PHARMACEUTICAL WRITING FOR FRENCH < > ENGLISH TRANSLATORS

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Note: This article accompanied a live session at an American Translators Association conference in 2002. Some information may be out of date, but the concepts and terminology are still valid.

Abstract: Pharmaceuticals are a multi-billion dollar, multi-national industry – perfect for translators. And while pharmaceutical writing may be considered a "subset" of medical writing, it is a wide-ranging field in and of itself, 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 U.S. Food and Drug Administration (FDA), Health Canada/Santé Canada and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) as well as national regulatory bodies in Europe. On the positive side (for translators), heavy regulation engenders LOTS of paper! Documents generated during the drug development and approval processes include: informed consent forms, protocols, investigator's brochures, case report forms, preclinical study reports, package inserts, and journal articles. 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 United States, and some of the documents generated by these processes.

1. DRUG DEVELOPMENT AND APPROVAL IN THE UNITED STATES

1.1 Selecting a Compound

Nearly all new drugs travel the same path from laboratory bench to pharmacy shelf. (Medical devices follow a similar route.) 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 syntheses; and
- drug modeling.

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

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1.2 Preclinical Testing

Our lead compound shows real potential, so we proceed to preclinical evaluation [note: no hyphen]. **Preclinical testing** (***étude / toxicologie / pharmacovigilance préclinique***) is performed in animals and cell lines, and so is also referred to as the **nonclinical phase** (***phase nonclinique***) of a study because it does not involve human subjects. As suggested by the French terms, preclinical 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 buying stock…yet.

1.3 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, and can be translated in various contexts as *sûreté, innocuité, tolérance*, even *effets indésirables* and *pharmacovigilance*.) Now we submit an **Investigational New Drug Application,** or **IND** (***une demande d'autorisation de nouveau médicament de recherche***) to the FDA. (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 purpose of the IND is to allow interstate shipment of unapproved drugs, and is required before beginning human trials in the U.S. 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.

1.4 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* although the former are actually more common.] These phases are set up differently, each having a unique purpose and thus its own set of tests… and documents, which we'll look at later. In a nutshell:

In a Phase 1 study we:
- establish safety in a small number of healthy volunteers (20-80) (with the exception of 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; and
- conduct **dose-ranging** (***études de dosage***) studies to establish the upper level of tolerability, 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;
- conduct some further PK studies;
- establish a minimum dose that is maximally effective;
- measure **clinical endpoints** (***critères d'évaluation*** (ou ***d'efficacité***) ***cliniques***); and
- 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.

In a **Phase 3** study (sometimes called a "**pivotal study**"(***étude 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 bénéfice-risque***);
- administer the drug in its **market image**, i.e. the **route of administration** (***voie d'administration***), **formulation** (***préparation***, not *dosage!)*, color, etc. in which it will be sold; and
- collect data to support proposed labeling.

Phase 3 studies can last several years.

1.5 NDA

Much to our (and our stockholders') satisfaction, our compound has beaten the odds – it ameliorates or cures a medical condition without harming the patient – 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)**. In Europe it is called a ***dossier d'autorisation de mise sur le marché (AMM)***. 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. A year may not sound like a lot when compared to the 10-15 years it takes to develop a new drug, but remember that the patent clock started ticking when we filed our IND several years ago.

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 **not-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 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!

1.6 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. The term of our patent runs for 17 years. Although the Patent Term Restoration Act may grant us some additional time, we still need to manufacture and deliver our product widely and quickly in order to recoup some of the US $500 million or so we spent on development — not to mention the NDA filing fee that can run US $1,000,000 or more!

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."] GMP is the law, so we must follow it carefully or risk the same civil and criminal consequences that result from breaking any law.

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 **Office of Prescription Drug Promotion (OPDP,** formerly the 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 postapproval requirements, especially **adverse drug reaction** (**ADR**) (***évenement 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.

2. DOCUMENTS GENERATED BY THE ABOVE PROCESSES

2.1 New Molecular or Chemical Entity

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.

2.2 Preclinical Studies

Pharmacologic work begins with a screening process, using in vitro and in vivo studies to determine if the compound demonstrates measurable pharmacological effect. Included here are: **pharmacodynamics** (***pharmacodynamie***); **toxicology studies** (***études toxicologiques)*** i.e. 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** (***mutagénicité***), **teratogenicity (*tératogénicité***), and **carcinogenicity** (***cancérogénicité, carcinogénicité***); and **PK studies** (***études pharmacocinétiques***) [note: k → c] and **bioavailability** (***biodisponibilité***). 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 in the United States, preclinical screening and testing need only comply with the U.S. Animal Welfare Act, until a manufacturer begins to compile safety data for submission to the FDA, at which point **Good Laboratory Practices**, or **GLP** (***bonnes pratiques de laboratoire, BPL***) take effect. The major provisions of GLP are:

- organization and personnel (especially the study director and the quality assurance unit);
- testing facility (including test substance handling areas, specimen and data storage, methods of dosage preparation, test substance accountability);
- testing facility operation (the standard operating procedures, or SOPs);
- test and control article characterization;
- the protocol and conduct of the nonclinical laboratory study (describing the design and purpose of the study, types of tests and analyses; note that protocols are study-specific whereas SOPs are facility-specific);
- records and reporting (summary, testing methods, results, conclusions, plus raw data); and
- equipment design (design, maintenance, calibration).

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 documents pertaining to the above.

2.3 Investigational New Drug Application

The IND has numerous sections, including:

- A **general investigational plan**, giving a brief description of the overall plan for investigating the drug, 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***), summarizing nonclinical and clinical studies and providing the investigators with information about the new drug, especially the risks to which subjects will be exposed. The IB is legally considered "labeling" (more on this later), and thus is comparable to the prescribing information provided for a marketed product. ICH 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 (*préparation***) (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.

- Additional relevant information; drugs that are radioactive or have the potential for abuse are subject to additional requirements.

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, not just when the drug is being marketed – thus the complexity and detail of the CMC section.

2.4 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 **Comité de Protection des Personnes** (**CPP**); this was formerly known as the CCPPRB, *le Comité Consultatif de Protection des Personnes dans la Recherche Biomédical**e*** — 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***).
  According to the International Clinical Studies Support Center (icscc.org), 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 submitting 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 can be read and understood 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 and 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, and a statement that participation is voluntary and a refusal to participate in or a withdrawal from the study will involve no 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 / adherence** ***(observance / adhésion)***, 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. measures),** ***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." Note that some GCPs are regulations, while others are guidelines.

2.5 New Drug Application

This is the biggie. A European *dossier de demande d'autorisation de mise sur le marché* is typically several hundred pages long. A new drug application in the U.S. is literally thousands of pages long, because the FDA requires total disclosure. This means that all of the data collected from the trial must be submitted, while in Europe ICH guidelines state that submission of a representative sample of the data is sufficient. [Note: even though the FDA is a party to ICH, their policy of total disclosure will not change. However, the **Common Technical Document (CTD)** will probably replace the NDA.] The parts of an NDA, per the **Code of Federal Regulations (CFR),** are:

- a summary (often 100-200 pages)
- technical sections: CMC, nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, microbiology, clinical data, statistical data, 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 certified translations to be provided of any required documentation that is in 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.

2.6 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. Many times these articles fall under the rubric of "promotional material" too, but they are also legitimate scientific works, and as such are (usually) 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 be reasonably **attributed** to (***imputable à***) the product.

3. CONCLUSION

This overview of drug development and approval offers translators a foundation in the basics of the pharmaceutical industry. In the session we plunged into the troubled waters of *faux amis* and other potentially confusing terminology. That PowerPoint presentation is available on the French Language Division website of the ATA.

References

1. Mathieu, Mark. *New Drug Development: A Regulatory Overview*. Cambridge, MA: PARAXEL International Corp.,1990.

2. Day, Simon. *Dictionary for Clinical Trials*. West Sussex, England: John Wiley & Sons Ltd., 1999.

3. Nahler, Gerhard. *Dictionary of Pharmaceutical Medicine*. Springer-Verlag, Austria: Springer-Verlag Wien New York, 1994.

4. *The Merck Manual, 17th Edition.* Whitehouse Station, NJ: Merck Research Laboratories, 1999.

5. *Le Manuel Merck, Troisième Edition*. Paris: Editions d'Après, 2000.

6. American Medical Association. *Manual of Style, 9th Edition*. Chicago, IL: Williams & Wilkins, 1998.

7. Biron, Pierre. *La pharmacovigilance de A à Z.* Montréal: Université de Montréal, 1999.