The Challenges of Working in the HY06 Production Environment

Abstract

The HY06 production environment presents a unique human factors engineering problem. Production specialists must perform many of their duties at 2 - 8 ºC. This issue is compounded by the fact that the production environment is an ISO 8 controlled cold-cleanroom, and traditional clothing cannot be worn in the area. This paper discusses the challenges associated with this environment and the solutions to overcome those challenges.

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Introduction

ISTA Pharmaceuticals, Inc (ISTA) is a specialty pharmaceutical company developing novel drugs for use in treatment of diseases of the eye. One of these products is Vitrase® (Ovine Hyaluronidase 200 units/mL and Ovine Hyaluronidase 6200 units/mL). Vitrase is clinically used as a spreading agent. When combined with certain injectable anesthetic agents, Vitrase "spreads" the agent to the tissue faster, producing a more effective anesthetic block. The active pharmaceutical ingredient (API) for Vitrase is HY06. In August of 2005, Company A notified ISTA that they were exercising their contractual right to withdraw from the supplier agreement to produce HY06 at their facility in the United Kingdom. As of August 2007, ISTA will no longer be able to obtain HY06 from the UK facility. An Operations team performed an extensive "make versus buy" analysis and proposed that the manufacture of HY06 be transferred to a new facility to be constructed adjacent to the ISTA corporate offices in Irvine, CA. This proposal was approved by the board and necessitated the creation of multiple project teams to support the change of manufacturing location. Up until this time, ISTA had been a virtual company that exclusively used contract-manufacturing operations to produce commercial products. Building a facility to support the production of the HY06 material was a complete departure from the previous business plan. Performing manufacturing operations on site has produced a number of human factor engineering problems not previous encountered by this company. One of the major obstacles to overcome is the challenge of learning to work in the cleanroom environment required to produce the HY06 material.

Technical Challenge Part One

The HY06 material is produced from an extract of ovine tissues procured in New Zealand. Pharmaceutical products produced from animal tissue extracts have the potential risk of containing prions associated with transmissible spongiform encephalopathy (TSE). The most well known TSE is Bovine Spongiform Encephalopathy (BSE), or "mad cow disease". New Zealand is rated as having the most highly developed bio-security programs in the world today and the lowest risk of producing animals with TSE. To further mitigate the risk of contaminating API with prions associated with TSE, the manufacturing facilities are designed as "cleanrooms". The cleanroom facilities are designed to reduce transmission of potential contamination from one area to another through the use

of High Efficiency Particulate Air filters (HEPA), cascading pressure differentials between rooms, strict adherence to gowning requirements and stringent cleaning procedures. In the integrated circuit industry, dust particles can be the cause of circuit failure. In the pharmaceutical industry, the particles are associated with viable or living contaminants. Viable contaminants (bacteria, fungi, viruses) attach to particles by a variety of methods and may lead to contamination of the product if they are not controlled. Estimates are that as many as 25 percent of particles have bacteria attached to them. In an unoccupied, disinfected cleanroom, the HEPA filters will maintain the room at whatever particle concentration the air handling systems were designed to support. The air handling systems continually re-circulate and filter room air and are capable, if properly maintained, of removing 99.97% of particulate contamination > 0.3 µm. The difficulty occurs when humans enter the rooms. As living, breathing organisms we are constantly shedding aerosolized fluids and particles of hair and skin that contaminate the environment. Studies have shown the following contamination levels are commonly associated with routine activities:

Table 1

Activity	**# Particles/Minute**	**Number of Bacteria**
Standing	100,000	25,000
Sitting (moderate movement)	1,000,000	250,000
Walking	7,500,000	1,875,000

(Robert Reich Seminar, 2004)

Contamination with the human element in a cleanroom is controlled by teaching proper cleanroom behavior (minimizing movement, minimizing talking, etc.) and by simply covering the human body. Depending upon the cleanroom classification the employee is working in, layers of cleanroom clothing are used to minimize the shedding of skin and hair cells. Hair coverings and facemasks provide additional contamination control. Cleanroom clothing is designed to cover the body but not add contamination (either viable or non-viable particles) to the environment. The materials of construction for these garments are carefully selected to not shed particles.

Technical Challenge Part Two

The second challenge presented by producing pharmaceutical products from tissue extracts is that many of the processes must be performed at low temperature so that degradation of the extracted material does not occur. In the case of the HY06 process, many of the manufacturing steps must be performed at 2-8 ºC. This means that manufacturing employees must spend long periods of time (potentially several hours per day) working in very cold conditions. This presents its own set of challenges. Iowa State University's Department of

Environmental Health and Safety has stated that working at cold temperatures produces a number of deleterious effects upon workers including decreased mobility due to vaso-constriction, loss of concentration, and the potential for hand and arm vibration syndrome (Iowa State). The report also states that working in cold temperatures exacerbates the physiological effects of working in static postures (standing or sitting in one location) due to the circulatory effects brought on by the cold temperatures and increases the possibilities of injury due to these postures. A health guide released by Canada's province of British Columbia (BC Health) states that chronic stress and anxiety are experienced by workers that must perform their duties in cold conditions. Exposure to low humidity and cold temperatures also dries mucous membranes. The body reacts to this condition by increasing mucous secretions. This can lead to coughing and sneezing, which dramatically add to the level of airborne particles and bacteria.

Moderate activities (Table 1) have been demonstrated to produced as many as 1.87 million bacteria per minute released into the room. The number of bacteria released as a result of a cough or sneeze is truly amazing (see Table 2).

Table 2

Activity	**# Particles/Minute**	**Number of Bacteria**
Sitting (moderate movement) – from Table 1, provided for comparison	1,000,000	250,000
Sneezing	N/A	10,000,000 – 20,000,000
Coughing	N/A	35,000,000 – 50,000,000

(Robert Reich Seminar, 2004)

Particles and bacteria released as part of normal activities have a tendency to be dispersed throughout the cleanroom environment evenly. A cough or sneeze produces a bolus of bacteria that may settle directly onto the surface of products being manufactured.

How Cold is it?

Numerous sources from the United Kingdom (union guidelines) state that 16 ºC is the minimum temperature that workers should endure for long periods. Hypothermia has been observed in people who were at temperatures of approximately 10 ºC for extended periods.

Although the recorded temperature of the HY06 cold-cleanroom may be 2 - 8 ºC, the perceived temperature of the room is not easy to establish. How cold the

body perceives the temperature to be is compounded by wind-chill. Air moving across exposed skin cools the body faster than static air.

Numerous windchill guidelines exist. A commonly accepted table is presented in Table 3.

Table 3

Wind Speed (mph)	Perceived Temperature			
0	40 °F	35 °F	30 °F	25 °F
5	36 °F	31 °F	25 °F	19 °F
10	34 °F	27 °F	21 °F	15 °F
15	32 °F	25 °F	19 °F	13 °F

(Adapted from NOAA index)

In a typical cleanroom, as many as 100 air changes per hour may be used to maintain particulate counts at the required levels. This fast moving air will produce an artificial wind-chill. Although the temperature range of the room may be 2-8 ºC, the workers may perceive the room to be much colder. An estimate of the airspeed in the room based upon 100 air changes per hour is 10mph. Using standard windchill calculators, the perceived temperature of the room may be as low as -2 °C. This very low temperature makes the risk of working in this environment even greater. It is critical that an effective method of protecting employees from this stressful environment be devised.

Dealing with Cold Temperatures

The obvious solution to working at cold temperatures is to be properly clothed. Although the following data (Table 4) are based upon survival in cold water, it does present an effective comparison between the effects of cold on a clothed individual and on an unclothed individual.

Table 4

Temperature (ºC)	Survival Time – Nude (Hours)	Survival Time – Clothed (Hours)
-10	4.1	>24
-20	2.5	15.4
-30	1.8	8.6

(Tikuisis)

At -10 ºC, when clothed, the survival time is six times that of an unclothed individual. Immersion in water robs the body of heat faster than being dry simply

because body heat is more effectively transferred from the body to water than to air. Even so, proper clothing goes a long ways to increasing comfort, the ability to carry out simple functions and ultimately survival.

Working at cold temperature is obviously a human factors engineering issue. Normally to mitigate this issue, two factors would need to be considered: reducing the time spent at cold temperatures and providing proper clothing for the worker. For individuals working in the HY06 production facility, the solution is not so simple.

The HY06 Working Environment Challenge

HY06 is a pharmaceutical product, which must be manufactured in accordance with the Good Manufacturing Practices (21CFR Parts 210 and 211) and FDA Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Center for Drug Evaluation and Research, August 2001). Certain aspects of the process must be documented “real time” by a production specialist. Workers must spend time monitoring the HY06 process in the cold environment.

The other problem is that working in a cleanroom dictates the type of clothing that must be worn. The need to keep particles at a minimum necessitates wearing lightweight, synthetic fiber clothing specifically designed for cleanroom use. Warm jackets and coats made of natural fibers would shed massive numbers of particles into the environment and cannot be worn. The following factors must therefore be considered in developing an appropriate remediation to the human factors engineering problem presented by this working environment:

1. Warm clothing that will not shed in the low particle environment
2. Time restrictions for working in the area that are sensitive to the regulatory requirements of producing API
3. Education for the workforce in the effects of working at cold temperatures and how to recognize the signs of hypothermia.

Current HY06 Gowning Procedure

The HY06 cold-cleanroom is an ISO 8 classified room. The International Standards Organization classifies cleanrooms by the maximum number of particles greater than 0.5 microns that are allowed per cubic meter of air. The limit for an ISO 8 room is 100,000 particles/m^3 (ISO Standard 14464-1). Typical gowning for an ISO 8 room is haircover, facial hair cover, smock, shoe covers and gloves. All of these garments are constructed of lightweight, synthetic, non-particle shedding fabrics. Due to the risk of TSE contamination of the product when moving from one area to another, ISTA has increased the gowning

requirements to cleanroom facility dedicated uniforms (i.e. scrubs) and dedicated shoes.

HFE Remediation – Solution Part One

Vaso-constriction in the extremities is the body's survival mechanism to shuttle blood to the body core and protect the vital organs. The other area the body purposely protects by re-directing blood flow is the brain. Because of the lack of natural insulation on the head and neck, up to 40% of body heat is lost through the head (University of Maine). To counteract the effects of working at cold temperatures, it is critical to warm the core and the head. To meet the requirements of working in the cold-cleanroom, any garment chosen would have to be lightweight, constructed of synthetic fibers and not prone to shedding particles or retaining moisture that might increase the possibility for bacteria and fungi to "grow" on the material.

Numerous discussions with the manufacturing staff in the HY06 facility have led to the following solutions. Ski vests with a nylon exterior and a synthetic insulation have been procured. Although these garments should shed very few particles, they will be worn under the cleanroom smock to even further reduce the possibility of material shedding. Synthetic material "ski-caps" have also been purchased that must be worn under the cleanroom head cover. Both of these garments are low particulate shedding and will serve to keep the core and head warm.

As an additional precaution against the spread of bacteria from coughing or sneezing, the wearing of facemasks will be mandatory. Normally a facemask is not required in an ISO 8 room; however, the possibility of increased mucous secretions due to the cold temperature overrides the normal procedures followed in this room classification.

HFE Remediation – Solution Part Two

Any time limits placed upon working in the room need to take into consideration the regulatory requirements of manufacturing products according to the cGMP regulations. Based upon guidelines from the Department of Energy (DOE) for working in cold temperatures, a schedule has been established for the cold-cleanroom of no more than one hour in the room followed by at least one hour of time at normal room temperature. A review of the master batch record (instructions for producing API) has indicated that all processes required to be carried out in the cold-cleanroom should be able to be performed within one hour sessions. Setting the time limit will help remediate the effect of working at the cold temperatures but will not have a negative regulatory effect upon the production of the material.

HFE Remediation – Solution Part Three

One of the best ways to correct any problem is to provide education on the nature of the problem, how to recognize the problem and how to deal with the negative effects. A training program is being prepared to educate the manufacturing staff on the effects of working at cold temperatures, how to recognize the symptoms of hypothermia in themselves and their co-workers and the steps the company has taken to help protect the employees from the effects of working in the cold. The training material will be written into a standard operating procedure that all employees working in this area will be required to read and understand.

Summary

The above steps present a comprehensive solution to an unusual and complex human factors engineering problem. The physiological effects of the cold have been minimized by providing additional clothing and limiting the time working in the area. These solutions were devised to protect the employee and not compromise the product being produced. The educational program that is being developed will provide further remediation to the problem. The FDA's 2004 guidance document entitled "Guidance to Industry: Quality Systems Approach to Pharmaceutical Good Manufacturing Practice Regulations" (FDA - 2004) encourages pharmaceutical companies to carefully consider all aspects of pharmaceutical products and to develop systems that keep the quality of the product at the forefront. The burden for solving quality issues is placed squarely on the shoulders of management. In the case of the HY06 clean-coldroom, simply having the employees wear wool sweaters and fur hats would have solved their problem. But that simple solution would have compromised the environmental quality of the manufacturing area and, ultimately, the product itself. In the case of the HY06 environment, management working with the employees working in the area arrived at a solution that protected the employees and the product.

References

Reich, R.R. Working in a Cleanroom Environment. (2004) Personal attendance at seminar.

Iowa State University, Department of Environmental Health and Safety. Occupational Health - Cold Temperatures. Retrieved from IAS website July 1, 2006. http://www.ehs.iastate.edu/cms/default.asp?action=article&ID=84

British Columbia Health, Cold Temperature Exposure. Downloaded from BC Health website July 1, 2006. http://www.bchealthguide.org/kbase/topic/symptom/colde/overview.htm

NOAA NWS Windchill Chart. Downloaded from NOAA website. http://www.noaa.gov/om/windchill/index.shtml

Tikuisis,P.(1995), International Journal of Biometrology, 39(2):94-102

Good Manufacturing Practice Regulations (1978), 21 CFR Parts 210 and 211. Retrieved from GPO access website July 15, 2006, http://www.gpoaccess.gov/cgi-bin/cfrassemble

Guidance for Industry, Q7A Good Manufacturing Guidance for Active Pharmaceutical Ingredients. Retrieved from FDA website July 15, 2006. http://www.fda.gov/cder/guidance/4286fnl.htm

University of Maine, Cold Weather Field Guide. Retrieved from website July 15, 2006. http://www.umaine.edu/sem/fieldworktraining/coldweather.htm

Department of Energy Guidelines. Retrieved from website July 15, 2006. http://www.eh.doe.gov/docs/hasp/100032.htm

Guidance for Industry, (September 2004), Quality Systems Approach to Pharmaceutical Good Manufacturing Practice Regulations. Retrieved from FDA website July 15, 2006. http://www.fda.gov/cder/guidance/6452dft.htm