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Original article

The requirements for manufacturing highly active or sensitising drugs comparing Good Manufacturing Practices

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Summary. *Background:* To date there exist no internationally recognised Good Manufacturing Practices (GMP) that clearly outline universally accepted standards for manufacturing highly active or sensitising ingredients. The pharmaceutical industry is faced with a twofold problem: determining which drugs need dedicated production areas and identifying the different regulations required in different countries. The aim of this paper is to find, by comparing the current regulations of the various Regulatory Agencies, the differences between containment requirements for the production of highly active or sensitising ingredients. *Methods:* An analysis of the following Regulatory Agencies' GMPs was performed: Europe (EMA), China (CFDA), Mexico (COFEPRIS), United States (FDA), Canada (Health Canada) Brazil (ANVISA), India (CDSCO), PIC/S and WHO in order to examine the differences in terms of containment requirements set by the different Regulatory Authorities for the manufacture of highly active or sensitising ingredients. *Results:* Our analysis found that the majority of Regulatory Agencies require that beta-lactams (sensitising materials) be produced in dedicated and segregated facilities. For "certain" highly active pharmaceutical ingredients (APIs), COFEPRIS, FDA, HC, EMA, PIC/S and WHO require that they be produced in facilities similar to those required for beta-lactams, while CDSCO, CFDA and ANVISA require that production takes place in segregated areas. Further differences between the Agencies have emerged regarding classes of highly APIs that require dedicated production. *Conclusion:* A study of GMP adopted by Regulatory Agencies has uncovered significant differences, in particular concerning containment requirements for the production of APIs. For this reason, the harmonisation of GMP following up-to-date quality standards based on cutting-edge science which are globally applicable is fundamental and will benefit companies and patients alike. Pharmaceutical companies would not be obliged to follow requirements enforced by the State in which they intend to manufacture a product, and patients would benefit from high-quality drugs regardless of their place of production. (www.actabiomedica.it)

Key words: Good Manufacturing Practices, highly active or sensitising drugs, cross-contamination, mix-ups, Regulatory agencies, Quality Risk Management

1. Introduction

The overmedication is often associated with an increase in the likelihood of making mistakes, abuse or non-compliance (1). Some people take medication without a prescription (2) or simply after consulting social media, and consequently risk being exposed to misleading and even dangerous information (3-6).

Highly active or sensitising ingredients require special rules for their production as accidental contamination with other materials could have serious consequences for the health of patients and because

they could also represent an occupational hazard to personnel who come into direct contact with these substances during all phases of production (7-9). Just as for regulations that concern the production and handling of some foodstuffs, even more care must be taken for medicines. Among the greatest dangers related to the manufacturing of any drug, and in particular during the production of those classed as highly active or sensitising, we find cross-contamination and mix-ups. Above all, GMPs stress the issue of contamination by substances which could be damaging to health, therefore the production of some products (in particular, sensitising and/or highly active ones) is required to take place in dedicated areas in order to ensure a clear-cut separation of these substances from other materials (10).

However, as there are no global GMP harmonising measures, some states require specific operating conditions for the manufacture of "certain" substances, while other states have different requirements, so that the only way to understand exactly what is meant by "certain" is by relying on an efficient Pharmaceutical Quality System within the organisation. Even in pharmaceutical companies, personnel can exhibit superficial behaviour caused by improper conservation practices or the inappropriate handling of substances during the production of medicines or supplements (11-13). At times this can be attributed to work-related stress, high levels of which have often been observed in these professions or linked to bad lifestyle choices that can increase improper behaviour (14, 15).

To assess the danger of cross-contamination and mix-ups, especially during the production of highly active or sensitising ingredients, pharmaceutical companies should resort to ICH Q9 Quality Risk Management guidelines. Quality Risk Management (QRM) is an essential instrument that all companies should use to perform a broad spectrum study aimed at determining any possible risks related to the production cycle of each drug. In the case of highly active or sensitising ingredients, if acceptable risk levels are not achieved for their production in multi-product plants, it is the duty of the quality assurance system to adopt precautionary measures during the production process (i.e. dedicated or partially isolated areas), especially when there is a high risk for cross-contamination and mix-ups which could be dangerous for the patient's health and/or if the Acceptable Daily Exposure (ADE) of a drug has values which could be hazardous to personnel.

The ADE shows the highest dose for each substance that is unlikely to cause an adverse health event or undesirable physiological effects if an individual is exposed to this dose or a lower dose every day for a lifetime (16, 17).

GMP in various countries do not list all the drugs that require dedicated production areas, nor the different levels of isolation required for processing certain drugs. In Europe, the European Medicines Agency (EMA) harmonises GMP belonging to the twenty-eight members of the European Union, though internationally there are still no universally harmonized guidelines; in fact, the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH), the *Pharmaceutical Inspection Cooperation/Scheme* (PIC/S) and the *World Health Organization* (WHO), were created precisely with the intent to harmonise different existing guidelines. Hence the pharmaceutical industry is faced with a twofold problem: it must determine which drugs need dedicated production and identify for each one regulatory differences required by different countries (10).

This study will examine issues concerning the manufacture of highly active and sensitising drugs in various Regulatory Authorities and will also analyse and compare GMP in order to highlight similarities and differences with the aim of identifying the most recent practices. Data may be useful to create a universally accepted standard for the production of these types of drug.

2. Materials and methods

GMPs issued by the following regulatory agencies were studied: Europe (EMA), China (CFDA), Mexico (COFEPRIS), United States (FDA), Canada (Health Canada), Brazil (ANVISA), India (CDSCO), PIC/S and WHO. The study was carried out in order to assess differences regarding containment requirements by different regulatory authorities for the production of the following categories of drugs: hormones, immu-

nosuppressants, cytotoxic agents, highly active pharmaceutical ingredients (APIs), biological preparations, steroids, sensitising pharmaceutical materials, antibiotics, cephalosporins, penicillin, carbapenems, beta-lactam derivatives. On the basis of this, we compared the different classes of drugs and the type of containment required by each regulatory agency.

3. Results

3.1 Segregation Requisites for producing highly active or sensitising ingredients according to the different regulatory authorities

Table 1 shows the results of the study with the categories of drugs for which different regulatory agencies require production in dedicated and/or segregated facilities.

The regulatory requirements adopted by various countries worldwide only partially define the different segregation levels essential for the production of certain classes of drugs and, as can be seen in Table 1, in classifying them adjectives such as: "*Certain*", "*Some*", "*Others*" are often used, the meaning of which is not always clearly given.

3.2 Requisites for the production of highly active or sensitising ingredients imposed by various regulatory authorities.

Brazil. The *Agência Nacional de Vigilância Sanitária* (ANVISA), provides the following guidelines, "*Technical Regulation of Good Manufacturing Practices of Drugs (2010), Resolution - RDC n. 17*", requires that production takes place in dedicated facilities for: sensitising pharmaceutical materials, biological preparations (eg: live microorganisms), cephalosporins, penicillin and carbapenems and "*other*" beta-lactam derivatives; therefore, monobactams and carbapenems could be included in this category. But it is specified that: "*In some cases, such as highly sensitising materials, segregation should also occur between them*". The production of certain highly APIs, such as some antibiotics,

Table 1. Regulatory Authorities and classes of drugs requiring segregation for production

Pharmaceutical substances	Brazil ANVISA	China CFDA	Mexico COFEPRIS	USA FDA	Europe EMA	Canada HC	India CDSCO	WHO	PIC/S
Hormones	X certain	X certain (contraceptives)	X (of biological origin)	X certain	X certain	X certain	X (sexual)	X certain	X certain
Immunosuppressants			X		X certain	X certain			X certain
Cytotoxic agents	X	X certain	X	X certain	X certain	X certain	X	X certain	X certain
Highly API	X certain	X certain	X others	X certain	X certain	X certain	X	X certain	X certain
Biological preparations	X	X	X	X	X certain	X certain	X	X	X certain
Steroids				X certain	X certain	X certain		X certain	X certain
Sensitising pharmaceutical materials	X	X	X	X certain	X certain	X certain	X	X	X certain
Antibiotics	X some				X certain	X certain	X certain	X some	X certain
Cephalosporins	X	X	X	X	X	X	X	X certain	X
Penicillin	X	X	X	X	X	X	X	X	X
Carbapenems	X	X		X	X	X certain	X		X
Beta-lactam Derivatives	X others	X		X	X	X certain	X		X

certain hormones and cytotoxic substances, should be carried out in segregated areas (18). For some classes of drugs (hormones and highly APIs), the terms "*some*" and "*certain*" are used but the meaning of these words has not been clarified by ANVISA. Therefore to determine which compounds should be included among the "some" and "*certain*" QRM must be consulted, which means resorting to case-by-case risk evaluation.

China. The *State Food and Drug Administration* (CFDA) is the Chinese regulatory authority that oversees safety in the management of food, cosmetics and pharmaceutical products. The GMPs are provided by the CFDA in the "*Good Manufacturing Practice 2010*" (19). This revised version of the Chinese GMPs, published in 2010, has been updated and is more comprehensive compared to the previous edition. For example, it has introduced the principles of QRM based on ICH Q9 standards. Despite the latest revision, Chinese GMPs remain mainly focused on the phases of production of the finished product. According to Chinese GMPs, there must be dedicated and self-contained premises available for the production of medicines like: sensitising pharmaceutical materials, biological preparations, beta-lactam antibiotics, contraceptive hormones (Art 46.3), certain cytotoxic agents and certain highly APIs.

Mexico. The regulatory authority that publishes Mexican GMPs is the *Comisión Federal Para la Protección contra Riesgos Sanitarios* (COFEPRIS) in the NOM-059-SSAI-2006 "*Buenas prácticas de fabricación para establecimientos de la industria químico farmacéutica dedicados a la fabricación de medicamentos*" (20). The rules set out in the guidelines are based on both European and FDA standards (both are quoted in the list of references). In 2014, COFEPRIS added Annex 20 to the GMPs, which is essentially the same as the ICH-Q9 in QRM; this attachment provides instructions for a systematic approach to QRM that facilitates compliance with GMPs and other quality requirements (21).

According to these GMP, the production of penicillin, cephalosporins, cytotoxic agents, immunosuppressants and hormones of biological origin must be completely independent and self-contained; furthermore, biological and microbiological processing must be physically separate. Regarding hormones, only those of biological origin must be produced in self-contained areas and there is no mention of those of synthetic origin. Cephalosporins and penicillin must be produced in areas that are completely independent and self-contained but there is no reference to the type of production necessary for beta-lactam derivatives. Highly active or sensitising ingredients, although not explicitly mentioned, are definitely among those at high risk mentioned in Art 8.2.16 (20).

USA. GMP regulations in the United States are enforced by the FDA through the Federal Register (mainly CFR Title 21, parts 210 and 211) and numerous industry guidelines. Areas of application of the American GMP is defined in the FDA regulations 21 CFR 210.1 where it is established that the rules cited must be considered the "*Minimum current GMP*" (22, 23). According to the FDA's GMP, the industrial production of penicillin must take place in totally dedicated areas of several buildings or even in the same building (CFR 21 Part 211.42-d). The "*Guidance for Industry Non-Penicillin Beta-Lactam Risk Assessment: a CGMP Framework for Preventing Cross Contamination*" states that the production of sensitising non-penicillin beta-lactams must be treated in the same way (24). The FDA has published internationally harmonized guidelines for highly potent APIs (*FDA, 2016, Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry*). In the FDA Q7 Guidelines published in 2016 it is specified that dedicated production areas should be used for manufacturing sensitising materials such as penicillin or cephalosporins, and that this should also be considered when infectious, highly active or toxic materials are involved (for example certain steroids or certain cytotoxic anti-cancer drugs) (25). In 2018, the FDA published an additional handbook: "*Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Questions and Answers Guidance for Industry*"(26); this document was written in collaboration with PIC/S and its aim was to clarify doubts concerning the interpretation of several sections of the FDA Q7 guidelines published in 2016. Regarding the highly active or sensitising ingredients, the ideas that can be found in the FDA Q7 Guidelines from 2016 are repeated. Further information can be obtained

from the "*Food and Drug administration compliance program guidance manual program*" (Ch.56) (27). Although GMP specify in numerous sections which rules must be followed for the production of penicillin and biological drugs, there are no specific manufacturing rules for other classes of drugs (as, for example, in the case of highly potent APIs). In the FDA's GMP it has not been clearly stated that the production of "*certain*" highly potent APIs must be carried out in dedicated areas, but this can be deduced by numerous references made in other documents, such as, for example, in the FDA's answer P-0069 to *Foley & Lardner's petition* (28).

Europe. In Europe, the EMA harmonises GMPs from the twenty eight members of the European Union in *Eudralex Volume* 4, which due to the number and complexity of its clauses should be considered a combination of the best and most current manufacturing procedures. The latest version, published in 2015, leaves the manufacturer a wider margin with which to assess risks (29).

The decision whether or not to use dedicated facilities covers all the categories that pose a risk and is still required in the following cases:

"a. The risk cannot be adequately controlled by operational and/ or technical measures,

b. Scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

c. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method" (Chap. 3.6).

Therefore, beta-lactam antibiotics remain the only type of drugs for which the EMA requires *a priori* production in dedicated areas. Regarding all other drugs, the manufacturers must carry out a careful analysis of the risks involved in their production in order to assess whether they can be produced in multi-product plants or whether dedicated facilities must be used for their manufacture. This assessment must take into account the toxicological as well as the pharmacological parameters of the product (30).

Canada. The regulatory agency that promotes GMP in Canada is Health Canada (HC) through the "*Good manufacturing practices guide for drug products - GUI-0001, 2018*" (31). The introduction specifies that the handbook was written with the intent of harmonising GMP regulations with those of other countries as well as the WHO, PIC/S and ICH; indeed, some of the definitions in the glossary have been taken from the regulations of these Agencies. The Guidelines for active pharmaceutical substances are dealt with in a separate section:"*Health Products and Food Branch Inspectorate; Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (API) - GUI-0104*" (32). In the Canadian GMP, which are similar to *Eudralex* guideline, the fact that any sort of cross-contamination poses a certain risk for patients is considered noteworthy and consequently the need to pay particular attention to any substance that is produced is emphasised. Moreover, it is clearly stated that the production of certain classes of sensitising materials, including penicillin and cephalosporins, must occur in dedicated areas (31). Hence other classes of beta-lactam antibiotics including carbapenems and "*other beta-lactam deivatives*" need to be further assessed by the manufacturer to establish the most suitable type of containment. In the "*Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (API) - GUI-0104*" it is stated that for the production of certain classes of drugs, such as steroids and cytotoxic anti-cancer agents, dedicated areas should be considered, unless validated inactivation and/or cleaning procedures are established and maintained, but there is no obligation to carry out production in segregated areas when certified procedures that guarantee the quality of the products and prevent the risk of cross-contamination are in place (32).

In short, the latest Canadian Guidelines repeat the topics already addressed in the *Eudralex* Guidelines regarding the need to perform a recorded risk assessment (*QRM*) concerning both the pharmacological and the toxicological aspect for any substance that is produced in order to control the risk of cross-contamination. But the Canadian Guidelines mention only two categories of materials for which production in dedicated areas is compulsory.

India. The *Central Drugs Standard Control Organization* (CDSCO) is the Indian Regulatory Agency which, with the promulgation of SCHEDULE

M "*Drug and Cosmetics Act*", contains GMP for both drugs and cosmetics. Furthermore, the guidelines combine requirements for highly APIs with those of other medicines (33). The rules are also divided according to the different ways in which products are administered. It is obvious that the complexity and number of sections included in SCHEDULE M are fewer compared to other GMPs studied. The fact that the one volume contains all the regulations regarding the production of such different substances (medicines and cosmetics) underlines how Indian GMPs are much less specific than the EMA GMP. The way in which production plants are designed is fundamental in order to avoid any chance of contamination between the different products. Indian GMPs call attention to the location of the pharmaceutical plant in order to avoid contamination from outside agents. Regarding the use dedicated and self-contained areas, Indian practices state the need to design separate areas for: beta-lactams (with no exceptions), highly active materials, sex hormones, some antibiotics, cytotoxic and oncology products.

World Health Organisation (WHO). The WHO is a specialized UN Agency that deals with international public health. The requirements for the production of drugs containing highly active or sensitising substances are listed in the "*WHO Technical Report Series, No. 957, Annex 2 (2010)*", in the "*WHO Technical Report Series, No. 957, 2010 Annex 3 (2010)*" and in the "WHO *Technical Report Series, No. 986, Annex 2 (2014)*" (34-36). The version of GMP developed by the WHO is used by the pharmaceutical industries and by the sector's supervising authorities in over 100 countries worldwide. These GMP are to be considered general rules, as it is clear that they are not exhaustive in the treatment of topics such as safety precautions for the health of personnel and the environment, aspects that are normally covered by national laws. In its "*Technical Report Series No. 986 (2014)*", the WHO specifies which elements are essential in an effective quality management system, stressing aspects like self-inspection and quality audits similar to those required by the EMA. Regarding ingredients that require production in dedicated areas, neither the "*WHO's Technical Report Series, No. 986, Annex 2 (2014)*" nor the "*No. 957 Annex 3*" mention Beta-lactam derivatives, only penicillin and cephalosporins. According to "*WHO Technical Report Series, No. 986, Annex 2 (2014)*" and "*WHO Technical Report Series, No. 957, Annex 2 (2010)*", the production of sensitising materials and biological preparations must be carried out in dedicated areas; furthermore, it is stated that certain highly active materials, such as some antibiotics, hormones, some steroids, cytotoxic substances and other non-pharmaceutical products should not be manufactured in the same building. Further instructions can be found in the "*WHO Technical Report Series, No. 957, 2010 Annex 3*": these are Guidelines that regulate the good practices that should be applied to facilities that deal with pharmaceutical products (including active pharmaceutical ingredients that contain dangerous substances such as some hormones, steroids or cytotoxic substances). The handbook underlines the fact that the production of certain products containing dangerous substances should generally occur in separate, dedicated and independent buildings. The "*WHO Technical Report Series, No. 986, Annex 2 (2014)*" states that dedicated facilities are required for the production of "certain" hormones, whereas in the "*Guideline to the inspection of hormone product manufacturing facilities*" (2008) the word "certain" in paragraph 3.4 is not used. Indeed it says that: *"Hormone facilities should be separate, dedicated facilities and should not form part of any other non-hormone facility. They may be in the same building as another facility but should be separated by a physical barrier and have separate entrances, staff facilities, air-handling systems, etc"* (37). On the other hand, in terms of GMP requisites, paragraph 4.1 of the same handbook reads that not all hormone products are equally potent and that a risk assessment should be carried out to determine the potential hazards to operators and to the environment.

Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Co-operation Scheme (PIC/S). PIC and PIC/S are two international tools created to improve the cooperation between the regulatory authorities and the pharmaceutical industry in the field of GMP. The aim of PIC/S is, fundamentally, to achieve the following goals: mutual recognition of the inspections, harmonisation of the GMP requisites, uniform control systems, training

inspectors, facilitating networking and mutual confidence. EMA and PIC/S cooperate to better harmonise the GMP at an international level, sharing resources and avoiding the duplication of efforts. To date 54 members, including Europe, the United States, Canada and both WHO and EMA adhere to the PIC/S and the number continues to increase. PIC/S develops and maintains a GMP guide that must be used by its members and is the PIC/S' main tool for harmonisation. In terms of GMP requisites, the PIC/S GMP handbook is identical to the EU GMP guidelines. The "*Guide to Good Manufacturing Practice for Medicinal Products PART I (PIC/S; 2018)*" contains the PIC/S' requirements for the production of highly active or sensitising ingredients (38). In PIC/S Guidelines, just as in the *Eudralex* Guidelines, the question of whether or not to use dedicated facilities is extended to all those categories which might present a risk and this remains a requirement in the cases listed in paragraphs a, b and c in Chapter 3.6, which cite exactly what is written in the *Eudralex volume 4* (2015) (29). In short, the PIC/S GMP Guidelines reiterate the topics already presented both in the *Eudralex* Guidelines and the Canadian Guidelines regarding the need for a recorded risk assessment (*QRM*) for both pharmacological and toxicological aspects in order to control the risk of cross-contamination. Unlike the *Eudralex* Guidelines, though, in the "*Guide to Good Manufacturing Practice for medicinal products PART II (PIC / S; 2018)*" the PIC/S GMPs list other categories of drugs which should be produced in dedicated areas, in particular: some steroids and cytotoxic anti-cancer agents (39).

3. Discussion

In order to clarify the different types of containment required by Regulatory Agencies to avoid the possible risks associated with the production of the aforementioned classes of drugs, it is important to understand the meanings of the terms used in the regulations adopted by different States. The *International Society for Pharmaceutical Engineering* (ISPE), an international society of engineers that supports pharmaceutical companies in designing and manufacturing pharmaceutical products, provides specific definitions concerning the different types of facilities and the types of containment required in the "*Risk-Based Manufacture of Pharmaceutical Products*" Handbook. In particular, this publication gives precise definitions for: dedicated area, dedicated building/facility, self-contained area and segregation (40).

All the GMP studied clearly forbid the production of penicillin in multipurpose areas, that is to say where other classes of drugs are manufactured. GMPs clearly state that this class of drugs must be manufactured in physically separate and dedicated facilities, although COFEPRIS, HC, FDA and WHO specify that it is not necessary to use separate buildings (20, 23, 31, 35). Hence, production can take place according to the option shown in Fig. 1. The GMP adopted by EMA, PIC/S, China, Mexico, USA, Canada and India regulate the production of cephalosporins in dedicated and separate facilities, designed in the same way as illustrated in Fig. 1 (19, 20, 25, 29, 31, 33, 38). In its Technical Report Series the WHO, No. 957

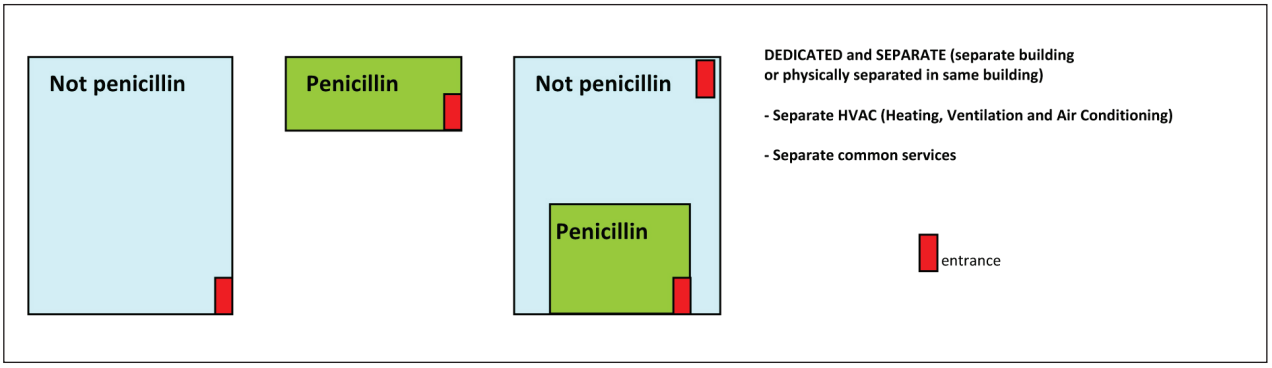

Figure 1. Facilities used for the production of sensitising materials

(2010, Annex 2), states that dedicated areas should be used for the production of cephalosporins; therefore, all compounds that belong to the latter class of drugs do not require segregation during the manufacturing process (34). Mexican and WHO regulations do not specify what sort of containment is necessary for the production of all beta-lactam derivatives, even though these classes of medicines are included among ones classed as sensitizing, consequently requiring production in facilities similar to those described for penicillin (20, 34-36).

3.3.2 *Production for highly potent APIs*

The GMP we studied provide specific indications for the production of "certain" highly potent APIs, except in the case of the Indian Regulatory agency which does not use the adjective "certain" (33). The type of containment required during the entire productive cycle of some classes of drugs belonging to this category varies depending on the Regulatory agency studied. The Mexican, USA, Canadian, European PIC/S and WHO Regulatory Organisations for example, require that the production of "certain" highly potent APIs take place in facilities designed in the same way as those meant for sensitising materials, that is to say totally dedicated and separate facilities (20, 25, 28, 29, 32, 34-39). In particular, EMA, PIC/S and WHO require this type of containment if QRM procedures prove that it is the only sort of containment capable of preventing events such as mix-ups and cross-contamination; otherwise it could be sufficient to adopt another form of control like, for example, dedicating areas and equipment to particular production phases and/or packaging. On the contrary, the Indian, Chinese and Brazilian Regulatory agencies regulate the production of "certain" highly potent APIs in dedicated manufacturing areas meant for the production of a given class of drugs (within the same building/facility where other medicines are produced), but designed in such a way as to prevent cross-contamination and guarantee that the product is not exposed to the adjoining areas, without having to be completely separate from other buildings (18, 19, 33).

Differences found between the GMP do not only involve the type of containment required but, as can be seen in Table 1, also refer to which class of highly potent API needs appropriate containment.

The Chinese, Brazilian, Mexican, Canadian, European, USA, PIC/S and WHO GMP regulate the production of "certain" hormones; among those classed as "certain", the CFDA (Chinese Regulatory Authority) mentions that contraceptives must be produced in dedicated and self-contained facilities; this is a significant distinction required by the CFDA and is not expected for the manufacturing of "other" hormones, which, on the contrary, can be produced in segregated areas within the same facility (18-20, 29,

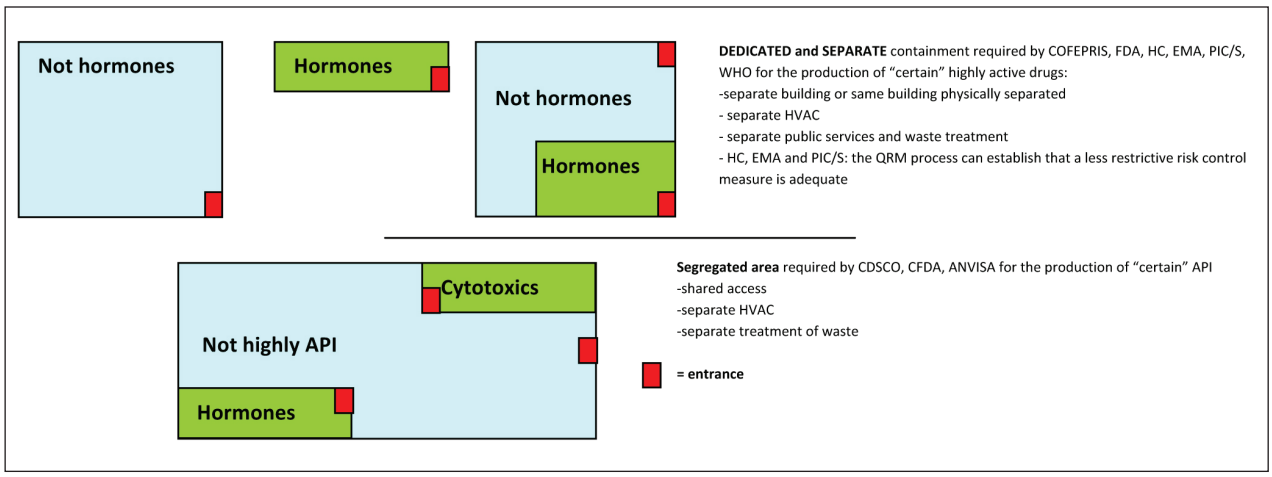

Figure 2. Facilities used for the production of highly APIs

31, 36-38). COFEPRIS is the only agency specifying that hormones of biological origin must be produced in separate and dedicated facilities, whereas the CDSCO only requires production in segregated areas for sex hormones (20, 33).

All GMP studied have specific containment rules for the production of cytotoxic medicines, although differences can be observed between them. CFDA, EMA, FDA, HC, PIC/S and the WHO only regulate the type of production required for "certain" cytotoxic agents (19, 25, 29, 32, 34, 36, 39). On the contrary, China, Mexico and India require that this type of drug be produced in a totally dedicated and separate facility (19, 20, 33). The USA, Brazil, Canada, PIC/S and WHO clarify that dedicated areas are sufficient, this does not imply a complete separation from other adjacent facilities (18, 25, 32, 34-36, 39). According to the EMA the choice of containment must be established by the manufacturer through adequate risk assessment, thus not necessarily requiring that these drugs be manufactured in contained facilities/areas (29).

Only the Mexican Regulatory Agency (COFEPRIS) requires that all immunosuppressants be manufactured in independent and self-contained facilities (20). ANVISA requires special containment rules for immunosuppressants exclusively when the active ingredient (raw material) is being produced (18). The European, Canadian and PIC/S GMP, which extend the risk assessment to any type of substance produced, refer the type of containment required for this class of drug to the manufacturer (29, 31, 38).

4. Conclusions

In various parts of the world the regulatory framework regarding GMP has evolved, but there are still significant differences between the various regulatory agencies concerning segregation requirements for the production of highly active or sensitising ingredients. Few scientific papers on this topic have been published and no critical analysis of the various regulations has yet been performed. A comparative study of GMP of some of the most important Regulatory agencies has shown that there are points of agreement and others of discord regarding the segregation required for the production of highly active or sensitising ingredients. In particular, regarding sensitising ingredients and especially penicillin, all GMP studied clearly forbid their production in areas where other classes of drugs are produced, necessitating their manufacture in dedicated and segregated facilities. According to most of the aforementioned regulatory agencies, cephalosporins, carbapenems and "*Other beta-lactam derivatives*" represent categories of sensitising ingredients which must be produced in facilities designed in a similar manner to those for the production of penicillin.

Regarding highly APIs, the type of containment required by each product varies in the Regulatory Authorities we studied. As can be observed in Figure 2, COFEPRIS, FDA, HC, EMA, PIC/S and WHO require that "certain" highly potent APIs be manufactured in facilities which have similar characteristics to those required for the production of sensitising ingredients, whereas CDSCO, CFDA and ANVISA require that "certain" highly potent APIs be manufactured in segregated areas, without requiring total separation from other facilities. EMA, PIC/S and HC in particular require that the above-mentioned type of containment be adopted only if the QRM procedures guarantee that it is the only type of containment capable of preventing mix-ups and cross-contamination; otherwise it could be sufficient to use another form of control such as dedicated areas and equipment for particular stages of the production and/or packaging. The Agencies also show some differences regarding the classes of API that require dedicated production areas.

In defining the levels of segregation for the different categories of drugs, and in particular for many of the classes of highly APIs, the Regulatory Agencies we studied used terms like "certain", "some", "others", often without any reference to their specific meaning. In these cases, it is up to the pharmaceutical industry to choose the most suitable containment measure by means of risk analysis. The use of these adjectives without providing a specific definition of their meaning obviously leaves too much room for individual interpretation which could potentially have a negative impact on both the safety and efficiency of the production processes. The problem should be overcome using unambiguous terminology with precise refer-

ences. In 2015, the EMA and later on PIC/S and HC updated their GMP by adding the need to use QRM procedures to their regulations in order to choose the most suitable facility for the production of all classes of drugs that could represent a risk. Moreover, they have introduced new criteria for the risk analysis of products based on toxicological and pharmaceutical parameters.

It became obvious that up to this moment, unlike other Regulatory Authorities only EMA, PIC/S and HC have regulations that define a specific operative method in order to assess the type of facility which should be used in the production of the highly active or sensitising ingredients mentioned in this paper.

The other regulations, as can be seen in Table 1, do not provide specific indications concerning the type of segregation required for these cases. As previously mentioned, in the case of sensitising ingredients such as beta-lactams, the majority of Regulatory Authorities require dedicated production, though in truth, even if a beta-lactam production plant were to be abandoned, its re-use would be nearly impossible. Nevertheless, advanced cleaning techniques could solve this problem. Takahashi et al., in their article "*Case Study: Beta-Lactam Decontamination and Cleaning Validation of a Pharmaceutical Manufacturing Facility*", describe the successful transformation of a facility previously used for manufacturing cephalosporins (41).

Various Regulatory Agencies require that some categories of highly potent APIs be manufactured in a dedicated or segregated facility from the very start, creating further costs for the manufacturing company, which would be forced to build this type of facility in order to comply with the regulations required by the Authority. This would encourage delocalization of productive activities, as a company might choose to manufacture in States where GMP are less restrictive, substantially cutting production costs. Unfortunately, this might result in a loss of quality for the finished product and an increase in risks for personnel who could be exposed to the effects of reduced quality standards and last but not least the end users.

The constant evolution of pharmaceutical legislation is aimed at finding innovative solutions for the production of highly active and sensitising materials, an approach that is not limited to the application of strict rules but that includes a risk analysis able to identify critical guidelines to focus on adopting appropriate safety measures for individual drugs and not just their class.

Consequently there is a need to bring legislation that does not support this approach up to date. Harmonising different regulations would be desirable, since by following a single QRM procedure a company could produce and market its products in every nation in the world in accordance with the best quality standards. A further problem is represented by the lack of official translations of the regulations, which facilitates mistakes due to an incorrect interpretation of regulations (7). Besides the language barrier, there is an obvious need to achieve a "Common scientific language", with which to standardise requisites enforced by the various Authorities according to available scientific evidence.

It is clear from the above that it is possible to improve the current status of drug production for the benefit of companies and users, reducing costs and increasing benefits and safety for all those involved.

The present study focuses on significant differences between some of the major GMP Regulation Agencies concerning the production of highly active and sensitizing pharmaceutical products, placing a special emphasis on the consequences of these differences and the urgent need to harmonise GMP to guarantee that the standards they provide are clear, up-to-date and globally applicable. A first step towards this goal might be provided if pharmaceutical companies collaborate to create a network of companies who conform to a set of standards.

Harmonisation will not happen without complication but needs to be achieved as soon as possible to ensure quality standards are met for medicinal products and patient safety is guaranteed.

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