DEVELOPMENT OF BIOTECH PRODUCTS

Biotechnology products come from many sources – for hundreds of years, animals and plants have been engineered into new varieties or breeds to create new products. For example, livestock pancreases have been ground up and used as a source of insulin (protein) to treat diabetes or the use of foxglove plant as a source of digitalis, a chemical used to regulate an irregular heart rate.

Harnessing the Potential of Materials Produced in Nature – Scientists have significantly improved access to naturally occurring products that occur in small amounts and are impractical to extract from a natural source.

Modeling the Research and Development of a Potential Product –
1. Estimate Market Size
2. Identify Product Sources
3. Creating a Comprehensive Product Development Plan (CPDP) – Companies use a CPDP to decide whether to pursue development of a potential product. For an accurate evaluation, significant research is conducted to identify the market and estimate the potential profit.
   - Does the product meet a critical need? Who will use the product?
   - Is the market large enough to produce sufficient sales? How many customers are there?
   - Does preliminary data support that the product will work? Will it do what the company claims?
   - Can patent protection be secured? Can the company prevent other companies from producing it?
   - Can the company make a profit on the product? How much will it cost to make it? How much can it be sold for?

ACTIVITY 1: Exploring Potential Products – Imagine you work in a biotech lab. Select a product from the table below or find a potential product and gather data to complete the CPDP review.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>NewLeaf potato</td>
<td>Protects potatoes from insects</td>
</tr>
<tr>
<td>Purafect Protease</td>
<td>Protein-digesting enzyme</td>
</tr>
<tr>
<td>Endless Summer tomato</td>
<td>Slow-ripening tomatoes</td>
</tr>
<tr>
<td>Bovine Somatotropin</td>
<td>Growth hormone for livestock</td>
</tr>
<tr>
<td>t-PA</td>
<td>Dissolves blood clots</td>
</tr>
<tr>
<td>HER2 antibody</td>
<td>Recognizes and marks breast cancer cells</td>
</tr>
<tr>
<td>Besifloxacin</td>
<td>For “pink-eye” treatment</td>
</tr>
<tr>
<td>Bollgard cotton</td>
<td>Insect-resistant cotton</td>
</tr>
<tr>
<td>Chymax</td>
<td>Enzyme curdles milk for cheese production</td>
</tr>
</tbody>
</table>

Conduct research and construct a chart that addresses all the criteria of the CPDP – include the elements below:
- Product Name
- Product Function – What individuals or industry will use it? For what purpose?
- Data to support claims that it will work
- Size of the Market – Number of potential customers
- Potential Sales Price – Potential profit?
- Patent Info – Existing patents? Companies working on it?

*Adapted from “Biotechnology: Science for the New Millennium” by Ellyn Daugherty.*
Producing Products – It takes approximately 15 years to develop, test and market an rDNA product before it can be brought to market. Preliminary testing and designing a development process may take up to 10 years.

1. A potential product must be identified then an assay is developed to recognize the presence and activity of the product. Next, determination of genetic engineering and production methods for the product are established. Scientists try to determine what cells to transform and how to regulate the genes once they are in the new cells.

2. A purification process is developed so the product can be isolated from other cells products. The R&D procedures are scaled-up to manufacturing volumes and it takes several years to produce volumes large enough to market.

3. During manufacturing, products must be produced under the supervision and rules of the FDA (Food and Drug Administration). Manufacturing must meet the FDA’s Good Manufacturing Practices (GMP) guidelines to ensure safety and purify. The product produced during scale-up are purified and formulated into the final version to be used by customers.

4. The final formulation or product must be tested during clinical trials. Clinical trials are also guided by FDA regulations and may take 3 to 5 years to complete. If a product demonstrates safety and efficacy during the clinical trials, the FDA can approve it for marketing and sales.

ACTIVITY 2:
Product Pipeline Study – No matter what the product of a biotech company, the goal is to get the product to market as quickly as possible. Often there is a period of R&D where a great deal of money is invested in attempting to produce a product on a small scale. Must testing is conducted, as the protocols for small-scale and large-scale production are determined. If the product is a pharmaceutical, it must undergo strict testing (clinical trials), under the guidance of the FDA, before it can be marketed. It takes 10 to 15 years for a company to take a product through all these steps. The product pipeline is different at every company, but it follows the basic outline below.

- Identify a potential product.
- Complete R&D with assay development and quality control.
- Manufacture on a small scale.
- Continue testing for safety and efficacy (including Phase I, II and III clinical trials for pharmaceuticals).
- Market the product.

As a sales and marketing specialists would do, study and report on a product that has been recently, or is about to be, brought to market.

1. Select a product from the table and research the product. Use these questions to lead your research.
   - What is the structure and function of the product?
   - What market will it serve and how large is the market?
   - When is the product first expected to reach the market?
   - What obstacles are there, if any, to reaching the market?
   - How far along is it in the product pipeline?
   - What has been its history in the product pipeline?
   - Are there any concerns or cautions about the production of the product?
   - How much money is expected to produce for the company?
   - Are any other companies in serious competition to bring this product to market?
   - Is there any other interesting information?

*Adapted from “Biotechnology: Science for the New Millennium” by Ellyn Daugherty.
2. Create a presentation, outline or graphic organizer that clearly describes the history, structure, function, market, pipeline status, potential profit, concerns and competition for your product. Include a slide that has a product pipeline diagram.

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Description/Treatment of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roundup Ready soybeans</td>
<td>Monsanto Canada, Inc</td>
<td>Herbicide resistant soybeans</td>
</tr>
<tr>
<td>Recombinant Human beta nerve growth factor</td>
<td>ProSpec-TanyTechnoGene</td>
<td>Stimulates nerve cell growth</td>
</tr>
<tr>
<td>Pulmozyme</td>
<td>Genentech, Inc</td>
<td>Cystic Fibrosis medication</td>
</tr>
<tr>
<td>Boilgard cotton</td>
<td>Monsanto Comany</td>
<td>Insect resistant cotton</td>
</tr>
<tr>
<td>Nutropin</td>
<td>Genentech, Inc</td>
<td>Human growth hormone</td>
</tr>
<tr>
<td>Hercpetin</td>
<td>Genentech, Inc</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>FLAVR SAVR tomato</td>
<td>Calgene, Inc</td>
<td>Slow-ripening tomato</td>
</tr>
<tr>
<td>EPOGEN</td>
<td>Amgen, INC</td>
<td>RBC production for anemia</td>
</tr>
<tr>
<td>Kogenate</td>
<td>Bayer Corp</td>
<td>Hemophilia</td>
</tr>
<tr>
<td>INTEGRA dermal regeneration template</td>
<td>Integra LifeScience Corp</td>
<td>Artificial skin</td>
</tr>
<tr>
<td>Humalog</td>
<td>Eli Lilly and Company</td>
<td>Treatment for diabetes</td>
</tr>
<tr>
<td>Proleukin IL-2</td>
<td>Chiron Corp</td>
<td>Kidney carcinoma</td>
</tr>
<tr>
<td>Glucobay</td>
<td>Bayer Corp</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Spezyme starch enzyme</td>
<td>Genecor International, Inc</td>
<td>Starch-digesting enzyme</td>
</tr>
<tr>
<td>Retavase</td>
<td>Centocor, Inc</td>
<td>Thrombolytic agent</td>
</tr>
</tbody>
</table>

**BRINGING A PRODUCT TO MARKET**

**Biomanufacturing** – commercial volumes of a product are produced, purified and formulated. Procedures are different depending on the product, but same general steps. Broth cultures of cells producing protein are moved through a series of processes – fermentation or cell culture, harvest/recovery, protein purification, formation, filling/packaging.

**Recovery & Purification & Formation:** Protein is separated and purified from other proteins using centrifugation, filtrations and chromatography. The method of harvesting depends on whether the protein is intracellular or extracellular.

- **Intracellular proteins** are made and function inside the cell – to harvest, the cells must be burst open. Detergents can be used to open the cell, but it denatures many proteins and difficult to isolate protein. Sonication uses high-frequency sound waves to break open the cells – disadvantage -- thousands of proteins are released making it hard to isolate and purify.
- **Extracellular proteins** are made in the cell and function outside the cell – much easier to isolate. Recovery begins by separating the protein from cell debris, either by filtering or centrifugation.

- Purification is accomplished through column chromatography – contains resin beads that separate molecules based on size, shape, charge or chemical nature. Pressure-pumped columns are used to treat large volumes. The final product is run through a series of filters to concentrate the product and to remove small contaminate molecules – ultrafiltration. Tangential flow filtration (TFF) is used – protein solution is fed into a membrane lined tube.
- After ultrafiltration, a relatively pure protein is ready for formulation – into liquid, powder, tablets, etc. – and then filled into desired packing.

**Product Quality Control** – Companies must be certain the product is high quality. As the product is scaled-up, manufactured and purified, technicians must monitor its concentration, purity and activity to ensure that it meets certain standards. The Quality Control (QC) and Quality Assurance (QA) departments monitor the characteristics and performance of the products.

*Adapted from “Biotechnology: Science for the New Millennium” by Ellyn Daugherty.*
QC departments handle product quantity and testing during product development – before the sample is close to marketing.

QA departments deal with quality objectives such as how certain objectives are met and reported, both internally and externally – especially as product is closer to marketing.

1. QC receives samples from fermentation, cell cultures or other manufacturing areas. These samples undergo the same assays that were performed during R&D. Testing may be conducted on animals – necessary to safely bring drugs to the human market. At instrumentation companies, QC measures different variables on instruments and reagents – technicians may use a mass spectrometer to validate reagents purity and performance.

2. If product is pure and properly formulated, the company can start steps to market the product.
   - If the product is industrial enzymes or research instruments, the sales staff can begin advertising and selling the product as long as EPA and USDA requirements are met.
   - If the product is pharmaceutical, an **Investigational New Drug (IND) Application** must be filed with the FDA. An IND Application describes the structure, specific function, manufacturing process, purification process, preclinical testing, formulation and specific application of the proposed pharmaceutical. The company submits an IND Application in anticipation of clinical testing, an FDA requirement for approval of a drug for market.

3. Clinical trials may take from 2 to 5 years. Clinical trials conducted on human are used to determine the safety and efficacy of the product. The trials are designed based on a set of protocols – type of people accepted, procedures, dosages and study duration. Throughout the trials, companies continue to develop and perform assays on human serum and plasma to determine dosage for greatest efficacy.
   - Clinical trials are performed in phases: Phase I – small sample of high-risk patients test a new drug for safety, dosage range and side effects. Phase II – study group is expanded to several hundred subjects and additional safety, dosage and efficacy testing is completed. Phase III – study group is expanded to thousands; safety and efficacy testing continues. Treatment’s effectiveness and its safety are compared to existing drug therapies. Phase IV – after the product has been marketed for a period of time, FDA requires trials to provide better safety and efficacy based on larger population.
   - Clinical trials are most often double blind – researchers and subjects don’t know which treatment the subjects are receiving: the new test drug or the placebo.

4. Once a company proves safety and efficacy, a marketing application is composed to include all the product descriptions and clinical trial results. The application is sent to the FDA for review and approval. The FDA approval requires site visits to manufacturing companies to check for Good Manufacturing Practices (GMP). The FDA approval takes 1 to 2 years.

**Activity 3:**
The QA Department at a pharmaceutical company is responsible for meeting all the regulatory guidelines by the FDA. For most biotechnology products, ISO 9000, an international standard of policies for products and services, is used as a guide. Describe why ISO 9000 is important to biotechnology manufacturing. [http://asq.org/learn-about-quality/iso-9000/overview/overview.html](http://asq.org/learn-about-quality/iso-9000/overview/overview.html)

**Activity 4:**

*Adapted from “Biotechnology: Science for the New Millennium” by Ellyn Daugherty.*
MARKETING AND SALES

Administrative, financial, legal and scientific staff meets regularly to assess and develop the company’s goals. A long-term plan outlines a company’s R&D scheme and business strategies with the intent of maximizing company value. The goals of R&D include decisions about the products and how many products should be in the pipeline at one time.

Marketing – As soon as the product receives all necessary approvals, it can be sold. The sales department is to advertise and publicize the product to an appropriate audience such as physicians or industries. Factors that affect product sales include: effectiveness of marketing team, pricing, patent protection, timing of FDA approval or rate of market penetration for competitive products.

Proprietary/Patent Rights – A company may invest millions of dollars in development of a product. At any time, individuals or companies could steal protocols or production information to begin producing or marketing the product. To protect against intellectual theft, companies proceed in two ways: Most companies require their employees to sign a proprietary- rights contract – employee agrees to keep secret the R&D of the company’s product. A company will move to secure a patent protection for a product under development. Gaining and retaining patent protection is of constant concern. Patent disputes can interfere with bringing products to market.

Product Application – Once a product is being synthesized and approved, the company will look into other applications of the product. If another application is found, a company can save thousands in R&D costs. Sometimes a company changes a product on a molecular level, resulting in different versions and different applications. Each product version must complete rigorous testing, but the R&D costs are reduced once the safety has been proved for the first application.

BIOTECHNOLOGY INDUSTRY & RESEARCH

Funding Biotechnological Advancements –

<table>
<thead>
<tr>
<th>Type of Organization</th>
<th>Funding Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large biotech &amp; pharm companies</td>
<td>Profits from sales of existing products</td>
</tr>
<tr>
<td>Small biotech companies and start-ups</td>
<td>Venture capital and government grants</td>
</tr>
<tr>
<td>Academic institutions, research institutions, hospitals and government labs</td>
<td>Government grants and other funding, foundations, endowments and charities</td>
</tr>
</tbody>
</table>

Sharing of Scientific Information – Scientists constantly challenge and question each other’s data and their discourse results in high-quality research. Scientific discoveries are most reliable when different laboratories using different methods come to the same conclusions. Scientists share their discoveries through peer-reviewed publications, conferences, meetings and seminars.

Patents – allow the inventors a set time period (usually 20 years) to make back the money they invested and prevent others from using the invention during the patent period. In exchange for these rights, the invention must be disclosed and shared with the scientific community. If others wish to use the product, they need to negotiate terms and permission to use or license the product.

*Adapted from “Biotechnology: Science for the New Millennium” by Ellyn Daugherty.*
Governmental Regulations of Biotechnology – Biotechnology is highly regulated by many governmental agencies to ensure research is performed safely, products are safe and effective, and that neither the products nor their manufacturing processes harm the environment. In the U.S., the main agencies governing biotechnology are:

- FDA – responsible for ensuring that food is safe; drugs are safe and effective.
- EPA – protect human health and the environment.
- USDA – responsible for ensuring that agriculture is protected.
- OSHA – responsible for regulating the safety of workers in the workplace.

Regulation of Genetically Modified Organisms – National Institutes of Health (NIH) regulates the use of GMOs in research labs. FDA regulates GMOs in the food supply. The FDA does not require food containing GMOs to be labeled if the food is “substantially equivalent” to the conventional variety in terms of its nutritional content and health effects. In Europe and Japan, if GMOs exceeds 1% of all the ingredients, the food must be labeled. Field testing of GM plants is mainly regulated by the Animal and Plant Health Inspection Services (APHIS), an agency of the USDA. The EPA is involved in regulating the cultivation of GM crops, the impact GMOs have in industry on the environment and regulates microorganisms used in agriculture.

Regulation of Products in Health Care – FDA regulates drugs, medical devices and diagnostic tools – concerned with safety and efficacy. All new drugs must receive approval from the FDA at each clinical trial stages. Preclinical trials must be performed using good laboratory practice (GLP) which ensures the research and the data meet an internationally recognized level of quality.

Industry Practices – industry standards help global business because they harmonize business practices around the world.

- Good Laboratory Practices (GLP) is a quality system used for non-clinical health and environmental safety studies. GLP is used to develop test data on the properties and safety of chemicals, biological molecules so they can be relied upon with confidence among countries. GLP requires that studies be performed according to its specifications and requires that a QA program be in place to ensure compliance.
- Good Manufacturing Practices (GMP) is a set of principles for ensuring the quality and safety of manufactured products used in health care. As with GLP, training, record-keeping, archiving, data monitoring, SOPs and equipment maintenance are important. GMP is enforced by the FDA.

*Adapted from “Biotechnology: Science for the New Millennium” by Ellyn Daugherty.*
ACTIVITY 5:
Create a flow chart that diagrams the major steps in an rDNA protein product that is destined to become a pharmaceutical. [http://www.fda.gov/drugs/newsevents/ucm130961.htm](http://www.fda.gov/drugs/newsevents/ucm130961.htm)

Research & Development
- Product Identification – examples of products and how they are found.
- Assay Development – examples of how assays are developed to identify/quantify the product.
- Genetic Engineering – examples of genetically engineered cells used to produce the product.

Manufacturing
- Fermentation/Cell Culture – description of how small amounts of genetically engineered cells are grown in increasingly larger volumes under strict regulations (scale-up)
- Recovery/Harvest – examples of how a product is purified on a large scale from cell cultures
- Product Formulation – examples of the variety of formulations possible for a product

Marketing
- Product Testing/Clinical Trials – examples of testing required before patients use a product.
- FDA Approval – process by which agent is judged safe for use and distribution.
- Regulations – any regulations set by federal agencies

HS-AB-6: Assess current trends, ethical, legal, and regulatory issues related to the development of biotechnology products.
6.1 Monitor scientific journals, Internet sources, mass media, and industry associations to identify current trends and policy issues in biotechnology.
6.2 Distinguish between marketing material and experimentally validated information.
6.5 Describe intellectual property rights, technology transfer, and how biotechnology is funded.
6.7 Describe the role of federal regulatory agencies and the Code of Federal Regulations applicable to biotechnology (e.g., FDA [Food and Drug Administration], 21 CFR [Code of Federal Regulations], EPA [Environmental Protection Agency], NIH [National Institute of Health], USDA [United States Department of Agriculture], etc.) and the relationship to international regulatory systems (e.g., ICH, etc.).
6.8 Explain the phases of clinical trials and requirements for obtaining FDA product approval.
6.9 Define the purpose of quality assurance, quality control, method validation, documentation, current Good Manufacturing Practices and Good Laboratory Practices.
6.10 Document and keep accurate records according to regulatory requirements.

*Adapted from “Biotechnology: Science for the New Millennium” by Ellyn Daugherty.