CHAPTER 3 REGULATION OF DRUG MANUFACTURERS AND ENHANCEMENT TO THE GOOD MANUFACTURING PRACTICES SCHEME

Overview

3.1 This chapter describes the current licensing system for drug manufacturers in Hong Kong and sets out the Review Committee's findings and recommendations on areas for improvement.

Current Licensing System for Drug Manufacturers

3.2 Drug manufacturing is defined under the Ordinance as "the preparation of pharmaceutical products for sale or distribution, but shall not include the individual dispensing on a prescription or otherwise of any pharmaceutical products". To ensure that drugs produced are safe, efficacious and of good quality, drug manufacturers must first obtain a licence. The licensing authority is the Pharmacy and Poisons (Manufacturers Licensing) Committee ("the Manufacturers Licensing Committee") under the Pharmacy and Poisons Board.

Licensing Requirements

3.3 The licensing requirements to be met in awarding a manufacturer licence and during licence renewal include –

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

(b) proper labelling 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 related records.

Since 2002, compliance with the Good Manufacturing Practices (GMP) has become an additional important licensing condition.

Good Manufacturing Practices

3.4 GMP is a quality assurance approach used by the drug manufacturing industry worldwide to ensure that products are consistently produced and controlled according to appropriate quality standards. Most countries have adopted the GMP guidelines promulgated by the World Health Organization (WHO), although countries such as the United States, European Union and Australia have drawn up their national GMP guidelines which are recognized to be of a standard higher than the WHO guidelines. 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 end products alone.

3.5 A GMP manufacturer should have adequate premises, spaces, laboratories, personnel, storage facilities 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 complying 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.

3.6 GMP specifies the recruitment of three key personnel in the manufacturer, namely the Authorized Person (AP) responsible for product release, head of production and head of quality control. In the Hong Kong context, the AP position must be filled by a registered pharmacist with at least one year of relevant experience in pharmaceutical manufacturing or quality control. As regards the other two heads, they must have at least one year of relevant experience if they have a pharmacy degree; two years of relevant experience if they have a higher diploma in pharmacy-related subjects; or three years of relevant experience if they have a degree in a relevant science subject. In addition, any change in the three key personnel must be approved by the Manufacturers Licensing Committee.

3.7 Of the 25 licensed manufacturers in Hong Kong, 24 are GMP certified to perform the manufacturing of various kinds of medicines. The remaining one is GMP certified to perform the packaging of pharmaceutical products only, which is regarded as part of a manufacturing process by leading drug regulatory authorities.

Processing of Licence Applications

3.8 Upon receipt of a licence application, DH inspectors will first study and assess the information in the application carefully. If the applicant has met the licensing requirements on paper, DH will inform the applicant to proceed with site preparation, staff recruitment and training; and then conduct on-site inspection. When DH is satisfied that the applicant has fulfilled all licensing conditions, a report will be put up to the Manufacturers Licensing Committee for decision. A licence is valid for one year and is renewable annually.

Monitoring and Inspections

3.9 To ensure compliance with the licensing requirements, licensed manufacturing premises are regulated by means of GMP inspections conducted by two DH inspectors at least once a year. Each inspection lasts for two days. During the inspection, all different GMP aspects will be audited for compliance against a checklist and product samples will be taken for analysis.

3.10 For minor non-compliance with any licensing conditions, the manufacturer will be verbally reprimanded and instructed to remedy the situation. For more serious non-compliance, the case will be submitted to the Manufacturers Licensing Committee which may revoke the licence or suspend it for such period as it thinks fit. If non-compliance with the law is found, prosecution action will be initiated. Convicted persons are liable to a maximum penalty of $100,000 and two years' imprisonment. The Manufacturers Licensing Committee may take further disciplinary action against the licensee after conviction, including the issue of a warning letter and further revocation or suspension of licence.

Consultancy Study on Hong Kong's GMP

3.11 Since Hong Kong's GMP has been in use since 2002 and may need updating in content, DH commissioned an overseas GMP expert from Australia in May 2009 to conduct a consultancy study on Hong Kong's GMP in the light of the latest practices in leading world drug regulatory authorities. The overseas consultant has made a number of recommendations, which were discussed first in the DH Task Force before putting forward to the Review Committee for consideration.

Microbiological Hazards on Drug Manufacturing

3.12 The Europharm drug incident has revealed the microbiological hazards in drug manufacturing. Shortly after the incident, DH set up an Expert Group, with Professor YUEN Kwok Yung, Head of the Department of Microbiology of University of Hong Kong as an expert advisor, to identify and evaluate microbiological hazards in the drug production process; and then propose an enhanced model for microbiological monitoring in drug manufacturing in Hong Kong. The Expert Group formulated an enhanced model and tested out this enhanced model in Europharm Laboratoires Company Limited. Based on the trial-run results, the Expert Group has refined the model and recommended that the model be implemented in all drug manufacturers in Hong Kong.

3.13 Under the proposed model, microbiological tests should be performed on all batches of high risk raw materials, prior to the use of the batch, and every six months thereafter, until the batch is used up. The holding time of granules prior to tabletting should be as short as possible, with an upper limit of not more than 48 hours. If a manufacturer intends to adopt a holding time beyond 48 hours for any product, the holding time to be adopted for that product must be supported by validation studies data. Furthermore, manufacturers should establish a more stringent in-house microbial limit for each product. Full microbial limit tests should be performed on every batch of every finished product before release for sale. Microbiological testing should also be included in the stability study programmes of all pharmaceutical products.

Findings and Recommendations

I. GMP Consultant's Recommendations

3.14 The Review Committee has considered and **endorsed the majority of the GMP consultant's recommendations** as follows –

(a) Upgrade of Hong Kong GMP Standards

3.15 It is recommended that DH should upgrade Hong Kong's current GMP licensing standards by a phased approach to PIC/S (Pharmaceutical Inspection Co-operation Scheme[1]) standards over a period of about four years to reflect changes in industry technology and to be on par with international best practice.

[1] The Pharmaceutical Inspection Co-operation Scheme is an international agreement between pharmaceutical regulatory authorities of different countries or territories which provide an active and constructive co-operation in the field of GMP. This is to be achieved by developing and promoting harmonized GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitate co-operation and networking for competent authorities and international organisations. There are currently 37 participating authorities including the majority European Union countries, Australia, Singapore, etc.

During the transition period, Hong Kong's GMP licensing standards should first be upgraded to 2007 WHO standards in about two years' time.

3.16 It is recommended that DH commissions a consultant to assist local drug manufacturing industry in progressing towards the PIC/S standards. Furthermore, DH should adopt international GMP guidance documents for implementation by the industry, develop an information website and set up an industry liaison group with industry participation.

(b) Control over Imported Drugs

3.17 It is recommended that DH should require imported drugs to comply with the same standards once local drugs attained the PIC/S standards, i.e. they should have GMP certificates issued by PIC/S member countries. For drugs of other places without recognized GMP certificates, their manufacturing premises must be inspected by either DH inspectors or a third party approved by the Pharmacy and Poisons Board to certify that their GMP standards is equivalent to the PIC/S standards before they could be allowed to import into Hong Kong.

(c) Control over the Use of Active Pharmaceutical Ingredients and Testing Laboratories

3.18 It is recommended that DH strengthens the control of the use of Active Pharmaceutical Ingredients (APIs) and contract laboratories by local manufacturers. For APIs not produced by manufacturers certified to have PIC/S standards, APs should be responsible for inspection of the manufacturing premises of APIs to certify the quality of APIs as well as retention of the inspection reports for DH examination. Besides, only laboratories licensed by DH or accredited by a third party in lieu could be used by local manufacturers for product testing. In this connection, DH should work out with relevant experts the licensing requirements and inspection checklist for contract laboratories.

(d) Tightening up the Qualification Requirements for AP and other positions

3.19 To ensure that the APs and the heads of production and quality control are capable of discharging their duties, the Review Committee **recommends** strengthening their experience requirement as follows –

- for AP: from at least <u>one</u> year of relevant working experience to at least <u>three</u> years;

- for the heads of production and quality control: from at least one year to at least two years for pharmacy degree holders and from at least two years to at least three years for holders of higher diploma in pharmacy-related subjects.

For degree holders of a relevant science subject, the Review Committee recommends no change to the three years' experience requirement to be eligible as the head of production or quality control.

3.20 The Review Committee considers that it is part of PIC/S requirements as well as a worldwide trend that the AP or equivalent position of manufacturers is filled by the most qualified person in possession of the relevant knowledge and experience dependent on the product characteristics and manufacturing needs of individual manufacturer. In many developed countries, the APs are not necessarily pharmacists. The Review Committee **recommends** that a formal set of criteria regarding the qualifications of the AP be set, a licensing or listing scheme to be established, alongside with the introduction of a structured training programme and a mechanism to ensure that APs will take responsibility for the quality, safety and efficacy of their drug products. The tightening up of the entry requirements of AP will raise the product manufacturing and quality control standards of local manufacturers.

3.21 In the meantime, the position of AP will still be required to be filled by pharmacist with relevant experience. The Review Committee notes that a pharmacist acting as AP is bound by both the responsibilities of AP as laid down under GMP and the disciplinary mechanism of the Pharmacy and Poisons Board against his professional status. Such a "double gate-keeping mechanism" is desirable for the protection of public health.

3.22 In the longer run, the Review Committee **recommends** empowering the Pharmacy and Poisons Board to maintain an AP register and remove any AP from the register should he be found incompetent to perform the AP role. The Pharmacy and Poisons Board should adhere to the usual open and transparent procedures in taking disciplinary actions against an AP and allow the AP concerned to make representations. The Review Committee also **recommends** DH to consult the Department of Justice (DoJ) on the feasibility of including the registration mechanism of APs in the Pharmacy and Poisons Ordinance.

3.23 When the above registration system for APs is in place and additional formal certified GMP training has been developed, consideration will be given to allowing non-pharmacists with the required experience and training to assume the position of AP.

3.24 The Review Committee **recommends** DH to liaise with the University Grants Committee and the universities offering pharmacy courses with a view to launching Master degree course(s) in drug manufacturing similar to the one being developed by the Chinese University of Hong Kong as soon as possible. DH should then monitor the supply of graduates from these courses and draw up an implementation timetable in consultation with the manufacturing industry for allowing non pharmacists to be APs.

(e) DH Inspection and Licensing Processes

3.25 It is **recommended** that DH upgrades the inspection and licensing processes to PIC/S standards in one year's time, including the establishment of an internal quality management system in line with the PIC/S requirements. In addition, the inspection reports should model on the PIC/S risk-rating and evidence-based report format. The portion of GMP-related duties of DH inspectors should be raised from the current 20% to not less than 50% of their work and the number of inspections should increase. While most of the inspections to manufacturing premises should remain announced, some unannounced inspections should be introduced. Further, one of the two inspectors in the inspection team should be retained for subsequent inspections to facilitate effective follow-up on irregularities identified.

3.26 DH should arrange the necessary training to staff and provide additional manpower support to implement the GMP consultant's recommendations in this regard.

3.27 The Review Committee also notes that DH inspectors do not have expertise on every aspects of drug manufacturing process. The Review Committee therefore **recommends** that DH sets up a multi-disciplinary GMP inspection team with professionals of other related disciplines like biochemists, chemists, engineers, microbiologists, etc. dependent on the production environment of manufacturers.

(f) Training Programme

3.28 It is **recommended** that structured, practical and continuous training programmes be developed for all levels of players in the GMP system including DH inspectors, APs, production and quality control heads, and shop floor level workers. Specifically, training programme for APs should be mandatory with content approved by DH. Training records for different levels of staff of manufacturers should be kept for auditing by DH as part of GMP inspections.

II. Invitation of AP to attend Board Meetings of Manufacturers

3.29 The Review Committee has also discussed the pros and cons of requiring AP to be a board member of manufacturers. On the pros side, the Review Committee notes that by sitting on the board, the status of AP can be elevated and the AP can ensure that his authority in respect of product quality and release will not be interfered with. Besides, the AP being a professional can help to ensure that decisions of the board will not be made on commercial interests alone. Furthermore, the AP can draw the board's attention to product quality issues and guide the board to take a proactive approach in avoiding drug incidents, instead of just playing a gate-keeping role.

3.30 On the other hand, the Review Committee notes that under GMP, the AP already has the final authority in respect of product release and even the board cannot interfere with the decisions of AP in this regard. If the AP is on the board, he will be diverted by business considerations and may compromise his professional role in respect of product quality control. Besides, AP being a pharmacist may not be able to undertake the business responsibilities of a board member, nor is it fair for AP to bear the business liabilities of a board member.

3.31 The Review Committee also notes that according to research of DH, there are no countries mandating manufacturers to put the AP or equivalent on the board of directors. It may constitute an unreasonable interference to the business decisions of manufacturers. From the perspective of good corporate governance, it is more important to establish a communication channel between AP and the management.

3.32 Taking into consideration the pros and cons, the Review Committee **recommends** DH state in the licensing condition that local manufacturers should either (a) appoint the AP as a board member; or (b) invite the AP to attend board meetings and allow the AP to speak and have his remarks put on record where safety, efficacy and quality issues of products are concerned. The recommendation should be put on trial for two years and then reviewed.

3.33 To further protect the authority of APs, the Review Committee **recommends** that a code of practice (COP) be introduced to govern the conducts of both the manufacturers and the APs. DH should prepare the COP in consultation with the industry and other stakeholders. The COP should state, inter alia, that AP has ultimate responsibility on product safety and that AP is required to certify every batch of finished products in compliance with GMP standard and registered particulars before release for sale. Compliance with COP should be a licensing condition.

III. Enhanced Model for Microbiological Monitoring of Pharmaceutical Products manufactured in Hong Kong

3.34 The Review Committee has considered the proposed model by the Expert Group on better monitoring of pharmaceutical products manufactured in Hong Kong, and **recommends** that all local manufacturers be required as a licensing condition to implement the proposed model in order to better guarantee safety and quality of finished products. The enhanced microbiological monitoring model covers raw materials, granules, finished products and stability studies.

Raw Materials

3.35 Manufacturers should perform microbiological tests on all batches of high risk raw materials prior to the use of the batch, and every six months thereafter, until the batch is used up. If a manufacturer wishes to test in other time intervals, it has to provide justifications for approval by DH.

Granules

3.36 Manufacturers are required to limit the holding time for in-process granules to not more than 48 hours before tabletting. If a manufacturer intends to adopt a holding time beyond 48 hours for any product, it must first seek approval from DH with support of validation studies data.

Finished Products

3.37 Manufacturers should set a more stringent in-house alert level for microbial burden of each product to be two times one $\log_{10}$ value lower than the pharmacopoeial limits, as compared with the common practice of one $\log_{10}$ lower value. If a manufacturer intends to adopt other alert level, it must first seek approval from DH with justifications.

3.38 Manufacturers are required to conduct full microbial limit tests on every batch of every finished product before release for sale. If the test results of five successive batches of a product meet the in-house standards, manufacturers are allowed to reduce the testing to every 5^{th} batch. However, at a minimum, manufacturers should still perform one batch test every six months. If any test result shows deviation from the longitudinal trend of previous results, manufacturers must conduct investigation, record the investigation result in writing and take all necessary remedial measures to restore the test result within the in-house standards.

Stability Studies

3.39 Manufacturers should include microbiological testing in the stability study programmes of all pharmaceutical products.