

COURSE LOGISTICS

INSTRUCTOR

- _____
- Contact info:
 - E-mail: _____
 - Telephone: _____
- Office: Granite Tech. Institute (GTI), Rm 259
- Office hours: _____

COURSE DESCRIPTION

- 3-credit hours, Interdisciplinary Gen Ed, survey
- Intro to biotechnology product manufacturing
- Focus on:
 - History of the industry
 - Required multidisciplinary approach for success
 - Details of manufacturing process
 - Legal, social, and ethical issues
- Exposure to local biomanufacturing companies
- Explore careers

COURSE FORMAT

- Lectures
- Class discussions
- Tours of local companies / guest speakers
- Student presentations
- Assignments
- Hands-on activity



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POLICIES, TOPICS, & GRADING

- See syllabus for details



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IMPORTANT DATES

- Last day to add: _____
- Last day to drop with 100% refund: _____
- Last day to withdraw, no refunds; "W" on transcript: _____



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"INCOMPLETE"

- Given for extenuating circumstances only with proper documentation
- Must be "passing" at time of request
- Must have completed course activities equaling more than 65% of total points (see syllabus)
- Must work with instructor to develop a contract for completing remainder of work
- Must fulfill contract within 1 year of "I" grade
- Failure to fulfill contract → "E" grade



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EMERGENCY INFO



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EVACUATION PROCEDURES

- Leave building calmly but immediately
- Exits
 - Only one way out to hall
 - Nearest stairwell vs. Other stairwells
- Pre-determined outside meeting place: to be designated by instructor at time of evacuation
- Assistance needed? Inform instructor !!
Assistance plan



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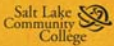
OTHER FACILITY ISSUES

- Power outage
 - Class is not automatically cancelled
 - Will attempt to finish class if possible
- Weather-related closures
 - Will follow official SLCC closure decisions
 - Hotline: 957-INFO (957-4636)



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OTHER PROGRAM-RELEVANT INFO



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IT'S NEW !!

- New training program
- New programmatic awards:
 - Certificate of Completion – 30 credits
 - Diploma – 47 credits
 - Associate of Applied Science – 65-69 credits
- New BMAN courses – currently 8 different ones
- Patience & feedback appreciated



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PROGRAM FUNDING

- Dept of Labor Community-Based Job Training (CBJT) grant : ~ \$ 2 million, used for
 - Facility remodel (mostly)
 - Training program / course development
 - New equipment purchases (some)
- Additional funding sources: WIRED (DoL), USTAR, other Utah state \$\$ (GSD)
- Grant objectives / timeline
- Progress & outcome reporting



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STUDENT SURVEYS

- Absolutely critical to program:
 - Provides info for progress & outcome reporting
 - Helps with course & program improvement
- Please help by completing



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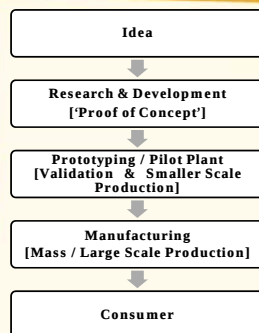
WHAT IS BIOMANUFACTURING ?

DEFINITIONS

- Biomanufacturing = manufacture of biotechnological products
- Biotechnology
 - Strict definition = use of biological processes to solve problems or make useful products
 - e.g. use of microorganisms for environmental clean-up ("bioremediation")
 - Broader / simpler definition = biology-based technology
 - e.g. use of yeast to make bread and wine

BIOTECH – BIOMAN RELATIONSHIP

- Biotechnology = research & development (R&D) oriented
- Biomanufacturing = production oriented
- Continuum
- Different, but complementary, skill sets required



<http://bio.org>

- Excellent resource for biotech-related info
- Biotechnology Industry Organization (BIO)
- 2008 Guide to Biotechnology
 - <http://bio.org/speeches/pubs/er/>
 - Downloadable pdf file
- Highlights
 - Biotech background
 - Industry timeline
 - Summary of technologies & applications



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2008 GUIDE TO BIOTECHNOLOGY

- Biotechnology: A Collection of Technologies
- Biotechnology Industry Facts
- Time Line
- Biotechnology Policy Milestones
- The Technologies and Their Applications
- Biotechnology Tools in Research and Development
- Health-Care Applications



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2008 GUIDE TO BIOTECHNOLOGY (cont.)

- Therapeutic Development Overview
- Agricultural Production Applications
- Agricultural Biotech Products on the Market
- Food Biotechnology
- Industrial and Environmental Applications
- Consumer Products Made with Industrial Biotechnology Development
- Examples of Industrial Enzymes



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2008 GUIDE TO BIOTECHNOLOGY (cont. 2)

- Preparedness for Pandemics and Biodefense
- Other Uses
- Ethics
- BIO Statement of Ethical Principles
- Intellectual Property
- Biotechnology Resources
- Glossary



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INDUSTRY FACTS

- Refer to handout from
<http://bio.org/speeches/pubs/er/statistics.asp>
- Large, diverse industry
- Many important and innovative accomplishments
- Great career opportunities available



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<http://iambiotech.org>

- A BIO project
- An excellent technical resource for all things biotech
 - Sister web site is great educational resource:
<http://www.whatcanbiotechdoforyou.com>
- Get / stay connected with biotechnology & biomanufacturing



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HISTORY OF BIOTECHNOLOGY



Step Ahead.

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TIMELINE

- Refer to handout from <http://bio.org/speeches/pubs/er/timeline.asp>
- Important events highlighted



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ASSIGNMENTS



Step Ahead.

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ASSIGNMENT 1

Research a current biotechnology product and prepare a 10-minute presentation for the class.

- Include:
 - Why you picked this product
 - Description of product and its use(s)
 - General description of the manufacturing process – specialized technology / equipment / methodology needed?
 - Legal / social / ethical implications of product



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ASSIGNMENT 1 (cont.)

- Purposes:
 - Learn about different biotech applications
 - Begin to learn about the manufacturing process
 - Practice research skills
 - Practice verbal communication and presentation skills
 - Share your 'excitement' of a biotech product
- Worth **150 points** toward 1000 point total
- **Be prepared to begin present next week & bring presentation on a flash drive**



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GRADING

- Points will be given for:
 - Content, specifically:
 - Why you picked this product
 - Description of product and its use(s)
 - General description of the manufacturing process – specialized technology / equipment / methodology needed?
 - Legal / social / ethical implications of product
 - Presentation organization and flow
 - Presenter's skills



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ASSIGNMENT 2

What area of biotechnology / biomanufacturing are you interested in? have an aptitude for? Write a 1-page (double-spaced, 10 point font) explanation of why you have an interest in this biotech area.

- Purposes:
 - Learn about the different biotechnology sectors
 - Practice written communication
- Worth **50 points** toward 1000 point total
- **Due in 2 weeks**



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Biotechnology Industry Facts

- The biotechnology industry emerged in the 1970s, based largely on a new recombinant DNA technique whose details were published in 1973 by Stanley Cohen of Stanford University and Herbert Boyer of the University of California, San Francisco. Recombinant DNA is a method of making proteins such as human insulin and other therapies in cultured cells under controlled manufacturing conditions. Boyer went on to co-found Genentech, which today is biotechnology's largest company by market capitalization.
- Biotechnology has created more than 200 new therapies and vaccines, including products to treat cancer, diabetes, HIV/ AIDS and autoimmune disorders.
- There are more than 400 biotech drug products and vaccines currently in clinical trials targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS and arthritis.
- Biotechnology is responsible for hundreds of medical diagnostic tests that keep the blood supply safe from HIV and detect other conditions early enough to be successfully treated. Home pregnancy tests are also biotechnology diagnostic products.
- Agricultural biotechnology benefits farmers, consumers and the environment by increasing yields and farm income, decreasing pesticide applications and improving soil and water quality, and providing healthful foods for consumers.
- Environmental biotech products make it possible to clean up hazardous waste more efficiently by harnessing pollution-eating microbes.
- Industrial biotech applications have led to cleaner processes that produce less waste and use less energy and water in such industrial sectors as chemicals, pulp and paper, textiles, food, energy, and metals and minerals. For example, most laundry detergents produced in the United States contain biotechnology-based enzymes.
- DNA fingerprinting, a biotech process, has dramatically improved criminal investigation and forensic medicine. It has also led to significant advances in anthropology and wildlife management.
- The biotech industry is regulated by the U.S. Food and Drug Administration (FDA), the Environmental Protection Agency (EPA) and the Department of Agriculture (USDA).
- As of Dec. 31, 2006, there were 1,452 biotechnology companies in the United States, of which 336 were publicly held.*
- Market capitalization, the total value of publicly traded biotech companies (U.S.) at market prices, was \$360 billion as of late April 2008 (based on stocks tracked by BioWorld).
- The biotechnology industry has mushroomed since 1992, with U.S. health care biotech revenues from publicly traded companies rising from \$8 billion in 1992 to \$58.8 billion in 2006.*
- Biotechnology is one of the most research-intensive industries in the world. U.S. publicly traded biotech companies spent \$27.1 billion on research and development in 2006.*
- There were 180,000 employed in U.S. biotech companies in 2006.*
- The top five biotech companies invested an average of \$170,000 per employee in R&D in 2007.
- In 1982, recombinant human insulin became the first biotech therapy to earn FDA approval. The product was developed by Genentech and Eli Lilly and Co.
- Corporate partnering has been critical to biotech success. According to BioWorld, in 2007 biotechnology companies struck 417 new partnerships with pharmaceutical companies and 473 deals with fellow biotech companies. The industry also saw 126 mergers and

Source: Biotechnology Industry Organization website - <http://bio.org/speeches/pubs/er/statistics.asp>

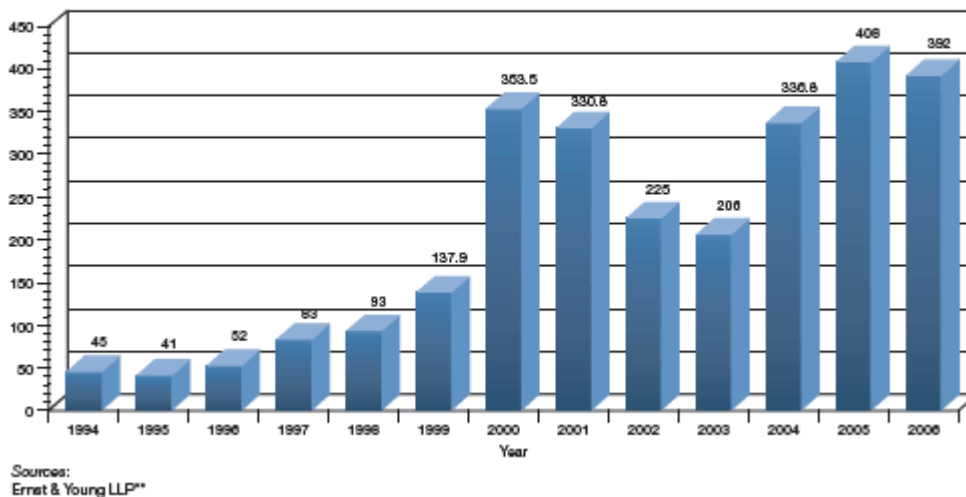
acquisitions.

- Most biotechnology companies are **young companies developing their first products and depend on investor capital for survival**. According to BioWorld, biotechnology attracted more than \$24.8 billion in financing in 2007 and raised more than \$100 billion in the five-year span of 2003-2007.
- The biosciences - including all life-sciences activities - employed 1.3 million people in the United States in 2006 and generated an additional 7.5 million related jobs.**
- The average annual wage of U.S. bioscience workers was \$71,000 in 2006, more than \$29,000 greater than the average private-sector annual wage.**
- The Biotechnology Industry Organization (BIO) was founded in 1993 to represent biotechnology companies at the local, state, federal and international levels. BIO comprises more than 1,200 members, including biotech companies, academic centers, state and local associations, and related enterprises.

* New data are expected in mid-2008 from Ernst & Young, which publishes an annual global overview of the biotechnology industry.

[See the 2008 BIO-sponsored Battelle Memorial Institute report.](#)

Market Capitalization, 1994-2006*



* Amounts are in U.S. dollars in billions

Source:

Ernst & Young LLP

U.S. Biotech Industry Statistics: 1994–2006*

Year	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997	1996	1995	1994
Sales	45.3	39.7	28.1	28.4	24.3	21.4	19.3	16.1	14.5	13	10.8	9.3	7.7
Revenues	53.5	48.5	43.8	39.2	29.6	26.6	26.7	22.3	20.2	17.4	14.6	12.7	11.2
R&D Expense	22.9	16.6	19.6	17.9	20.5	15.7	14.2	10.7	10.6	9.0	7.9	7.7	7.0
Net Loss	3.5	1.4	6.8	5.4	9.4	4.6	5.6	4.4	4.1	4.5	4.6	4.1	3.6
No. of Public Companies	336	331	331	314	318	342	339	300	316	317	294	260	265
No. of Companies	1,452	1,475	1,346	1,473	1,466	1,457	1,379	1,273	1,311	1,274	1,287	1,308	1,311

Source:

Ernst & Young LLP annual biotechnology industry reports, 1995–2006. Financial data based primarily on fiscal-year financial statements of publicly traded companies.**

*Amounts are U.S. dollars in billions.

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Source:

Ernst & Young LLP, annual biotechnology industry reports, 1995–2006. Financial data based primarily on fiscal-year financial statements of publicly traded companies.**

U.S. Public Companies by Region, 2006

REGION	NO. PUBLIC COS.	MARKET CAP*	REVENUE*	R&D*
San Francisco Bay Area	69	\$145,553	\$17,668	\$7,486
New England	60	\$62,956	\$10,384	\$3,919
San Diego	38	\$20,916	\$3,352	\$1,432
New Jersey	28	\$28,556	\$1,747	\$802
Mid-Atlantic	23	\$17,111	\$2,061	\$1,270
Southeast	19	\$5,301	\$544	\$271
New York State	17	\$8,863	\$1,373	\$685
Mid-West	8	\$1,161	\$121	\$90
Pacific Northwest	15	\$4,928	\$196	\$521
Los Angeles/Orange County	11	\$81,585	\$14,692	\$4,898
North Carolina	9	\$2,017	\$328	\$191
Pennsylvania/Delaware Valley	12	\$7,140	\$2,078	\$603
Texas	11	\$1,495	\$160	\$170
Colorado	6	\$1,847	\$296	\$195
Utah	2	\$1,454	\$160	\$170
Other	8	\$1,526	\$384	\$107

* Amounts are in millions of U.S. dollars.

Source:

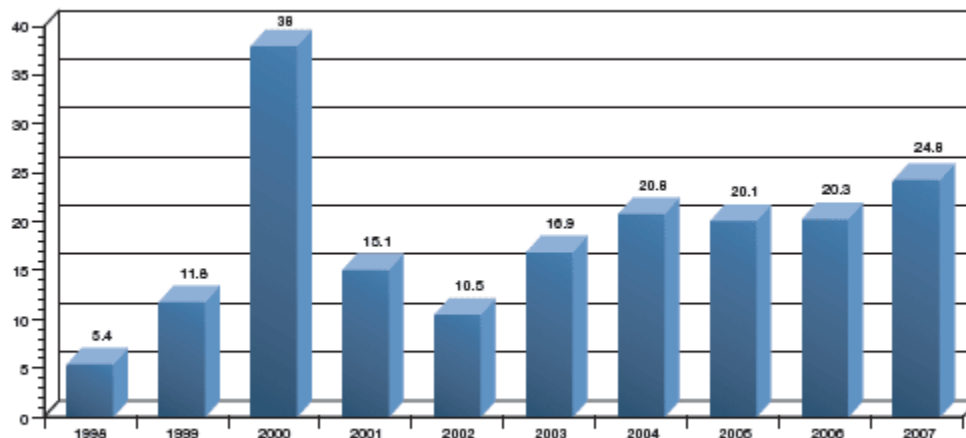
Ernst & Young LLP

* Amounts are in U.S. dollars in billions

Source:

Ernst & Young LLP

Total Financing, 1998–2007 (in billions of U.S. dollars)



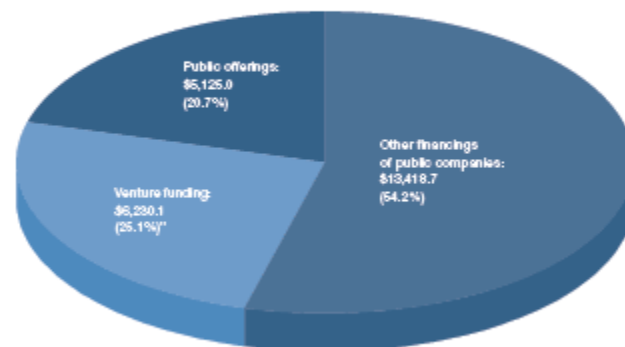
Source:
BioWorld

Source:
BioWorld

Total: \$24,773.8 Million
(all figures in millions)

Biotech Industry Financing

Total: \$24,773.8 Million
(all figures in millions)



Source:
BioWorld

Source:
BioWorld

Biotechnology Time Line

8000 B.C.

- Humans domesticate crops and livestock.
- Potatoes first cultivated for food.

4000-2000 B.C.

- Biotechnology first used to leaven bread and ferment beer, using yeast (Egypt).
- Production of cheese and fermentation of wine (Sumeria, China and Egypt).
- Babylonians control date palm breeding by selectively pollinating female trees with pollen from certain male trees.

500 B.C.

- First antibiotic: moldy soybean curds used to treat boils (China).

A.D. 100

- First insecticide: powdered chrysanthemums (China).

1322

- An Arab chieftain first uses artificial insemination to produce superior horses.

1590

- Janssen invents the microscope.

1663

- Hooke discovers existence of the cell.

1675

- Leeuwenhoek discovers bacteria.

1761

- Koelreuter reports successful crossbreeding of crop plants in different species.

1797

- Jenner inoculates a child with a viral vaccine to protect him from smallpox.

1830-1833

- 1830-Proteins discovered.
- 1833-First enzyme discovered and isolated.

1835-1855

- Schleiden and Schwann propose that all organisms are composed of cells, and Virchow declares, "Every cell arises from a cell."

1857

- Pasteur proposes microbes cause fermentation.

1859

- Charles Darwin publishes the theory of evolution by natural selection. The concept of carefully selecting parents and culling the variable progeny greatly influences plant and animal breeders in the late 1800s despite their ignorance of genetics.

1865

Source: Biotechnology Industry Organization website - <http://bio.org/speeches/pubs/er/timeline.asp>

- Science of genetics begins: Austrian monk Gregor Mendel studies garden peas and discovers that genetic traits are passed from parents to offspring in a predictable way-the laws of heredity.

1870-1890

- Using Darwin's theory, plant breeders crossbreed cotton, developing hundreds of varieties with superior qualities.
- Farmers first inoculate fields with nitrogen-fixing bacteria to improve yields.
- William James Beal produces first experimental corn hybrid in the laboratory.
- 1877-A technique for staining and identifying bacteria is developed by Koch.
- 1878-The first centrifuge is developed by Laval.
- 1879-Fleming discovers chromatin, the rod-like structures inside the cell nucleus that later came to be called chromosomes.

1900

- Drosophila (fruit flies) used in early studies of genes.

1902

- The term immunology first appears.

1906

- The term genetics is introduced.

1911

- The first cancer-causing virus is discovered by Rous.

1914

- Bacteria are used to treat sewage for the first time in Manchester, England.

1915

- Phages, or bacterial viruses, are discovered.

1919

- First use of the word biotechnology in print.

1920

- The human growth hormone is discovered by Evans and Long.

1928

- Penicillin discovered as an antibiotic: Alexander Fleming.
- A small-scale test of formulated *Bacillus thuringiensis* (Bt) for corn borer control begins in Europe. Commercial production of this biopesticide begins in France in 1938.
- Karpechenko crosses radishes and cabbages, creating fertile offspring between plants in different genera.
- Laibach first uses embryo rescue to obtain hybrids from wide crosses in crop plants-known today as hybridization.

1930

- U.S. Congress passes the Plant Patent Act, enabling the products of plant breeding to be patented.

1933

- Hybrid corn, developed by Henry Wallace in the 1920s, is commercialized. Growing hybrid corn eliminates the option of saving seeds. The remarkable yields outweigh the increased costs of annual seed purchases, and by 1945, hybrid corn accounts for 78 percent of U.S.-grown corn.

1938

- The term molecular biology is coined.

1941

- The term genetic engineering is first used, by Danish microbiologist A. Jost in a lecture on reproduction in yeast at the technical institute in Lwow, Poland.

1942

- The electron microscope is used to identify and characterize a bacteriophage-a virus that infects bacteria.
- Penicillin mass-produced in microbes.

1944

- DNA is proven to carry genetic information-Avery et al.
- Waksman isolates streptomycin, an effective antibiotic for tuberculosis.

1946

- Discovery that genetic material from different viruses can be combined to form a new type of virus, an example of genetic recombination.
- Recognizing the threat posed by loss of genetic diversity, the U.S. Congress provides funds for systematic and extensive plant collection, preservation and introduction.

1947

- McClintock discovers transposable elements, or "jumping genes," in corn.

1949

- Pauling shows that sickle cell anemia is a "molecular disease" resulting from a mutation in the protein molecule hemoglobin.

1951

- Artificial insemination of livestock using frozen semen is accomplished.

1953

- The scientific journal Nature publishes James Watson and Francis Crick's manuscript describing the double helical structure of DNA, which marks the beginning of the modern era of genetics.

1955

- An enzyme involved in the synthesis of a nucleic acid is isolated for the first time.

1956

- Kornberg discovers the enzyme DNA polymerase I, leading to an understanding of how DNA is replicated.

1958

- Sickle cell anemia is shown to occur due to a change of a single amino acid.
- DNA is made in a test tube for the first time.

1959

- Systemic fungicides are developed. The steps in protein biosynthesis are delineated.

ALSO IN THE 1950s

- Discovery of interferons.
- First synthetic antibiotic.

1960

- Exploiting base pairing, hybrid DNA-RNA molecules are created.

Source: Biotechnology Industry Organization website - <http://bio.org/speeches/pubs/er/timeline.asp>

- Messenger RNA is discovered.

1961

- USDA registers first biopesticide: *Bacillus thuringiensis*, or Bt.

1963

- New wheat varieties developed by Norman Borlaug increase yields by 70 percent.

1964

- The International Rice Research Institute in the Philippines starts the Green Revolution with new strains of rice that double the yield of previous strains if given sufficient fertilizer.

1965

- Harris and Watkins successfully fuse mouse and human cells.

1966

- The genetic code is cracked, demonstrating that a sequence of three nucleotide bases (a codon) determines each of 20 amino acids. (Two more amino acids have since been discovered.)

1967

- The first automatic protein sequencer is perfected.

1969

- An enzyme is synthesized in vitro for the first time.

1970

- Norman Borlaug receives the Nobel Peace Prize (see 1963).
- Discovery of restriction enzymes that cut and splice genetic material, opening the way for gene cloning.

1971

- First complete synthesis of a gene.

1972

- The DNA composition of humans is discovered to be 99 percent similar to that of chimpanzees and gorillas.
- Initial work with embryo transfer.

1973

- Stanley Cohen and Herbert Boyer perfect techniques to cut and paste DNA (using restriction enzymes and ligases) and reproduce the new DNA in bacteria.

1974

- The National Institutes of Health forms a Recombinant DNA Advisory Committee to oversee recombinant genetic research.

1975

- Government first urged to develop guidelines for regulating experiments in recombinant DNA: Asilomar Conference, California.
- The first monoclonal antibodies are produced.

1976

- The tools of recombinant DNA are first applied to a human inherited disorder.
- Molecular hybridization is used for the prenatal diagnosis of alpha thalassemia.
- Yeast genes are expressed in *E. coli* bacteria.

Source: Biotechnology Industry Organization website - <http://bio.org/speeches/pubs/er/timeline.asp>

- The sequence of DNA base pairs for a specific gene is determined.
- First guidelines for recombinant DNA experiments released: National Institutes of Health-Recombinant DNA Advisory Committee.

1977

- First expression of human gene in bacteria.
- Procedures developed for rapidly sequencing long sections of DNA using electrophoresis.

1978

- High-level structure of virus first identified.
- Recombinant human insulin first produced.
- North Carolina scientists show it is possible to introduce specific mutations at specific sites in a DNA molecule.

1979

- Human growth hormone first synthesized.

ALSO IN THE 1970s

- First commercial company founded to develop genetically engineered products.
- Discovery of polymerases.
- Techniques for rapid sequencing of nucleotides perfected.
- Gene targeting.
- RNA splicing.

1980

- The U.S. Supreme Court, in the landmark case *Diamond v. Chakrabarty*, approves the principle of patenting organisms, which allows the Exxon oil company to patent an oil-eating microorganism.
- The U.S. patent for gene cloning is awarded to Cohen and Boyer.
- The first gene-synthesizing machines are developed.
- Researchers successfully introduce a human gene-one that codes for the protein interferon-into a bacterium.
- Nobel Prize in Chemistry awarded for creation of the first recombinant molecule: Berg, Gilbert, Sanger.

1981

- Scientists at Ohio University produce the first transgenic animals by transferring genes from other animals into mice.
- Chinese scientist becomes the first to clone a fish-a golden carp.

1982

- Applied Biosystems, Inc., introduces the first commercial gas phase protein sequencer, dramatically reducing the amount of protein sample needed for sequencing.
- First recombinant DNA vaccine for livestock developed.
- First biotech drug approved by FDA: human insulin produced in genetically modified bacteria.
- First genetic transformation of a plant cell: petunia.

1983

- The polymerase chain reaction (PCR) technique is conceived. PCR, which uses heat and enzymes to make unlimited copies of genes and gene fragments, later becomes a major tool in biotech research and product development worldwide.
- The first genetic transformation of plant cells by TI plasmids is performed.
- The first artificial chromosome is synthesized.
- The first genetic markers for specific inherited diseases are found.
- First whole plant grown from biotechnology: petunia.
- First proof that modified plants pass their new traits to offspring: petunia.

1984

- The DNA fingerprinting technique is developed.

Source: Biotechnology Industry Organization website - <http://bio.org/speeches/pubs/er/timeline.asp>

- The entire genome of the human immunodeficiency virus is cloned and sequenced.

1985

- Genetic markers found for kidney disease and cystic fibrosis.
- Genetic fingerprinting entered as evidence in a courtroom.
- Transgenic plants resistant to insects, viruses and bacteria are field-tested for the first time.
- The NIH approves guidelines for performing gene-therapy experiments in humans.

1986

- First recombinant vaccine for humans: hepatitis B.
- First anticancer drug produced through biotech: interferon.
- The U.S. government publishes the Coordinated Framework for Regulation of Biotechnology, establishing more stringent regulations for rDNA organisms than for those produced with traditional genetic modification techniques.
- A University of California-Berkeley chemist describes how to combine antibodies and enzymes (abzymes) to create pharmaceuticals.
- The first field tests of transgenic plants (tobacco) are conducted.
- The Environmental Protection Agency approves the release of the first transgenic crop-gene-altered tobacco plants.
- The Organization of Economic Cooperation and Development (OECD) Group of National Experts on Safety in Biotechnology states: "Genetic changes from rDNA techniques will often have inherently greater predictability compared to traditional techniques" and "risks associated with rDNA organisms may be assessed in generally the same way as those associated with non-rDNA organisms."

1987

- First approval for field test of modified food plants: virus-resistant tomatoes.
- Frostban, a genetically altered bacterium that inhibits frost formation on crop plants, is field-tested on strawberry and potato plants in California, the first authorized outdoor tests of a recombinant bacterium.

1988

- Harvard molecular geneticists are awarded the first U.S. patent for a genetically altered animal-a transgenic mouse.
- A patent for a process to make bleach-resistant protease enzymes to use in detergents is awarded.
- Congress funds the Human Genome Project, a massive effort to map and sequence the human genetic code as well as the genomes of other species.

1989

- First approval for field test of modified cotton: insect-protected (Bt) cotton.
- Plant Genome Project begins.

ALSO IN THE 1980s

- Studies of DNA used to determine evolutionary history.
- Recombinant DNA animal vaccine approved for use in Europe.
- Use of microbes in oil spill cleanup: bioremediation technology.
- Ribozymes and retinoblastomas identified.

1990

- Chy-Max™, an artificially produced form of the chymosin enzyme for cheese-making, is introduced. It is the first product of recombinant DNA technology in the U.S. food supply.
- The Human Genome Project-an international effort to map all the genes in the human body-is launched.
- The first experimental gene therapy treatment is performed successfully on a 4-year-old girl suffering from an immune disorder.
- The first transgenic dairy cow-used to produce human milk proteins for infant formula-is created.
- First insect-protected corn: Bt corn.
- First food product of biotechnology approved in U.K.: modified yeast.
- First field test of a genetically modified vertebrate: trout.

1992

- American and British scientists unveil a technique for testing embryos in vitro for genetic abnormalities such as cystic fibrosis and hemophilia.
- The FDA declares that transgenic foods are "not inherently dangerous" and do not require special regulation.

1993

- Merging two smaller trade associations creates the Biotechnology Industry Organization (BIO).
- FDA approves bovine somatotropin (BST) for increased milk production in dairy cows.

1994

- First FDA approval for a whole food produced through biotechnology: FLAVRSAVR™ tomato.
- The first breast cancer gene is discovered.
- Approval of recombinant version of human DNase, which breaks down protein accumulation in the lungs of CF patients.
- BST commercialized as POSILAC® bovine somatotropin.

1995

- The first baboon-to-human bone marrow transplant is performed on an AIDS patient.
- The first full gene sequence of a living organism other than a virus is completed, for the bacterium *Hemophilus influenzae*.
- Gene therapy, immune system modulation and recombinantly produced antibodies enter the clinic in the war against cancer.

1996

- The discovery of a gene associated with Parkinson's disease provides an important new avenue of research into the cause and potential treatment of the debilitating neurological ailment.

1997

- First animal cloned from an adult cell: a sheep named Dolly in Scotland.
- First weed- and insect-resistant biotech crops commercialized: Roundup Ready® soybeans and Bollgard® insect-protected cotton.
- Biotech crops grown commercially on nearly 5 million acres worldwide: Argentina, Australia, Canada, China, Mexico and the United States.
- A group of Oregon researchers claims to have cloned two Rhesus monkeys.

1998

- University of Hawaii scientists clone three generations of mice from nuclei of adult ovarian cumulus cells.
- Human embryonic stem cell lines are established.
- Scientists at Japan's Kinki University clone eight identical calves using cells taken from a single adult cow.
- The first complete animal genome, for the *C. elegans* worm, is sequenced.
- A rough draft of the human genome map is produced, showing the locations of thousands of genes.
- Five Southeast Asian countries form a consortium to develop disease-resistant papayas.

ALSO IN THE 1990s

- First conviction using genetic fingerprinting in the U.K.
- Discovery that hereditary colon cancer is caused by defective DNA repair gene.
- Recombinant rabies vaccine tested in raccoons.
- Biotechnology-based biopesticide approved for sale in the United States.
- Patents issued for mice with specific transplanted genes.
- First European patent on a transgenic animal issued for transgenic mouse sensitive to carcinogens.
- 2000
- First complete map of a plant genome developed: *Arabidopsis thaliana*.
- Biotech crops grown on 108.9 million acres in 13 countries.
- "Golden rice" announcement allows the technology to be available to developing countries in hopes of improving the health of undernourished people and preventing some forms of blindness.

Source: Biotechnology Industry Organization website - <http://bio.org/speeches/pubs/er/timeline.asp>

- First biotech crop field-tested in Kenya: virus-resistant sweet potato.
- Rough draft of the human genome sequence is announced.

2001

- First complete map of the genome of a food plant completed: rice.
- Researchers with China's National Hybrid Rice Research Center report developing a "super rice" that could produce double the yield of normal rice.
- Complete DNA sequencing of the agriculturally important bacteria *Sinorhizobium meliloti*, a nitrogen-fixing species, and *Agrobacterium tumefaciens*, a plant pest.
- A single gene from *Arabidopsis* inserted into tomato plants to create the first crop able to grow in salty water and soil.

2002

- The first draft of a functional map of the yeast proteome, an entire network of protein complexes and their interactions, is completed. A map of the yeast genome was published in 1996.
- International consortia sequence the genomes of the parasite that causes malaria and the species of mosquito that transmits the parasite.
- The draft version of the complete map of the human genome is published, and the first part of the Human Genome Project comes to an end ahead of schedule and under budget.
- Scientists make great progress in elucidating the factors that control the differentiation of stem cells, identifying over 200 genes that are involved in the process.
- Biotech crops grown on 145 million acres in 16 countries, a 12 percent increase in acreage. More than one-quarter (27 percent) of the global acreage was grown in nine developing countries.
- Researchers announce successful results for a vaccine against cervical cancer, the first demonstration of a preventative vaccine for a type of cancer.
- Scientists complete the draft sequence of the most important pathogen of rice, a fungus that destroys enough rice to feed 60 million people annually. By combining an understanding of the genomes of the fungus and rice, scientists can elucidate the molecular basis of the interactions between the plant and pathogen.
- Scientists are forced to rethink their view of RNA when they discover how important small pieces of RNA are in controlling many cell functions.
- Japanese pufferfish genome is sequenced. The pufferfish sequence is the smallest known genome of any vertebrate.
- Scientists at Stony Brook University in New York assemble a synthetic virus, polio, using genome sequence information. The project raises ethical and security questions.

2003

- Researchers find a vulnerability gene for depression and make strides in detecting genetic links to schizophrenia and bipolar disorder.
- GloFish®, the first biotech pet, hits the North American market. Specially bred to detect water pollutants, the fish glows red under black light thanks to the addition of a natural fluorescence gene.
- Worldwide biotech crop acreage rises 15 percent to hit 167.2 million acres in 18 countries. Brazil and the Philippines grow biotech crops for the first time in 2003. Also, Indonesia allows consumption of imported biotech foods, and China and Uganda accept biotech crop imports.
- The U.K. approves its first commercial biotech crop in eight years. The crop is a biotech herbicide-resistant corn used for cattle feed.
- The U.S. Environmental Protection Agency approves the first transgenic rootworm-resistant corn, which may save farmers \$1 billion annually in crop losses and pesticide use.
- An endangered species (the banteng) is cloned for the first time. 2003 also brought several other cloning firsts, including mules, horses and deer.
- Dolly, the cloned sheep that made headlines in 1997, is euthanized after developing progressive lung disease. Dolly was the first successful clone of an adult mammal.
- Japanese researchers develop a biotech coffee bean that is naturally decaffeinated.
- China's State Food and Drug Administration grants the world's first regulatory approval of a gene therapy product, Gendicine, developed by Shenzhen SiBiono GenTech. The product delivers the p53 gene as a therapy for squamous cell head and neck cancer.

2004

Source: Biotechnology Industry Organization website - <http://bio.org/speeches/pubs/er/timeline.asp>

- The FDA approves the first anti-angiogenic drug for cancer, AVASTIN® (bevacizumab).
- The FDA clears a DNA microarray test system, the AmpliChip® Cytochrome P450 Genotyping Test, to aid in selecting medications for a wide variety of common conditions.
- An RNA-interference product for age-related "wet" macular degeneration becomes the first RNAi product to enter a clinical trial.
- The United Nations Food and Agriculture Organization endorses biotech crops and states that biotechnology is a complementary tool to traditional farming methods that can help poor farmers and consumers in developing nations.
- The National Academy of Sciences' Institute of Medicine finds biotech crops do not pose any more health risks than do crops created by other techniques, and that food safety evaluations should be based on the resulting food product, not the technique used to create it.
- FDA finds biotech wheat safe after a food safety review.
- Monsanto introduces low-linolenic soybeans (produced through conventional breeding methods) that will reduce or eliminate trans fatty acids in processed soybean oil.
- Chicken genome sequenced by the Chicken Genome Sequencing Consortium.
- First cloned pet, a kitten, is delivered to its owner.
- Laboratory rat genome is sequenced.
- Researchers complete the sequence of the chimpanzee-humanity's closest primate relative.
- The Canadian biotech company Iogen achieves the first commercial production and delivery of bioethanol, producing the fuel with biotech enzymes and wheat straw.
- California voters pass Proposition 71, which supports embryonic stem cell research with \$3 billion in funding over 10 years.

2005

- Researchers at the University of Georgia successfully produce a cow cloned from the cells of a carcass.
- FDA for the first time approves a drug for a specific race. The drug, NitroMed's BiDil®, treats congestive heart failure in self-identified black patients. The company hopes a genetic test can be developed to identify patients likely to benefit, regardless of race.
- The Energy Policy Act is passed and signed into law, authorizing numerous incentives for bioethanol development.
- The National Institutes of Health in December launches a pilot project to determine the feasibility of The Cancer Genome Atlas. The ultimate goal would be a complete map of the genomic changes involved in all types of human cancer.
- Using new genome sequence information, scientists at the Centers for Disease Control & Prevention partially synthesize the flu virus that killed at least 20 million people worldwide in 1918-1919.
- Scientists at Harvard University report success in converting skin cells into embryonic stem cells through fusion with existing embryonic stem cells.
- USDA, Monsanto and Genaissance Pharmaceuticals announce a joint soybean genome project.
- The British government approves the Equine Fertility Unit's research in using nuclear transfer in horse cloning.
- On May 7, the one billionth acre of biotech seed is planted.
- The World Health Organization (WHO) issues the report Modern Food Biotechnology, Human Health and Development, which states biotech foods can contribute to enhancing human health and development. According to the report, biotech foods can increase crop yield, food quality, and the diversity of foods which can be grown in a given area. They lead to better health and nutrition and thereby help raise health and living standards.
- The British research firm PG Economics Ltd. finds that the global use of biotech crops has added \$27 billion to farm income, and greatly reduced agriculture's negative impacts on the environment.
- The National Science Foundation, USDA, and the Department of Energy award \$32 million to a team of university and private laboratory researchers to sequence the corn genome.
- A consortium of scientists led by the National Human Genome Research Institute publishes the dog genome, which belongs to a 12-year-old boxer.
- Global biotech crop acreage reaches 222 million acres.

2006

- A team of researchers headed by the University of Illinois receives a \$10 million federal grant to complete the sequence of the swine genome. The project is expected to be completed within two years.
- In his State of the Union address, President Bush expresses support for bioethanol made from agricultural wastes. "Doesn't it make sense," he asked, "to determine whether or not we can use these raw materials to make something out of nothing so that we continue the advance of ethanol and so the market for ethanol expands throughout the United States?"

Source: Biotechnology Industry Organization website - <http://bio.org/speeches/pubs/er/timeline.asp>

- The National Institutes of Health begins a 10-year, 10,000-patient study using a genetic test that predicts breast-cancer recurrence and guides treatment. Patients whose cancer is deemed unlikely to recur will be spared chemotherapy. The genetic test, Oncotype DX™ was developed by the biotech company Genomic Health and is already commercially available.
- In January, the American Dietetic Association (ADA) publishes a reaffirmed statement of support on agricultural and food biotechnology. The ADA states that agricultural biotechnology techniques can enhance the quality, safety, nutritional value, and variety of food available for human consumption while increasing the efficiency of food production, food processing, food distribution, and environmental and waste management.
- Dow AgroSciences announces it has received the first regulatory approval for a plant-made vaccine from USDA's Center for Veterinary Biologics. The vaccine protects poultry from Newcastle disease, and is the first plant-made vaccine to be approved.
- Renessen LLC, a joint venture of Monsanto and Cargill, receives approval from USDA to begin selling the first crop improved through biotechnology with added benefits for use in animal feed. The product, Maveria™ High Value Corn with Lysine, has been improved to grow with increased levels of lysine, an amino acid that is essential for animal diets, especially those of swine and poultry.
- USDA awards \$5 million to a consortium of public wheat breeders and 18 universities for wheat genome research.
- Researchers develop biotech pigs that produce high levels of omega-3 fatty acids. The biotech pigs were developed by inserting the "fat-1" gene that comes from the roundworm *Caenorhabditis elegans*. The biotech pigs were cloned, and six of the 10 clones produced increased levels of omega-3 fatty acids, which are believed to ward off heart disease.
- The World Trade Organization issues a confidential final ruling on the U.S./Canada/Argentina challenge against the European Union (EU) on approval of new biotech crops. According to news reports, the ruling concludes that the EU breached its trade commitments with respect to 21 agricultural biotechnology products-including types of oilseed, rape, maize and cotton.
- The French agriculture ministry authorizes 17 new field tests for biotech corn and tobacco crops.

Sources:

Access Excellence

Biotech 90: Into the Next Decade, G. Steven Burrill with the Ernst & Young High Technology Group

Biotechnology Industry Organization

Genentech, Inc.

Genetic Engineering News

International Food Information Council

ISB News Report

International Service for the Acquisition of Agri-Biotech Applications

Texas Society for Biomedical Research

Science

Science News

The Scientist

REVIEW FROM PREVIOUS WEEK

- What is the definition of *biotechnology*?
- How would you describe the way a biotechnology *idea* becomes translated to a *product for the end user / consumer*?
- What are 3 specialty fields / areas of biotechnology?



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COMPANY TOURS (Preview)



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GOALS

- Exposure to several different local biomanufacturing companies
- Exposure to different biomanufacturing sectors



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MAKE THE MOST OF THE TOUR

- Prior to the tour date, research the company on the internet
 - What product(s) does the company make?
 - How long in business?
 - Volume of business (\$\$\$ or units per year)
 - Do they have R&D? or strictly production?
- Make a list of specific questions
 - Details of a product's manufacturing process?
 - How many employees?
 - Employment opportunities? e.g. # of positions? in what dept or area? future company expansion?



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ASSIGNMENTS RELATED TO COMPANY TOURS

1. **Tour summaries:** a few paragraphs each
 - To obtain student input on tours
 - What did you learn?
 - Did the tour help with a career decision?
 - What questions did you have before and after the tour? Answered?
2. **Local company survey:** 3-page double spaced, 10-point font
 - Survey **3 other local biomanufacturing** companies, each representing a different sector
 - Describe what each company manufactures
 - Compare and contrast the companies
 - What do you like/dislike about them / their product(s)?



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ASSIGNMENTS RELATED TO COMPANY TOURS (cont.)

- Due dates:
 1. The **tour summaries (50 points)**: all 3 summaries due by _____; can submit early if desired (instructor recommended)
 2. The **local company survey (150 points)**: due by _____



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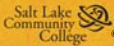
GRADING

- Points will be given for:
 - Content
 - Refer to recommended content on previous slide
 - Additional content may be added – be imaginative / creative (e.g. you are a news reporter writing about a local company – what's interesting about it?)
 - Written communication skills
 - Grammar
 - Report organization and flow



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BIOTECHNOLOGY APPLICATIONS – PRESENTATIONS



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ASSIGNMENT

Research a current biotechnology product and prepare a 10-minute presentation for the class.

- Include:
 - Why you picked this product
 - Description of product and its use(s)
 - General description of the manufacturing process – specialized technology / equipment / methodology needed?
 - Legal / social / ethical implications of product



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ASSIGNMENT (cont.)

- Purposes:
 - Learn about different biotech applications
 - Begin to learn about the manufacturing process
 - Practice research skills
 - Practice verbal communication and presentation skills
 - Share your 'excitement' of a biotech product
- Worth **150 points** toward 1000 point total
- Be prepared to begin presenting this week



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GRADING

- Points will be given for:
 - Content, specifically:
 - Why you picked this product
 - Description of product and its use(s)
 - General description of the manufacturing process – specialized technology / equipment / methodology needed?
 - Legal / social / ethical implications of product
 - Presentation organization and flow
 - Presenter's skills



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GRADING (cont.)

- Total points possible = **150**
- Instructor responsible for **100**
- Students responsible for **50**
- Class discussions to give constructive feedback



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COMPANY TOURS



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REMINDERS

- See handout for company locations and dates
- Research company prior to tours (see web sites on handout); make a list of questions
- Meet by front doors about 10-15 minutes early
- Wear appropriate clothing: pants, closed-toed shoes
- Bring notepad & pen; no bags, backpacks, etc.
- Take notes for tour summaries assignment – due _____



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BIOTECHNOLOGY APPLICATIONS – PRESENTATIONS (cont.)



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GRADING

- Points will be given for:
 - Content, specifically:
 - Why you picked this product
 - Description of product and its use(s)
 - General description of the manufacturing process – specialized technology / equipment / methodology needed?
 - Legal / social / ethical implications of product
 - Presentation organization and flow
 - Presenter's skills



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GRADING (cont.)

- Total points possible = **150**
- Instructor responsible for **100**
- Students responsible for **50**
- Class discussions to give constructive feedback



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MORE INFO ?

- Reading in textbook:
 - Communication Skills: Chapter 5



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TEXT READINGS

- For ***Manufacturing Process Overview*** topic coming up – reading in advance:
 - Production Basics – Creating Products : Section 8.1
 - Production Planning & Workflow : Chapter 12
 - Production Components : Chapter 13
 - Controlling & Documenting Production – Documenting the Process : Section 14.2
 - Packaging & Distributing Products : Chapter 15
 - Continuous Improvement : Chapter 16



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REVIEW FROM PREVIOUS WEEKS

- What were 3 highlights of the company tours?
- What were 3 surprises of the company tours?



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MANUFACTURING PROCESS OVERVIEW

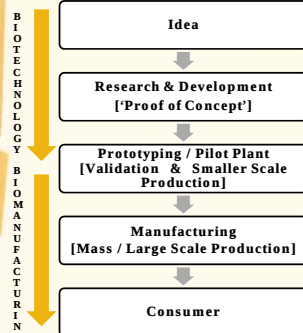


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MAKING A BIOTECH PRODUCT

- Prototyping / Pilot Plant phase = product transfers from R&D to production
- Biomanufacturing can begin during this transfer phase
- Scale up issues must be resolved during transfer phase



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PRODUCTION PLANNING

- Identify resources required
 - Materials
 - People
 - Equipment & tools
 - Facilities
 - Time
 - \$\$\$
- Identify processes required
 - Process = any operation or technique used to transform materials into products
 - Involves technology : engineering and science considerations



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RAW MATERIAL ACQUISITION

- Identify source(s)
- Qualify vendor
 - Regulatory compliance
- Purchase raw materials
- Inspect incoming raw materials
 - Released for use if meet specifications
 - Quarantined / rejected if not
- Add to inventory: traceability!



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PRODUCTION RUN

- Verify all raw material availability
- Schedule production run
- Line clearance before starting
- Follow appropriate work instructions
 - Approved
 - Most current
- Manage resources throughout



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PRODUCTION RUN (cont.)

- Product must meet desired specifications / requirements
- Monitor / control production to ensure quality
- Complete batch record with production run
- Typically, entire run = one “LOT” or “BATCH”
- Deviations? Get approval & document



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PRODUCT COMPLEXITY

- Some products are made from smaller parts/subassemblies
 - May be made in-house or by a supplier/vendor
 - Finished product company has bears overall responsibility over parts/subassemblies used – importance of vendor qualification
- Subassemblies can be made
 - Prior to final product – “stocked”
 - Just in time for use in final product
- Traceability is critical !!



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PACKAGING AND LABELLING

- Package product appropriately
 - Maximize product stability
 - Sterility concerns?
- Label product appropriately (labels & product inserts)
 - Must follow federal regulations
 - All claims must have supporting data



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INSPECTION AND RELEASE

- Finished product inspected to ensure quality and consistency
 - Various levels of visual checks – cross-referenced with documentation
 - May include testing: sampling vs. 100% testing
 - Verify product meets desired specifications / requirements



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DISTRIBUTION AND CUSTOMER SUPPORT

- Sales and marketing – can tie in to R&D
- Warehousing
- Shipping
- Customer service / technical support



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CONTINUOUS IMPROVEMENT

- Can always improve on any and all phases of manufacturing:
 - Resource scheduling
 - Shifts
 - Equipment maintenance
 - Production
 - Supply chain management
 - Inventory: transit, material, work-in-progress, buffer, finished goods
 - Lean manufacturing
 - Just-in-time manufacturing
 - Quality assurance



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PRODUCTION – MORE SPECIFICALLY

WORK FLOW & FACILITIES

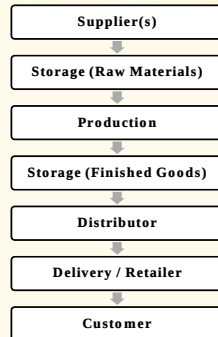
- Work flow is impacted by facility layout
 - Typical layouts: product vs. process
- Cellular layout: newer, lean philosophy
 - Work cell = combination of process and product layout
 - Flexible, so amenable to customization as needed
 - Typically 3-12 workers per cell, CROSS-TRAINED !
 - Cell is responsible for all aspects of product – output & quality
- Line balancing: assignment of tasks at a station/cell to maximize efficient output

MATERIALS INVENTORY

- Types of inventory:
 - Transit
 - Raw materials / parts
 - Work-in-process (WIP)
 - Buffer = safety stock
 - Maintenance repair and operations (MRO) = machine parts & tools
 - Finished goods (FG) = final product
- Inventory costs \$\$\$: carrying costs vs. shortage costs

SUPPLY CHAIN

- Supply chain management = coordination of supply chain elements to maximize efficiency and profit
- Effective management results in:
 - Shorter lead times
 - Reduced inventory costs
 - Faster response to demand changes



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TIME COSTS \$\$\$

- Time includes
 - Supplier lead times
 - Equipment set-up
 - Scheduled maintenance
 - Production
 - Unexpected events: breakdowns/repairs, delivery delays
- Minimizing downtime → minimizes costs
 - Preventative maintenance vs. repairs (aka corrective maintenance)
 - Maximize use of production equipment
 - Maximize quality



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PRODUCTION SYSTEMS

- Two main types:
 - PUSH system :
 - Triggered by forecasted demand
 - Forecast must be accurate: errors cause shortages or excess
 - Changes are difficult once production has begun
 - May have large WIP inventory
 - PULL system :
 - Triggered by customer orders
 - Only the necessary materials are moved downstream: signaled by a *kanban* ("card" in Japanese), a visual signal
 - Works best if stations are close and workers cross-trained
 - Small WIP inventory so material delays affect production



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PRODUCTION SYSTEMS (cont.)

Characteristic	Push System	Pull System
Production trigger	Forecasted demand	Customer demand
Buffer and WIP inventory size	Large	Small
Production run length	Long	Short
Product changeover speed	Slow	Fast
Effect of supply disruption	Can continue until WIP inventory is exhausted	Stops until supply is replenished
Speed of response to demand change	Slow	Fast
Effect of scheduled maintenance	Depends on WIP inventory	Production stops



From: High-Performance Manufacturing, Glencoe/McGraw-Hill, 2006 edition, pg.306
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PRODUCTION SYSTEMS (cont. 2)

- Adaptations of PULL system:
 - Agile manufacturing:
 - Uses flexible automation – minimal changes in tooling / software
 - Cross-training is critical
 - Allows rapid development of new products
 - Just-In-Time (JIT) production:
 - Reduces inventory and waste by balancing material flow
 - Permits temporary buffer inventory
 - Biggest risk = interruption of material flow; good supply chain management is critical (e.g. multiple suppliers)



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DOCUMENTATION

- Absolutely critical to the production process
- Types of production documents include
 - SOPs
 - WIDs
 - Work orders
 - Batch records
 - Maintenance records
 - Testing records
 - Shipping records
- Written documents are most typical, but moving to electronic documentation



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DOCUMENTATION (cont.)

- Purpose of documentation include:

- Provides a reference for every action
- Provides a reference for results of every measurement / test
- Ensure all procedures and regulations were followed
- Help all workers understand the process
- Provides a means of communication between teams / groups within a company
- Identifies opportunities for improvement
- Provides justification for change
- Provides a way to trace materials, especially for corrective action



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MORE INFO ?

- Reading in textbook:

- Production Basics – Creating Products : Section 8.1
- Production Planning & Workflow : Chapter 12
- Production Components : Chapter 13
- Controlling & Documenting Production – Documenting the Process : Section 14.2
- Packaging & Distributing Products : Chapter 15
- Continuous Improvement : Chapter 16



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CRITICAL FUNCTIONS

- Discussion:

Identify critical functions in the manufacturing process and explain why they are critical

Relate to company tour observations when possible



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MANUFACTURING PROCESS OVERVIEW (cont.)

IN-CLASS PRACTICAL ACTIVITY

- Prepare a batch of chocolate chip cookies using a SOP and batch record
- Purpose:
 - To experience a simulated manufacturing process
 - Learn to follow and use SOPs and batch records
 - Practice good manufacturing practices, proper documentation, quality assurance / control, and regulatory compliance
- Worth **150 points**

RULES OF ENGAGEMENT

- Work as a group, but you must fill in your own batch record
- You may **talk quietly within your group** but **not to students in other groups**
- **Be clean** when you work
- **No** tasting of ingredients or dough
- Bake at least enough cookies for each student and instructor to have 1 cookie from your batch (you may discard the remaining dough to speed things up)

REVIEW FROM PREVIOUS WEEKS

- How would you describe the process of taking an idea and turning it into a sellable product?
- Name 3 phases of the manufacturing process.
- What is meant by “supply chain management”, and what are the benefits of doing so?
- Describe the 2 main types of production systems in terms of the trigger for production.
- What did you learn from the “cookie activity”?



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DISCIPLINES INVOLVED IN BIOMANUFACTURING



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MULTIDISCIPLINARY

- Biomanufacturing involves a number of different disciplines, including but not limited to:
 - The sciences
 - Engineering
 - Business



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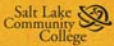
IN-CLASS ASSIGNMENT

- Consider your biotechnology product presentation – list all the disciplines and sub-disciplines involved in its development and manufacture, and specify how these disciplines are involved
- Class discussion of each list
- Worth **10 points**



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EVENTS IN THE WORLD OF BIOTECHNOLOGY & BIOMANUFACTURING



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TIMELINE

- Lists significant events for biotechnology & biomanufacturing



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IN-CLASS ASSIGNMENT

- Maintaining chronology, sort timeline events into one of the following categories:

- ☐ Research / technology / tools
- ☐ Agricultural / food products
- ☐ Environmental / industrial products
- ☐ Medical devices
- ☐ Pharmaceuticals
- ☐ Other ?

- Worth **20 points**



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ASSIGNMENT

Now that you have gotten a thorough exposure to the field of biotechnology

- Write a **1-page biotechnology interest paper** describing
 - o an aspect of biotechnology that most interests you
 - o why you are interested
 - o how this relates to your general interests and aptitudes
- Worth **50 points** and due _____



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REVIEW FROM PREVIOUS WEEK

- What can you say about the disciplines involved in biomanufacturing?
- Name 3 significant events in biotechnology / biomanufacturing that interest you.



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JOB AND DEPARTMENT ROLES IN BIOMANUFACTURING



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MAKING A BIOTECH PRODUCT

- Prototyping / Pilot Plant phase = product transfers from R&D to production
- Biomanufacturing can begin during this transfer phase
- Scale up issues must be resolved during transfer phase

BIOTECHNOLOGY
BIOMANUFACTURING

Idea



Research & Development
['Proof of Concept']



Prototyping / Pilot Plant
[Validation & Smaller Scale Production]



Manufacturing
[Mass / Large Scale Production]



Consumer



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JOB FAMILIES

- Quality
- Regulatory
- Facilities
- Product / Process Development (pilot plant)
- Manufacturing

- Clinical Development (pharma)
- Discovery Research (R&D)



Life Science Career Alliance (Philadelphia, PA)
http://www.lscalliance.org/pdfs/Biotech_Pharma_careers.pdf
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ASSIGNMENT

- Research a position of interest to you in one of the 3 job families in biotechnology / biomanufacturing
- Write a **1-page long career survey** about your chosen position (refer to syllabus for assignment requirements)
- Worth **50 points** and due _____
- Purpose:
 - ✓ Practice written communication skills
 - ✓ Explore potential job / career paths



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EQUIPMENT AND PROCESSES USED IN BIOMANUFACTURING



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WORK AREAS

- Material handling / warehousing
- Production
- Testing
 - Quality control / assurance
 - Validation
 - Calibration
- Packaging



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MATERIAL HANDLING

- Forklifts
- Specialized containers ?
- Software databasing system
- Segregated storage areas/systems



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PRODUCTION

- Presses
- Mixers – dry & wet
- Dispensers – weight & volume
- Clean rooms
- Molders
- Extruders
- Assembly machines
- Bioreactors



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TESTING

- Microbiology equipment: culturing, cell harvesting, cell lysis, bioburden
- Spectroscopy systems: chemical analyses (e.g. FTIR)
- Chromatography systems:
 - Liquid (LC, HPLC) vs. Gas (GC) for identification or purification
 - May be coupled to a mass spectrometer (MS) for more sensitive detection
- Measuring devices / systems
- Calibration systems for assorted measuring devices



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PACKAGING

- Form-fill-seal
- Bottling line – solids & liquids
- Tubing line
- Vacuum sealer



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ASSIGNMENT

- Research a piece of “biotechnology manufacturing equipment” of interest to you
- Create a 5-minute PowerPoint presentation (use websites and other visual aids) describing your findings for **next week’s class** (bring on **flash drive**)
- Focus on :
 - What the equipment is used for in biotech. / bioman.
 - Standard features vs. special / optional features
 - How the equipment works & special usage considerations



Worth **20 points**
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REVIEW FROM PREVIOUS WEEK

- What are the main job families in biomanufacturing?
- Equipment & processes used in biomanufacturing – student presentations



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PRODUCT QUALITY AND QUALITY MANAGEMENT SYSTEM



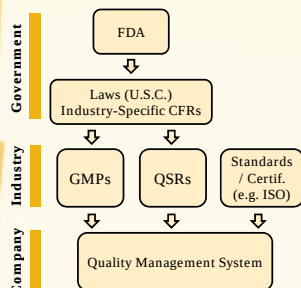
Step Ahead.

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THE “TRICKLE DOWN” EFFECT

A tight relationship exists between

- ☐ the FDA [regulating body]
- ☐ the Laws [US Code]
- ☐ the Code of Federal Regulations (CFRs) - gov't agency promulgated
- ☐ Good Manufacturing Practices (cGMPs)
- ☐ Quality System Regulations (QSRs)
- ☐ Standards / Certifications (e.g. ISO)
- ☐ Quality Management System



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PRODUCT QUALITY

- Begins with design specifications & requirements
- Is the responsibility of all employees
- Quality Department has an important role
 - Quality assurance : “preventative”
 - Quality control : “corrective”
 - Quality engineering : “preventative” & “corrective”



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QUALITY MANAGEMENT SYSTEM

- A plan focusing an organization's efforts on product quality and meeting customer needs
- Specifically:
“a set of policies, processes, and procedures required for planning and execution (of production / development / service) in the core business area of an organization”
[from: http://en.wikipedia.org/wiki/Quality_management_system]
- Provides a process approach for project execution



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QUALITY MANAGEMENT SYSTEM (cont.)

- Enables an organization to **identify, measure, control, and improve** various core processes that will lead to improved business performance
- Essentially, what an organization implements to manage processes/activities so that the products meet the organization's objectives:
 - Satisfying customer requirements
 - Complying with regulations



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QUALITY MANAGEMENT SYSTEM (cont. 2)

- Example : Total quality management (TQM) – a system that
 - ❑ Is built around an effort to improve quality
 - ❑ Involves the entire organization
 - ❑ Ensures customer satisfaction
- ** an outdated quality management system
- Usually designed to meet industry/sector-specific ISO requirements / standards (permits certification);
 - o ISO standards = model to follow
 - o incorporates “best practices”



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QUALITY MANAGEMENT SYSTEM (cont. 3)

- Based on FDA / CFRs / QSRs / ISO standards, the QMS should include methods of :
 - ✓ Training & qualifying personnel
 - ✓ Controlling product design
 - ✓ Controlling documentation & records
 - ✓ Controlling purchasing
 - ✓ Identifying & tracing product at all production stages
 - ✓ Defining & controlling production & processes
 - ✓ Defining & controlling inspection / measuring / test equipment



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QUALITY MANAGEMENT SYSTEM (cont. 4)

- ✓ Validating processes
 - ✓ Accepting product
 - ✓ Controlling nonconforming product
 - ✓ Instituting corrective & preventative actions
 - ✓ Controlling labeling & packaging
 - ✓ Servicing production equipment
 - ✓ Using statistical techniques
- These items are evaluated for ISO certification



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QUALITY MANAGEMENT SYSTEM (cont. 5)

- ISO standards' operating principle :

PDCA Cycle :



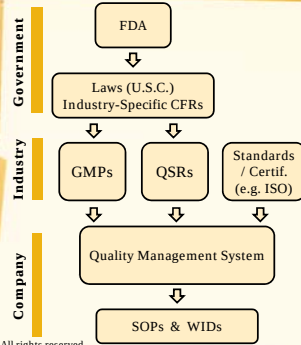
- **Plan** : establish objectives & make plans to achieve them
- **Do** : implement plans (do what you planned)
- **Check** : measure results (i.e. measure/monitor how actual achievements meet planned objectives)
- **Act** : correct / improve plans and how they are implemented



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THE “TRICKLE DOWN” EFFECT (cont.)

A company's set of Standard Operating Procedures and Work Instruction Documents is derived from its quality management system, and all laws & regulations, industry guidances, standards governing QMS's



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QMS vs. SOPs & WIDs

- Can think of:
 - Quality management system as the “rule book”
 - SOPs & WIDs as the “play book”



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ASSIGNMENT

- Select one of the following chapters of the Medical Device Quality Systems Manual at <http://www.fda.gov/cdrh/dsma/gmpman.html> :

< see list provided by instructor >



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ASSIGNMENT (cont.)

- Scenario :
 - ☐ You are the Quality Assurance Director at medical device company and responsible for new employee training on Quality Systems so that they can work in compliance with federal regulations
 - ☐ Identify critical points of information you must pass on to the new employees
- Write a **1 to 2-page “training guide”** summarizing important points (bullets) from selected chapter to share **next week**



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REVIEW FROM PREVIOUS WEEK

- What is a quality management system (QMS)?
- Name 3 topics that a QMS should cover.
- What are the 4 parts of the PDCA cycle?
- How do GMPs relate to the CFRs and to WIDs?



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PRODUCT QUALITY AND QUALITY MANAGEMENT SYSTEM (cont.)

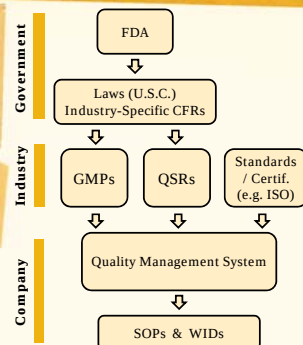


Step Ahead.

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THE “TRICKLE DOWN” EFFECT

- Review of previous discussion



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ASSIGNMENT

- Select one of the following chapters of the Medical Device Quality Systems Manual at <http://www.fda.gov/cdrh/dsma/gmpman.html> :

< see list provided by instructor >



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ASSIGNMENT (cont.)

- Scenario :
 - ☐ You are the Quality Assurance Director at medical device company and responsible for new employee training on Quality Systems so that they can work in compliance with federal regulations
 - ☐ Identify critical points of information you must pass on to the new employees
- Write a **1 to 2-page “training guide”** summarizing important points (bullets) from selected chapter to share



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QUALITY ISSUES – CASE STUDIES



Step Ahead.

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CASE STUDIES

- Helpful method of examining
 - Consequences of quality issues and noncompliance with FDA regulations / cGMPs
 - Poor manufacturing activities & decisions
 - FDA investigations
 - Product recalls
 - FDA enforcement of regulations
 - Continuous improvement – for a product, company, industry (best practices), and the FDA



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FDA WEB SITE

- <http://www.fda.gov/default.htm>
- Great source of information, such as
 - Current science & research
 - Regulations and laws
 - Product recalls & alerts
 - Product approvals !!
 - Criminal investigations
 - Consumer information
 - Manuals, regulatory publications, and reports



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PEANUT CORPORATION OF AMERICA – CASE STUDY

- *Salmonella* Typhimurium in PCA peanut products
- Class examination and discussion of
 - Investigational timeline
 - Outbreak and source identification
 - Regulatory actions
 - FDA inspection observations (Form 483)
 - Corrective / preventative actions
 - Legal, social, & ethical impacts



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PEANUT CORPORATION OF AMERICA – CASE STUDY (cont.)

- Purposes :
 - To examine PCA quality errors made and their consequences
 - To examine PCA's / FDA's / CDC's / various states' actions to the *Salmonella* Typhimurium contamination
 - To propose potential corrective / preventative actions for PCA
 - To examine, from an ethical and legal standpoint, the laws / regulations governing the biomanufacturing industry and how PCA chose to run its business



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ASSIGNMENT

For **next class**, read the following documents and prepare for class discussion (**75 points**) :

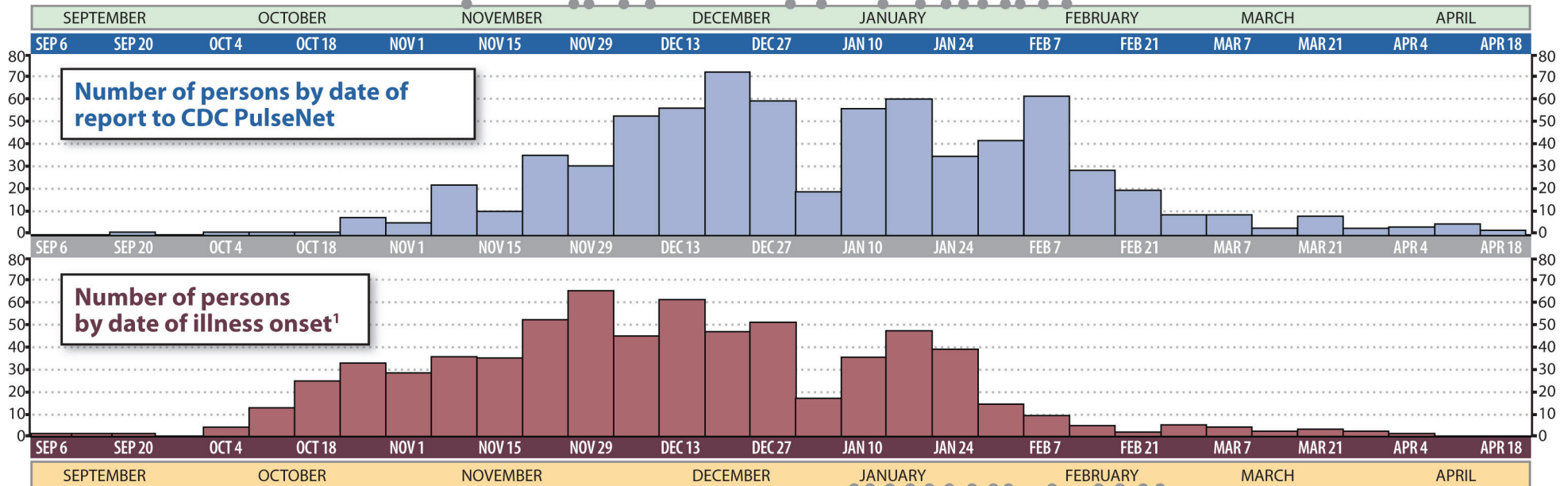
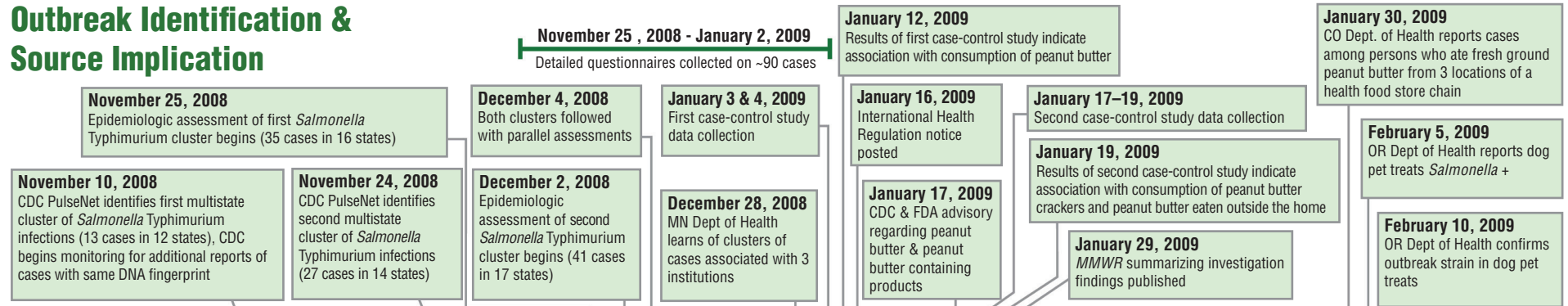
- *Timeline of Infections: Multistate Outbreak ...*
- *Salmonella Outbreak Investigations: Timeline for Reporting Cases*
- *Salmonella Strains Tables for Outbreak Related to Peanut Butter and Peanut Containing Products*
- *FDA Inspectional Observations Form 438 for Peanut Corp. of America Plainview, Blakely, GA inspection 01/09/2009 – 02/05/2009*
- *FDA Inspectional Observations Form 438 for Peanut Corp. of America Plainview, TX inspection 02/04/2009 – 02/26/2009*



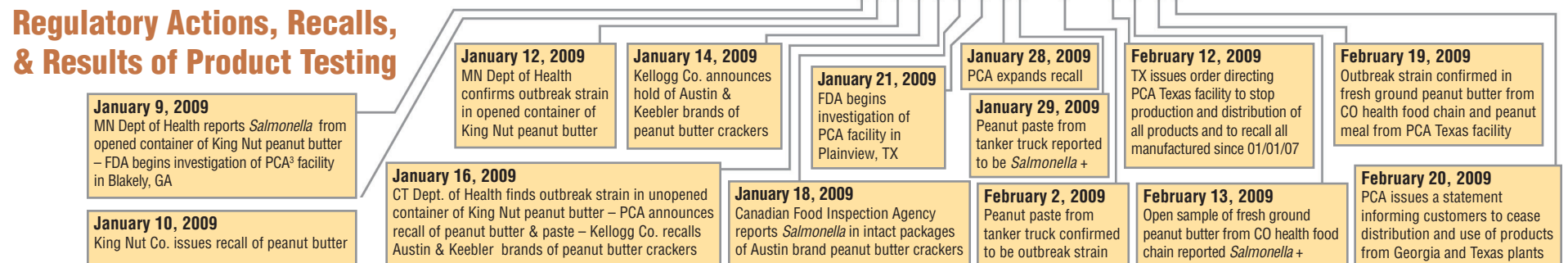
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Timeline of Infections: Multistate Outbreak of Salmonella Infections Associated with Peanut Butter and Peanut Butter-Containing Products — United States, 2008–2009

Outbreak Identification & Source Implication



Regulatory Actions, Recalls, & Results of Product Testing



¹Some illness onset dates have been estimated from other reported information

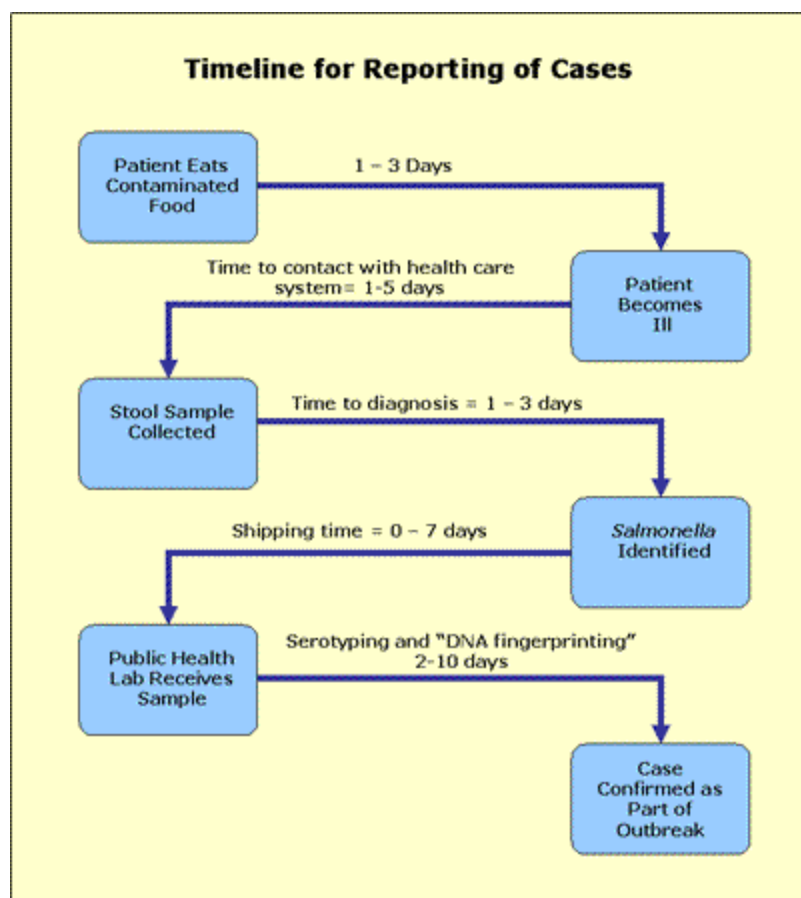
²There is an inherent delay between the date that an illness starts, and the date that the case is reported to public health authorities. It typically takes 2–3 weeks for *Salmonella* infections. That means that someone who got sick last week is very unlikely to have been reported yet, and someone who got sick three weeks ago may just be reported now.

³Peanut Corporation of America



Salmonella Outbreak Investigations: Timeline for Reporting Cases

To find cases in an outbreak of *Salmonella* infections, public health laboratories serotype the *Salmonella* bacteria and perform a kind of “DNA fingerprinting” on *Salmonella* laboratory samples. Investigators determine whether the “DNA fingerprint” pattern of *Salmonella* bacteria from one patient is the same as that from other patients in the outbreak and from the contaminated food. Bacteria with the same “DNA fingerprint” are likely to come from the same source. Public health officials conduct intensive investigations, including interviews with ill people, to determine if people whose infecting bacteria match by “DNA fingerprinting” are part of a common source outbreak.



A series of events occurs between the time a patient is infected and the time public health officials can determine that the patient is part of an outbreak. This means that there will be a delay between the start of illness and confirmation that a patient is part of an outbreak. Public health officials work hard to speed up the process as much as possible. The timeline is as follows:

<http://www.cdc.gov/salmonella/reportingtimeline.html>

1. **Incubation time:** The time from eating a contaminated food to the beginning of symptoms. For *Salmonella*, this is typically 1-3 days, sometimes longer.

2. **Time to contact with health care provider/doctor:** The time from the first symptom until the person seeks medical care, when a diarrhea sample is collected for laboratory testing. This time may be additional 1-5 days, sometimes longer.

3. **Time to diagnosis:** The time from when a person gives a sample to when *Salmonella* is obtained from it in a laboratory. This may be 1-3 days from the time the sample is received in the laboratory.

4. **Sample shipping time:** The time required to ship the *Salmonella* bacteria from the laboratory to the state public health authorities that will perform serotyping and “DNA fingerprinting”. This usually takes 0-7 days depending on transportation arrangements within a state and the distance between the clinical laboratory and the public health department. It should be noted that the diagnostic laboratories are not required by law to forward *Salmonella* isolates to the public health labs and not all diagnostic laboratories forward any isolates unless specifically requested.

5. **Time to serotyping and “DNA fingerprinting”:** The time required for the state public health authorities to serotype and to perform “DNA fingerprinting” on the *Salmonella* and compare it with the outbreak pattern. Serotyping may take up to 3 days. The “DNA fingerprinting” can be accomplished in 2 working days (24 hours). However, many public health laboratories have limited staff and space, and experience multiple emergencies at the same time. Thus, this process may take 1-10 days for both serotyping and “DNA fingerprinting” together.

The time from the beginning of the patient’s illness to the confirmation that he or she was part of an outbreak is typically about 2-3 weeks. Case counts in the midst of an outbreak investigation are therefore always preliminary and must be interpreted within this context.

Page last modified: June 24, 2008

Content Source: **National Center for Zoonotic, Vector-Borne, and Enteric Diseases (ZVED)**

Page Located on the Web at <http://www.cdc.gov/salmonella/reportingtimeline.html>

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Salmonella

[Salmonella](#) > [Salmonella Outbreak Investigations](#) > [Investigation Update: Outbreak of Salmonella Typhimurium Infections, 2008–2009](#) > [Salmonella Strains Tables for Outbreak Related to Peanut Butter and Peanut Containing Products](#)

Salmonella Strains Tables for Outbreak Related to Peanut Butter and Peanut Containing Products

The three tables below summarize the several different strains of *Salmonella* identified during the outbreak investigation related to peanut butter and peanut containing products in January, 2009. For more information on the PFGE process, see "[How the PFGE Process Works](#)".

Table 1: The outbreak strain† of *Salmonella* Typhimurium has been found in ill humans and in food samples during this outbreak investigation. These strains have been confirmed by CDC's [PulseNet](#).

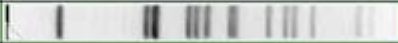
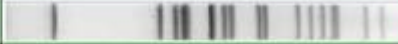
Location(s) of Sample	Salmonella Serotype	DNA Fingerprint ID (PFGE Pattern*)	PFGE Image	Source in Which Strain was Found
Multiple States	Typhimurium	JPXX01.1818		Ill humans
Multiple States	Typhimurium	JPXX01.1825		Ill humans
Multiple States	Typhimurium	JPXX01.0459		Ill humans
Canada	Typhimurium	JPXX01.1818		Austin brand Toasty Peanut Butter Crackers purchased in the United States
Connecticut	Typhimurium	JPXX01.1825		Unopened container of King Nut brand creamy peanut butter
Connecticut	Typhimurium	JPXX01.0459		Unopened container of King Nut brand peanut butter
Georgia	Typhimurium	JPXX01.1818		King Nut brand crunchy peanut butter
Michigan	Typhimurium	JPXX01.0459		Closed container of King Nut brand peanut butter
Michigan	Typhimurium	JPXX01.0459		Unopened container of King Nut brand creamy peanut butter
Minnesota	Typhimurium	JPXX01.1818		Open container of King Nut brand creamy peanut butter
Minnesota	Typhimurium	JPXX01.1825		Open container of King Nut brand creamy peanut butter
North Carolina	Typhimurium	JPXX01.0459		Retained PCA peanut paste sample
Ohio	Typhimurium	JPXX01.1818		Opened container of King Nut brand creamy peanut butter

[Click on image for larger map view.](#)

†These bacteria are grouped as a single outbreak strain even though they have slightly different DNA fingerprints (red rectangle). They are indistinguishable by all other laboratory tests, and they are part of the same outbreak. For example, *Salmonella* Typhimurium bacteria with these different patterns collected from sick people during the outbreak were indistinguishable by a different method used by PulseNet, called multi locus variable number tandem repeat analysis (MLVA). MLVA is a method used for the genetic analysis of particular microorganisms, such as bacteria like *Salmonella*. It is one of the new tools of forensic microbiology.

* standardized molecular subtyping (or "DNA fingerprinting") of bacteria by pulsed-field gel electrophoresis (PFGE)

Table 2: *Salmonella* strains of other serotypes than Typhimurium have been found in food and in environmental samples during this outbreak investigation. These strains have been confirmed by CDC's PulseNet ([link to PulseNet](#)) and are NOT associated with an increase in human illness.

Location of Sample Origination	Other <i>Salmonella</i> Serotypes	DNA Fingerprint ID (PFGE Pattern *)	PFGE Image	Source in Which Strain was Found
Georgia	Mbandaka	TDRX01.0011		PCA plant in Blakely, Georgia - Floor crack
Georgia	Senftenberg	JMPX01.0089		PCA plant in Blakely, Georgia - Floor crack
Georgia	Tennessee	JNXX01.0011		unopened container of King Nut brand peanut butter
Minnesota	Tennessee	JNXX01.0026		unopened container of King Nut brand peanut butter

[Click on image for larger map view.](#)

Table 3: These *Salmonella* strains were reported by the company to have been isolated from the Peanut Corporation of America's Blakely, Georgia production plant. DNA fingerprinting (PFGE) results are not available for these strains. *Salmonella* serotype Anatum has not been associated with a recent increase in human illness. Because DNA fingerprinting (PFGE) patterns are not available, we are unable to determine if the Typhimurium serotype is the outbreak strain or not, and if it is not, whether it is associated with an increase in human illness.

Location of Sample Origination	Other <i>Salmonella</i> Serotypes	DNA Fingerprint ID (PFGE Pattern *)	PFGE Image	Source in Which Strain was Found
Georgia	Typhimurium	not determined	not available	peanut paste
Georgia	Anatum	not determined	not available	peanut butter, peanut meal and peanut granules

[Click on image for larger map view.](#)

* standardized molecular subtyping (or "DNA fingerprinting") of bacteria by pulsed-field gel electrophoresis (PFGE)

Page last modified: January 29, 2009

Content Source: [National Center for Zoonotic, Vector-Borne, and Enteric Diseases](#)

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Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333, USA
800-CDC-INFO (800-232-4636) TTY: (888) 232-6348, 24 Hours/Every Day - cdcinfo@cdc.gov (TTY)

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DISTRICT ADDRESS AND PHONE NUMBER 4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax: (214) 253-5314 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 02/04/2009 - 02/26/2009* FEI NUMBER 3005090079	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Roy V. Creasy, Jr., Trustee, US Bankruptcy Court for the Western District of VA		
FIRM NAME Peanut Corporation of America (PCA)	STREET ADDRESS 3601 North I-27	
CITY, STATE, ZIP CODE, COUNTRY Plainview, TX 79073	TYPE ESTABLISHMENT INSPECTED Peanut Processor/Manufacturer	
This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.		
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:		
OBSERVATION 1		
Effective measures are not being taken to exclude pests from the processing areas and protect against the contamination of food on the premises by pests. Specifically, on 2/11-12/09, the following signs of rodent activity were observed.		
a) In a crawl like space between a false ceiling and the primary roof of the building other signs of rodent activity were observed. The false ceiling covered the kitchen/old lab rooms and the whole and split blanching processing areas. The ducting for the redskin removal (b) (4) (referred to as [REDACTED]) system was located in this area. The end cap of one of these ducts was open providing a passageway for rodents to access the blanching equipment below. Approximately 6 dead mice were found in this false ceiling area; b) A dead mouse stuck to a glue trap located at the wall/floor junction in the room off the west end of the kitchen/old lab rooms. The mouse appeared to have died recently; c) What appeared to be rodent excreta pellets (REP) were observed on the countertops of the south most room of the kitchen/old lab area; d) Unprotected possible rodent/pests entryways were observed at the ceiling/wall junction along the south and west walls next to the southwest corner of the mezzanine room; e) What appeared to be REPs too numerous to count were observed in the cabinet under the sink in the south most kitchen/old lab room; f) In the cabinet north of the dishwasher in the north most room of the kitchen/old lab rooms I counted approximately 27 REPs; g) More, what appeared to be REPs were observed in the cabinets under the bottom drawer in the south most room of the kitchen/old lab rooms; in an area 1" X 2" behind the bottom drawer in this cabinet I counted approximately 30 rodent excreta pellets;		
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Toby H. Hill, Investigator <i>Toby H. Hill</i> Elvia J. Cervantes, Investigator <i>Elvia J. Cervantes</i> Akbar Javed, Investigator <i>Akbar Javed</i> Paul E. Frazier, Investigator <i>Paul E. Frazier</i>	DATE ISSUED 02/26/2009
FORM FDA 483 (04/03)		
PREVIOUS EDITION OBSOLETE		
INSPECTIONAL OBSERVATIONS		
PAGE 1 OF 2 PAGES		

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Roy V. Creasy, Jr., Trustee, US Bankruptcy Court for the Western District of VA		
FIRM NAME Peanut Corporation of America (PCA)	STREET ADDRESS 3601 North I-27	
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h) Another dead mouse was found just outside the south most doorway of the kitchen/old lab rooms at the east corner of the corridor leading from the mezzanine area into the kitchen/old lab rooms. This mouse also appeared to have recently died; i) What appeared to be a bird's nest was observed in the wall/ceiling metal support beam at southwest corner of the mezzanine area.		
OBSERVATION 2 Failure to operate fans and other air-blowing equipment in a manner that minimizes the potential for contaminating food, food-contact surfaces, and food-packaging materials. Specifically, The (b) (4) filters (similar to the metal used on a cooking grill) of the air-makeup system were littered with feathers, lint, dust, and miscellaneous foreign debris. This observation was made on 2/11/09. In this room where the air makeup equipment is housed, a strong negative pressure is created. This negative pressure had drawn redskins and other debris from the false ceiling area into the room. The false ceiling is also where significant signs of rodent activity were observed. A bed of redskins approximately 1" deep were accumulated on the floor of the air makeup room in the northwest corner. The air-makeup system is designed to maintain a positive air pressure in the plant's peanut processing areas to prevent air infiltration from the raw peanut pre-clean processing areas. There was nothing to prevent the redskin and other foreign debris from being drawn into the air-makeup system and carried into the non-raw peanut processing environment via air inflow. The room that houses the air-makeup system is located off the northwest corner of the mezzanine in the upstairs area.		
OBSERVATION 3 Failure to clean food-contact surfaces as frequently as necessary to protect against contamination of food. Specifically,		
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Toby H. Hill, Investigator <i>THH</i> Elvia J. Cervantes, Investigator <i>ef</i> Akbar Javed, Investigator <i>AJ</i> Paul E Frazier, Investigator	DATE ISSUED 02/26/2009
FORM FDA 483 (04/03) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 2 OF 7 PAGES		

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
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FIRM NAME Peanut Corporation of America (PCA)		STREET ADDRESS 3601 North I-27	
CITY, STATE, ZIP CODE COUNTRY Plainview, TX 79073		TYPE ESTABLISHMENT INSPECTED Peanut Processor/Manufacturer	
On 2/9/09, at the following equipment food contact surface sites, an appreciable buildup of peanut fines, meal, chunks, or paste (some gooey other solidified) was observed: Granulation Room Sites a) Dump station discharge chute for elevator # (b) (4) located on east wall of granulation; b) Intake chute of (b) (4) vibrator shaker located in the granulation room; c) Discharge chute of peanut meal bin in granulation room; d) Inside surface of bin feeding grinder at the discharge chute gate; Processing Area e) Inside rear surface of south feed for (b) (4) (camera sorting machine aka electric eyes) machine; nozzle # (b) (4) f) Inside rear surface of middle feed for (b) (4) (camera sorting machine aka electric eyes) machine; nozzle # (b) (4) g) Inside rear surface of north most feed for (b) (4) (camera sorting machine aka electric eyes) machine; identified as nozzle # (b) (4) h) Inside rear surface of south most feed for (b) (4) (camera sorting machine aka electric eyes) machine; identified as nozzle # (b) (4) i) West most cylindrical (approximately (b) (4)" in diameter) roller of split blanching machine located at southeast corner of blanching processing area; top center of roller sponged; Oil Roasting Processing Area j) Accumulation of roasted peanut debris on oil roasters cooling tunnel conveyor belt; k) Southwest corner of hand-sorting conveyor belt beyond oil roaster's cooling tunnel; peanut debris collect at edge of belt underneath a 2" wide protective strip; l) Inside surface of oil roaster's pack-off chute; m) Inside surface of peanut meal tote transfer funnel; accumulation of meal on chute rim and throughout the inside surfaces of the funnel; n) Inside surface at southwest corner of gravity table discharge chute; gravity table is located diagonally off the northeast corner of oven roaster;			
SEE REVERSE OF THIS PAGE		EMPLOYEE(S) SIGNATURE Toby H. Hill, Investigator <i>T.H.H.</i> Elvia J. Cervantes, Investigator <i>E.J.C.</i> Akbar Javed, Investigator <i>A.J.</i> Paul E. Frazier, Investigator	
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CITY, STATE, ZIP CODE, COUNTRY Plainview, TX 79073		TYPE ESTABLISHMENT INSPECTED Peanut Processor/Manufacturer	
o) Inside wall at the southeast corner under lid of whole peanut blancher # (b) (4) p) Inside west wall of the second section from the middle of whole peanut blancher # (b) (4) q) Top stair plate (peanuts fall down as bin fills) inside east most bin feeding split blancher; peanut debris accumulated on corners of stair; r) Split blancher discharge chute that dumps into vibrating conveyor; Pre-clean Processing Area s) 90 degree turn of vibrating conveyor leading to elevator that feeds de-stoner holding bin; peanut debris accumulated in corners and jagged surfaces.			
OBSERVATION 4 Failure to maintain buildings and physical facilities in repair sufficient to prevent food from becoming adulterated. Specifically, Roof leaks where rain water was observed dripping into the plant's peanut processing areas were observed at the following locations: a) Roof leaking in pre-clean area above the space between the gravity shaker and raw peanut tote dump station; leaking water was observed running down roof support pole on east side of raw peanut tote dump station; b) Roof leaking at overhead hanging doorway leading from pre-clean area to oven roasting area; the dripping water was landing on the top side of the opened (spooled) overhead hanging door; drip splatter could potentially contaminate the conveyor belt running near the ceiling from the pre-clean bins to the oven; c) Roof leaking in the hallway diagonal to the northeast of the doorway leading to oil roasting and granulation processing areas; d) Roof leaking in work in process (WIP) area and pooling on the floor between organic and oil-stock storage areas approximately 20' off oil-stock storage area's southwest door; e) Roof leaking in WIP area and pooling on the floor below between storage areas identified as "Q" and "R" approximately 1' west of "Q"; f) Roof leaking in (WIP) area and pooling on the floor below between storage areas identified as "Q"			
SEE REVERSE OF THIS PAGE		EMPLOYEE(S) SIGNATURE Toby H. Hill, Investigator <i>THH</i> Elvia J. Cervantes, Investigator <i>EC</i> Akbar Javed, Investigator <i>AJ</i> Paul E. Frazier, Investigator	
		DATE ISSUED 02/26/2009	
FORM FDA 483 (04/03) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 4 OF 7 PAGES			

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DISTRICT ADDRESS AND PHONE NUMBER 4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax: (214) 253-5314 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 02/04/2009 - 02/26/2009* FEI NUMBER 3005090079
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Roy V. Creasy, Jr., Trustee, US Bankruptcy Court for the Western District of VA		
FIRM NAME Peanut Corporation of America (PCA)	STREET ADDRESS 3601 North I-27	
CITY, STATE, ZIP CODE, COUNTRY Plainview, TX 79073	TYPE ESTABLISHMENT INSPECTED Peanut Processor/Manufacturer	
and "R" approximately 1' east of "R"; g) Potential roof leak in northeast corner of north most room in the kitchen/old lab room; puddle of water observed on floor of room. Paint chipping and peeling observed on ceiling over the dumping equipment located at northwest corner of the receiving/pre-clean area.		
OBSERVATION 5 Failure to clean non-food-contact surfaces of equipment as frequently as necessary to protect against contamination. Specifically, On 2/9/09, at the following equipment non food-contact surface sites, an appreciable buildup of peanut fines, meal, chunks, or paste (some gooey other solidified) was observed: a) Drive chain upper sprocket of cup elevator # (b) (4) located directly over moving elevator cups (Processing Area); b) Drive chain sprocket of cup elevator # (b) (4) in granulation room; site located next to moving elevator cups (Processing Area) c) Elevator in granulation room at southwest corner of granulation room; accumulation on northeast inside wall of sprocket directly next to moving elevator cups (Granulation Area); d) Drive chain sprocket of elevator # (b) (4) located north of the blanching area beside the (b) (4) sorting machine; peanut debris on sprocket was directly over elevator cups (Processing Area). Additionally, the (b) (4) Mode (b) (4) Vacuum-Packaging Machine was not cleaned (b) (4) both externally and internally as prescribed in the machine's operation manual. This piece of equipment was used to vacuum seal both repackaged product from the Blakely, GA facility and products manufactured at the Plainview, TX facility.		
OBSERVATION 6 Failure to dispose of adulterated food in a manner which protects against the contamination of other food. Specifically,		
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Toby H. Hill, Investigator <i>THH</i> Elvia J. Cervantes, Investigator <i>ef</i> Akbar Javed, Investigator <i>AJ</i> Paul E. Frazier, Investigator	DATE ISSUED 02/26/2009

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On 2/4/09, when conducting our initial walkthrough of the facility, various lots of recalled peanut product, specified as originating from the Blakely, GA plant, were palletized and placed among all other finished product lots designated as outgoing shipments. These products were not appropriately segregated, quarantined, or placarded as "on hold" or "defective". The potential for inadvertent shipment existed.																							
OBSERVATION 7 Devices and fixtures are not designed and constructed to protect against recontamination of clean, sanitized hands. Specifically, The hot water foot-operated valve of the hand-washing sink at the primary entrance to the food processing area was not shutting off after use. To shut off the valve, the foot pedal had to be jiggled or pulled upward.																							
OBSERVATION 8 There is no assurance that raw materials which are susceptible to contamination with aflatoxin or other natural toxins comply with current FDA standards before being incorporated into food. Specifically, Upon review of records (aflatoxin COAs with incoming lot and/or laboratory peanut received logbook) specific to positive aflatoxin test results for the lots listed below, no records were found with the positive aflatoxin COAs to verify that the raw peanut lots initially testing positive for aflatoxin had been reconditioned and later tested and confirmed to be below FDA aflatoxin standards and action levels. These said lots of raw peanuts were processed into finished peanut products that were sold for human consumption. <table style="width: 100%; border-collapse: collapse; margin-top: 20px;"> <thead> <tr> <th style="text-align: center;">PCA Raw Peanut Lot #</th> <th style="text-align: center;">Date Received</th> <th style="text-align: center;">PCA Raw Peanut Lot #</th> <th style="text-align: center;">Date Received</th> <th style="text-align: center;">PCA Raw Peanut Lot #</th> <th style="text-align: center;">Date Received</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">2061</td> <td style="text-align: center;">11-12-08</td> <td style="text-align: center;">1937</td> <td style="text-align: center;">06-10-08</td> <td style="text-align: center;">2008</td> <td style="text-align: center;">09-04-08</td> </tr> <tr> <td style="text-align: center;">2043</td> <td style="text-align: center;">10-20-08</td> <td style="text-align: center;">1919</td> <td style="text-align: center;">05-21-08</td> <td style="text-align: center;">2009</td> <td style="text-align: center;">09-04-08</td> </tr> </tbody> </table>						PCA Raw Peanut Lot #	Date Received	PCA Raw Peanut Lot #	Date Received	PCA Raw Peanut Lot #	Date Received	2061	11-12-08	1937	06-10-08	2008	09-04-08	2043	10-20-08	1919	05-21-08	2009	09-04-08
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER

4040 North Central Expressway, Suite 300
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Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

02/04/2009 - 02/26/2009*

FEI NUMBER

3005090079

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Roy V. Creasy, Jr., Trustee, US Bankruptcy Court for the Western District of VA

FIRM NAME

Peanut Corporation of America (PCA)

STREET ADDRESS

3601 North I-27

CITY, STATE, ZIP CODE, COUNTRY

Plainview, TX 79073

TYPE ESTABLISHMENT INSPECTED

Peanut Processor/Manufacturer

2026	09-26-08	1892	04-10-08	2011	09-06-08
2006	09-04-08	1899	04-25-08	1752	09-19-07
1985	08-07-08	1877	04-01-08	1753	09-20-07
1967	07-18-08	1879	04-02-08	1758	09-24-07
1959	07-18-08	1880	04-30-08	1733	09-11-07
1961	07-09-08	1883	04-04-08	1744	09-14-07
1963	07-11-08	1874	03-26-08	2013	09-10-08
1944	06-18-08	1852	02-29-08	2049	10-28-08
1932	06-20-08	1826	01-23-08	2005	09-03-08
1949	06-26-08	1956	07-02-08	2007	09-04-08

*** DATES OF INSPECTION:**

02/04/2009(Wed), 02/05/2009(Thu), 02/09/2009(Mon), 02/10/2009(Tue), 02/11/2009(Wed), 02/12/2009(Thu), 02/13/2009(Fri), 02/14/2009(Sat), 02/26/2009(Thu)

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OF THIS PAGE**

EMPLOYEE(S) SIGNATURE

Toby H. Hill, Investigator *Toby H. Hill*
Elvia J. Cervantes, Investigator *Elvia J. Cervantes*
Akbar Javed, Investigator *Akbar Javed*
Paul E. Frazier, Investigator

DATE ISSUED

02/26/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DISTRICT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax: (404) 253-1202 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 01/09/2009 - 02/05/2009*
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Sammy L. Lightsey, Plant Operations Manager		FIR NUMBER 1036857
FIRM NAME Peanut Corporation Of America	STREET ADDRESS 14075 Magnolia St	
CITY, STATE, ZIP CODE, COUNTRY Blakely, GA 39623-1881	TYPE ESTABLISHMENT INSPECTED Peanut Roaster/Peanut Butter and Paste Manufacturer	
This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.		
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:		
OBSERVATION 1		
Failure to manufacture foods under conditions and controls necessary to minimize the potential for growth of microorganisms and contamination.		
Specifically, the firm's private laboratory microbiological testing found the following:		
Salmonella Typhimurium: Peanut paste under lot # 8278 was found contaminated with Salmonella Typhimurium by private laboratory testing conducted by the firm. After the firm retested the product and received a negative status, the firm shipped (b)(4) of the product in interstate commerce. Additionally, this peanut paste was manufactured on 9/26/08 from (b)(4) lb. totes of roasted peanuts received on 9/25/08. The lots of roasted peanuts received on 9/25/08 were also used to produce the following products that were also shipped in interstate commerce: (b)(4) totes were used to manufacture (b)(4) peanut butter under lot # 8276; one tote was used to manufacture peanut butter for (b)(4) under lot # 8277 and (b)(4) (b)(4) under lot # 8277.		
Creamy Stabilized Peanut Butter, manufactured on 8/11/08 (producing both lots #8220 and #8224), tested positive for Salmonella by (b)(4) received the PCA sample for these lots on 8/12/08 and issued a report of positive results on 8/27/08. The isolate from this sample was sent to (b)(4) and was confirmed as Salmonella Anatum. The firm then had this lot retested at both (b)(4) and (b)(4) with both labs finding negative results. However, PCA had already shipped into interstate commerce the following: An 8/15/08 shipment of (b)(4) lbs. (invoice #0107013) creamy stabilized peanut butter under lot #8220 went to (b)(4)		
Lot #8268, Peanut Meal and Medium Chopped Peanuts, manufactured on 9/24/08, tested positive for Salmonella by (b)(4) (b)(4) received this PCA sample on 9/25/08 and issued a report of the positive results on 10/6/08. This sample was confirmed by (b)(4) as Salmonella Anatum. However, PCA had already shipped into interstate commerce the following lots before lab results were known: On 9/24/08 a shipment of (b)(4) lbs. (invoice #302583) of peanut meal under		
AMENDED		
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Janet B Gray, Investigator Darcy E. Brillhart, Microbiologist Sandra I. Gaul, Investigator Robert P. Neligan, Investigator Lesley K. Satterwhite, Microbiologist Theresa L. Stewart, Investigator	DATE ISSUED 02/05/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
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FIRM NAME Peanut Corporation Of America	STREET ADDRESS 14075 Magnolia St	
CITY, STATE, ZIP CODE, COUNTRY Blakely, GA 39823-1881	TYPE ESTABLISHMENT INSPECTED Peanut Roaster/Peanut Butter and Paste Manufacturer	
lot#8268 to (b)(4) On 9/25/08 a shipment of (b)(4) lbs. (invoice #1057536) medium chopped granules under lot #8268 went to (b)(4) Lot #8168, Medium Chopped Peanuts and Peanut Meal, manufactured on 6/16/08 tested positive for Salmonella by (b)(4). (b)(4) received the PCA sample for this lot on 6/17/08 and issued a report with the positive results on 6/23/08. The firm resubmitted a sample to (b)(4) on 6/21/08 with a report issued on 6/23/08 as negative. This firm had shipped the following product into interstate commerce prior to receiving the sample results on 6/23/08: A shipment on 6/18/08 of (b)(4) lbs. (invoice #662837) of peanut meal under lot #8169 went to (b)(4). On 6/20/08 this firm shipped approximately (b)(4) lbs. (invoice #61108) of peanut meal under lot #8169 to (b)(4). Lot #8161A, Small Chopped Peanuts, manufactured on 6/9/08, testing positive for Salmonella by (b)(4). (b)(4) received the PCA sample for this lot on 6/10/08 and issued a report with the positive results on 6/16/08. This firm resubmitted a sample to (b)(4) on 6/18/08 which was found to be negative per a report issued 6/21/08. PCA had already shipped product from lot# 8161A in interstate commerce before the positive results were known on 6/16/08. On 6/10/08 a shipment of approximately (b)(4) lbs. (invoice #MRB6408) of small chopped peanuts under lot #8161 went to (b)(4). On 6/13/08 a shipment of (b)(4) lbs. (invoice #11114-3) of small chopped peanuts under lot #8161 went to (b)(4). Lot #8028, Peanut Paste, manufactured on 1/25/08 tested positive for Salmonella by (b)(4). (b)(4) received the PCA sample for this lot on 1/26/08. However, also on 1/26/08 PCA shipped (b)(4) lbs. (invoice #4503605302) of peanut paste under lot #8028 to (b)(4). Salmonella (no strain identified): Medium Chopped Granules manufactured on January 24, 2008 under lot # 8024 tested positive for Salmonella by a private laboratory. After the firm retested the product and received a negative status, the product was shipped in interstate commerce. Lot # 7206, Small Chopped Peanut Granules, manufactured on or around 7/26/07, tested positive for Salmonella by (b)(4). (b)(4) received the PCA sample on 7/26/07 and issued a report of the positive results on 7/30/07. PCA had already shipped approximately (b)(4) lbs. (invoice #736434-001) of small chopped peanuts under lot #7206 to (b)(4). (b)(4) on 7/27/07 before the lab results were obtained. Lot #7192A, Small Chopped Peanuts, manufactured on 7/11/07, tested positive for Salmonella by (b)(4). (b)(4) received the PCA sample for this lot on 7/12/07 and issued a report of the positive Salmonella results on 7/18/07. Two more samples of this lot were submitted to both (b)(4) and (b)(4). The (b)(4) follow-up sample of this lot submitted on 7/18/07 was classified negative on 7/19/07. The (b)(4) follow-up sample of this lot		
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	RPN	
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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DISTRICT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax: (404) 253-1202 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 01/09/2009 - 02/05/2009*
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FIRM NAME Peanut Corporation Of America	STREET ADDRESS 14075 Magnolia St	
CITY, STATE, ZIP CODE, COUNTRY Blakely, GA 39823-1881	TYPE ESTABLISHMENT INSPECTED Peanut Roaster/Peanut Butter and Paste Manufacturer	
submitted on 7/18/07 was classified as positive for Salmonella. Records show that PCA shipped product from this lot prior to receiving the analytical results on 7/18/07. On 7/12/07 a shipment of approximately (b)(4) lbs. (invoice #LALIT70507) of small chopped peanuts under lot #7192 went to (b)(4). Also, on 7/12/07 a shipment of (b)(4) lbs. (invoice #732153-001) of small chopped peanuts under lot #7192 went to (b)(4). Lot #7190B, Medium Chopped Peanuts, manufactured on 7/9/07, tested positive for Salmonella by (b)(4). (b)(4) received two PCA samples for lot #7190B on 7/10/07 and 7/12/07. Both samples were positive with the lab reports issued on 7/16/07 and 7/18/07 respectively. The following shipments were released into interstate commerce before the final lab results were obtained: On 7/11/07 a (b)(4) lb. shipment of medium chopped peanuts (invoice #100986) under lot #7190 went to (b)(4). On 7/12/07 a (b)(4) lb shipment of medium chopped peanuts (invoice #18049-30) under lot #7190 went to (b)(4). On 7/13/07 a shipment of (b)(4) lbs of medium chopped peanuts (invoice #31810) under lot #7190 went to (b)(4) and on 7/13/07 a (b)(4) lb shipment of medium chopped peanuts (invoice #759) under lot #7190 went to (b)(4). Additionally, the firm made the following shipments on or after the positive Salmonella results were obtained: On 7/18/07 a shipment of (b)(4) lbs. of medium chopped peanuts (invoice #21479) under lot #7190 went to (b)(4) and on 7/24/07 a shipment of approximately (b)(4) lbs. of medium chopped peanuts (invoice #10872-2) under lot #7190 went to (b)(4). Lot # 7190 B19-JR, Oil-Roasted Salted Jumbo Peanuts (b)(4) manufactured on 7/9/07 tested positive for Salmonella by (b)(4). (b)(4) received the PCA sample for this lot on 7/10/07 and issued a report of the positive results on 7/16/07. On 7/12/07 PCA submitted a second sample to (b)(4) of the same lot (#7190 B19-JR) and received a negative status for Salmonella on 7/16/07. The following shipments were released by PCA into interstate commerce before final lab results were known: A 7/10/07 shipment of (b)(4) lbs. (invoice #12131) oil roasted salted jumbo peanuts under lot #7190 went to (b)(4). A 7/12/07 shipment of (b)(4) lbs. (invoice #213157) oil roasted salted jumbo peanuts under lot #7190 went to (b)(4). A 7/12/07 shipment of approximately (b)(4) lbs. (invoice #213158) oil roasted salted jumbo peanuts under lot #7190 went to (b)(4). A 7/13/07 shipment of approximately (b)(4) lbs. (invoice #11463) oil roasted salted jumbo peanuts under lot #7190 went to (b)(4). Lot # 7157 Small Chopped Peanut Granules, manufactured on 6/7/07, tested positive for Salmonella by (b)(4). (b)(4) received the PCA sample on 6/7/07 and issued a report of the positive results on 6/13/07. However, PCA had already shipped (b)(4) lbs (invoice # 721676-001) of small chopped peanuts under lot #7157 to (b)(4) on 6/7/07 before the lab results were obtained.		
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FORM FDA 483 (04/03) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 3 OF 8 PAGES		

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FIRM NAME Peanut Corporation Of America	STREET ADDRESS 14075 Magnolia St	
CITY, STATE, ZIP CODE, COUNTRY Blakely, GA 39823-1881	TYPE ESTABLISHMENT INSPECTED Peanut Roaster/Peanut Butter and Paste Manufacturer	
OBSERVATION 3		
Failure to perform mechanical manufacturing steps so as to protect food against contamination.		
Specifically, this firm recognizes the roasting step as the control point for eliminating microbiological contamination in raw materials. However, this firm has not established the effectiveness of the temperature, volume, or belt speed specific to this roaster to assure it is adequate as a kill step for pathogenic bacteria. Additionally, the firm's records of the roaster's temperature are inadequate in that dates have been left off of several circular recording charts. For example, in August 2008 three days of recording charts were not dated; in September 2008 two recording charts were not dated; in October 2008 six charts were not dated; in November 2008 24 days of recording charts were not dated; and in December 2008 and January 2009 no temperature recording charts were dated.		
OBSERVATION 4		
Failure to store finished food under conditions that would protect against microbial contamination.		
Specifically, on 1/9/09 (b)(4) lb. totes of raw peanuts were observed to be stored directly next to (b)(4) lb. totes of finished, roasted peanuts in the firm's production/packaging room. The totes of finished product included the following: Honey Roasted Peanuts under lot # 8339; Dry Roasted Peanuts under lot # 9002; Peanut Meal under lot # 9005; and Dark Roasted Peanuts (paste line) under lot # 9009. The (b)(4) lb. totes of raw peanuts were all under lot # 40147. On 1/26/09, an additional (b)(4) lb. tote of raw peanuts under lot # 16195-08 was observed to be stored in the production/packaging room along with the same lots of finished goods listed above. It was visually difficult to discern which of these totes were finished products and which were raw products.		
The above totes of finished product were stored within 15 feet of a floor crack where an environmental swab was collected on 1/10/09 and found positive for Salmonella Senftenberg.		
Also, one environmental swab collected on 1/10/09 from the finished product cooler floor (beside the south wall) was found positive for Salmonella Mbandaka. The swab location was within 3 feet of pallets of finished product.		
Mold was observed growing on the ceiling and walls in the firm's cooler used for finished product storage. In addition, water stains were observed running down from the cooling unit fans in the cooler. On 1/10/09, pallets of finished product were stored directly beneath this unit.		
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FIRM NAME Peanut Corporation Of America	STREET ADDRESS 14075 Magnolia St	
CITY, STATE, ZIP CODE, COUNTRY Blakely, GA 39823-1001	TYPE ESTABLISHMENT INSPECTED Peanut Roaster/Peanut Butter and Paste Manufacturer	
OBSERVATION 5		
The plant is not constructed in such a manner as to allow ceilings to be kept in good repair. Specifically, on 1/10/09 there were open gaps observed as large as 1/2" x 2 1/2 feet at the air conditioner intakes located in the roof of the firm. Water stains were also observed on the ceiling around the air conditioner intakes. Additionally, there were water stains and streaks located on the edges of the skylights where rain water has been leaking into the firm. All of these openings were located in the production/packaging room. Totes of finished, roasted product and a roasted nut packaging line are located directly underneath these areas.		
OBSERVATION 6		
The design of equipment and utensils fails to preclude the adulteration of food with contaminants. Specifically, a felt material is present on the final roller at the roaster's discharge. This material cannot be adequately cleaned or sanitized. Also, the rework kettle in the peanut butter room had openings (2" x 3") at the top exposing the peanut butter to open conditions.		
OBSERVATION 7		
Proper precautions to protect food and food-contact surfaces from contamination with microorganisms cannot be taken because of deficiencies in plant construction and design. Specifically, the firm is not equipped with a ventilation system to prevent cross-contamination by providing a negative room pressure in the facility. A negative room pressure would direct air flow from the finished product areas into the negative pressure room (raw peanut receipt and staging area), ensuring that contaminated air does not escape to other parts of the facility. The raw peanut receipt/staging area, peanut paste tanker line, peanut roasters, and the peanut granule line are housed in the same open room with no segregation. In addition, the honey roasted peanuts, considered to be finished product, are filled into		
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SEE REVERSE OF THIS PAGE	EMPLOYER(S) SIGNATURE Janet B. Gray, Investigator Darcy E. Brillhart, Microbiologist Sandra I. Gaul, Investigator Robert P. Neligan, Investigator Lesley K. Satterwhite, Microbiologist Theresa L. Stewart, Investigator	DATE ISSUED 02/05/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		
DISTRICT ADDRESS AND PHONE NUMBER 60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax: (404) 253-1202 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 01/09/2009 - 02/05/2009* FEI NUMBER 1036857
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Sammy L. Lightsey, Plant Operations Manager		
FIRM NAME Peanut Corporation Of America	STREET ADDRESS 14075 Magnolia St	
CITY, STATE, ZIP CODE, COUNTRY Blakely, GA 39823-1881	TYPE ESTABLISHMENT INSPECTED Peanut Roaster/Peanut Butter and Paste Manufacturer	
boxes utilizing a hopper in the "kitchen area", this location is where the raw peanuts enter the roaster, again no segregation. Raw peanuts are filled into boxes utilizing a hopper located in the Production/Packaging room. This hopper is positioned above the packaging line for the small party packs of roasted peanuts. There is no segregation of raw and finished product in this area.		
OBSERVATION 8 Devices and fixtures are not designed and constructed to protect against recontamination of clean, sanitized hands. Specifically, the sink located in the peanut butter room is used interchangeably as a point for cleaning hands and utensils and for washing out mops.		
OBSERVATION 9 Failure to conduct cleaning and sanitizing operations for utensils and equipment in a manner that protects against contamination of food. Specifically, on 1/12/09 a build-up of product residue was observed on grinders, hoppers, and support beams on the peanut paste tanker line. Also, pieces of the yellow and black caution sign on the (b)(4) mill were flaking off into the catch pan for product under the mill. On 1/9/09, the dry ingredient staging area above the peanut butter room was dirty with a heavy build-up of different powdery ingredients on all exposed surfaces. This is an open area of the ceiling located directly above the dry ingredient hopper and ribbon mixer. On 1/9/09, a mesh-type conveyor was observed to be stored in the firm's equipment/utensil wash room, which was used as a catch-all storage area for buckets, stainless steel pipes, removable pumps, removable Y-spouts, and floor mats. The insides and end rollers of this conveyor were covered with a slimy, black-brown residue. Additionally, the bottom sections of the wash room walls had areas of mold.		
AMENDED		
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Janet B Gray, Investigator <i>JBG</i> Darcy E. Brillhart, Microbiologist Sandra I. Gaul, Investigator Robert P. Neligan, Investigator <i>RPN</i> Lesley K. Satterwhite, Microbiologist Theresa L. Stewart, Investigator	DATE ISSUED 02/05/2009

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OBSERVATION 10 Effective measures are not being taken to protect against the contamination of food on the premises by pests. Specifically, on 1/9/09 a live roach and several dead roaches were observed in the firm's wash room. This wash room is adjacent to the production/packaging area. Also, the bumper pads used for sealing the trailers against the bay doors were inadequate in that openings of 6 inches or more were observed along the sides and tops of the trailers. These trailers, containing raw or roasted product in totes, can be left backed up to the bay doors for 5-7 days allowing these openings to exist.		
* DATES OF INSPECTION: 01/09/2009(Fri), 01/12/2009(Mon), 01/13/2009(Tue), 01/14/2009(Wed), 01/15/2009(Thu), 01/16/2009(Fri), 01/19/2009(Mon), 01/20/2009(Tue), 01/21/2009(Wed), 01/22/2009(Thu), 01/23/2009(Fri), 01/26/2009(Mon), 01/27/2009(Tue), 02/05/2009(Thu)		
AMENDED		
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QUALITY ISSUES – CASE STUDIES (cont.)

CASE STUDIES

- Helpful method of examining
 - Consequences of quality issues and noncompliance with FDA regulations / cGMPs
 - Poor manufacturing activities & decisions
 - FDA investigations
 - Product recalls
 - FDA enforcement of regulations
 - Continuous improvement – for a product, company, industry (best practices), and the FDA

FDA WEB SITE

- <http://www.fda.gov/default.htm>
- Great source of information, such as
 - Current science & research
 - Regulations and laws
 - Product recalls & alerts
 - Product approvals !!
 - Criminal investigations
 - Consumer information
 - Manuals, regulatory publications, and reports

PEANUT CORPORATION OF AMERICA – CASE STUDY

- *Salmonella* Typhimurium in PCA peanut products
- Class examination and discussion of
 - Investigational timeline
 - Outbreak and source identification
 - Regulatory actions
 - FDA inspection observations (Form 483)
 - Corrective / preventative actions
 - Legal, social, & ethical impacts



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PEANUT CORPORATION OF AMERICA – CASE STUDY (cont.)

- Purposes :
 - To examine PCA quality errors made and their consequences
 - To examine PCA's / FDA's / CDC's / various states' actions to the *Salmonella* Typhimurium contamination
 - To propose potential corrective / preventative actions for PCA
 - To examine, from an ethical and legal standpoint, the laws / regulations governing the biomanufacturing industry and how PCA chose to run its business



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PEANUT CORPORATION OF AMERICA – CASE STUDY (cont.)

Class discussion (75 points) :

- *Timeline of Infections: Multistate Outbreak ...*
- *Salmonella Outbreak Investigations: Timeline for Reporting Cases*
- *Salmonella Strains Tables for Outbreak Related to Peanut Butter and Peanut Containing Products*
- *FDA Inspectional Observations Form 438 for Peanut Corp. of America Plainview, Blakely, GA inspection 01/09/2009 – 02/05/2009*
- *FDA Inspectional Observations Form 438 for Peanut Corp. of America Plainview, TX inspection 02/04/2009 – 02/26/2009*



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ASSIGNMENT

For **next class** (part of **75 points**), read the following documents :

- *FDA Inspectional Observations Form 438 for **Utah Medical Products, Inc.** inspection 02/02/2004 – 03/03/2004*
- *US District Court, District of Utah Case No. 2:04-CV-733 BSJ [**USA vs. Utah Medical Products, Inc.**]*
- *FDA Establishment Inspection Report for **Neways, Inc.** inspection 08/18/2008*



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Establishment Inspection Report

Neways, Inc

Salem, UT 84653-9365

FEI:

1000149898

EI Start:

08/18/2008

EI End:

08/18/2008

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SUMMARY

The inspection of this dietary supplement manufacturer and re-packer was conducted as a directed inspection, under FACTS assignment 962442, operation ID 3795338 and per the Domestic Food Safety Compliance Program, 7303.803.

The previous inspection was conducted on February 18th, 2003 and classified as NAI. No form FDA-483, Inspectional Observations, was issued.

The current inspection covered sanitation and verification whether or not the firm uses (b) (4) radiation during their manufacturing and repackaging of dietary supplements.

The firm was repackaging a dietary supplement called Life Enhancer during this inspection.

At the conclusion of the inspection, a close out meeting was held with management. No form FDA-483, Inspectional Observations, was issued.

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No refusals were encountered and no samples were collected.

(b)(4)

Post inspectional correspondence should be sent Mr. Eric Larsen, CEO, Neways International, 2089 Neways Dr., Springville, UT 84663. The FMD-145 should be addressed to Mr. Eddie Mendivil, Vice President Quality Assurance, 150 East 400 North, Salem, UT 84653.

ADMINISTRATIVE DATA

Inspected firm: Neways, Inc
Location: 150 E 400 N
Salem, UT 84653-9365
Phone: 801-423-2800
FAX:
Mailing address: 150 East 400 North
Salem, UT 84653

Dates of inspection: 8/18/2008
Days in the facility: 1
Participants: Becky L Bhan, Investigator

At the beginning of the inspection credentials were presented and a form FDA-482, Notice of Inspection, was issued to Mr. Eddie Mendivil, Vice President Quality Assurance.

At the conclusion of the inspection, a closeout meeting was held with Mr. Mendivil, (b)(6), PA and Ms. Payne.

There were no other inspectors or government agencies present during this inspection.

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Establishment Inspection Report

Neways, Inc
Salem, UT 84653-9365

FEI: 1000149898
EI Start: 08/18/2008
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HISTORY

The firm is part of Neways International. The headquarters is located at 2089 Neways Dr., Springville, UT 84663. Neways International warehouses are located throughout the world.

The firm has been in business since 1992.

The firm has approximately (b) (4) employees.

(b) (4)
(b) (4) A cleaning is conducted after each repackaging event. The firm operates (b) (4)
(b) (4)

The firm has registered under the Bio-Terrorism Act.

The firm consists of (b) (4) buildings that are approximately (b) (4) square feet.

The previous inspection was conducted on February 18th, 2003 and was classified as NAI. No form FDA-483, Inspectional Observations, was issued.

INTERSTATE COMMERCE/ JURISDICTION

According to management, the firm ships approximately (b) (4) of their products to (b) (4)
(b) (4) Products are shipped using various shipping carriers (see exhibit 1).

The firm receives bulk tablets and capsules from (b) (4)
(b) (4) (see exhibit 2).

In addition to dietary supplements, the firm manufactures body soaps, shampoos, toothpaste, lotions, lipstick, and many other products. Management provided a list of all dietary supplements manufactured and repackaged at the Salem Plant (see exhibit 3).

All products are sold directly to distributors located throughout the world. Sales strategies are similar to those of (b) (4)

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

At the beginning of the inspection, credentials were displayed and a form FDA-482, Notice of Inspection, was issued to Mr. Eddie Mendivil, Vice President Quality Assurance. Mr. Mendivil has

Establishment Inspection Report

Neways, Inc
Salem, UT 84653-9365

FBI: 1000149898
EI Start: 08/18/2008
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the responsibility for all quality assurance and quality control of operations in the Salem Plant. A copy of the organizational chart is included (see exhibit 4). Mr. Mendivil reports directly to Mr. Larsen, CEO. Mr. Mendivil was present during the entire inspection and provided information related to manufacturing, storing, receiving, and distribution of products.

I also met with the following individuals during the inspection:

- Ms. Tonya Payne, Document/Regulatory Auditing Manager. Ms. Payne is responsible for all regulatory affairs and document storage. Ms. Payne reports directly to Mr. Mendivil.
- (b)(6), PA Regulatory Auditing Supervisor. (b)(6), PA is responsible for all in house audits and advises management of any deficiencies in manufacturing and maintenance at the Salem Plant. (b)(6), PA reports directly to Mr. Mendivil.

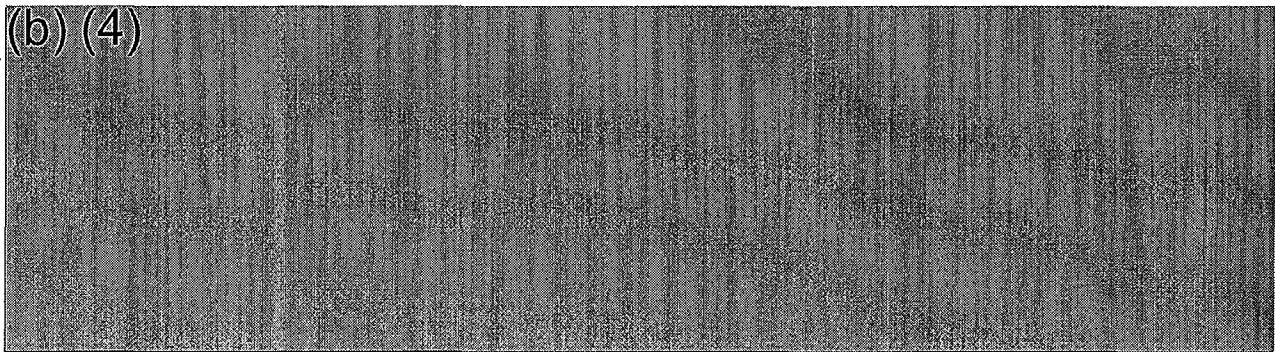
FIRM'S TRAINING PROGRAM

The firm has (b)(4) current good manufacturing training for all employees. Training is also conducted when there are changes in standard operating procedures.

MANUFACTURING/DESIGN OPERATIONS

Raw materials for mixing and bulk materials for repackaging are received in (b)(4) and placed into a quarantine area. Raw materials are then transferred to a staging area where samples are taken in a hepa filtered room and then tested for heavy metals and microorganisms. The firm does their own in-house testing (see exhibit 5). The firm does not test for irradiation of its raw materials, however documents were provided to me showing it is against company policy to accept irradiated raw materials (see exhibit 5). After test results are negative for microorganisms and heavy metals they are transported to the manufacturing areas.

(b)(4)



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Establishment Inspection Report

Neways, Inc
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During this inspection I observed bulk repackaging of a dietary supplement called Life Enhancer. This product was being manufactured for distribution (b) (4) (see exhibit 6). No products were being manufactured at the time of this inspection for distribution in the US.

The firm's pest control is managed by (b) (4) and checks are conducted every (b) (4). They use traps, lights, and external spraying. I did not observe any pest activity during this inspection.

A reconciliation exam was conducted on bulk tablets that are repackaged for sale as Life Enhancement. No discrepancies were observed (see exhibit 7).

MANUFACTURING CODES

The lot code is embossed on the external part of the bottle. The lot code is followed by an expiration date that consists of two numeric numbers that represent the month and a slash with four numeric numbers that represent the year.

COMPLAINTS

Complaints are handled at the Springville Headquarters. According to management no complaints have been filed since the last inspection in 2003.

RECALL PROCEDURES

The firm has a recall procedure and conducts annual mock recalls. According to management no recalls have been conducted since the last inspection in 2003.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

No objectionable conditions were observed and no form FDA-483, Notice of Inspection, was issued.

REFUSALS

No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT

I discussed with management two reports provided to me by the (b) (4) (see attachment 4). These reports stated that *Neways Green Qi* (lot code 575889) and *Neways Feeling Good* (lot codes 577129 & 575230) products tested positive for ionizing radiation. I stated to management their products had tested positive and they advised me they did not irradiate any of their products. They also stated it was against company policy and provide in writing to their suppliers a document stating that irradiation is not permitted. Management advised me that they were going to conduct their own investigation. I asked them if any "Green Qi" or

Establishment Inspection Report

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"Feeling Good" product was distributed in the US and they stated that some had been distributed and they would notify the people that those products may be irradiated. No lot numbers that tested positive were distributed in the US.

A copy of the "What You Need to Know about Registration of Food Facilities" was provided to Mr. Mendivil and I briefly discussed with him food security information.

ADDITIONAL INFORMATION

This firm primarily repackages bulk dietary supplements that are made by third parties. During the course of the inspection I wore a (b) (4) provided by the FDA and no radiation was detected. I did not observe any devices that could irradiate products.

(b) (4)

(b) (4)

(b) (4) to determine if these

(b) (4) Neways third party ingredient suppliers were irradiating at their facilities. Follow up trace back investigations were conducted at (b) (4)

(b) (4)

SAMPLES COLLECTED

No samples were collected.

EXHIBITS COLLECTED

Exhibit 1, shipping carriers, dated 18AUG08 (b) (4)

Exhibit 2, third party manufacturers, dated 18AUG08 (b) (4)

Exhibit 3, dietary supplement product list, dated 18AUG08 (7pp)

Exhibit 4, Organizational Chart, dated 18AUG08 (1p)

Exhibit 5, Quality Assurance and Control documents (b) (4)

Exhibit 6, Product Labeling (b) (4)

Exhibit 7, Reconciliation Documents (b) (4)

ATTACHMENTS

FDA-482, Notice of Inspection, dated 18AUG08 (1p)

Attachment 2, Copy of the assignment, dated 15AUG08 (1p)

Attachment 3, (b) (4)

Attachment 4, (b) (4)

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Establishment Inspection Report

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08/18/2008

ORIGINAL

Becky L Bhan, Investigator

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 6th & Kipling St. (P.O. Box 25087) Denver, CO 80225-0087 (303) 236-3000 Fax: (303) 236-3100		DATE(S) OF INSPECTION 02/02/2004 - 03/03/2004*
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Kevin L. Cornwell, Chairman & CEO		FEI NUMBER 1718873
FIRM NAME Utah Medical Products, Inc	STREET ADDRESS 7043 South 300 West	
CITY, STATE, ZIP CODE, COUNTRY Midvale, UT 84047-1048	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer	

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

A process whose results cannot be fully verified by subsequent inspection and test has not been validated and approved according to established procedures.

For example,

- a) Extrusion molding processing parameter operation control limits (i.e. heating zone, die, adaptor and clamp/gate temperatures, variac setting, screw RPM, head pressure, puller and cutter speed, and laser micrometer setting) are not supported by an examination of their relationship to the true control limits (edge of failure).
- b) Injection molding processing tolerance limits (temperatures, pressure, speed, injection time) have not been challenged, there is no documentation to support that test sampling plan was based upon a statistically valid rationale and there is no documentation to support that process equipment was properly installed. Validation activities have not been conducted on the programmable logic control system utilized to establish actual operating parameters of the injection molding equipment. This was observed for injection molded part
- c) The material drying process has not been qualified or validated. The drying process includes a 1 hour dry time at a temperature of 200 degrees Fahrenheit (BOO Process Number 1000, Operation 1000, Work order number 1000 dated 1/1/04) documented that material was dried at 200 and 200 degrees Fahrenheit between 1/1/04 and 1/1/04 Work order number 1000 dated 1/1/04 documented that material was dried between 200 and 200 degrees Fahrenheit between 1/1/04 and 1/1/04. The material specification sheet states 200 degrees Fahrenheit. 1000 documented runs) were reviewed between 1/1/04 and 1/1/04 for injection molded part

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03/03/2004

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
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- d) The annealing process qualification associated with injection molded part is not complete in that data/documentation does not exist associated with the operations as follows:
- the test. The current Bill of Operations (Process No. to procedure Manufacturing procedure Operation states to anneal parts entitled "HEAT ANNEALING PROCEDURE", Rev. dated (section states to preheat oven to degrees Fahrenheit (section) and place trays in preheated oven for minutes (section
- Additionally, this same test report documents qualification for the bonding process used to assemble PVC tubing to connectors in the Deltran assembly. The raw data supporting this summary report was not retained.
- e) Bond qualification for the revision adhesive was last done on Bond qualification for the rev. dated was last done as part of revision The firm was unable to provide data to demonstrate that these bond process qualifications support the current process.
- f) There is no maximum time established for pre-extrusion drying of the used to mold the Assembly respectively.

OBSERVATION 2

Acceptance procedures to ensure that specified requirements for in-process product are met were not documented.

- a) Injection molded parts (P/N were not processed in accordance with procedure number Revision entitled "STATISTICAL PROCESS CONTROL CHART PROCEDURE FOR MOLDING" dated Section states to (above UCL or below LCL). Processing above the UCL was observed in work orders for injection molded parts) manufactured between The established product characteristic specification parameters for are nches.

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DISTRICT ADDRESS AND PHONE NUMBER

DATE(S) OF INSPECTION

FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

FIRM NAME

STREET ADDRESS

CITY, STATE, ZIP CODE, COUNTRY

TYPE ESTABLISHMENT INSPECTED _____

DATE ISSUED

FORM FDA 483 (07/00)

PREVIOUS EDITION OBSOLETE

INSPECTIONAL OBSERVATIONS

PAGE 3 OF 7 PAGES

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DEPARTMENT OF HEALTH AND HUMAN SERVICES	
FOOD AND DRUG ADMINISTRATION	
DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6th & Kipling St. (P.O. Box 25087)	02/02/2004 - 03/03/2004*
Denver, CO 80225-0087	FBI NUMBER
(303) 236-3000 Fax: (303) 236-3100	1718873
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
TO: Kevin L. Cornwell, Chairman & CEO	
FIRM NAME	STREET ADDRESS
Utah Medical Products, Inc	7043 South 300 West
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Midvale, UT 84047-1048	Medical Device Manufacturer

from the ~~Complaint Handling System~~ to generate reports for the MRB ~~Spreadsheets~~ Reviews including the
reports such as ~~Validation Master Plan schedule, updated on~~, indicates the Test Protocol is in the ~~the firm's Software~~ phase and
designates the criticality as high for ~~the firm's Software~~

c) The ~~X~~ system, Version ~~X~~, has not been validated for its intended use as follows:

The firm's Software Validation Master Plan schedule, updated on ~~11/1/2017~~, does not indicate the current status of the Test Protocol and designates the criticality for planning priority and planned completion date as follows:

WMM 3/3/04

The corrective and preventive procedures addressing the analysis of sources of quality data to identify existing and potential causes of nonconforming product or other quality problems were not defined.

Specifically, the Corrective and Preventive Action procedure, Document ~~XXXX~~, Revision ~~X~~ Revision Date ~~XXXX~~ does not define how data will be presented to the Materials Review Board (MRB), CAPA Committee, for effective analysis. For example:

a) The MRB Review reports include data analysis on
The procedure does not define how the failure codes are used by the company and what the failure codes represent in relation to data analysis of the CAPA and complaint handling systems.

1. As an example, 12 complaint records were documented for the electrodes not fitting into pencil, which was described as the same problem, but ~~X~~ different failure codes were used to document the type of failures in the complaint records. The Corrective Action Report (CAR) Number ~~X~~ Origination Date ~~X~~ identifies the complaint issues as the same for the complaint records.

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2. Complaint ☒ , dated ☒ for Electrical Surgical Unit ☒ , was assigned failure code ☒ however failure analysis revealed that the ☒ complaint ☒ , dated ☒ , for ☒ , was assigned failure code ☒ however failure analysis also revealed that the unit had no sound because ☒

b) The ☒ MRB Review reports include data analysis on the ☒ The procedure does not define how the number is obtained or what the number represents, such as the number is the actual number of hard copy complaint records, the actual number of devices/units alleged as defective by the complainant, the number of devices/units returned and tested, or number of complaints confirmed.

OBSERVATION 5

Not all of the actions needed to correct and prevent the recurrence of nonconforming product and other quality problems have been identified.

Corrective/Preventive Action Request, CAR NO. ☒ was opened ☒ closed ☒ , and affectivity verified on ☒ and ☒ concerning the ☒ The MRB CAPA meeting minutes and CAR ☒ file, does not document the product lot numbers involved with this defect, and does not document the rationale for releasing these lots for distribution.

OBSERVATION 6

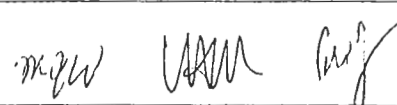
Complaint handling procedures for receiving, reviewing, and evaluating complaints have not been defined.

For example:

The Customer Complaint Investigation procedure, Document No. ☒ , Revision ☒ Revision Date ☒ , does not define the process of how the recent complaint history is evaluated and/or does not require the recording, in the individual complaint file, of how the recent complaint history and/or service history was evaluated for that particular complaint. For example:

a) ☒ : complaint records, received since ☒ were reviewed and the documentation in the complaint records did not include the information of how the recent complaint history was evaluated or performed.

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CITY, STATE, ZIP CODE, COUNTRY Midvale, UT 84047-1048	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer	

1. Complaint Number ☒ Received Date ☒ documents that the complaint history for the past ☒ was searched and no similar incidents were found. The procedure does not describe the process of a complaint history search. The complaint record, Number ☒ does not document how the complaint history was searched, such as searching in ☒ by generating a report by product; using a report generated from ☒ to aid in the identification of hard copy complaint files and manually reading each complaint description; using the MRB ☒ Reports data generated every ☒ or pulling and reading of all hardcopy complaint files without the aid of a complaint list generated from ☒

2. Complaint Number ☒ Received Date ☒ documents that the complaint history for the past ☒ revealed ☒ occurrences of bent loops found. The procedure does not describe the process of a complaint history search. The complaint record, Number ☒ does not document how the complaint history was searched, such as searching in ☒ by generating a report by product; using a report generated from ☒ to aid in the identification of hard copy complaint files and manually reading each complaint description contained in the hard copy files; using the MRB ☒ Reports data generated every ☒ or pulling and reading of all hardcopy complaint files without the aid of a complaint list generated from ☒ Also, the procedure and/or complaint record do not document or define what the ☒ occurrences represent, such as whether the number represents hard copy complaint records; number of units/devices allegedly reported by the complainant in all the complaint records searched; number of units/devices returned and tested; and/or number of confirmed units/devices defective or confirmed problems.

- b) A review of ☒ customer complaint records received since ☒ for the FINESSE Electrical Surgical System device noted ☒ different described scenarios for ☒ look back reviews, including ☒ complaints where there is no indication that a look back was done as part of the complaint investigation. The ☒ look back descriptions are noted below followed by the total number of complaints where each was observed as follows: ☒

OBSERVATION 7

The device history record does not include complete acceptance records that demonstrate the device is manufactured in accordance with the device master record.

A review of four ☒ work orders (device history records), manufactured after ☒ revealed the following ☒ errors that were not detected during the review and approval of the device history records.

- a) The following error was not detected during review and approval of Device History Record: Extrusion molding batch, product test samples for work order ☒ Assembly ☒ were selected by production personnel according to an obsolete sample scheme.

SEE REVERSE OF THIS PAGE	<i>mgw</i> <i>UAM</i> <i>fig</i>	DATE ISSUED 03/03/2004
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PURGED

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 6th & Kipling St. (P.O. Box 25087) Denver, CO 80225-0087 (303) 236-3000 Fax: (303) 236-3100		DATE(S) OF INSPECTION 02/02/2004 - 03/03/2004*
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Kevin L. Cornwell, Chairman & CEO		FBI NUMBER 1718873
FIRM NAME Utah Medical Products, Inc	STREET ADDRESS 7043 South 300 West	
CITY, STATE, ZIP CODE, COUNTRY Midvale, UT 84047-1048	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer	

b) The time ☒ was put into the dryer was not recorded on the bill of operations (BOO) for Assembly #
☒ work order ☒ as required by this BOO. This is done to establish conformance with the minimum
drying time of ☒ specified for this polymer.

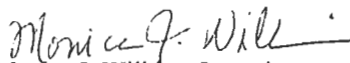
*** DATES OF INSPECTION:**

02/02/2004(Mon), 02/03/2004(Tue), 02/04/2004(Wed), 02/05/2004(Thu), 02/06/2004(Fri), 02/07/2004(Sat), 02/09/2004(Mon),
02/10/2004(Tue), 02/11/2004(Wed), 02/12/2004(Thu), 02/17/2004(Tue), 02/23/2004(Mon), 02/24/2004(Tue), 02/25/2004(Wed),
02/26/2004(Thu), 02/27/2004(Fri), 03/01/2004(Mon), 03/02/2004(Tue), 03/03/2004(Wed)

FDA EMPLOYEES' NAMES, TITLES, AND SIGNATURES:


Lori A. Medina, Investigator


Ralph W. Jernsdal, Investigator


Monica J. Wilkins, Investigator

PURGED

SEE REVERSE OF THIS PAGE	DATE ISSUED 03/03/2004
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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF UTAH, CENTRAL DIVISION

* * * * *

UNITED STATES OF AMERICA,)
)
Plaintiff,)
)
vs.)
)
UTAH MEDICAL PRODUCTS, INC.,)
a Utah corporation; KEVIN L.)
CORNWELL and BEN D. SHIRLEY,)
individuals,)
)
Defendants.)

Case No. 2:04-CV-733 BSJ

MEMORANDUM OPINION & ORDER

FILED
CLERK, U.S. DISTRICT COURT
October 21, 2005 (12:36pm)
DISTRICT OF UTAH

* * * * *

This matter was tried to the Court from September 26 through October 4, 2005. Arnold Allan Gordus of the Department of Justice and Claudia J. Zuckerman of the Office of Chief Counsel for the Food & Drug Administration appeared on behalf of plaintiff United States of America (“United States”). Daniel G. Jarcho, Cass W. Christensen, and Daniel L. Russell, Jr., of McKenna Long & Aldridge LLP, appeared on behalf of defendants Utah Medical Products, Inc., Kevin Cornwell and Ben Shirley (collectively “Utah Medical”).

INTRODUCTION

On behalf of the Food and Drug Administration (“FDA”), the United States seeks a permanent injunction against Utah Medical under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 332(a), regarding alleged violations of the Quality System Regulation (“QSR”), 21 C.F.R. Part 820 (2004). Utah Medical is a corporation organized under the laws of Utah, with its

principal executive offices at 7043 South 300 West, Midvale, Utah 84047. Defendant Kevin L. Cornwell is the Chairman and Chief Executive Officer of Utah Medical. Mr. Cornwell is involved in the day-to-day operations of Utah Medical and has authority over all of the Company's operations, including the design, manufacture, packing and storage of Utah Medical's devices. Mr. Cornwell is ultimately responsible for Utah Medical's compliance with all applicable laws and regulations. Mr. Cornwell performs his duties at the Company's principal offices, within the jurisdiction of this Court. Defendant Ben L. Shirley is the Vice President of Quality Assurance and Product Development at Utah Medical and is involved in the day-to-day activities of Utah Medical. Mr. Shirley is also responsible for compliance with the QSR at Utah Medical's Utah facility. Mr. Shirley performs his duties at the Company's principal offices, within the jurisdiction of this Court.

Utah Medical develops, manufactures, and markets a broad range of disposable and reusable specialty medical devices. Utah Medical's current product line includes devices for labor and delivery, neonatal intensive care, gynecology, urology, electrosurgery and blood pressure monitoring. Utah Medical regularly manufactures devices from components that it receives in interstate commerce and introduces finished devices into interstate commerce. Utah Medical also manufactures "components," as defined at 21 C.F.R. § 820.3(c) (2004),¹ because it manufactures parts or subassemblies that are intended to be included as part of finished, packaged and labeled medical devices.

The two main methods by which Utah Medical manufactures its components are its

¹"Component means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device." 21 C.F.R. 820.3(c) (2004).

extrusion process and injection molding process. “Extrusion” is a process in which plastic is extruded, or pushed, through a fixed die (or orifice) in order to assume its final shape. “Injection molding” is a process in which liquified plastic is injected into a mold cavity in order to assume its final shape. The entirety of Utah Medical’s extrusion and injection molding operations are devoted to component manufacturing. No products other than components are manufactured with Utah Medical’s extrusion or injection molding operations.

Utah Medical sells the large majority of the components it manufactures to other entities, including its wholly-owned subsidiary in Ireland (Utah Medical Products, Ltd.), to be used by these other entities in the manufacture of finished products.² For example, in 2004, Utah Medical manufactured a total of 29,549,139 units of injection-molded or extruded components. In the same year, Utah Medical sold approximately 73% of these molded or extruded components to other entities, to be used by the other entities in the manufacture of finished products. In the case of the Irish subsidiary, the manufacture of finished medical device products (and the use of those products) occurs solely outside of the United States.³ Some of the companies that purchase components manufactured by Utah Medical do not manufacture medical devices.⁴

Utah Medical asserts that it has a comprehensive quality system, intended to comply with all Quality System Regulations provisions. As part of its quality system, Utah Medical has

²Because the burden of ensuring the quality of components rests upon the finished device manufacturer (*see* 21 C.F.R. 820.80), the QSR does not regulate Utah Medical’s components to be sold to manufacturers of finished products.

³The QSR does not regulate devices made and distributed outside of the United States. *See* 21 C.F.R. 820.1(a)(2).

⁴But here, the United States’ case focuses on the production of plastic components that are incorporated in medical devices.

implemented a broad range of protocols, policies, and procedures to design, produce, test, and distribute quality components and medical devices. The FDA has inspected Utah Medical several times since 2001. During certain inspections, the FDA has issued written observations by FDA inspectors on Forms FDA-483. A Form FDA-483 is a list of concerns observed by an FDA inspector during the course of an inspection. The investigator's observations are subject to review and response by the Company and are further reviewed by other FDA personnel before the FDA makes a decision whether it believes the Company complies with applicable law and regulations.

This is an unusual case. The safety of the products manufactured by Utah Medical has never been at issue.

Even though product safety is a non-issue, the relief originally sought by the United States was to stop Utah Medical's products from entering commerce because of alleged persistent deficiencies of the Utah Medical in complying with the applicable quality system regulations (21 CFR § 820), and asserting that a failure to comply by definition produced an "adulterated" product and subjected the product and the persons responsible for the product to "regulatory action." In short, the United States asked that Utah Medical be ordered to stop the sale of product until Utah Medical complies with the regulation 21 CFR § 820 "*and in a manner that has been found acceptable to FDA.*" (See Complaint, (emphasis added) ¶¶ IA and IB at 10.)

During the extended process carried on by the parties and by the Court in passing on motions and during the pretrial conference, and during the trial itself, the United States on the record softened the relief that it sought to simple regulatory compliance, and abandoned the more draconian relief of stopping sales of product defined as adulterated.

The relief early sought by the United States assumed that compliance with the regulations “and in a manner satisfactory to the FDA” are the same. But Utah Medical has asserted full compliance with the regulations and insists that the FDA misreads its own regulations.

The specific questions before the court, as set forth in the Pretrial Order, are three:

Issue No. 1(a): Whether Utah Medical has properly validated its extrusion and injection molding processes.

Issue No. 1(b): Whether Utah Medical has properly validated the software programs used as part of production or the quality system.

Issue No. 2: Whether Utah Medical properly processes complaints with regard to lookbacks and failure codes.

ANALYSIS

According to Mr. Cornwell, Utah Medical was originally founded in 1978 and went public in 1983. The QSR was adopted October 7, 1996 with an effective date of June 1, 1997.⁵

The regulations are characterized by the United States as general and flexible so as to cover a broad spectrum of products and activities, and that the regulations place a great deal of responsibility on a manufacturer to adopt and document internal practices and procedures which ensure the safety of the product. That general characterization is acquiesced in by Utah Medical.

For the most part, the substantive issues relate to the word “validation” as used in the regulations, the manner in which practices and procedures may be “validated,” and whether the practices and procedures of the Utah Medical have been “validated” as required by the

⁵ See 61 Fed. Reg. 52602-01, 52654, 1996 WL 565309 (Oct. 7, 1996).

regulations.

The United States asserts that the best source of validation information as to “current good manufacturing practice” is found in two publications: (1) *The Quality System Compendium*, (Assoc. for the Advancement of Medical Instrumentation, 1998) (Pl.’s Exh. 47); and (2) *Quality Management Systems - Process Validation Guidance*, 2d. ed. (The Global Harmonization Task Force, January 2004) (Pl.’s Exh. 99), and assert that such have been incorporated by the regulations. The regulations were effective in 1997. They do not expressly incorporate any industry publication, nor have they been amended to expressly include “future practices” which may be of benefit. Of course, it is fundamental that the regulations state the applicable law.

Medical device manufacturing is a heavily regulated industry, and rightfully so.

The applicable statute empowering the Secretary to promulgate regulations is found at 21 U.S.C. § 360j(f)(1)(A) and (B), and provides as follows:

(A) The Secretary may, in accordance with subparagraph (B), *prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, pre-production design validation (including a process to access the performance of a device but not including an evaluation of the safety or effectiveness of a device), packing, storage, and installation of a device conform to current good manufacturing practice, as prescribed in such regulations*, to assure that the device will be safe and effective and otherwise in compliance with this chapter.

(B) Before the Secretary may promulgate any regulation under subparagraph (A) he shall—

- (i) afford the advisory committee established under paragraph (3) an opportunity to submit recommendations to him with respect to the regulation proposed to be promulgated;
- (ii) afford opportunity for an oral hearing; and
- (iii) ensure that such regulation conforms, to the extent practicable, with internationally recognized standards defining quality systems, or parts of the standards, for medical devices.

* * * *

21 U.S.C. § 360j(f)(1)(A)(B) (1999). (Emphasis added.)

Pursuant thereto, regulations were effective June 1, 1997 and are found at 21 C.F.R. Part 820 (2004). The United States asserts that Utah Medical has failed to comply with 21 C.F.R. §§ 820.75(a), 820.75(b), 820.70(i), 820.250(b), 820.100(a)(1), 820.90(a), 820.198(a), 820.70(a), 820.80(c) and 820.80(e) (2004). Utah Medical asserts full compliance.

Definitions found at 21 C.F.R. § 820.3(z) state:

(z) *Validation* means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

(1) *Process validation* means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

21 C.F.R. § 820.75 reads:

§ 820.75 Process validation.

(a) Where the results of a process cannot be fully verified by subsequent inspection and test, *the process shall be validated with a high degree of assurance and approved according to established procedures.* The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.

(b) Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.

(1) Each manufacturer shall ensure that validated processes are performed by qualified individual(s).

(2) For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be documented.

(c) When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented. (Emphasis added.)

21 C.F.R. § 820.70(i) reads in pertinent part as follows:

(i) *Automated processes.* When computers or automated data processing systems

are used as part of production or the quality system, the manufacturer shall *validate* computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented. (Emphasis added.)

21 C.F.R. § 820.198 reads in pertinent part as follows:

§ 820.198 Complaint files.

(a) Each manufacturer shall maintain complaint files. Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that:

(1) All complaints are processed in a uniform and timely manner. . . .

21 C.F.R. § 820.250 states as follows:

§ 820.250 Statistical techniques.

(a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.

(b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.

As this matter progressed, it became clear to the court that the question is not whether the Utah Medical in times past fully and technically complied with the regulations, but whether Utah Medical is currently in compliance.

Past activities of the parties are of some help in discerning the need, if any, for a court order as sought by the United States.

Since about 2001, there has been an ongoing interplay between the agency and Utah Medical through the FDA oversight process of inspections, written observations by inspectors, responses by Utah Medical, review by District Directors and others, disagreements with the observations, purported “corrective actions” by the Utah Medical, and the gathering and

furnishing of documents of various kinds to satisfy the FDA.

1. Utah Medical Adequately Validates its Manufacturing Process in accordance with the Quality System Regulations.

The United States' proffered experts testified that Utah Medical has not properly validated its extrusion or injection molding processes used to make plastic parts. The United States generally contends that there is insufficient documentation demonstrating: (a) a proper installation of the extrusion and injection molding equipment; (b) proper calibration of the extrusion and injection molding equipment; (c) proper establishment of process parameters for the extrusion and injection molding processes; (d) adequate monitoring of critical dimensions of products manufactured through the extrusion and injection molding processes; (e) adequate inspection and testing of products manufactured through the extrusion and injection molding process; and (f) "edge of failure" testing of its processing parameters. The United States' experts stated that, according to industry standards, "process validation requires three separate elements known as "installation qualification" (IQ), "operational qualification" (OQ), and "performance qualification" (PQ). But at trial, the United States' experts repeatedly testified that it was the Company who must establish and maintain a quality system that is appropriate for the specific medical devices designed or manufactured.⁶

First, as to installation validation, the machines used for injection and extrusion have been in place and producing product for many years.

Currently, manuals and drawings contained therein are on hand and available. In an effort to "validate" "installation" which took place years earlier, Utah Medical used its own

⁶21 C.F.R. 820.5 reads "[e]ach manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part."

engineers to go through a comparable testing process in 2004.

Though done years after actual installation, the in-house engineers checked out the installation over a period of months and documented what they did over a period of months. They determined that the machines were properly installed. To the Court, that seems perfectly adequate. It verifies currently the validity of what was done at installation. The movie can't be run backwards, nor the clock turned back. The current effort by Utah Medical, of course, is to ensure product safety by doing now and providing documentation of a comparable "installation" series of tests. Such complies with the regulation. So much for installation.

Utah Medical establishes its processing parameters in part during the design phase of its manufacturing process. *See* 21 C.F.R. 820.75(b). Utah Medical identifies critical dimensions for all of its extruded and injection molded products. Utah Medical calibrates its extrusion and injection molding equipment on a regular, periodic basis, following established, documented procedures. This calibration work is done periodically and regularly by outside vendors. Utah Medical employs a statistical process control procedure to monitor and control its extrusion and injection molding process, by which samples of component parts are inspected at regular intervals. Process parameters are established and followed, and inspection occurs. All steps are documented.

The United States also asserts that process validation is deficient due to an absence of "edge of failure" testing, or in other words, testing of at what point process parameters do not work. But each product has design and operational specifications; each has an operation sheet provided to machine operators with specification limits presented by the engineer; each has a history sheet which is kept; each has a specification sheet, and designated temperature ranges,

speed of a particular run, pressure, as well as the stated directions from suppliers of raw material for the use of raw material. Measurement by laser beam is instantly available on tubing. There is a plethora of documentation as to what is to be done and what is done each step of the way.

“Edge of failure” testing to demonstrate what does not work makes no sense when engineers have specified what does work and what has worked over years of operation.

Moreover, assembled products are all visually inspected, often more than once prior to shipment to customers.

For the reasons stated above, the Court finds that Utah Medical has adequately validated its manufacturing processes in accordance with the Quality System Regulations.

2. Utah Medical Adequately Validates its Software in compliance with the Quality System Regulations.

The United States expert Daniel Olivier testified that Utah Medical has not validated software that it uses in production or its quality system in accordance with “industry standards.” He suggested that Utah Medical was deficient in three ways: (a) failure to document an intended use for each software program requiring validation; (b) improper sequencing of test protocols and test reports, in that certain test protocols were finalized after the relevant test reports; and (c) the existence of a so-called “Y2K” problem.

Utah Medical presented substantial testimony and documentary evidence that it validates its software for the software’s intended use. Date discrepancies of a trivial nature and Y2K matters were easily explained by later drafts, interlineations, or typographical errors unrelated to validation. The undisputed hands-on testimony confirmed that the intended use of the software used by Utah Medical is adequately documented and the software is tested properly.

3. Utah Medical Has a Uniform Complaint Handling Process in compliance with the Quality System Regulations.

The United States experts testified that: (a) Utah Medical does not assign “failure codes” to complaints in a uniform manner; and (b) Utah Medical’s “look-back” analyses are not performed in a uniform manner. A “look-back” refers to the company’s investigation of new complaints by looking back at prior complaint files that may be relevant to the current issue or complaint under review. A “failure code” is a code assigned by a Utah Medical employee to generally characterize the issue associated with each complaint. Once again, the United States asserts that this process does not comport with “industry standards.”

Utah Medical has established uniform procedures for implementing corrective and preventive action in accordance with 21 C.F.R. § 820.100(a). The company employs a detailed and uniform procedure that it follows for receiving, reviewing, and evaluating complaints. Utah Medical has documented its complaint-handling procedure. (*See* Def.’s Exh. 318.) Utah Medical uses “failure codes” merely as an internal general trending tool. The Company groups complaints not by failure codes, but by a corrective action number, allowing people to review similar complaints, if any, according to the corrective action number. These complaints are initially the responsibility of one individual, Russell Pope. The company holds regular weekly meetings to discuss complaints. In addition, complaints are periodically reviewed by the Chief Executive Officer, Kevin Cornwell.

Utah Medical is in compliance with Quality System Regulations as to complaint handling under 21 C.F.R. § 820.90(a) and § 820.198(a).

The question here is whether the processes and procedures used by Utah Medical to

currently produce product comply with the applicable regulations. The answer is yes, they do. That is a different question than whether Utah Medical has historically, from 2001, always been in full technical compliance.

It seems to me that a recurring problem in this extended and in some instances “nit-picking” case is a failure of the regulator and the regulated to communicate. It appears to me they have often talked past each other and, while using the same words, have meant entirely different things. This seems to be a common characteristic of both, arising in part because of the general nature of the regulations themselves, which have the virtue of generality and the vice of imprecision. This endemic problem is perhaps augmented by decision-makers who themselves rely too much on inspectors’ reports without taking a fresh look themselves at ongoing changes made by Utah Medical in response to questions raised.

Each of the parties, of course, has a point. Utah Medical in times past may have lacked documentation of the particular kinds they now say are readily available, such as injection molding manuals and drawings. Utah Medical may well have applied an incorrect electronic label to a complaint, but the complaint process itself was both uniform and effective. Even counsel for the United States acknowledged that if computer labels were not used at all, the complaint handling process would be satisfactory.

The court has been impressed, for the most part, by the diligence of agency oversight. The court has been impressed as well by the Utah Medical’s design of product, its record-keeping of each step along the way, the acceptance in the market of its products, the Company’s uniform processing of complaints, and the manner in which change is made in practice and procedure as a result of complaint handling.

As this case progressed, the court wondered how it had evolved into a litigation with hundreds of exhibits, endless depositions, and high-cost “experts.”

The common mission of the manufacturer and the regulating agency is a safe product and the adoption of manufacturing processes which ensure safety.

Product safety is not an issue in this case. Processes and procedures are. “Validation” is the key word, and has often been noted, “many roads lead to Rome.”

The fact that the road chosen by Utah Medical may be different in degree than that thought to be appropriate by a regulator, does not mean that it is wrong, or in violation of the regulations. The regulations talk of current manufacturing practice. “Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulations.” 21 C.F.R. § 820.1(a).

The regulations were promulgated in 1997 with no express incorporation of industry standards. The suggestions found in *The Quality System Compendium* and *Quality Management Systems - Process Validation Guidance* may be of some value as evidence of some standards suitable for some manufacturers, but in no sense are specifically embraced by the regulations, nor have changes been made in the regulations to incorporate them. The statute, of course, talks of “current good manufacturing practice, as prescribed in such regulations.” 21 U.S.C. § 360j(f)(1)(A)(B) (1999).

Without a doubt, the United States captured Utah Medical’s attention in the past, and whatever modest deviations from *regulations* may have occurred in times past no longer exist at present. It makes no sense for the court to order Utah Medical to do something they are already doing.

Utah Medical's pending motions are mooted by this Opinion.

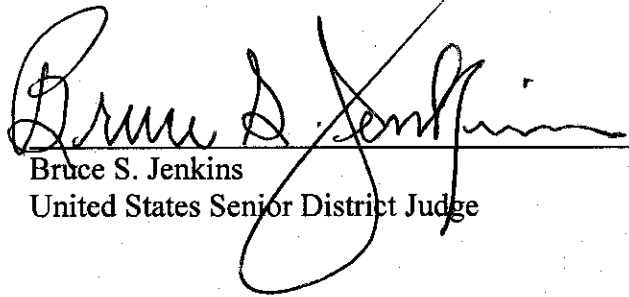
Petition DENIED, and case DISMISSED.

SO ORDERED.

Let judgment be entered accordingly.

DATED this 21 day of October, 2005.

BY THE COURT:



Bruce S. Jenkins
United States Senior District Judge