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INTRODUCTION

1.1 INSPIRATION

This project was first conceptualized at a most unlikely place: at a visit to an *Inspiring Impressionism* exposition at the Denver Art Museum in 2008. The exhibition focused on the impressionists as students of earlier masters. They immersed themselves in these earlier masterpieces and then incorporated the insights they had gained and added their own techniques to convey the same subject matter in profound new ways. My 20 years as a process chemist at Syntex and Roche are much like the years the impressionists spent camped out in front of the works of the masters. The insights gained could be conveyed by presenting the theory and concepts of process research and development, but there are many well-worn reference books that collectively accomplish that objective. My experience has been that process chemistry is a roller-coaster ride, with tremendous highs and lows, where you learn theory and concepts, as needed, on the fly, from your colleagues and from those reference books (while meeting seemingly unattainable milestones and timelines). The aim of this book is to convey some of this experience by immersing the reader in the process chemistry of some of the most valuable pharmaceuticals we are fortunate to have available today. The masterpieces in this book are the top-selling drugs in the United States in 2007–2008. These are Lipitor®, Nexium®, Advair Diskus®, Prevacid®, Plavix®, Singulair®, Seroquel®, Effexor XR®, Lexapro®, and Actos®, all "blockbuster" drugs, generating more than $1 billion in revenue for their owners each year (Figure 1.1).[1]

I have no previous detailed knowledge of the process chemistry of most of these drugs. Why choose these as the subject matter? First, there is currently intense interest in the process chemistry of these drugs. Second, if I had detailed unpublished knowledge about these drugs, I would be bound by a secrecy agreement to discuss only information already in the public domain. Third, having no financial stake in any of these drugs or their process technology, I can be completely (and refreshingly) objective. I am not "selling" the value of any target or proprietary technology to a patent agency or a pharmaceutical manufacturer.

After a detailed review of the process chemistry for Plavix® and Nexium®, these will not be included. The process chemistry for Plavix® is omitted because I have published and patented process work and have detailed knowledge of the manufacturing process for Ticlid®. The antiplatelet drug Ticlid® is an adenosine diphosphate (ADP) receptor inhibitor with the same thienopyridine core as Plavix® (Figure 1.2).[2] The process chemistry for Nexium® is omitted because Prevacid® and Nexium® have the same core and there is considerable overlap in their process chemistry. Advair Diskus® has two active ingredients: salmeterol and fluticasone. The process chemistry of salmeterol is included. The process chemistry of fluticasone would be better presented "in context" with the process chemistry of other valuable steroids.

With this format, will this book touch on every important aspect of process chemistry in the pharmaceutical industry? If you carefully studied the techniques used to create 10 masterpieces at the art museum would you become an art

Pharmaceutical Process Chemistry for Synthesis: Rethinking the Routes to Scale-Up, By Peter J. Harrington

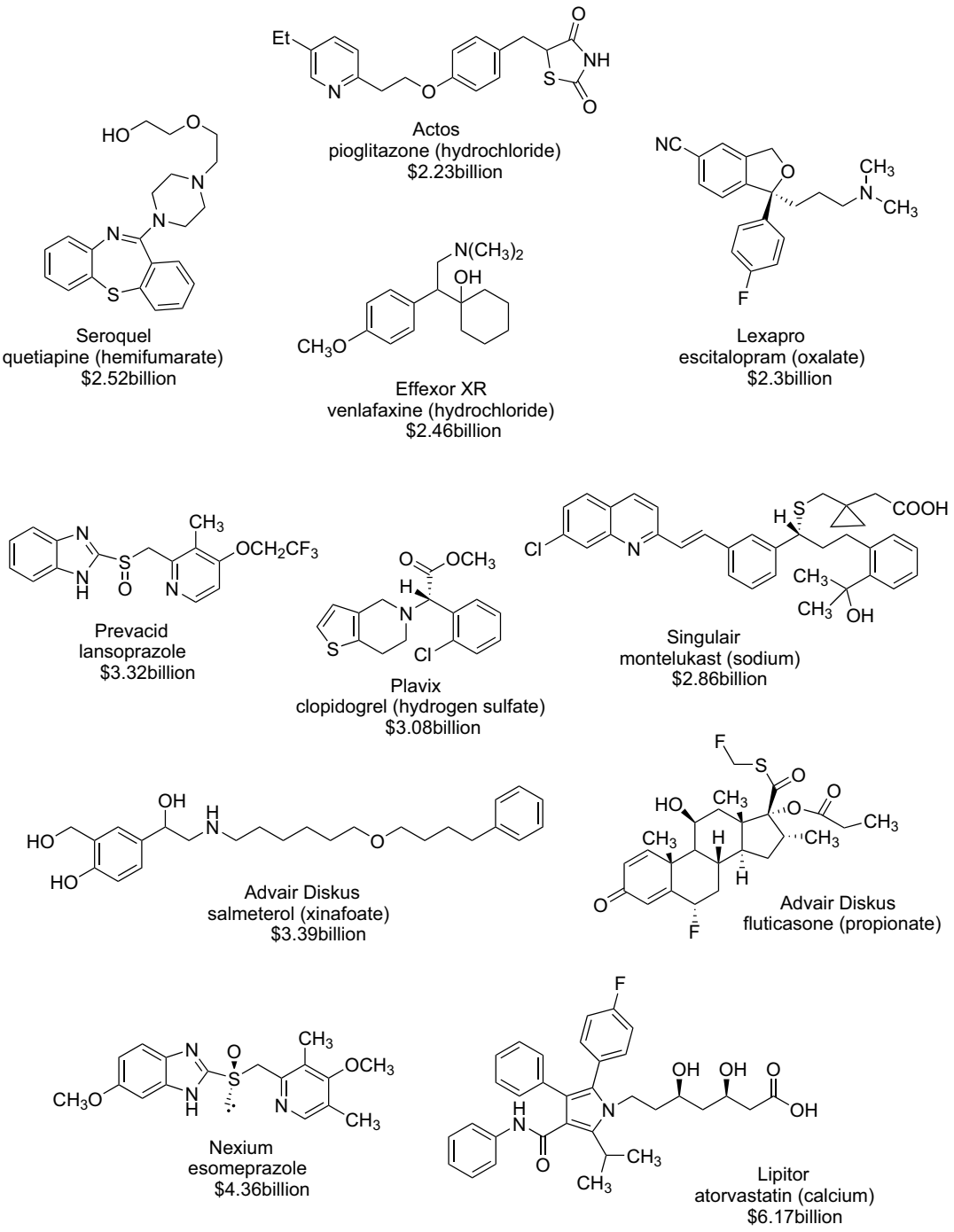


FIGURE 1.1 The top-selling drugs in the United States in 2007.

expert? Most people would say no. Would you be better able to utilize the techniques in your own paintings? Most people would say yes. The scientific objective of this book is then twofold: to identify one "best" process for manufacturing these blockbuster drugs and to highlight the strategies and methodology that might be useful for expediting the process research and development of the blockbusters of the future.

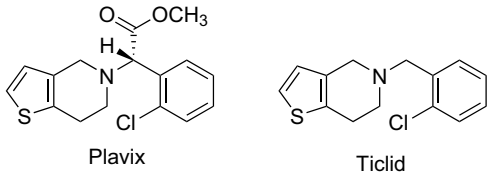


FIGURE 1.2 The close structure similarity between the antiplatelet drugs Plavix® and Ticlid®.

1.2 INFORMATION SOURCES

This project must begin with meaningful and realistic objectives. A consistent strategy will be used to define, retrieve, and review the relevant literature. The process chemistry presented is based on published experimental data harvested from patents and journal publications. The majority of the information is taken from U.S., European (EP), and World (WO) patents. Other country-specific patents are included if they are cross-referenced several times, do not have a U.S./EP/WO equivalent, and are available in English, French, or German. Working with a finite production budget, information from Chinese (CN) and Japanese (JP) patents is taken from *Chemical Abstracts.* Journal articles are often published in tandem with patents and offer the same experimental procedures and data. Key journal articles offering information not found in the patent literature are included. The presentation is weighted to emphasize the process patents and publications and the marketplace information published in the past decade.

It is likely that at least a few details of the process chemistry of a valuable pharmaceutical may be carefully guarded as a trade secret. Speculation about unavailable data will be clearly marked as such. Legal questions such as who owns a particular patented process, how long they will own it, or how valid are their patent claims are important questions that should be directed to a legal expert. The answers to these questions are outside the scope of this book.

A quick SciFinder® search (January 1, 2009) for the Prevacid® structure, for example, revealed approximately 1700 references. A review using this number of references for each target cannot be accomplished in a realistic time frame. A solution to this is to structure search for the building blocks unique to each target. The building blocks selected for Prevacid® are shown in Figure 1.3. The building block structure searches provide the first generation of references. The cross-references from the first generation are then used and the process repeated until the cross-reference loop is completed. For Prevacid®, this structure search approach reduced 1700 references to a manageable 200 references. The structures searched are provided at the end of each chapter. No effort was made to update the chapters completed first.

Process chemistry is so multidimensional that there will inevitably be important points overlooked. I welcome your comments and suggestions for improving the content and format of future publications.

1.3 CONTENT AND FORMAT FOR PRESENTATION

The content of each chapter will vary according to the information harvested from the references. For example, one chapter emphasizes the manufacturing route selection while another focuses on conversion of the penultimate intermediate to the final target. This variable content accurately reflects the range of tasks assigned to process chemists. Your role in a process research and development team may be early route selection in one project. Your role may be late troubleshooting of a difficult crystallization to produce a target that filters well and meets crystal size and purity specifications in another. Your role might involve working closely with procurement specialists or engineers in the early route selection or with analytical and regulatory specialists on the difficult crystallization.

Just as the chemical transformations are central to the manufacturing process, the process chemist is the hub of manufacturing process research and development. The process chemist does not have to be an expert in the related specialties of marketing strategy, patent law, procurement, environmental health and safety, analytical chemistry, formulation, regulatory affairs, and engineering and facilities but he must be knowledgeable enough to identify questions best answered working in close collaboration with these experts. Answers will sometimes be offered to questions best answered by these experts with the understanding that the answer is meant to trigger a discussion with the expert.

Each chapter is written to stand alone. Chapters 2–9 can be read in any order. While the content for each chapter will vary, the same format will be used to present the available information. Each chapter begins with an *overview of current and past marketplace information* for the target. This discussion is included to emphasize that the process research and development team cannot work in a vacuum. The team should receive detailed updates at regular intervals on the market potential of the target, the timing of the delivery, and new clinical and post-launch data that may impact the market potential and timing of the delivery. This

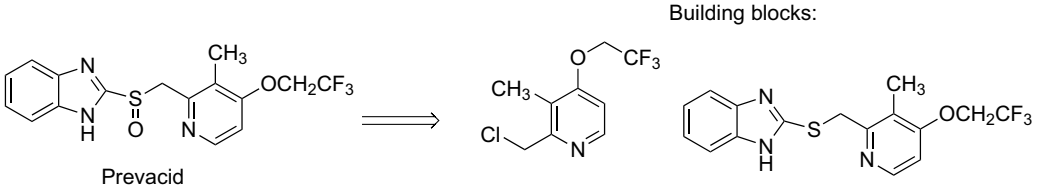


FIGURE 1.3 Building blocks searched to provide references to process chemistry for Prevacid®.

information might come from a marketing or business development expert.

To minimize repetition, retrosynthetic analysis will not be used to stage the synthesis discussion. To emphasize the modularity of pharmaceutical manufacturing, the synthesis discussion in each chapter starts with identification of raw materials. These *raw materials* are usually commercially available or can be produced in a few steps from commercial materials.

Every process begins with *commercially available raw materials*. A price is provided for each raw material *that contributes at least one atom to the target* when that raw material first appears in the discussion. Since suppliers and prices for raw materials are in constant flux, all prices quoted are taken from the 2007–2008 Aldrich catalog. It is my intention that these prices will give a "snapshot" of a relative price and availability at this point in time. Quoting an Aldrich catalog price should suggest scheduling a preliminary communication with a procurement group. This communication would include estimates of the quantity and purity specifications, a preferred delivery date, and any special shipping and handling requirements. Other raw materials, for example, acids, bases, reagents used to create protecting groups or leaving groups, drying agents, filter aids, and decolorizing carbon are not priced since expensive materials might be replaced by less expensive alternatives.

The raw material prices are only intended for "back-of-the-envelope" calculations. Detailed cost calculations should include vendor-guaranteed raw material prices and labor and overhead (LOH) costs for the manufacturing site and are beyond the scope of this book.

Aldrich catalog names are used for all starting materials and *ChemDraw 11.0*® is used to generate names for all process intermediates. With the intention that each sentence can stand alone, full chemical names are used in the text in many cases. Process intermediates and products are each assigned a number to facilitate correlation of the names with the structures in schemes and figures. An example of a stand-alone sentence is taken from the Seroquel® discussion.

> The reaction of 11-chlorodibenzo[*b*,*f*][1,4]thiazepine **(25)** with 2-(2-(piperazin-1-yl)ethoxy)ethanol **(26)** (2.0 equivalents) in refluxing toluene is complete in 8 h.

Patent procedures often contain *data gaps*. These can be separated into two categories. A major data gap is missing information that would certainly have been generated but was not included in the process description. Examples of major data gaps are a missing quantity for one reagent of several or a missing volume for the reaction solvent. Major data gaps are clearly identified in the discussion, and where possible, an attempt is made to fill the gaps with information gleaned from another source. A minor data gap is information presented in a format that requires a translation. For example, reagent quantities might be quoted only in weights or volumes. This gap is filled by converting reagent quantities into *equivalents*. In process chemistry, an equivalent simply refers to the number of moles of reagent per mole of limiting reagent. Equivalents in this book are calculated to the nearest 0.1.

Solvents and *reaction temperatures* are critically important process characteristics. These are included in each reaction description. After selecting a best process, the process solvents used are revisited to emphasize the importance of minimizing the number of process solvents and to highlight the solvents commonly used in a pharmaceutical manufacturing plant. Temperatures in the range of 20–30°C, or "ambient," are standardized as 25°C in the reaction descriptions. Very low temperatures (<-70°C) require that expensive liquid nitrogen be available locally and that liquid nitrogen storage facilities be available on site. Expensive circulating fluid and energy are required to achieve and maintain very high reaction temperatures (>160°C). Examples of a reaction description and a process solvent review are taken from the Actos® discussion.

> The condensation of 4-(2-(5-ethylpyridin-2-yl)ethoxy)benzaldehyde **(19)** with thiazolidine-2,4-dione (1.2 equivalents) and pyrrolidine (1.0 equivalent) in methanol at 45°C is very efficient even after multiple precipitations and isolations for purity upgrade (95% yield). The process solvents are toluene, THF, ethanol, isopropanol, and water, all solvents commonly used in a pharmaceutical manufacturing plant.

It is assumed that all operations involving combustible organic materials are performed *under nitrogen* and that all chemical mixtures are *stirred*. This is not specifically stated in the procedures described.

When there are many similar procedures, they will be presented in a *parallel format* to facilitate comparison and highlight the differences. Material presented in parallel format is usually preceded by a summary of the trends and results. An example of parallel formatting is taken from the Effexor XR® discussion.

> A mixture of 1-(2-amino-1-(4-methoxyphenyl)ethyl)cyclohexanol **(34)**, 88% formic acid (5.0 equivalents), and 36% aqueous formaldehyde (3.1 equivalents) in water (96 L per kg **34**) is refluxed for 21 h.
>
> A mixture of 1-(2-amino-1-(4-methoxyphenyl)ethyl)cyclohexanol **(34)**, formic acid (6.3 equivalents), and paraformaldehyde (2.9 equivalents) in water (7.9 L per kg theoretical **34**) is refluxed for 24–48 h.

When the discussion leads to a choice between two very similar processes, the analysis may be taken to an even greater level of detail. An example of information on this next level is *volume throughput*. The discussion at this next

level should be prefaced with the understanding that throughputs are rarely the focus of patent procedures, that some assumptions must be made, and that some questions (e.g., solubility and viscosity) can only be answered in the laboratory.

Nowhere is the phrase "time is money" more apt than in a manufacturing plant. Patent procedures typically quote reaction times in the range of 30 min to 24 h. I would suggest that a *reaction time* of 2 h is close to ideal, slow enough to allow for efficient heat transfer to or from the reaction vessel and to allow for sampling and an offline completion check. Any unusually long reaction times in key procedures will be identified and the potential for reducing these times may be addressed.

A great deal of process research and development effort is spent streamlining the transitions from one reaction to the next. For this reason, *workup procedures* are presented in detail to highlight potential scale-up problems. There may be product stability issues that will only become apparent during a scale-up or there may be a concentration at reduced pressure to a solid residue. When the workup description does not add to the discussion, it may be omitted or abbreviated to a "routine workup." In a routine workup, the reaction is quenched with water, dilute bicarbonate, or dilute brine and then extracted into an organic solvent (toluene, ethyl acetate, or dichloromethane). There may be several extractions. The combined organic layers are optionally dried ($MgSO_4$ or Na_2SO_4) and the solvent removed at reduced pressure to produce an oil or solid residue.

Drying agents such as sodium sulfate or magnesium sulfate are routinely used in the laboratory but rarely used at pilot plant scale. Drying agents used in the experimental procedure are omitted from the process descriptions in this book. The process chemist must use the water-wet solution or rely on (design in) an azeotropic distillation to remove water from the solution.

Purity analysis is critically important in process chemistry, yet often is not included in patent experimental procedures. The centrifuge may be filled to capacity with product but remember: *If the material does not meet specifications, the yield is zero.* To be consistent with this important tenet, yield and purity data are quoted when available. In the absence of purity data, the yield is quoted if the product is precipitated, chromatographed, crystallized, or distilled. Crude yields of early intermediates are included when other data suggest that the yield is an accurate reflection of efficiency of the reaction. HPLC area% data will be used for completion checks but not for purity analysis. Purity data for process intermediates are rounded to 0.1%. Purity data for the final drug substance, if available, are rounded to 0.01%.

Physical data such as boiling point or melting point are provided for process intermediates if those data are critical for determining the suitability of the process. For example, the crystallization and isolation of a solid with a low melting point ($<50^{\circ}C$) may be more challenging. The distillation of an oil at high temperature and low pressure ($>150^{\circ}C$ at <1 mmHg) may not be a viable option.

Every effort will be made to identify undesirable reagents and intermediates. These include *carcinogens*, *lachrymators*, *sensitizers*, and *malodorous chemicals*. Information on these chemicals will be quoted from *material safety data sheets* (MSDS) to substantiate the objection to use of the chemical. The date accessed and online reference to the MSDS are not included in the references. *The most current version of the MSDS should be reviewed before working with any chemical*. An example of an MSDS review is taken from the Prevacid® discussion.

> Vanadium(V) oxide is considered to be a carcinogen.[82] All vanadium compounds should be considered toxic.[83] The toxicity depends on the valence state and the solubility of the compound. For example, vanadium(V) oxide (V_2O_5) is considered to be five times as toxic as vanadium(II) oxide (V_2O_3). The first concern in handling these vanadium catalysts is exposure to dust. For vanadium(V) oxide, the OSHA permissible exposure limit (PEL) for vanadium respirable dust is 0.5 mg/m^3 (ceiling) and for vanadium fume is 0.1 mg/m^3 (ceiling), and the ACGIH threshold limit value (TLV) is 0.05 mg/m^3.

The "no stone left unturned" level of detail is chosen to accurately reflect the day-to-day concerns and activities of a process chemist. It is also intended that the level of detail is sufficient to allow the reader to make an informed process decision without revisiting the original experimental description for additional details.

Text boxes are used to elaborate on the logic behind a process decision. They are largely the author's personal preferences honed by trial and error in the laboratory and pilot plant over 20 years. Text box topics include setting starting material specifications, solid addition to a reaction mixture, stability of intermediate mixtures produced during sequential reagent charges, compatibility of materials of construction with reaction conditions, concentration at reduced pressure, acceptable volume throughputs, estimating volume throughputs from gram-scale procedures and kilogram-scale procedures, identifying first/second-generation side products for workup design, distillation of high-boiling polar aprotic solvents, routine safety testing of lab distillation bottoms, self-accelerating decomposition temperature (SADT), alternatives to dichloromethane, "one-pot" procedures, the importance of hold points, mixtures of sulfonic acids and methanol, alignment of economic and environmental incentives, selecting reaction variables for design space studies, analysis of suspensions, why polymorphs are important, and deconvoluting polymorph literature. While the same text box topic could be inserted at many points in the book, each topic appears only once and where it is most

relevant. An example of a text box is taken from the Singulair® discussion.

> Now that the challenges of producing 7-chloroquinaldine (**3**) are understood, a specification for 5-chloroquinaldine (**4**) in the starting material must be set and the fate of the side products from 5-chloroquinaldine (**4**) produced in the following step(s) must be determined. Our first inclination, as synthetic chemists, is to demand high-purity starting material. However, it would be prudent to invest some time up front to demonstrate efficient rejection of the side product from 5-chloroquinaldine (**4**). These data will empower us to use a lower grade of 7-chloroquinaldine (**3**) that will be available at a better price.

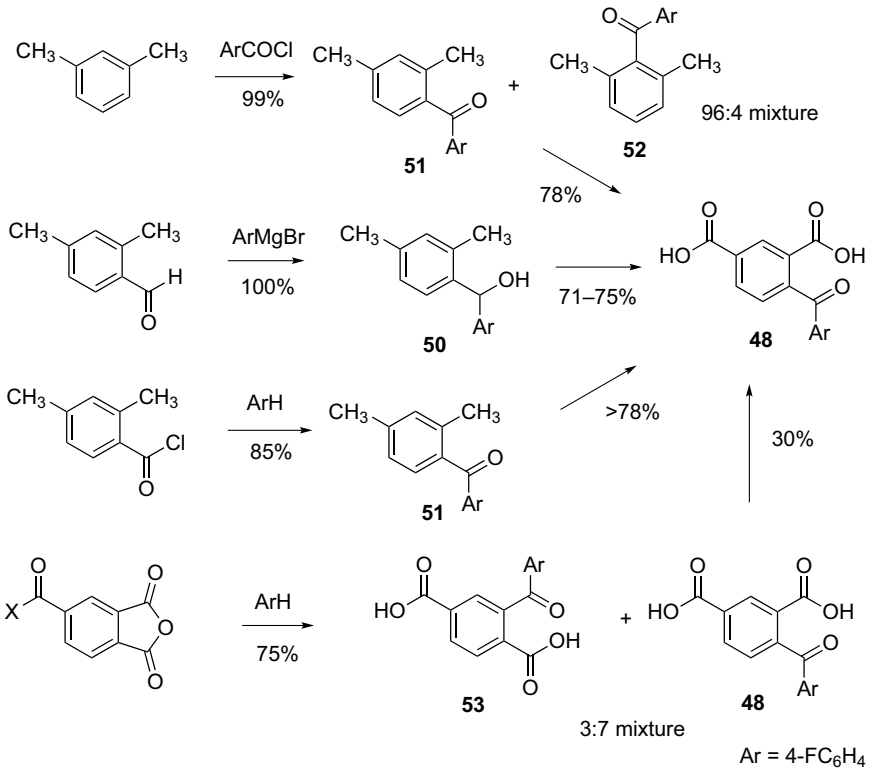
Schemes immediately follow the chemistry discussion. Since reagents and conditions are provided in the text and since many of the transformations can be performed using more than one combination of reagents and conditions, these are not included in the schemes. The highest yield or an appropriate yield for each transformation is provided under the reaction arrow. For example, see the scheme from the Lexapro® presentation (Scheme 1.1).

A section on *trade secrets, impurities, and analytical methods* is sometimes used to capture valuable process information that does not appear in the earlier chemistry review sections but might prompt valuable additional discussion.

Finally, the *best process available* offers criteria for selecting the process and uses the criteria to arrive at a single route as the standard for comparison. This best process is an amalgamation of the best available process steps and is intended to serve as a basis for further discussion rather than to end it.

For most of the targets, the method developed for generating the limited reference set intentionally minimizes the publications in other important areas, including *crystallization*, *polymorphism*, *particle size*, *storage stability*, and *formulation* of the final drug product. The Lexapro® presentation is expanded to include a detailed discussion on crystallization and polymorphism. The Lipitor® discussion includes a discussion of amorphous and crystalline polymorphs and the drying and storage stability of the final drug product.

A suitable formulation is most efficiently attained by the process chemist working in close collaboration with a formulation group. The involvement of the process chemist might end with developing crystallization, drying, and milling procedures to deliver the desired polymorph of the target to the formulation group with acceptable storage stability



SCHEME 1.1 A scheme from the Lexapro® presentation.

and a well-defined particle size range. Formulation is outside the scope of this book.

How reproducible are the patent experimental procedures at the heart of this project? Comparing similar procedures side by side certainly makes it easier to find inconsistencies. The inconsistencies are pointed out and corrections for typographical errors may be suggested. An example is taken from the Effexor XR® discussion.

> Palladium on carbon (10% w/w, 50% water-wet) (50 g Pd per kg **17**) is added to a mixture of 2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)acetonitrile **(17)** and hydrochloric acid in methanol (8 L per kg **17**), presumably at 25°C. (*Note*: The amount of hydrochloric acid charged is quoted as "1–3 moles" or 10–29 equivalents. This is presumably a typographical error.)

If a quoted yield can't be reproduced is the best process still viable? *The underlying principle for selecting the process is still valid*. An optimistic process chemist would respond: if you can get 50%, you can get 80%. If you can get 80%, you can get 90%. All that is required is motivation and development time.

1.4 SPECIALIZATIONS: BIOTRANSFORMATIONS AND GREEN CHEMISTRY

Some readers will be disappointed that a particular specialization in process chemistry does not receive more attention. The presentation is weighted based solely on how many of the patents and publications deal with that specialization. For example, a chiral alcohol intermediate in the Singulair® discussion can be produced by a microbial reduction.

> There are five options for the asymmetric reduction: microbial reduction to (*R*)-alcohol **31** with the novel microorganism *Microbacterium* MB5614 (ATCC 55557) and a Mitsunobu inversion,[50,32] microbial reduction to (*S*)-alcohol **32** with *Mucor hiemalis* IFO 5834,[51] reduction to (*S*)-alcohol **32** with borane–THF catalyzed by an oxazaborolidine,[32] reduction to (*S*)-alcohol **32** with diisopinocampheylchloroborane,[43] and ruthenium-catalyzed transfer hydrogenation to produce (*S*)-alcohol **32**.[52] Since the microbial reduction patents provide only milligram-scale procedures and are more than 10 years old, we will focus on the chemical methods.

While the process chemist is not an expert in green chemistry, the process chemist plays a pivotal role in the *implementation* of green chemistry on a plant scale. The terms *green or greener* may be used to denote a process that is superior in its qualitative or quantitative adherence to one or more of the *Twelve Principles of Green Chemistry*.[3]

1.5 IMPACT ON PROCESS CHEMISTRY IN THE FUTURE

Rethinking the step-by-step *manufacturing process* is the overriding theme of this book. A secondary objective of this book is to increase awareness about the *process by which we transition from one supplier to multiple generic suppliers*. A long-standing interest in this transition dates back to the 1980's second-generation process research and development for (*S*)-naproxen, now sold as Aleve®.[4] After reading this book, it will be clear that there may be an incentive to regress to inferior process technology and that the regression is often accompanied by an increase in the environmental impact of manufacturing the drug. This regression is the inevitable consequence of the normal progression of patent protection for a new drug: the patents for the drug itself and the medicinal chemistry route(s) to the drug are followed, often over the course of many years, by a series of process patents from the manufacturing group. These process patents protect key steps in one or more finely honed manufacturing processes for many years beyond expiration of the drug patent. Unless groundbreaking new and directly applicable synthetic methodology is discovered in the 10 years after the drug manufacturing process was first put online, new manufacturing processes may offer little that is new and improved. Process regression is science in reverse, a step back for a society that celebrates and rewards innovation.

1.6 AUDIENCE

Synthetic chemists interested in manufacturing these top-selling drugs are the primary audience for this book. Another audience is graduate students with a specialization in organic synthesis. In many university interview trips in search of the next generation of process chemists, it became clear that most graduate students have no idea what a process chemist does. With instructor-added emphasis on synthetic strategy and control, this book could provide the core information for an interactive one-semester graduate course in process chemistry. Where is the academic value of learning process chemistry? Process research is mechanism based, it requires an in-depth analysis and understanding of reaction kinetics and thermodynamics, and it pushes the limits of established synthetic technology. Process research generates unexpected results, results considered improbable during the project planning phase, and results that are often the basis of valuable process patents.

Another intended audience for this book is process chemists always in search of *methods proven on scale-up*. Looking for a method for nitrile reduction to a primary amine? What better place to look than in the chapter on Effexor XR®. Methods are compared and contrasted for creating a chiral secondary alcohol from a ketone

(Singulair®), oxidation of a sulfide to sulfoxide (Prevacid®), and introducing an amino group using an ammonia surrogate (salmeterol of Advair Diskus®).

Discovery chemists seeking a strategy to protect their investment in a new drug might review the strategies generic manufacturers used to develop noninfringing processes. Generic drug manufacturers eager to design and implement new manufacturing processes can map out the company-specific patent strategies used to protect new drugs. The environmental chemist will find useful information on the environmental impact of drug manufacturing for these specific targets and for small-molecule drugs in general. Finally, the consumer activist will find useful information on the cost to produce these blockbuster drugs.

ACKNOWLEDGMENTS

Thanks to Chemical Abstracts® for a grant of 115 tasks/1 year used for the structure searches. Journal articles were obtained through the interlibrary loan (ILL) program. Thanks to the ILL program coordinator, Sandra Richmond, at the Louisville Public Library for her time and support. Current and past marketplace information for each target was developed working in collaboration with Karen Ingish, reference librarian at the Louisville Public Library. A special thanks to Karen for her enthusiasm and her invaluable contribution. Thanks to Dr. Dave Johnston and Dr. Neal Anderson for their sage advice and support for this project. Finally, Rosemarie and Jack, my home team, there are no words of thanks I can offer to tell you how much I appreciate all that you did. This book is dedicated to you, Jack. No man could ask for a finer son.

At the beginning of this project, it was clear that this would be a journey of a thousand miles. You will be gratified with expectations met in some cases and surprised by unexpected selectivity in others. You will delight in the victory of efficiency of some manufacturing processes and be left dissatisfied with the state of affairs of others.

> A journey of a thousand miles begins with a single step.
>
> Lao-tsu (604–531 B.C.)

REFERENCES

1. Accessed at www.drugs.com/top200.html.
2. (a) Harrington, P.J.; Sanchez, I.H. *Synth. Commun.* **1993**, *23*, 1307.(b) Harrington, P.J.; Sanchez, I.H.EP 522956(1/13/1993).
3. Accessed at www.epa.gov/greenchemistry.
4. Harrington, P.J.; Lodewijk, E.L. *Org. Process Res. Dev.* **1997**, *1*, 72.