent drugs are purchased from multiple suppliers where available. Of the off-patent drug items purchased by HA, about 350 items are from local manufacturers.

29. In accordance with HA policy, other than in exceptional circumstances, only drugs registered with the DH are purchased. Selection of drugs (patented or generic) is based on compliance with all quality requirements, i.e. registration with DH; accreditation of GMP of the manufacturing site; and detailed product specific information, such as product master formula, method of assay, finished product specification and stability data. For generic drugs, bioequivalence data is also required to ensure equivalence with patented drugs. All the listed quality requirements are based on the requirements of the WHO. HA also conducts product testing.

30. The HA's Drug Selection Committee, an independent committee consisting of physicians, clinical pharmacologists and pharmacists from HA, DH, the private sector and a university, independently selects generic products for the HA to ensure product quality and safety.

RECENT INCIDENTS ON PHARMACEUTICAL PRODUCTS

31. Recent incidents concerning pharmaceutical products in Hong Kong have caused great public concern and called into question public confidence on the adequacy and performance of the existing regime for the regulation and control of pharmaceutical products -

(a) **The incident on fungal contaminated Allopurinol**. The University of Hong Kong announced on 6 March 2009 that four batches of Allopurinol 100mg tablets produced by a

local manufacturer, the Europharm Laboratories Ltd. (Europharm), were contaminated with Rhizopus microsporus. On 9 March 2009, DH ordered the local manufacturer to recall all Allopurinol tablets from the market as laboratory analysis of the samples of the affected four batches of Allopurinol confirmed the presence of Rhizopus. DH's investigation revealed that during the production process, there was prolonged storage of granules prior to tabletting.

(b) **The recall of drugs which had failed stability testing**. DH on 11 March 2009 instructed another local manufacturer, Marching Pharmaceutical Ltd. (MPL), to recall a total of 216 pharmaceutical products as the label expiry dates of these products were not substantiated by laboratory data. The Manufacturers Licensing Committee of the Board on 12 March 2009 suspended the manufacturer's license of the company for one month to facilitate investigations into the operation of the company. The case had also been reported to the Police as during the course of DH investigations, certain irregularities in the documents submitted by the company were found.

(c) **Supply of unregistered pharmaceutical products**. It was found on 16 March 2009 that part of the pharmaceutical products (metformin tablets packed in 50x10's blister which are a kind of diabetic drug) supplied to HA by a local manufacturer, Christo Pharmaceuticals Ltd, had yet to be registered by DH. DH's investigation is ongoing.

(d) **Suspected unlicensed packaging of pharmaceutical products**. On 19 March 2009, DH investigated a case which involved suspected unlicensed packaging of Amitriptyline tablets (a drug for depression) by Unipharm Trading Company, which is a drug importer with no drug manufacturing licence. The tablets were imported by the company from a licensed drug manufacturer in the United Kingdom. DH has instructed the company to recall the products from public hospitals, public clinics, private hospitals, private doctors and pharmacies. DH's investigation is ongoing.

(e) **Pharmaceutical products supplied to HA not matching with the declaration in label**. On 22 March 2009, DH

instructed a licensed drug importer "Luen Cheong Hong Ltd" to recall two batches of "Water for Injections" produced by the Indonesian subsidiary of a Japanese company, Otsuka, and supplied to HA, the volume of which did not match with the declaration in label. DH's investigation is ongoing.

32. As an immediate measure, DH has already commenced targeted inspection to all the 25 local manufacturers. Prioritization is based on risk assessment, with manufacturers which are sister companies of those manufacturers involved in recent incidents to be inspected first. The emphasis of the inspection would be on the licensees' demonstration of their diligence in assuring the safety, efficacy and quality of their products, particularly the identification and control of microbiological hazards.

COMPREHENSIVE REVIEW ON THE REGULATORY REGIME

Setting up of a Review Committee

33. In the light of the recent drug incidents, the Administration considers that in order to ensure patient safety, protect public health, and restore public confidence, a comprehensive review on the existing regulatory regime for the regulation and control of pharmaceutical products is necessary to identify gaps and areas for improvement.

34. The Secretary for Food and Health announced on 19 March 2009 the setting up of a Review Committee, which will be chaired by the Permanent Secretary for Food and Health (Health) and comprise members from the pharmaceutical sector, medical profession, academia, patient groups and consumer representatives, amongst others. The Review Committee will conduct a comprehensive review on all the relevant issues including safety and quality assurance of drugs, standard and practices of the pharmaceutical industry, and whether there is a need for legislative amendments. To support the work of the Review Committee, the Director of Health has set up a Task Force to comprehensively review the existing control of the drug supply chain, including manufacturers, importers, wholesalers and retailers, as well as the control of drugs. An Expert Group on Microbiological Hazards on Drug Manufacturing will also make proposals to the Task Force. Their recommendations will be put to the Review Committee for deliberations. The Department of Health will enlist the assistance of a reputable overseas authority to assist and advise on the work of the Task Force.

The views from the relevant stakeholders will be sought and duly taken into account in the course of the review.

Review Framework

35. The review of the existing regulatory regime would involve both DH and HA and cover the following major areas -

(a) The governance and internal audit system of local manufacturers, including sister companies;

(b) Scope of GMP, including microbiological safety and quality requirements, and review of the Standard Operating Procedures, for quality assurance;

(c) Enhancement of the GMP inspections on local manufacturers and review of the checklist used by DH inspectors when conducting inspections with a view to yielding measurable and accountable audit results;

(d) Effective penalty system to ensure GMP compliance, which may include a demerit point system capable of proportionate penalty ranging from for example written warnings, announcement of serious noncompliance cases, suspension or termination of licences;

(e) Establishment of a robust microbiological vigilance system on the part of the manufacturers with standards set by DH for microbiological testing;

(f) Assessment of the additional work involved and the resulting resource implications in support of the enhanced regulatory framework;

(g) Proposals for legislative amendments, if required;

(h) Comprehensive review on HA's procurement policy for pharmaceutical products, covering both new and renewal of contracts, to ensure stability of supplies as well as quality assurance;

(i) Effective system in HA to assess product quality and suppliers' capacity and to ensure regulatory compliance

when sourcing supplies of pharmaceutical products;

(j) Consider introducing mandatory requirement for sample testing and trial run in the drug procurement process in HA, especially those drugs intended for high-risk patients;

(k) Inputs from clinicians in drug procurement process and a system to gather users' feedback in HA; and

(l) Standardized procurement and supply procedure of drugs to private hospitals and private doctors to ensure safety and accountability.

36. The Task Force led by the Director of Health and the Review Committee chaired by the Permanent Secretary for Food and Health (Health) will examine in details the issues set out in the above review framework with a view to formulating specific recommendations for implementation. We will announce the Committee membership shortly and will have the first meeting in early April. It is expected to complete the review in six to nine months' time.

ADVICE SOUGHT

37. Members are invited to note the contents of the paper.

Food and Health Bureau
Department of Health
Hospital Authority
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