INFORMATION NOTE

Regulations governing the definition, registration and manufacture of medicinal products in the European Union

1. Introduction

1.1 In Hong Kong, the regulation of pharmaceutical products has aroused public concerns in recent years. Pharmaceutical products are also known as medicinal products in some jurisdictions like the European Union ("the EU"). At the meeting held on 17 June 2014, the Bills Committee on Pharmacy and Poisons (Amendment) Bill 2014 requested the Research Office to study the regulatory framework in the EU governing (a) the definition and registration system of medicinal products; and (b) the manufacture of medicinal products and the qualification requirements for qualified persons.[1] The purpose of this information note is to provide information on the above for Members' reference.

2. Legislative framework

2.1 In terms of regulation of medicinal products, all 28 Member States of the EU are bound by a single set of legislation (Directives) and regulations. In the EU, regulation of medicinal products is the same both for human and veterinary products. However, the legislation is covered by two Directives, both originating from 2001: (a) Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use; and (b) Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to veterinary medicinal products.

[1] Qualified persons are known as authorized persons in Hong Kong.

2.2 The EU legislation and regulations set out, among other things, (a) the definition of medicinal products; (b) the registration system to obtain the marketing authorization for medicinal products for human use and veterinary medicinal products; (c) the post-authorization safety study; and (d) the regulations governing the manufacture of medicinal products and the qualification requirements for qualified persons.

3. Definition of medicinal products

3.1 In the EU, a medicinal product (other than food supplements[2]) for human beings is defined as:

(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.[3]

3.2 For the veterinary medicinal product, it is defined as:

(a) any substance or combination of substances presented as having properties for treating or preventing disease in animals; or

(b) any substance or combination of substances which may be used in or administered to animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.[4]

---

[2] Article 2(a) of Directive 2002/46/EC defines a "food supplements" as "foodstuff the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities".

[3] See Article 1(2) of Directive 2001/83/EC, as amended in Directive 2004/27/EC.

[4] See Article 1(2) of Directive 2001/82/EC, as amended in Directive 2004/28/EC.

4. Registration system for medicinal products

4.1 No medicinal product may be placed on the market in the EU unless a marketing authorization has been issued by the competent authority of a Member State for its own territory (national authorization)[5] or by the European Medicines Agency[6] for the entire EU (Union authorization). The medicinal products with the Union authorization are recorded in the register of the European Commission.[7]

National authorization

4.2 In order to obtain a national authorization, an application must be submitted to the competent authority of a Member State. In cases where national authorizations are requested for the same medicinal product in more than one Member State, there are two possible routes available for the simultaneous authorization: decentralized procedure and mutual recognition procedure.

Decentralized procedure

4.3 In the decentralized procedure, a company can apply for simultaneous authorization in more than one EU Member State of a medicinal product that has not yet been authorized in any EU Member State. The company must first submit an application in all the Member States where it intends to obtain marketing authorization at the same time. It will choose one of the Member States to act as the Reference Member State for assessing the application.

---

5 In the EU, the competent authority of a Member State is the medical regulatory authority of that Member State. For example, the competent authority in the United Kingdom is the Medicines and Healthcare Products Regulatory Agency.

6 As an agency of the EU, the European Medicines Agency is responsible for protecting and promoting public and animal health through the evaluation and supervision of medicines for human and veterinary use. It also conducts scientific evaluations of medicines developed by pharmaceutical companies for use in the EU.

7 The European Commission is the EU's executive body and represents the interests of Europe as a whole (as opposed to the interests of individual countries).

4.4 The Reference Member State will liaise with the other Member States where the company wishes to market the medicinal product (known as Concerned Member States), as well as providing them with an assessment report on the medicinal product, the summary of product characteristics, and a draft label and package leaflet. If the Reference Member State and Concerned Member States both agree on the application, they will each issue a national marketing authorization.

Mutual recognition procedure

4.5 In the mutual recognition procedure, a medicinal product is first authorized in one EU Member State in accordance with the national procedures of that country. The authorization holder then submits a request to the Concerned Member States for simultaneous recognition of this authorization. He or she must inform the Member State which has issued the authorization (i.e. the Reference Member State) and the European Medicines Agency. The Reference Member State must forward the assessment report on the medicinal product, the summary of the product characteristics as well as the label and package leaflet to the Concerned Member States. The Concerned Member States will then decide whether to recognise the market authorization already granted by the Reference Member State.

When the Member States disagree

4.6 When one or more Member States cannot recognize the assessment and product information prepared in decentralized procedure or an authorization already granted under mutual recognition procedure, the disagreement is referred to the Coordination Group for Mutual Recognition and Decentralized Procedure for Human Medicinal Products.[8] If the Member States still fail to reach agreement with the coordination group, the matter is referred to the Committee for Medicinal Products for Human Use ("CHMP")[9] of the European Medicines Agency for arbitration, where there is a detailed reasoning for the disagreement. The applicant may appeal against any negative decision by CHMP and bring the case to the European Commission for final decision.

---

[8] According to Article 27(2) of Directive 2001/83/EC and Article 31(2) of Directive 2001/82/EC, the coordination group shall be composed of one representative from each Member State.

[9] In case where veterinary medicinal products are concerned, the matters may be referred to the Committee for Medicinal Products for Veterinary Use for arbitration.

Union authorization

4.7 For certain medicinal products, it is mandatory to submit the applications to the European Medicines Agency for the Union authorization via the centralized procedure. In the centralized procedure, successful applicants will receive one European approval which is valid in all the 28 Member States of the EU.

4.8 According to Article 3(1) of Regulation (EC) No 726/2004, Union authorization is required for a medicinal product that: (a) is derived from biotechnology and other high-tech processes; (b) contains new active substances[10] intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases; or (c) is a type of designated orphan medicines intended for the treatment of rare diseases. Applicants may also seek the Union authorization for certain new medicinal products[11] and generic medicinal products for paediatric use.

Post-authorization safety study

4.9 For both national and Union authorizations, the competent authority of a Member State may impose an obligation on the authorization holder to perform a post-authorization safety study. The study is to (a) identify, characterize or quantify a safety hazard; (b) confirm the safety profile of the medicinal product concerned; and (c) measure the effectiveness of risk management measures.

4.10 Once the post-authorization study has been completed, a final report must be submitted to the national competent authority requesting the study or the Pharmacovigilance Risk Assessment Committee ("PRAC"). PRAC is a committee of the European Medicines Agency tasked with assessing and monitoring safety issues for human medicines. PRAC may make recommendations, after which the Member States agree on a position to be adopted in this regard. The resulting agreement is then published on the EU post-authorization study register by the European Medicines Agency.

[10] "Active substance" is defined as any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis. See Article 1(3a) of 2001/83/EC.

[11] The new medicinal product is required to be a new active substance, constitutes a significant therapeutic, scientific or technical innovation, or is in any other respect in the interest of patients at the EU level.

Renewal of marketing authorization

4.11 Marketing authorizations granted in the EU or in individual Member States have an initial duration of five years. After these five years, the marketing authorization may be renewed on the basis of a re-evaluation of the risk-benefit balance. In this connection, the marketing authorization holder is required to provide the European Medicines Agency or the national competent authority concerned with a consolidated version of the files in respect of quality, safety and efficacy (including all variations introduced since the marketing authorization was granted) at least nine months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period unless the European Commission or the national competent authority concerned decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

5. Manufacture of medicinal products

5.1 In the EU, all Member States take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of a manufacturing authorization. The authorization is required for both total and partial manufacture, and for the various processes of dividing up, packaging (including primary and secondary packaging) or presentation.[12] In order to obtain a manufacturing authorization in a Member State, an application must be submitted to the competent authority of that Member State. After approving the application, the Member State is required to record the authorization information in the database managed by the European Medicines Agency.

Application for manufacturing authorization

5.2 In order to obtain the manufacturing authorization, an applicant is required to:

(a) specify the medicinal products to be manufactured and the place where they are to be manufactured;

[12] See Article 40 of Directive 2001/83/EC.

(b) have appropriate premises, technical equipment and control facilities;

(c) have the services of at least one qualified person responsible for ensuring that the requirements set out in the marketing authorization and the legislation in force are met; and

(d) provide the approving Member State with relevant supporting information as necessary.

Obligations of manufacturers

5.3 The holder of a manufacturing authorization is required to fulfil obligations[13] such as to:

(a) have the services of staff who comply with the legal requirements existing in the Member State concerned;

(b) supply the authorized medicinal products only in accordance with the legislation of the Member States concerned;

(c) give prior notice to the competent authority of any changes he or she may wish to make to any of the information supplied in connection with his or her manufacturing application;

(d) allow the agents of the competent authority access to his or her premises;

(e) comply with the principles and guidelines of good manufacturing practices ("GMP") for medicinal products and use only those active substances manufactured in line with GMP;

(f) immediately provide the competent authority and the authorization holder of medicinal products with any information revealing that the medicinal products covered by his or her authorization have been falsified or are suspected of having been falsified;

[13] See Article 46 of Directive 2001/83/EC.

(g) check that the manufacturers, importers or distributors supplying him or her with active substances are registered with the competent authority in the Member State in which they are established[14];

(h) check the authenticity and quality of active substances and excipients[15]; and

(i) enable the qualified person to carry out his or her duties, and inform the competent authority in the event that this person is replaced.

Qualified person

5.4 As stipulated in the *EU guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*[16], the main duties of a qualified person[17] are to:

(a) ensure that each batch of medicinal products manufactured is checked as well as the requirements set out in the marketing authorization and the relevant legislation in force are met; and

(b) ensure that each production batch of medicinal products coming from other countries has undergone full analyses, tests and checks to ensure the quality of medicinal products meet the requirements of the marketing authorization. The qualified person is required to certify in a register or equivalent document that each production batch satisfies the requirements as set out in the legislation.

[14] Active substances may only be imported if (a) they are manufactured in line with GMP, and (b) they are accompanied by written confirmation from the competent authority in the third country in question.

[15] "Excipients" is defined as any constituent of a medicinal product other than the active substance and the packaging material. See Article 1(3b) of 2001/83/EC.

[16] See European Commission (2013), paragraph 2.6 of Chapter 2.

[17] The responsibilities of a qualified person may be delegated, but only to other qualified person(s).

Academic requirements for qualified persons

5.5 A qualified person must have a degree, diploma, or other formal qualification awarded on completion of a university course of study, or a course recognized as equivalent by the Member State in which it is studied, which:

(a) is a completed four years of theoretical and practical study, or a shorter study (e.g. of three years recognized as equivalent by the Member State concerned), in one of the following disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, and biology; and

(b) the course should at least include one of the following core subjects: (a) experimental physics; (b) general and inorganic chemistry; (c) organic chemistry; (d) analytical chemistry; (e) pharmaceutical chemistry (including analysis of medicinal products); (f) general and applied medical biochemistry (medical); (g) physiology; (h) microbiology; (i) pharmacology; (j) pharmaceutical technology; (k) toxicology; and (l) pharmacognosy.

5.6 However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year, including a training period of at least six months in a pharmacy open to the public and a final examination at university level.

Practical experience requirements for qualified persons

5.7 A qualified person is required to have acquired practical experience over a period of at least two years[18] in one or more authorized manufacturers in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.

[18] The requirement of the practical experience duration may be reduced by one year if the university course lasts for at least five years, and may be reduced by 1.5 years if the course lasts for at least six years.

References

1. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001. (2009) *Community code relating to veterinary medicinal products (Consolidated version: 18/7/2009).* Available from: http://ec.europa.eu/health/files/eudralex/vol-5/dir_2001_82_cons2009/dir_2001_82_cons2009_en.pdf [Accessed July 2014].

2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001. (2012) *Community code relating to medicinal products for human use (Consolidated version: 16/11/2012).* Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf [Accessed July 2014].

3. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002. (2002) *Approximation of the laws of the Member States relating to food supplements*. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:183:0051:0057:EN:PDF [Accessed July 2014].

4. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004. (2004) *Amendments to Directive 2001/83/EC on the Community code relating to medicinal products for human use*. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf [Accessed July 2014].

5. Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004. (2004) *Amendments to Directive 2001/82/EC on the Community code relating to veterinary medicinal products*. Available from: http://ec.europa.eu/health/files/eudralex/vol-5/dir_2004_28/dir_2004_28_en.pdf [Accessed July 2014].

6. European Commission (2013) *EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*. Available from: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm [Accessed July 2014].

7. European Commission. (2014a) *Legal framework governing products for human use in the EU*. Available from: http://ec.europa.eu/health/human-use/legal-framework/index_en.htm [Accessed July 2014].

8. European Commission. (2014b) *Pharmaceuticals – Community Register*. Available from: http://ec.europa.eu/health/documents/community-register/html/index_en.htm [Accessed July 2014].

9. European Commission. (2014c) *The rules governing medicinal products in the European Union*. Available from: http://ec.europa.eu/health/documents/eudralex/index_en.htm [Accessed July 2014].

10. European Medicines Agency. (2014) *Applying for EU marketing authorization*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Brochure/2011/03/WC500104233.pdf [Accessed July 2014].

11. European Union. (2014a) *Community code relating to medicinal products for human use*. Available from: http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21230_en.htm# [Accessed July 2014].

12. European Union. (2014b) *Community code relating to veterinary medicinal products*. Available from: http://europa.eu/legislation_summaries/food_safety/animal_health/l21231_en.htm [Accessed July 2014].

13. International Society for Pharmaceutical Engineering. (2009) *Regulatory Framework – EMEA*. Available from: http://www.pharmaceuticalengineering.org/knowledge-briefs/regulatory-framework-emea.pdf [Accessed July 2014].

14. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004. (2013) *Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Consolidated version: 05/06/2013)*. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_2013_en.pdf [Accessed July 2014].

Prepared by YU Chun-ho
Research Office
Information Services Division
Legislative Council Secretariat
3 July 2014
Tel: 2871 2142