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# Basic good manufacturing practices (GMP), special conditions and inspection processes in the Covid19 (SARS-CoV-2) pandemic

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**ABSTRACT**: The COVID-19 pandemic has severely impacted the world economy, businesses and global health. Exceptional situations are evident in the food, cosmetics and pharmaceutical production in the supply chain, where many businesses have been shut down completely following government restrictions. In the pandemic process, it has become much more important to ensure hygienic products and employee safety and to deliver quality and healthy products to the consumer. In extraordinary conditions, it is necessary to provide additional contributions to the principles of good manufacturing practices. With the additional measures to be taken during the epidemic period, a healthy and safe operation can be brought to production. In addition, the assurance system can continue to function despite restrictions and failing audits. In addition to the updated guides, the development of roadmaps specific to the epidemic period for production may provide the advantage of being ready for problems.

**KEYWORDS**: Covid19; GMP; GDP; production, pandemic, inspecion, guide, SARS-CoV-2

## INTRODUCTION

GMP is a set of practices designed to produce accurate, clean, high-quality, stable, controlled and traceable products for manufacturing and product owners. It determines and controls the quality and reliability of the place of production, environment, materials, equipment and production process, personnel and raw materials. Covering the pharmaceutical, cosmetic and food industries, GMP also includes detergents and cleaning products. The human factor in the manufacture of cosmetic products; There are international guidelines that allow effective control of the technical and administrative factors that affect product quality and manufacturers of cosmetic products. These guidelines are used to guide the establishment of the plans and activities necessary for the effective operation of the quality management system. For example, Good Manufacturing Practices for cosmetics are qualified in ISO 22716 standards to verify compliance of the business management system with the requirements of the European Cosmetics Regulation and to gain access to the European market (1).

Good manufacturing practice is the responsibility of the top management of the manufacturing company and refers to the conditions required to ensure adequate facilities for personnel, equipment and machinery. The first step of GMP is the establishment of a quality management system. The aim of the quality management system is to establish a unique quality system adapted to the activities of the manufacturer and the quality of its products. To implement quality management at the production level, this system includes the organizational structure, commitments, available resources, procedures, and processes. An internal organization chart and job descriptions are established. Thus, each employee knows his or her duties, specific tasks, and position within the organization. Within the quality management system, there must be the necessary infrastructure for production, sufficient space, the necessary equipment and competent personnel (2,3).

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## 1. GENERAL CONDITIONS OF GOOD MANUFACTURING PRACTICES AND PANDEMIC MEASURES

### 1.1. Staff status

Job descriptions are created according to tasks and represent several people who know their responsibilities. Competence is important in a system of good manufacturing practices. At control points such as quality control and production, the same personnel should not be responsible for two tasks. It should be determined whether the personnel supervising or performing the production or control of the products have the necessary education, training, and/or experience to perform the tasks assigned to them. To this end, the appropriate technical and GMP training should be repeated for the personnel concerned, and their qualifications should be regularly reviewed and documented (personnel qualification). In addition, personnel in direct contact with raw materials, in-process materials, finished products, or contact surfaces should wear clean clothing appropriate for the task at hand, as well as the necessary protective clothing (e.g., uniforms, gloves, safety glasses, and hair caps).

Personnel should maintain appropriate personal hygiene and stay away from sources of microbiological contamination (e.g., wounds and infected sores). To this end, staff hygiene and cleaning training should be repeated at intervals. Eating, drinking, or tobacco use should be confined to appropriate, designated areas away from storage and processing areas. Only authorized personnel should be allowed access to production, storage, and product control areas. These authorizations must be registered and traceable (4).In pandemic conditions, employees who come to the workplace should be screened in some way. The appropriate level of screening may vary depending on the overall spread of the virus and other risk factors. It may be questioned if employees have symptoms of COVID-19, have recently traveled, or have been in close contact with someone who has tested positive for COVID-19 or has similar symptoms. Employees should be encouraged to stay home if they are ill. Those whose symptoms are suspicious should not be forced to come to work. Management can use a non-contact precision infrared thermometer (IR thermometer) to take employee temperatures (38°C or higher). In the case of seasonal and temporary workers, they should be carefully monitored. Control of workplace hazards associated with the virus is critical, as symptomatic scans cannot detect infected but asymptomatic individuals. Similarly, the safety of the place where the scan is performed and the person performing the scan should be ensured (5,6).

Disposable gloves do not replace hand washing in ensuring personal hygiene of the personnel. SARS-CoV-2 can also contaminate the virus through disposable gloves. Removing disposable gloves can also contaminate hands. Therefore, proper donning and removal of gloves is essential. In addition, employees should wash their hands for at least 20 seconds and in accordance with the washing instructions before putting on disposable gloves. Care should be taken not to create a false sense of security due to the use of gloves and to wash hands frequently enough (7-10).

*1.1.1 Ensuring hand hygiene*

The establishment should have hot water, liquid soap, disposable paper towels and non-contact trash cans and appropriately placed hand washing stations. Employees should wash their hands frequently (at least 20 seconds) as indicated in the instructions for use. Non-contact hand sanitizers may be used as an additional precaution, but should not replace proper hand washing. An alcohol-based hand sanitizer with an alcohol content of at least 60% should be used. Hand sanitizers can be used in areas where hand washing is not possible (11-13).

*1.1.2 Use of face masks*

During the epidemic, it is recommended to use face masks in crowded environments where it is difficult to maintain social distance measures. Mask use is mainly for asymptomatic workers who can unknowingly spread the virus. The World Health Organization recommends that workers wash their hands with soap and water before putting on a mask. Both mouth and nose should be covered with a mask, and there should be no space between the face and the mask. Personnel should avoid touching the mask during use; otherwise, hands should be washed or disinfected. The mask should be changed as soon as it becomes damp, dirty, or torn, and disposable masks should not be reused (14,15). Personal face masks should not be worn for more than one day. Performance has been shown to be reduced when a disposable mask is worn for more than 4 hours (16). Care should be taken when removing the mask. It should be removed from the back (without touching the front of the mask) and thrown into a closed container. Hands should then be washed with soap and water.

*1.1.3 Physical distancing measures*

Maintaining physical distance is one of the important factors in preventing the transmission of the virus. *The WHO defines the physical distance as 1 m and the CDC defines it as 2 m (17,18). Workers can become infected through close contact in production lines, receiving and packaging areas, sampling and quality control rooms, and common areas such as conference rooms, break rooms, locker rooms, restrooms, hallways, and entryways (19). Close contact means being within approximately 2 m of a COVID-19-positive person for more than 15 minutes (20). Maintaining physical distance helps slow the spread of COVID-19.

**1.2. Condition of buildings and facilities**

All areas where activities will take place must be designed, constructed and protected in accordance with international standards and requirements. Pressure differences between areas, area temperatures, humidity and ventilation, quality of lighting products should not affect the products during their production or storage. For this reason, HVAC (Heating, ventilation and air conditioning conditions) systems should be designed in accordance with the cleanliness class (sterile, non-sterile) of the product to be produced, and the level of impact on the environment and human beings. While designing HVAC systems, air filtration stages, air duct materials, duct sealing, air cycle numbers in production areas, desired particle and microbiological limits in the air in production areas should be taken into consideration. After the system is commissioned, qualification tests should be carried out (21).

The suitability of the air quality of the production areas (Particle, Pressure differences, Temperature, Humidity and Microbiology loads) should be tested periodically and documented. Buildings must provide adequate size and adequate organization to avoid selection errors (i.e. mixtures) or cross-contamination between consumables, raw materials, intermediate formulations (i.e. in-process materials) and finished products. Adequate pollution and pest controls should be carried out against animal contamination such as rodents, insects or birds, or other objectionable substances caused by unsanitary conditions. Service purchases can be made for tracking and combating. Processes should be recorded so that they can be tracked.

Floors, walls and ceilings should be made of smooth, easily cleanable surfaces. Adequate lighting and ventilation, control screening, filtering, dust, humidity, temperature and bacteriological controls can be designed when necessary (22).

It is not appropriate to use a fan within the scope of Covid-19 measures in offices and areas that do not need air conditioning. Ventilation of workplaces with central ventilation systems should be arranged in a way to ensure fresh air circulation, maintenance of ventilation systems and filter changes should be done in accordance with the manufacturer's recommendations. Flow should be provided from the contaminated area to the clean area in such a way that mechanical airflow is prevented. Cleaning, maintenance and repair of the filters of the ventilation system should be done periodically [23].

Equipment and machinery should be located so that they do not pose a potential risk to the quality of materials, machinery and personnel movements. In order to serve the purpose of the activity effectively, equipment and machinery should be maintained. Periodic maintenance should be done once a year or more in order to be efficient enough.

There should be a closed and locked area within the facility where wastes will be kept separately. Raw materials, semi-finished products, primary packaging, secondary packaging materials and wastes generated in production should be transferred from different areas.

*1.2.1 Measures that can be taken within the facility during pandemic processes.*

The following recommendations for Common Areas, Corridors and Personnel Control can be followed.

• Using doors that open without touching within the facility or opening doors with limbs such as elbows, knees, hips and feet reduces the spread of the virus from hands where the virus is concentrated.
• If the number of employees in the closed office area is high, the areas can be divided or separated.
• Waiting and communications in the corridors can be minimized.
• It can be divided into times to prevent crowding in areas such as locker rooms, cafeterias and parks that can be crowded at once.
• Hand-free washing can be provided with foot-operated taps in hand washing units.
• Surfaces to be contacted in areas where uniforms will be changed can be reduced.
• Dirty uniforms and clean ones can be kept separately.
• A distance of 1-2 m should be maintained between each worker throughout the facility in the production environment.

*WHO: World Health Organisation- Dünya Sağlık Örgütü
**CDC: Centers for Disease Control and Prevention - Hastalık Kontrol ve Korunma Merkezleri

• Distance monitoring and distance instructions can be written on the processing area lines.
• Spaces can be left between workstations, which may require reducing the speed of production lines.
• Visual cues (eg floor markings) can be provided to remind workers to maintain physical distance.
• The number of personnel in the food preparation area can be limited.
• Shifts can be extended with less staff to avoid crowds.
• Working groups or teams can be organized to reduce interaction between personnel.
• Video calls can be provided instead of face-to-face by using technological facilities.
• Video applications or phone calls can be used to avoid face-to-face contact during shift changes.
• In order to minimize contact with more than one person, materials such as pens, knives, clipboards, kitchen utensils can be allocated to everyone.
• The number of people working and accumulating in social areas can be reduced.
• A single trained employee can be assigned to serve the employees, instead of taking food from a common container where more than one employee's utensils are touched by more than one person.
• Refrigerator handles/sinks and faucets/kitchen areas/microwave and vending machine buttons can be disinfected frequently.
• Foot-mounted disinfectant stations can be placed in every different area.
• Signs promoting hand hygiene and physical distancing may be posted for staff (16,24).

### 1.3 Methods (procedures) and instructions

Each manufacturer creates its own system of procedures and production instructions. Institutional structure and production quality are taken into account in the procedures. Procedures and production instructions should be properly defined. All flow steps should be written down, and Standard Operating Procedures (SOPs) should be established, describing general approaches and policies. Instructions containing specific working methods and rules specific to the process and equipment should be created. SOP and instructions should be updated and renewed at certain time intervals. The SOP and instructions should comply with current guidelines and include these guidelines in content. The general rule in the GMP Documentation system should be ***'Write What You Do, Do What You Write'*.**

Processes refer to the necessary and sufficient development steps to be applied during the production of the product. It should be ensured that these operations are carried out under suitably controlled conditions.

According to GMP, conditions in accordance with product standards and quality must be provided in production areas. Measures should be taken against possible risks and production should be guaranteed to ensure the same conditions. Therefore, it is necessary to follow the procedures and instructions for each stage of the process. Critical points must be controlled and all processes must be traceable. It should be seen that the responsible persons perform their duties and follow the work responsibly both in the production and control stages. Personnel must have sufficient information, data and instructions in all operations within the facility. Correct implementation, control and documentation of the following parameters directly related to production and products should be provided.

### 1.4 Production parameters

*1.4.1 Water*

Monitoring and quality of water, which is one of the main ingredients of production and ensures cleanliness, is very important. Quality and standardized water must be provided to ensure conformity of the finished product. For this purpose, systems such as deionization, reverse osmosis, filtration and distillation systems can be used. The production of water within the facility should be done according to the procedures written in detail. Water systems should be monitored to ensure proper chemical and microbiological quality. The installation should be placed from the water production to the production area in such a way that there is no stagnation and dead spots. If necessary, a closed-circuit system can be created with continuous circulation. There should be no risk of contamination in the environment. Water should not be kept in a closed system for a long time. Materials, motors, pumps, etc. should not effect the water quality. Materials that are open to corrosion, suitable for microbiological growth and have blind spots should not be used. Water pipes should be identified by appropriate markings such as cold, hot, demineralized water, cleaning water or steam, and their flow directions should be indicated.

In GMP, the quality of the final water can be Pure Water (PW), Ultra Pure Water (UPW), Water for Injection (WFI). The conductivity, temperature, pH, TOC (Total Organic Carbon) etc. quality parameters limits of these waters are clearly stated in the GMP standard. (25,26)

*1.4.2 Acceptance of raw materials and materials*

Depending on the rules, specifications for raw materials should be established to ensure that they meet the appropriate standards and specifications. Descriptions in the instructions should be descriptive and detailed, and storage conditions should be specified. There should be sampling studies, testing and analysis methods for acceptance criteria. (Cosmetic guidelines are not as strict as GMP in drug status, and in many countries it is sufficient to simply get the specifications.)

Prohibited and restricted cosmetic ingredients (ie color additives and preservatives) must be distinguished before supplying the raw materials.

The following recommendations can be considered for the transportation and acceptance of raw materials and materials under pandemic conditions.

• Have a driver handle the transport of items and materials.
• Implementation of applications that reduce or eliminate the contact between the driver and the facility.
• Advising drivers to stay off-site and/or in their vehicles.
• Shrink the packaged raw materials and limit the unwinding of the tight film packaging by the receiving personnel, not by the production personnel.
• Ensuring that the driver washes or disinfects their hands before and after unloading the cargo, as well as the receiving and delivering employees.
• Use of face masks when physical distancing cannot be applied.
• Minimize shared items for signing shipping documents.
• Implementation of appropriate hygiene and sanitation protocols when using reusable containers and carriers (24).

*1.4.3 Storage*

All raw materials, packages, finished products and intermediate products should be stored and monitored under appropriate conditions. In order to guarantee the stability of the products throughout the shelf life, all parameters that come into contact with the product must be stored under appropriate conditions. Materials required for production (all starting materials, semi-finished products, bulk products and finished products, quarantine products, released products) must be stored according to their quality and in appropriate conditions to ensure efficient lot identification and stock rotation. Temperature and humidity should be in storage conditions. There should be defined rejection areas where non-conforming products are separated. Quarantine areas where raw materials, packaging and finished products are kept should be determined during the control (3).

*1.4.4 Purchasing processes*

All materials for production (raw materials, product components, semi-finished products, bulk products, packaging materials, unpackaged products) must be purchased within the framework of certain procedures and in accordance with their technical documents. Critical points should be checked and recorded when receiving materials. Control criteria should be made according to the numbers and methods specified in the instructions.

According to extraordinary conditions, possible crisis situations in the world supply chain should be evaluated and alternative supply plans should be created according to possible breaks in the supply chain.

Records must contain the following information to identify the product purchased:

• Shipment document and product name written on the material,
• The name given to the product within the company (if different from the name given by the supplier) and/or the product code,
• Delivery date,
• Supplier's name, batch number,
• Total amount and number of material received,
• Depending on the quality performance system, internal batch number after acceptance, verification used in the delivery of purchased products, supplier or subcontractor verification should be done.
• Transportation and internal identification of raw materials, product components and other materials should be done according to established procedures.

Samples for analysis and tests; should be made by authorized persons to take samples. Equipment and methods should be used in accordance with written sampling instructions for sample quantities and to prevent contamination and deterioration of the material.

*1.4.5 Weighing*

Raw materials must be weighed under the same production conditions, in accordance with the production formula. Weighings should be recorded and weighed by another personnel (double check). Labels and quantities describing the product should be written on the weighed materials. The containers in which the weighing is made must be clean in accordance with the cleaning instructions. Weighing cups specific to each material can also be used. Starting materials and auxiliaries must be weighed precisely and protected from contamination. Who carried out the weighing operation should be recorded and identified by signature. Weighing authorization should be given to certain personnel.

In pandemic conditions, contact surfaces should be minimized and attention should be paid to maintaining distance in weighing areas.

*1.4.6 Mixture preparation*

Production should be done in accordance with the written instructions. The materials to be taken into production and their quantities, the conditions under which production will take place and for how long (such as temperature, mixing speed and time) should be defined. The materials are placed in the equipment that has been previously checked for cleaning, paying attention to the quantities and sequences specified in the formula and flow chart. While the equipment is running, the process is controlled by taking samples from the points specified in the instructions and in certain numbers. The batch number of this production is written on the labels. The follow-up signatures of the operators performing the production and quality controls should be included in the production notes. The product that receives control approval can be filled. During pandemic processes, attention should be paid to hygiene rules and contact surfaces should be minimized.

*1.4.7 Filling and packaging*

Filling and packaging processes should be specified in the instructions. Before starting packaging operations, appropriate checks should be made to ensure correct installation and equipment use as planned. Filling is carried out in controlled primary packs (primary packaging). It is very important to avoid the risk of mixing/contact with the packaging material or a product/material contamination from the previous filling and packaging process itself or its components. To ensure these precautions, the necessary controls should be defined in the instructions. Packaged products should be labeled on the production line or kept in a controlled manner if they are to be made well after the production process. Products should be kept under quarantine while controls are made on finished products. If there is a secondary packaging (secondary packaging), this process is included in the control process.

It is stated that the risk of spreading from food products or packaging is very low, since the survival time of corona viruses on surfaces is generally short (27). However, it has been determined that the virus can survive up to 9 days on different surfaces. Therefore, as a precaution, contact with the eyes and respiratory organs should be avoided after contacting the packages during primary or secondary packaging (28).

*1.4.8 Release*

Finished products must go through an acceptance process to see their suitability before being released to the market. Different control methods are possible according to the nature of the product, production method and quality system. Products must not be placed on the market without sales approval following the procedures of conditions clearly defined by the business. These procedures and conditions may also be included in the subcontractor agreement. Products must be released by the responsible person. Released products should be registered and tracked in warehouses with the lot number to be distributed to the market (29).

*1.4.9 Distribution*

Transport instructions should be available to guarantee the quality of products stored under appropriate conditions. In order for the finished products to be placed on the market, they must comply with the standards defined by the legislation and the relevant technical regulations. If contract manufacturing takes place in another production facility as a subcontractor, attention should be paid to the GMP system and production compliance. The manufacturer should take responsibility at critical points related to production. Records should be archived and kept by both the manufacturer and the product owner.

### 1.5 Contract manufacturing

If the product owner plans to have his products produced in another production place under his own brand, contract manufacturing should be done with this production facility. Instructions and specifications for raw materials and product ingredients, formulations and production workflow must be properly defined to maintain the quality of the product. For this reason, an agreement should be made between the contractor and the subcontractor regulating the obligations of both parties. It is the employer's responsibility to evaluate the subcontractor's ability to make contract manufacturing in order to carry out the necessary procedures. The employer must submit to the subcontractor all the information regarding the details of the obligations regarding the manufacturing stages with a written contract. The subcontractor must comply with pre-arranged official requirements and fully comply with the agreed technical requirements. The subcontractor must carry out any control and inspection that the employer may request as specified in the contract. If necessary, the control of production and quality control processes during production can be added to the contract by mutual agreement.

It is necessary to agree on the hygiene rules to be followed during the pandemic process. If the personnel is to be present in the factory on behalf of the company that produces to control the production process and records, depending on mutual agreement, they should act in accordance with the precautions of the manufacturer (19).

### 1.6 Quality assurance system

The quality assurance system in the production process includes all the activities of the manufacturer. In order to reduce, eliminate and prevent the problems that may arise in quality, some activities should be carried out by both the production unit and other departments that have a direct or indirect relationship with production. These activities are part of the quality assurance system. System activities according to departments are as follows; The Production Unit must regulate and comply with the instructions and procedures clearly defined by the authorized departments. Production personnel should be encouraged to report any non-compliance and compliance criteria violations. Along with other processes related to the subject, the analysis of quality inconsistencies and the implementation of correction, prevention, development, monitoring and evaluation activities as a result of the analysis should be ensured. It should be seen that there are responsible persons at every level and that the system is traceable. Records must be kept and maintained.

Measures and action plans to be taken due to extraordinary conditions and force majeure should also be recorded. In order for these records to be perceived and applied correctly by the employees, trainings and reminder activities should be organized (20,29,30).

### 1.7 Purchasing management

*1.7.1 Purchasing department*

Responsible for managing the purchasing process. The execution of the quality system in this area is based on the efficient management and direction of the resources that are important for production. Resources include raw materials, product components and, if necessary, manufacturing machinery. It should take part in the follow-up of resources in partially or completely contract manufacturing processes such as filling or packaging. All requests and research and development issues related to the continuity of product quality should be carried out in coordination with the production and quality units. The operational obligations of the unit should be clearly stated. These obligations can be listed as follows.

- Raw materials, product components, etc. to edit the relevant features and specifications.
- Approving and periodically evaluating suppliers and subcontractors in terms of quality assurance,
- Arranging the conditions for the relationship and exchange (support, audit, etc.) between the company and the supplier,
- Considering the audits made by the supplier or subcontractor,
- Arranging provisions on technical issues to be included in the contract (type of audit to be performed, acceptance or rejection criteria, steps to be taken in case of violation of compliance or in case of changes, etc.),
- Other requests such as price, delivery time and instructions, and after-sales service if necessary.

*1.7.2 Purchasing documents*

They must clearly describe the product. In addition, obligations regarding order preparation, type of information or conditions to be specified should be clearly defined in the procedures. Additional measures regarding the transportation, protection and delivery of the materials requested according to the pandemic conditions should be put in writing.

### 1.8 Maintenance and repair

Maintenance and Repair Unit is the unit responsible for the installation, repair and maintenance of the lines. It takes part in the purposeful design, assembly, installation and protection of production machines within the quality system without affecting the product quality. The machines should be placed in such a way that they do not hinder the movement and should be properly cleaned. All these operations must be carried out according to pre-prepared standard operating procedures. The operating instructions of the machines and the precautions to be taken in case of failure should be specified in the quality system. Maintenance of production machines should be done regularly by the authorized department within the company or by outsourcing the maintenance contract.

Companies that receive services from outside should be informed about acting according to pandemic conditions. Facilities and equipment must be kept intact and in working order. Maintenance records and documentation should be kept (20).

### 1.9 Hygiene rules and prevention of pollution

The finished product should not adversely affect the health of the consumer. It should not cause deterioration in product quality due to microorganisms. Since the risk of microbiological contamination varies by product (for example: less contamination in perfumes compared to creams), different production steps should be used in accordance with industrial hygiene conditions. In every part of the factory, buildings, installations and equipment must be kept in good hygienic conditions, just as raw materials, product components, bulk products, unpackaged and finished products. Different activities should often be organized to avoid the risk of stagnant water, dust, insects and other animals in the production area. These activities should be cleaned and disinfected in accordance with the design and usage conditions by outsourcing if necessary. It should be ensured that personnel comply with certain rules and work instructions regarding personal hygiene. To identify the nature and source of any contamination for product contamination, measures should be taken to eliminate these sources of contamination. The plant and equipment must not present any risk for any product contamination and/or deterioration. The facility must be kept clean and tidy. Detergents should not come into contact with cosmetic products. Any cross contamination should be avoided (20,30,31).

In pandemic conditions normal routine cleaning with soap and water, and hygiene against germs and dirt on the surfaces are provided. In this way, the risk of spreading the COVID-19 infection is reduced, while disinfectants kill germs on surfaces. Killing germs on a surface after cleaning can further reduce the risk of infection spreading (32). When working with chemicals, the manufacturer's instructions should be followed, paying close attention to the contact time, concentration, method of application and whether it is safe for use on surfaces that come into contact with the product (33,34).

All production equipment that comes into contact with the product should be cleaned using validated methods. Sanitization and sterilization processes should be carried out in the equipment and lines where sterile products are produced. Sanitization should be done with WFI quality water, and sterilization should be done with sterile clean steam obtained from WFI water, in compliance with temperature and time limits.

### 1.10 Education

In order to ensure effective quality control in production, sufficient knowledge, experience, competence and motivation should be provided to the personnel. For this reason, first of all, the training needs of all personnel, regardless of their position within the company, should be determined. A personnel training plan should be established.

The trainings should be in accordance with the profession and responsibilities of the personnel working in a certain department, taking into account the technical knowledge and experience. As a result, all key and manufacturing personnel must be fully trained in the methods and competence required to perform the different processes (weighing, mix preparation, production, industrial hygiene, in-process controls, maintenance, etc.). These training courses should be given by the company or external training organizations within the framework of a program. This plan should be regularly reviewed, monitored, recorded and evaluated.

It is very important to share how to take and implement measures in pandemic conditions within the institution. Informative trainings should be organized and guides should be prepared to guide employees. These guidelines should be accessible and understandable. Graphics, images and videos can be used. In face-to-face training, physical distance should be followed or distance education tools should be used (19,35).

## 2. EVALUATION OF RESULTS AND PANDEMIC CONDITIONS IN GOOD MANUFACTURING PRACTICES

Using the results of GMP allows measuring quality in production. On the other hand, corrective-improving-preventive actions provide the opportunity to monitor the results. In the light of this information, an analysis of the causes of possible errors should be made in order to decide which corrective-improving-preventive measures to take.

Being aware of the crises and opportunities brought about by extraordinary conditions will create awareness in terms of the continuity and evaluation of the processes. Projected and unforeseen risks to personnel, crew and equipment can define the magnitude of the potential impacts of the pandemic. There may be additional measures to be taken according to these situations.

In case of complaints, only reasoned complaints should be considered and party records should be examined. Complaints should be recorded. If necessary, corrective-improving-preventive actions should be taken according to the complaints (36,37).

## 3. AUDIT AND PANDEMIC CONDITIONS

GMP audits can normally be carried out on a regular basis by specially appointed authorized auditors, or they can be carried out independently and in detail upon request. Inspections are carried out at production sites, suppliers' workplaces or contract manufacturing sites. Inspection is generally carried out through the quality system. The purpose of the audit is to comply with good manufacturing practices and, if necessary, to recommend corrective-improving preventive actions. The results of the inspections are sent to the company management and reported to the personnel who passed the inspection. If there are deficiencies, improvement activities should be arranged. Checks should be made to ensure that remedial measures have been taken. Records of every operation performed in the facility setup and equipment should be kept in accordance with the established rules and conditions (20).

In the extraordinary conditions that have changed with the Covid19 pandemic, the conduct of inspections has also undergone some changes. Different measures and updated control mechanisms have been developed from country to country. Despite the restrictions, inspections continue during the pandemic. In March 2020, when the outbreak was first described as a pandemic by WHO, the FDA announced that it was temporarily suspending all domestic and foreign routine surveillance facility inspections and would resume mission-critical inspections whenever possible. In July 2020, it was announced that domestic inspections would be carried out with a road map under certain conditions (38).

In audit practices in Australia, remote and/or mixed audits are used by using the hybrid method model. In the new audit processes, communication tools and desktop review of information are made using remote, virtual review. In some cases, a mixed approach is used, which includes a desktop inspection and an in situ inspection under controlled conditions. There may be an on-site inspection in places where the safety equipment can be taken completely, and it is also considered to conduct inspections at a later date in places where there may be a security risk.

Efforts have been made to minimize the potential risks inherent in on-site inspection, where social distancing may be difficult to achieve. The continuity of production and economy was ensured without interrupting the inspection and permit processes. Safe use of therapeutic products by consumers has been supported by surveillance (39).

Due to travel restrictions related to the pandemic, supervisory authorities often conduct remote assessments. It is expected that foreign inspections will increase again when the transitions from country to country are more free. The European Federation of Pharmaceutical Industry and Associations (EFPIA) has implemented the inspection guide in the pandemic, which is also recognized by the Pharmaceutical Inspection Cooperation Program (PIC/S), which works on the international development and implementation of harmonized GMP standards and quality systems in medical product inspections. Guidance on "COVID-19 Risk Assessment for Routine Onsite Inspections" (PI055-1) was also published on July 15, 2021 (40,41).

With the joint proposal of the European Commission, EMA (European Medicine Agency) and HMA (Head of Medicines Agencies), it has been decided to extend the validity of GMP certificates, timed production and import permits, and the validity of GDP (Good Distribution Practices) certificates until the end of 2021. However, this stretch does not mean that manufacturers and importers waive their obligations to comply with GMP and GDP standards. The supervisory authorities in the EU have stated that they will remain vigilant to ensure the quality of medicines available to patients in the EU. Audits, including remote

assessments, can be initiated and appropriate regulatory actions should be planned in case of non-compliance (42).

In our country, GMP inspections abroad have been suspended due to restrictions of pandemic conditions. The duration of GMP certificates has been extended to 30 June 2021 without application. It has been announced that if the overseas production site is in a PIC/S member country and an inspection has been carried out there, the inspection results will be accepted, provided that the inspection right is reserved (43).

One of the important elements of auditing is internal auditing. With limited opportunities, its importance has increased even more in the time period when on-site inspections decreased, especially during the epidemic. In order to ensure the compliance and continuity of the production and quality conditions with GMP, the company's self-inspection, detecting the deficiencies according to the current conditions and creating corrective and preventive actions regarding these support the quality system (44,45,46).

## 4. RESULTS

GMP is a set of rules that must be in the production of products that directly affect human health, such as the pharmaceutical, cosmetic and food industry. In order for a product to be effective and safe, starting from raw materials and packaging materials, until it reaches the consumer, there must be systematic practices. Within the scope of these rules, general principles regarding Quality Management, Personnel, Facility and Equipment, Documentation, Production, Quality Control, Contract Manufacturing, Complaints and Product Withdrawals and Internal Audits have been determined.

Redesigning an existing facility according to GMP rules can be more difficult and problematic than the processes in a new factory setup. For this reason, it is necessary to design flexible installations by anticipating the situations that will arise in a new plant installation.

Before a new GMP production facility is established, it should be ensured that the products to be produced in this facility are classified, the human-environment interactions and requirements are well analyzed, the production quantities are determined and the equipment and infrastructure are used efficiently. In order for the system installation and applications to be long-term, preliminary audit, managerial, physical and operational development needs should be determined. As a result of the preliminary audit, studies and action plans are prepared to meet the training needs and development needs related to the management system. In line with this plan, employees are provided with physical conditions, basic documentation requirements and competencies.

The extraordinary circumstances of the pandemic have affected or partially hindered the conduct of on-site inspections of existing national and international security measures and travel restrictions, GMP and GDP. Mitigation measures were first taken in inspections to ensure that standards of good practice were followed and vital production continued. However, in order to maintain product safety, risk assessment was carried out and inspection roadmaps were updated according to pandemic conditions. It has been foreseen that the upcoming near periods may pass under epidemic conditions, and it has become necessary to take systematic measures and to create updated guidelines for legislators. In the pandemic, the unique GMP and GDP requirements of food, cosmetics, pharmaceuticals and vaccine productions have brought along unique measures for the health and safety of employees and for consumers to use safe products. On the other hand, it has been seen how the supply chains will be negatively affected by the closure of borders and customs, and it has been understood how difficult it is to ensure continuity in the pandemic.

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