

# DELAWRITER

The quarterly newsletter of AMWA-DVC

Delawriter Editors

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## Highlights of 23rd Annual AMWA-DVC Princeton Forum

### Clinical Pharmacology in Drug Development: What Medical Writers Need to Know

*By Danielle Ippolito*

How does a drug work? What does the body do to a drug? What does the drug do to the body? How does a drug behave in combination regimens? Medical writers reviewed the key clinical pharmacology studies that answer these questions in a presentation by Linda LaMarre, BS, MS (Principal Documentation Director, Bristol-Myers Squibb) at AMWA-DVC's 23rd Annual Princeton Forum on Saturday, May 4, 2019.

#### Key Concepts

Clinical pharmacology studies investigate how the body affects the drug (pharmacokinetics) and how the drug affects the body (pharmacodynamics). Medical writers convey the results of these studies in key documents that support the new drug application and product label. When considering how drugs transit through the body, pharmacokinetic studies evaluate drug absorption into the blood, distribution from blood to extravascular fluids and tissues, metabolism to either an active or a more readily excreted form, and elimination via urine, bile, feces, or breath.

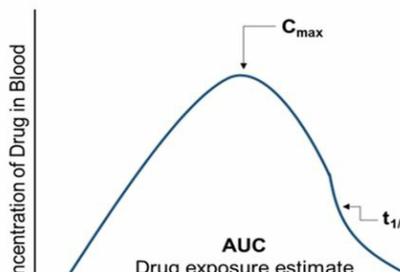
Drug-drug interactions can occur if one drug interferes with another's metabolism via hepatic cytochrome P450 (CYP) enzymes or other mechanisms. For example, coadministration of phenobarbital and warfarin is contraindicated because phenobarbital induces CYP450 enzymes that metabolize warfarin, thereby lowering plasma warfarin levels below the acceptable therapeutic range. Liver or kidney damage could also affect a drug's metabolism or elimination, and may be a consideration for making dosing adjustments in susceptible individuals.

#### Pharmacokinetics Analysis

In early clinical studies, characterizing drug pharmacokinetics requires intensive blood sampling at multiple time points and non-compartmental analysis. Later in clinical development, pharmacokinetic sampling may be undertaken at fewer, select time points. Pooling data from multiple studies can facilitate the development of population pharmacokinetic models that assess the effects of covariates such as age, weight, sex, and kidney function on a drug's pharmacokinetic profile.

Pharmacokinetic parameters derived from concentration-time plots define absorption and elimination profiles of a drug (Figure). Key parameters include maximum concentration in plasma ( $C_{max}$ ), time to reach maximum plasma concentration ( $T_{max}$ ), time for drug concentration to decrease to 50% ( $t_{1/2}$ ), minimum concentration ( $C_{min}$ ), and the area under the concentration-time curve (AUC). AUC estimates overall drug exposure, providing an indicator of the duration

Concentration-vs-time Curve:  
Key Pharmacokinetic Parameters



#### In This Issue

- [Princeton Forum](#)
- [Clinical Pharmacology](#)
- [Real World Evidence](#)
- [Regulatory Submissions](#)
- [The Fine Art of Procrastination](#)
- [Upcoming Events](#)

#### Quick Links

[AMWA National](#)

#### QUICK NOTES

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The DELAWRITER needs contributing authors for the quarterly publication. *Have an idea for an article?* *Haven't used that byline recently?* If so, please contact the [editorial team](#).

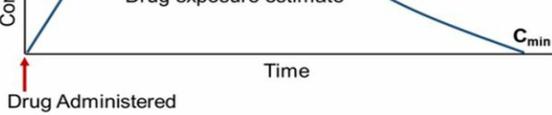
#### Quarterly Quotes

*The skill of writing is to create a context in which other people can think.* - Edwin Schlossberg

*The way to get started is to quit talking and begin doing.* - Walt Disney

*Words do two major things: they provide food for the mind and create light for understanding and*

and intensity of a drug's effect. When given in multiple doses, a drug reaches steady-state concentrations when rates of elimination equal administration, usually after 4 to 5 times the t1/2 value. Total drug exposure may be affected by many factors, including route of administration, formulation, food effects, interactions with other drugs, patient age, kidney/liver function, and body weight.



AUC, area under the concentration-time curve; Cmax, maximum concentration in plasma; Cmin, minimum concentration; Tmax, time to reach maximum plasma concentration; t1/2, time for drug concentration to decrease to 50%..

### Pharmacodynamics

Pharmacodynamics studies describe the relationship between the drug and its effect on the body. Mechanistically, pharmacological targets for drugs are usually receptors on the cellular surface or within the cytoplasm, although other mechanisms are possible (eg, altering physiological physical/chemical properties or a normal metabolic, synthetic, or signal transduction pathway). Pharmacodynamic drug-drug interactions result when two drugs (1) compete for the same receptor (pharmacological), (2) act at different receptors to potentiate or diminish an effect (physiological), or (3) react with each other and prevent interaction with the pharmacological targets (chemical). At a pharmacological target, dose-response relationships are fundamental to identifying the appropriate dosing window in a given regimen, with the goal of achieving an adequate therapeutic response with minimal side effects and/or drug interactions. In pharmacodynamics terminology, potency measures the amount of drug needed to produce an effect; efficacy defines the drug's ability to produce a desired response; and therapeutic index describes the relative safety of the drug and is calculated by dividing either the drug's median toxic or lethal dose by its median effective dose. Evaluating dose-response relationships early in drug development facilitates dose selection in later clinical trials, and provides guidelines for adjusting dose for intrinsic (eg, age) or extrinsic (eg, concomitant medications) covariates.

### Clinical Pharmacology Documents: Opportunities for Medical Writers

Clinical pharmacology studies span the lifecycle of drug development, from preclinical to clinical (Phases 1 through 3) studies and post-approval (Phase 4), and support the New Drug Application (NDA) or New Biologic Application (BLA). Clinical pharmacology studies are part of the Common Technical Document (CTD), which was designed to provide technical documentation in a common format between Europe, the United States, and Japan. The CTD includes pharmacometric reports (Module 5, Clinical Study Reports) and studies including (1) formulation/manufacturing changes, dosage strengths, food effects, and analytical/validation methods (Module 2.7.1, Biopharmaceutics, Analytical Methods) and (2) drug interactions, human pharmacokinetic and pharmacodynamic parameters, routes of absorption, distribution, metabolism, and elimination, pharmacometrics, and dose selection/administration (Module 2.7.2, Clinical Pharmacology Studies). Medical writers may also draft other regulatory documents containing key clinical pharmacology endpoints, from investigator brochures to pediatric investigator plans, and documents for communicating with health authorities (eg, briefing books, meeting requests, scientific advice documents, and response queries).

Overall, LaMarre's comprehensive overview showed medical writers how clinical pharmacology studies support drug applications by identifying key pharmacokinetic and pharmacodynamic parameters that describe how the drug affects the body and vice versa.

Danielle Ippolito, PhD, CMPP, MWC is a medical writer at PharmaWrite® Medical Communications, LLC, in Princeton, New Jersey.

## Real World Evidence: What Writers Need to Know

By Daniel Zinshteyn

Dramatic advancements in data storage, internet usage, and mobile computing have transformed the healthcare industry this past decade. The massive shift towards digitization has spurred the development of studies based on "Real World Evidence," or RWE. Nancy Connolly, MPH and Chris Pericone, PhD (Janssen Scientific Affairs, Real World Analytics & Alliances) provided a detailed look at the use of RWE in medical writing at AMWA-DVC's 23rd Annual Princeton Workshop on May 4, 2019. Their presentation, "Introduction to Real World Evidence," covered the basics of RWE, as well as various challenges associated with conducting and communicating RWE studies. They also guided workshop attendees through worksheets designed to reinforce their understanding of RWE.

RWE refers to information that is not sourced from a typical clinical research study. This may include data gathered from insurers, healthcare providers, product/disease registries, and even wearable devices. One of the obvious advantages to RWE studies is the reduction in cost and length relative to clinical trials. While clinical trials take years and cost tens of millions of dollars, retrospective RWEs can be performed quickly and at a fraction of the cost. It is this quick and affordable turnaround of RWE studies that makes them particularly useful at various stages of clinical development. Rather than replace clinical trials, RWE studies are being used to inform trial design before launch and to influence treatment choices after launch.

RWE studies are also crucial for addressing concerns that are not typically covered in clinical settings. These include economic concerns such as the cost of treatment to patients, and humanistic concerns including reductions of symptoms not typically measured in clinical trials, treatment satisfaction, or impact on quality of life. These studies also address clinical outcomes, typically in the form of biomarkers, symptoms, side effects,

life. These studies also address clinical outcomes, typically in the form of biomarkers, symptoms, side effects, and mortality; these clinical outcomes are reported in most databases. RWE studies require careful consideration of the questions being asked, the type of data used, and the proper way to analyze the acquired data in order to address the question of interest. For example, if a study was designed to measure the risk of emergency room visits among elderly users of a drug, then the study could utilize claims data from Medicare-insured patients. In another example, investigators seeking to measure the incidence of a mild symptom could gather data from a smartphone app for people with the condition. These examples demonstrate how RWE studies can be utilized to determine specific information about a drug or patient population.

For a number of research questions, the most useful aspects of RWE are those first two words: "Real World". Clinical trials address whether a treatment is effective in a controlled, clinical setting in a subset of patients who meet classification criteria for the disease; RWE studies can help to inform how the treatment affects patient outcomes in practice. RWE studies can tell investigators whether the treatment plan is effective in a real-world setting, where economic and human factors can influence the implementation of the treatment plan.

The workshop instructors also detailed a number of considerations that must be taken into account when designing RWE studies. For example, because RWE data are not randomized, care must be taken to avoid bias. Also, RWE studies may not be suitable for tracking patient outcomes over a long period of time, as patients often change insurance or healthcare providers. Adherence is a key concern with RWE studies because adherence is typically self-reported or inferred from prescribed and/or filled medications.

Understanding data sources is key to successful utilization of RWE. Two of the most common sources for RWE are administrative claims databases and electronic health records (EHR). Administrative claims databases are generated by insurance providers. They record all data for which a claim is submitted, including doctor's visits, medications filled, and tests/treatments ordered. EHRs, which typically include fewer patients, detail patients' entire health records, disease severity, and lab results, but fail to include cost data (eg, charges to insurance). Although often costly or inaccessible, integrated databases are a particularly useful RWE source because they integrate EHRs from healthcare providers and administrative claims from insurance providers for the same individuals.

RWE studies have increased in prominence in recent years and are sure to remain a key component of drug design and regulation. It is important for medical writers to be aware of these studies, particularly with regard to data sourcing and experimental design. Speaking as someone who is new to medical writing, I am excited to learn more about this field and am grateful to Connolly and Pericone for presenting an excellent introduction (and more) on RWE.

Daniel Zinshteyn, PhD is based in Philadelphia and is just starting a career in medical writing. He recently graduated from Cornell with a PhD in genetics.

## The Medical Writer's Role in Regulatory Submissions

By Julie Kirkwood

The application to market a new drug in the United States is so big that, prior to the digital age, a pharmaceutical company would hire a U-Haul truck to drive all the necessary documents to the FDA in Bethesda. There was that much paper.

The common technical document (CTD), which is the application dossier, is now submitted electronically. The planning and creating the hundreds of documents and thousands of pages is a tremendous undertaking for a medical writing team, according to Mark Bowlby, PhD, principal regulatory writer at Synchrogenix, a contract research organization that specializes in medical writing and regulatory affairs.

Bowlby presented an overview of the regulatory submissions process from the medical writer's perspective at the AMWA-DVC's 23rd Annual Princeton Workshop in May 2019. He explained the common types of submissions and discussed strategies for structuring content, managing timelines, and ensuring consistency across documents.

### Types of Submissions

Medical writers are responsible for many types of documents in the drug development process. For new drug applications, the International Council for Harmonisation (ICH) provides guidelines that guide the content and formatting of these documents, specifically the ICH Efficacy Guidelines and Multidisciplinary Guidelines. Medical writers prepare Clinical Study Reports and the Integrated Summary of Efficacy and Integrated Summary of Safety, which are summaries that involve combined analyses from multiple studies. Medical writers also prepare the Summary of Clinical Efficacy and the Summary of Clinical Safety (limited to about 400 pages when combined with the Summary of Biopharmaceutics and Summary of Clinical Pharmacology), and the Clinical Overview (less than 50 pages). There are also documents related to quality and non-clinical studies, which may be written by scientists or by medical writers.

In addition to drug applications, medical writers prepare documents such as Investigator's Brochures and Protocols that are submitted with the Investigational New Drug (IND) application to begin human trials. Also, medical writers support interactions with regulatory authorities at multiple points in the drug development

process and may prepare briefing books for these meetings.

### Writing Strategies

To prepare a regulatory document, medical writers typically begin with a template that serves as an outline for the required content. After creating a document shell, which outlines the content in more detail and has placeholders for table and figure headings, writers may consult an example document from a different submission by the same sponsor to get a sense of the length and level of detail of the various subsections. Also, they will review the ICH guidelines related to the document and look at the statistical analysis plan and any source documents.

When creating documents, Bowlby recommends looking back over the minutes from discussions with FDA over the years. Any issues that have been raised by FDA in the past should be addressed proactively. Also, he recommends creating a lexicon to use across all the various documents in the submission. The lexicon is a list of phrases, style notes, and formatting conventions that the team has approved. The lexicon should be a living document that is continually updated throughout the project.

For managing timelines, the first step is for a medical writer to arrange a kick-off meeting with the sponsor to determine a target submission date, then plan dates for each document, keeping in mind any rate-limiting components and areas with a high number of studies. The medical writer can help keep the process on track by leading effective revisions meetings. Some tips from Bowlby:

- Make an agenda based on the reviewers' comments in the document, covering the most important comments first.
- Don't end the meeting until you, as the medical writer, have all your questions answered. "That really is the writer's meeting," Bowlby said. "Don't let anyone tell you otherwise."

### The Submission Lead

In terms of structuring the medical writing team, Bowlby says having a lone medical writer authoring all the documents in a submission is impossible. Instead, his team appoints a submission lead (ie, a medical writer who coordinates the other medical writers). The submission lead's job is to ensure consistency of strategy and messaging across documents, manage timelines, and fill in for other writers as needed. This writer is essentially the subject matter expert on medical writing within the team of contributors to the submission.

For a medical writer interested in becoming a submission lead, Bowlby's advice is to first gain experience writing individual documents, such as protocols, clinical study reports, and investigator's brochures, then work up to summary-level documents, perhaps collaborating with a more experienced medical writer. For a first project as a submission lead, try a small submission with a familiar team and product. An IND application is a good choice because it tends to be smaller and more contained. As you gain confidence as a submission lead, advance to larger projects and new therapeutic areas.

Julie Kirkwood is a medical writer in the cardiac core laboratory at ERT, a global data and technology company that helps minimize risk in clinical trials. She lives in Rochester, NY.

## Highlights of AMWA-DVC Freelance Workshop, March 16th, 2019

### The Fine Art of Procrastination

By *Curtis Briggs*

Kelleen Flaherty, MS, MWC, CMPP, an adjunct assistant professor of biomedical writing at the University of the Sciences in Philadelphia, assured the AMWA Freelance Workshop audience that procrastination is actually universal-not only the bane of writers, but of all kinds of people in all kinds of occupations. In fact, a Google search for memes about procrastination yielded over 6 million results.

Taking an ersatz scientific approach to deconstructing procrastination, Flaherty presented some highly imaginative-in her words, completely fake-neurochemical models of both productivity and procrastination. In Flaherty's productivity model, a neurotransmitter called productin is manufactured in the time management axon. Productin binds to receptors on the postsynaptic membrane, the productivity neuron depolarizes, and productivity ensues. In the procrastination model, productin molecules do not bind to the postsynaptic membrane for one of several reasons: (1) productin receptor blockade (the writer has time management skills but a situational block gets in the way); (2) catalytic degradation of productin (time management skills are lost due to social media or daydreaming); or (3) reuptake disorder (time management skills are not used because of fear). These models were so convincing that Flaherty had to keep reminding the audience that this was not real science.

Flaherty discussed the results of an online survey about procrastination that she conducted with AMWA members, Facebook users, and University of the Sciences faculty and students. She was surprised by the volume and emotional intensity of survey responses. Heartfelt responses from the survey came in lengthy emails and attachments. In them, writers described the emotional and physical toll of procrastination, including stress, loss of self-confidence, self-worth, and sense of purpose, as well as guilt, shame, despair, and poor health. One respondent wrote, "It is a real hindrance to my life, and it has cost me time, trust, money, and

health." Another claimed, "If anyone has a drug to cure it, I will sell my kidney for it."

Fear and its close relatives-perfectionism, lack of self-confidence, anxiety, obsessive compulsive disorder/attention deficit disorder (OCD/ADD), apathy, depression, feeling overwhelmed-were most often cited as the root causes of the self-destructive and compulsive patterns of procrastination. Additional causes were cited, including problems with concentration or focus, unrealistic expectations and self-delusion about deadlines, or needing absolute quiet and an environment free of distractions in order to work. Working from home was seen as a mixed blessing, providing more flexibility, but not necessarily an environment conducive to work.

Survey respondents described their typical methods of procrastination, including social media, exercising, eating, napping, daydreaming, organizing, or cleaning: "And now, since I have a deadline, I must go and alphabetize the contents of my refrigerator."

Because procrastination and its corresponding emotional distress feed each other, both need to be addressed concurrently, using cognitive tools as well as time management and productivity strategies. Flaherty presented a Cognitive Behavioral Therapy Model in which the writer learns to challenge and control self-defeating thoughts ("OMG, I'll never get this done!" or "I am a lazy failure!"), as well as how to break the workload into manageable parts and use self-soothing strategies like exercise, meditation, yoga, and music.

Flaherty presented time management strategies with a "6 Rs of Behavioral Coping" model:

1. Rules: Make a timeline; create a list, prioritizing one thing per day; limit social media; "just do it."
2. Routine: Know when you work best; keep the same daily routine, with a regular sleep/wake/work schedule.
3. Ritual: Work in timed blocks; use a journal; create to-do lists with sub-categories that you update regularly.
4. Research: Consult self-help literature for coping strategies; consider medical options.
5. Review: Access online tools, tips, and checklists; review your journal; do self-evaluation of skills and process (what works and what doesn't).
6. Reward: Check off tasks on lists; take a break; mentor/help others; do something fun or creatively fulfilling.

Flaherty emphasized "the power of the almighty list," with its power to reduce anxiety. She suggested keeping a running list at hand (including by the bed at night), and getting down thoughts as soon as they occur. She demonstrated dividing up tasks on the list by More Important, Less Important, Fast, or Not Fast. At the same time, she cautioned not to give your list too much power or let it make you feel overwhelmed.

Preparation and organization before starting are critical, including ensuring that you have the materials and information you need, estimating time, building in "disaster strategies," and starting before the starting date.

All these strategies will help you avoid the quicksand of procrastination as well as earn neurochemical rewards: relief, euphoria, happiness, and a sense of peace. You'll also be better able to cope with the next project.

Curtis Briggs, owner of Working Words Inc., is a freelance medical writer, editor, and copywriter, and provides training and coaching in writing and critical thinking, primarily for pharmaceutical and biopharmaceutical clients.

## Upcoming Education and Networking Events for our Members

### AMWA National Conference November 6-9, 2019 in San Diego, CA

Discounted registration for the National Conference is available until August 31, 2019.



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### 2019 MAACME 9th Annual Conference



The Mid-Atlantic Alliance for Continuing Medical Education (AMACME) Annual Conference is designed to meet the educational needs of CME professionals working in a variety of settings. The 2019 MAACME Annual Conference will be held November 20-21, 2019 at the Sheraton Harrisburg Hershey Hotel. Day 1 will be an all-day session, "CME 101: The Nitty-Gritty of Accredited Continuing Medical Education and Adult Education" followed by a fun welcome reception. Day 2 will begin with a keynote from ACCME Vice President of Education and Outreach, Steve Singer, PhD. The full agenda and registration information is available at [www.maacme.org](http://www.maacme.org). Group rates expire October 29, 2019. If interested in learning CME, here's a great opportunity to expand your knowledge and skills.

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