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Quality risk assessment due to the introduction of a new fermentation process in a certified multiproduct facility

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ABSTRACT

The development of Genetic Engineering has made it possible to obtain a large number of novel molecules expressed through the recombinant DNA technology in *Escherichia coli*. After selecting the producing strain, preparing the cell banks and designing the production process to obtain the active ingredient, while meeting the quality standards according to the pharmaceutical form that will be used, clinical studies are required to demonstrate the proof of concept and safety. Clinical assessments are then required in human beings, and Good Manufacturing Practices (GMP) must therefore be met to ensure product quality and safety for the patient. This paper shows the application of the quality risk assessment on introducing a new fermentation process to obtain a novel product in a certified multiple product plant. Risk assessment was therefore applied, using quality tools and basic observation techniques. The potential faults involved in the introduction of this new technology were identified and assessed. In this case we identified intermediate risks for the quality of the process, which will be mitigated during technology transfer, and low risks for the facility. Therefore, this production may be carried out within this production facility, which will save resources and time.

Keywords: Quality risk evaluation, *Escherichia coli*, multi-product facility

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RESUMEN

Evaluación de los riesgos a la calidad por la introducción de un nuevo proceso de fermentación en una planta multiproducto certificada. El desarrollo de la Ingeniería Genética ha propiciado la obtención de un gran número de moléculas novedosas que han sido expresadas mediante la tecnología del ADN recombinante en *Escherichia coli*. Una vez seleccionada la cepa productora, elaborado los bancos de células y diseñado el proceso productivo para la obtención del ingrediente activo, cumpliendo con los atributos de calidad acorde a la forma farmacéutica a emplear, deben realizarse los estudios no clínicos para demostrar las pruebas de concepto y seguridad. Posteriormente es necesario realizar la evaluación clínica en seres humanos, por lo que el proceso debe cumplir con las Buenas Prácticas de Fabricación (BPF) para garantizar la calidad del producto y la seguridad del paciente. En este trabajo se muestra la aplicación de la evaluación de los riesgos a la calidad en la introducción de un nuevo proceso fermentativo para la obtención de un producto novedoso en una planta multiproducto certificada. Para ello se aplicó la valoración de riesgo, con apoyo de herramientas de calidad y técnicas básicas de observación. Se identificaron y se evaluaron los fallos potenciales que implicaría la introducción de esta nueva tecnología. En este caso se identificaron riesgos medios hacia la calidad del proceso, que se mitigarían durante la transferencia tecnológica y riesgos bajos hacia la instalación. Por tanto esta producción pudiera llevarse a cabo en esta unidad productiva, lo cual implicaría un ahorro de recursos y de tiempo.

Palabras clave: Evaluación de riesgo a la calidad, *Escherichia coli*, plantas multiproducto

*I*ntroduction

The Pharmaceutical Quality System (PQS) [1], recommends a Management System for the industry based on the concepts of ISO 9000, in line with the Good Manufacturing Practices (GMP) and complemented with the quality design studied during the Pharmaceutical Development stage [2] and the Quality Risk Management (QRM) [3], through the life cycle of the product [4]. QRM is included as a management tool of the Enterprise, and one of its greatest benefits is an improved knowledge of the processes and products, resulting in the scientific bases for decision making.

In recent years the Cuban biopharmaceutical industry has started to publish a certain number of papers related to the application of QRM in industrial production in a proactive and active form. These include: risk analyses to different technologies for the production of monoclonal antibodies used as reagents to obtain the anti-hepatitis B recombinant vaccine [5]; application of risk analyses to the production of recombinant proteins expressed in *Escherichia coli* [6]; the application of risk analyses in the preparation of solutions of the Quimi-Hib® vaccine [7] and the application of risk analyses to quality aspects in the production of tablets [8].

Tools that will be used to establish a decision making process based on science and practice are required

1. International Council for Harmonization. ICH Harmonised Tripartite Guideline Quality.Q10. Pharmaceutical Quality System. 2008.

2. International Council for Harmonization. ICH Harmonised Tripartite Guideline Quality Q8. Pharmaceutical Development. 2005.

3. International Council for Harmonization. ICH Harmonised Tripartite Guideline Quality Risk Management Q9. Federal Register. 2006; 71(106):32105-6.

for the application of the Quality Risk Analysis (QRA); these must be transparent, reproducible and must have been selected and well documented [9]. The cutting-edge tools include: Hazards and Operability Analysis (HAZOP), Fault Tree Analysis (FTA), Failure Modes and Effects Analysis (FMEA), Failure Modes, Effects and Criticality Analysis (FMECA), and support tools [10]. Basic tools such as brainstorming, teamwork, flow diagram, 6Ms (Materials, Machine, Measurement, Man, Methods and *Millieu* (environment)), identification and evaluation of possible risks can also be used [3, 10, 11].

A key element in risk assessment is defining the most appropriate tools that will be used. In general, there is no single option for a given evaluation process; in that case the selection of a risk tool is based on: the depth of the analysis required, the complexity of the topic and the experience in its application [3, 10-12]. The preliminary risk analysis is another basic method for information collection. It is a simple and inductive analysis method aimed at identifying the risks, risk situations and events that may harm a certain activity. It is recommendable to apply it at the early stages of development of a process, i.e., when there is little information on the details of the design or of the operation procedures. It may frequently be a precursor of new studies and offer information on the specifications of the design of the process [3, 10, 11].

Brainstorming is used as a support method. This tool is a means to bring together a large set of ideas and evaluations classified by a team. It helps to promote the free conversation of a group of specialists with knowledge and experience to identify the potential faults and associated risks, as well as the decision making criteria and treatment options. Moreover, it may be used with other risk assessment methods, or alone as a technique to stimulate creative thought in relation to any stage of the risk management process. Since this tool emphasizes imagination, it is very useful in identifying the risks of new technologies where there are no enough data, or when new problem solutions are needed [11, 13].

The process for research and development of new pharmaceuticals ends at the commercial production scale, where the volumes and regulatory requirements are increased. At the development stage, before carrying out technology transfer to the production scale, the feasibility for its introduction in the final facility must be analyzed, assessing alternatives such as: building a new production plant or evaluating an already existing facility [14].

The pharmaceutical and biopharmaceutical production facilities may have different types of classifications depending on the production route required for the product [15, 16]. These include:

Dedicated facilities: the production of a single product is carried out.

Multipurpose plant: here the products do not necessarily follow the same sequence or need to have all stages of the production process, and different products are obtained at the same time, and also, the same product may follow different routes through the plant.

Multiplant: it has the structure of two or more multiproduct plants that operate in parallel.

Multiproduct plant: here all products follow similar sequences through all stages of production and several similar products are obtained.

Currently the biopharmaceutical companies prefer a design of facilities favoring production efficiency so that they could respond better to demands. In principle, the investment is aimed toward a balance between common sense and the regulation scope, in order to reduce the time taken to launch the plant so that the novel products would soon be available in the market [17].

The operation of multiproducts plants offer advantages for the biological manufacturing systems since they have facilities that make a better use of the installed capacities, decrease the costs of investments for the introduction of new production processes, a faster inclusion in the market and a better use of labor [16].

The aim of this paper is to model the identification of the possible risks involved in the proposal of introducing a new fermentation process for manufacturing a novel biological product through the use of *E. coli* in a certified multiproducts plant, for manufacturing the injectable active pharmaceutical ingredients (API). A comparison is made with the process used in this plant considered to be the worst case scenario.

Setting up the QRA conditions

Selection of the consultant team

A working team of seven persons was formed by selection. We considered their knowledge, practical expertise in the biological manufacturing environment, creativeness, the possibility of their true participation, their problem resolution capacity or flexibility, their abstraction ability, response capacity, group behavior, orientation capacity and logical response. In order to work with the experts, meetings were held to complement their training in relation to the new process and the operational system of the facility. Furthermore, interactive seminars were made where the training was shared between the Technological Development Administration, having the scientific knowledge of the new process, and the staff of the receptor unit that have good command of the operational system of the facility [17].

Risk assessment using quality tools

In order to carry out the identification, analysis and assessment of risks found in the proposal for the introduction of the new manufacturing process, to obtain a novel biomolecule in a multiproducts plant, the following basic tools were applied:

- *Teamwork*: it was carried out by several individuals where each one plays a role but all have a common aim. This is a type of psychological working conditions that has one of the greatest positive influences in the workers because it enhances comradeship;
- *Brainstorming*: this is a is a group technique used to produce original ideas on a topic or a certain problem that may arise in a relaxed environment [18];
- *Flow diagram*: this cover a series of related activities with the aim of turning raw materials into products. The process includes the value of the inputs; it is composed of tasks or activities and has a start and

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an end. For the analysis of a process it is essential to have a diagram that schematically represents the different activities taking place in the working process and the working objects up until they become finished products [19];

- *6Ms*: These are based on the analyses of the machinery, labor, measures, methodology, materials and the environment [14, 20] and risk assessment [21, 22] classified in three levels [20]: low risks that do not affect the quality of the process; intermediate risks, that could affect the quality of the process but may be mitigated through preventive decision making; and high risks, which are not acceptable. For the analyses, all risks identified are treated with the same priority.

QRA for the introduction of the new fermentation process in a multiproducts facility

After establishing the fermentation process at a pilot scale, the levels of production must be increased, as well as enhancing the regulatory standard of the production facilities to favor patient safety.

Here we identified a plant that operated through campaigns, and carried out stages of fermentation and cell rupture of five recombinant protein molecules expressed in *E. coli*. Therefore, we considered the possibility of incorporating the production of the new campaign process within the facility, thus reducing cost and time of the research development stage.

Forming the expert team

The team of seven members that were selected according to the previously mentioned criteria are shown in the table 1.

During the initial exchanges with the experts, the aims, the processes that would be analyzed and the characteristics of the process that would be introduced, as well as the tool that would be used, including the flowchart and 6Ms, were defined. After identifying the risks, three levels were assessed and classified as previously described.

Identifying the possible risks

The elements analyzed for the identification of the possible risks associated to the operations of the new process, if the introduction of the process is to take place in the multiproducts plant, are shown in table 2.

To carry out the identification of the possible risks during the introduction of the new production process in the multiproducts facility [5], the performance of the 6Ms were considered in each one of the stages of the production process:

Labor

Although the staff operating the multiproducts plant is qualified in GMP, it is not trained for the implementation of the new technology.

Possible risk identified: the staff is not trained in the new process to be introduced.

Materials

The materials used in each step of the process are dedicated according to the products and they are permanently properly identified for their implementation. However, the risk of contamination should be considered, this involves the entrance of new biological material to the facility (working cell bank, WCB).

Possible risk identified: contamination by introducing of a new biological material.

Table 1. Team of experts and their expertise for Quality Risk Assesment of a multiproduct facility

Role	Professional competence	Professional profile	Years of experience
Leader	Chemical Engineer. Master of Biotechnological Process Engineering	Specialist in Fermentations	26
Member	Chemical Engineer. Master of Biotechnological Process Engineering	Specialist in Fermentations and validation	21
Member	Chemical Engineer. Master of Biotechnological Process Engineering	Specialist in Chemical Analysis	22
Member	Pharmacologist Master of Trends in Contemporary Biotechnology	Specialist in Quality Assurance	14
Member	Chemical Engineer. Master of Biotechnological Process Engineering	Specialist in Validation	23
Member	Veterinary Surgeon Master of Drug Technology and Control	Specialist in Documentation	20
Member	Microbiologist Master of Microbiology	Microbiology Laboratory Specialist	25

Machinery

The equipment required for the production of the new process is available at the facility; however, there are pieces of equipment that are non-dedicated, since we are dealing with a multiproducts plant.

Possible risk identified: not detected.

Methodology

The general operation procedures for the plant are established; however, the fermentation process has not been set up and there is no documentary package approved for the new product, in line with the multiproducts facility.

Possible risk identified: the process is not established at the production scale and the documentary package is lacking.

Measuring

Compendious methods and validated analytical techniques are used.

Possible risk identified: not detected.

Assesing the risks

Once the possible risks were identified, they were properly assessed as follows.

The staff is not trained in the specific operations of the new production process

The staff plays a key role in the operations of the biopharmaceutical industry; personnel must therefore be selected, trained, qualified and have a high level of responsibility in the work they carry out [16, 23]. During the technology transfer process, mixed personnel are used: those from the facility that performs the transfer and has scientific knowledge of the process,

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Table 2. Aspects analyzed for the identification of possible risks of the process based on the 6Ms

Aspect	Operations*	Machines and equipment	Working methods	Material	Environment	Measurement
1	Cell bank storage	Calibrated and qualified freezer	Qualified	Released cell banks, separated by production and identified	Nearby surroundings: Grade D environmental monitoring approved	Controlled temperature. Periodical verification: viability, purity, plasmid stability and level of expression
2	Pre-inoculum and inoculum	Unidirectional flow cabin and thermostated shaker (not critical, not dedicated) calibrated and qualified	Control of operation parameters, pre-inoculum handling (approved procedures)	Dedicated glassware	Close surroundings: Grade A Nearby surroundings: Grade C	Temperature, stirring, microbiological purity
3	Fermentation of culture inoculum	Reactor (critical and not dedicated) calibrated and qualified	Control of operation parameters (approved procedures)	Dedicated materials (venting filters, gaskets and diaphragms) and system tubing	Close surroundings: Controlled environment Nearby surroundings: Grade D	Temperature, stirring, pH, optic density, conductivity, microbiological purity, concentrations of total protein and proteins of interest
4	Harvest	Centrifuge and reactor (critical and not dedicated) calibrated and qualified	Control of operation parameters (approved procedures)	Dedicated tubing	Close surroundings: Controlled environment Nearby surroundings: Grade D	Stirring, temperature, feeding flow, weight of the biomass
5	Biomass washing	Centrifuge and reactor (critical and not dedicated) calibrated and qualified	Control of operation parameters (approved procedures)	Dedicated tubing	Close surroundings: Controlled environment Nearby surroundings: Grade D	Stirring, temperature, feeding flow, weight of the biomass
6	Biomass storage	Calibrated and qualified freezer	Biomass storage (approved procedures)	Sealed bags, separated and identified	Nearby surroundings: Grade D Environmental Monitoring Program approved	Temperature, biomass weight

* All the operations were run by qualified personnel

as well as those from the receptor unit, trained in the general operations of this facility. Therefore, the complementation of training is required to cover the lack of knowledge and experience of the new production process carried out during the technology transfer. This risk level is considered to be *intermediate*.

Contamination due to the introduction of new biological material

Here a strain of *E. coli* (Gram negative, non-sporulating bacteria, coccobacillus) is used, which is similar to those employed for certified productions in the facility. The WCB was made with sterile culture media and materials; the equipment used, such as the autoclave and the unidirectional flow cabinet are qualified; the environment was monitored during the preparation of the cell bank through the exposed plate method, the volumetric analyzer and the contact plate, giving satisfactory results. The staff preparing the WCB used the approved procedures and they were trained for this activity. Furthermore, the WCB was characterized by microbiological and compendious molecular biology techniques to ensure the well characterized cell origin, and it was released by the Quality Management and Regulatory Issues Division [6]. For this reason, this risk was scored as *low*.

It should be pointed out that in the fermentation processes using sporulating Gram positive bacteria, Doherty [15] recommends that the process should be carried out in dedicated facilities.

Process was not established at the production scale and there is no documentary package

For the transfer to the productive scale, a scaling-up is carried out in which the new operation conditions are established and the adjustment lots are made to verify the new parameters. On establishing the conditions, the specific documentation of the process is prepared.

Similar productions have been previously transferred to this facility and they have given satisfactory results. Hence, it is considered that the production staff should have enough experience to address this task. In this study, this risk can be mitigated through training complementation, which is characteristic of the entire technology transfer process. Therefore, the risk is assessed as *intermediate*.

Cross-contamination through the use of non-dedicated equipment

A comparison was made to assess the possible risk, between the new fermentation technology and the production of recombinant proteins (worst case) at the multiproducts plant.

The aspects analyzed to determine the production in the 'worst case' were: cellular concentration (fermentation), form of recombinant protein expression, the expression levels of the recombinant protein (percentage), culture time per lot and injectable administration routes in both cases. The comparison of these characteristics between both productions is shown on table 3.

It is observed that the new technology uses the same host (*E. coli*), and therefore, the biological risk of the microorganism used in both cases classifies as Group I according to the guidelines for Biotechnology cleaning validation [24]. The culture of the new

24. Parenteral Drug Association. Points to Consider for Biotechnology Cleaning Validation. Technical Report No. 49; 2010.

Table 3. Aspects analyzed for the evaluation of the production established as the worst case scenario

Aspects	Production established as the worst case scenario	Production that will be established
Host cell	*Escherichia coli* strain W3110	*Escherichia coli* strain W3110
Cellular concentration (fermentation)	Humid weight of 22-25 g/L	Approximate humid weight of 12-14 g/L
Form of expression of the recombinant protein	Insoluble intracellular	Insoluble intracellular
Expression levels of the recombinant protein (%)	15-20	15-20
Culture time per lot (h)	18-20	12-14
Administration route	Parenteral	Parenteral

process reaches a lower final cellular concentration and less duration time. In both cases, the protein is expressed in an insoluble intra-cellular form; therefore, the recombinant molecule must not be in contact with critical surfaces of the equipment in any of the two cases. Both molecules are intended to be administered by the parenteral route for its biopharmaceutical application.

The following conclusions can be reached from the analyses of all these elements: the production established beforehand as the 'worst case' can remain as such. Furthermore, the procedures for the sanitation of the non-dedicated equipment established at the plant may be used for the new productive process. These procedures have been validated with the production established as the "worst case". Sodium hydroxide and ortho-phosphoric acid at a high temperature (80 ºC) and one hour of exposure time are used during the sanitation of the machinery. When proteins are in contact with acids or alkali, they are irreversibly degraded to peptides and amino acids of much smaller chains, their solubility in water is significantly increased and biological activity is decreased. The level of proteolysis is directly proportional to the increase in temperature and to the time of exposure to these agents. Hence, it is not possible, in many cases, to detect the original molecule by specific methods and the use of analytical techniques determining the total organic carbon concentration (TOC) is recommended [23].

At the end of the sanitation of the non-dedicated equipment, during the change of the campaign, visual inspections of the surfaces are made, as well as the determination of TOC, pH and conductivity of the rinsing water, where traces of residues of the products and sanitation agents may be detected. These values are compared to those of the point of use of purified water [16, 24].

Assuming that the new technology that is established would become the 'worst case', since: the protein is expressed in an extracellular manner and it is therefore in direct contact with the critical surfaces of the non-dedicated equipment, the levels of expression, cell growth, culture time of the new process or both, would be greater to those of the production declared in the facility, the cleaning and sanitation procedures for the machinery should then be modified and validated. López *et al*. [16] carried out a similar risk analysis where the new technology became the 'worst case' and they proposed the increase in the concentration of sodium hydroxide. The temperature or exposure time to alkali or acid solutions could also be increased, favoring the degradation of proteins [23].

For more information on the possible cross-contamination, a performance evaluation was carried out during 11 campaign changes using the values of pH, conductivity, TOC of rinsing water and TOC of the swab of surfaces of non-dedicated equipment with the most difficult access. Results are shown in the figure.

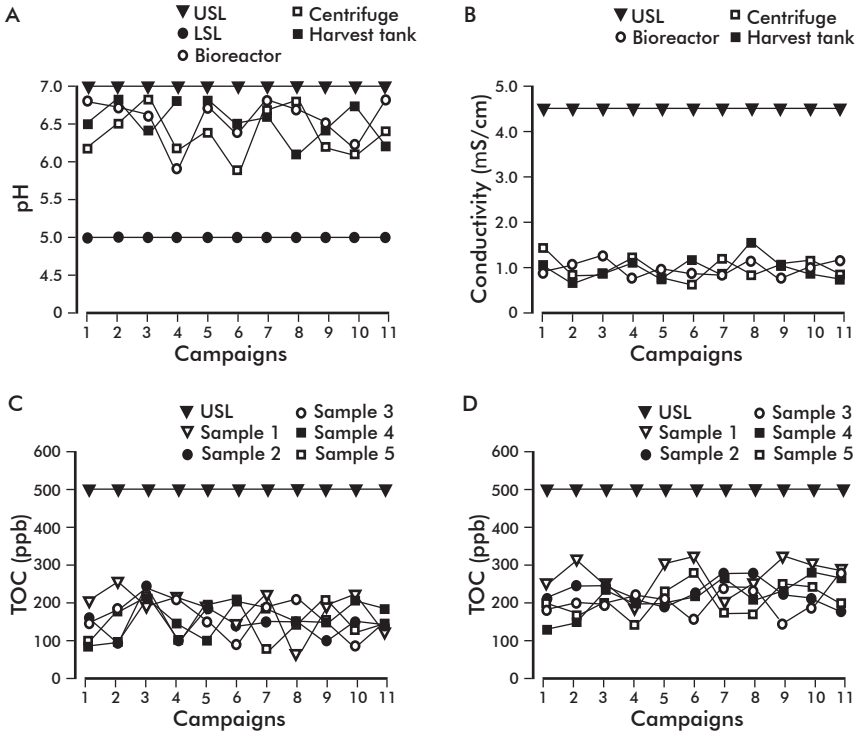

Figure. Behavior of the sanitation of the non-dedicated equipment during 11 campaign changes in a multiproduct production facility. A) pH of the rinsing water. B) Values of conductivity of the rinsing water. C) Total organic carbon concentration (TOC) values of the rinsing water. D) TOC values of the swab at the points having the most difficult access. USL, LSL: Upper and lower specification limits, respectively.

It is observed that in all cases the pH, conductivity and TOC values during the 11 campaign changes were within the specification limits. These results show that the sanitation procedures for non-dedicated equipment, as well as the work of the personnel that carry out this activity, were satisfactory. Therefore, the analyses of the above results show that for the machinery, the level of risk of cross-contamination would be *low*.

Conclusions

The possible risks associated to the process and the multiproduct facility were identified, with a total of four risks; two were evaluated as intermediate risks (training of personnel and documentary package of the new process) and two would have a low score (contamination with biological materials and cross-contamination). Since high risks affecting the quality of the process within a certified multiproducts plant were not identified, the technology of the new production in the assessed facility may be carried out. It is therefore possible to reduce the cost and time of the Research & Development stages and clinical trials, and this would therefore increase the time of the exclusivity of the product in the market.

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