*Macedonian pharmaceutical bulletin, 68 (Suppl 1) 597 - 598 (2022)*
*Online ISSN 1857 - 8969*
*DOI:10.33320/maced.pharm.bull.2022.68.03.286*
*Short communication*

# Cross-contamination in pharmaceutical industry: types, measures and good practices

Kosara Lutovska*, Marija Glavas Dodov

*Institute of Pharmaceutical technology, Faculty of Pharmacy, Ss. Cyril and Methodius University in Skopje, Mother Tereza 47, 1000 Skopje, North Macedonia*

## Cross-contamination in pharma industry

In pharmaceutical companies there are risks of cross-contamination in case of poorly designed and operated air handling systems and dust extraction systems; inadequate procedure for personnel and equipment and not proper cleaning of equipment; not proper sealing, separation and storage of raw materials as well as problems with water purification. System of standards - GMP (Good Manufacturing Practices) requirements provide production of safe and controlled medicinal products. With planning and practice of appropriate Quality Management System-QMS, contamination and cross-contamination could be prevented.

Medicinal products manufacturing should be in a controlled clean aseptic or sterile conditions. Medicinal products are meant to prevent or treat illnesses or diseases, improve the patient's health and save his/her life.

*Cross-contamination risk points mapping*. The cross-contamination risk points that are considered are: materials; equipment; personnel; premises; layout of facilities; HVAC system and water. Standards should be implemented in order all the listed risk points are verified and to ensure aseptic or sterile conditions. This will ensure medicine quality and safety, which directly affects the patient's health and life.

*Equipment.* The production equipment should be composed of material compatible with the characteristics of the process and the product (EudraLex, 2014), and it is required to be in compliance with ISO 13485 – Quality management system for the production of medical devices. Parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive. According to GMP guidelines, it should be designed, located and maintained in a way that could be easily and thoroughly cleaned according to detailed and written procedures (EudraLex, 2014). Pharmaceutical manufacturers are required to establish a fully documented written cleaning procedure for each piece of processing equipment in accordance with FDA 21 CFR Part 211.67 (FDA, 2022).

*Personnel.* According to GMP and WHO guidelines, there should be hygiene instructions and personal health checks to maintain the quality of the product and to prevent contamination and cross-contamination (WHO, 2014).

Standard operational procedures for personal hygiene (washing hands, changing clothes, disinfecting shoes and hands, sterile clothing) are mandatory. Moreover, protective garments should be worn when handling starting materials and exposed products. Once garments become wet or dirty, they should be replaced with clean, freshly laundered garments. The clothing should comply with EN-SFS 14065 - European Standard for Hygienic Quality of Protective Clothing (Lindström 2020; WHO, 2014).

Personnel flow is also important when it comes to preventing cross-contamination. Personnel and materials should not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone. (EudraLex, 2013).

*Premises.* Manufacturing rooms should be well designed in order to ensure adequate cleaning and minimizing the cross-contamination in compliance with ISO 14644 - International standard to design, construct, validate and operate a cleanroom (EudraLex, 2014). According to GMP, premises are divided in 4 types: storage, production, quality control and ancillary area. General requirements useful to prevent cross-contamination are: adequate space should be provided for logical and orderly placement of equipment and free movement of personnel; the walls and floors of the areas should be free from cracks; points of dust accumulation like 90 ° angles areas or less; premises should be carefully maintained; premises should be cleaned and where applicable disinfected; doors should be kept shut to keep

*kosaralutovska@gmail.com

the pressure differences; spills should be cleaned up immediately (EudraLex, 2014; Gad, 2008; GMPSOP, www.gmpsop.com).

*Layout of facilities*. The design of a pharmaceutical company facility should always be developed in a way that the material, product, personnel flow is taken into consideration (Gad, 2008).

There are several types of layouts: *1).* Perimeter manufacturing and center warehouse. The center of the facility is a storage (raw materials, packaging components, and bulk stocks), and the outer perimeter is for manufacturing and packaging. Advantage: space conservation, negative side: risk of contamination and cross-contamination; *2).* Circular flow layout consists receiving, approved raw materials, components storage and dispensing on one side, and manufacturing, quarantine, bulk stock, and packaging across a central corridor; *3).* The straight line flow layout design would be the best alternative to minimize the cross-contamination or mix-ups. The main disadvantage is that an additional space would be required.

*HVAC system.* According to the GMP, the heating, ventilation and air-conditioning (HVAC) system should be designed to provide clean and controlled conditions for manufacturing, as well as to prevent the cross-contamination (WHO, 2018). HVAC system has an effect on room pressure, pressure differentials, and pressure cascades (ISPE, 2009). The pressure differential should be designed in a way the direction of airflow is from the clean area, resulting in dust containment (WHO, 2018). With the aim to provide spatial segregation airlocks could be created. Depending on the desired airborne flow direction with the different pressure between rooms there can be created a cascade, a bubble and a sink (ISPE, 2009).

There are levels of protection and recommended filtration - the filters should relate to the EN1822 and EN779 test standards. The HEPA filters should be in complains with EN1822 classification of at least H13 or equivalent (WHO, 2006).

*Water.* In order to achieve the microbial criteria and to avoid biofilm growth, the water system should be in compliance with ISO 22519 (specifies design, materials selection, construction and operation of purified water and water for injection, pretreatment and membrane-based production systems). The European Pharmacopoeia (Ph. Eur. 10) has set quality standards for three grades of water (water for injections, purified water and water for preparation of extracts. All systems, should have appropriate recirculation and turnover to assure the system is well controlled chemically and microbiologically; they should be monitored regularly; and water pipes should be sanitized and stored according to written procedures (WHO, 2012).

## Conclusion

GMP standards should be implemented within a pharmaceutical company in order all aspects of possible contamination and cross-contamination to be considered and prevented. Reducing the possibilities of the cross-contamination ensures adequate and safe conditions for production of quality, pure and controlled medicinal product. Ultimately, this will provide safe patient treatment and the potential risks of medicinal products will be minimized.

## References

EudraLex., 2013. The Rules Governing Medicinal Products in the European Union, Vol. 4. Pt.1, Chapter 2. Available at: untitled (europa.eu).

EudraLex., 2014. The Rules Governing Medicinal Products in the European Union, Vol. 4. Pt.1, Chapter 3. Available at: chapter_3_0.pdf (europa.eu).

FDA, 2022. Available at: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-211/subpart-D/section-211.67

Gad, C.S., 2008. Pharmaceutical Manufacturing Handbook, Regulations and Quality. John Wiley and Sons Inc., New Jersey, pp. 818-819 and pp. 821.

GMPSOP. Available at: www.gmpsop.com. Accessed on: April 15, 2022. https://group.lindstromgroup.com/contamination-control-in-the-pharmaceutical-industry-eguide-download.

ISPE, 2009. Available at: Good Practice Guide: Heating, Ventilation, & Air Conditioning (HVAC) | ISPE | International Society for Pharmaceutical Engineering.

Lindström, 2020. Available at: https://lindstromgroup.com/in/article/pharmaceutical-contamination-types-causes-and-prevention/.

WHO, 2006. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Who Press, Geneva, pp. 55-56 Available at: untitled (who.int).

WHO, 2012. Available at: Annex 2 WHO good manufacturing practices: water for pharmaceutical use.

WHO, 2014. Available at: https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/trs986annex2.pdf?sfvrsn=320c9e62_1&download=true.

WHO, 2018. Available at: trs1010-annex8-who-gmp-heating-ventilation-airconditioning.pdf.