

## Pharmaceutical Writing for French<>English Translators

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Pharmaceutical are a multi-billion dollar, multinational industry—perfect for translators. Pharmaceutical writing is a wide-ranging field encompassing not just pharmacology but everything from statistics, medical ethics, epidemiology and biometry, to packaging and marketing. This industry is heavily regulated, which is both a boon and a bane for translators. Numerous regulatory documents and guidelines exist—from the Food and Drug Administration (FDA) in the U.S., and the International Conference on Harmonisation (ICH) and national regulatory bodies in Europe b u t they are not always consistent. On the positive side (for translators), heavy regulation generates LOTS of documentation! As it would be impossible to do the entire industry justice in one sitting, I will concentrate on just a few areas here: an understanding of the processes of drug development and approval with a focus on the U.S., and some of the documents generated by these processes.

### **Drug Development and Approval in the United States** **Selecting a Compound**

Nearly all new drugs travel the same path from laboratory bench to pharmacy shelf. We begin with a new chemical entity or a new molecular entity (here we go with the abbreviations—NCE and NME) (*nouvelle entité moléculaire*, not usually abbreviated in French). An NME is a novel patentable

compound never before approved as a medicine in the United States. We can use a variety of methods to identify a lead compound (*tête série*), i.e., one that has promise. From the simplest (and the one with the lowest odds of success) to the most complex (and expensive, with the highest rate of success), these methods are:

- random screening
- combinatorial chemistry and screening
- targeted synthesis
- drug modeling.

Let's keep our fingers crossed: only 20 in 5,000 compounds that are screened enter the next phase, preclinical testing.

### **Preclinical Testing**

Our lead compound shows real potential, so we proceed to preclinical evaluation (note: no hyphen). Preclinical testing (*toxicologie préclinique ou pharmacovigilance préclinique*) is performed in animals and cell lines, and so is also referred to as the nonclinical phase (*phase nonclinique*) of a study. As suggested by the French terms, pre-clinical testing includes pharmacology and toxicology studies, primarily to assess safety. It is estimated that between 95% and 99% of new therapies do not make it past the preclinical stage, so we aren't telling Martha Stewart to buy stock...yet.

## Filing an IND

Our compound, code-named “Wonderpill,” has demonstrated a promising efficacy and safety profile (*profil d’efficacité et sécurité*). [“Safety” is a tricky term for English– French translations, as it can be translated as *sûreté, innocuité, ou tolerance.*] Now we submit an Investigational New Drug Application, or IND (*une demande d’autorisation de nouveau médicament de recherche*) to the FDA. INDs are required before beginning human trials in the United States. (Why it isn’t called an “INDA” I cannot say. To further confuse matters, an IND is also known as a Notice of Claimed Investigational Exemption for a New Drug!) The FDA does not approve an IND. It has 30 days to review the document, during which time it carefully examines the protocol to ensure that human subjects will not be exposed to unnecessary risks, and that Phase 2 and 3 trials are adequately designed to provide the necessary data. If the agency is not satisfied, it will contact a sponsor and issue a clinical hold (*bloquer la demande*) until any problems or questions are resolved.

## Clinical Development

No news is good news. Our pharmaceutical company hasn’t heard from the FDA within the 30-day limit. Now we may proceed with clinical (i.e., human) trials (*essais cliniques*). Clinical development is commonly divided into four phases, cleverly named “Phase 1,” “Phase 2,” “Phase 3,” and “Phase 4.” [Note: You will see these terms written with both Roman and Arabic numerals; the latter are used in the *AMA Manual of Style* and *The Merck Manual*.]

## In a Phase 1 study we:

- Establish safety in a small number of healthy volunteers (20-80). The exceptions are AIDS and oncology drugs, which are not tested in healthy subjects because they are too toxic.
- Conduct clinical pharmacology (*pharmacologie clinique*), pharmacodynamics (*pharmacodynamie*), and pharmacokinetic (PK) (*pharmacocinétique*) studies to study how the drug is tolerated, metabolized, and excreted.
- Conduct dose-ranging (*études de dosage*) studies to establish the upper level of tolerability, which is the maximum tolerated dose (*dose maximale tolérée*). Phase 1 studies last several months.

## In a Phase 2 study we:

- Establish short-term safety, but concentrate on efficacy for the intended indication (i.e., medical condition) in the so-called diseased or intended population (*population visée*) (50-200 patients) at different doses and regimens.
- Establish a minimum dose that is maximally effective.
- Measure clinical endpoints (*critères d’évaluation [ou d’efficacité cliniques]*).
- Control our compound against placebo (*contrôlé par placebo*) or comparator (*comparateur*) (existing drug or standard therapy). Phase 2 studies last from several months to two years.

## Phase 3

In a Phase 3 study (sometimes called a

“pivotal study” (*etude pivotale*), depending on how it is set up) we:

- Establish substantial evidence to confirm and expand on the safety and efficacy of the drug in a larger diseased population (from several hundred to several thousand patients).
- Assess the benefit: risk ratio (*rapport beneficerisque*).
- Administer the drug in its market image—the route of administration (*voie d’administration*), formulation (*preparation*), color, etc., in which it will be sold.
- Collect data to support proposed labeling.

Phase 3 studies can last several years.

## **NDA**

Much to our (and our stockholders’) satisfaction, our compound has beaten the odds and is ready to be submitted to a regulatory agency for review. In the U.S., this submission is called a New Drug Application (NDA). It is called a dossier d’autorisation de mise sur le marché (AMM) in Europe. Unlike the IND, an NDA must be approved by the FDA before a drug can be marketed. This approval process usually takes about one year. However, if our drug qualifies for so-called “fast track” review (the FDA awards this designation to drugs that “are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs”), the process may take only six months.

After many months of nail-biting and checking the mailbox, we finally hear from the FDA. We’re still anxious, knowing that the agency sends out three kinds of action letters: a approvable letter (the application is insufficient to justify approval); an approvable letter (the application substantially

meets requirements for approval and can be approved provided certain changes are made and/or additional information is included); and an approval letter (the drug is considered approved as of the date of the letter). Only rarely does a company receive an approval letter without first receiving an approvable letter. The envelope please...yes! Wonderpill has been approved!

## **Marketing and Phase 4 Studies**

While champagne flows over in R&D, the manufacturing department is gearing up. One of our considerations back in the discovery phase, when we were determining formulation, was the feasibility of bulk production. Naturally, as part of their mandate to protect public health, regulatory bodies have an interest in our manufacturing methods, and have laid out some specific requirements for us to follow. These are set forth in the Good Manufacturing Practices (GMP) (*bonnes pratiques de fabrication, BPF*). [Acronym note: You will often see CGMP or cGMP; the “c” stands for “current.”] *En gros*, GMP deals with quality control and purity issues.

Now that Wonderpill has been approved, we can start an advertising campaign and send our sales representatives into the field to tout its marvels to physicians. We can’t say just anything, of course. All promotional materials must be approved by the FDA’s Division of Drug Marketing, Advertising, and Communications (DDMAC). Nor can we stop monitoring the effects of our drug on people. At this point, we want to gather data about the broader experience with the drug in the

general population, both for marketing purposes (a.k.a. Phase 4 study) and for ongoing safety and epidemiological purposes (a.k.a. postmarketing surveillance [*pharmacovigilance*], especially when conducted or mandated by a regulatory body). [Note: Translators may run across the term “seeding study” in older texts. This is an outdated term for Phase 4 studies that were primarily marketing tools and had little scientific merit.] As a responsible pharmaceutical manufacturer, we abide by all of the government’s post-approval requirements, especially adverse drug reaction: (ADR) (*événement indésirable médicamenteux*, *EIM*) reports. Of course, we hope there won’t be many of these, and that Wonderpill will offer a happier, healthier life for millions of people and millions of dollars for us.

### Documents Generated by the Above Processes NME/NCE

As stated in the definition given earlier, NMEs are new compounds, so translators may see patent applications, along with highly specialized chemistry and biology reports.

### Preclinical Studies

Translators will encounter validation protocols for the various processes and equipment used, and reports on the *in vivo* and *in vitro* studies. These studies focus on toxicology, and thus include reports on single-dose or acute studies (*études aiguës*); subacute or subchronic studies (*études subaiguës*); chronic studies (*études chroniques*); multiple-dose (*doses multiples*) or dose-ranging studies (*études de dosage*); as well as mutagenicity (*mutagenicity*), teratogenicity (*teratogénicité*), and carcinogenicity (*cancero-*

*généicité*, *carcinogénicité*). Research at this stage also includes pharmacodynamics (*pharmacodynamie*), bioavailability (*biodisponibilité*), and PK studies (*études pharmacocinétiques*) [note: *k*→*c*].

In the losing battle against acronymania, PK studies are also known as ADME studies, for absorption, distribution, metabolism, excretion (*absorption, distribution, métabolisme [biotransformation], élimination*). French-to-English translators will be tempted to render the “E” of ADME as “elimination,” especially late at night under a tight deadline. Avoid this temptation!

We should note here that when a manufacturer begins to compile safety data from preclinical studies for submission to the FDA, Good Laboratory Practices, or GLP (*bonnes pratiques de laboratoire*, *BPL*), are in effect.

GLP essentially provide for quality control of the preclinical facility, personnel, and data. If preclinical studies have been conducted in another country, then the manufacturer must demonstrate to the FDA that the testing labs followed GLP, so many translators have seen these types of documents. The full text of the guidelines can be found in English, French, and Spanish at [www.olis.oecd.org/olis/1998d/oc.nsf/LinkTo/env-mcchem\(98\)17](http://www.olis.oecd.org/olis/1998d/oc.nsf/LinkTo/env-mcchem(98)17).

### IND

The IND has numerous sections, including:

- A general investigational plan, giving a brief description of the overall plan for investigating the drug, and the scale and kind of clinical studies to be conducted during the following year.
- The investigator’s brochure (**brochure de l’investigateur ou brochure**

**du chercheur [Canada]**), summarizing **everything** known about the drug at that point in time. ICH (*CIH, conference internationale d'harmonisation*) guidelines *E6: Good Clinical Practice: Consolidated Guidance* describe the information an investigator's brochure should contain.

- Clinical trial protocols (*protocoles des essais cliniques*): the scientific plan for studying the drug and the statistical analyses of the results, including directions to doctors, nurses, and lab personnel for correct implementation of the study.
- Chemistry, manufacturing, and control information (CMC), detailing the identity, strength, purity, and quality of the drug substance (*principe actif*) and drug product (*preparation*) (as you can see from the French, these are not the same thing), and how these will be consistently obtained by the manufacturer. The drug's stability (*stabilité*) is also described. Guidelines state that any placebo used in a trial must mimic the study drug in appearance, flavor, odor, etc., so its composition, manufacture, and control must also be described here.
- Pharmacology and toxicology information, including: a) the pharmacology and mechanism of action (*mécanisme d'action*) of the drug as well as the ADME study results; b) an integrated summary of the toxicology results to support the safety of the proposed trial; and c) a statement that GLP regulations were followed.
- Previous human experience with the investigational drug. If the drug has been tested or marketed in other countries, those safety and efficacy data must be submitted to the FDA, in English.

Although the FDA realizes that manufacturing methods may change when production changes from pilot scale to

large-scale production, companies are required to comply with GMP during clinical trials, and not just when the drug is being marketed. Thus, the complexity and detail of the CMC section.

## Clinical Development

Before a clinical trial can begin, it must receive approval from the Institutional Review Board (IRB), a.k.a. the Independent Ethics Committee (*IEC [approbation du comité d'éthique]*). In France, approval must be obtained from the CCPPRB, *le Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale* (so, sometimes those acronyms do come in handy!).

Commonly translated documents from this stage of a drug trial include:

### Clinical Study Protocol (*protocole de l'étude clinique*)

The International Clinical Studies Support Center provides a clear explanation at [www.icssc.org/protocol\\_development.htm](http://www.icssc.org/protocol_development.htm): "The protocol document describes the framework under which the study is conducted. A well-written protocol must:

- State the rationale and objectives for the research.
- Describe the study design and methodology to be utilized.
- Define the study population.
- Protect participants' rights while in the study.
- Outline the procedures to be followed throughout the course of the study.
- Present data monitoring, management, and analysis plans to ensure high quality data.
- Describe the procedures for submit-

ting reports to institutional review boards (IRBs), data and safety monitoring boards (DSMBs), and/or sponsoring institutions." Amendments to protocols are common.

### **Informed Consent Form (*formulaire de consentement éclairée*)**

Before a subject can be enrolled in a study, he or she must sign a consent form. As a rule, consent forms should be written so that they are readable by people who have not completed high school. They must include:

- A statement that the study involves research and is experimental.
- The purpose of the research.
- The duration of a subject's participation in the study.
- The study procedures.
- A description of foreseeable risks or discomforts.
- A description of benefits that can reasonably be expected.
- Mention of confidentiality measures.
- Contact name(s) for any questions.
- A statement that penalty or loss of benefits to the person.

### **Case Report Forms (CRFs) (*cahiers d'observation*)**

A file is kept on every subject enrolled in every phase of a clinical trial. CRFs are critical, as they contain all of the data that will be used to address the research question, and thus enable a drug (*or device or procedure*) to be eligible for approval. This file usually includes: an eligibility checklist of inclusion and exclusion criteria (*critères d'inclusion et d'exclusion*); medical history (*anamnèse*); physical examination(s); laboratory data;

study drug administration and compliance (*observance*); a list of concomitant medications, adverse events, and efficacy measures (*endpoints or outcome measures [critères d'efficacité, critères d'évaluation]*); and surrogate endpoints (s. outcomes, s. mesures, *critères de substitution, CS*).

In this phase of the investigation, the sponsor must comply with Good Clinical Practices, GCP (you guessed it, *les bonnes pratiques cliniques, BPC*). **Interestingly, GLP are more** stringent than GCP! The definition of GCP in the ICH *Guidelines Glossary* is: "A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected." A good website for GCP in the U.S. is [www.sqa.org/Committees/CS S/gcpref.html](http://www.sqa.org/Committees/CS%20/gcpref.html). For European GCP, the Pharmacos site has the complete text, in numerous languages, at <http://pharmacos.eudra.org/F2/eudralex/vol-1/home.htm>.

### **NDA**

This is the biggie. A new drug application in the U.S. is literally thousands of pages long. The parts of an NDA, per the Code of Federal Regulations (CFR), are:

- A summary (often 100-200 pages).
- Technical sections: CMC, non-clinical pharmacology and toxicology, human pharmacokinetics and bioavailability, microbiology, clinical data, statistical data, and pediatric use.
- Samples and labeling.

- Case report forms and tabulations.
- Other (of interest to us as translators, because it includes such things as foreign marketing history).

Labeling, included in the CMC section of the NDA, is another area often involving translation. It is important to note that the FDA makes a distinction between label and labeling. The first term refers only to what is actually affixed to the product container (*l'étiquetage*), and the second refers to any other written material accompanying the product. Most often, labeling refers to the package insert, PI (*la notice*), but includes all other packaging. All labeling must be approved by the FDA.

Client education note: The FDA requires that "certified" translations be provided of any required documentation that is in a foreign language! It may also require a back translation, especially for languages the agency considers "esoteric." Japanese, for example, is considered an esoteric language by the FDA.

### Marketing and Phase 4 Studies

Numerous marketing materials are prepared in anticipation of FDA approval of a drug, and flood the relevant print, radio, and television waves immediately thereafter. Promotional materials, both for the general public and for specialized physicians, are considered "labeling" by the FDA, and are tightly regulated. They are usually written by specialized advertising companies to comply with these regulations. In my experience (i.e., into English), such documents are not often translated.

More frequently translated, and much more interesting, are journal articles. These tend to be well written, especially those submitted to prestigious, peer-reviewed journals. I

love to translate journal articles!

A significant postmarketing activity is pharmacovigilance. Reporting is often voluntary, such as in MedWatch, the "FDA Safety Information and Adverse Event Reporting Program." Note that although the term "adverse event" is used, these reports are often called ADRs (*EIM*) because reactions can reasonably be attributed to (*imputable a*) the product.

### Conclusion

This overview of drug development and approval offers translators a foundation for understanding the pharmaceutical industry. For more information, I have prepared a PowerPoint presentation on this subject, which can be downloaded from ATA's French Language Division website ([www.americantranslators.org/divisions/FLD/fldhome.htm](http://www.americantranslators.org/divisions/FLD/fldhome.htm)), along with a French and English glossary of acronyms and initialisms.

### References

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## Use Your Words

Finally, I'd like to share a few tips about business etiquette that may seem self-evident, but which are often not observed.

"May I?" *Always ask first* if you want to use someone as a reference, if you're thinking about introducing yourself to one of their business partners, etc. It can be disquieting to learn that someone has acted on information learned through a confidential business relationship. There's probably nothing that will sour a relationship faster than even a whiff of violated confidentiality.

"Thank you." Whenever someone helps you out, at least call to personally thank them, or better yet, send a handwritten note. When a local client of mine recommends my services and I get the job, I always invite the "old" client out to lunch. It's a great thank you and an opportunity to catch up and cement the relationship.

Remember, it's called *networking*, not grab-and-run or me-first. Your objective is not just to find more business for yourself, but to promote the well-being of your business while promoting the well-being of your clients, colleagues, and friends. When you read an ar-

ticle about a company or issue you know a client is interested in, give them a call or fax it over to them. They'll appreciate the information and the fact that you thought of them. There are a million other examples you'll discover as you apply some creative thinking to develop business relationships, and that's what it's all about.