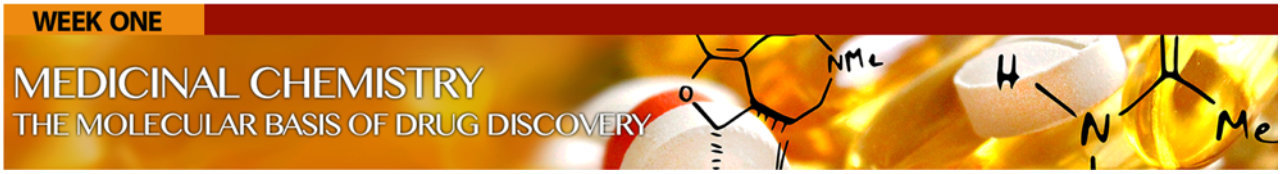


Welcome to Week 1

Starting week one video

Please watch the online video (1 minutes 7 seconds).

OPTIONAL-Please participate in the online discussion forum.

Chapter 1 - Pre-Regulatory Medicine

Introduction to Chapter 1

Chapter 1 contains three subsections.

- Natural Products
- Synthetic Drugs
- Need for Regulation

At the conclusion of this chapter, you should have an appreciation for the types of drugs that have been used throughout history and up to the late 1930s. You should also understand the challenges faced by drug regulatory agencies as they try to enforce the creation of a safe and effective drug supply.

OPTIONAL-Please participate in the online discussion forum.

1.1 Natural Products

Ephedrine video

Please watch the online video (7 minutes, 6 seconds).

A condensed summary of this video can be found in the *Video summary* page.

OPTIONAL-Please participate in the online discussion forum.

Pharmacophores in drugs

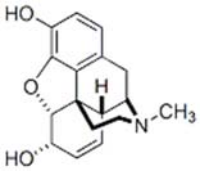
Background: The phenethylamine compounds mentioned in the video are relatively small structures with an easily identified pharmacophore. Pharmacophores in drugs can be considerably more complex.

Instructions: Read the passage concerning compounds that contain the same pharmacophore elements as morphine. Use the information to answer the questions that follow the text.

Learning Goal: To examine a molecule's structure and determine whether a molecule contains a specified pharmacophore.

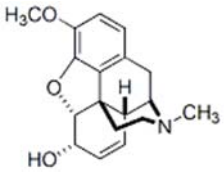
Opiates, Opioids, and Their Pharmacophores

A notable natural product that can be traced to the early history of humankind is morphine (**1**). Morphine is found in opium, the residue that seeps from damaged poppy seed pods. Morphine is a complex alkaloid with very potent **analgesic** (pain relieving) properties. Beyond offering pain relief, morphine is also highly addictive.



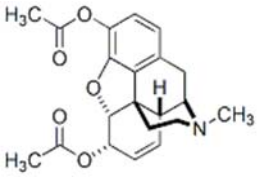
morphine
1

Morphine is not the only compound found in opium. Opium contains approximately two dozen other compounds including codeine (**2**). Morphine and codeine are both known as **opiates**. Opiates are naturally occurring compounds that share the same activity as morphine.

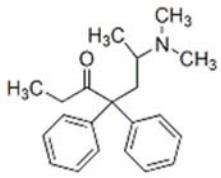


codeine
2

A number of compounds similar to morphine and codeine can be synthesized in a lab. Some are prepared by modifying morphine itself. Examples of synthetic and semi-synthetic morphine analogues include heroin (**3**) and methadone (**4**). These unnatural compounds with morphine-like activity are called **opioids**. Methadone looks very little like morphine, but it is still considered an opioid because of its biological activity.



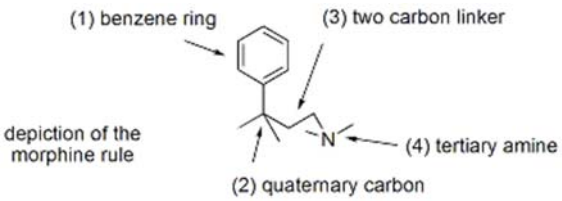
heroin
3



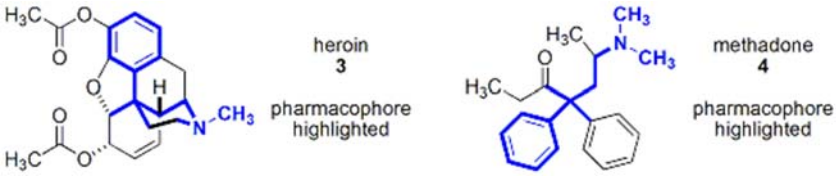
methadone
4

Almost all opiates and opioids share common structural features known as the **morphine rule**. The morphine rule stipulates the structural requirements for a compound to have morphine-like activity. Specifically, the morphine requires a compound to have (1) a benzene ring (2) attached to a

quaternary carbon connected by (3) a two-carbon spacer to (4) a tertiary amine. These structural elements describe the pharmacophore of morphine.



The pharmacophore cores of heroin and methadone are shown below traced in blue.



Collectively the opiates and opioids play a key role in pain management. Because of their addictive properties, opiates and opioids are not suitable for long-term use. For certain situations, such as post-operative surgery pain, they are very effective and safe.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

Regulation of herbal dietary supplements?

Background: Many herbal medicines have been used for thousands of years and continue to be used today. The herbal medicine, or herbal supplement, industry is very loosely regulated in the United States as well as most nations.

Instructions: Read the linked article below from *BMC Medicine* concerning the quality of herbal supplements in the marketplace. Use the information in the article to answer the questions that follow.

Learning Goal: understand purity issues within the herbal supplement industry.

A recent article in *BMC Medicine* reported that possibly a high percentage of herbal supplements contain little or none of the supposed active plant material.

Please return to the online course and read the article to which the above paragraph refers.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

1.2 Synthetic Drugs

Sulfa drugs video

Please watch the online video (6 minutes, 23 seconds).

A condensed summary of this video can be found in the *Video summary* page.

OPTIONAL-Please participate in the online discussion forum.

Early synthetic drugs

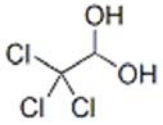
Background: Around the middle to late 1800s, organic chemistry had advanced sufficiently to allow the preparation of organic molecules as drugs.

Instructions: Read the passage of text below on three very early synthetic drugs.

Learning Goal: To gain exposure to the early important synthetic pharmaceuticals.

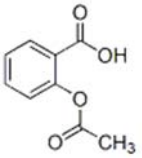
Below are three very early synthetic drugs.

- chloral hydrate
  Chloral hydrate (**1**) is a solid formed by the reaction of trichloroacetaldehyde and water. The compound is a potent sedative. Once its properties were discovered around 1870, chloral hydrate was used widely in medicine. Chloral hydrate was prone to abuse, and solutions of chloral hydrate became called "knock-out drops" or a "Mickey Finn". The phrase "slip him a Mickey" became synonymous with using chloral hydrate to incapacitate a person for ignoble ends.



chloral hydrate
1

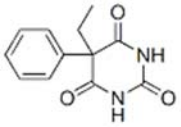
- aspirin
  Aspirin (**2**) was first prepared around 1900 by a scientist at Bayer. It is an effective analgesic, antipyretic (reduces fever), anti-inflammatory, and anticoagulant (reduces blood clotting). The name Aspirin is still under trademark protection in some parts of the world. In those jurisdictions the generic form of the compound is referred to as acetylsalicylic acid, or ASA.



aspirin
2

- phenobarbitol
  Phenobarbitol (**3**) is an anticonvulsant. Phenobarbitol was discovered around 1900 during a

flurry of early research in the area of barbiturates as anticonvulsants and sedatives. Phenobarbitol continues to be used widely today, especially in less developed nations.



phenobarbitol
3

OPTIONAL-Please participate in the online discussion forum.

Pharmacophore of sulfonamide antibiotics

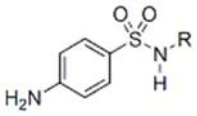
Background: Sulfanilamide is the parent molecule of the sulfa drug class. The simple structure of sulfanilamide very nearly describes the pharmacophore of the sulfa drugs.

Instructions: Read the text below and use the information to answer the questions on the pharmacophore of sulfa drugs.

Learning Goal: To identify sulfonamide antibiotics based upon their structural features.

As an early class of drugs, sulfonamide antibiotics have been extensively explored. Literally thousands of different sulfonamides were prepared and tested in the 1930s and 1940s. Through these studies, the pattern of activity and pharmacophore for sulfonamide antibiotics became clear.

The pharmacophore for sulfonamides (**1**) consists of a 4-aminosulfonamide core with tolerance for aryl and acyl groups on the sulfonamide nitrogen. Almost all sulfonamide antibiotics follow this simple model.



sulfonamide
pharmacophore
1

R = H, aryl, heteroaryl, acyl

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

1.3 Need for Regulation

Elixir Sulfanilamide tragedy video

Please watch the online video (7 minutes, 33 seconds).

A condensed summary of this video can be found in the *Video summary* page.

OPTIONAL-Please participate in the online discussion forum.

Continued issues with diethylene glycol

Background: Since 1938 the US Food and Drug Administration has held increased powers of oversight over the safety and effectiveness of pharmaceuticals in the United States. The drug regulatory agencies of other nations hold very similar roles and powers.

Instructions: Read the text below and the accompanying report from the World Health Organization and answer the subsequent questions.

Learning Goal: To understand the complexities and risks that international trade creates for drug regulatory agencies trying to maintain a safe drug supply.

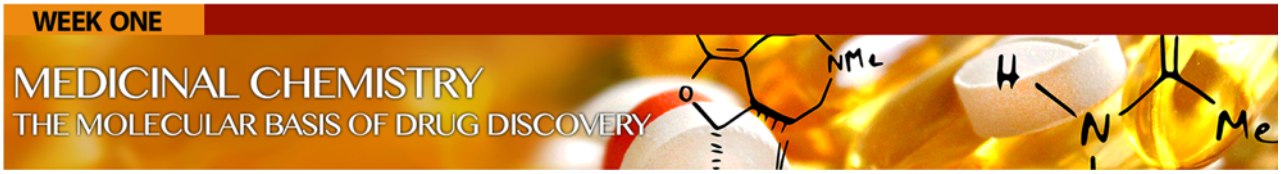
Diethylene glycol played a deadly role in the Elixir Sulfanilamide tragedy. Unfortunately diethylene glycol continues to be found in medicines despite the efforts of drug regulatory agencies. In 2006 many people, likely several hundred, died in Panama after taking cold medicine containing diethylene glycol.

Read the linked bulletin from the World Health Organization and answer the questions below

Please return to the online course and read the bulletin to which the above paragraph refers.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.



Chapter 2 - Drug Discovery: From Concept to Market

Introduction to Chapter 2

Chapter 2 contains three subsections.

- Phenotype- vs. Target-Based Drug Discovery
- Drug Development Outline
- Intellectual Property

At the conclusion of this chapter, you should understand the different stages of development for a drug. You should also know the difference between generic and branded drugs as well as the role of patents in drug discovery.

2.1 Phenotype- and Target-Based Drug Discovery

Phenotype vs. target video

Please watch the online video (6 minutes, 20 seconds).

A condensed summary of this video can be found in the *Video summary* page.

OPTIONAL-Please participate in the online discussion forum.

Mixing target and phenotype

Background: In their traditional forms, target-based drug discovery tends to rely upon in vitro testing for lead optimization, and phenotype-based drug discovery leans upon in vivo testing.

Instructions: Read the passage below on how phenotype-based drug discovery programs often blend with target-based techniques.

Learning Goal: To understand that different approaches to drug discovery can frequently blur together.

A strength for phenotype-based drug discovery is that the compounds of interest are known to be active because their activity has already been observed in a living organism. The reliance on in vivo testing, however, is a significant hindrance for phenotype-based drug discovery. The in vivo tests are more involved and longer than in vitro tests, and the lead optimization process is slower as a result.

A more ideal situation would be to start with a compound with known in vivo activity and the ability to optimize its potency with quick in vitro screens. This ideal situation is a cross between

phenotype- and target-based drug discovery and most often begins with the phenotype model and switches over to the target method.

The phenotype model begins with an observed effect in vivo. The compound that causes the effect is the lead molecule. Instead of continuing the program with improving the lead with more in vivo testing, the drug discovery group works to discover the protein to which the molecule binds in the body. In other words, the discovery group seeks out the target responsible for the biological activity. Once the target is known, a molecular biology group will attempt to develop a biochemical binding assay to test the ability of a molecule to bind the target. Newly prepared compounds are then tested with the rapid in vitro binding assay.

In this blended model, the discovery group can be more confident that the final molecule will have activity in animals. Additionally, the improvement of the activity of the lead will be accelerated because it is being accomplished with in vitro methods. When performed properly (not easy!), the blended approach can combine the best of both drug development methods. Drug programs that discover their leads through phenotype-based observations, regardless of how they later optimize the lead, are typically categorized as phenotype-based discovery programs.

OPTIONAL-Please participate in the online discussion forum.

Support for phenotype-based drug discovery

Background: The topics of phenotype- and target-based drug discovery can be very divisive. Both methods of drug development have very vocal supporters and detractors. There has recently been a push for a renewed emphasis on phenotype-based methods.

Instructions: Read linked article from *Science Business eXchange* and answer the subsequent questions.

Learning Goal: To gain an appreciation and understanding for phenotype-based drug discovery in a medicinal chemistry course that will emphasize target-based drug discovery.

A recent article in *Science Business eXchange* discusses developments in phenotype-based drug discovery.

Please return to the online course and read the article to which the above paragraph refers.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

2.2 Drug Discovery Outline

Drug discovery outline video

Please watch the online video (8 minutes 22 seconds).

A condensed summary of this video can be found in the *Video summary* page.

OPTIONAL-Please participate in the online discussion forum.

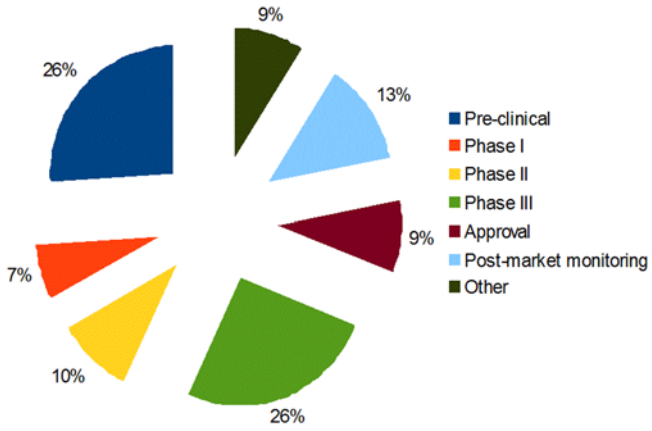
The cost of doing business

Background: The total cost of bringing a drug to market is highly debated, but the most reliable estimates seem to place the figure at around US$1 billion or higher.

Instructions: Read the text below and use the information to answer questions in a subsequent unit.

Learning Goal: To learn about the cost of the different stages of drug development.

According to DiMasi et al.,[1] the costs of a drug can be broken down as shown below.



Note that the pre-clinical stages of drug discovery, which can take years, only account for approximately one quarter of the total costs. The expenses begin to accrue quickly with the clinical trials. Phase III typically costs the most because of the very large number of patients involved. In Phase I and Phase II, volunteers and patients are intensely monitored. The costs of Phase I and Phase II might be lower than Phase III, but the per patient costs are higher in the early phases.

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1. DiMasi, J. A.; Hansen, R. W.; Grabowski, H. G. The Price of Innovation: New Estimates of Drug Development Costs. *J. Health Econ.* **2003,** *22,* 151-185.

OPTIONAL-Please participate in the online discussion forum.

The risk of failure

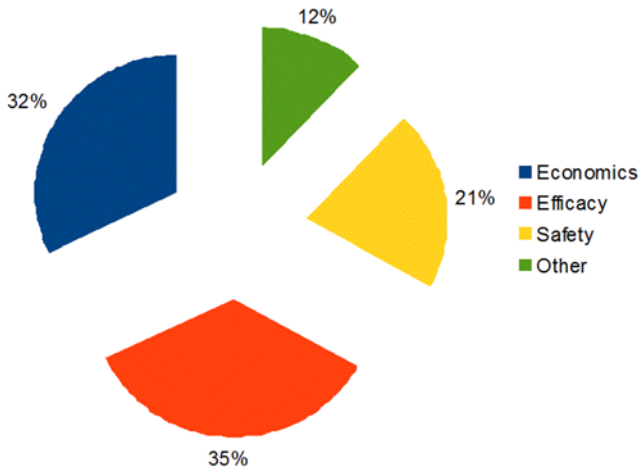
Background: Most attempts to develop a drug end in failure. Since the costs of bringing a drug to market are high, even failures in the early stages of a drug program add significant costs to a drug company.

Instructions: Read the text below and use the information to answer questions in a subsequent unit.

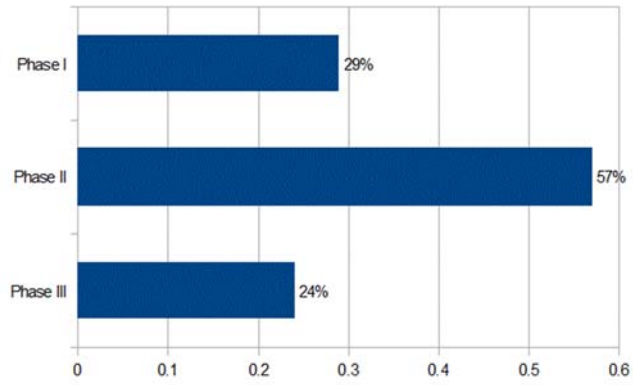
Learning Goal: To learn about the different reasons for failures in drug development.

A widely mentioned statistic is that, for every 10,000 compounds that are analyzed in a drug discovery program, only 5 will be tested in humans as clinical candidates, and only 1 will be approved as a drug. The origin of these figures is hard to trace, but we can make an attempt. In a target-based drug discovery program, it would not be uncommon to screen a million or more molecules in a library. Perhaps the top 1% in terms of binding to the target might be selected as hits in the screen. That cut-off would give 10,000 hits. Of these 10,000 compounds, 5 (following optimization) might be advanced to the clinic with just 1 becoming a drug.

According to DiMasi et al.,[1] the primary reasons for failure of a drug discovery effort in the United States from 1981 to 1992 are listed below. These figures would be for leads that make it into animal testing.



DiMasi further gives the failure rates for compounds that make it into the different clinical trials. Note that the failure rates are cumulative. Therefore, a clinical candidate has a 29% of failure in Phase I. If it clears Phase I, it then has a 57% of failure in Phase II.



One way to examine this bar graph is to consider the probably for success of a drug. If a clinical candidate has a 29% chance of failing in Phase I, then it has a 71% chance of *success* in Phase I. Similarly, it will have a 43% and 76% chance of success in Phase II and Phase III, respectively. With this interpretation, a drug will have a 23% (0.71 × 0.43 × 0.76) chance of completing all the trials. A 23% chance corresponds to somewhere between a 1-in-4 or 1-in-5 chance of success.

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1. DiMasi, J. A. Risks in New Drug Development: Approval Success Rates for Investigational New Drugs.*Clin. Pharmacol. Ther.* **2001,** *69,* 297-307.

OPTIONAL-Please participate in the online discussion forum.

Questions on cost and failure

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

2.3 Intellectual Property

Patents and branding video

Please watch the online video (7 minutes 17 seconds).

A condensed summary of this video can be found in the *Video summary* page.

OPTIONAL-Please participate in the online discussion forum.

Composition of matter in action

Background: Patents are a type of intellectual property. While they are invaluable to the drug industry for the exclusive rights they afford, patents are legally very complex.

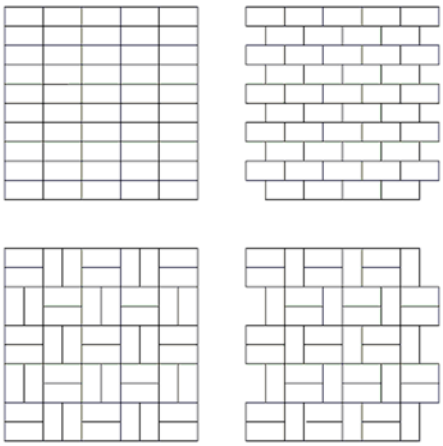
Instructions: Read the passage below for one example of how the composition of matter patent is used in the drug industry.

Learning Goal: To learn about composition of matter patents and crystal polymorphs.

Crystalline Polymorphs of Ranitidine[1]

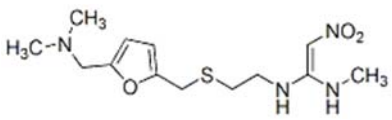
Drugs are normally protected with a composition of matter patent. Surprisingly, some drugs require multiple different composition of matter patents. Multiple patents are needed when a drug exists in multiple, different crystalline forms. These different forms are called **polymorphs**.

In polymorphs the same molecule can pack together in different orientations and patterns. Each pattern is a different polymorph. A simple example of polymorphs can be found with bricks, which can be stacked in various patterns as pavers. A few patterns are shown below. Molecules can stack in different patterns in much the same fashion.



Because polymorphs can have different physical properties (e.g., solubility and melting point), a drug company must be able to control which polymorph of a drug is being synthesized.

Ranitidine (**1**) is a drug that treats acid reflux. In 1978 Glaxo, the discoverer of ranitidine, obtained a composition of matter patent on the compound. At the time, the term of patents was 17 years from the date of issue. Therefore, Glaxo's patent on ranitidine was set to expire in 1995, or 17 years after 1978.



ranitidine
1

As Glaxo continued to research ranitidine, a second polymorph was discovered. Glaxo obtained a composition of matter patent on the second polymorph, called Form 2, in 1985. The Form 2 patent would expire in 2002.

Glaxo ultimately marketed ranitidine as Form 2 under the name of Zantac. During the 1980s Zantac was a blockbuster drug, and its success continued into the 1990s.

Around 1990 a company called Novopharm, a generic drug manufacturer, started to develop a generic form of ranitidine. Novopharm hoped to capitalize on Form 1 of ranitidine because the patent on Form 1 would expire in 1995. During their research, chemists at Novopharm tried to make the original, Form 1 polymorph of ranitidine based on the Glaxo procedures. To their surprise, the Novopharm chemists could only prepare Form 2. Novopharm reasoned that if Form 2 was known all the way back in 1978 in the first work on ranitidine, then the 1985 Form 2 patent was not valid. Novopharm pushed ahead and applied to the FDA to market generic ranitidine in 1995, corresponding to the expiration of the Form 1 (perhaps Form 2) patent.

Glaxo then sued Novopharm for planning to market ranitidine's Form 2, on which Glaxo held a patent until 2002. A third-party lab was called in to prepare Form 1 of ranitidine from Glaxo's 1978 Form 1 patent. The lab successfully reproduced the procedure to make Form 1, and Glaxo won the case.

Novopharm went back to work and managed to reproduce the Form 1 procedure. Novopharm then filed paperwork with the FDA to market generic ranitidine (Form 1) starting in 1995, the year of expiration of Glaxo's Form 1 patent.

Glaxo again sued Novopharm. This time, Glaxo claimed that Novopharm's Form 1 of ranitidine likely contained impurities of Form 2. If so, then marketing this mixture would violate Glaxo's exclusive rights to Form 2. Novopharm provided evidence that their ranitidine was free of Form 2, and Novopharm won the case.

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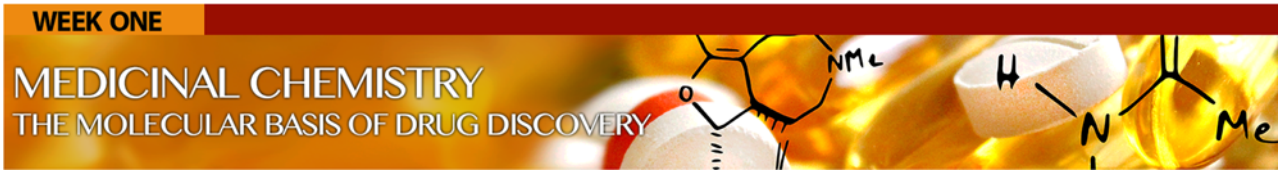
1. Bernstein, J. Polymorphism and Patents from a Chemist's Point of View. In Hilfiker, R. (Ed.)*Polymorphism: In the Pharmaceutical Industry.* Weinheim, Germany: Wiley-VCH, 2006, Chapter 14.

OPTIONAL-Please participate in the online discussion forum.

Global complications with patents

Background: The interpretation and implementation of patent law varies from one country to another.

Instructions: Read the linked article from *The Economist* and answer the subsequent questions related to patents.



Learning Goals: To understand how patents affect drug profitability around the world.

A recent posting on the website of *The Economist* covers a key patent ruling in India.

Please return to the online course and read the posting to which the above paragraph refers.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.