Participant & Facilitator Guide

MAKING THE CALL: QUALITY IN BIOMANUFACTURING

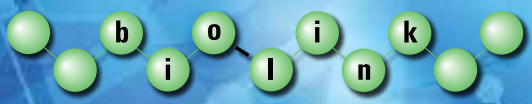
AN INTERACTIVE VIDEO

See the impact of employee decisions in a fictional biotech company

QC Analyst

Upstream Technician

Upstream Supervisor



The Interactive Video *Making the Call* and the companion Participant/Facilitator Guide were produced collaboratively by Bio-Link and Pellet Productions

Making the Call: Quality in Biomanufacturing

About this Guide:

This Guide contains background information to support the interactive video production (Interactive), ***Making the Call: Quality in Biomanufacturing***, which is freely available online at franklinbiologics.org. This Interactive is an educational tool designed to teach participants about working in a regulated biomanufacturing environment. It is a story about a fictional biopharmaceutical company, Franklin Biologics (Franklin), and a fictional drug, Squabanin. Franklin is a mid-sized contract bioprocessing firm, which means that other companies hire Franklin to manufacture their drugs.

In this Interactive, participants choose to play one of three characters working at Franklin. Through a series of video vignettes, participants follow their character through his/her work routine, contributing to the manufacturing of Squabanin. Each scene terminates at a decision point—choices that would have to be made on the job. Participants choose one of the options presented and, in the next video vignette, can immediately see the consequences of their decisions. Different outcomes, some good, some not, will unfold depending on their choices. This Interactive is a safe place to explore what it means to work in a biopharmaceutical company. If a participant makes a wrong choice, no one's life is at stake, millions of dollars are not really lost, and no one really loses their job. Through this Interactive, participants will come to understand the culture and expectations of working in a company that produces life-saving drugs.

This Guide, which accompanies the Interactive, begins with a few technical notes. The next part of the Guide introduces the story of Franklin Biologics; the drug, Squabanin; and the lead characters in the Interactive. The next, more extensive part of the Guide, provides background information that may be useful to those unfamiliar with biomanufacturing, quality systems, and the Food and Drug Administration (FDA). Facilitators might want to provide all these sections to participants in advance as background.

In the Interactive, participants take on the role of one of the lead characters and make decisions for that character. These decisions are discussed in the final part of this Guide. We suggest that participants do not read this section in advance of playing one or more characters.

The Interactive was created by Bio-Link in collaboration with Pellet Productions. Bio-Link is the Next Generation National Advanced Technological Education Center of Excellence for Biotechnology and Life Sciences. Bio-Link originated in late 1998 with funding from the National Science Foundation. Bio-Link supports educational programs that prepare skilled technicians to work in high-tech fields that drive the U.S. economy. Pellet Productions creates compelling media for clients world-wide and is an accomplished producer of innovative educational programming.

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TECHNICAL NOTES

This Interactive is hosted by YouTube at **franklinbiologics.org** and can be played on any internet-enabled computer. Each clip will automatically play to its conclusion, but it is possible to pause the action by clicking on the ▶. It is also possible to drag the horizontal scroll bar at the bottom of the screen to go forwards or backwards in the video.

There is a drop-down menu on the left side of the screen that makes it possible to jump to a particular scene for a particular character and each of the possible outcomes for that scene. With a few exceptions, each scene involves a dilemma that the character must resolve. This menu is intended to be helpful to facilitators who may wish to discuss a specific scenario without playing through an entire character. We recommend that participants do not use this menu to jump around until they have played one or more characters from beginning to end.

INTRODUCTION TO THE INTERACTIVE PRODUCTION: THE STORY AND THE MAIN CHARACTERS

THE STORY

The chief executive officer of Franklin Biologics is facing a crisis she never thought would occur in her career. She explains:

> *"Last month we lost a major batch of drug product for a client. A big client. And it was our fault. A lot was hanging on that batch—our reputation. Our bottom line. The mistake cost us millions. Worse still, the FDA found major violations resulting in actions against the company. And the lawsuit, well…I never thought I'd be at the helm while a company went down like this."*
>
> *"Except, I'm not. This is all fiction. It never actually happened. But it could. In this Interactive, you can set back the clock, and change the way this whole thing plays out. Step into the shoes of one of three characters working at Franklin Biologics, and make real-world decisions about quality. You can choose to play an Upstream Production Supervisor, a Production Technician, or a Quality Control Analyst. All of them have critical roles in making our products—and each of them has to adhere to strict guidelines for quality. Are you up for the challenge? Can you stop this disaster from happening?"*

Making the Call: Quality in Biomanufacturing, is a story about a fictional biopharmaceutical company, Franklin Biologics, and a fictional drug, Squabanin. Franklin is a mid-sized contract bioprocessing firm, which means that other companies hire Franklin to manufacture their drugs.

Biopharmaceutical companies are complex, challenging—and ultimately rewarding places to work. These companies produce pharmaceutical products that improve the quality of life for millions of people. If every employee makes the right decisions, then products can be manufactured successfully. But if anyone makes poor choices, the company's products may be adversely affected, which can harm or even kill patients, damage the company, cost millions, and adversely affect every employee's career. In this story, Stilton Pharmaceuticals, Franklin Biologic's biggest (and prickliest) client, has just placed a major, time-sensitive order for the injectable biopharmaceutical product, Squabanin. However, after a change in leadership at Stilton, the company is considering pulling its contract with Franklin. Franklin executives fear that if anything goes wrong with this batch, the company will lose its biggest client and millions of dollars, causing a wave of layoffs.

In this Interactive, you will choose to play one of three characters working at Franklin. Through a series of video vignettes, you will follow your character through his/her work routine, contributing to the manufacturing of Squabanin. Each scene terminates at a decision point—choices that would have to be made on the job. You will choose one of the options presented and, in the next video, can immediately see the consequences of your decision. Different outcomes, some good, some not, will unfold depending on your choices. This Interactive is a safe place to explore what it means to work in a biopharmaceutical company. If you make a wrong choice, no one's life is at stake, millions of dollars are not really lost, and no one really loses their job. As you participate in this Interactive, you will come to understand the culture and expectations of working in a company that produces life-saving drugs.

Alicia Sandoval CEO

THE MAIN CHARACTERS

CORINNE LAWTON, Associate Production Technician. After high school, Corinne worked at a variety of retail jobs. She was a hard worker and was appreciated by her employers, but none of her jobs were intellectually stimulating and she did not feel that she was contributing to the world.

Corinne always liked science in high school, particularly biology, but she was not very good at math so she did not think she could ever have a career in science. That changed after a visit to a counselor at her local community college where she learned about a program in biomanufacturing. Corinne was nervous about attending college and it was difficult for her financially. After much deliberation she did enroll in the biomanufacturing program. At the community college, she discovered that her hard work and positive attitude made her a great student. Math never came easily to her, but it began to make sense when she could see the applications of math in her biomanufacturing courses.

After completing her community college degree, Corinne landed her job at Franklin Biologics. Now she feels that the work she does is important and fascinating and she thinks she might continue her education and get a Bachelor of Science degree from a local university.

QUESTIONS: INTRODUCTION, THE MAIN CHARACTERS, CORINNE

If you play Corinne, consider the challenges and rewards of her work. Corinne has a great deal of responsibility for the successful manufacture of Squabanin. Every task that she performs is essential for making the product. How would you feel in this role?

KEVIN TURNER, QC (Quality Control) Microbiology Analyst. Kevin is a relatively new employee at Franklin Biologics. He has a four-year Bachelor of Science degree from a major university where he was an excellent student. He majored in microbiology and he completed a challenging senior research project, but he did not have any relevant work experience and had difficulty finding a job after graduation. He worked for a while in his family's business and then heard about a biomanufacturing certificate program at his local community college. He completed the certificate program and, with help from his instructors at the community college, was able to land the job at Franklin Biologics.

Kevin enjoys his job at Franklin and likes working in a team environment. But he is finding that this company environment is quite different than he expected, based on his academic experiences. In his academic lab at the University, Kevin had a great deal of autonomy and made many decisions on his own. At Franklin, there are established procedures that must be strictly followed. While Kevin has been finding some opportunities at Franklin to be creative, his everyday work is governed by these established procedures.

QUESTIONS: INTRODUCTION, THE MAIN CHARACTERS, KEVIN

If you play Kevin, what do you think might be the challenges and rewards of this type of laboratory work where there are established procedures that must be followed?

ASEEM KOMANI, Upstream Production Supervisor. Aseem has a degree in chemistry from a university. He has worked six years at Franklin Biologics, first as a technician and then as a production supervisor. Aseem is a nice person and a dedicated employee who wants his team to be successful. Aseem has a family and job security is very important to him. Aseem wants to do what is best for the company, for his family, and for his employees; sometimes he is not sure how to balance them all.

QUESTIONS: INTRODUCTION, THE MAIN CHARACTERS, ASEEM

If you play Aseem, consider the responsibilities, pressures, and rewards of a management position. How can Aseem best ensure the success of his team? How can he make sure that the people he supervises have the resources they need to grow professionally? How can he balance the requirement to make products quickly and properly with the need to support his workers? If his employees make a mistake, does he have any responsibility for their error?

BIOMANUFACTURING & BIOPHARMACEUTICALS

OVERVIEW

Pharmaceuticals ***are agents with therapeutic activity in the body that are used to treat, prevent, or correct injuries, diseases, and disorders.*** In this Guide, we use the common term, "drug," as a synonym for "pharmaceutical."

Many familiar drugs, like aspirin or cortisone for insect bites, are small molecules that are chemically synthesized in factories. Biopharmaceuticals are a different category of drug. Most biopharmaceuticals are composed of proteins that are large, complex molecules that cannot (at least at this time) be chemically synthesized in a chemical factory, ***Figure 1***. Rather, proteins are manufactured by living cells.

Let's consider how proteins might be used as drugs. Every living organism is comprised of one or more cells and these cells make many proteins. Moving, thinking, eating, or doing any other task as a living being requires the work of proteins. There are many different proteins, each with its own job in the cell. It makes sense that, since proteins are necessary for cellular function, they sometimes can be administered to patients to treat disease. For example, some people have diabetes because their pancreas does not produce enough of the protein, insulin, to control the level of sugar in their body. Their disease can be controlled by Humulin, a drug form of insulin. Insulin is just one example of a biopharmaceutical. There are many others that are used to treat diverse illnesses including cancer and autoimmune diseases.

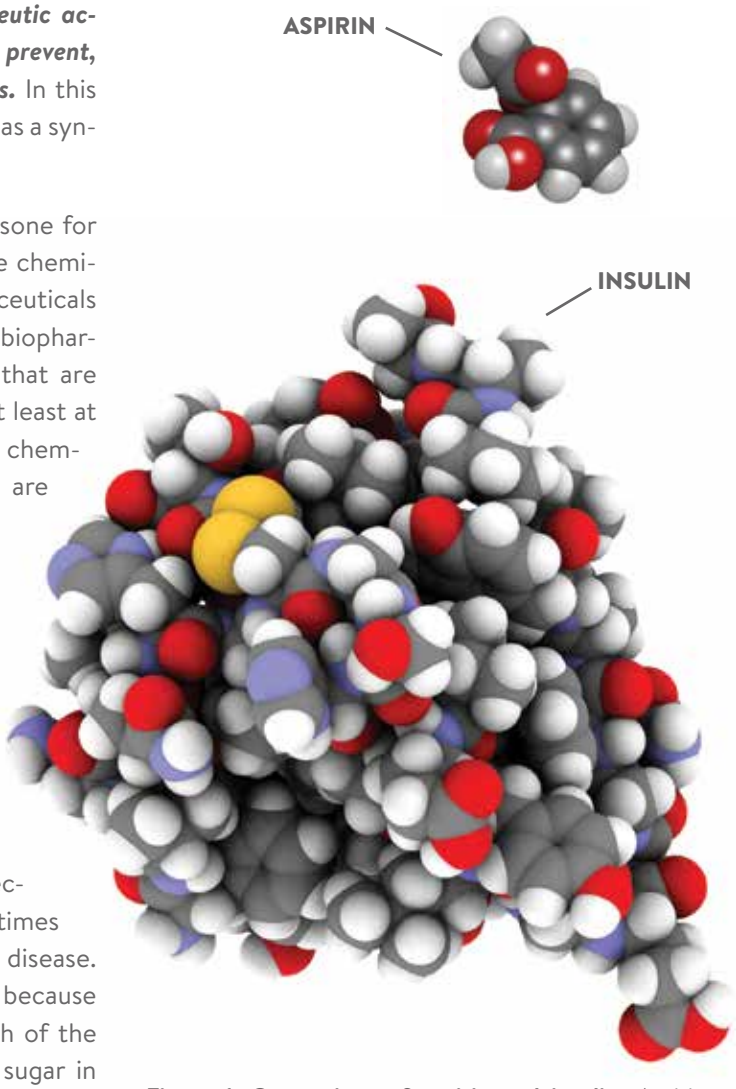


Figure 1. Comparison of aspirin and insulin. *Aspirin, shown at the top, is a small, relatively simple drug molecule that is chemically synthesized in factories. Insulin, which is one of the smaller biopharmaceuticals, is shown below aspirin. It is a much larger and more complex molecule than aspirin.*

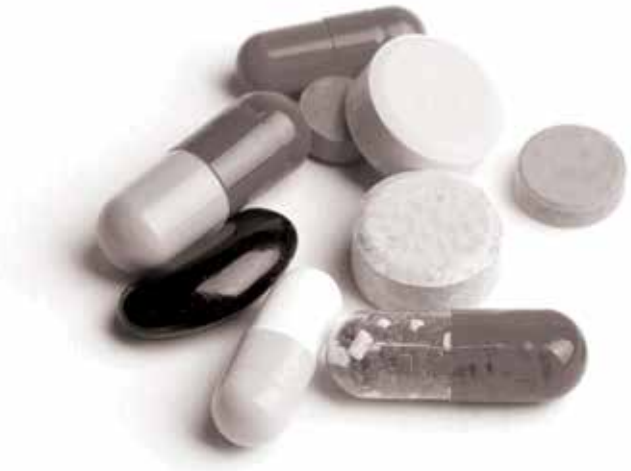
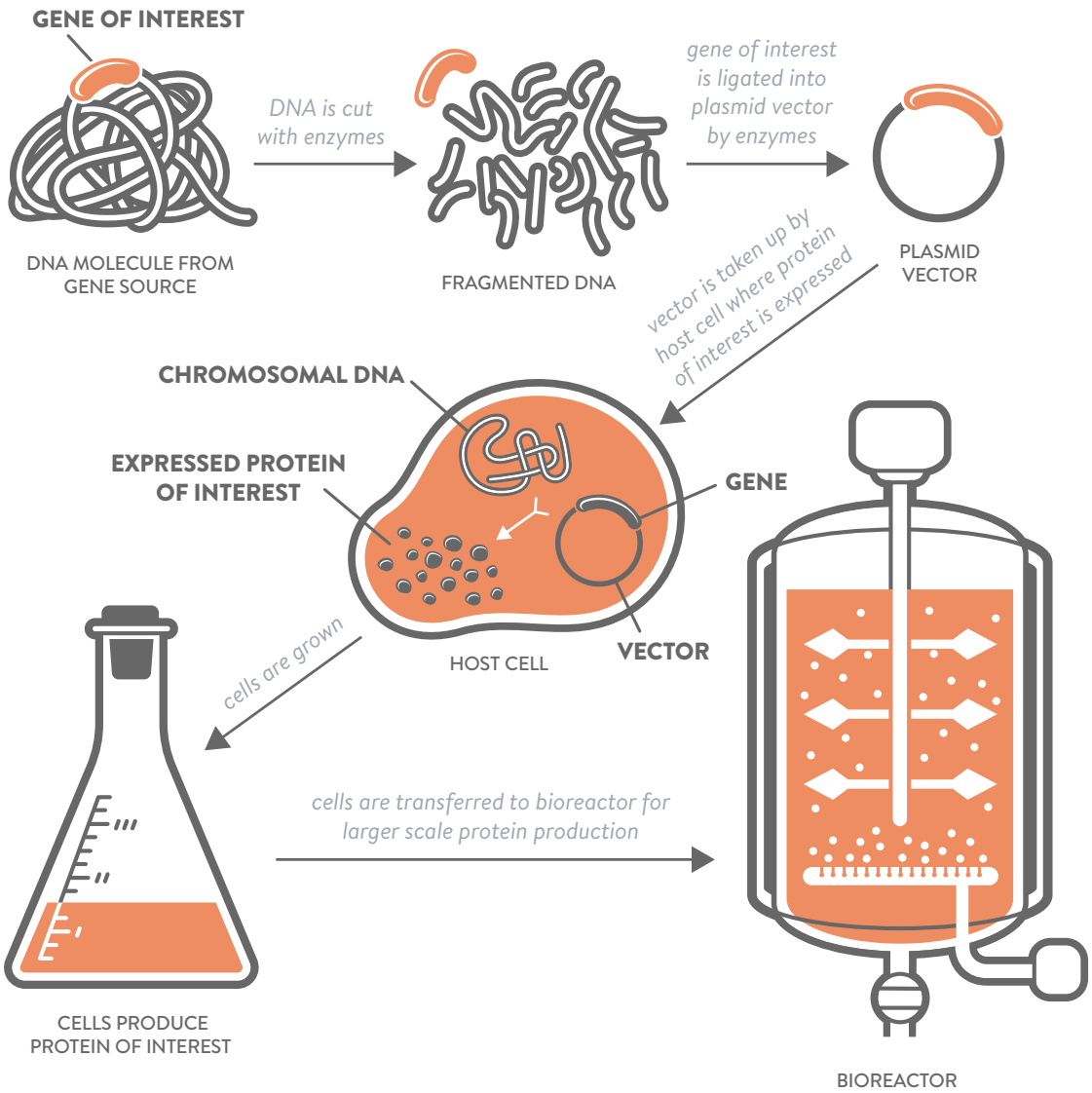


Figure 2. (opposite) Genetic engineering of cells. *In biopharmaceutical manufacturing, a gene of interest is isolated that codes for a protein that can be used therapeutically. The gene of interest is inserted into a vector that is taken up by host cells. The host cells then are able to make the protein of interest. The host cells are grown initially in small flasks or containers. Once there are many cells, they are transferred to a bioreactor where they manufacture the biopharmaceutical protein product.*

Pharmaceutical companies cannot manufacture protein drugs in chemical factories; instead they must use living cells as "factories." In industrial settings, these cells are contained in flasks or vessels. The cells are suspended in, and nourished by, a watery medium that contains the nutrients needed for life. Thus, for our purposes we will define **biopharmaceuticals** ***as protein drugs that are manufactured in industry using living cells.*** **Biomanufacturing** ***is the process in which biopharmaceutical products are manufactured by these cells.*** In this Guide, we use the term "bioprocessing" as a synonym for biomanufacturing.

The cells that are used as factories in biomanufacturing are often genetically engineered. **Genetic engineering** ***involves taking genetic information (DNA) from one organism and transferring it to another.*** In biomanufacturing, scientists genetically engineer special types of cells that grow well in vats or vessels outside of any living organism. They transfer to these cells the genetic information that codes for the protein that will be used as a drug. These genetically engineered "host cells" are grown in vessels and produce the protein of interest in large quantities; thus the term "bio"manufacturing, ***Figure 2.*** Squabanin is a fictional biopharmaceutical made by genetically modified cells that, in our interactive world, can be used to treat a serious, imaginary disease.



Biomanufacturing is divided into two phases:

Upstream Processing ***is the phase that occurs over a period of days or weeks during which time the host cells grow, divide, and produce a protein drug product.***

Downstream Processing ***occurs after the product is made by cells and involves a series of steps that purify the drug product away from the cells and other contaminants and make it into a form that can be administered to patients.***

Corinne, Aseem, and Lorenzo work in upstream processing. Therefore, we will consider this phase in more detail. If you are curious about downstream processing, we recommend the resources on the NBC2 website, as cited in the Online Resources section (p. 36).

UPSTREAM PROCESSING

Before our story begins, scientists had genetically engineered host cells to contain the gene that codes for Squabanin. Scientists placed their genetically engineered cells into small vials that were stored in tanks filled with liquid nitrogen. Liquid nitrogen is very cold (-198° C) and placing the vials in this environment allows the cells to be stably stored for a long time. As our story begins at Franklin Biologics, technicians remove a vial of the frozen host cells and thaw the cells to begin a production run of Squabanin. They introduce the cells into liquid nutrient medium. Initially, the thawed vial provides a small number of cells that can be grown in a small flask. Over a period of days, the cells grow and multiply in this favorable environment. As the cells divide, there are more and more cells that are divided into bigger and bigger flasks containing liquid nutrient medium, *Figure 3.*

Figure 3. Scaling-up from small to larger flasks. *A frozen vial provides relatively few cells that can be grown in the small flask on the right. As the cells divide, larger and larger flasks are required.*

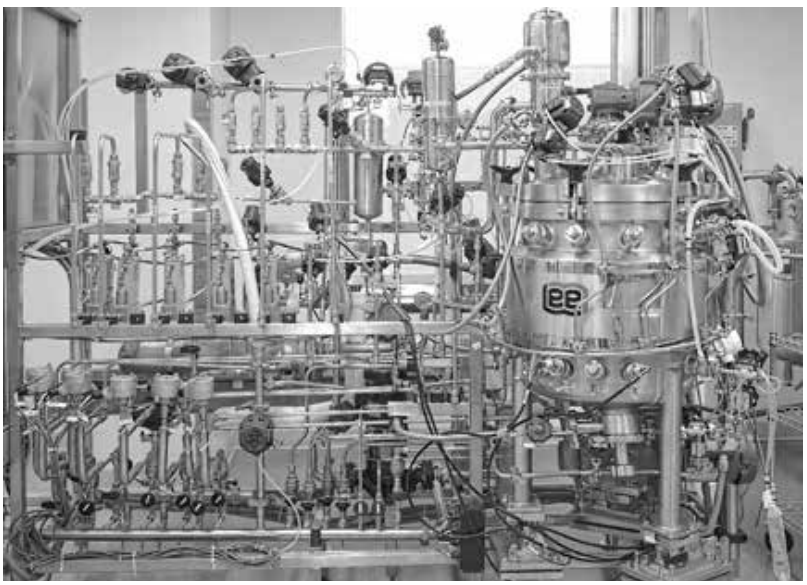


Figure 4a. The 100 L bioreactor that Corinne, Lorenzo, and Aseem operate. *The vessel containing the cells is on the far right. Details of the various parts of the bioreactor are shown in Figures 5 and 6.*

When the cells become too numerous to fit in flasks, they are moved to a bioreactor. ***The cells that are moved to the bioreactor are termed the*** **inoculant.** **Bioreactors** ***are vessels that can hold large numbers of host cells and allow precise control of environmental conditions to promote cell growth and productivity***, *Figure 4a, b.* Bioreactors come in many sizes ranging from those that hold only one liter of cells to those with vessels that are several stories tall and hold tens of thousands of liters. A **seed bioreactor** ***is a relatively small bioreactor***.

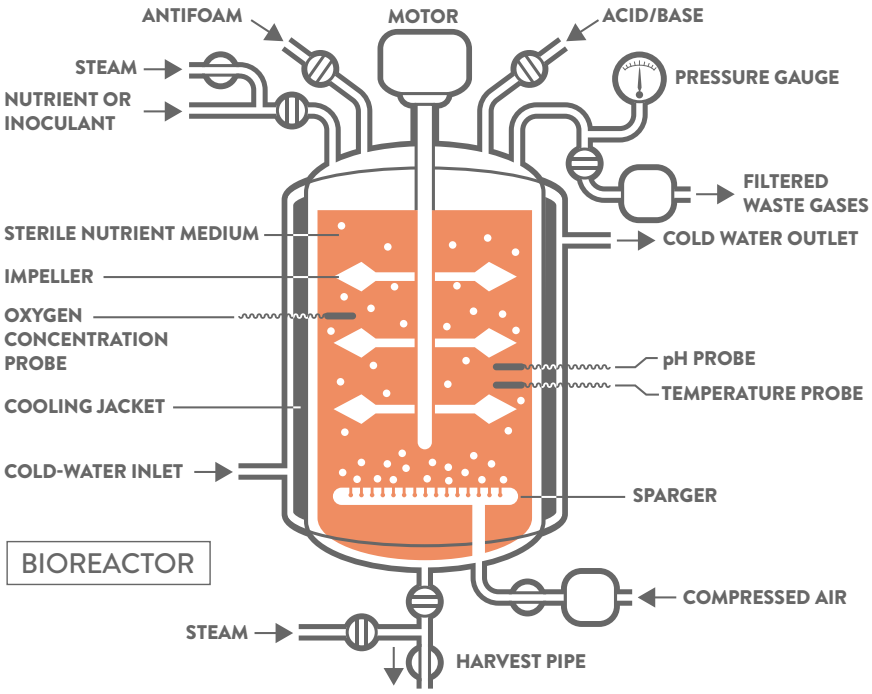


Figure 4b. ***A schematic diagram of a bioreactor.***

Normally, the cells that are grown in the seed bioreactor are eventually moved into a larger production bioreactor. In the Interactive, you see Corinne, Lorenzo, and Aseem working with a seed bioreactor. **Scaling-up** ***is the process in which a relatively small number of cells are allowed to multiply and are moved into progressively larger and larger vessels.***

All living cells have specific requirements for life and growth. These requirements are relatively easy to provide to the limited number of cells growing in a flask. But the number of cells that can be grown in a flask is not nearly enough to make sufficient protein to treat patients. When cells are moved into bioreactors, controlling their environment requires:

- Aeration and oxygenation
- pH control
- Temperature control
- Ability to add substances (e.g. nutrients) during the process and before
- Adequate mixing to provide nutrients and air throughout the vessel

If any of these factors is not properly controlled, the cells may not grow; they may not produce sufficient protein; and, in a worst case, a batch of product may be ruined. Additionally, when working with a bioreactor, the withdrawal of sterile samples for testing and the harvesting of the cells at the end of the run without contamination are requirements. Bioreactors are engineered to provide for all these requirements. Bioreactors have probes that continuously monitor the pH, temperature, and oxygen level inside the vessel. These conditions are adjusted as needed. For example, if a probe detects that the oxygen level has dropped too low, the amount of aeration is increased. Usually the probes are connected to computers that automatically control the conditions inside the bioreactor, ***Figure 7.*** However, even with computer monitoring and control, humans must still oversee the process.

Before cells and their nutrient medium are introduced into the bioreactor, the vessel, filters, and all the piping leading into and out of the bioreactor must be cleaned and then sterilized. This is accomplished by introducing cleaning agents to the system, followed by steam, which is very hot and under high pressure. This cleaning/sterilizing process involves connecting the bioreactor to a portable clean-in-place (CIP) skid, ***Figure 8***. The skid is moved next to the bioreactor and attached to it. In ***Figure 6***, you can see a "header" which is a single piece of pipe with a number of valves. The cleaning and sterilizing agents come into the bioreactor through this piping, controlled by the valves. Temperature probes verify that the desired high temperatures are achieved for the required amount of time to sterilize the vessel.

Figure 5. The Bioreactor Vessel. *The host cells at Franklin Biologics are mammalian cells and so, like our own cells, they need to be maintained at 37° C (98.6° F). This is achieved with a fluid filled "jacket" that surrounds the vessel; the fluid in the jacket can be heated or cooled as needed. The jacket is visible as a protuberance around the vessel. Some of the tubing that you see alongside the vessel is part of the heat exchanger that allows the fluid temperature to be adjusted. In this figure, you can also see the ports where probes are inserted at the bottom of the vessel. At the top of the vessel are other ports used for adding nutrients, anti-foam, and other substances. A sampling port is on the far-right side of the vessel. At the bottom of the vessel is the valve that can be opened to harvest the cells, connected to the harvest line. Foam is a special consideration. Aeration and agitation inside the vessel cause a layer of gaseous bubbles to form at the top of the bioreactor; this is foam. Antifoaming agents are added to the vessel through an addition port to reduce the foam. In a worst case, the foam gets so high that pressure builds in the vessel until foam and liquid are released through a pressure release valve at the top of the vessel. At this point the batch is ruined and there is a mess to clean up. To help avert this problem, there are probes at the very top of the vessel that detect the presence of foam and sound alarms if the foam is too high.*

LEGEND

FIGURE 5

- (A) Addition parts
- (B) Jacket to control temperature
- (C) Harvest line
- (D) Monitoring probes
- (E) Harvest valve
- (F) Sampling valves and port

FIGURE 6

- [A] Valves relating to cleaning and sterilizing
- [B] Header for cleaning
- [C] CO_2 sparge
- [D] O_2 sparge
- [E] Air sparge
- [F] Mass flow controllers
- [G] Temperature probes

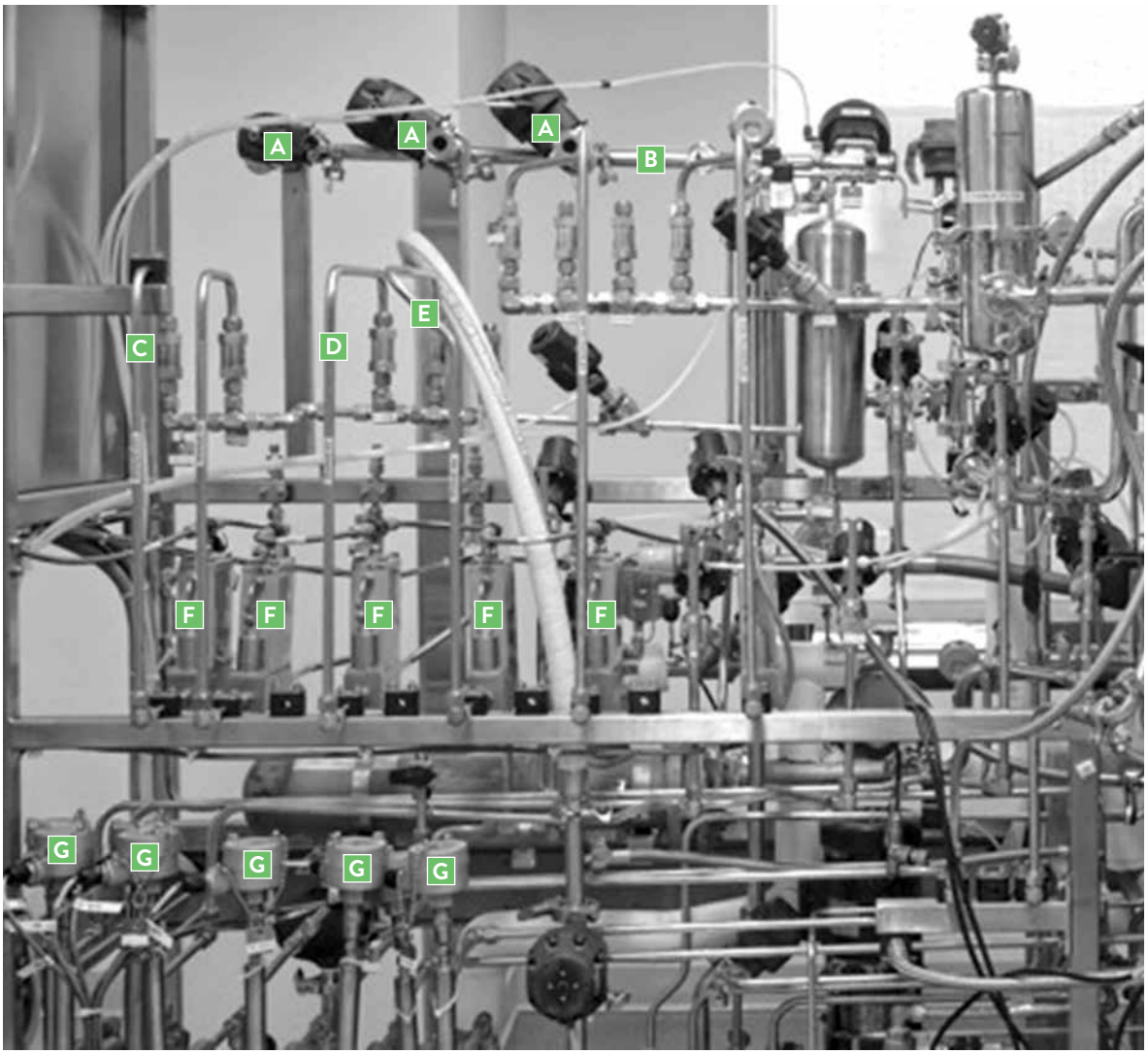


Figure 6. To the left of the vessel are the environmental controls of the bioreactor. *pH is controlled by the addition of liquid sodium bicarbonate, if the pH drops too low, or gaseous carbon dioxide if it rises too high. Cells require oxygen. There are lines to add pure oxygen and purified air (both with special filters that prevent the introduction of any contaminants). In this figure, you can see the lines through which air, oxygen, and CO_2 enter the vessel. Behind each line is a gray box, the mass flow controller, that measures and controls the amount of gas being sent to the bioreactor. You can also see the header that is associated with cleaning, the valves that control the entry of cleaning agents, and the temperature probes that monitor temperature during sterilization.*

Figure 7. *Interface that allows human operators to interact with the computer that is controlling environmental conditions in the bioreactor.*

Figure 8. *Clean-in-place movable skid with controller panel on the right and lines that can be attached to equipment on the left. Tanks that hold cleaning agents are behind the skid, not visible in this photo.*

QUESTIONS: BIOMANUFACTURING & BIOPHARMACEUTICALS

1. In what scene(s) are Corinne and Lorenzo working with the seed bioreactor?
2. How are the cells transferred from one place to another, for example, from the seed bioreactor to the main bioreactor?
3. What happens if Corinne accidentally sets the bioreactor to the wrong pH?

THE REGULATION OF PHARMACEUTICAL/ BIOPHARMACEUTICAL MANUFACTURING

In order to understand the culture of workplaces like Franklin Biologics, you must know something about the regulations (laws) that govern pharmaceutical manufacturing. Poorly manufactured drugs can harm or even kill patients. Therefore, the manufacture of pharmaceuticals, including biopharmaceuticals, is closely regulated by the government. Every person who works at Franklin Biologics is impacted by these regulations throughout their workday.

The government has not always been concerned with pharmaceutical manufacturing. Around the turn of the 20th century, "snake oil" salesmen loudly advertised remedies of dubious value, *Figure 9*. At best these remedies might contain alcohol, at worst they were deadly.

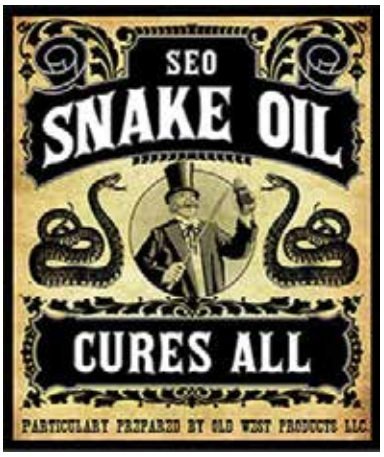


Figure 9. *Before government regulations of drug manufacturing, many preparations were useless, harmful, and sometimes deadly. (Image from the archives of the Food and Drug Administration)*

In 1906 Upton Sinclair recorded filthy conditions and unacceptable practices in the food industry in his novel, ***The Jungle***. People were outraged by Sinclair's exposé and, as a result, the original **Food Drug and Cosmetic Act (FDCA) was passed by Congress in 1906 to prevent the commerce of unacceptable food and drugs.** The 1906 FDCA authorized regulations to ensure that food and pharmaceutical manufacturers did not adulterate their products with filth or mislabel them, but it did not deal with the safety or effectiveness of drugs.

In 1927 the government decided that it was necessary to have a separate law enforcement agency to enforce regulations relating to food and drugs. Without an agency in charge of enforcement, it was impossible to guarantee that manufacturers complied with the FDCA. This policing agency became the **Food and Drug Administration (FDA)** in 1930. The FDA today has the authority to inspect pharmaceutical manufacturers and to initiate actions against those that do not comply with the laws. These actions range from public letters outlining violations all the way to criminal prosecution of pharmaceutical manufacturers.

In 1937 a batch of the antibiotic, sulfanilamide, was dissolved in the deadly industrial solvent, diethylene glycol. There were 358 poisonings and 107 deaths, mostly children. As a result of this incident, the **revised Food, Drug and Cosmetic Act was passed in 1938 which, for the first time, required drugs to be tested for safety before release to the public.**

In 1955 some children vaccinated with polio vaccine contracted paralytic polio. Fifty-one people were paralyzed and ten died. The problem was traced to one manufacturer who apparently did not properly inactivate the virus used to make the vaccine. This incident and others like it led to increased factory inspections and testing of the safety of products before their release to the public.

In 1963 the first set of Good Manufacturing Practices, GMP, regulations were published. These regulations guide companies in the production of safe and effective drugs. A number of injuries and deaths in the 1960s and 1970s caused by contaminated products led to the **revised GMPs in the late 1970s**. With some modifications, these regulations are the ones followed today by all manufacturers who make pharmaceuticals for the United States market and they are enforced by

the FDA. These regulations are usually referred to as the cGMPs, where "c" stands for "current." The goal of these regulations is to ensure that all pharmaceutical products are **safe, reliable, and effective**.

The cGMPs cover many interwoven aspects of an organization including: personnel (e.g.; how people are hired and trained), buildings and facilities, equipment, control of processes to manufacture products, packaging and labeling, laboratory testing, and more. These regulations are written in a manner that is general enough to apply to all pharmaceutical companies and institutions that make drugs. For example, here is a portion of a regulation that relates to quality control testing:

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release.

You can see that this regulation clearly requires that companies producing pharmaceutical products test those products to see that they are satisfactory. The regulation, however, does not say exactly what those tests might be. This is because the tests that might be used to confirm the composition of a batch of aspirin, for example, are quite different than the laboratory tests that might be used to determine the composition of a protein biopharmaceutical. Thus the cGMP regulations are written broadly; it is up to every regulated company to apply those regulations to their own situation. This requires that the company maintain a comprehensive quality system, as is discussed in the next section.

QUALITY SYSTEMS

OVERVIEW

Creating a quality pharmaceutical product requires systems to integrate and control incoming raw materials, manufacturing processes, employee activities, equipment operation, equipment maintenance, quality control testing, and many other factors. Every company must have its own **quality system,** ***which includes the organization, structure, responsibilities, procedures, processes, and resources for ensuring the quality of a product.*** The details of every quality system vary because every company is different, but all quality systems in pharmaceutical manufacturing aim to make products that comply with FDA regulations and are safe, reliable, and effective.

Quality assurance (QA) ***is a division in a company whose job is to help the organization develop its quality system and comply with it.*** The people who work in QA help the company maintain a culture of quality, a mindset of doing things right and not cutting corners. **Quality control (QC)** ***is typically a subdivision within QA which is responsible for laboratory testing.*** The interactive character, Kevin Turner, works in QC.

In the next sections we will consider in more detail specific aspects of a quality system that are particularly important for understanding the Interactive.

DOCUMENTATION

"The palest ink is better than the best memory."

– Chinese proverb

Complete and honest documentation is the foundation of a quality system. Documentation is a system of records where a record is anything that provides permanent evidence or information about past events. Documentation may be tangible, such as forms and information recorded on paper. It may also be electronic, that is, recorded using a computer. Documentation also refers to methods of verifying that tasks were performed in a certain way and that results and products are of good quality. Every quality system requires a complex system of documents that are used throughout the organization. One of the important jobs of QA is to oversee this complex system. There is not any single cGMP regulation that cov-

ers documentation; rather, documentation is so integral to maintaining quality that it is mentioned repeatedly throughout the regulations. Here is an example of a regulation that includes a requirement for documentation:

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedures shall be followed.

Documents must be honest, secure, and verifiable. It must not be possible to change a record once it is made. Standard practices have evolved in order to meet these requirements. Sometimes these practices are called "good documentation practices" (gdps). These practices are summarized in *Table 1*. Several decision points in the Interactive relate to gdps because following these practices is of critical importance.

Table 1 GOOD DOCUMENTATION PRACTICES*

RULE 1 RECORDS MUST BE ACCURATE, LEGIBLE, AND UNDERSTANDABLE

To accomplish this, perform these actions:

- Write legibly.
- Define abbreviations.
- Paginate all forms and documents with the page number and the total number of pages (e.g., page 2 of 10). This helps ensure that no pages get lost or omitted over time.
- Avoid ditto (") marks or arrows when recording repetitive information.

RULE 2 RECORDS MUST RECORD EVENTS WITH CLEAR AND VERIFIABLE DATES

To accomplish this, perform these actions:

- Date every record (e.g., every label, signature, and page of a laboratory notebook).
- Never "backdate"; show the actual date.
- Use the format that is required in your organization (e.g., April 15, 2010 or 4/15/2010). Note that conventions for dates vary in different countries.

RULE 3 DOCUMENTS MUST BE SECURE AND SAFE FROM NATURAL DISASTER, THEFT, AND ACCESS BY UNAUTHORIZED INDIVIDUALS

To accomplish this, perform these actions:

- Use filing cabinets and locks to protect paper documents.
- Use software security and organization to safeguard electronic documents.

**These rules are not found in any official document or regulations. The rules, as they are stated here, are common practices compiled from a number of sources.*

RULE 4 RECORDS MUST BE ATTRIBUTABLE TO A PARTICULAR INDIVIDUAL

To accomplish this, perform these actions:

- Sign every record to identify the person making the record and to attest to the truth of the data recorded.
  - A traditional signature is used with paper documents.
  - An electronic signature is used for computer records. This typically requires entering a unique user ID and password. Everything recorded onto the computer while that individual is logged on is attributed to that person. In situations requiring more assurance of an individual's identity, sophisticated authentication methods, such as voice recognition and retinal scans, can be used.
- Never sign a document for another person or log in as another person.
- Never sign before you have completed a task.

RULE 5 DOCUMENTS MUST PROVIDE INFORMATION FOR TRACEABILITY

Traceability *means that all the materials used in an experiment or analysis, or used in making a product, and all associated documents can be identified.*

To accomplish this, perform these actions:

- Identify all chemicals, equipment, documents, samples, and other items with unique identification numbers, tags, or labels.
- Always record complete information about all chemicals, equipment, documents, samples, etc. when the item is used.

RULE 6 RECORDS SHOULD NOT BE CAPABLE OF BEING ALTERED, EITHER ACCIDENTALLY OR INTENTIONALLY

To accomplish this, perform these actions:

- Enter data directly onto the correct form or into your laboratory notebook, never onto a piece of scrap paper or the back of your hand.
- Always use permanent ink.
- Cross out mistakes with a single line so that the original recording is visible. Never use whiteout; never write over data to obscure it. In many organizations, corrections must be initialed, dated, and briefly explained.
- Draw a line through any unused space in a laboratory notebook so that no one can add anything later. If a whole page is supposed to be blank, label the top of the page as "intentionally left blank."
- If you are filling out a form and a blank does not apply, write NA, "not applicable." Do not leave any fields empty as this can be interpreted as missing data or accidentally omitted data.
- Electronic documents require a software method of tracking modifications to data to ensure that original recordings are not erased. If someone legitimately tries to add information to a record, the computer must be programmed to "know" that this act is legitimate and to show both the original record and the revision.

You may find it helpful to categorize the many types of documents into those that are "directive" and those that "collect data." Directive documents tell personnel how to do a task, identify a material, or define something. Data collection documents facilitate the recording of data and provide evidence that a directive document has been properly followed.

Standard operating procedures (SOPs) are a type of directive document that provide a step-by-step outline of how a task is to be performed. Everyone in the organization follows the same, most current version of SOPs to ensure that tasks are performed correctly and consistently. SOPs describe what is required to perform the task, who is qualified to perform the task, who is responsible for the task, safety considerations, record requirements, and other related information. An example of a portion of an SOP from Franklin Biologics is shown in the Document Manual *(p. 27, Figure 10)*.

Another important type of document that you see in use in the Interactive is a batch record. Batch records are used in manufacturing to direct operators in how to formulate or produce a product. They also contain blanks to fill in as operators perform tasks and therefore they are both directive and data collection documents. The batch record is a critically important document in a production environment. A portion of a batch record from Franklin Biologics is shown in the Document Manual *(p. 28, Figure 11)*.

A third type of document you see being used in the Interactive is a form. Forms are data collection documents that are filled in as some task is performed. Usually forms accompany SOPs that direct the performance of the task. Forms appear in the Interactive in the quality control laboratory where they are used to document analyses that are performed. The form is used for collecting data including: what samples were tested, information about those samples, what test method was used, by whom, when, what result was obtained, and what happened as a result of the analysis. An example of a Franklin Biologics QC form is shown in the Document Manual *(p. 32, Figure 12)*.

QUESTIONS: QUALITY SYSTEMS, OVERVIEW & DOCUMENTATION

1. See if you can find instances where characters do not follow proper good documentation practices.
2. See how many documents you can find as you participate in the Interactive. For each one, state in which scene it is shown and whether the document is a directive document, a data collection document, or both. Note that there are scenes where the characters are using a batch record that directs the production of Squabanin and records the details of production. In the video, you will not see the actual batch record itself, only the notebook in which it is held. State which scenes involve this batch record.
3. Explain the slogan, "do what you say, say what you do." As you participate in the Interactive, look for examples of choices where the characters do or do not follow this maxim. If they do not, what are the consequences?
4. The commitment to quality must begin at the very highest levels of authority at an organization. Who is at the highest level of authority at Franklin Biologics? Does this character appear to be committed to quality? How can you tell?

CONTAMINATION: A CRITICAL ISSUE IN BIOMANUFACTURING

Our world is filled with **microbes**, ***tiny microscopic bacteria and fungi***, and also viruses. Scientists estimate that each person has as many as 40 trillion bacterial cells residing on their skin and in their gut; this is more than the number of cells estimated to comprise a person's body. A single gram of soil may contain billions of microbes and viruses. The air that surrounds us and that we breathe in and out is similarly teeming with microscopic organisms and viruses. The presence of all these microbes is not a cause for alarm; it is possible to live a healthy life totally unaware of the microscopic world around us—unless one works in biomanufacturing. If even a single one of these trillions of microbes accidentally enters a bioreactor, it can divide and quickly overrun the host cells, thereby ruining the batch. It is even more serious if these microbes or viruses wind up in a final injectable drug; these contaminants can harm or kill patients. And, in fact, this has tragically happened. You may have seen these real headlines in recent years: "Pharmacists to Plead Guilty in Deaths from Contaminated Drugs," "Fungal Meningitis Sickens More than 800 Patients, 64 Die," "Microbial Contamination in Blood Thinning Medication May Have Caused Uncontrollable Bleeding and Death." Biomanufacturing requires stringent safeguards to prevent cells and products from being contaminated by any of the contaminants teeming on workers, in the air, and in dust and dirt.

"Biomanufacturing requires stringent safeguards to prevent cells and products from being contaminated by any of the contaminants teeming on workers, in the air, and in dust and dirt."

Contamination is an issue in all pharmaceutical manufacturing, but it is particularly problematic for biopharmaceuticals because these drugs are biological molecules. Biological molecules are damaged by heat. This means that microbes cannot be removed from biopharmaceuticals using methods that involve high temperatures, as is possible with some other medical products. The way to avoid contamination of biopharmaceuticals is to prevent contaminants from entering in the first place. It is also essential that testing is performed routinely during manufacture to make sure that no contaminants have been inadvertently introduced.

In the Interactive you will see some ways in which operators work to minimize the chance of contamination. The first method is "gowning." People are probably the biggest source of contamination in biomanufacturing. As previously noted, everyone harbors vast numbers of microbial cells on their skin, hair, breath, and clothing. One way to minimize the chance of contamination from people is to cover the skin, hair, and clothing of workers with sterile gowns, booties, headgear, and gloves. In ***Corinne, Scene 1*** you will see Corinne and Lorenzo **gown**, ***that is, don special clothing that minimizes the spread of contaminants from the worker***. The gowns (including booties and headgear) are sterile until removed from their packaging. When operators gown, they carefully put on the suit while avoiding touching the outside of the suit with their hands or their clothing. Sterile gloves are worn while gowning and generally, the gloves that are worn to put on the gown are replaced at the end of gowning. Once gowned, operators step over a bench; one side of the bench is the "dirty" side. The other side, the "clean" side, leads to the production suite. It is important for operators to make sure their booties do not touch the floor on the dirty side to avoid tracking bacteria and other agents into the production suite.

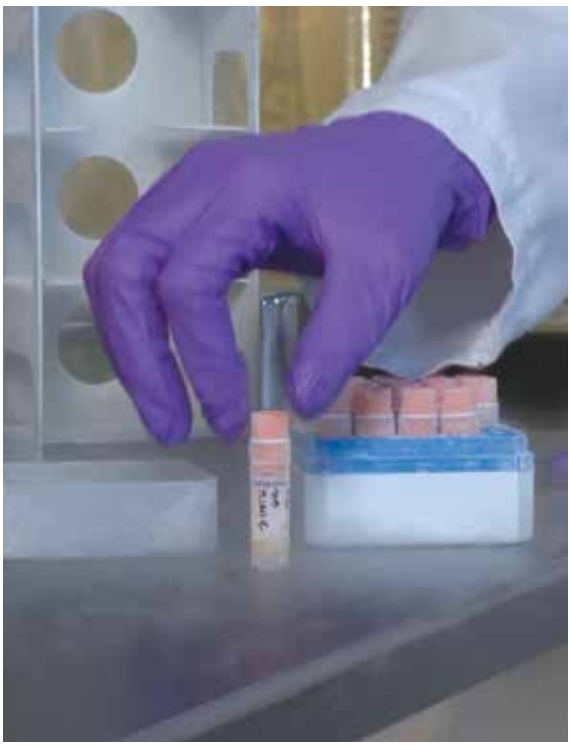
Once gowned, Corinne and Lorenzo enter the production suite, which is a **clean room**, ***a specially engineered space that, in combination with special behaviors by workers, reduces the chance of contaminating a product.*** Clean rooms have a number of design features, such as air filtration and easily cleaned surfaces, which discourage the proliferation of microbial contaminants. Gowning is one of the important ways in which workers reduce contaminants coming into the clean room space. All walls, ceilings, and surfaces are regularly disinfected in cleanrooms following special procedures. Note that cleanrooms are not **sterile**, ***where sterility is the absence of living things***, nor are they entirely contaminant-free. As long as

humans are present, the room cannot be entirely free of all microbes and particles. Therefore, as another layer of protection, the cells that make biopharmaceuticals are enclosed in cleaned, sterilized vessels that are carefully designed to prevent the introduction of contaminants. Operators must be knowledgeable and work properly with these vessels to prevent contaminants from entering them.

In the Interactive you will see workers routinely wearing gloves. Gloves are worn for two reasons: 1. to protect the product, in this case Squabanin, from contaminants on the workers' hands, and, 2. to protect the worker from harmful chemicals or agents used in production. In a situation where gloves are worn for the second reason, workers must always be aware that their gloves may be contaminated with the harmful agent. Thus, in this situation, either everyone must wear gloves at absolutely all times (no exceptions), or gloves must be removed and/or changed when handling telephones, light switches, pens, computer keyboards and mice, etc. Otherwise the harmful agent may be moved from one person's gloves to another person's hands. When gloves are worn solely to protect the drug product, people tend to wear them when answering a phone or working on a computer, as you might notice in the Interactive.

Endotoxins are a particularly problematic type of potential contaminant. **Endotoxins** ***are byproducts formed by some types of bacteria***. Endotoxins are dangerous to humans and can cause high fever, septic shock, and even death. Endotoxins are a special hazard because they are difficult to destroy and can be present even when all bacteria are removed from a product. Therefore, pharmaceutical companies must routinely test for the presence of endotoxins in addition to the presence of the microbes that produce them.

Preventing contamination is thus multi-faceted and includes: production suites that are properly cleaned and maintained; sterilizable vessels to hold the cells while making product; and trained technicians who know how to work so as to minimize the chance of contamination.



QUESTIONS: QUALITY SYSTEMS, AVOIDING CONTAMINATION

1. As you participate in the Interactive, look for examples of how people use gloves. Why do you think they are using gloves? How do you use or not use gloves in your school labs or your workplace? Do you think that gloves are used properly all the time where you go to school or work?
2. As you participate in the Interactive, look for scenes involving endotoxin testing. What happens if endotoxins are present and quality control testing fails to detect them?
3. As you participate in the Interactive, see how many situations you can find that relate to the issue of contamination.

QUALITY CONTROL & RETESTING

Quality control is a laboratory function. Quality control analysts test in-process samples that are taken during the period of time when the product is being manufactured. In-process testing helps ensure that any problems that arise during manufacturing are caught as quickly as possible. Analysts also test final product samples to be sure the product meets all its specifications before it is released for customers. QC analysts might also test for contaminants in the production environment (e.g. floors and surfaces). They may conduct tests of incoming raw materials to ensure that these are what they are supposed to be, are uncontaminated, and are suitable for use in manufacturing. The people who work in quality control labs are very important in assuring the quality of products and must be honest and meticulous in their work.

When QC tests are run in the lab, analysts must know what the expected or desired result is. For example, perhaps the purity of a final product must be within the range of 98% to 100%. If the purity test of a batch of final product gives a result of 97%, this is an out-of-specification (OOS) result. Thus, an out-of-specification result is one that falls outside the specified range. Every company must have a procedure for dealing with OOS results because they may indicate a serious problem.

Retesting is a term used in quality control when a lab test is repeated. In the past, quality control technicians were sometimes allowed or even encouraged to repeat an OOS laboratory test. The reasoning was that the OOS result may simply have been the result of an error made by the laboratory analyst. Sometimes, in poorly run laboratories, people kept testing samples over and over again until they got the result they wanted. This practice of retesting without identifying an actual laboratory error is strictly forbidden by cGMP regulations. While it is true that an unexpected lab result may be due to an error in running the test, it may also be due to a problem with the product. Thus, whenever an OOS result is obtained, the analyst and supervisor must first review the documentation associated with the test to see if there is a clearly defined laboratory error. The test can then be repeated if, and only if, a documented laboratory error is found. If the analyst and supervisor cannot identify a laboratory error, then the cause of the OOS result must be formally investigated and whatever problem is found must be dealt with and documented. In some cases, this might mean discarding a batch—an expensive but sometimes necessary solution.

QUESTIONS: QUALITY SYSTEMS, QC

1. As you participate in the Interactive, look for examples of quality control testing. What happens if analysts find contaminants?
2. Look for the issue of retesting in the Interactive. Why is it forbidden to retest a sample without following a formal procedure?

DEVIATIONS

Sometimes, even when a company has well-defined processes and skilled personnel, something unexpected occurs during manufacturing. Perhaps a test of a product or in-process sample yields an out-of-specification result. Possibly there is a malfunction in a piece of equipment. Perhaps an operator erroneously adjusts a valve. A **deviation** ***is a departure from what is expected, for example, a procedure was not followed, or a specification was not met***. Every company needs clear procedures to deal with such deviations. This process will always require specific documentation to record the event and what is done about it. This documentation will typically include: a description of the deviation, the reason for the deviation, an explanation of any corrective actions that needed to be taken, and any preventive actions that need to be taken to prevent the problem from happening again. When a deviation is relatively minor and QA determines it will have no impact on the product, an intensive investigation may be unnecessary. But in more serious cases, a formal investigation will need to occur. Every company must have a Corrective and Preventative Action (CAPA) system. **CAPAs** ***are specific and detailed plans created to deal with a deviation, find out why it occurred, and avoid or accommodate such deviations in the future.***

QUESTIONS: QUALITY SYSTEMS, DEVIATIONS

1. The Interactive deals with dilemmas, hence, nearly every scene potentially leads to a deviation. Find two examples of deviations and how they were or were not handled properly. What procedures are in place for handling problems; how do these procedures affect each character?
2. In the Interactive, the character Vanessa Clark works in QA. In which scenes does she interact with the characters? What is her role in these scenes?

INTEGRITY

Chris Bellerive, a real person and a professional with many years of experience in the biopharmaceutical industry, tells this story:

"Working in this industry is all about integrity because we can make bad decisions. When I first got into the industry it was all about the money for me. I was a plumber by trade, but I got into biomanufacturing so I could come home clean and make good money. But as I worked on the development of Humira [a prescription drug to treat severe diseases including rheumatoid arthritis] and we started to bring in the patients for clinical studies, they showed us videos of how these patients couldn't even tie their shoes or feed themselves, and then when they're on this drug it improves their quality of life and they're tying their own shoes and juggling—that was the eye-opener, what we're doing, what sort of product we're making. That's when I knew that we improve the quality of life for people."

"No quality system, no matter how well constructed, will work if people are not honest and do not work with integrity. Integrity is the bedrock of a quality system."

No quality system, no matter how well constructed, will work if people are not honest and do not work with integrity. Integrity is the bedrock of a quality system.

THE DECISION POINTS

An Important Consideration:

The following section discusses the decision points in the Interactive. This information is intended to be helpful to facilitators guiding discussion. ***We suggest that participants wait to read this section until they have played one or more characters.***

In the Interactive the "right" answer is often intuitively obvious. But it is more important to appreciate why these are the right answers than it is to answer correctly. This involves understanding the possibly severe consequences of making the wrong decision. As is evident from the discussion on page 15, in a worst case, a wrong decision made by a biomanufacturing employee can cause harm or death to patients. Even if patients are not harmed, poor decisions can have severe economic consequences. For example, a company might lose a batch of product whose raw materials cost upwards of a million dollars and whose value is far more. Poor decisions might cause a company to lose an important contract, as is the concern at Franklin Biologics. Wrong decisions also open the company to sanctions by the FDA. Recall that government regulation of medical products evolved to protect people from harmful and even deadly substances. The FDA enforces these regulations and can impose sanctions on companies that do not comply. The first level of FDA sanction is a letter written to the company that outlines errors observed by FDA inspectors auditing the company. These letters are publicly available and can adversely impact the company's reputation. More serious offenses or failure to correct problems can lead the FDA to seize product and/or impose fines. In particularly egregious situations, company employees have been convicted in court and imprisoned. Finally, at the personal level, an employee who makes wrong decisions might be fired. It is important for Interactive participants to understand how seemingly small decisions can have a major impact on a product, a company, and their career. Facilitators might want to encourage participants to sometimes make the wrong decision to see these consequences.

"It is important for Interactive participants to understand how seemingly small decisions can have a major impact on a product, a company, and their career."

Several of the dilemmas in the Interactive relate to documentation because documentation is the foundation of any quality system. Documentation is how an organization "says what it does and proves that it does what it says." Documentation cannot function properly if employees fail to complete documents, are inaccurate in their documentation, or, worse still, do not tell the truth. Consider ***Corinne, Scene 4*** and ***Kevin, Scene 5***. It is easy to inadvertently make a mistake when recopying information; doing so therefore violates good documentation practices (see page 17). Such a mistake would cause documentation to be inaccurate. This kind of mistake would be impossible to catch in a later document review if the original post-it notes or batch record had been discarded. Laboratory instructors might want to relate this principle to class laboratory notebooks because novice students often erroneously want to write in pencil or take notes on separate sheets of paper to keep their lab notebooks "neat and pretty."

In ***Aseem, Scene 4***, Aseem might think he knows what units of measure were used by Lorenzo, but since he was not present, he cannot be sure. If, for example, Lorenzo accidentally added 1 g of a ma-

terial when he should have added 1 mg, he would have added 1000 times too much of this substance. An error like this would likely have adverse consequences. If the error were not caught, the batch would probably be ruined; in a worst case, patients could be harmed. This kind of mistake could be easily caught in a review process if Lorenzo accurately recorded the units he used. Possibly the batch could even be salvaged. But, if Aseem fills in the "correct" units, the mistake would not be easily caught. Even if problems were observed with the batch, it would be hard to trace them back to Lorenzo's original error because the documentation would indicate that he made the material properly.

Corinne, Scenes 2 and 5, refer to witnessing. Witnessing is a process in which a second person watches a critical process being performed to ensure that it is done correctly. The practice of witnessing was instituted because people can be distracted or tired and make inadvertent errors. Witnessing by a second person is a control that helps to prevent such errors. If Corinne signs that she has seen a task being done when she was not actually present ***(Scene 2)***, then, she has lied, which can jeopardize the product and can lead to her being fired. An underlying principle of working in a quality environment (and, indeed in any workplace) is: it is critical to work honestly and with integrity.

Many scenes in the Interactive relate to the importance of following established procedures. To a novice, this strict adherence to procedures might seem unduly rigid. But, drug products have a very long (and expensive) "life cycle" that includes years of development; testing in test tubes, cells, and animals; and finally testing in humans. A product is only approved and released for general use if it is found to be safe and effective throughout this testing cycle. During the long development period, procedures are established to make the drug product with its particular therapeutic characteristics and specifications. Once a product has been tested and approved, it is critical to manufacture it in a way that consistently results in the same drug product every time. Alterations in a procedure that seem minor to those working in production might affect the final product in an unforeseen way. It is therefore not allowable to alter a procedure without following an established and controlled process.

Raw materials are those substances that go into producing the final product. Ensuring that these raw materials meet their own specifications is an important part of maintaining a consistent and controlled manufacturing environment. FDA requires that raw materials be tested and approved before they are used in production. Every company must have a process in place to quarantine raw materials that have not yet been tested and to release them to production once they have passed their tests. Those working in production must follow this procedure, as is discussed in ***Aseem, Scene 5*** and ***Corinne, Scene 7***. Facilitators might point out that companies usually have a locked cage or room in which to store raw materials that have not yet been approved for use. Only after

raw materials are tested, approved, and labeled as approved, can they be removed by authorized personnel from the quarantine area.

Contamination prevention is another area where it is essential to follow established procedures.

During the development period for a product, methods are established to prevent contaminants from entering the product and to test for contamination that might have occurred. Once these methods have been devised, it is necessary to follow them. ***Corinne, Scenes 1 and 8*** and ***Kevin, Scenes 2 and 3*** are relevant here.

The issue discussed in ***Kevin, Scene 7***, relates to following established procedures that guide retesting in a quality control environment. These requirements may seem odd to anyone who has worked in a research laboratory or in a teaching laboratory. Researchers, teachers, and students know that people often make errors when performing laboratory analyses and it is normal practice to redo a test that provides an unexpected result. But, things are different in a quality control lab where an unexpected result might signal that a drug product is unsafe or defective. It has happened that analysts in drug companies have been allowed or encouraged to keep repeating a test until they got the result they wanted. This is sometimes called "testing into compliance" and can result in a dangerous product being released to the public. FDA forbids retesting unless a supervisor is notified and a specific lab error can be identified or unless a full-scale investigation of a product is being performed. Every company must have an established procedure that analysts must follow when they obtain an unexpected test result.

Aseem, Scenes 6 and 7; Corinne, Scene 8; and ***Kevin, Scene 6*** are about responding thoughtfully to problems, such as equipment alarms. Sometimes unexpected things occur and there might not be a perfect procedure in place to guide one's behavior. Facilitators might want to use these scenes to point out that even though biomanufacturing is a type of manufacturing and it is guided by strict procedures, working with cells that make drugs is never entirely routine. There are often challenges and opportunities to troubleshoot and problem solve. Facilitators might also want to note that the scene with Kevin emphasizes the importance of teamwork—biomanufacturing is very much a team activity.

The Interactive is not a cGMP training course; it does not cite explicitly the Code of Federal Regulations that controls pharmaceutical and biopharmaceutical manufacturing. However, it should be clear that these regulations do impact everyone who works at the company. For example, ***Aseem, Scene 2*** refers to mandatory, ongoing cGMP training.

Finally, we encourage facilitators to have discussions about the rewards of working in biomanufacturing and its challenges. In many parts of the country and the world there are career opportunities in biomanufacturing. It is therefore valuable to have participants think about whether this type of work might be a good fit with their personality and skills.

FRANKLIN BIOLOGICS

Operation of Balance: BRP 88

Effective Date: 7/22/10

SOP Identification: BRP8762

Revision Number: 1.0

Prepared by (author) Joseph Nonic Date 9/13/11

Reviewed and Approved by Roberta Santos Date 9/21/11

Reviewed and Approved by June Hagimoto Date 9/22/11

1 PURPOSE

Describes routine operation of Balance Type BRP 88.

2 SCOPE

The routine (daily) operation and use of Balance model BRP 88 by laboratory analysts.

3 DEFINITIONS

NA

4 REFERENCES

Manufacturer's bulletin No 2

5 MATERIALS, REAGENTS, EQUIPMENT

NIST Traceable standard mass set (2000 grams); part number SMS 100. Set must have been checked by metrology department within the last year.

6 RESPONSIBILITY

Training level of "Operator 2" or greater is required for use of this equipment.

7 HAZARD COMMUNICATION

NA

8 PROCEDURES

Frequency: Daily before use

Form: Balance Instrument record (QF 15.3.6.3)

8.1 Before calibration and verification, the balance must be switched on for at least 20 minutes to allow the internal components to come to working temperature.

8.2 Check that the leveling bubble is centered

8.2.1 If the bubble is off center. Adjust the leveling feet to bring back to center.

8.3 Check that the balance is clean

… and so on

Figure 10. Example of portion of a SOP.

FRANKLIN BIOLOGICS

Batch History Record
Lysis Solution – VP SP-0207-00

Part No: SP-0207-00D
Superseded: 11/7/09
Effective: 6/10/16
Revision Level: B
DRF #: 989

Batch Number: _____ Exp. Date: _____
(6 months from the date of manufacture)

Date of Manufacture: _____

1.0 Bill of Materials

REAGENTS	PART NO.	LOT NO.	EXP. DATE	*STANDARD QUANTITY	MULT BY	QTY USED
Tris base	RR-0111-00			11 g		
EDTA	RR-0040-00			3.7 g		
N-lauryl-sarcosine	RR-0088-00			50.0 g		
Sodium dodecyl sulfate (SDS)	RR-0095-00			5 g		
ProClin 150	RR-0176-00			1 mL		
HCl, 1 N	RR-0171-00			~50 mL		
Water, deionized	RR-0116-00	N/A	N/A	Enough to bring to 1 L		

* Standard formula is for 1000 mL = 1 L

Figure 11. Example Batch Record.

FRANKLIN BIOLOGICS

Batch History Record
Lysis Solution – VP SP-0207-00

Part No: SP-0207-00D
Superseded: 11/7/09
Effective: 6/10/16
Revision Level: B
DRF #: 989

Batch Number: _____

1.1 Accountability

Amount Requested		Amount to QC (10 mL)	
Amount Manufactured		Amount to Retention (long-term storage) (10 mL)	
Amount Lost/Discard		Other _____	
		Yield	

1.2 Comments

_____

_____

_____

2.0 Materials/Equipment/Reference Documentation

None

NOTE *The operator will initial each step when it is completed. Some critical steps are witnessed and the witness also initials and dates the record.*

3.0 Procedure

NOTE: The solution may be allowed to stir overnight in a sealed container to ensure that all reagents are completely dissolved.

3.1 _____ Add approximately ¾ the volume of water and a stir bar to a glass container. Start stirring.

3.2 _____ Weigh and add Tris base.

Witness to Tris addition: _____ Date:_____

3.3 _____ Weigh and add EDTA. Stir to dissolve.

Witness to EDTA addition_____ Date:_____

3.4 _____ Weigh and slowly add N-lauryl sarcosine.

Witness to sarcosine addition:_____ Date:_____

3.5 _____ Weigh and add SDS. Stir until dissolved.

Witness to SDS addition: _____ Date: _____

Figure 11. Example Batch Record.

FRANKLIN BIOLOGICS

Batch History Record
Lysis Solution – VP SP-0207-00

Part No: SP-0207-00D
Superseded: 11/7/09
Effective: 6/10/16
Revision Level: B
DRF #: 989

Batch Number: _____

3.0 Procedure

NOTE: The solution may be allowed to stir overnight in a sealed container to ensure that all reagents are completely dissolved.

3.6 _____ Measure and add ProClin. Mix well.

Witness to ProClin addition: _____ Date:_____

3.7 _____ Adjust the pH to 7.9 – 8.1 at 20-25 C with 1 N HCl as required.

Starting pH _____ Temp _____ ˚C

Vol. HCl added _____

Final pH _____ Temp _____ ˚C

3.8 _____ Adjust to final volume with water.

3.9 _____ Filter through 0.45 μm filter unit. An optional glass fiber prefilter may be used. If flow becomes restricted, change glass fiber prefilter as needed.

Source of filter unit: _____ Lot #: _____

Source of filter unit: _____ Lot #: _____

3.10 _____ Label container with description, part number, lot number and expiration date. Store at room temperature in a quarantine area pending QC testing.

3.11 _____ Remove two 10 ml aliquots of the Lysis Solution. Label one as QC and the other as RETENTION. Submit the samples and the completed Device History Record to the QC department.

3.12 _____ Comments:

Prepared by: _____ Date:_____

Reviewed by: _____ Date:_____

Manufacturing Authorization

4.0 Specifications/Test Methods

4.1 Appearance Determination (DT-0001):

4.1.1 Acceptable appearance = Clear, colorless solution substantially free of particulate matter; foams upon shaking.

4.1.2 Observed appearance = _____

Figure 11. Example Batch Record.

FRANKLIN BIOLOGICS

Batch History Record
Lysis Solution – VP SP-0207-00

Part No: SP-0207-00D
Superseded: 11/7/09
Effective: 6/10/16
Revision Level: B
DRF #: 989

Batch Number: _____

4.2 pH Determination (DT-0002):

4.2.1 Acceptable pH = 7.9 – 8.1 at 20-25 ˚C

4.2.2 Starting pH _____ Temp _____ ˚C

4.3 Osmolality Determination (DT-0003):

4.3.1 Acceptable mean osmolality = (230 – 250)

4.3.2 Observed osmolality= #1 _____

#2 _____

#3 _____

MEAN _____

Performed by: _____ Date: _____

4.4 Accepted: Yes_____ No _____

Accepted by: _____ Date: _____

5.0 Storage/Stability

Store tightly capped at room temperature. Stable for 6 months from date of manufacture.

6.0 Final Disposition

❍ PASS ❍ FAIL

By:_____ Date: _____ *QA Authorization*

Figure 11. Example Batch Record.

FRANKLIN BIOLOGICS

Bioburden Analysis

Effective Date: 7/22/10
Form: F6724
Revision Number: 1.0

Test Requested _____ **Requested By** _____

QC # Assigned _____ **Assigned By** _____

SOP Identification: BRP6724

Completed by QC

Test Method: ***Bioburden Analysis*** Test Date_____

Alert Limit; ≥5 CFU/mL / Action Limit ≥10 CFU/mL

Test Result: _____

Comments ❍ N/A

_____

_____

_____

Specification Section

❍ Meets Specification ❍ Fails Specification / Investigation Number: _____

Comments ❍ N/A

_____

_____

_____

Accepted by: _____Date: _____

Accepted by: _____Date: _____

Figure 12. A portion of a form that is used in the quality control lab.

ADDITIONAL RESOURCES

SCENE-BY-SCENE OUTLINE

This scene-by-scene outline is included to assist facilitators who may wish to focus on a particular dilemma or topic. It is possible to skip to any video by using the menu on the left side of the Franklin Biologics website. However, we suggest that participants play at least one character through from beginning to end before using this outline to move around in the Interactive.

Overview: ***Welcome and overview of biomanufacturing process***

Opening Scene- ***The Bad Day that didn't happen (hopefully!)***

Main Menu: Each of the 3 main characters have multiple scenes as follows:

Corrine Introduction: *Meet Corrine*

Scene 1: Honesty and integrity: Gowning with Lorenzo, foot goes down on dirty side

1a: Ignore it—he only touched the ground for a few seconds
1b: Tell him to redo with clean booties

Scene 2: Dealing with unexpected: Rufus the dog is hit by a car

2a: Hurry up and finish procedure before leaving
2b: Let Lorenzo handle it
2c: Tell Aseem about the problem

Scene 3: Career choice discussion with donuts

Scene 4: Documentation: You make a mistake in documentation

4a: Put a single line through it
4b: Start over with fresh batch record forms
4c: Scribble over it so it can't be read

Scene 5: Honesty and integrity. Witnessing, inoculation of the seed bioreactor

5a: Add media and record weight on own
5b: Wait until Aseem returns
5c: Ask Lorenzo to verify your work

Scene 6: Following procedures: Transfer from seed bioreactor to 2000L bioreactor, pH adjustment issue

6a: Bring up concern with supervisor
6b: Let it go—no big deal

Scene 7: Following procedures: Expired reagent (control of raw materials)

7a: Go ahead with clean-in-place
7b: Contact materials department about replacing the fluid

Scene 8: ***Things go wrong: Ready to harvest the batch and transfer cells from bioreactor, possible contamination***

8a: Talk to Aseem
8b: Mention to Lorenzo
8c: Nothing—valve not open long enough

Scene 9: Congratulations—you and the team are successful!

Aseem Introduction: *Meet Aseem*

Scene 1: The Supervisors' Meeting

Scene 2: Following procedures: cGMP refresher training

2a: Hold off on the training
2b: Do the training now

Scene 3: Following procedures: On the job training for Lorenzo is slowed by his questions

3a: Postpone training
3b: Answer questions even though it puts you behind schedule
3c: Tell him to pay attention but instruct him to save questions for another time

Scene 4: Documentation: You find Lorenzo has been sloppy in his documentation

4a: Pull Lorenzo aside and discuss it directly
4b: Talk to colleague in QA about how to handle it
4c: Correct documents yourself

Scene 5: Following Procedures: A week later—seed bioreactor has been inoculated; time to add media but scan says pending release

5a: Tell your team to document and use anyway
5b: Call materials release coordinator to find out what the problem is

Scene 6: Things go wrong: Foam alarm on bioreactor; Lorenzo asks for help

6a: Try antifoam, seems to help
6b: You decide it's a glitch—keep an eye on it
6c: Troubleshoot the alarm now—alert manager, engineering, etc.

Scene 7: Things go wrong: Corrine is setting up harvest lines and calls you over

7a: Follow up with Corrine and ask her to show the line that she might have opened
7b: Dismiss error and move on as planned
7c: Re-steam line as a precaution, just in case

Scene 8: Congratulations—you and the team are successful!

Kevin Introduction: *Meet Kevin*

Scene 1: Asseem and Kevin talk in the hallway

Scene 2: Contamination: The telephone-touch sequence

2a: Document error, change gloves
2b: Start over with remaining sample fluid

Scene 3: Contamination: Review is coming up—should you tell supervisor about cell phone issue

3a: Document and tell supervisor
3b: Document and keep mistake to yourself

Scene 4: Things go wrong: Running out of pipet tips; hit the side of the jar

4a: Ignore it and keep working
4b: Ask John to get more tips

Scene 5: Documentation: John is writing raw data on Post-it notes

5a: Press issue with John
5b: Quietly talk to supervisor
5c: Ignore it—John has been working there a lot longer than you have

Scene 6: Teamwork: Temperature alarm goes off while you are working

6a: Ignore it: you are busy and want to go home on time, not your samples
6b: Go over and check it out yourself

Scene 7: Following procedures, retesting: Testing samples from seed culture for endotoxin

7a: Find procedure for positive test result
7b: Redo test
7c: Alert production staff

Scene 8: Congratulations—you and the team are successful!

ONLINE RESOURCES

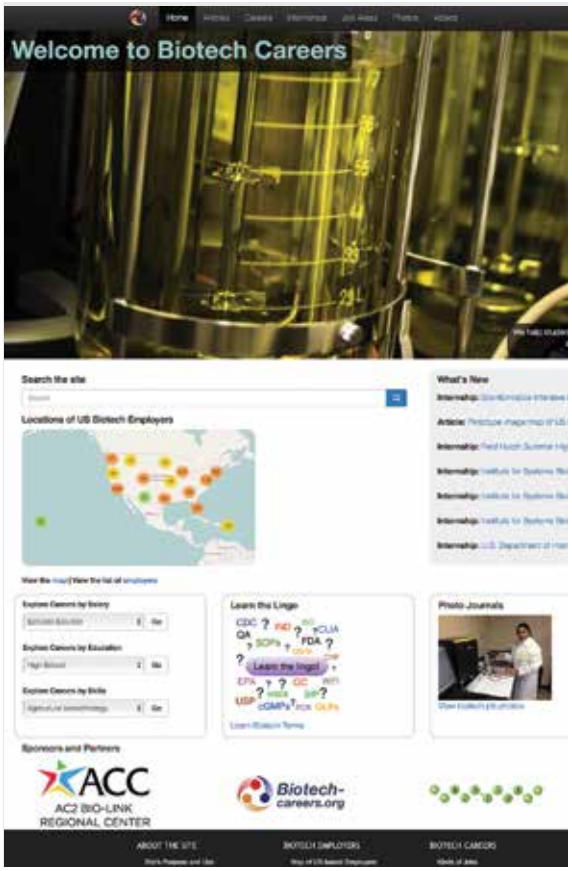
Bio-Link

bio-link.org

Bio-Link is the Next Generation National Advanced Technological Education Center of Excellence for Biotechnology and Life Sciences. Bio-Link originated in late 1998 with funding from the National Science Foundation. Bio-Link supports educational programs that prepare skilled technicians to work in the high-tech fields that drive the U.S. economy. Bio-Link provides webinars, conferences, and workshops for faculty enhancement. Bio-Link's website contains a number of useful resources for instructors, students, and individuals interested in learning more about biotechnology careers. In particular:

Instructors may find the Bio-Link Courses-in-a-Box useful. Two quality/regulatory affairs courses are posted at: **bio-link.org/home2/courses**

For career exploration visit: **biotech-careers.org**



NBC2

biomanufacturing.org

The Northeast Biomanufacturing Center and Collaborative (NBC2) is a National Science Foundation Advanced Technological Education regional center that has been in existence since 2005. Over the past ten years, NBC2 has worked with industry subject matter experts to develop a suite of curricular materials including a biomanufacturing lab manual, an ***Introduction to Biomanufacturing*** textbook, several process-specific short lab manuals and a complete list of skill standards and competencies for biomanufacturing technicians. This material and much more is available to you at their website.

NBC2 offers several professional development opportunities for college and high school faculty including ***BIOMAN*** conferences and ***Protein is Cash*** workshops that provide faculty with learning modules that can be added to existing courses or programs. Over the years, the Center has expanded its focus to include curriculum materials and hands-on experiences in the areas of biofuels, industrial biotechnology and stem cell technology.

ATETV

atetv.org

ATETV is an award-winning web-based video series and interactive network designed to connect students and professionals with careers in advanced technology.

ATETV is a product of Pellet Productions.

SUGGESTED ANSWERS TO QUESTIONS

QUESTIONS: INTRODUCTION, THE MAIN CHARACTERS, CORINNE [P.6]

If you play Corinne, consider the challenges and rewards of her work. Corinne has a great deal of responsibility for the successful manufacture of Squabanin. Every task that she performs is essential for making the product. How would you feel in this role?

ANSWERS: INTRODUCTION, THE MAIN CHARACTERS, CORINNE [P.6]

Everyone will have his/her own answer to this question. It is important to think about how one feels handling this type of responsibility.

QUESTIONS: INTRODUCTION, THE MAIN CHARACTERS, KEVIN [P.7]

If you play Kevin, what do you think might be the challenges and rewards of this type of laboratory work where there are established procedures that must be followed?

ANSWERS: INTRODUCTION, THE MAIN CHARACTERS, KEVIN [P.7]

Everyone will have his/her own answer to this question. All the characters have a great deal of responsibility. Kevin performs analyses, the results of which might cause a batch to be discarded or have other serious impacts in a biomanufacturing environment. It is therefore essential that he performs his work with care and with adherence to established procedures. Some individuals find this type of responsibility to be rewarding and enjoy working in a laboratory environment where there are established procedures and expectations. Others may not like this type of responsibility or may prefer to work in an environment where there is more flexibility in day-to-day procedures. The rewards of this work include helping people/saving lives, good benefits, and interesting work that requires technical expertise.

QUESTIONS: INTRODUCTION, THE MAIN CHARACTERS, ASEEM [P.7]

If you play Aseem, consider the responsibilities, pressures, and rewards of a management position. How can Aseem best ensure the success of his team? How can he make sure that the people he supervises have the resources they need to grow professionally? How can he balance the requirement to make products quickly and properly with the need to support his workers? If his employees make a mistake, does he have any responsibility for their error?

ANSWERS: INTRODUCTION, THE MAIN CHARACTERS, ASEEM [P.7]

There are various answers for this question. In terms of the rewards of this position, besides for the obvious financial incentive, people who work in biomanufacturing often feel good about making products that help improve the quality of lives for others. Managers must balance the needs of the company with the personal needs of the people they supervise. They must strive to create an environment that helps employees do a good job. Aseem has responsibility for ensuring on-going staff training and must set a tone that encourages personal growth. Participants might provide various details as to how Aseem can create this environment.

QUESTIONS: BIOMANUFACTURING & BIOPHARMACEUTICALS [P.14]

1. In what scene(s) are Corinne and Lorenzo working with the seed bioreactor?
2. How are the cells transferred from one place to another, for example, from the seed bioreactor to the main bioreactor?
3. What happens if Corinne accidentally sets the bioreactor to the wrong pH?

ANSWERS: BIOMANUFACTURING & BIOPHARMACEUTICALS [P.14]

1. In ***Corinne, Scene 5***, Corinne and Lorenzo are getting ready to fill the seed bioreactor with growth medium.
2. Cells are transferred through "lines," that is, tubing. This tubing is often made of flexible plastic that can be sterilized. The flow of cells and culture medium into the tubing is controlled by valves.
3. Cells have an optimal pH at which they produce the maximum amount of product. If the pH is not optimal then the manufacture of product will be adversely affected. The most likely problem would be a reduction in the yield of product.

QUESTIONS: QUALITY SYSTEMS, OVERVIEW & DOCUMENTATION [P.19]

1. See if you can find instances where characters do not follow proper good documentation practices.

2. See how many documents you can find as you participate in the Interactive. For each one, state in which scene it is shown and whether the document is a directive document, a data-collection document, or both. Note that there are scenes where the characters are using a batch record that directs the production of Squabanin and records the details of production. In the video, you will not see the actual batch record itself, only the notebook in which it is held. State which scenes involve this batch record.

3. Explain the slogan, "do what you say, say what you do." As you participate in the Interactive, look for examples of choices where the characters do or do not follow this maxim. If they do not, what are the consequences?

4. The commitment to quality must begin at the very highest levels of authority at an organization. Who is at the highest level of authority at Franklin Biologics? Does this character appear to be committed to quality? How can you tell?

ANSWERS: QUALITY SYSTEMS, OVERVIEW & DOCUMENTATION [P.19]

1. In ***Corinne, Scene 4***, one of the incorrect options is to rewrite a document in order to correct a mistake.

   Aseem, Scene 4, deals with mistakes in documentation. Lorenzo has not filled in documents properly. A particular error is his failure to record the units of measurement. It is important to always record units. It is incorrect for Aseem to fill in the missing information because he did not actually do the work.

   Kevin, Scene 5, deals with raw data. Raw data are original observations. It is critical that raw data are recorded in the proper medium, for example, on the proper form, in a batch record, or in a laboratory notebook. It is never correct to recopy raw data from the wrong place to the proper place. This is a similar problem as was shown in ***Corinne, Scene 4***.

2. In ***Corinne, Scene 2***, Corinne and Lorenzo are following an SOP that directs them in how to calibrate a pH meter. This is a directive document. It is also possible that this procedure is part of the batch record.

   In ***Corinne, Scene 4***, Corinne is filling out a form that documents the results of in-process tests. This is a data-collection document.

   In ***Corinne, Scenes 6 and 8***, Corinne and Lorenzo are shown following the directions in a batch record. Batch records are both directive and data-collection documents.

   Corinne, Scene 7, shows a label. Labels are a type of documentation. Labels are directive documents in that they identify a material and provide information. Labels may include expiration dates, as in this scene, and these dates direct staff as to whether or not the material can be used.

ANSWERS: QUALITY SYSTEMS, OVERVIEW & DOCUMENTATION *CONT.* [P.19]

In ***Aseem, Scene 5***, we see Aseem and Corinne following a batch record which is both a directive and data collection document. Similarly, in ***Aseem, Scenes 7 and 8*** we see this batch record.

In ***Kevin, Scene 7,*** there are forms visible on the counter. It would be common practice for analysts to record results on standardized forms. These are therefore data collection documents.

3. Many answers are possible but any answer should include some reference to documentation. Documentation is a way that an organization states what it does and provides evidence that people did what they said they would do. This slogan emphasizes the importance of honesty and integrity. Various scenes could be cited relating to this slogan. For example, in ***Corinne, Scene 2***, Corinne cannot sign off on Lorenzo's work if she did not actually see it being done. If she does so, the company could face sanctions from the FDA, a batch could be rejected, and she could face disciplinary action. ***Aseem, Scene 4,*** is a similar situation in which Aseem is filling in information that he did not actually witness. Lorenzo must say what he did (including the units of measurement).

4. Alicia Sandoval is the CEO of Franklin Biologics. It is her responsibility to ensure that all staff are committed to making quality products. She appears to be committed to quality in her remarks to new employees and her remarks during meetings.

QUESTIONS: QUALITY SYSTEMS, AVOIDING CONTAMINATION [P.21]

1. As you participate in the Interactive, look for examples of how people use gloves. Why do you think they are using gloves? How do you use or not use gloves in your school labs or your workplace? Do you think that gloves are used properly all the time where you go to school or work?

2. As you participate in the Interactive, look for scenes involving endotoxin testing. What happens if endotoxins are present and quality control testing fails to detect them?

3. As you participate in the Interactive, see how many situations you can find that relate to the issue of contamination.

ANSWERS: QUALITY SYSTEMS, AVOIDING CONTAMINATION [P.21]

1. Gloves are used by staff whenever they are in the production suite. They do so to protect the drug product from contamination by skin cells, oils, dirt, and microbes on their skin.

ANSWERS: QUALITY SYSTEMS, AVOIDING CONTAMINATION *CONT.* [P.21]

2. ***Kevin, Scene 7,*** deals with endotoxin testing. Endotoxins have the potential to harm or even kill patients if they are present in a drug.

3. In ***Corinne, Scene 1***, we see Lorenzo accidentally touch his booty on the "dirty" side of the bench. A contaminated booty can track microbes into the production suite.

   Corinne, Scene 8, deals with lines that are used to transfer cells from one place to another. These lines must be sterile, otherwise the cells will be contaminated.

   Kevin, Scene 2, deals with contamination. In this case, Kevin touches his cell phone and then begins to work in the cell culture hood, thereby possibly contaminating the cells with which he is working. Similarly, in ***Kevin, Scene 4***, when working in the cell culture hood, it is essential that the pipet tips never touch anything other than the cells and culture medium. Otherwise the tips may be contaminated by microbes on the surfaces of the hood and objects in the hood.

QUESTIONS: QUALITY SYSTEMS, QC [P.22]

1. As you participate in the Interactive, look for examples of quality control testing. What happens if analysts find contaminants?

2. Look for the issue of retesting in the Interactive. Why is it forbidden to retest a sample without following a formal procedure?

ANSWERS: QUALITY SYSTEMS, QC [P.22]

1. All of Kevin's scenes relate to the quality control lab.

2. Researchers who work in research laboratories and science teachers know that people often make errors when performing laboratory analyses and it is normal practice to redo a test that provides an unexpected result. But, things are different in a quality control lab in a company where an unexpected result might signal that a drug product is unsafe or defective. It has happened that analysts in drug companies have been allowed or encouraged to keep repeating a test until they got the result they wanted. This is sometimes called "testing into compliance" and can result in a dangerous product being released to the public. FDA forbids retesting unless a supervisor is notified and a specific lab error can be identified or unless a full-scale investigation of a product is being performed. Every company must have an established procedure that analysts must follow when they obtain an unexpected test result.

QUESTIONS: QUALITY SYSTEMS, DEVIATIONS [P.23]

1. The Interactive deals with dilemmas, hence, nearly every scene potentially leads to a deviation. Find two examples of deviations and how they were or were not handled properly. What procedures are in place for handling problems; how do these procedures affect each character?

2. In the Interactive, the character Vanessa Clark works in QA. In which scenes does she interact with the characters? What is her role in these scenes?

ANSWERS: QUALITY SYSTEMS, DEVIATIONS [P.23]

1. One might choose to discuss any of the dilemmas in the Interactive. For example, in ***Aseem, Scene 5***, a material is accidentally released to production before it has been fully tested. In this situation, Aseem has two choices. He can document and use the material anyway or take extra time and check with the materials department. If he uses the material, he must file a deviation report. Unfortunately, in this story, the medium turns out to be unsuitable and ruins the batch. The proper way to handle this dilemma is to get more information before proceeding.

2. ***Aseem, Scene 4***, deals with documentation errors. The QA department reviews documentation and therefore is involved in this scenario. Ms. Clark, in this case, advises Aseem to work with Lorenzo to improve his documentation.

   In ***Corinne, Scene 2***, Ms. Clark deals with a serious violation of procedure, where Corinne signs off on work that she did not actually witness. Observe that this is a case where this decision is dishonest, which is not acceptable even in times of stress.

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Worcester Polytechnic Institute (WPI)

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