DRUG DESIGN, DEVELOPMENT, AND DELIVERY:
An Interdisciplinary Course on Pharmaceuticals

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For the past five years, Georgia Tech's School of Chemical and Biomolecular Engineering (ChBE) has offered an innovative interdisciplinary course in drug design, development, and delivery, also known as the D4 course. This course was developed due to changes in chemical engineering education over recent years, as well as needs within the pharmaceutical industry for an interdisciplinary approach to the development of novel drugs and formulations. It is offered as part of the biotechnology option track, an undeclared certificate offered to ChBE undergrads. One biotech elective is required for all students in the biotech option, and this course satisfies that requirement. The D4 course also meets requirements in the Department of Biomedical Engineering and the School of Chemistry and Biochemistry; both principal course instructors serve as adjunct faculty in one of these additional schools. The course provides the additional advantage of offering instruction in the important biotech area of pharmaceutical development. Aspects of this type of biotech development, such as drug manufacturing and drug delivery, are underserved in university curricula and consequently offer interesting opportunities for employment of graduates.[1, 2]

The D4 course was developed through the leadership of the Georgia Tech Center for Drug Design, Development, and Delivery (CD4). CD4 is composed of close to 40 faculty with interests in the drug development process. The authors serve as its director and co-director. Ten to 15 doctoral students in CD4 receive fellowships each year from a long-standing training grant from the Department of Education GAANN program. The D4 course was created to serve these CD4 graduate students, ChBE undergraduates taking the biotech option, and undergraduates from other departments interested in pharmaceuticals. As discussed below, a balanced interdisciplinary mixture of students is assured through admissions restrictions.

This article aims to provide information on the D4 course's structure, its contents, and the instructional philosophy behind it, with the hope that this framework may be directly useful to others or might be adapted to other courses geared towards the pharmaceutical and other industries.

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GOALS OF THE COURSE

The overarching goal of the D4 course is to give students insight into the drug development process in the pharmaceutical industry.[3,4] Without specific training, it is not necessarily obvious how to apply chemical engineering principles to this highly specialized field, as the pharmaceutical industry has its own unique culture based on the critical needs of providing drugs that are both safe and effective. For example, while the development process might often be complex and inefficient, the drug product must be of extremely high purity. During the drug development process, activities must be documented much more extensively than in other industries. In addition to the detailed structure of the pharmaceutically active ingredient itself, the Food and Drug Administration (FDA) requires its manufacturing process to be set even before the completion of clinical trials. Once the manufacturing process is set, it is expensive and time-consuming to make major changes, such as switching raw materials or adding or dropping steps for downstream processing. There are also the variables introduced by having drug delivery in the hands of the consumer and the need to assure safe and reliable compliance. Due to these unique circumstances, there is a need for this course to address the application of biochemical and engineering principles to this industry.

The specific objectives of this course are to (i) appreciate critical issues, perform analysis, and make quantitative calculations related to drug design, drug development, and drug delivery; (ii) integrate concepts from drug design, development, and delivery and appreciate their interdependence; (iii) understand the different phases of the pharmaceutical process; (iv) appreciate the role of alternative methods and broader implications of the pharmaceutical process; and (v) communicate with professionals in the pharmaceutical community.

The three parts of the pharmaceutical industry covered in the course are drug design, development, and delivery. Drug design, which is drawn largely from chemistry, involves synthesis of the active ingredient beyond the discovery synthesis. Development involves manufacturing and formulation, which focuses on chemical engineering principles in both industrial chemistry and biotechnology. Multiple disciplines, including biomedical engineering, are often involved in drug delivery, the step in which both the route of administration and drug distribution within the body need to be determined and controlled. One of the goals of the training within the course is to highlight the interdisciplinary connections involved in the pharmaceutical development process and thereby train students to have an impact on the industry by taking an integrated approach that streamlines the drug development process.

The D4 course focuses on actual drugs and the processes and issues surrounding their delivery, whether successful or failed, including continual references to actual drug substances (the active ingredient alone) or drug products (active ingredient and delivery vehicle). The class also is kept interesting and relevant through occasional guest lectures by experts in the field. During the final phase of the class, we examine four case studies to apply the general lessons covered in the first part of the class to specific scenarios in industrial and medical practice. Each case study is analyzed for strengths and weaknesses of current and alternative approaches. This emphasis on real industry examples enables both students and instructors to consider the broader impact of the material and the educational philosophy within healthcare, economics, and other fields.[5]

The course instructors, and many of the TAs and guest lecturers involved in the course, have significant industry experience. Both main instructors have worked for pharmaceutical companies and so are able to bring real-world experience to the course material. TAs, often selected from among graduate students with prior experience in the pharmaceutical industry, have to be more active, interested, and knowledgeable than in a typical survey course. They put in extended hours to explain material to students lacking detailed background in transport phenomena or bioorganic chemistry, and are confronted with group dynamics in connection with the project-team phase of the class. The lectures on drug design are given by a professor from Georgia Tech's School of Chemistry and Biochemistry, and the lectures on drug development and drug delivery are given by the instructors of the D4 course. Supplementary lectures on pharmacology and clinical trials (by Emory University School of Medicine faculty) and on pharmaceutical marketing (by an industry colleague) are included to continually reinforce the broader significance of course material. This emphasis on real-world relevance explains the success of the course with students who are mostly seniors and graduate students often about to enter industry positions.[6]

Existing courses on pharmaceuticals at other universities are typically more narrowly focused, for example, on medicinal chemistry aspects of drug design and discovery or on formulation aspects of drug delivery systems. We are not aware of any other course that integrates drug design, development, and delivery in a single course, and explores their connections in the context of broader societal impacts.

COURSE STRUCTURE AND SYLLABUS

Because student interest is high and the class fills easily, we have chosen to restrict enrollment to a limited number of students from each major department: approximately 10 students each from the School of Chemical and Biomolecular Engineering, School of Chemistry and Biochemistry, and Department of Biomedical Engineering. Around 10-15 seats are reserved for GAANN Fellows, as the class is a requirement of the fellowship program. The remaining 10 seats are filled by graduate students from various departments. Thus, the class is designed to serve 54 students, approximately 60% undergraduate and 40% graduate, who can then be divided

into 18 interdisciplinary teams of three students each for the case study projects.[7-9] This structure guarantees that the students will be working and communicating with colleagues of other disciplines, just as they would in industry. The class is highly interactive, with interaction and questions not only between students and instructors but, especially during the project-team phase, between the students themselves.

As summarized in Table 1, the course begins with an overview of pharmaceutical development that features goals, timelines, and constraints that guide the industry. Because of the interdisciplinary nature of the course, we also include optional refresher lectures on biochemistry for engineering students and diffusion for chemistry students. The only prerequisite for the course is one semester of biochemistry. Next, drug design, development, and delivery (*i.e.*, the three Ds) are covered for two to three weeks each. Finally, the student-led case studies are developed and presented.

The Three Ds

During the overview section of the course, the instructors describe the integrated process of drug development from discovering the active ingredient to its formulation into a dosage form, its manufacture using suitable reaction pathways, its assessment in clinical trials, the FDA approval process, and its introduction into the market. One lecture tells the story of three innovators in the drug delivery field—Robert Langer, David Edwards, and Alejandro Zafaroni—and presents innovative drug delivery systems in the context of the technical and human factors that influenced their development and ultimate impact on medicine. Another lecture deals with the development process and business context of the pharmaceutical industry and portrays the risks in developing novel pharmaceuticals, as tight regulations by the FDA, rigorous testing of candidate compounds, and often long and involved clinical trials to prove safety and efficacy result in high failure rate of candidates and thus very high expenses for every successful new drug.

The drug design module presents key ideas behind the search for a compound testable in the clinic and thus able to be manufactured on large scale. Concepts such as binding of a small-molecule inhibitor to an enzyme or to a receptor are covered, as well as varying the structure of a lead compound to improve characteristics such as inhibition constant, stability, or bioavailability. Rules for the molecular properties of successful drug candidates are discussed, most notably Lipinski's Rule of Five.[10]

TABLE 1
D4 Course Syllabus

CLASS MEETINGS	SECTION	SELECTED TOPICS
Classes 1 – 4	Introduction	Challenges and current methods of drug design, development, and delivery; successful examples; tutorials; homework 1
Classes 5 – 8	Drug Design	Overview of protein-ligand interactions and enzyme catalysis; enzyme inhibition and drug design; quiz; homework 2
Classes 9 - 13	Drug Development	Manufacturing & process development; small molecule manufacturing; development of protein therapeutics and vaccines; quiz; homework 3
Classes 14 - 18	Drug Delivery	Pharmacokinetic modeling; methods of delivery; drug delivery device commercialization case study; quiz; homework 4
Classes 19 - 20	Pharmacology and Clinical Trials	Guest lecturers; quiz
Spring Break	Plant Trip to Puerto Rico (optional)	–
Class 21	Pharmaceutical Marketing	Guest lecturer
Classes 22 - 23	Case Study I: Ocular Dorzolamide	Synthesis by conventional and novel chemoenzymatic routes; topical delivery; molecular design
Classes 24 - 25	Case Study II: Contraceptive Hormone Patch	Chemical and microbial synthesis; transdermal and other delivery methods
Classes 26 - 27	Case Study III: Leuprolide Implant	Solid-state and enzymatic synthesis; polymeric controlled release; broader impacts
Classes 28 - 30	Case Study IV: Insulin	Delivery and production methods; stability issues
Final Exam Week	Final Exam	Derived largely from case studies

The first lecture of the drug development module lays out the challenges of drug manufacturing and formulation, one of which is the preeminence of purity over yield, which requires catalysts with exquisite selectivity. After the initial lecture, one lecture each is spent on manufacturing of small molecules, therapeutic proteins, and vaccines. Foci for each, respectively, are the design of environmentally benign processes to decrease both costs and ecological footprint for small molecules; the complex downstream processing to a pure, virus-free, therapeutic protein; and the comparison of eggs and cell culture for the manufacture of drug substance for vaccines. Another challenge is the necessity of formulation to preserve the structural and functional integrity of the drug product for at least

two years in the container identical to the one for selling the drug, so one lecture deals with issues of formulation.

The drug delivery module starts with a lecture on methods used to design, formulate, and manufacture conventional pharmaceutical dosage forms, with special emphasis on oral tablets and capsules, and also presents mathematical analysis of drug pharmacokinetics. The subsequent lectures address controlled release, transdermal, ocular, and other routes of drug delivery in detail. The final lecture presents a detailed discussion of the development of microneedle drug delivery systems at Georgia Tech and in industry, which emphasizes the challenges of bringing a product forward from the initial idea stage through clinical introduction.

TABLE 2
Attributes of Current and Past D4 Course Case Studies

Product name (company)	Active ingredients	Delivery method
Trusopt® (Merck)	Dorzolamide	Eye drops
Ortho Evra® (Johnson & Johnson)	Ethinyl estradiol, Norelgestromin	Transdermal patch
Lupron Depot® (Abbott)	Leuprolide acetate	Injectable implant
Exubra® (Pfizer)	Insulin	Inhalation
Testoderm® (Alza)	Testosterone	Transdermal patch
Procardia-XL® (Pfizer)	Nifedipine	Oral osmotic pump

Products covered in case studies in the class have included drugs for a range of indications, such as cancer reproduction, ocular disease, heart disease, and diabetes. Each year the course includes four case studies, and every case study investigates at least two of the three Ds, most often development and delivery (Table 2).

Each case study is analyzed by a team typically of two undergraduates and one graduate student from at least two but typically three different disciplines. By the time the case study teams are formed, the students have already taken some quizzes and handed in homework, and the instructors can thereby balance teams according to known strengths and weaknesses of students.[11, 12]

The scope of the case study assigned to each group is intentionally broad so that the students will do their own research, on the basis of a few lead publications provided by the instructors, and develop their own analysis. One week before the project is due, each team meets with one of the instructors to outline the presentation, make their case, and receive feedback. When the group presents its case study to the class, total contact time is 40 minutes per team, with 20 minutes of presentation involving all three team members, followed by 20 minutes of Q&A primarily by the students, with supplemental questioning by the instructors.

Case Study Example: Ortho-Evra® patch (Johnson & Johnson)

One of the case studies focuses on the Ortho-Evra contraceptive patch, which provides an opportunity to evaluate competing methods of drug synthesis during the design phase, development issues related to cost-effectiveness and safety, and challenges of transdermal delivery and resulting medical issues. Introduced in 2001, Ortho-Evra® is a transdermal contraceptive patch manufactured and marketed by Ortho-McNeil-Janssen Pharmaceuticals, a subsidiary of Johnson and Johnson.[13] It contains a progesterone analog, norelgestromin, and an estrogen analog, ethinyl estradiol, that are released continuously during each week that the patch is worn. Initially, Evra® was a great success, taking a significant share of the contraceptives market by providing simple and reliable birth control using a once-per-week patch. Post-marketing clinical studies, however, showed that the total estrogen dose from the Evra® patch was significantly larger than that administered by conventional birth control pills, possibly posing increased cardiovascular risks.[14] Because the patch and the pill produced similar estrogen levels in the clinical trials, a change in the manufacturing process during scale-up to commercial production is suspected. These issues led to lawsuits and a huge decline in Evra® sales.[15] In response, J&J has changed product labeling and continues to market the patch.

In the student presentations, one of the student teams is charged with evaluating the transdermal patch technology used to make Evra® by considering the nature of the skin barrier, the medical suitability of controlled drug release across skin, and the advantages and disadvantages of different patch designs. Another team takes on alternative methods of contraceptive hormone delivery, including oral tablets, subcutaneous implants, intrauterine devices, and other approaches. Hormone synthesis is considered as well: for both ethinyl estradiol and norelgestromin, the conventional methods are chemical synthesis starting from residual materials from plants, such as sitosterol, stigmasterol, and phytosterol from soybeans or tall oil, the latter itself a residue from pulping. The potentially disruptive technology is a biotechnological synthesis route combining fermentation and enzymatic steps, possibly combined with a few purely chemical steps.

In addition to the many interesting technical issues associated with this case study, there is a rich set of business, medical, social, and political issues as well. For example, the business decision to continue marketing the product with updated labeling, rather than reformulating the patch to administer the intended estrogen dose, is addressed. The ethical implications of this decision are also discussed, along with the broader issue of access to contraception and associated disparities around the world.

Pharmaceutical Industry Plant Tour

During spring break of the semester the course is offered, there is an optional five-day trip to visit pharmaceutical industry plants in Puerto Rico, which is one of the largest worldwide sites for pharmaceutical manufacturing.[16, 17] During the trip, students tour manufacturing facilities and packaging plants to see at least 10 different pharmaceutical and biotechnology manufacturing processes.[18] Groups have visited Amgen, Eli Lilly, Johnson & Johnson, Merck, Pfizer, and Wyeth, and seen small-molecule drug synthesis, protein fermentation and purification, drug formulation, sterile operations, and product packaging. The tour ends with a visit to Bacardi, which features a technical tour of the fermentation and distillation processes at the world's largest rum distillery. In their free time, students also kayak through a bioluminescent bay, become familiar with Old San Juan, and broadly experience a cultural environment different from the U.S. mainland.

GRADING, ASSESSMENT, AND CHANGES IMPLEMENTED

D4 course grades are based primarily on the student teams' oral and written project reports and a final exam derived largely from the case studies. A series of homework assignments and quizzes during the initial phase of the course also contribute to the grade.

At the end of the semester, students assess the course through anonymous surveys. As shown in Figure 1, numerical evaluations have been highly positive, indicating that students found the course to be well structured and implemented.

Written comments, however, have also shown that students find the course challenging in some ways. A strength and weakness of the course is that it requires interdisciplinary knowledge and instruction rooted in strong chemistry and engineering fundamentals.[7, 8] Often, criticism focuses on the perception that material from the student's own major got short shrift in comparison to materials from other majors. Student comments also reveal group dynamics during the team projects to be a weak point of the students' skill set.[9]

Changes implemented as a result of student assessments include the addition of tutorials on biochemistry and diffusion basics early in the course to assure common ground among the students. Also, due to comments about sometimes uneven contributions to group work, each group member now submits to the instructors an anonymous e-mail about the percentage of work done by each member. Instructors check discrepancies, and the result has an impact on the final grade. Since this change was implemented, group cooperation has increased.

SUMMARY

The instructors developed a course on drug design, development, and delivery in response to Georgia Tech's specific need for a class on pharmaceuticals for advanced undergraduate students and graduate students in CD4 and the pharmaceutical industry's general need for scientists and engineers trained in the interdisciplinary field of pharmaceuticals. To balance breadth with depth, we extensively use a case study format, which enables teaching the integrated process of pharmaceutical development in the context of real product examples with their associated technical details and broader societal impacts. This use of a subject overview coupled with focused case studies is common in law, medicine, and business education but is not often employed in engineering courses. It is believed that the general structure of the D4 course is useful not only for material relating to the pharmaceutical industry but could also be used for engineering courses related to other industries.

When implementing such a course, the involvement of instructors and teaching assistants with industry experience is critical, as is the creation and use of relevant case studies

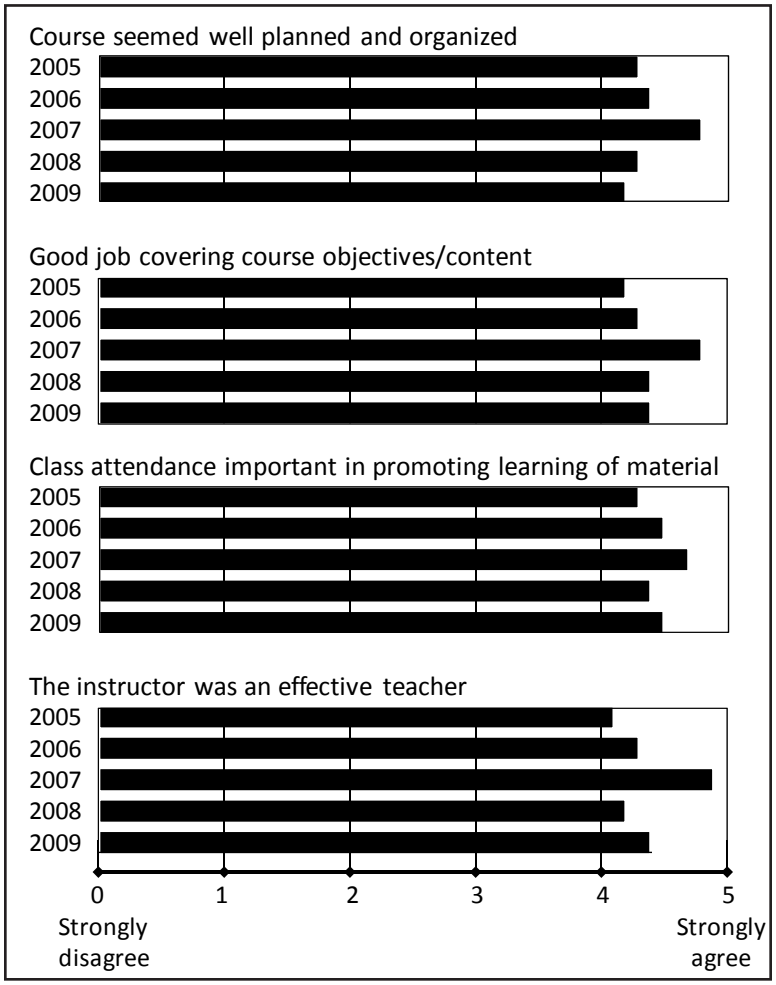

Figure 1. *Summary of end-of-semester student survey results from D4 course.*

with published literature, especially in a course for which there is no textbook. To provide real insight and understanding in a field, the D4 course was based on the philosophy that both course instruction and content must include the key disciplines related to the pharmaceutical development process. It is vital both for engineering education and industrial practice to focus on interdisciplinary knowledge and collaboration, which looks beyond typical classroom instruction and organization within a major. Students trained in the D4 course are well positioned to enter the pharmaceutical industry with the integrative interdisciplinary perspective that will likewise prepare them for entry into other fields as well.

REFERENCES

1. Block, D.E., "Teaching Biotech Manufacturing Facility Design and Regulatory Compliance: Better Equipping Students for a Maturing Industry," *Chem. Eng. Educ.*, **35**(3), 188 (2001)
2. Lee-Parsons, C.W.T., "A Biochemical Engineering Course Taught in the Context of Drug Discovery to Manufacturing," *Chem. Eng. Educ.*, **39**(3), 208 (2005)
3. Lipsky, M.S., and L.K. Sharp, "From Idea to Market: The Drug Approval Process," *J. Am. Board Fam. Pract.*, **14**, 362–367 (2001)
4. Meadows, M., "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective," Food and Drug Administration, Rockville, MD (<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm>)
5. Armstrong, R.C., "A Vision of the Chemical Engineering Curriculum of the Future," *Chem. Eng. Educ.*, **40**(2), 104 (2006)
6. Farrell, S., R.P. Hesketh, M.J. Sevelski, K.D. Dahm, and C.S. Slater, "Membrane Projects With an Industrial Focus in the Curriculum," *Chem. Eng. Educ.*, **37**(1), 68 (2003)
7. Newell, J.A., S.H. Farrell, R.P. Hesketh, and C.S. Slater, "Introducing Emerging Technologies into the Curriculum Through a Multidisciplinary Research Experience," *Chem. Eng. Educ.*, **35**(4), 296 (2001)
8. Armstrong, M., R.L. Comitz, A. Biaglow, R. Lachance, and J. Sloop, "Interdisciplinary Learning for Chemical Engineering Students from Organic Chemistry Synthesis Lab to Reactor Design to Separation," *Chem. Eng. Educ.*, **42**(4), 193 (2008)
9. Adams, J.U., "Drug Discovery and Development: A Complex Team Sport," *Science,* **319** (5868) Advertising Supplement (2008)
10. Lipinski, C.A., F. Lombardo, B.W. Dominy, and P.J. Feeney, "Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings," *Adv. Drug Deliv. Rev.*, **46**(1-3), 3 (2001)
11. Felder, R.M., G.N. Felder, and E.J. Dietz, "The Effects of Personality Type on Engineering Student Performance and Attitudes," *J. Eng. Educ.*, **91**(1), 3–17 (2002)
12. Felder, R.M., and R. Brent, "Understanding Student Differences," *J. Eng. Educ.*, **94**, 57-72 (2005)
13. Goa, K.L., G.T. Warner, and S.E. Easthope, "Transdermal Ethinylestradiol/Norelgestromin: A Review of Its Use in Hormonal Contraception," *Treat. Endocrinol*, **2**(3), 191 (2003)
14. Jick, S.S., K.W. Hagberg, R.K. Hernandez, and J.A. Kaye, "Postmarketing, Study of ORTHO EVRA and Levonorgestrel Oral Contraceptives Containing Kormonal Contraceptives with 30 mcg of Ethinyl Estradiol in Relation to Nonfatal Venous Thromboembolism," *Contraception*, **81**(1), 16 (2010)
15. Phelps, J.Y., and M.E. Kelver, "Confronting the Legal Risks of Prescribing the Contraceptive Patch with Ongoing Litigation," *Obstet. Gynecol.,* **113**(3), 712 (2009)
16. Pharmaceutical Industry Association of Puerto Rico (<http://www.piapr.org/>)
17. Pharmaceutical market report (Puerto Rico), Caribbean Update, Aug.1, 2007
18. Ostafin, A.E., D. LaClair, and H.T. Schmidt, "A Course in Bioprocess Engineering: Engaging the Imagination of Students Using Experiences Outside the Classroom," *Chem. Eng. Educ.*, **37**(3), 180 (2003) ❐