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Impact of written drug information in patient package inserts: Acceptance and impact on benefit/risk perception

Thesis submitted as partial fulfilment of the requirements for the Degree of Doctor in Medical Sciences

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There is, upon the whole, nothing more important in life than to find out the right point of view with which things should be looked at and judged, and then to keep to that point.

Von Clausewitz
[(cited by J. Ziman. Reliable knowledge: An exploration in the grounds for belief in science. Cambridge University Press, 1978.]

To Mieke

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Preface

In the early 1980s, the Belgian Health Authorities decided to provide an understandable insert with written drug information, to be enclosed with every package of every medicine dispensed in the country. In doing so, the Belgian government anticipated upcoming European regulations.

In 1985, Prof. Marc Bogaert, Professor of Clinical Pharmacology at Ghent University and member of the Belgian Drug Registration Committee, invited me to join a small group of experts, called upon to give sound recommendations for the editing of patient package inserts. I was then a practicing physician in the city of Ghent, with 7 years of practice experience, and a member of the Research Organisation of the Flemish Scientific Association of General Practitioners. While working on the committee, I realised what an tremendous task it was for the more than 200 pharmaceutical companies to revise the data sheets and to edit a *patient package insert* (PPI) for the more than 5,000 drugs in Belgium.

When all was well under way, a scientific evaluation programme of the introduction of PPIs in Belgium was started. In 1988, the kick-off for the programme was given with an international scientific symposium at the University of Ghent[1], where world experts gathered to discuss the framework and the objectives of the evaluation programme. I served as a part time coordinator of this programme, with Chris Van haecht as a full time researcher. In 1992, he defended his doctoral thesis on this subject[2].

Later on, I continued the work on written drug information at the Heymans Institute, with several new studies, while remaining a practicing family physician till today. This thesis is an overview of the research carried out over a period of 18 years.

Summary

This thesis discusses the patient package insert (PPI), a folded sheet of paper in the drug package with a text which is supposed to be comprehensible for the general public. The PPI contains information on how the drug must be taken, on the risks of taking the drug, and a limited amount of information on what the drug is for.

Belgium was the first country in Europe, together with Switzerland, to introduce PPIs. PPIs were first introduced in 1988 and the process was completed in 1992.

In Europe, health authorities decided in 1992 that all medicinal product packages should contain a comprehensible insert. This decision is slowly but surely being implemented in all European countries. Similar developments did not take place in the US and other parts of the world, where medicines are distributed in bulk and dispensed without much information, even when dealing with powerful prescription drugs.

During the introduction of PPIs in Belgium, a research programme was conducted to evaluate this change in the way drug information was provided in the drug distribution system. This thesis provides an overview of the studies carried out during that period. In addition, a number of other descriptive studies of the flow of drug information in specific patients groups is provided. Finally, a number of experimental studies is presented, which evaluate the impact of written drug information on patients' benefit/risk perception.

The acceptance of a drug distribution system with mandatory PPIs in all drug packages will be evaluated on the basis of Belgium's relatively long and well-documented experience with PPIs. We address the following questions: what is the percentage of patients who read, accept and appreciate PPIs; what happens when a country changes from technical inserts with difficult jargon to comprehensible PPIs; what do we know about the impact of PPIs on patients knowledge and feelings about their drugs?

In this thesis, an attempt is made to understand the mental processing of drug information which precedes patients' decisions and coping strategies, necessary for successful drug treatment. The question here is whether the PPI is capable of influencing the benefit/risk perception of patients. A further step is to study the impact of the PPI on behaviour. Here, other questions are at stake. Does the PPI have an impact on patients' reporting of health problems and side-effects, on their ability to carry out a treatment correctly and safely, on their adherence to therapy at the beginning of treatment, and on their motivation to continue crucial therapy? These questions are addressed only to a limited extent in this work, as we have focused on the preceding cognitive process of benefit/risk perception.

This thesis is composed of 4 parts: an introductory section, two sections with results from the various studies, and a closing section with a discussion, recommendations and final conclusions. In annex 1, we add six facsimiles, one for each of the six publications which make up the formal basis of this thesis. However, these core publications are also reported in a slightly simplified and condensed way in the two middle sections, but this time placed within the wider context of the thesis and in a style similar to the other studies reported here.

In the introductory section, the aims of this collection of studies are described. First, we review the literature on patients' objective and subjective needs for drug information. We define the notion of the patient package insert, along with its characteristics and functions. We review what is known about the impact of the PPI on patients level of knowledge about medicines. The history and current status of insert programmes in Europe, the US and other parts of the world are given. Afterwards, we focus on the introduction of the PPI in Belgium between 1988 and 1992, as this was the background setting for this thesis.

The introduction ends with a short overview of the theoretical models used to design the studies presented here and an outline of the structure of this thesis.

In Part II, descriptive studies are presented, which were carried out before, during and shortly after the introduction of PPIs in Belgium.

In Chapter 1 of Part II, we present the 1988 population survey in Belgium, among adults from 18 to 64 years old, with door-to-door interviews. This study was carried out just before PPIs were introduced, at the end of a period of 25 years of drug distribution with more or less incomprehensible technical inserts (TIs). Results showed that a high percentage of patients (around 90%) claimed to read the TI, and to find it useful. There were some complaints about readability. The specific role of the insert was acknowlegded, in addition to the role of the physician and the pharmacist.

In Chapter 2 of Part II, a report is given of a mail questionnaire study among Belgian physicians. Most physicians apparently underestimated the percentage of patients reading the insert.

Three types of physicians were discovered in a cluster analysis: somewhat older physicians, overtly negative towards the PPI, but engaging frequently in personal verbal instructions on drug use; somewhat younger physicians, welcoming the PPI as a relief from providing routine information; and physicians with mixed feelings towards the PPI, because they observed their patients more thoroughly and observed positive as well as negative effects of the insert.

In Chapter 3 of Part II, we present a study in nursing homes with an observation of a sample of residents and an interview with their attending nurses. In these nursing homes, drug utilisation was high. The insert was not

distributed to residents. Even cognitively fit residents had lost their autonomy over the use of their drugs. The nurses made only limited use of the insert as a source of drug information.

Chapter 4 of Part II starts with a description of the linguistic tools developed in the Belgian PPI Programme (writing style guides, multilingual glossary of technical and popular medical terms and a computerised readability test for the French and the Dutch language). In addition, an overview is given of eleven supplementary studies: a mail questionnaire study among regulatory affair managers, a repeat of the 1988 population study in 1991, two consecutive clinical registration studies among hypertensive patients in general practice, five studies among specific population groups, two studies on drug distribution in nursing homes and hospitals, and finally a quality evaluation of a sample of Belgian inserts in 2000.

The regulatory affairs managers are the authors of PPIs within the pharmaceutical industry. The survey demonstrated that they underestimated (as did the physicians) the percentage of patients reading the insert. Their opinion on the usefulness of this source of information was generally positive with some reservations.

The repeat of the population survey in 1991 confirmed the high percentage of readers. In addition, it was clear that the introduction of PPIs was well underway (39% penetration), and was proceeding smoothly and unnoticed.

In the two consecutive clinical registration studies among hypertensive patients on chronic therapy, somewhat lower reading percentages were found, although they were still high. There was little difference in (high) satisfaction according to the type of insert (TI or PPI). However, we observed a somewhat higher level of spontaneous reporting of health problems and side-effects among the PPI readers.

In the descriptive studies among the elderly, a paradox was observed of higher drug consumption and lower subjective need for drug information. Among socially active elderly people, a wide range of information sources was observed, with the PPI still playing a prominent role. Frail elderly people living at home and no longer able to leave their houses were found to have lost contact with the pharmacist, while paramedical caregivers took over as information providers. Among the elderly in acute geriatric wards, the role of the PPI disappeared, in a setting with poor drug information. Among healthy adolescents, the PPI played a prominent role, in the relatively rare instances when a medicinal drug was taken.

The analysis of a small sample of Belgian inserts from the year 2000 indicates that some linguistic improvements have been made (shorter sentences, less jargon) but the length, content, and quality of the Belgian PPIs remains variable, eight years after their introduction.

In Part III we present the experimental studies, focusing on how patients perceive the benefits and risks of their medicines.

In Chapter 1 of Part III (published as the chapter of a book), the relation between drug information, benefit/risk perception and patient compliance is explored, in the light of a new, precise method for measuring patient compliance (electronic monitoring).

In Chapter 2 of Part III, we report on a study where this new measurement technique was applied in a randomised clinical trial, comparing atenolol with lisinopril in the treatment of hypertension. Both treatment groups were further divided into two subgroups: one subgroup without an insert, and one subgroup with a hybrid PPI (in which typical side effects of the two drugs were mixed). This study was originally designed and monitored by a pharmaceutical company, but we added the element of testing the impact of written drug information. There were deficiencies in the blinding of allocation of patients to treatment in this study. Some general practitioners broke the randomisation as they preferred not to give beta-blockers to elderly patients. Hence there were no conclusive results. However, the methodological lessons from this study are discussed, and some hypotheses for further research are suggested.

In Chapter 3 of Part III, we report on an experimental psychology study in healthy volunteers, predominantly women. A PPI with a benefit section (a short paragraph of approximately 80 words on the benefit of the drug) was tested against a normal PPI (as customary, without a benefit section) and against no PPI. For this study, three scenarios were tested (cisapride for acute, benign digestion problems; itroconazol for fungal toenail infections; risperidon in the chronic treatment of psychosis). In each scenario, approximately 90 patients were divided into three experimental groups and given no insert, a normal PPI or a PPI with a benefit message. Subjects who did not receive an insert rated the benefit of the medicine higher than its risks, but scored low on the knowledge test. Subjects who received a normal PPI knew more about the medicine, but rated lower on the benefit/risk. Subjects who received a PPI with a benefit message knew more about their medicine, and consistently rated the benefits higher than the risks. These findings were consistent in the three scenarios.

In Chapter 4 of Part III, we report on a randomised clinical trial with an anti-inflammatory drug among patients with acute pain from a benign trauma. Half of the patients received their drug with the existing technical insert (basically incomprehensible), and the other half received their drug with a PPI (same content, same lay-out, but shorter sentences and less jargon). In both groups the insert was read by a similar high percentage of patients. The satisfaction with the insert was high in both groups, but patients reading a PPI rated lower on the benefit/risk ratio, and had more spontaneous reports of health problems and side effects. Finally, we discuss the design of a study

where we tried to combine a number of the elements described above. This study was halted, however, because of recruitment problems, probably caused by a design that may have been overly ambitious to conduct the study.

In Part IV, the closing section, the relevant results of the properly conducted studies are discussed in relation to other findings in the literature. In addition, hypotheses for further research are formulated. A number of recommendations are made concerning the liability issue and the production and testing of better PPIs. We make a plea to embed PPIs in the new information media, in the context of more general health policy and patient education efforts.

The following final conclusions were drawn.

Patient package inserts are an essential part of modern drug distribution systems and a tool for patient education and health policy. Routinely provided inserts are read by the vast majority of patients and have a positive impact on patient satisfaction, regardless of their quality.

A drug distribution system with patient package inserts has been accepted and welcomed by the population.

High quality patient package inserts have a positive impact on knowledge about drugs in those patients who read the insert. This has been proven in research by others and confirmed in our studies.

The effects on readership, satisfaction, and on knowledge alone may warrant their automatic provision, each time a medicinal product is dispensed, with or without prescription, in spite of the slightly higher distribution costs. These are strong arguments for the universal application of the European system of mandatory and comprehensible patient package inserts. Additional claims of positive behavioural effects of PPIs on patient compliance have barely been demonstrated. There is little evidence to ascertain that current PPIs reduce medication errors and off-label use, increase the observance of precautions, and stimulate adequate reactions when side-effects occur.

Benefit/risk perception is an important cognitive concept for understanding patients mental processing of written drug information in patient package inserts. Direct measurement of benefit/risk perception with more validated tools is necessary to comprehend the relation between benefit/risk perception and behaviour. This may be crucial to design (and retest) better patient package inserts, to help patients make informed and shared decisions about adherence to drug treatment, and to assist them in the proper and safe continuation of treatment. One instrumental aspect of writing better PPIs may be the introduction of an elaborate benefit section. By combining benefit messages and risk messages in the patient package insert, improved transfer of information and a more balanced benefit/risk perception may be achieved.

Samenvatting in het Nederlands

Dit werk gaat over de bijsluiter ingesloten in de verpakking van geneesmiddelen, met een tekst die bedoeld is om voor het grote publiek verstaanbaar te zijn. De patiëntenbijsluiter bevat informatie over hoe het geneesmiddel moet worden genomen, wat de risico's zijn van het gebruik, en tot op zekere hoogte waarvoor het geneesmiddel dient.

België speelde in 1988 een pioniersrol in Europa door samen met Zwitserland als eerste patiëntenbijsluiters in te voeren. Die omschakeling liep tussen 1988 en 1992.

In Europa werd in 1992 besloten dat alle geneesmiddelenverpakkingen zo'n verstaanbare bijsluiter moesten bevatten en geleidelijk aan werd dit ook overal in Europa gerealiseerd. Amerika en andere delen van de wereld kenden deze evolutie niet. Daar worden geneesmiddelen nog veel in bulk verpakt en dikwijls zonder veel informatie verdeeld, ook als het gaat om krachtige geneesmiddelen op voorschrift.

Tijdens de introductie van de patiëntenbijsluiter werd in België een evaluatieprogramma opgezet om de omschakeling op de voet te volgen. Dit werk bevat een overzicht van alle studies die toen werden opgezet. Ook een aantal andere beschrijvende studies worden hierin verwerkt, omdat ze een licht werpen op hoe specifieke groepen patiënten zich informeren over hun geneesmiddelen. Tot slot worden ook een aantal experimentele studies besproken, die dieper peilen naar de invloed van geneesmiddeleninformatie op de manier waarop patiënten zich een voorstelling maken van het voordeel en het risico van hun geneesmiddel (voordeel/risico perceptie).

Vanuit de ervaring in België wordt gepoogd een uitspraak te doen over de aanvaardbaarheid van de verplichte aanwezigheid van een patiëntenbijsluiter in alle geneesmiddelenverpakkingen. Daarbij stellen we ons een aantal vragen. Hoeveel patiënten lezen, aanvaarden en waarderen de bijsluiter? Wat gebeurt er als een land omschakelt van moeilijke naar verstaanbare bijsluiters? Is die omschakeling in België gelukt? Wat weten we over de invloed van de patiëntenbijsluiter op de kennis, emoties en percepties van patiënten over hun geneesmiddelen?

In dit werk is gepoogd om een beter begrip te krijgen van de invloed van de bijsluiter op de mentale processen die voorafgaan aan de beslissingen en handelingen van patiënten wanneer ze geneesmiddelen gebruiken. De vraag is hier of de patiëntenbijsluiter de perceptie van patiënten over het voordeel en het risico van geneesmiddelen kan beïnvloeden. Een verdere stap is uit te maken hoe de bijsluiter inwerkt op gedrag. Dat kan gaan over het melden van gezondheidsproblemen en bijwerkingen, over het vermogen om de behandeling juist en veilig uit te voeren, over de aanvaarding van het geneesmiddel bij de start van een behandeling en over de motivatie om een

noodzakelijke behandeling verder te zetten. Hiervoor zijn in dit werk slechts enkele aanzetten gegeven, omdat we ons toegespitst hebben op de studie van de cognitieve processen van voordeel/risico beleving die voorafgaan aan beslissingen van patiënten.

De thesis bevat vier delen: een inleidend deel, twee delen met de resultaten van de verschillende studies en een afsluitend deel met bespreking, aanbevelingen en conclusies. Achteraan zijn in annex de copies toegevoegd van de zes publicaties waarop deze thesis formeel is gebaseerd. In het boek zelf wordt de verslaggeving van deze 6 publicaties ook gegeven, maar dan wel geplaatst in de context en met een eenheid van stijl, die ook is toegepast voor de andere studies in dit werk vermeld.

Het inleidende deel omschrijft eerst het doel van de onderzoeken die hier worden voorgesteld. Daarna worden de literatuurgegevens over de objectieve en subjectieve nood aan geneesmiddeleninformatie bij patiënten besproken. Dan worden de kenmerken en de functies van de bijsluiter besproken, samen met wat er reeds lang is geweten over de invloed van de bijsluiter op feitelijke kennis over het geneesmiddel. De geschiedenis en de huidige stand van zaken rond bijsluiterprogramma's in Europa, Amerika en enkele andere landen wordt toegelicht. Daarna gaan we dieper in op de introductie van de bijsluiter in België, tussen 1988 en 1992, omdat dit toch de achtergrond was voor dit werk. Om de inleiding af te ronden, worden kort de theoretische modellen geschetst die werden gehanteerd bij het uittekenen van de studies. Tenslotte wordt ingegaan op de structuur van dit werk.

In het tweede deel worden de beschrijvende studies voorgesteld, die werden uitgevoerd vóór, tijdens en kort na de introductie van de bijsluiter in België.

In Hoofdstuk 1 van Deel II wordt een bevolkingsonderzoek van 1988 in België voorgesteld, bij volwassenen van 18 tot 64 jaar, met huis-aan-huis interview. Dit onderzoek werd uitgevoerd net voor de introductie van patiëntenbijsluiters, na 25 jaar geneesmiddelendistributie met nagenoeg onbegrijpelijke technische bijsluiters. Uit de resultaten bleek dat deze technische bijsluiter door de grote meerderheid van de patiënten (87%) gelezen werd. De bijsluiter werd ook gewaardeerd als nuttig, met beperkte klachten over leesbaarheid, en met een aparte rol, naast deze van arts en apotheker.

In Hoofdstuk 2 van Deel II wordt gerapporteerd over een bevraging via de post bij Belgische artsen. Hieruit bleek dat artsen onderschatten hoeveel patiënten de bijsluiter lezen. Via een clusteranalyse werden drie types artsen beschreven: wat oudere artsen die ronduit negatief stonden tegenover de bijsluiter, maar die zelf de moeite doen om veel mondelinge instructies te geven; wat jongere artsen die de bijsluiter als een verlichting van hun informatietaak zien; tenslotte artsen die gemengde gevoelens hebben tegenover de bijsluiter, omdat ze scherp op de reacties van patiënten letten, en dus zowel positieve als negatieve gevolgen zien.

In Hoofdstuk 3 van Deel II beschrijven we hoe aspirant-verplegers uitgestuurd werden naar Vlaamse rusthuizen om een staalkaart te maken van het geneesmiddelengebruik onder de bejaarde bewoners. In het rusthuis was het verbruik hoog, en bleek de bijsluiter te verdwijnen uit de distributie. Zelfs cognitief fitte bewoners verloren hun autonomie over het geneesmiddelgebruik. Alleen de behandelende verpleegkundigen hanteerden de bijsluiter nog enigszins als bron van informatie.

In Hoofdstuk 4 van Deel II belichten we eerst de taalkundige hulpmiddelen die in het kader van het Belgische bijsluiterprogramma werden ontwikkeld (schrijfadviezen, meertalige woordenboeken van moeilijke en makkelijke medische termen en een leesbaarheidstest voor bijsluiters in het Nederlands en het Frans). Daarna volgt een kort overzicht van elf bijkomende beschrijvende onderzoeken.

Het gaat om een bevraging via de post van de schrijvers van de bijsluiter (regulatory affairs managers), een herhaling in 1991 van de bevolkingsenquête van 1988, twee opeenvolgende registratiestudies in huisartsenpeilpraktijken van huisartsen in 1989 en 1990, vijf studies in specifieke bevolkingsgroepen (sociaal-actieve bejaarden, kwetsbare bejaarden in de thuiszorg; bejaarden op geriatrische ziekenhuisafdelingen, en gezonde adolescenten), twee studies over geneesmiddelendistributie in bejaardentehuizen en in ziekenhuizen, en tenslotte een beoordeling van de kenmerken van de Belgische bijsluiters in 2000. We lichten de kerngegevens van elk van deze onderzoeken hier telkens toe.

De schrijvers van de bijsluiter binnen de farmaceutische industrie bleken al evenzeer als de artsen te onderschatten hoeveel patiënten de bijsluiter lezen. Hun oordeel over het nut van dit informatiemedium was evenwel genuanceerd positief.

In het herhaald bevolkingsonderzoek werden de hoge leespercentages bevestigd. Ook was duidelijk dat de introductie van de patiëntenbijsluiter goed opschoot (39% penetratie) en probleemloos en onopgemerkt verliep.

In twee opeenvolgende klinische registratiestudies bij hypertensiepatiënten werden iets lagere, maar toch nog hoge leespercentages gemeten. Er was weinig verschil in (hoge) tevredenheid naargelang van het type bijsluiter, maar wel een hogere graad van spontane melding van gezondheidsproblemen en bijwerkingen bij de lezers van de patiëntenbijsluiter.

In de studies bij bejaarden werd de paradox aangetoond tussen hoger geneesmiddelenverbruik en dalende behoefte aan geneesmiddeleninformatie bij deze groep. Terwijl bij sociaal-actieve bejaarden nog een ruime waaier aan informatiekanalen bestond met nog steeds een prominente rol voor de bijsluiter, vernauwde dat bij kwetsbare bejaarden in de thuiszorg, die niet meer het huis uit konden; ze verloren contact met de apotheker en de paramedische zorgverleners namen over. Bij bejaarden in acute geriatrische afdelingen

verdween de rol van de bijsluiter, in een informatie-arme omgeving. Bij gezonde adolescenten bleek de bijsluiter een prominente rol te spelen, naast ouders, arts en apotheker, in de uitzonderlijke gevallen waar toch een geneesmiddel werd genomen.

Uit de analyse van een kleine staalkaart bijsluiters uit het jaar 2000 blijkt duidelijk dat doorgaans wel enkele taalkundige ingrepen zijn gebeurd (kortere en minder ingewikkelde zinnen, minder jargon), maar dat de lengte, de inhoud en de kwaliteit van de Belgische patiëntenbijsluiters erg variabel blijft, ook acht jaar na hun introductie.

In deel III worden de experimentele onderzoeken besproken die zich toespitsen op de manier waarop patiënten het voordeel en het risico van geneesmiddelen beleven.

In Hoofdstuk 1 van Deel III wordt een overzichtsartikel (gepubliceerd als hoofdstuk in een boek) besproken over de relatie tussen geneesmiddeleninformatie, voordeel/risico beleving, en therapietrouw, en dit in het licht van een nieuwe, precieze techniek voor de meting van therapietrouw (electronische monitoring).

In Hoofdstuk 2 van Deel III wordt die techniek toegepast in een gerandomiseerd klinisch onderzoek waar atenolol wordt vergeleken met lisinopril bij de behandeling van hypertensie. Beide behandelingsgroepen werden nog eens onderverdeeld in twee groepen: een subgroep zonder bijsluiter en een subgroep met een hybride bijsluiter (waarin typische bijwerkingen van beide geneesmiddelen in één tekst verenigd werden). Deze studie werd uitgevoerd door een farmaceutisch bedrijf en het luik over de bijsluiter werd er aan toegevoegd. Bij het toevallig blind toewijzen van de patiënten tot één van beide groepen liep iets mis. Sommige artsen doorbraken de randomisatie omdat ze liever geen beta-blokker gaven aan oudere patiënten. Daarom waren er uit deze studie geen echte conclusies te trekken. Wel wordt de opgedane methodologische ervaring belicht en worden enkele hypotheses voor verder onderzoek geformuleerd.

In Hoofdstuk 3 van Deel III wordt een experimentele psychologische studie besproken met gezonde vrijwilligers (overwegend vrouwen). Een bijsluiter met een voordeelboodschap (een paragraaf van ongeveer 80 woorden) werd getest tegenover geen bijsluiter en tegenover de gewone bijsluiter (zonder noemenswaardige voordeelboodschap). Dit onderzoek werd uitgevoerd met drie scenarios (cisapride bij acute, banale spijsverteringsklachten; itroconazol bij schimmelbesmetting van teennagels; risperidon bij chronische behandeling van psychosen), telkens met ongeveer 90 proefpersonen verdeeld over drie experimentele groepen (geen bijsluiter; normale patiëntenbijsluiter; patiëntenbijsluiter met voordeelinformatie). Proefpersonen die geen bijsluiter kregen bleken het voordeel van het geneesmiddel hoog in te schatten, maar scoorden laag op de kennistest. Proefpersonen die een gewone bijsluiter kregen wisten meer over het geneesmiddel, maar scoorden de voordeel/risico

verhouding lager. Proefpersonen die een bijsluiter kregen met voordeelinformatie wisten meer over het geneesmiddel en bleven de voordelen hoger inschatten dan de nadelen. Deze bevindingen waren consistent in de drie scenario's.

In Hoofdstuk 4 van Deel III wordt een gerandomiseerde klinische studie gerapporteerd met een ontstekingsremmer bij patiënten met acute pijn door een banale kwetsuur. De helft van de patiënten kreeg het geneesmiddel met de bestaande technische bijsluiter (in principe moeilijk verstaanbaar), de andere helft kreeg de patiëntenbijsluiter (zelfde inhoud, zelfde lay-out, maar eenvoudiger geschreven). Uit de resultaten bleek dat in beide groepen de bijsluiter evenveel gelezen werd, dat de tevredenheid over de bijsluiter even hoog was, maar dat bij de patiënten met een patiëntenbijsluiter de voordeel/risico beleving toch negatiever was. In dezelfde groep werden er meer gezondheidsklachten spontaan gerapporteerd en werd er meer een verband gelegd met het geneesmiddel. Ter afronding werd in Deel III nog het ontwerp besproken van een studie waarin gepoogd werd veel van de bovenstaande elementen te verenigen. Deze studie lukte evenwel niet, wellicht door de ambitieuze opzet.

In het afsluitend deel IV sommen we de relevante resultaten van de goed uitgevoerde beschrijvende en experimentele studies nog eens op en bespreken deze in relatie met literatuurgegevens. Ook suggereren we hypotheses voor verder onderzoek. We formuleren een aantal aanbevelingen met betrekking tot de problematiek van aansprakelijkheid en de productie en het testen van betere bijsluiters. We bepleiten de inbedding van bijsluiters in de nieuwe media, in een context van gezondheidspolitiek en patiëntenopvoeding.

De conclusies luiden als volgt.

Patiëntenbijsluiters zijn een essentieel onderdeel van moderne systemen voor de distributie van geneesmiddelen, maar ook een instrument voor patiëntenopvoeding en gezondheidspolitiek. Bijsluiters die routinematig bij de aankoop van een geneesmiddel ter beschikking worden gesteld, worden gelezen door de patiënt en beïnvloeden de tevredenheid van de patiënt positief, ongeacht hun kwaliteit. Het lezen van een patiëntenbijsluiter van hoge kwaliteit heeft een bewezen positieve invloed op het kennisniveau over het geneesmiddel. De effecten op leesgedrag, tevredenheid en kennis zijn op zichzelf al een voldoende argument om een patiëntenbijsluiter te verstrekken, telkens er een geneesmiddel wordt afgeleverd, of dit geneesmiddel nu op voorschrift is of niet, en ondanks de ietwat hogere distributiekosten. Dit zijn sterke argumenten om het Europese systeem met verplichte verdeling van verstaanbare bijsluiters te veralgemenen. Beweringen dat patiëntenbijsluiters bijkomende positieve effecten zouden hebben op therapietrouw zijn niet echt onderbouwd. Ook is de evidentie schaars voor de stelling dat de huidige bijsluiters medicatiefouten en het oneigenlijk gebruik van geneesmiddelen

zouden verminderen, een betere naleving van waarschuwingen zouden bewerkstelligen, of meer adequate reacties op bijwerkingen zouden stimuleren.

De voordeel/risico perceptie van het geneesmiddel door de patiënt is een belangrijke schakel in de verwerking van de geneesmiddeleninformatie in bijsluiters. Voordeel/risico perceptie kan direct gemeten worden. Voor die meting dienen gevalideerde meetechnieken ontwikkeld te worden.
Dat is nodig om de relatie tussen kennis, begrip en gedrag bij het gebruik van geneesmiddelen te doorgronden en om betere bijsluiters te ontwerpen en te testen. Betere bijsluiters kunnen patiënten helpen samen met de arts gedeelde beslissingen te nemen (op basis van voldoende informatie) rond het opstarten van een behandeling. Ze kunnen patiënten ook kunnen helpen bij het juist en veilig verderzetten van de behandeling. Een belangrijk aspect bij het schrijven van betere bijsluiters is de invoering van een korte paragraaf met voordeelinformatie. Door informatie over voordeel en risico te integreren in een verstaanbare bijsluiter, zou een verbeterde overdracht van informatie kunnen gecombineerd worden met een meer gebalanceerde beleving van het voordeel en het risico van het geneesmiddel door de patiënt.

Part I

Introduction

L'homme a inventé la parole pour cacher ses idées.
Prince De Talleyrand

1 Aim of the present thesis

Every year, billions of boxes of prescription medication are dispensed in the Western industrialised world. In Europe, each of these boxes contains an extensive folded sheet of paper, the patient package insert (PPI). This official drug labelling document lists in understandable terms the indications, contraindications, side-effects of the medication and other benefit and risk messages, to be read by the patient or his proxy, before the start of therapy or later while taking the medication. In this system of distributing drugs, the pharmaceutical companies assemble branded cardboard packages of fixed pack size, including the medication in fixed strength (in blisters or bottles) and the patient package insert. These branded packages are then distributed to the pharmacies, to be dispensed to patients. This drug distribution system for ambulatory care is called unit-of-use distribution or original pack dispensing.

The efforts of writing, submitting, printing and distributing patient packages insert slightly add to the cost of distribution, as dispensing pharmaceuticals in bulk to pharmacies may be somewhat cheaper. The question is what the rationale is for consuming so much paper and ink and for spending the incremental cost of the distribution of a patient package insert in every box of medication.

This thesis aims to assess the impact of distribution of written drug information in original pack dispensing on:

- the acceptance of the patient package insert by the patient
- the benefit/risk perception of the patient.

Acceptance of drug information and benefit/risk perception are cognitive processes, preceding behaviors such as noncompliance, medication errors made by patients, inadequate reactions of patients to side-effects. These behaviors may have a more direct impact on clinical outcome of the patients, but are not the main focus of this study. We considered that a better understanding of preceding cognitive processes was necessary to understand behavioral responses and to design more effective interventions.

We decided to focus in this thesis on two cognitive processes: acceptance of written drug information (or patient satisfaction with information) and benefit/risk perception.

For the focus on acceptance of patient package inserts by the public, two motives were predominant. Firstly, acceptance is a key factor in evaluating the usefulness of a drug distributing system based on prepacked medicines with inserts versus a drug distribution system based on bulk medicines without information. Patient satisfaction (with drug information in general and with insert in particular) may be considered as a goal on its own, as it is an instrument to enhance patient compliance.

Secondly, opinion leaders among physicians and in the pharmaceutical sector are still making unsubstantiated statements about low percentage of patients reading the insert and high percentages of dissatisfaction and that it was time to replace "experience-based statements" with empirical evidence.

Our focus on benefit/risk perception was motivated by the possibility to further upgrade the quality of the communication in patient package inserts and to design intervention studies on the impact of written drug information on patient behavior , using inserts with a proper balance between risk and benefit information.

This thesis is based on 6 peer-reviewed first author publications, and a report of other relevant studies in which the author was involved. These studies were conducted between 1988 and 1997 and published between 1991 and 2002. Most of the research was related to the introduction on a national scale of patient package inserts in Belgium between 1989 and 1992.

In this thesis we focus on communication about prescribed allopathic medicines, formulated from active substances, synthesised by chemical reactions, or extracted in sufficient quantities from natural medicinal sources.

We have limited ourselves primarily to communication to patients on prescription medication in ambulatory care.

The following topics will be addressed in the introduction:

- Drug information needs of patients
- Information on patient package inserts
- The introduction of the patient package insert in Belgium
- Theoretical models about the impact of written drug information
- The structure of this thesis.

2 Drug information needs of patients

2.1 Objective need for (written) drug information?

It is well known that the level of knowledge about drug therapy in general and about medicines which patients are currently taking in particular is poor

among the population, especially in the polymedicated elderly,[3][4][5][6][7][8][9][10][11][12] but by no means exclusively among the elderly.[13]

In the years prior to the shaping of the European legislation on patient packages inserts, minimal requirements of what a patient needs to know to use a medicine correctly were formulated for over-the-counter medicines[14] and for prescription medicines.[15]

These minimal requirements constitute an extensive body of knowledge on indications, side-effects, dosage regimen, precautions, warnings, contraindications and storage instructions, to be conveyed to the patient.

In contrast to the field of written drug information, formal minimal requirements for drug information to be delivered to the patient by physicians or pharmacists have not been established yet, except for general recommendations concerning the professional role of health care providers with regard to patient education,[16] and the duty to inform patients about proposed therapy.[17]

It is clear that these official requirements for drug information set a high standard to the amount of information to be transferred, especially with regard to risk information. They establish an extensive and rather complex collection of information items that should be transferred to fulfil the need for drug information.

Evidence in the literature clearly indicates that the traditional sources of oral drug information, the physician and the pharmacist, do not suffice to ensure the adequate transfer of minimal drug information to patients, especially with regard to risk information.

Observations of discourse between physicians and patients have revealed that the time devoted to information transfer regarding drug therapy is short in routine consultations.[18] In general practice, consultations tend to be short (between 6 and 20 minutes),[19] during which the patients must expose the reason for encounter, the physician must ask questions, examine the patient, and come to a diagnosis and a therapy plan. This must be discussed, agreed upon and explained. A recent study estimated that the time spent to medications is about one fifth of the consultation time.[18]

The short interaction between the physician and the patient is a potentially stressfull event for the patient, where the senses have to process extensive information in a highly emotional context, under time constraints and where drug therapy information is but one of the points of focus. Patients may forget the information,[21] and strong emotions (fear, anxiety, relief, dissatisfaction, satisfaction) may reduce the receptivity of the patient to information.[22] While the doctor explains about how to take the drug, the patient may be wondering about the consequences of the diagnosis, how it will affect his/her life and work: in such conditions the patient may completely miss the message.

Physicians and pharmacists who engage in information giving must overcome a number of hurdles. They often received no or ineffective training in communication skills.[23] There is an educational, cultural and linguistic gap between the physician and the patient.[24][25][26][27][28][29] Finally, the scientific

concepts of the doctor and the layman's framework of ideas differ substantially.[30]

The low prevalence, the low quality, and the low effectiveness of information giving activities does not facilitate communication about medication between the patient and the health care provider.

Moreover, there is little communication between physicians and pharmacists in routine medical practice, and hence a risk of conflicts in information from two trusted sources, as the pharmacist is unaware of the contents of the discussion during consultation.[31][32]

On these theoretical grounds, it may be argued that there is an objective need for a trustworthy source of drug information in the drug distribution process.

2.2 Subjective need for (written) drug information?

Judging from studies that have directly measured patients' preferences about health information, the answer to the question "do patients want drug information" is a clear and definite "yes".[33][34][35][36][37][38][39][40][41][42][43][44] The majority want (more) drug information, with a special interest in risk information, even concerning infrequent risks,[45][46][47][48] contrary to what the physicians think about this matter.

Discussion about and reporting of side-effects are prominent subjects on the voiced or unvoiced agenda of patients to be discussed during consultation.[49]

The source of drug information which patients undoubtedly prefer is the physician.[37][44][50][51][52] In most of the studies cited above, the pharmacist is mentioned as the second preferred source, at some distance behind.

This desire for drug information from the physician pertains as much to procedural information (how to take the drug) as to the effectiveness (how does the drug work) and the safety of therapy (what are the risks of treatment and what to do in case of side-effects). The biggest "information gap" is perceived in the two latter areas.[33] There is also a desire for information on treatment alternatives.[34][53]

The third preferred source of drug information is the patient package insert, at least in countries where it is available. In countries where it is not available, people would welcome its provision.[42][44][54]

Additional sources of drug information are relatives and friends and the media. In quantitative surveys, the role of the social network around the patient is minimised. In qualitative research, personal contacts seem to be somewhat more important.[30][55] The information provided by the media about benefits and risks of medications has been described as inadequate, incomplete and biased by industry sources,[56] or as alarmist in times of crises.

In sharp contrast with the data on the subjective desire for information, a number of studies have indicated the passivity of patients when information needs were not fulfilled, both in asking questions or requesting written

information during consultation, as well as in seeking information after the consultation, especially with regard to risk information, the information need most often unfulfilled.[57]

A number of possible reasons have been listed for this passivity:[57]

- Patients do not want "to bother" the physician
- Low level of information search, even for high involvement items, is a general feature of consumer behaviour
- Patients perceive barriers, based on the physicians' behaviour
- The cost of getting information elsewhere is perceived as too high
- The ability to find information elsewhere is perceived as too low.

It is beyond the scope of this thesis to comment in greater detail on segmentation analyses. We will quote Morris, author of two of such analyses presented here: "Segmenting patients according to risk information seeking patterns helps us understand how risk information is differently sought by various groups of patients. When this segmentational analysis is done, however, we see an overwhelming passivity of patients, when obtaining therapeutic advice." However, we will demonstrate in the next paragraphs that patients display an overwhelming tendency to read written drug information, provided it is readily available.[58][59]

There is overwhelming evidence that:

- most patients express a subjective need for written drug information, especially for risk information
- most patients are interested in receiving patient package inserts
- the majority of patients read patient package inserts, whenever these are offered, even if the quality of the document is substandard.

In our view, the intensity, focus and motivation of reading reflects a genuine interest in seeking risk information as a coping strategy to deal with threatening illness and its therapy.

In original pack dispensing distribution systems, the small minority of non-readers is composed of at least three groups:

- risk avoiders
- healthy individuals with little experience of illness, who are not (yet) interested in medicine(s)
- elderly people who have emotionally adapted to chronic therapy and are no longer interested in drug information, even when (they know that) their level of knowledge is insufficient.

Each of these groups will require suitable attendance by other means, beyond the scope of the PPI.

Among the patients who read PPIs there are two predominant groups:

- passive patients, longing for information, but not actively asking the health care provider for information or for a share in the decision making, nor seeking information when (unvoiced) questions remain unanswered

- active patients, longing for information and participation in decision making, who would have departed on an information hunt for other sources, if no PPI was provided.

3 The patient package insert (PPI)

3.1 Definition of the PPI

The medium we have selected is the patient package insert, a sheet of paper folded inside a prepacked *medicinal product package*, in the framework of the *unit-of-use drug distribution model*. In this model, medicines are distributed in packages with a fixed number of units of a fixed strength, under a brand name, under the responsibility of a marketing authorisation holder, and with an outer container, intrinsically linking a package insert to the medicine.

The patient package insert is information from an authoritative source, as its content is approved by the regulatory authorities, sometimes after long discussions between the health authorities, experts from the scientific medical community and the pharmaceutical company.

The patient package insert is clearly an instrument of mass communication, controlled by registration authorities and pharmaceutical companies. However, the patient who receives and reads the insert has been targeted to receive this specific piece of information by prescription from a physician and/or delivery from a pharmacist.

Patient package inserts have a word count varying from 500 to 2000 words. They are longer than the label on the outside of a medication box, which is limited to major instructions or warnings. PPIs are usually shorter than brochures or pamphlets with extensive information.

The patient package insert is derived from the scientific data sheet or the Summary of Product Characteristics. This official labelling document is kept with the regulatory authorities, as a reference document for the different forms of drug information, derived from it for communication with professionals or patients or the general public. In the past in some countries, the text of the scientific data sheet was transcribed (sometimes in a slightly abbreviated version) into a technical insert (TI). This was the case in Belgium between 1964 and 1988. The text of the TI is usually somewhat longer than the text of the PPI, as technical information for the professional or sometimes vital information is left out in the PPI.

The content of the PPI is fixed for the average patient (or groups of patients). Adaptation of its content to the gender, age, literacy level, and cultural background of the recipient is not possible. Its target is the patient with a disease (or risk profile), for whom the need exists to take a medicine with preventive, symptom-relieving or healing properties. It is not a do-it-yourself manual, but shares many of the characteristics of instructional user

manuals, as for the operation of electronic equipment or software applications, or for assembly of construction kits. It is not its purpose to promote non-medicinal therapeutic interventions, but rather to support the relationship of the patient with the prescribing physician and/or the dispensing pharmacist. Its tone, however, differs substantially from the oral persuasive communication often practiced by physicians and pharmacists, in order to convince patients of the need to take the medicine as directed. It is a unique, and supposedly balanced mixture of tips for patients on the proper use of the medicine (procedural instructions), of warnings (risk information), and of information on the potentially beneficial effects (benefit information). It is unique, because in no other industrial branch are products released with such a full and readily available account of the potential risks of the product (longer and more explicit than the warning labels for tobacco products, alcoholic beverages, and dangerous chemical substances).

In short, the concept of the patient package insert brings together four important notions:

1. the notion of linking the chemical substance (the medicine) and the information that goes with it (the insert) into one branded product (the package) in the course of retail distribution
2. the notion of authoritative medication information, approved by health regulatory agencies, after consensus with pharmaceutical companies and medical experts
3. the notion of balance between risk and benefit information
4. the notion of intentional, and legally enforced readability.

3.2 The context in which the PPI is used by patients

Other information channels around the patient

In the information network surrounding the individual patient, there are many oral information sources, each playing its role. Health professionals, i.e. physicians and pharmacists, are the information sources preferred by the patients.[60][51] Field studies, however, have demonstrated that information from these sources is limited, especially with regard to risk communication.[61][62] Traditionally, there has been very little cooperation between physicians and pharmacists in bringing information about medications to the patient.[63][64]

A social network of relatives, neighbours, and friends surrounds the patients. Patients consult this network when in trouble, e.g. when deciding whether to seek professional help, or to start (or to continue) taking medicines. The media influence the patient directly and indirectly through the social network. Some of the information provided by these sources is repetitive, some is conflicting, some diverges from accepted knowledge. Patients can actively seek information in books, magazines, and on the Word Wide Web.

Encounters with patient information sources on a time axis

It is instructive to plot the encounters of the patient with information sources on a time axis. First, the patient decides to go and see the doctor. During this encounter he/she will receive some information from the doctor, and a prescription. Then the patient goes to the pharmacy, again with the possibility to obtain information. An important moment comes when the patient returns home with the dispensed medication and has to decide whether or not to take the medicine. At that moment the patient might read the insert. The insert may also be important at a later point on the time axis. The time of onset of side-effects is often unpredictable. However, an appropriate and swift reaction of the patient is often crucial, to limit the harm caused by side-effects. With some side-effects, e.g. allergic reactions, the patient should stop the medication and consult the physician promptly. With other side-effects, the patient should continue the medication, because abrupt halting might be hazardous. For some side-effects, the physician should be informed as soon as possible, for others only at the next scheduled checkup.

note Some argue that the patient should have access to all the necessary information before buying the medicine from the pharmacist. It is possible that modern techniques of information providing will – or do already – alter the normal flow of events described here.

It is obvious that some important decisions in the therapeutic process are left to the patient. At such moments of doubt, it might be convenient for the patient to consult the patient package insert, provided the box and its content have not been thrown away. This is one of the reasons for having an insert in every box, even for chronic therapy, despite the environmental strain this potential waste of paper might cause, and despite the small but significant incremental cost of the distribution system.

3.3 The quality of the scientific data sheet and the quality of the patient package insert

The scientific data sheet is the official summary of the huge amount of information that is available when the medication is registered, and it should reflect the accumulating evidence of its benefits and risks, as more and more patients are exposed to the drug, in the years after the release of the drug onto the market.

The quality of the scientific data sheet is determined by:

- the art and science of clinical pharmacology, pharmacovigilance, pharmaco-epidemiology, pharmaco-economics and outcomes research, all fairly new disciplines, called upon to produce a balanced account of the risks and benefits of medicines
- the quality of the interaction between the regulatory authorities, pharmaceutical companies, and medical experts.

The quality of patient package insert is determined by:

- the quality of the scientific data sheet
- the communication skills of the medical communication officer (or regulatory affairs manager or medical director) within the pharmaceutical company (or his/her ability to seek and find the right consultants)
- the company policy and the national regulatory policies, determined by the local balance between the legal, regulatory and educational function of the PPI.

3.4 The functions of the PPI

3.4.1 The legal function of the patient package insert

Liability currently has the most profound impact on the content and style of the PPI. The document is seen as a protection against liability claims, and as such, will always be reviewed by the company's lawyer. It is the primary reason why the pharmaceutical industry claims the responsibility of authorship of the document, while the regulatory authorities restrict themselves to reviewing the document and approving its content, after seeking expert advice from the medical community.

In Europe, liability issues are governed by the EEC Product Liability Directive (85/374/EEC), which states in Article 6 that: "A product is considered to be defective when it does not provide the safety which a person is entitled to expect, taking all circumstances into account, including: the presentation of the product ...".

"Presentation of the product" means the full disclosure of instructions for use, necessary to reduce the risk of the product, and of all possible side-effects. The Directive introduces the principle of strict liability within the European Union, which means liability of the producers for damage caused by their products without their fault or negligence, if labelling or instructions for use do not correspond to knowledge available in medical science.[65] Very few cases of liability, solely based on poor labelling, ever went (successfully) to court in Europe. Nevertheless, the reaction of the European pharmaceutical industry, and the lawyers advising them, has been to overload the inserts of their products with detailed information about side-effects. It is not certain that this policy will really protect companies from claims regarding new and unexpected side-effects. These long enumerations include the obligatory list of frequently occurring minor side-effects (even those not occurring more often than with placebo), to every adverse event ever reported anecdotally (even if it occurred only once, and causality was never properly assessed). Under those circumstances, it is difficult to translate the side-effect section of the scientific data sheet into an understandable, meaningful and not too frightening message that is helpful to the patient.

3.4.2 *The regulatory function of the patient package insert*

The patient package insert has become more than a passive conveyor of the current state of available information. It has also become an instrument of regulatory policy. When facing a safety crisis caused by the emergence of a signal of a potential serious adverse reaction to a marketed drug, the regulatory authorities traditionally have three options. They can play it safe and withdraw the product from the market, thereby protecting future patients from harm. Or they can take a risk and leave the product on the market, so as not to endanger the important investments. However, there is a third option, often a way out of impossible dilemmas. The regulatory authority can officially request a change in the scientific data sheet. This can then be communicated to the health professionals by "Dear Doctor" letters and other means. In cases where patient package inserts are available in the distribution system, direct communication with the patients taking the drug can be achieved by a mandated change in the document, whether or not enforced by some method of emphasis. This is an example of the use of information as an instrument of regulatory policy.[66] In a number of instances this approach has permitted the regulators to prevent or successfully cope with media crises. It explains why the regulators tend to exert thorough control over the structure and content of this official document.

The European Directive 92/27/EEC goes to great lengths to define the number of sections, the content of the sections and the order of sections in what is officially called the "User Leaflet". Moreover, this legislation is a clear choice for the full information patient package insert, with little or no loss of information, as compared with the scientific data sheet. This is especially true for the section on side-effects, warnings, and contraindications. These sections are the main targets for regulatory control, to check whether there are no important omissions. In addition, regulatory authorities check whether the enumeration and formulation of official indications is correct. In practice, in Europe, regulatory authorities have not allowed long sections on the benefit of the medication, probably in fear of the administrative workload for checking and debating this section.

3.4.3 *The educational function of the patient package insert*

The patient package insert is an instrument to fulfill the patients' right to know, a right claimed by consumer organisations in Western Europe and to a lesser extent in the USA.

In an early review of 8 studies looking into the impact of PPIs without any additional intervention, knowledge was improved in 7 studies, especially with regard to less commonly known information such as precautions, side-effects, or special warnings.[67]

In a later review, looking into 32 studies, (many with multiple interventions) only one study was found where there was no knowledge gain comparing subjects receiving a PPI to those who did not receive one.[68]

A review of this issue in 1998[38] focused on studies in the UK,[7][8][69][70] and more specifically on the Southampton studies, published between 1987 and 1990.[71][72][73] These studies confirmed that patients who had received a leaflet (a PPI) were again more knowledgeable (and more satisfied).[74] This series of studies, partially sponsored by the King's Fund, had a strong impact on the Association of the British Pharmaceutical Industry and on Britain's position during the passing of the European Directive on patient information in 1992.

The studies described above were non-randomised intervention studies, mostly testing intervention versus no intervention.

The impact of leaflets on knowledge was also confirmed in a number of studies in pre-post design.[74][75][76][77]

For a thorough discussion of the differential impact on knowledge of different aspects (background information, instructions, side-effects) we refer to the thesis of van der Waarde.[78]

Few comparative evaluations of the differential impact of technical inserts (TIs) versus patient package inserts (PPIs) have been conducted. First attempts were made in Switzerland in the study by Rupf.[79] A recent large scale randomised double blind comparison (N=1560) of TI versus PPI was conducted in Spain, with knowledge assessment by a questionnaire distributed to patients, to be filled in at home (possibly with the insert at hand). The questionnaire focused on *procedural* items. The mean proportion of correct answers was 45.7% in the TI group and 75.5% in the PPI group. The odds ratio of answering more than 70% of the questions correctly was 13.5 (CI95 10.5-17.5).[80]

The complicated relationship between verbal and written information has been discussed elsewhere,[67][81][82][83][38] strongly suggesting that verbal information reinforces the effect of written information on knowledge, but that physicians and pharmacists tend to engage in persuasional efforts and procedural information rather than in risk communication.

3.5 The history of the PPI

3.5.1 Historical developments in Europe

A start of drug registration

In the early 1960s Western Europe was the theatre for a crisis with the drug thalidomide (a drug for nausea in pregnancy), causing the birth of thousands of children with malformations primarily of the arms *(focomelia)*.[84] In the following years most countries in Western Europe installed a formal procedure to have drugs registered and evaluated by a Drug Registration Authority.[85] The *European Union* (EU) issued a *Directive* in 1965, which fixed the outline of a scientific data sheet, also called *Summary of Product Characteristics*

(SmPC), to be delivered by the company for every new drug brought forward for registration.[86]

Southern European countries regulated that this scientific data sheet should be put into the branded boxes of medicines (the dominating way of dispensing medicines in these countries). In the Northern European countries, where medicines were distributed in *bulk dispensing* (taken from big containers and dispensed in small white paper bags or caps), this obligation was not enforced. In 1975 the concept of the patient package insert was introduced in European legislation, but without immediate practical consequences. Meanwhile, the quality but also the sophistication of the scientific data sheet grew with the growing regulatory impact on the drug development process. By 1985, all drugs, including those registered before the thalidomide crisis, needed to have a scientific data sheet and have this sheet revised every five years. In those countries where the scientific data sheet was contained in the medication package, there was strong pressure of the consumer movement for a more understandable patient package insert.

The European pharmaceutical industry did not oppose the concept because the British industry considered the insert an essential part of original drug dispensing (dispensing of medicines in branded fixed boxes). That was the reason why the British government for once did not say no to a proposal for European regulation, and backed the crucial decision of the Council of Health Ministers, under the Belgian Presidency in 1988.[85] In 1992, the Directive 92/27/EEC was passed introducing mandatory patient package inserts in all countries of the European Union (EU).

The legal road to patient package inserts in Europe

We will limit ourself to the enumeration of and brief comment on the different Directives, relevant to this subject:

- Directive 65/65/EEC (O.J. 22 of 9.2.1965), which decreed that an application for marketing authorisation should contain a Summary of Product Characteristics (SmPC), and, in addition, a draft of a package leaflet, in countries where one is to be enclosed, similar to the SmPC.
- Directive 75/319/EEC (O.J. L 147 of 9.7.1975), which introduced the concept of a patient package insert, without making it mandatory, but specifying minimum information required when enclosed.
- Directive 83/570/EEC (O.J. L 332 of 28.11.1983), which further specified the content of the SmPC for new marketing authorisations from 1986 on and, in addition requiring a similar SmPC for all existing drugs (even those registered before 1964) before the end of 1990.
- Directive 92/27/EEC (O.J. L 113 of 30.4.92), which made the provision of a patient package leaflet (in accordance with the SmPC), mandatory in all member states in all dispensed medicine boxes.

The situation in the European countries in the early eighties
In the United Kingdom, in the Netherlands, and in most of the Scandinavian countries the concept of written drug information was unknown to the population (except for some voluntary initiatives). In Denmark, the inclusion of written information in the drug packages was even explicitly forbidden. In Belgium, as in Germany and in the Southern European countries, at the end of the 1980's, patients were familiar with (technical) inserts in the drug distribution process. Germany passed a decree to create two types of inserts (PPI and TI) in 1986, but was not able to solve the problem of an excessively long side-effect section due to liability issues.[65] France had a similar provision since 1985, but the PPI was rather short and devoid of useful information (e.g. a side-effect section could be limited to: "in case of problems, consult your physician").

Joossens (1990) presents an overview of the status of written drug information in the 12 member states for the European Union of Consumer Associations.[87] The conclusions are:

- the European Union was still far away from achieving complete, standardised, up-to-date, available, legible and readable information for patients
- there were three types of countries: countries with no inserts, countries with technical, unintelligible inserts (TIs), and countries with (unsatisfactory) patient package inserts (PPIs)
- information in the inserts from products with the same active ingredients differed substantially across Europe, as far as side-effects, contra-indications and dosages were concerned.

Joossens also points out that research had shown that technical inserts were basically unintelligible to patients. Despite this fact, research in Belgium, Switzerland and Italy has shown that these technical inserts are both read by the majority of citizens, and judged useful. This paradox was considered indicative of the great need for information about medicines among patients, a need unmet by the then current drug information practices in Europe. This influential report undoubtedly had a great impact on the developments in Belgium and in Europe.

3.5.2 Historical developments in the US

The USA escaped from the *thalidomide* crisis because the Food and Drug Administration (FDA) had not yet registered thalidomide when the epidemic of malformations became obvious elsewhere in the world. The USA had no tradition of written drug information inside packages, and drugs were predominantly dispensed in bulk with some limited labelling instruction on the white paper bag (e.g. "to be taken twice a day"). During the late 1960's, the FDA introduced patient package inserts for *isoprotorenol* (an inhalation drug

for asthma attacks, often used erratically by patients), and later in the early 1970's for oral contraceptives.[88] In 1984, the Patient Labelling Project was initiated to conduct research and evaluation studies and to design a full scale implementation plan. During the final weeks of the Carter Administration, the FDA issued final regulations for a 3-year PPI pilot programme covering 10 drug classes. However, once the Reagan Administration took office, the PPI pilot programme was immediately put on hold, with preference given to the development of voluntary private sector initiatives.

The rationale of the FDA to propose a mandatory PPI was based on economic assumptions. The FDA referred to the costs of hospitalisations caused by inappropriate use of prescription medications, estimated at 78.6 billion USD annually for the USA, an amount almost equal to the actual drug budget itself.[89][90] However, the evidence that drug related hospital hospitalisations or medication errors are (even partly) caused by the lack of written drug information is not substantial.

One of the reasons for opposition to PPIs in the US was the liability issue. There are fundamental differences between the legal systems of the USA and Western Europe. The USA has a Common Law system, where legal doctrine is created from actual rulings of the court, while most European countries have a Napoleontic System, where the Law is a result of parliamentary activity, interpreted by the judges. Plaintiffs who have experienced harm from the use of pharmaceutical products are more likely to go to court in the USA, maybe because of the higher probability of winning cases and higher ensuing compensation. The lawyers of the pharmaceutical companies in the USA have built a specific defence against liability claims. They argue that physicians and pharmacists are the first information sources of the patients (the learned intermediaries), who have the responsibility to inform the patient of the inherent risks of the pharmaceutical product. The companies have the duty to inform the health professionals but should not intervene between patients and their caregivers. This peculiar legal doctrine continues to dominate the approach in USA courts. However, the basis of this doctrine (the doctor and the pharmacist will provide the patient with the necessary risk information) is refuted by the results of studies, which have clearly shown that health professionals engage only very seldom and very superficially in risk communication during routine practice.[61][62][91]

Nevertheless, this legal doctrine is probably a major reason why in the American drug distribution system information from the scientific data sheet has not found its way into the drug packages in the form of patient package inserts. As the scientific data sheet was never intended to be inserted into the medication boxes, it grew longer and longer. This reflects the legal interest of debates on the exact wording of indications, because the document was more used as a reference document in conflicts over off-label use and inappropriate benefit claims in pharmaceutical promotion to prescribers and direct-to-consumer advertising.[92] Pharmaceutical advertising paradoxically is far more frequent in the US media, compared to Western Europe.

3.6 Current status of PPI programmes in the world

3.6.1 The regulatory situation in Europe

After the 1992 legislation on patient information, the European Commission invited a Consumer Association expert (Luc Joossens, the same expert who conducted the comparative study of leaflet quality in 12 European countries in 1990[93]) to provide recommendations for the legibility of labels and leaflets of medicinal products. In this document, a rather small type size was proposed (8 pica points for monolingual leaflets and 7 pica points for multilingual leaflets, each with one pica point leading).[94] This document was later followed by a formal guideline on readability, adopted in 1998.[95]

The European Agency for the Evaluation of Medicinal Products (EMEA) created an internal working group, called the Quality Review of Documents group (QRD). This group issued templates, reference documents and guidance on user testing for centrally authorised products, as well as guidance on various other aspects of terminology and style, the provision of general health information in PPIs, and guidance to address the paediatric or incapacitated patient. The positive aspect of this process was that a dialogue developed between EMEA and the industry about the aim and methods of user testing. However, a rather superficial method of testing was proposed.[96] Nevertheless, this resulted in an unprecedented level of user testing of product information, and a certain build-up of expertise. Moreover, the industry and the EMEA successfully discussed the linguistic review of product information within the timetable of a marketing authorisation application. Indeed, because of the tight schedule of a marketing application and because of the translation problems with the nine official languages of the European Union, it proved difficult for companies to allocate sufficient attention to the linguistic quality of patient package inserts in the early stages of the marketing authorization. Fortunately, EMEA decided to simplify the reviewing process and to implement a new process for the linguistic review of product information of products submitted to the European (centralised) registration procedure. The assessment of the content is based only on the English language version of the Summary of Product Characteristics and package leaflets. As soon as an official opinion is made (normally on day 210 of the application), a linguistic review process of translations starts (maximum 40 days), with input from the member states.[97]

A development worth mentioning was the initiative of the Dutch regulatory authorities to allow pharmaceutical companies to adopt "house-styles" for the development of PPIs of all their products. This house style can diverge from the European templates, provided it is underpinned by user testing.[98]

A joint EMEA/industry group started the PIM project (Product Information for Medicines), a first attempt to bring the production, review, and publication process of formal patient information into the technical realm

of structured document management systems, using the Extensible Markup Language XML, a standard for content management and Internet applications.

Another EMEA project, called Medication Information Network for Europe (MINE) aimed to provide European citizens with a database of all the medicinal products on the European market, including the text of the PPI, but unfortunately this project failed, as did all of its predecessors.[99]

Although no new formal reevaluation of the current situation regarding patient information in the different European countries has been made (except for small studies in a limited number of countries[100]), it seems that progress has been made in the availability of PPIs in countries where they did not previously exist.[101] In these countries and in countries with a long tradition of PPIs, the quality and congruity of drug information for patients has not increased.[102][103][104][105][106][107][108] For companies producing PPIs for the member states, differences in national regulations may have increased rather than decreased over the past decade.[109]

After the Treaty of Maastricht in 1992, the development of a public health approach became possible in the European institutions. A thorough review of European pharmaceutical legislation was undertaken by the European Commission, setting in motion a long constitutional approval process in the European Union, to be finished by 2004. As part of this process, three developments deserve to be mentioned.

- a concerted effort between the regulatory authority and patient advocate groups
- the G10 High Level Medicines group
- the tense debate in the European parliament on direct-to-consumer advertising.

The EMEA and its commission for drug approval, the Committee for Proprietary Medicinal Products (CPMP), has started a concerted action with patient advocate groups and consumer associations about communication with patients on issues of drug approval and drug safety. In a series of meetings between 2002 and 2004, a plan of action is to be established regarding pro-active pharmacovigilance, product information, transparency and dissemination of information.[110]

On the political front, the European Commission engaged in a wide consultation in the G10 High Level Medicines Group on innovation and provision of medicines, created in 2000 to explore ways of improving the competitiveness of the European pharmaceutical industry, while encouraging high levels of health protection. A formal meeting was organised in Luxembourg (December 2001), by the Directorate General of Health and Consumer Protection with patient advocate groups and different stake-holders, to discuss the issue of patient information. In the final report of May 2002 with recommendations for action, a chapter is devoted to patients, with a recommendation concerning the distinction between information and

advertising, public-private partnerships, adequately funded patient advocate groups, optimal pharmacovigilance, and, finally, review of the legislation regarding patient information leaflets (Recommendation 11).

All of this was the prelude to an intense political debate about the possible introduction of direct to consumer advertising in Europe, against the background of a thorough revision of European regulations regarding medicines.[112] In April 2002, in an unusual coordination effort, European consumer groups, patient advocate organisations, an international federation of mutualities (semi-public health insurers), and the International Society of Drug Bulletins formed a "Medicines for Europe Forum" to promote a responsible public-health-oriented policy towards medicines in general and support for independent drug information to professionals and patients in particular.

In October 2002, the European Parliament voted on legislation, forming the legal framework for human medicines throughout the European Union in years to come.

There was also an amendment by the Commission to allow the industry to advertise medicines for HIV/AIDS, asthma and diabetes. This amendment was rejected by a vote of 494 to 42, as it was felt that the proposal would weaken the EU's ban on advertising prescription-only medicines to the public. The Parliamentary Committee on Environment, Public Health and Consumer Policy called on the Commission to outline a comprehensive consumer/patient information strategy, ensuring good quality, non-promotional and reliable information about medicines and other treatments. In 2003, the dialogue with consumer organisations and the EMEA was resumed.[110]

It remains to be seen whether the issue of high quality, independent, transparent and easily accessible product information (including PPIs) will remain high on the agenda of both regulatory health authorities and patient advocate groups. The arrival of 10 new member states may absorb a lot of energy of all the constituencies, now that the number of official languages is to rise from 11 to 19 languages in 25 member states. The Council Meeting on Employment, Social Policy, Health and Consumer Affairs in Brussels, in December 2003, adopted a forceful and detailed Council Resolution on "Pharmaceuticals and public health challenges - Focusing on the patients" which may set the agenda for progress in this area at the European level for the coming years.[112]

3.6.2 The regulatory situation in the United States of America

In 1995, a new confrontation between the voluntary and mandatory approach originated, when the FDA announced the MEDGuide project, reinforcing as its target that by 2000 75% of the patients to whom drugs are dispensed should receive written drug information.[113] In February 1996, the FDA held a workshop on prescription drug information, to confirm its intention to move forward in this area. In December 1996, an action plan for the provision of

useful prescription medicine information was put forward to Secretary Donna E. Shallala of the Department of Health and Human Services. This action plan stimulated both private and governmental initiatives and provided a new plan for strict evaluation of the private sector approaches.[114]

The MedGuide programme was finally adopted in 1998[115] and the FDA remained active in revising drug labelling and patient information for several drug groups, including antibiotics[116] and oral oestrogens.[117][118]

In 2000, research surveys should have provided conclusions about the success of voluntary programmes of drug information distribution, as announced in health care targets, e.g. for menopausal women taking oestrogens. At this point, the Clinton Administration was moving to its end. Al Gore (a well known advocate of readability issues in communication between state, companies and the citizen) was campaigning against George Bush. Since the Bush Jr. Administration took over, the fate of governmental drug information initiatives looks bleak for some time to come.[119]

Surprisingly, much research on this issue has been carried out in the US, but so little action was undertaken at the regulatory level. On the other hand, Europe undertook a major regulatory change in drug distribution on a rather scant evidence base. Maybe reluctance to regulatory change is greater in the USA, because the constituencies know that once decided, rules get implemented. In Europe, laws and directives are voted with elegant ease and little preparation, but few seem to mind that implementation stalls and differs from what was envisioned.

3.6.3 The regulatory situation in other parts of the world

Although Japan has a long history of packaging inserts,[120] current medical practice still seems to be dominated by a paternalistic approach to patients by dispensing physicians. The development of the role of the pharmacist in drug information is ongoing.[121] Cultural factors among patients and health care providers with regard to drug information might be different.[122][123][124] The pharmaceutical industry has Drug Information Centres which give direct response to consumer inquiries.[125] In 1997, the law obliged manufacturers and drug distributors to provide information. Voluntary drug information activities are coordinated by the RAD-AR Council, a consortium of scientists and the pharmaceutical industry.

In 1992, the Australian Federal Government adopted legislation to ensure that Consumer Medicines Information (the Australian version of the PPI) would be available for all new and existing drugs by 2004. This goal has been met by intense collaboration between the parties involved, some of them initially reluctant.[126][127] In an early phase, information design experts were consulted, resulting in excellent recommendations, frameworks, vocabularies and testing procedures.[128][129][130] Peculiar to the Australian approach is that the policies to provide consumers with high quality information are part of a

larger public health approach to quality use of medicines.[131] Some doubts remain about the level of effective distribution of the (excellent) inserts, despite subsidizing of pharmacies to install specially designed laser-printers at the point of dispensing.

In Canada, patient package inserts have been made mandatory as part of the marketing authorisation for a large number of drugs, all inhalers and patches and self-administered biologicals. An excellent guide for producing well designed PPIs was published by the Canadian Public Health Association in 2002.[132]

In Israel, patient oriented package inserts became legally mandatory in 1979, in 3 languages (Hebrew, Arabic and English), with several revisions since.

For the sake of completeness, we list some reports from South America and Asia on the subject.[133][134][135]

3.6.4 Recent research meetings on PPIs

On the scientific front, interest in the subject has been kept alive, with experts meeting in two Drug Information Association (DIA) symposia, held in London in 2000 and in Bruges in 2002; the 2nd international Shared Decision Making conference in Swansea, UK (2003); a workshop from the health information design network in 2003 in Coventry, UK; and symposia at the 2002 and 2003 meetings of the International Federation of Pharmacy FIP in Nice, France, and Sydney, Australia.

4 The introduction of PPIs in Belgium and its evaluation

4.1 Some background information about Belgium

For a good understanding of the research presented here, it is important to be familiar with some key characteristics and peculiarities of Belgium, a country with a complex governemental structure, and of its patient package inserts. Belgium is a small but densely populated country, situated at the crossroads of Europe, with 10 million inhabitants and 3 official national languages. These languages are:

- Dutch, the language of the Dutch-speaking part of Belgium (6 million inhabitants)
- French, the language of the French-speaking part (4 million inhabitants)
- German, the language of a small number of villages (40.000 inhabitants) near the eastern border

Belgium has been a kingdom with a parliamentary democracy since 1830, but has been occupied at different times in history by the armies and administrations of every dominant nation in Europe, and hence it has been subjected to a variety of cultural influences. In no other country have the French and Anglo-saxon medical traditions interacted with such intensity.

4.2 Characteristics of the Belgian drug distribution system

Technical inserts were gradually introduced in Belgium from 1964 on, when a Drug Registration Committee was installed, after the thalidomide crisis. These inserts were in fact the scientific data sheets (sometimes in a somewhat shortened version), inserted inside the boxes distributed to the patients. Over 90% of the medication dispensed in the pharmacies (which hold a monopoly to dispense medication) is dispensed as branded boxes with a fixed pack size and a fixed strength of content (the remaining 10% being ready-made formulations by the pharmacist, a tradition which is almost extinct). Unfortunately, for legal reasons, it was decided that technical package inserts, regardless of their place of distribution in the country, needed to be printed in the 3 official languages. This decision is indicative of the priority given to the language problem by the regulators. This had a number of consequences. In order to keep the sheet of paper inside the medication packages down to a reasonable size, the text was printed in small print size, on the thin paper used for Bibles, and with a dense and dull layout, with a sometimes cluttered aspect in the order of the three language versions. The Belgian technical inserts did not have a side-effect section as long as the one in the German inserts. They were longer and more informative than the French inserts, which basically did little more than refer patients to the physician in case of problems.

4.3 The legal road to PPIs in Belgium

The wheels of the process were set in motion in Belgium by a law (amending the basic medicines Act of 1964) passed in 1983 (Act of 21.06.1983), followed by two royal decrees in 1984 (R.D of 23.7.1984; R.D. of 9.7.1984). The health administration prepared for a huge operation of revision of all the technical data sheets for all drugs (including drugs on the market prior to 1964), to begin in 1986, as requested by Europe (see above). In addition, the administration knew that new legislation was on its way regarding the provision of understandable information to patients. An expert committee was set up to investigate whether and how the revision operation could coincide with the introduction of patient package inserts. Finally, in 1986 the new Minister of Health decided to go ahead with the operation. A Royal Decree was made on January 27, 1986, fixing the time schedule over one year for the introduction of drafts of PPIs. Belgium was by then the first country in Europe

to anticipate the upcoming European Directive of 1992, and to combine the process with the validation of the drug information on older products and the first wave of a 5-year revision cycle for all products. A few back-and-forward changes were made to the official wordings of the headers of the patient package inserts, and finally the Belgian legislation incorporated European Directive 92/27/EEC with the Royal Decree of 31.12.1992, as the first European country to legally and practically enact this piece of legislation. In the mean time, a new Belgian government had been formed, and the political interest in this project had vanished.

4.4 The characteristics of PPIs in Belgium

To understand the transition to patient package inserts which started in 1988, we must bear in mind two crucial features. Firstly, as stated above, it was a transition from an original drug dispensing system *with technical inserts* to an original drug dispensing system *with patient package inserts*. Secondly, the main difference between the patient package insert and the old technical insert was merely of a linguistic nature. Both texts have a similar overall look (in fact, rather dull) and are of similar length. Only when the text is read do the differences become apparent, essentially a reduction of jargon, and a reduction of the length and complexity of the sentences. Unfortunately, the requirement to have the insert in three official language was maintained, hence the type size of the Belgian inserts has remained small, sometimes less than 9 pica points, which is probably too small.

The following elements should be added:

- a clear choice for a full information insert
- structured in 16 items, expressed in simple, uniform titles, to provide the reader with a grid to scan the content
- a fixed order of items, with the order chosen to reflect the mental process of an individual reading the insert before the intake of the first dose
- omission of the section of the scientific data sheet on pharmacological properties
- a standardised reference to the pharmaceutical group to which the drug belongs, with some efforts to coordinate with the wording in the section on interactions
- no information on how the drug works or how drug action can be perceived (benefit information)
- long and unstructured lists of possible side-effects
- an informative, moderate tone, without any promotional messages.

The following additional characteristics are also important:

- the final responsibility and authorship of the insert lies with the pharmaceutical company

- the messages in the Belgian insert are targeted to a mentally healthy adult with a formal education to the age of 16 years
- the insert is explicitly positioned as an instrument in the patient-pharmacist-patient relation, and not a stand-alone, do-it-yourself guide
- the content of the insert is related to a specific drug, rather than to a drug class.

4.5 Characteristics of the Belgian implementation efforts

From 1984 till 1987, there was active involvement by scientific associations, consumer associations, and the pharmaceutical industry in the preparation phase of the Belgian transition to patient package inserts, with intense debate, particularly on the issue of final authorship (firmly claimed by the industry), and the inclusion or omission of a benefit message (claimed by the consumer organisations, but in practice declined by the regulatory agencies). Policy was finally firmly established in 1986, after a compromise was reached, with which none of the constituencies were fully happy, especially not the consumers.[136] Once decided, a rather technocratic process evolved, run by the Pharmaceutical Inspection and the Medical Information officers of the companies, in cycles of draft deposition, revision and final acceptance of more than 2,000 inserts. A description of the implementation efforts was presented at the 25th Annual Meeting of the Drug Information Association in Boston, USA in 1989, and published in the DIA journal in the same year.[137]

The goals of the PPI implementation were stated in the official motivation of the legislative process:

- to fulfil the right to know
- to enhance patient compliance
- to enhance patient participation in the health care process and to improve the rationality of the process of drug utilisation

Part of the implementation process was to provide help, assistance and tools to the writers of the patient package inserts. The medical information officers inside the companies were academically trained physicians and pharmacists, heavily using medical jargon. They had great difficulty writing in a simple style. Training courses for communication in plain language were organised, and a booklet on the subject was commissioned from a linguistic expert, focusing on drug information.[138][139] In addition, a trilingual glossary of technical and popular terms was edited.[140][141] First, a selection was made of some 1.400 medical jargon terms, which often turn up in scientific data sheets. A Dutch/French/German list of these technical terms was then made, and finally, for each of the technical terms, an appropriate popular term (or a short description) was sought in each language. The list had no normative character, but was intended to avoid a "Babel-like" multiplication of "popular" terms.

The validation of the drafts of the patient package inserts was organised in a two-step procedure. Firstly, there was a congruence check with the data sheet by the medical experts of the Pharmaceutical Inspection. Secondly, the readability of the text was evaluated. It was agreed that as the law said that inserts had to be understandable by the citizen, and so there was a need for a formal evaluation procedure to enforce this legal obligation. However, it was soon clear that the pharmaceutical industry would not accept refusals of drafts by civil servants, who themselves did not have a track record of clear and understandable communication. At that time, the only available example of a solution for this difficult situation was the USA Department of Defence Regulation DOD 3984X203, stating that manuals for guns, commissioned by the Navy, needed to be understandable by the average American private soldier, confirmed by a readability test.[142] After reviewing the literature on the pros and cons of existing readability tests, a research programme was commissioned to produce a context-specific computerised readability test (see chapter 4 of Part II). The readability of individual drafts was then screened by a medical doctor with linguistic training in medical communication. The computerised readability test was only used to confirm the identification of substandard inserts with low readability, and to document rejection decisions. A scanning system with Optical Character Recognition technology processed the drafts (with titles and technical sections obscured by markup) and was able to print a written result with an overall readability score, and with identification of technical terms and complex sentences. The very fact that the system was in place sent a signal to the medical departments of the pharmaceutical companies, indicating that the operation had to be taken seriously from a linguistic point of view.

The review process was organised in a time frame, taking one major therapeutic class after another. However, the control was performed on individual drafts for brands of different companies. There was no Document Management System available to compare e.g. the side-effect sections of different medicinal products, containing e.g. aspirin. Inevitably, inconsistencies crept in, weakening the fair enforcement of a minimum level of quality.

The first validated patient package inserts appeared in packages in 1987, and the transition process gradually evolved in the ensuing years, to be completed by 1993.

4.6 Evaluation of the introduction of PPIs in Belgium

In 1987, while we were involved in the implementation process, we proposed initiating an evaluation programme, and were able to convince the health authorities to fund the project.

Lilja lists a number of criteria which can be used to measure impact (here presented in a slightly adapted form):[143]

- reception rate
- receivers' satisfaction with the information provided

- changes in knowledge
- changes in attitude
- behavioural changes (compliance, different reporting of adverse drug reactions, more adequate reactions to adverse drug reactions)
- health effects (including reduction in adverse reactions)
- satisfactory balance between health information cost and benefits

We chose reception rate and satisfaction as two primary criteria, as we were fairly confident that the results would be positive. We skipped changes in knowledge as a criterion for our programme, as we considered that the impact on these aspects had already been clearly demonstrated in other research projects. It was considered too difficult to demonstrate impact on health outcome. We were always reluctant to add the impact on patient compliance to the list, as we knew how poor measurement validity was and how contradictory the literature results were in that respect. In contrast, we were genuinely interested in the impact on attitude and on behavioural changes with regard to adverse reactions (be they negative or positive). Hence, the longer list was shortened to 4 criteria:

1. reception rate
2. receivers' satisfaction with the information provided
3. changes in attitude
4. behavioural changes (reactions to adverse drug reactions).

5 Theoretical background to this thesis

5.1 A model for assessing acceptance of PPIs

Lilja lists a typology of evaluation studies suitable for this kind of research:[143]

- evaluations which concentrate on determining whether or not the programme was properly implemented
- evaluations which concentrate on determining whether the assumptions about the influential features of the information programme were correct or not
- evaluations which aim at determining the impact and suitability of the programme.

For designing descriptive studies of the acceptance of patient package inserts in the drug distribution system of Belgium (presented in Part II), we combined elements of each of these types of evaluation studies.

In the beginning, we tried to exploit as much as possible the circumstances of this natural experiment (a massive change in drug distribution on a national scale). We concentrated on descriptive studies, prior to the implementation of the programme and repeated during the programme. By the time we obtained our first results from these studies (reported in Part II), interest in the

programme had decreased by a swing in political mood in the country. Later on, we redirected our research to experimental studies (reported in Part III.)

5.2 Theoretical models for assessing impact of PPIs on benefit/ risk perception

In the fields of medical sociology, communication science, clinical psychology and health promotion a number of theoretical frameworks or models have been developed for explaining variations in health-related behaviours. These models can and have been applied to the field of patient compliance.[144] They can be grouped in two broad categories:

- Social Cognition Models for health behaviour based on beliefs and attitudes
- Clinical Psychology Models.

These models are briefly described in the following subsections.

5.2.1 Social Cognition Models

The most general theory, developed for the study of behaviour in general, but widely applied in health care is the Theory of Reasoned Action by Ajzen and Fishbein.[145] This model was further developed into the Theory of Planned Behaviour[146] by incorporating a new element, "perceived control", in fact "perceived behavioural control and barriers" (e.g. do I have sufficient skills to carry out the behaviour and will I be able to overcome the barriers I see to fulfil my intention to display the behaviour). This concept is rooted in Bandura's concept of self-efficacy[147] and also tries to incorporate the somewhat ill-fated notion of (health) locus of control.[148]

The problem is that this theory ends up looking like a loose container of intellectually different approaches, ranging from social determinism to cognitive expectancy-value models (used more successfully in the analysis of the drug choice process by physicians),[149] to attitude and motivation research and clinical psychology concepts. Its application in the health care sector has been focused rather on preventive measure for health status maintenance (such as exercise, diets, smoking, and using condoms); the application to patient compliance was less convincing.[144]

For historical reasons, what should also be mentioned is the Health Belief Model, originally directed at the desire of the individual to avoid a specific disease threat.[144][150][151] Many more revisions and the addition of modifying factors, combined with differences in *operationalisation* across the different studies make it difficult to draw conclusions about the viability of the model.[144][152]

For the sake of completeness, we should mention the extension of these social cognition models into the realm of health promotion and public health. The Health Action Model[153] incorporates political and ideological concepts of patient empowerment and the influence of mass-media. The PRECEDE/PROCEED model[154] is oriented towards the planning and evaluation of health promotion. These last two theories introduce the notion of enabling and reinforcing factors and mainly take the perspective of the macro-level of society.

5.2.2 Clinical Psychology Models

5.2.2.1 Stages of Change Models. In these models, it is acknowledged that interaction between cognition and behaviour is dynamic, rather than static, that adoption of a new behaviour follows a temporal pattern, with a succession of stages in an orderly process, and that different cognitions are important at different stages.[144]

The most prominent model is the Transtheoretical Model,[155] in which 5 progressive stages (precontemplation, contemplation, preparation, action and maintenance) are discerned.

Patient compliance with prescription medication can be also be seen as a consecutive process of different decisions.[156] First, the decision to go and see the doctor,[157][158][159] then the decision to start taking the medicine, and finally the decision to continue the treatment. These decisions are yes or no decisions and can be seen as a chain of Markov models, each with two probabilities (to take or not to take the action).[160] Whichever decision making theory is used, here are three consecutive, but different decisions to be looked at, probably each with their own stages and their own cognition processes.

5.2.2.2 Ley's studies on Cognition, Memory and Emotion. Philippe Ley was an psychologist who conducted a number of pivotal studies on doctor-patient communication and compliance and the role of verbal and written information to patients in the late seventies and early eighties. Although he never proclaimed any formal theory carrying his name, his research has greatly influenced many aspects (and more specifically the important aspects) of the theories described above. What follows is an attempt to summarise important notions of his work.

He was one of the first to acknowledge that following doctor's orders is not always the wisest decision for the patient, that many physicians prescribe inappropriately, and that physicians are reluctant to give vital information on risks of medicines and indeed fail to do so.[144]

He stressed the basic communication principle that verbal messages (if they are given at all) need to be understood and recalled. He provided evidence that failure to recall information from a physician-patient encounter is high, even immediately after the consultation. An important reason is that during

the short consultation, information processing by the patient is often hampered by emotion. Emotion can arise from fear or severe anxiety (concerning the diagnosis and the future), from dissatisfaction with the physician-patient interaction, because the patient's reason for encounter was not properly sought out or addressed, because information needs were not explored or addressed, or because the interactional style of the patient and the physician simply did not match. The basic message here was that negative emotion interferes with cognition and memory, leading to failure to recall information and inability to comply in a proper way, even if one wants to comply, which is unlikely if the preceding consultation was characterised by negative emotions.

On the other hand, patients leaving the surgery in a satisfied mood (pleased with the physician-patient encounter), would be more willing to comply with the prescribed medication, even if they have not received or do not recall enough information to be able to comply properly.

5.2.2.3 Leventhal's Self-Regulatory Model of Illness. This theory is about how people react to illness or health threats. Our account of the model is based on the original studies by Leventhal[161][162][163][164][165][166] and on other attempts at synthesis.[2][167] The fundamental premise is a view of the patient as an active problem solver, constantly monitoring internal and environmental signals, and attempting to close the perceived gap between current health status and a future goal state. Threatening internal and external signals will trigger two fundamental processes, viz. a cognitive response (a mental representation of the problem) and an emotional experience. These processes may interact but may also develop independently. Both the cognitive response and the emotional experience will lead to a sequence of first, an action plan for coping, and second, an appraisal of the outcome of this action plan. The results of carrying out the coping action may alter the representation of the illness, the emotional response and the appraisal process.

The internal stimuli may be physical sensations of symptoms of disease or bodily (mal)functions. External stimuli may be comments from relevant others about one's condition, health messages from the media, a result from screening programmes, a lab result or a diagnosis from a doctor.

The cognitive representation of the illness problem is a complex notion (still under development). Patients can make immediate interpretations of what the meaning of the experienced stimuli might be, based on past experiences, common knowledge, dominant cultural explanations for specific symptoms and lay disease theories. Patients responding cognitively to stimuli retrieve schemata of structured knowledge from memory, characterised by the identity (the key collection of symptoms of an illness and its label), cause (what the illness can be attributed to), consequences (interference with daily life, and time-line (expectation about the duration of illness). In addition, the characteristics of the treatments known for the illness can be retrieved.[165]

Situations where stimuli are unfamiliar and do not generate retrieval from long term memory into the working memory of known schemata, or where stimuli generate multiple schemata (with a worst and a best hypothesis) may arouse strong emotions.[164] When the illness episode is over, recent experience is integrated in the schemata, disappearing from the working memory but stored as past experience.

The theory of Leventhal (et al.) has been used several times in interventional research to change patient compliance[161][168][161169][170] and in the development of new measurement methods for the study of the cognitive representation of illness and medication.[163][171][164][172][165][173]

5.2.3 Relevance of these theoretical models to this thesis

These models were instrumental to our research in several ways, as they helped us to:

- focus on prescription-only medicines (Rx), rather than on over-the-counter medication (OTC)
- consider the consecutive decision processes for prescription medication taking
- see compliance as a process with a beginning, a middle and an end
- focus on benefit/risk perception of the treatment in the contemplation stage.

6 Structure of this thesis

After the introductory Part I, the results of our studies are described in the two middle parts of this thesis. In Parts II and III, a narrative report of the first author studies is given. Each of these parts consists of 4 chapters. The first three chapters of each part contain a vernacular description of first author articles (the facsimiles of the original publications of the six first author articles are enclosed in Annex 1), the fourth chapter contains a brief description of additional research in which the author of this thesis was involved but not as a first author.

In Part II, the focus is on the acceptance of patient package inserts during their introduction in Belgium, with descriptive studies, making use of the timeline of the Belgian PPI programme.

In Part III, the focus is on benefit/risk perception, reporting on interventional studies.

In Part IV, the general discussion, recommendations and final conclusions are given.

Part II

Descriptive studies in the Belgian Patient Package Insert Evaluation Programme

Everything put together, sooner or later falls apart.
Paul Simon

Part II provides a narrative account of the descriptive studies performed in the Belgian PPI Evaluation Programme from 1988 till 1998. The first chapter reports on a survey of the attitude of the Belgian population to (technical) inserts, just prior to the change in 1989. In the second chapter, we report on a 1991 survey of physicians, to explore their attitude toward patient package inserts, at that time an innovation. The third chapter describes a survey of drug utilisation and drug information flow in nursing homes, to see to what extent this part of the population is reached by written drug information. In the fourth chapter, the other studies of the Belgian PPI Programme (in which the author of this thesis participated but was not the first author) will be described.

We will discuss to what extent the explicit objectives of the Belgian PPI Programme were reached in the general conclusion in Part IV.

Chapter 1
Attitude of the public toward technical package inserts for medication information in Belgium

Originally published as: Vander Stichele RH, Van haecht CH, Braem MD, Bogaert MG. Attitude of the public toward technical package inserts for medication information in Belgium. DICP 1991;25:1002-106 (see facsimile 1 in Annex 1)

That must be wonderful. I don't understand it at all.
Moliere

Motives for this study
In our first formal study in the research programme on the impact of the introduction of patient package inserts (PPIs), we wanted to measure the attitude toward written drug information among the Belgian population, just prior to a major change in the drug distribution system on a national scale. The study was conducted a few months before the first PPIs began to appear in the medication packages on the Belgian market, to make a zero measurement of the situation at that time. This would later enable us to demonstrate the (beneficial) impact of that change, by repeating the measurement after the change.

Setting
Belgium is a Western European country, where the level of illiteracy is limited to less than 5% of the population. Patients in Belgium have become used to finding inserts in their medication packages since 1963. Drug distribution in Belgium occurs almost exclusively as original drug dispensing with a branded package, containing an insert. Between 1963 and 1988, that insert was always a technical insert (TI). This document, on thin paper used for bibles and folded into the package, was the scientific data sheet, written for the health care professional, heavily laden with medical jargon, basically unintelligible for the layman, but distributed in the medication package, and hence available to the patient, each time he or she bought a medication package.

Objective of the study
Our primary aim in conducting this study was to know whether Belgian patients read the technical insert (TI) and whether they were satisfied with it.

Time frame
June 1988, just prior to the change from TI to PPI.

Design
A descriptive, exploratory, cross-sectional population survey.

Participants
We wanted to select a representative sample of the Belgian population aged 18 years and older, stratified for Dutch speaking and French speaking citizens.

Method
We designed a questionnaire with closed questions, intended to be taken from citizens by trained interviewers, familiar with population surveys. The questionnaire was 84 items long, and took 30 minutes to answer. Patients' perceptions of the TI were explored with 5 point Likert statements (five possibilities to answer between "strongly agree" and "strongly disagree"). Patients were asked to chose one or more items from a closed list of motivations to read the insert (4 items) and topics of interest in the insert (9 items). Respondents were questioned for their preference for the future patient insert as to length and completeness in two separate questions.

We selected a random sample of 2×200 possible participants from the election registers of two major Belgian cities and their rural surroundings (each with a catchment area of approx. 950,000 inhabitants). We selected one Dutch speaking city in the northern part and one French speaking city in the southern part of Belgium. The trained interviewers visited the selected addresses and interviewed the adult person at home, willing to participate. In case of refusal or absence, the case was replaced with a new selection matching for sex and age, till the quota sample was complete.

The characteristics of the respondents were compared to the population characteristics and the results were weighted for those variables that showed a statistical difference (population percentage outside the confidence interval of the sample result).

Short overview of the results in the original publication
We recruited 398 participants, 200 Dutch speaking and 198 French speaking, with a slight underrepresentation of the elderly (60+) and the less well educated (schooling age no higher than 14 years). Seventeen % of the sample stated that they had not taken any medication in the past year.

The weighted percentage of citizens stating that they read the insert (TI) when purchasing and using a medicine was 87%. Nine % did not read the insert, neither did another person. Four % did not read it, but a relative did. This relative was either the wife for the husband, or the mother for the younger adults. Women read the TI more often than men did (93% vs 75%). Among the readers, 78% stated that they always read the insert, regardless of the severity of their illness or whether the medicine was on prescription or over the counter.

At least 5 items of the insert were read thoroughly by 83%. Attention of the readers was focused predominantly on risk information; viz. the side-effect section (read by 88%), contraindications (82%), indication – to check whether this matched the diagnosis – (79%), medication shelf life (76%). Another focus of attention was procedural information; how to take the medicine (85%), how much to take (85%), how long to take the medicine (57%). There was less interest in background information; how the medicine works (56%), composition of the medicine (39%).

The motive to read the TI was to be able to execute treatment properly (83%) to be reassured (57%), to know more about the medicine (50%), to decide whether or not to take the medicine (31%). Thirty-five % had more than two motives (always including the first motive).

The information contained in the insert was perceived by the readers as useful (86%) and complete (71%); 75% found it reassuring that a TI could always be consulted. Dissatisfaction was reported as difficulty to understand (57%), remember (52%), and read (45%). The insert was considered graphically dull by 69%. Induction of fear to take the medicine by reading the insert was reported by 31%, and 25% considered that confidence in the physician might be reduced by reading the TI .

With regard to medicines on prescription, 55% would ask the physician, 19% would stop taking the drug and 18% would continue to use the drug, if the insert mentioned a threatening side-effect; if the insert contained information that was not understood, 36% would turn to the physician, 33% to the pharmacist, and 15% would not look for further information. With regard to (over-the-counter) medicines, 26% would ask the physician, 43% would stop taking the drug, 16% would ask the pharmacist, if the insert mentioned a threatening side-effect; if the insert contained information that was not understood, 19% would ask the physician, 54% the pharmacist, and 13% would not look for further information.

If the content of the insert conflicted with the physicians' advice, 41% would contact the physician, 37% would follow the physicians' advice, 10% would ask the pharmacist.

Sixty-seven% of the patients preferred the insert to be short and 88% wanted the insert to be exhaustive.

Twenty % knew that new, more readable inserts would soon be introduced. Their source of information was the media, not the physician or the pharmacist.

Short overview of the discussion and conclusions in the original publication

There was a limited but obvious distortion of the representativity of the sample, caused by the quota sampling technique. This was corrected by a weighing technique, resulting in only a slight shift in the results. Because of the crude sampling technique and the limited sample size, this study is merely a temptative exploration of the attitude of the Belgian adult general public.

Several more specific descriptive studies were set up in elderly populations and in adolescents (see Chapter 4 of Part II).

The data on the reading level of the insert reflected people's intention and did not stem from observed behaviour. High levels of readership do not necessarily result in benefit in terms of increased knowledge or modified behaviour.

The level of readership observed was higher than we expected. The gender differences observed might indicate that women are interested in medication not only for themselves but also as gatekeepers for medical information for the family.

Equally surprising was the high level of satisfaction with the technical insert (TI), notwithstanding criticism about graphical quality, readability and legibility. Negative emotional impact was reported by less than one third of the readers. Disturbing reactions to conflicts between information sources seemed to be limited.

People react differently to information in inserts of prescribed medicines than to inserts of over-the-counter medicines.

A phenomenon such as the popularity of the Physicians' Desk Reference (a book on medicines for physicians) among American patients is virtually non-existent in Belgium.

The public wants an impossible compromise between concise and complete inserts.

It is difficult to understand how basically unintelligible medical jargon obtains such high levels of readership and satisfaction. Maybe, the very fact of providing written information is more important than the quality of the written information. Medical jargon may have a "magical" ring that satisfies patients, even if information transfer has not been achieved.

Improvement of readership levels and satisfaction levels by changing to patient package inserts (PPIs) was hardly to be expected in Belgium, given the initial high levels. Some gain could be attained in reducing complaints on poor readability.

Additional results from this study

We performed an analysis of differences in responses between Dutch and French speaking respondents. Only two items showed a statistically significant difference. We hesitated to stress these results, as an analysis of many variables may yield some positive results by mere chance, and because at that time we had no explanation for the findings. What we observed was that complaints about the vagueness of the text (as a proxy for understandability) were more frequent among the Dutch (55%) than among the French respondents (45%). On the other hand, the French speaking respondents reported complaints about legibility (47%) more frequently than the Dutch (33%).

An additional exploratory principal component factor analysis was performed to analyse the link between the different motivations to read the insert (4 items) and the topics of interest while reading the insert (9 items).

Three factors were found, resulting in a categorisation of the information in the insert:

- Risk information
- Procedural information
- Background information.

Interestingly, some topics of interest scored high on more than one factor. The item "indication" scored high on both risk information (is this the right medicine for me?) and high on background information (what is this medicine used for and how does it work?). The item "package shelf life" scored high on procedural information (how long can I keep this drug) and high on risk information (am I not taking an out-of-date medicine?). The item "dosage" scored high on procedural information (what is the right dosage to take?) and on risk information (am I not poisoning myself by taking too much of the medicine?).

Further discussion in the context of this thesis

The results of our first study indicated that there was little hope for substantial beneficial change by the introduction of the patient package insert. Apparently, the level of readership was already so high that little incremental gain was to be hoped for. On the other hand, it was reassuring that providing written information resulted in high penetration, even with a low readability level. We felt that the result was so important that it needed confirmation in a subsequent study.

It became clear to us that if change was to be documented and gain to be demonstrated, one had to look into reduction of complaints about readability. That meant that we needed a tool for the objective assessment of readability. We either had to look for an existing readability test or develop one ourselves, which we eventually did (see Chapter 4.1.2 of Part II).

We realised that could be a tricky measure of satisfaction with written information. Provision of written information in itself seemed to bring about satisfaction, despite the presence of medical jargon and despite the predominance of risk information. It was not impossible that enhancing the level of readability, by using simple words and shorter sentences, would heighten the emotional impact of the insert, and hence reduce satisfaction, instead of augmenting it. Our decision was to repeat the population survey, two years after the first survey (see Chapter 4.4.1 of Part II), but without the satisfaction measurement. We did however include satisfaction measurement in the coinciding intervention study (see Chapter 4.1 of Part III) conducted at the same time.

Another possible outcome parameter was the impact of a change from TI to PPI on patients' knowledge of the medicine. We decided not to focus on this issue, as it has already been addressed adequately in other research programmes in Europe and in the US. It seemed clear to us that more

understandable written information results in a better knowledge, and that there was no need for a replication of this finding in our studies.

There was a striking gender difference in the first population survey, and concluded that women are a legitimate target for research and information campaigns, regarding medication information. In future research, we would not hesitate to sometimes recruit exclusively female populations (see Chapter 3 of Part III).

The differences in appreciation of the TI between the French and Dutch speaking respondents puzzled us for a long time. Basically, these results suggested that Dutch speaking people complained more often that they did not understand the content of the insert, and that French speaking people complained more often that they could not read the insert. Eventually, we formulated the following hypothesis as an explanation for the findings. The Dutch language is a Germanic language. Medical words in Dutch are fundamentally different from the medical jargon, which has its etymological roots in Latin and Greek. Therefore, Dutch speaking people have a problem with many of the difficult terms in the technical insert, and are less likely to understand its content. The French speaking people on the other hand, have a lexicon that is much closer to medical jargon, but they are confronted with another problem. The French language is written in an alphabet with numerous diacritical signs. These are accents above or under some letters of the alphabet, changing the pronunciation of the letter and the meaning of the word to which the letter belongs. Examples are é, è, ê, à, ç and ô. A text edited in a diacritical language will become much less legible when printed in a smaller size. A Dutch speaking person with slightly impaired eyesight might still be able to read a Dutch text set in 9 pica points type size, while under the same conditions, a French speaking person would no longer be able to read the same text in French. Note that the German language has both problems: lexical distance from the medical jargon and many diacritical signs (ü, ö). We concluded that readability and legibility problems are language specific. Hence, if a readability test was to be developed, one had to be developed for Dutch inserts and one for French inserts, and that it would be an aberration to apply to Dutch and French texts simple readability tests developed for the English language (like the Flesch test), based on word and sentence length.

There were two consequences for our further research from our findings on the categorisation of information in the insert in risk information, procedural information and background information, based on an exploratory factor analysis. Firstly, our interest in aspects of balance between the positive and negative information (risk information and background (or benefit) information) was awakened (see Chapter 3 of Part III). Secondly, we used the insight in our own design of patient package inserts for intervention studies (see Chapters 2 and 3 of Part III). We used three rules of thumb while editing our inserts:

- combine procedural information with risk information
- combine background information with procedural information

- choose a consistent grammatical tense depending on the type of information.

In the first population survey, there were few signs of problematic interaction between information sources, more specifically between the information in the insert and the information of the prescribing physician. We anticipated that this might change as PPIs would soon turn up in packages. It seemed important to know the attitude of health professionals, more specifically physicians, as we focused our research on prescribed medicines. Therefore, we undertook a survey of the attitude of physicians, in the spring of 1990 (see Chapter 2 of Part II).

Finally, we had some doubts about the representativity of our population survey for the Belgian population. Children and adolescents up to the age of 17 were not represented. The number of people of 65 and older was too small to extrapolate on the attitude of the elderly, which are after all, the big consumers of medicines, with special drug information needs.[58]

Chapter 2
Attitudes of physicians toward patient package inserts for medication information in Belgium

Originally published as: Vander Stichele RH, De Potter B, Vyncke P, Bogaert MG. Attitude of physicians toward patient package inserts for medication information in Belgium. Pat Educ Counsel 1995;28:5-13. (see facsimile 2 in Annex 1)

Grebles' contradiction:
Eighty percent of people think of themselves
as above average automobile drivers.

Motives for this study
The prescribing physicians are the preferred information source for most of the patients.[51][174][175] Hence, we thought it would be helpful to know the attitude of Belgian physicians on the brink of the introduction of a renewed source of written information, in a major alteration of the drug distribution system. We considered to conduct a campaign towards the physicians, to ask their support for the introduction of the patient package insert (PPI).

Setting
Belgium has 35,000 physicians, with some 10,000 active general practitioners (GPs), for 10 million inhabitants. In the hospitals there is quite some outpatient activity, and many specialists (gynaecologists, paediatricians) have a private practice outside the hospital. Most patients regularly attend one general practitioner (often shared with the rest of the family) but there is no formal registration of the population with GPs. Direct access to specialist care is possible and often sought, especially for paediatric and gynaecological problems.

Objective of the study
Our primary aim was to explore possible differences in attitude to written medication information amongst physicians.

Time frame
Spring 1990, when one third of the medication packages on the market contained a PPI.

Design
A descriptive, exploratory, cross-sectional survey of practicing physicians.

Participants
We selected a sample of the Belgian practicing physicians, stratified for general practitioners and specialists.

Method
Together with a clinical psychologist and a communication scientist, we designed a questionnaire, within the theoretical framework of symbolic interactionism[176] (see part 2, introduction for explanation) along 4 dimensions:

- Observations of patient behaviour by the physicians
- Reported actual use of written information by the physician
- Physicians' perception of patient information behaviour
- Physicians' perception of the impact of the PPI.

The first two dimensions were observations that could be made directly by the physician, either on their own behaviour (5 items), or on the behaviour of patients (5 items). We asked for frequencies of observations on a five-point scale (daily, weekly, monthly, yearly, never). The last two dimensions were on subjective perceptions of patient behaviour that could not be directly observed by physicians. Here we asked for estimated percentages of patients, presumed to exhibit the behaviour (5 items), and for agreement or disagreement (strongly or moderately) with statements about possible patient behaviour (19 items).

The questionnaire was pretested by 10 physicians and took 20 to 25 minutes to complete.

The questionnaire was sent to 1,500 Dutch and French speaking general practitioners (an 8.2% random sample) and to 500 specialist in internal medicine (a 22.6% random sample), to enable for comparison between GPs and specialists.

One written reminder was sent to non-responders after 4 weeks.

We performed a *cluster analysis* to identify relevant subgroups among the respondents. In this mathematical procedure, the respondents are divided into groups (clusters) with similar answers to the questions. The characteristics of these newly formed groups are then analysed and an appropriate label is sought for each of the groups.

Short overview of the results in the original publication
The questionnaire was returned by 38.0% of the specialists and 23.5% of the GPs (overall response rate 27.5%, N=543)). The sample was representative for gender, age, language and workload. As no significant differences were found between GPs and specialists in internal medicine, their answers were concatenated in the subsequent analysis.

The large majority (88%) had heard of the existence of patient package inserts, mostly trough their medical journals and the media, occasionally from

patients or colleagues. In the preceding two months, 81% had read an insert, but only one third had read a patient package insert. Motives to read an insert were:

- to check whether a particular side-effect was listed (69%)
- to check what a patient had said about the content of the insert (52%)
- to know the precise formulation of the message in the insert (40%)
- to check for possible interactions (36%)
- to check the indication of the medication (32%)
- to know the composition of the medication (31%)
- other reasons (10%).

More than two thirds of the physicians had had at least one patient in the past month with whom she/he had discussed side-effects, with explicit reference to the insert, or a patient who had returned and asked for explanation of information from the insert. Half of the physicians reported a failure to start a prescribed medicine after reading the insert or request for another therapy.

In comparison with the situation 1 year earlier, 75% of the physicians did not see any difference, 1% perceived a decrease, and 24% an increase in the events described above. Of the physicians perceiving an increase, two thirds thought there was a causal relationship with the shift to PPIs.

Less then half of the physicians reported having advised a patient to read the insert, and one in five had read the insert together with a patient in the past month.

Only one third of the physicians thought that more than half of their patients read the insert. Very few physicians thought that more than half of their patients would understand the technical insert. When asked what in their opinion the majority of their patients would do in the case of a contradiction between their oral information and the information in the insert, the answer was:

- contact the physician to get further information (43%)
- do what the doctor told them (41%)
- contact the pharmacist to get further information (10%)
- look for clarification and stop therapy (8%)
- look for information elsewhere (family, friends, books) (5%)
- follow the instructions of the insert (2%).

The cluster segmentation resulted in a stable separation (segmentation) into three clusters, which were assigned the following names, after analysis:

- moderately positive physicians (CL1 20%)
- ambiguous to neutral physicians (CL2 44%)
- overtly negative physicians (CL3 36%).

The moderately positive physicians show little activity in writing personal notes with instruction on medication usage to the patient, and make only

limited attempts to block access to the PPI; 56% are younger than 40; the PPI is seen as a valuable information tool that reduces the need for oral information, brings about better patient compliance and more adequate reactions to side-effects.

The ambiguous to neutral physicians report substantial activity in writing personal notes and in discussing the PPI with the patient; 44% are younger than 40; the PPI is again seen as a valuable information tool, but it is too long and contains too much risk information, having a definite impact on patients' emotions, which are to be dealt with.

The overtly negative physicians regularly attempt to block access to PPIs, but, on the other hand, engage in writing personal notes. The PPI is seen as having negative impact (suggestion of side-effects, non-compliance) and is thought to make it more difficult to prescribe medicines with a high incidence of side-effects.

The widest differences among clusters were found in the perception of the impact of the patient package insert. We present the statements and two extremes of percentages per cluster of physicians agreeing with the statement:

- a patient will experience the side-effect read in the insert (CL1 62%; CL3 93%)
- the insert will help the patient to react more adequately in the case of unforeseen events (CL1 84%; CL3 33%)
- reading the patient package insert will enhance patient compliance (CL1 78%; CL3 25%)
- the patient package insert will reassure the patient (CL1 63%; CL3 15%)
- the patient package insert is superfluous, because I give the information orally (CL1 8%; CL3 70%).

Short overview of the discussion and conclusions in the original publication

There was a low response rate in this survey, possibly caused by the length of the questionnaire and "survey fatigue" among Belgian physicians. However, there was no bias for gender, language, age or workload. Nevertheless, we learned from this study that more effort is needed to assure better response in postal mail surveys to physicians by sending multiple mail and/or telephonic reminders. Because of the low response we refrained from extrapolating the frequencies of the clusters to the population of Belgian physicians.

We observed that 70% of the physicians estimate that less than half of the patients reads the insert. This is a clear underestimation by the physician of patients' readership of the written medication information (see Chapter 4 of Part II for further confirmation).

Diverging attitudes among physicians should be taken into account in the design of public information campaigns and in medical education programmes for communication skills training. In our first cluster, we found young physicians, who disturbingly seem to consider written drug information a substitute for oral information. In the third cluster, the

caricatural image of the older paternalistic physician is tempered by evidence of extensive personalised efforts to communicate instructional messages. In our second cluster, we find physicians more receptive to the behavioural signals of their patients, with consequently a clearer view of the emotions of patients while dealing with oral and written information. Our segmentation into three clusters goes beyond the classical dichotomy between physician paternalism and patient autonomy.

Physicians and pharmacists should explore ways to integrate the patient package insert into their communication strategies in routine practice.

Further discussion in the context of this thesis

The absence of significant differences between general practitioners and specialists in internal medicine with regard to attitude toward written medication information was unexpected. As 80% of the prescriptions in ambulatory care are issued by GPs, an information campaign aimed at physicians could concentrate on GPs, and a separate or different campaign for specialists would not be necessary.

Relatively few incidents were reported, although the penetration of the PPIs had already reached 30% at the time of the study.

Most physicians apparently considered the technical insert a fairly useless, poorly used information source. They were unaware of the high percentages of patients reading the insert. However, their attitudes towards the patient package insert were strikingly different. The first cluster seemed to predict a positive (although somewhat disturbing) impact as a substitute for oral information, relieving the physician of some of the burden of providing complex information on medicines. The third cluster considered the shift from TI to PPI as a mere aggravation of the existing situation, causing unnecessary additional effort by the physician to put the patient back on track, after having been thoroughly and purposelessly disturbed by the insert. The second cluster seemed to welcome the arrival of the PPI, as a sensible improvement of an existing information channel, but expressed doubts about the quality of the document, and estimated that the emotional impact of understandable information on patients would be greater. This was not necessarily considered a negative development, but patients would require more counselling.

At the time we reached our conclusions from this study, we considered the situation among the most important group (the prescribing physicians) complex and difficult to predict. There were many misunderstandings of reality, and diverging attitudes, all belonging to the realm of speculation. One thing was clear: that it was not going to be easy to involve the entire community of physicians in a programme for the implementation of patient package inserts. Moreover, the rate of penetration of the PPI was rather low (30% at the time of the study). It was impossible to predict at that time whether the Belgian PPIs would evolve into high quality communication tools, which one could recommend wholeheartedly to physicians. We

explored the design of intervention studies, implicating the prescriber, attracting attention to the PPI and inviting patients to read and discuss the insert with the physician. But we abandoned the idea, once it became clear that the Belgian effort in the PPI implementation programme would not be continued in the nineties. Meanwhile, a new minister with other priorities had taken over, after an election, which maintained the previous coalition of political parties, but reshuffled the departments.

Chapter 3
Medication utilisation and drug information in homes for aged persons

Originally published as: Vander Stichele RH, Mestdagh J, Van haecht CH, De Potter B, Bogaert MG. Medication utilization and drug information in homes for the aged. Eur J Clin Pharmacol 1992;43:319-321. (see facsimile 3 in Annex 1)

Motives for this study
We wanted to assess information sources and information needs of the elderly, residing in nursing homes, the population the least likely to be reached by patient package inserts.

Setting
Flanders, the Dutch-speaking part of Belgium, where the elderly of 65 and more years old comprise 17% of the population. Five % of these elderly reside in community nursing homes, most often in the vicinity of their previous residence. In these homes, elderly people with satisfactory functional and mental status live together with frail elderly, either demented or incapacitated by disease. Most institutionalised elderly are treated by general practitioners, often their own GP, who treated them before they entered the home.

Objective of the study
The aim of the study was to quantify the utilisation and knowledge of medicines among residents of nursing homes in Flanders, and to describe medication distribution and information activities inside the nursing home.

Time frame
February 1990.

Design
A observational, descriptive, exploratory, cross-sectional survey of nursing home residents.

Participants
Residents of Flemish homes for the aged.

Method
We worked with 23 experienced nurses, each working in a different nursing home, but meeting regularly for postgraduate training. Hence we constituted a

quota sample of the 23 nursing homes where these nurses were working. In each of the nursing homes, we made a random sample of 10 residents.

The 23 nurses were trained first to interview the nurse responsible for the selected resident, and then to assess the Activities of Daily Living Score and the functional and mental status of each resident. They reviewed the medication charts and identified how the medication was dispensed to each resident. Finally, residents were also interviewed directly, if possible and if permitted. For the assessment of the mental state no formal scales such as the NOSGER (Nurses' observation Scale for Geriatric Patients) Scale or Mini Mental Scale (both at that time in development) were used. However, the interviewers firstly assessed with a structured questionnaire the subjective appreciation of the nurse, responsible for daily care of the resident and secondly, the information from the medical chart as to mental orientation in time, place and person. The protocol was accepted by the Ethical Review Committee of Ghent University.

Short overview of the results in the original publication

Two directors refused to participate and one of the trained nurses fell ill. Two selected residents were lost to follow up. 198 patients were included in the study, with an interview of the nurse directly responsible for their care. Finally, 128 residents were interviewed directly, as communication with the other 70 residents was impossible because of dementia (55 patients) or communication problems such as aphasia and deafness (15 patients).

The characteristics of the 20 nursing homes selected were similar to those of nursing homes in general, although somewhat bigger institutions than average were selected (a mean of 81 residents per nursing home in our sample versus a mean of 61 in Flanders). Annual mortality was 30%. On average, there were 14 full time nurses per nursing home, 19 different GPs attending patients in the nursing home. Half of the nursing homes had a coordinating GP.

Among the 198 selected residents, 76% were female, and the mean age was 83 years (range 62-103, SD 7), with a distribution very similar to the general population of nursing home residents.

The distribution of the Activities of Daily Living score was (N=198):

- Score 3: fully independent for hygiene, feeding and moving around (49%)
- Score 4-5: minor deficiencies for one or two items (22%)
- Score 6-10: major deficiencies, requiring considerable resources of care (29%).

According to the judgement of the nurses who took care of the selected elderly, 28% were deeply demented, 13% slightly demented, and 59% were judged cognitively fit.

The nursed judged 42% of the residents as functionally and cognitively fit.

Twenty-three % of the residents were incontinent for urine, and 19% were also incontinent for faeces.

Symptoms of depression were present in 25% of the residents, 10% was hypochondriac, 3% euphoric, and 2% psychotic. Seven % had disruptive behaviour (aggression, regression, agitation).

Hearing problems were present in 27% of the residents (4% functionally deaf), and serious problems with reading in 33% (9% functionally blind).

The family regularly visited 57% of the residents. Eleven % received a regular visit from former neighbours and 7% from friends. The GPs visited 82% at least monthly (22% weekly).

The residents had a mean of 4.5 different medicines (range 0-12) on their medication chart. Only 4% did not take medicines (half of them because of therapeutic abstinence in terminal care); 47% had 5 or more medicines (polypharmacy). The number of medicines increased with age between 60 and 79 years (from 3.7 to 4.8), but stabilised from 80 years on at 4.3 medicines per resident.

Medication was ordered from community pharmacies in original drug dispensing packages, kept in ward rooms, and dispensed by the nurses. Nurses read the inserts of the medicines of 98% of the residents and kept the inserts of 77% of the residents in the nursing office.

Type of dispensing was as follows:

- medication mixed in food (16%)
- dispensed dose per dose with observation of swallowing (34%)
- dispensed dose per dose with retrospective control (35%)
- dispensed in the room per package, with autonomy of the patient over medication intake (11%)
- no medication (4%).

Thirty-two % of the residents were judged both cognitively and functionally fit, but lost autonomy over their medication.

The 128 residents who were able to respond to the interviewer were able to name (either by name, color or indication) 3.3 of the 4.7 medications on their list. We identified the following elements in the knowledge of their medication (*N*=128):

- knowledge of dosage regimen (81% of the residents)
- rough idea of indications (71%)
- notion of potential side-effects of their medication (4%).

The two most important information sources about their medicines were the family physician and the nurse. Four % or less mentioned relatives and friends or the pharmacist.

Short overview of the discussion and conclusions in the original publication

The small bias towards selection of somewhat larger institutions was probably caused by underrepresentation of small private nursing homes of less then 10 residents in our quota sample.

The findings about the level of drug utilisation and polypharmacy are in accordance with data from similar studies in the literature.

There is a contrast between the 42% of the residents judged cognitively and functionally fit by the nurses, on the one hand, and the 11% of the residents, who were allowed to order medication independently, keep the medication packages in their room, without intake control, and, hence, to remain autonomous about their medication intake. In a nursing home, there are good reasons to subject a number of patients with cognitive and functional deficits to a tightly organised distribution system, in which the provision and the intake of medicines is controlled by the nurses. However, this military distribution system seems to be applied indiscriminately to all residents, even those who are functionally and cognitively fit. This loss of autonomy might lead to a loss of interest in the medication and the end of the role of the patient as a partner in monitoring effects and side-effects of the medication. However, we have no further data on patients' preference for more autonomy neither on what the risks and costs would be of a more flexible medication management approach for those cognitive elderly, who aspire for greater autonomy in the handling of their medication.

Only the general practitioner and the nurse provide a limited and probably inadequate amount of medication information. As a result, the elderly know very little about the risks of taking drugs.

It is not easy to inform the institutionalised elderly about medicines. The educational background of the current generation of elderly is low; mental deficits, hearing problems, visual impairment and problems of verbal communication may hinder human interaction and information transfer. When elderly people lose responsibility over their own drugs, interest may subside. It is unlikely that a piece of flimsy paper with a small type size will contribute much to solutions in this context. To help the receptive elderly to deepen their knowledge of their own medication and to preserve or restore autonomy, an individual approach with oral messages is needed.[58]

The nurse in the nursing home is a suitable candidate to provide this tailored individual approach. The finding that these nurses intensively use the package insert as a personal source of medication information was unexpected.

Further discussion in the context of this thesis

In the outpost of health care, the nursing home, we came across both the limits of written medication information and its unexpected role as a source of medication information for the care taking nursing staff.

Chapter 4
Other descriptive research

In addition to the descriptive research reported in Chapters 1 to 3, a number of other studies were conducted within the framework of the Belgian PPI programme. This fourth Chapter of Part II outlines the remaining descriptive studies and application research.

4.1 Development of linguistic tools in the Belgian PPI Programme

Writing high quality, understandable PPIs within a pharmaceutical company is a formidable task, especially when the marketing director, the medical director, and the company lawyer are looking over one's shoulder. The pressure to launch the product onto the market quickly and if possible ahead of schedule is tremendous. Few companies are prepared to stall the introduction of a product for a lengthy discussion with the regulatory authorities over the wording of a few sentences in the PPI. PPI authors within companies were on unfamiliar territory when the Belgian authorities decided that Belgium would have PPIs a few years ahead of the other European countries. Writing style guides and vocabularies were published to assist authors of PPIs. However, to control and enforce compliance to good readability standards, a computerised readability test specific for PPIs was developed.

4.1.1 Writing style guide for patient package inserts

The objective of the Belgian Health Authorities was to make a contribution to alleviate the task of PPI authors, avoiding confusion and ensuring consistency in the structure of the PPI, the wording of the section headers of the PPI, and the use of popular terminology. A concise writing style guide in the Dutch and French language for written drug information was developed, in cooperation with experienced linguists.[138][139]

4.1.2 Trilingual (Dutch, French and German) vocabularies of technical and popular medical terms

A trilingual (Dutch, French, German) vocabulary of technical and popular medical terms was published.[140][141] This was a trilingual list of 1,400 technical medical terms frequently used in written drug information messages. Each term was then "translated" (vulgarised) in each language to a more

popular term, if appropriate. The list included terms for therapeutic groups. This was considered an important issue, because group terms are needed for cross-referencing with the item "interaction with other drugs". In addition, the list was indexed according to the International Classification of Primary Care. In retrospect, we found that this list was extensively used, although the quality of the "translation" was sometimes questioned. A Babel-like multiplication of divergent "popular terms" has probably been avoided.

note This exercise was repeated in 1993, after the European Union also adopted the principle of PPIs. A revision and extension of the trilingual vocabulary was commissioned. The Heymans Institute of Pharmacology and the Ghent Mercator School of Translators embarked on a low budget mission to extend the list of terms to 1830 entries (now based on a computerised frequency ranking of terms in a compendium of Summary of Product Characteristics). Each term was given a concise definition to avoid problems of *homonymity* (a term having more than one possible meaning, but with a different translation in another language). All terms were translated on the technical level into the then 9 official languages of the European Union. Each technical term was then vulgarised to a more popular term in each language, if appropriate.
This complex work was put on the World Wide Web as early as 1995, under the name "Multilingual Glossary of Technical and Popular Medical Terms", in nine European languages. Greek is not included in the web site: at that time it was too cumbersome to include the Greek alphabet on the web site. The site is still operational, and attracts some 1,500 visitors per day from all over the world. A number of major medical sites provide a link to this application. Its functionality stems from the programmed creation of thousands of internal links. This technical approach was quite suitable for the initial creation of the site in 1995. However, this now hampers the updating and maintenance process. A major revision of the site with a web-based, interactive group-authoring tool is planned. For a full discussion of the linguistic approach and translation difficulties, we refer to the web.

4.1.3 The development of the readability test

The Belgian Health Authorities realised that it was not enough to make a legal statement that inserts should be understood by the general public. Some mechanism had to be developed to check author's drafts and the chances that a draft would be understood by a sufficient number of people in the general public audience. Civil servants did not have the expertise to perform readability control. Disputes about the level of readability of a text would always remain in the realm of subjectivity. Application of general readability tests, aimed at a wide range of topics, were unlikely to be suitable for a highly structured patient package insert, focusing on a very specific subject. Development of a context-specific, computerised readability test would

facilitate law enforcement. In addition, it could be useful to authors as a pretest.

Before a computer programme could be created, the scientific basis of such a programme, viz. a suitable readability formula had to be created. This research was commissioned to the Department of Experimental Psychology of the Ghent University.[177]

In a field study with 432 Dutch speaking patients, the impact of terminological and grammatical text characteristics (assessable by computer analysis) on the readability of medication information was explored. The idea was to create a readability formula, composed of the selected variables, which would be able to predict the percentage of persons from a randomly selected group, who would understand a given patient package insert. This readability formula could then be integrated in a computerised text analysis tool for checking whether Belgian patient package inserts were understandable.

This research was only conducted for the Dutch language. (For the French language, an existing readability formula was adapted).[178] The full reports of these analyses were presented to a wider audience in 1994.[179]

The following 11 characteristics were selected for the study:

1. proportion of words longer than 8 characters
2. proportion of frequent terms
3. diversity index
4. the proportion of forbidden words
5. the sentence length in words
6. the average number of punctuation marks per sentence
7. the average number of finite verbs per sentence
8. the average number of finite verbs per hundred words
9. the proportion of auxiliary verbs
10. the proportion of prepositions
11. the proportion of gerund-like terms (verbs turned into nouns)

The first four variables assess the lexical complexity of the text. Long words and words not part of a basic general vocabulary make a text difficult to understand. When many different words are used in a text and few words are repeated, comprehension will be more difficult. Forbidden words were technical terms, present in the Trilingual Medical Vocabulary (see above), with a credible popular alternative. It was assumed that not using this alternative would not enhance readability. Flagging the forbidden words (from a list explicitly pertaining to written drug information) makes this readability test context-specific. This means it cannot be used for texts dealing with other subjects, but it may also ensure the power of the test in the appropriate context. The last 7 variables assess syntactical complexity, and try to flag long and complex sentences, which make comprehension of the text less likely. Complex sentences will contain more punctuation marks (such as commas), more auxiliary verbs, more prepositions (a fixed list in the Dutch language), more gerund-like terms (verbs or adjectives turned into nouns). Texts with

simple sentences will contain more finite verbs (conjugated verbs with a subject or imperatives).

Each of the 432 participants was given two inserts to read and then asked to answer 40 simple yes-or no questions. A rotation scheme for 18 different text in three levels of difficulty was made for distribution of the insert among the participants. In a multiple regression analysis the correlation between the text characteristics and the percentage of correct answers was analysed. The multiple correlation coefficient was .71 (95% confidence limits .65 to .86), with 50% of the variance explained.

An explained variance of 50% for variables, only pertaining to lexical and syntactical text characteristics, was considered to be a strong result. Also the fact that these variables needed to be present together to produce an optimal result was special. All the texts pertained to the field of written drug information (a homogeneous domain). As they were legally subjected to a particular structure, the texts were also standardised for semantic characteristics (the structure and the order of the information).

The validity of this readability test would be subject to change over time, if the general public was continuously and systematically exposed to high quality PPIs. Theoretically, the average medical knowledge and familiarity with medication information could improve and a new validation test would become necessary.

Further discussion in the context of this thesis

The computer routines to analyse text variables and the formula described above were implemented in a programme. Texts of patient package inserts could be entered in a computer by scanning with optical character recognition or by electronic transmission. The headings of the different sections of the inserts were excluded by adding mark up to the titles. The computerised readability test was able to analyse patient package inserts, compute the readability prediction, apply a cut-off criterion and then flag patient package inserts of poor quality. Together with the verdict, a number of general suggestions for improvement were given, based on linguistic characteristics (e.g. a list of replaceable forbidden terms).

This procedure was administratively enforced as a part of the control cycle of draft PPIs in the early phases of the implementation programme.[180] In the first year, I was in charge of checking readability as a human reader, with a concomitant check of the conformity of the PPIs to the scientific data sheet. The computerised readability test was used a few times, to confirm the detection of flagrant cases of low quality. It worked as an early warning signal in the beginning of the programme, but its cumbersome application was not sustained in later years. Transforming the programme into a web application would make the analysis more feasible and accessible on a wider scale.

The development of this readability test was an exercise in linguistics, helpful in the proofreading of over 2,000 drafts of PPIs during 1986 and 1987, and in writing experimental drafts of PPIs (see Chapters 2 and 4 of Part III).

4.2 Further exploration of the relevant constituencies: regulatory affairs managers

Motives for this study

In Belgium, the responsability for authorship of the patient package insert lies with pharmaceutical companies. Within the company it is the regulatory affairs manager who supervises the drafting of the Summary of Product Characteristics and the patient package inserts. He/she is also responsible for getting the draft through the approval process. In 1993, there was a symposium at the Heymans Institute, co-organised by the Belgian Consumer Association and the Belgian regulatory affairs managers, to discuss the transition from Belgian Patient Package Inserts to European User Package Leaflets (the term used in the 1992 EEC regulation). The present study was conducted in the months prior to the symposium. The results were presented at the symposium, but have not been published elsewhere.

Objective of the study

Our primary aim in conducting this study was to explore the attitude and experiences of Belgian regulatory affairs managers with regard to the impact of patient package inserts and the quality of the approval process.

> ***Setting:*** *Belgium, a country where technical inserts and patient package inserts of approximately 5,000 marketed branded packages need to be drafted, approved and updated every five years in three different languages.*
> ***Time frame:*** *1993, at the end of a 5-year cycle of the validation of old Summaries of Product Characteristics and the introduction of the Belgian Patient Package Insert, and at the start of new European legislation on written drug information.*
> ***Design:*** *An exploratory, descriptive mail survey.*
> ***Participants:*** *Information officers and regulatory affairs managers of the 120 small and big pharmaceutical companies in Belgium.*
> ***Method:*** *A mail questionnaire with 25 items (14 statements with 4 point agree/disagree Likert scales) and a section for open-ended remarks. The questionnaire was introduced by an official letter from the Heymans Institute of Pharmacology and the president of the Regulatory Affairs Managers Association. It was to be mailed back anonymously to the seat of the association. No reminders were sent.*

Results

Questionnaires were returned by 33 regulatory affairs managers. Eight were affiliated to a Belgian company, 8 US, 8 other European, 3 Swiss, 2 Scandinavian, 2 others and 2 independent consultants working for various companies. One in 3 respondents was male. Age was equally distributed over the decades (range 23 to 63). The majority of the respondents were Dutch speaking and 60% were pharmacists. The average number of fully processed PPIs per person was 37 (most of them not unconditionally accepted), with on average still 25 in the approval process at the time of the survey.

The vast majority (94%) were convinced that less than 50% of the patients understood the technical insert. Sixty-four % were convinced that less than 50% of the patients read the patient package insert. Opinions about the ability of the patients to understand the PPI varied. Half were convinced that the majority of patients understood it, half were convinced that the majority did not. The regulatory affairs managers tended to agree (strongly or moderately) with the following statements:

- it is good that the PPI is always available for the patient (100%)
- the PPI helps the patient to react more adequately to side-effects (97%)
- the PPI is useful to help them remember (81%)
- the PPI generates side-effects (66%) .

They had different opinions about the statements:

- the PPI stimulates compliance
- the text is legible
- the PPI is too long
- the PPI has a role to play in the information transfer to the patient.

And they tended to (strongly or moderately) disagree with the last statements:

- there is too much risk information in the PPI (64%)
- the PPI reassures the patient (73%)
- simplifying scientific information renders it incorrect (94%)
- the PPI stimulates automedication (97%)
- the health professional gives information, so the PPI is superfluous (97%)
- the PPI is useless (100%).

The writing style guides were generally well accepted by the regulatory affairs managers, but there was some criticism of the completeness and the validity of the vocabularies (see above). Lack of direct contact with insert assessors was deplored. Feedback from health authorities was often considered too little, too late, and sometimes inconsistent. Some respondents expressed the feeling that too much legalism was an obstacle for good communication with the patient. Poor legibility of inserts (set in small type size due to long texts in three languages) was considered a major impediment to communication.

Discussion and conclusion
Just like the physicians, the regulatory affairs managers underestimate the percentage of patients reading PPIs (see Chapter 2 of Part II). This misconception is probably detrimental to their job satisfaction. However, regulatory affair managers have a diversified perception of the impact of the PPI. Their attitude toward this communication medium is ambivalent, but on the whole positive, in spite of serious practical problems and extensive bureaucratic effort.

4.3 Follow-up studies of the implementation of the Belgian PPI Programme

During the years of transition from the technical insert (TI) to the patient package insert (PPI) in Belgium (1988 to 1993), a number of follow-up studies were planned, to confirm the gradual penetration of the PPI in the drug distribution system, to pick up possible unexpected phenomena, and to deepen our knowledge of the impact of written medication information. Here, we will present a population survey, mentioned in Chapter 1 of Part II, and a pre/post (during) clinical registration study among hypertensive patients in a general practice.

The transition from 100% technical inserts (TIs) to 100% patient package inserts (PPIs) in the medication boxes took place on the Belgian market between 1988 and 1992. The first population study was conducted in 1988 and repeated in 1991. The baseline clinical registration study was done in the spring of 1989, just before the start of the transition and repeated one year later in 1990, when the transition was in full swing.

4.3.1 Population study

note This study was only presented as an abstract.[181]

Motives for this study
The first population study in 1988 yielded the counter-intuitive finding that a vast majority of the general population reads inserts when using medicines. The finding merited scientific confirmation, as it was met with scepticism by the parties involved (see Chapter 2 of Part II).

Objective of the study
Our primary aim was to make stronger (corroborate and confirm) an ascertainment of the 1988 survey, i.e. a high level of readership of inserts in the general population. In addition, we wanted to measure the current penetration

of PPIs in the marketplace and monitor the public awareness of the ongoing change.

> ***Time frame:*** *January 1991*
> ***Design:*** *A confirmatory, descriptive survey*
> ***Participants:*** *A representative sample of 400 Belgian adults, stratified for Dutch and French speaking inhabitants*
> ***Method:*** *The method of quota sampling from the first survey was replicated in the same two Belgian cities (Ghent and Liège) and the surrounding country site. The investigators interviewed the respondents with a similar questionnaire, with some questions omitted and others added. Respondents were asked to show the packages of their current medication and the investigators determined whether the insert was a technical insert (TI) or a patient package insert (PPI). A difference of 10% or more in readership would be considered a relevant difference.*

Results

Data were collected from 403 respondents (200 Dutch speaking and 203 French-speaking), after ringing 775 doorbells (174 absent, 128 refusals, 55 outside the selection criteria and stratification quota, 15 interruptions during the interview). Fifty-two % were female, and the mean age was 42.7 years (SD 17.8: range 16-89), with a somewhat better representation of the elderly (60+), but again a slight overrepresentation of the higher educated. At the time of the interview, 35% of respondents was taking medicines, 22% had taken medicines during the last year, 43% had not been taken medicines for at least one year.

The vast majority of the respondents (95%) was familiar with the concept of a patient package insert and was able to give a definition or an enumeration of sections of the insert. In the following table, readership results of both the first and second surveys are compared.

Table 1: Level of readership of package inserts in two consecutive population surveys

DO YOU READ THE INSERT?	1988 (N=198)	1991 (N=203)
Yes, I do	89%	85%
No, but a relative does	7%	8%
No, neither does someone else	4%	7%

Only 16% knew of the existence of patient package insert at the time of the interview (in the previous study, 20% knew that patient package inserts were coming), and only 4% had stated to have read one.

At the end of the interview, the packages of the respondents currently taking medicines, were collected and the type of insert was determined. Thirty-nine % of the packages actually contained a patient package insert.

Discussion and conclusions

Resulting from bias, inherent to the method of quota sampling in door-to-door interviews, the characteristics of this sample differ slightly from the first survey population sample characteristics, viz. with regard to education level.

However, percentages of insert readership do not differ significantly between the two samples, which can be interpreted as a confirmation of the high readership, regardless of the type of insert.

The shift from TI to PPI was well under way in early 1991 (39% penetration), but had gone virtually unnoticed. The awareness of the PPI among 20% of the public in 1988 had certainly not risen in 1991, coinciding with diminished media attention to the subject in that period. People hardly knew what a patient package insert was, were not aware of having seen one, and did not recognise the PPIs in their medication boxes. One of the reasons was certainly that the nature of the change was predominantly linguistic, not typographical.

Further discussion in the context of this thesis

This study, presented as an abstract[181], illustrates the decline of the Belgian PPI implementation programme. Public attention to the subject was not sustained, because there was no public information campaign on the subject. The change was not visually obvious. However, one cannot conclude that the effect was nihil. A patient does not need to be conscious of change to undergo the impact of that change. However, it is possible that greater public awareness might have enhanced the impact of the change.

4.3.2 Two consecutive GP registration studies

note The full report of the joint analysis was part of the doctoral thesis by Van haecht,[1] and separate reports of the two studies were published.[182][183]

Motives for these studies

Belgian research on the impact of written medication information was carried out in the realm of the clinical setting by Chris Van haecht, who worked at the Heymans Institute during the PPI Evaluation Programme. He focused on the use of inserts by patients in a specific clinical setting, namely the treatment of hypertension in general practice. Two consecutive registration studies were set up, with identical design, and separated by 13 months, in a crucial phase of the shift from technical insert (TI) to patient package insert (PPI). The

emphasis shifted from describing to exploring relationships between reading the insert, the type of insert, and the occurrence of side-effects. Special attention was also given to the influence of the educational status of the patient.

Objective of the study
The descriptive aim was to determine the intensity with which patients read the insert of a medicine for a chronic asymptomatic disease (hypertension), and whether or not PPIs were read more carefully than TIs. The explanatory aim was to explore the link between reading the insert and reporting side-effects, and whether or not this link changed with the type of insert.

> ***Setting:*** *Antihypertensive patients in Flanders, Belgium, recruited by general practitioners, experienced volunteer participants in an epidemiologic network of sentinel practices, who engage in short term registration projects on varying topics (three to four projects per year).*
> ***Time frame:*** *First study in April 1989; second study in May 1990*
> ***Design:*** *Two episodes in a consecutive, cross-sectional, observational, clinical registration study*
> ***Participants:*** *a consecutive sample of patients, seen for a repeat prescription of antihypertensives during the registration period (one month). The estimated average of patients to be recruited was 20 in one month. One hundred GPs were invited to participate, in the hope that 25 would volunteer.*
> ***Method:*** *Physicians were asked to recruit antihypertensive patients in surgery and during house calls. Socio-demographic data, systolic and diastolic pressure, the date of first antihypertensive treatment and the list of antihypertensive medication currently used were recorded per patient. For each antihypertensive on the list, patients were asked whether they had read the insert (thoroughly or superficially) (recently or in the past). GPs also identified the type of insert for each antihypertensive, by requesting the insert from the current package and clipping it to the registration form. Finally, GPs recorded first spontaneous reports of general health problems (during the consultation) and then confronted patients with a checklist of 22 symptoms, described in popular medical terms (taken from published lists of side-effects of antihypertensives). Patients were asked whether they had experienced these symptoms (occasionally, often, daily) in the past month, and whether or not they thought there was a connection between the symptom and the use of antihypertensives (attribution). At the end, there was a short debriefing by the GP, to explain the*

purpose of the study and to correct possible misconceptions about side-effects.

Results

In episode 1, 28 GPs recruited 702 patients. In episode 2, 19 GPs recruited 407 patients (12 GPs participated twice, but there was very little overlap in patients). Characteristics of GPs and of patients were similar in both episodes, and similar to other samples of hypertensive patients in general practice. The percentage of higher educated patients was 9%, higher then in the first episode (p=.0.007). The average age in the first and second episode was respectively 64 and 65 years (SD 12) and the percentages of women were 67% and 70%; the percentages of lower educated patients were 74% and 67% (higher in women and in 65+ patients). Patients had been treated for hypertension on average for 9 years (SD 7). Sixty %, respectively 61%, were on monotherapy. The percentage of patients on beta-blockers and/or diuretics dropped from 63% to 55%, compensated by a rise in ACE-inhibitors and calcium antagonists from 20% to 30%. Penetration of the PPI had risen from 16% to 38%.

Intensity of readership was first assessed with the insert as *unit of analysis*.

Table 2: Intensity of readership of package inserts in two consecutive registration studies

WAS THE INSERT READ?	April 1989 (N=702)	May 1990 (N=407)
Never	33%	35%
Superficially in the past	31%	31%
Thoroughly in the past	36%	34%

There was no time trend in these data, neither did the intensity of readership differ significantly according to the type of insert, present in the packages (TI or PPI).

The data on intensity of readership was then regrouped to permit an analysis at the level of the patient. Patients were classified as “never readers”, “superficial readers” (when none of their inserts were read thoroughly, but at least one superficially, recently or in the past), or “thorough readers” (when at least one of their inserts were read thoroughly, recently or in the past).

Among the patients younger than 65 years of age (in the first episode), 29% never read the insert, versus 42% in the group of 65+; while 40% of the younger patients read the insert thoroughly versus 29% in the older group, a statistically significant difference. Results were again nearly identical in the second episode.

An even stronger association was found with educational level. In the first episode 1, 41% of the patients with lower educational level never read the insert and 7% read it thoroughly. Among patients with a higher educational

level 7% never read the insert and 69% read the insert thoroughly. The results were nearly identical in the second episode. It is well known that the elderly are less well educated for historical reasons. Logistic regression analysis revealed that the age effect was merely based on confounding by educational level, which was by far the strongest determinant of readership. There was no association between readership of the insert, on the one hand, and sex or type of insert, on the other hand.

There was a small, but significant time trend in the tendency of patients to report health problems to the physician, either spontaneously (after a general probing question), or systematically (by checking a list of health problems).

Table 3: Reporting of health problems by hypertensive patients. Comparison of two episodes

LABEL	April 1989 (N=702)	May 1990 (N=407)	Chi^2 test
% of patients reporting spontaneously (without prompting)	30%	36%	p=.02
Total % patients reporting health problems (after checking a list)	68%	75%	p=.04
% of patients attributing health problems to medication	24%	30%	p=.04

Reporting health problems was significantly associated with the demographical characteristic of "educational level" (not with sex and age). The higher the educational level, the more patients reported health problems, and attributed them to the medication. The overall percentages in the second episode were higher (see above), but the associations with educational level were comparable.

In the first episode there was no association between reading an insert and reporting and attributing health problems. In the second episode, there was a tendency toward a higher frequency of reporting spontaneously and attribution in the group of thorough readers, but this failed to reach significance.

A final subanalysis was made among the patients who read at least one insert superficially or thoroughly (N=449 in episode 1 and N=271 in episode 2). Here the association was investigated between the type of insert and reporting and attributing health problems.

In the first episode, spontaneous reporting and attribution was higher when a PPI was read. This association was not significant in the higher education stratum.

In the second episode, the overall frequency of reporting and attribution was higher and the penetration of the PPI had climbed from 18 to 36%. In this episode, the association with type of insert was significant for all three types of reporting. This association remained after stratifying for educational level, and

was prominent in the lower educated stratum. A multiple regression analysis confirmed that the type of insert and the educational level of the patient were two independent predictors.

In comparing the two episodes, it might be observed that the time trend of higher reporting was restricted to the group of PPI readers. In the first episode, the percentage of patients reporting was 72% versus 83% in the second episode, and for attribution it was 35% versus 41% respectively (both differences statistically significant).

Discussion and conclusions

The samples in the two episodes were comparable for demographic characteristics, except for a slightly higher number of higher educated patients in the second episode. As the two episodes were twelve months apart, the time frame had of course changed.

With these two consecutive studies, we showed the general trend of increasing penetration of patient package inserts (confirmed from other observational studies) in this particular clinical setting, which can be considered as an argument of face validity for these studies.

When turning to clinical practice, to experienced patients, and older patients, the picture of readership is different from the results in the population study presented in study 1, where 9 in 10 predominantly healthy and better educated adults stated to read the insert. There are still two thirds who read the insert one way or another, but the figures had decreased. Forty-one % with lower education state that they never read inserts.

Again we observed no difference in readership between the TI and PPI, neither in episode 1, neither in episode 2, despite the ongoing shift. Our interpretation was that the shift from TI to PPI is not consciously noticed by the patients, because of the lack of visual clues in design change. Another explanation might be the diminished media attention to this subject.

This study clearly indicates that educational level is a demographic characteristic of paramount importance. Higher educated patients read inserts more frequently and more thoroughly and report more health problems. The results do not warrant conclusions on whether higher educated patients actually experience more health problems.

The results on the frequency of health problems reporting in this study must be considered carefully. The health problems reported here are not related to hypertension, neither necessarily related to the antihypertensive drugs. These problems also tend to occur frequently in the general population. We used an unusual method of recording the reporting of health problems, first with a general prompt and then by repeating the inquiry with a checklist (this method is seldom used in clinical trials, because they may lead to misinterpretation of safety assessments of important new drugs). Hence, we found percentages of 68% and 65% of the patients reporting health problems. This is in contrast with the normally reported frequency of mild side-effects with beta-blockers of 10%.

As we were studying the impact of written drug information, we focused on the subjective perception of patients, which might be affected by suggestion (experiencing the side-effects mentioned in the insert just by reading them) or by incorrect attribution (linking to the drug bodily symptoms which are not related to the intake to the drug). This observational study is not able to distinguish between the different underlying mechanisms of health problem reporting (see further in Part III).

There were no obvious differences in reporting between patients who read the insert and those who did not. Interpretating this finding is difficult. Possible explanations are averaging to zero of opposing effects in TI and PPI readers or lack of power in the study (relatively few PPI readers, especially in the first episode).

Our interest in this study was in the relative difference between frequencies of subjectively perceived health problems between the PPI and the TI groups, not in the absolute frequencies. To determine whether a reported health problem is in fact an adverse drug reaction, a complex causality assessment is needed (which was not performed in this study).

We did pick up effects of the type of PPI (which can only be mediated through reading). We found effects both on the total reported (only in the second episode) and on attribution.

We did find higher attribution in the second episode. It could be caused by higher penetration, or by different education levels among patients, chance variation, or another time-related variable outside the scope of the study.

As often in science, this study provided a few answers, but raised more new questions, to be addressed with new and more sophisticated interventional studies.

In conclusion, the percentage of patients who read the insert is extensive, even in a group of elderly, chronic, and experienced users. The advent of the PPI has not changed this, either upwards of downwards. The higher educated patients tend to read inserts more often, and more thoroughly. Reading the PPI is associated with higher reporting and *attribution*, also in the group of the lower educated (the biggest group). This was found in both episodes, but overall reporting was higher in the second episode, coinciding with a higher implementation of the PPI. We formulated the hypothesis that the introduction of the PPI has an impact on the reporting of health problems (and hence potential side-effects). Experimental research is needed to test that hypothesis.

Further discussion in the context of this thesis

This study was pivotal in the evolution of the research in this project towards interventional studies. The results confirmed once again the high level of readership of inserts (regardless of their style), this time in a specific clinical setting. For the first time we discovered something that may have been an overall effect of the generalised introduction of the PPIs in Belgium. We observed a puzzling association between readability of the insert and higher

levels of communication between physicians and patients about adverse events (not necessarily adverse reactions). Finally, there was a hint that the educational level of the patient is an important variable that needs to be taken into account in further studies.

4.4 Descriptive studies in focused groups of patients

In addition to the study of the elderly in nursing homes (see Chapter 3), several other studies were performed to explore the way the elderly deal with medicines and information about medicines. In the past decade, medication utilisation by the elderly has been the subject of many studies of growing sophistication.[184] Nevertheless, we will briefly present three studies here, performed in connection with the Belgian PPI Evaluation programme, because they focus on the informational aspects of drug use by specific subgroups among the elderly. A fourth study will deal with healthy adolescents. These studies were performed by Master students, in collaboration with our department.[185][186][187][188] In fact, some of these data were collected well after the closing of the formal evaluation programme, but as their subject is little affected by the time frame, we want to present them, as their results offer additional perspectives. An overview of the studies focusing on the aspect of polypharmacy among the elderly has been published in Dutch.[189]

4.4.1 Socially active elderly, living at home

note This work was carried out in the context of a Master thesis by Marleen Bekaert and Alain Van Den Dungen.[186]

Objective of the study
Our primary aim in conducting this study was to explore the information channels and knowledge about drugs among the elderly, living at home, but mobile, and regularly leaving home to engage in social contacts.

> ***Setting:*** *Community centres for the elderly, run by city councils, (providing meals, coffee and refreshments, sports facilities, body care, educational training, entertainment, creative expression and meeting facilities), in two Dutch speaking cities (Ghent and Bruges) in Belgium.*
> ***Time frame:*** *February to April 1993.*
> ***Design:*** *An exploratory, descriptive cross-sectional survey by interview*

Participants: *Volunteers were recruited, in the afternoon, among the visitors of 60 years and older to the 17 centres in the two cities.*
Method: *Two trained interviewers asked 34 closed questions in a 15 minute interview. Respondents were asked whether they were currently taking medicines and if no, to name these medicines. In case the name was not know, the function or the colour and the shape of the individual medicines was asked. Knowledge of dosage regimen and side-effects was assessed. Respondents were recruited till a quota sample of 400 respondents was reached.*

Results
Interviews were taken from 400 older patients (4 refusals). The mean age was 72.3 years old (SD 6.7y, range 60-91 y). There were 49% men (38% married, 9% widowers, 2% single men) and 51% women (24% widows, 22% married, 5% single women). The percentage of respondents with a schooling age of more then 14 years was 7% among the 80+year old, 19% among the 75-79, 27% among the 70-74, 31% among the 65-69, and 31% among the 60-64 year old (the group of elderly who were 13 to 17 year old at the beginning of World War II in 1940). Women were less educated (21% with a school-leaving age higher than 14 years, versus 30% in men). One third lived alone. Of the other two thirds, 4% had a partner in need of constant care, 5% lived with their children or had their children still living with them, 1% lived with a brother or sister. One third had no outside help (or did not need it), one third only had cleaning help, and one third had various combinations of nursing help, help from family or neighbours, or cleaning help. Contact with the centre was on a daily basis for 45%, at least once a week for 50% and occasional for 5%.

Of the respondents, 83% stated that they were currently on medication (10% on 5 or more medications). Men listed a mean of 1.7 medications, women 2.6. Most illnesses were chronic (83%), most medicines were registered, allopathic medicines and given on prescription (96%). The majority of the medication was once taken daily (60%), 17% twice daily, 8% three times daily, 5% two to three times per week, 4% sporadically, and 6% when needed. The 860 medications listed by the elderly were communicated by name, colour, shape or function. Twenty-three % was not able to name any of their medications. Only 10% of the elderly were able to list at least one possible side-effect of at least one of their medications. Among the respondents currently taking medicines (N=333), 87% fetched the medication themselves at the pharmacy, 12% had someone else to fetch the medication, and 2% had a pharmacist who delivered at home. Eighty-four % were fully autonomous with regard to medication management (keeping and ordering stock, preparing for intake), 5% left it to the partner and 1% to others (children, neighbours, nurse). A medication chart was used by 3%, 10% used a day box and 2% a week box.

Twenty-two % had been hospitalised in the past year (3% twice and 1% three times). Three % were on a waiting list for the nursing home.

Respondents were asked whether their physician or pharmacists gave them medication information on what the medicine was for, how to take the medicine and what the side-effects were. Respondents mentioned that their physician mainly gave procedural information (how to take) (28% a little, 69% extensively), and explanation about the purpose of the drug (28% a little, 64% extensively). The perception of information activities by pharmacists were limited to procedural information (36% a little, 16% extensively) and even less about the function of the drug (15% a little and 13% extensively). Seventy-five % stated that they have not received any information about the risk of medications from either the pharmacist or the physician.

The package insert of their medications was read by 69% of the respondents, 2% had someone else read the insert to them, and 29% did not read the insert, neither was anyone asked to read the insert. Among the readers of the insert (N=282), the motive to read the TI was to be able to comply to therapy (89%), to be reassured (72%), to know more about the medicine (73%) or to decide whether or not to take the medicine (45%). The information contained in the insert was perceived by readers as useful (97%) and complete (89%); 85% found it reassuring that a TI could always be consulted. Dissatisfaction was reported as difficulties understanding (70%), reading (69%) and remembering (39%). The insert was considered graphically dull by 51%. Induction of fear to take the medicine by reading the insert was reported by 15%, and 11% thought that confidence in the physician might be reduced by reading the TI.

Important information sources are the prescribing physician (97%), personal experience (93%), the pharmacist (59%), the insert (59%), the media (21%). Family, friends and neighbours were hardly mentioned (1%).

The respondents were satisfied with their medication knowledge: 84% stated they know enough about their medicines (ranging from 69% in the 60-64 years group to 100% in the 85+ group). Thirty-one % would like to know more about their medication (9 in 10 through a more readable insert, 5 in 10 through the physician, 5 in 10 through the pharmacist and 2 in 10 through an educational meeting).

Discussion and conclusion

This was a study of information and knowledge about medication, not an attempt to measure drug utilisation objectively. Patient self-reporting may lead to underestimation.

Most of the socially active elderly take a substantial number of medications and know little about their risks, but do not seem to mind. The prescribing physician, and, to a lesser extent, the pharmacist, are considered to be important information sources. However, one cannot rely on these channels with regard to the transfer of risk information. The elderly consider the

package insert as an import source of information. However, their interest in medication seems to fade with growing age and disability, and to be mainly limited to procedural aspects. This situation cannot be solved solely by providing better inserts. If a more profound knowledge of the medication is considered desirable (from a general point of view or in specific cases of disease management) personalised and tailored educational interventions will be needed. Such interventions can only benefit from cooperation with preferred information sources, such as the prescribing physician and the pharmacist.

4.4.2 Frail elderly living at home

note This work was carried out in the context of a Master thesis by Anniek De Roep.[186]

Motives for this study
We had previously looked at two extremes in geriatric health care setting: elderly in nursing homes and socially active elderly living at home. Somewhere in between are elderly who still are at home, but only rarely leave their residence, and who require a lot of attention and health care resources. We wanted to find out whether the information needs of these patients differ.

Objective of the study
Our primary aim in conducting this study was to explore the information channels and knowledge about drugs among frail elderly living at home.

> ***Setting:*** *A community care organisation (Familiezorg Oost-Vlaanderen, of Christian denomination, but pluralistic) for intensive family and elderly assistance in the Dutch-speaking region of Belgium.*
> ***Time frame:*** *January to March 1994.*
> ***Design:*** *An exploratory, descriptive cross-sectional survey by interview*
> ***Participants:*** *One hundred patients in one community (Lokeren, 17,000 inhabitants) of one community care organisation were invited to participate. Inclusion criteria were age (65+) and being under the care of the organisation.*
> ***Method:*** *Fifteen professional family helpers were trained to interview 4 to 8 patients under their care in the region, with a question list similar to the one used in the study among socially active patients. In addition, permission was asked to collect information on monthly revenue (available from the administrative dossier in the community care organisation) and private medication expenses (available from the pharmacist).*

Results

Ninety-two patients were recruited (5 could not be interviewed because of hospitalization, 3 refused to participate). The mean age was 78 years (SD 7y, range 66-93 y). Seventy % were women (51% widows, 14% married, 5% single women) and 30% men (half of them married and half widowers). The percentage of respondents with a schooling age of more then 14 was 15%. Sixty % lived alone, 28% lived with their partner, 7% lived with their children or had their children still living with them, 1 had a spouse in the nursing home).

The care delivered by the community care organisation was the only family help (cooking and help with shopping) in 75%, only cleaning help in 15%, and both services in 5%. Thirty-eight % had, in addition to these services, a nurse, paying home visits.

The monthly income was less than 500 EUR (recalculated in current prices from Belgian francs in 1993) in 8%, between 501 and 1000 EUR in 64%, and more then 1000 EUR in 28%. There was a strong relation between the level of income and the educational level.

Of the respondents, 90% stated that they were currently on medication (43% on 5 or more medications), with a mean of 4.4 different medications per patient. Almost all medicines were chronic, on prescription (96%) and allopathic.

Monthly private spending on medication (in surplus of reimbursement) was 30 EUR or less in 49%, between 31 and 60 EUR in 24%, between 61 and 90 EUR in 20% and more then 90 EUR in 7%. The median number of drugs per patient was 4 in the income group below 1000 EUR/month and 6 in the group above 1000 EUR/month (p=0.02). Medication consumption was lower in the lower educated group, but this was confounded by income.

Among the respondents currently taking medicines (N=83), 62% had someone else to fetch the medication, 36% fetched the medication at the pharmacy themselves, and 2% had a pharmacist who delivered to their home. Seventy-four % was fully autonomous with regard to medication management (keeping and ordering stock, preparing for intake), 14% left it to the partner, 9% to the children, 2% to the nurse and 1% to the family helper. A medication chart was used by 2%, 3% used a day box and 5% a week box.

Thirty-three % had been hospitalised in the past year (21% twice). Eight % were on a waiting list for the nursing home. The remaining 92% firmly denied being on a waiting list.

Respondents mentioned that their physician gave procedural information (how to take medicines) (76% a little, 21% extensively) and explanation about the purpose of the drug (61% a little, 19% extensively). The perception of information activities by the pharmacists was limited; it mainly contained procedural information (58% a little, 11% extensively) and very little about the function of the drug (33% a little and 5% extensively). Seventy-three % state that they have not received any information about the risk of medications from either the pharmacist or the physician.

Respondents were satisfied with their medication knowledge: 86% stated that they knew enough about their medicines.

Discussion and conclusion

With regard to drug utilization, the frail elderly living at home more closely resemble the elderly in the nursing homes than the socially active elderly living at home. Nevertheless, few are anticipating transfer to the nursing home.

Two-thirds no longer had direct contact with the pharmacist, and, hence, were alienated from an important information source. Written drug information, often read by someone else, may play an important backup role in this situation. The expressed need for more medication information is rather limited.

There is a complex relation in polymedicated frail elderly between income, educational level, private drug spending, and medication utilization. Some elderly with a low income and a high drug bill apparently have to make tough choices (alone) between buying food and other essentials or buying medicines, probably resulting sometimes in non-compliance with crucial medication.

4.4.3 Elderly hospitalised in subacute geriatric wards

note This work was carried out in the context of a Master thesis by Bart Coingiez.[187]

Objective of the study

We wanted to explore the transfer of information about medication between the former residence and the hospital among elderly in subacute geriatric wards, assess the shifts in medication lists during hospitalisation, and assess the efforts to inform the patient about the current medication list during the hospital stay and at discharge.

> ***Setting:*** *Subacute geriatric wards in the hospitals of the city of Ghent, Belgium (a catchment area of 250.000 persons).*
> ***Time frame:*** *January 16 to February 16, 1995.*
> ***Design:*** *An exploratory, descriptive cross-sectional survey by chart review.*
> ***Participants:*** *All discharges in the participating wards during the index period.*
> ***Method:*** *One trained nurse reviewed the medical and nursing charts of discharged elderly, transferring data on medication and medication information to a portable computer. Entry of medication lists was facilitated by brand index, ensuring quick and accurate recognition of active ingredients, galenic form and strength and automatic conversion to the ATC/DDD drug*

classification. Patients were not interviewed directly and their cognitive status was not assessed.

Results

Six of the seven geriatric wards in Ghent participated. From the 202 available subacute geriatric beds, 224 elderly were discharged during the index period. The mean age was 82.1 years (SD 7.8y, range 59-101y), with 35% men.

Half of the patients were transferred from acute hospital wards, 43% from home and 7% arrived from a nursing home. The mean length of stay was 27.0 days (SD 25.7), with 72% of the patients staying less than 30 days (the limit of length of stay for full budgeting). Of the discharged elderly, 42% returned home, 17% were newly transferred to a nursing home, 16% died, 12% returned to the nursing home, 7% were hospitalised to acute wards and the remaining 6% were transferred to revalidation centres.

The mean number of different oral medications per patient was 5.3 at discharge (no medication 3%; 5 or more medications 56%).

In all patients admitted from nursing homes, it was possible to reconstitute from the medical or nursing charts the medication list prior to admission, either from a transcript of the medication list in the nursing home chart, or from a referral letter from the nursing home general practitioner (present in 94% and containing explicit information on medication in 75% of the cases). In patients admitted directly from home, information about medication prior to admission was present in 89% of the charts, either from questioning the patients or their next of kin, or from a general practitioners' referral letter (present in the ward chart in 81% and containing medication information in 64% of the cases). In patients transferred from other acute hospital wards, information about the medication list prior to admission to the acute ward was present in only 66% of the cases, with the GP referral letter absent or lost in 73% of the cases.

Among patients where it was possible to reconstitute the medication list prior to hospital admission, the mean number of different oral medications was 4.8 (no medication 8%, 5 or more medications 48%).

All discharged patients received a copy of the discharge medication list or a preliminary referral letter to the general practitioner, including discharge medication information. Patients received a limited supply (for a few days) of the discharge medication, without patient package inserts. We did not find evidence in the ward charts of formal discharge training for new chronic medication or for continuation of new (sub)acute medication, nor evidence of explanations given for discontinuation of former medication.

For some drug classes there was no difference before and after hospitalisation in the percentage of patients taking medicines pertaining to this class. This was the case for cardiovascular drugs in general (C) (58% post and 57% prior), for anxiolytics, hypnotics and sedatives (N05B+N05C)(43% prior and post), for digitalis (C01A) (19% prior and 20% post) and for

antipsychotics (N05A) (16% prior and post). For laxatives (A06), the percentage rose from 18% before admission to 29% at discharge. For drugs for peripheral vascular disease (C04A), the percentage dropped from 19% prior to admission to 14% at discharge. Antibiotics (J01) were given to 26% of the patients, mostly initiated during admission, to be continued after discharge in almost half of them.

Discussion and conclusion
The shift towards polypharmacy observed here during hospital admission may be caused by acute new illness or exacerbation of chronic illness, which triggered hospitalization. Opportunities for reduction of inappropriate therapy seem to be missed during hospitalisation (except perhaps for peripheral vasodilators). Use of laxatives rises, maybe because of immobilisation. When patients are transferred from other acute hospital wards, communication about prior medication between the treating general practitioner and the geriatrician does not seem optimal. Despite changes to the medication list, which are sometimes substantial, little information is given to the hospitalised patient at discharge, and the rescue supply at discharge is not accompanied with written drug information.

4.4.4 Healthy adolescents

note This work was carried out in the context of a Master thesis by Katrien Santy.[188]

Objective of the study
We wanted to explore occasional medication taking behaviour and the medication information behaviour of healthy adolescents, in the third grade of secondary education (normally 17-18 years of age).

> ***Setting:*** *Adolescents of the 2 last years (third grade) of secondary education in schools in West-Flanders, Belgium.*
> ***Timeframe:*** *Winter 2001-2002.*
> ***Design:*** *An exploratory, descriptive cross-sectional survey by self administered questionnaire.*
> ***Participants:*** *A sample of 616 adolescents from 7 schools, stratified for age, sex, type of school (general, technical, crafts-oriented) and type of school network (community or Catholic).*
> ***Method:*** *A questionnaire was developed based on "Health behaviour in School-Aged Children", an instrument used for international and longitudinal research.[190] Questionnaires were distributed during class (after approval of school management), with an informed consent document, to be signed by at least one parent, if the respondent was younger than 18 years old. The*

respondent was asked to fill in the questionnaire at home, and to return it, after a few days, to the class teacher in a sealed envelope. Entry of medication lists was facilitated by brand index, ensuring quick and accurate recognition of active ingredients, galenic form and strength and automatic conversion to the ATC/ DDD drug classification.

Results

We received 460 usable questionnaires, duly signed by at least one parent (a response rate of 75.7%), without significant differences between the study population and the respondents for the characteristics of stratification.

Twenty-two of the 460 respondents (4.8%) stated that they suffered from a chronic disease or serious health problem, and 3.9% reported taking medicines for this illness. Results are further given for the group of 438 "healthy" adolescents in the last two years of secondary school. Only 15.3% were older than 18 years. Male students represented 54.1%. Only 7.4% valued their health status as poor or very poor. Daily smokers represented 22%, occasional smokers 7%. More girls reported health complaints perceived almost every month to almost daily (as opposed to seldom or never).

Medication for headache had been taken at least once in the past month by 44%, the common cold 27%, abdominal pain 15%, nervousness 3%, sleep disorders 2%, and weight loss 1%. The percentages were somewhat higher among females, but only substantially (more than 20% difference) for headaches. Use of vitamins in the last month was reported by 29% and use of homeopathic medicines by 13%. The step towards intake of medication is taken within a few hours for headache and abdominal pain, within a day or two for cough and common cold, and only after one week for nervousness or sleep disturbances. Anticipating use of medicines is reported by 14%, and use without complaints (except for general unwellness) by 8%, mostly antipyretics, and to a lesser extent vitamins or homeopathic medicines. There was no question concerning the use of the contraceptive pill among girls. Of the respondents 46% felt no need to get additional information about the medication used, 30% turned to the patient package insert, 15% to the physician, 11% to the pharmacist, less than one percent to books or Internet. Only 3% of those students who turned to the insert stated that they did not really understand the insert.

Discussion and conclusion

The use of medication, and especially problematic use, might be underreported by the obligation to have the questionnaire signed by at least one parent. However, adolescents seem to be confronted with serious health problems relatively rarely. Their use of legal medication is generally not problematic. Over-the-counter (OTC) medications for minor complaints are occasssionally taken, often on their own initiative, and without much perceived need for

more drug information. Although the patient package insert is the most important information source in this age group, with little complaints about comprehensibility among the readers, its role is limited.

4.5 Studies on medication distribution in health institutions

Research into drug information is intricately linked with the study of the distribution process of medications, especially in institutional care. Again with the help of two Master students,[191][192] we were able to explore the setting of the nursing homes and the setting of hospital care.

4.5.1 Medication distribution in the nursing homes

note This work was carried out in the context of a Master thesis by Jean-Marie Clarebout.[191]

Objective of the study
We wanted to explore medication distribution practices for oral medication in Flemish nursing homes, Belgium.

> ***Setting:*** *Nursing homes in West-Flanders, Belgium, where 5% of 65+ inhabitants reside in nursing homes, mostly close to the former residence.*
> ***Time frame:*** *Winter 1994-1995.*
> ***Design:*** *An exploratory, descriptive study by direct observation and assisted questionnaire.*
> ***Participants:*** *A heterogeneous sample of 7 nursing homes.*
> ***Method:*** *Consent to participate in the study was asked from nursing homes management. A trained geriatric nurse visited the nursing home for direct observation with a structured observation list and questioned the head nurse responsible for medication management.*

Results
Two of the selected nursing homes refused to participate and were replaced by two other homes.

The size of the nursing homes ranged from 31 to 116 residents (mean 85). Small nursing homes had all their residents in one medication distribution unit. Larger homes were split into two or more distribution units. The smallest

unit (20 residents) was run by 1 nurse, the largest unit (93 residents) was run by 6 nurses.

Responsibility for the organisation of the medication distribution was assumed by one head nurse (or specially assigned medication nurse) in all homes, but daily distribution of medication was shared by several nurses and sometimes also with non-paramedical caregivers (evening, night, weekend, replacement of absence). Residents were supervised by their former general practitioners, hence nurses had to deal with 4 to 12 different physicians. Formal rules about nurse attendance during the physician's visit only existed in 3 homes.

In 4 homes, medications were delivered by several local community pharmacists on alternating role.

Medication is kept in a pharmacy cupboard at the nursing post in two parts: the collection of boxes, with packs belonging to one individual, on the one hand, and a non-individualised backup collection for occasional first aid or emergency medication, on the other hand. Access to medication is not strictly reserved for nurses in all homes and the medication cupboard is not always locked.

In all homes, one nurse per distribution unit (mostly the head nurse) is authorised to write an individual medication scheme for each resident, to be updated every month, based on oral or written instructions from the physician. This individual medication scheme is kept in the nursing chart. In some nursing homes, the information is copied manually several times (to make pharmacy orders or to give instructions).

Preparation for actual dispensing covered one week in three homes and one day in the other homes. This preparation was always performed by a nurse, but not always the head nurse or a specially designated nurse. For weekly preparation, week boxes (with 4 divisions per day) of 7 trays with cups (one tray for each day) were used. For daily preparation, a tray with cups was used in most cases. Pills were removed from their blisters during this preparation phase.

Actual dispensing was in four rounds (08.00 a.m.- 11.00 a.m. - 5.00 p.m. - 08.00 p.m.). The evening dispensing was almost exclusively for sleeping pills. Medication is either given personally to the patient, or set next to the patient with visual control of intake. Written information is not dispensed to the patients. Very few patients preserve any autonomy over their medication.

No formal systems for the control or reporting of medication errors were in place. Communication between physicians and nurses about side-effects and special intake procedures was limited. A (mostly outdated) drug compendium was kept in the unit, and package inserts were occasionally read but not collected systematically by the nurses.

Discussion and conclusion

In the 1995 Flemish nursing home, nurses were responsible for the correct distribution of medication to a relatively small and stable population, on

relatively stable but complex medication schedules. Their training for this task was limited, communication with the treating physicians not optimal, and formal systems to reduce medication errors were not available. Intervals between dispensing rounds are pharmacologically inadequate for medications to be given three times a day. The patient package insert is still present in the distribution process, but only available for the nurses, who do not use them systematically.

4.5.2 Medication distribution in hospitals

note This work was carried out in the context of a Master thesis by Kathleen De Sutter, and published (in Dutch).[192]

Objective of the study
We wanted to explore medication distribution systems and medication error management systems in Flemish hospitals

> ***Setting:*** *Secondary and tertiary care in Flanders, Belgium.*
> ***Timeframe:*** *February – March 1997.*
> ***Design:*** *An exploratory, descriptive study by interview with hospital pharmacists and head nurses*
> ***Participants:*** *We selected a convenience sample of 6 hospitals (2 tertiary university hospitals, 2 community and 2 private secondary hospitals).*
> ***Method:*** *A two-hour interview was carried out with the hospital pharmacist and a one-hour interview with two head nurses (one from a surgical department, one from a medical department). Direct observations were made of the medication distribution documents and depots in the departments of the nurses interviewed.*

Results
Five hospitals agreed to participate. One refused and was replaced by another volunteering hospital within the same stratum.

All hospitals worked with a distribution system from the central pharmacy to departmental depots. Hence, none of the hospitals worked with the internationally proposed standard of direct distribution from the central pharmacy of individual unit doses to the patient.

In three hospitals these depots were predominantly collections of individualised boxes with a small supply of maximum 4 to 5 days (and in addition a limited depot of non-individualised rescue medication). In the 3 other hospitals, there were predominantly general non-individualised depots (with individualised boxes for some special medication only).

In 6 of the 7 hospitals, prescription orders were processed manually to the nurse supervising the departmental depot and to the central pharmacy, mainly for billing purposes and a posteriori renewal of supplies.

Nurses kept a medication list in the nursing chart, often to be changed on the basis of oral orders from the physicians, and to be transcribed manually (sometimes several times) for actual dispensing orders on the ward.

Actual dispensing to patients was prepared on a daily basis (with removal of identifying blisters), and given to patients in individual doses, often by other nurses on different shifts.

In none of the six hospitals did any formal quality control programme for the prevention of dispensing errors exist.

Medication arrived at the ward from the central pharmacy in bulk, blisters or in units, with no written patient package insert available.

Discussion and conclusion

The sample in this study is too small to make generalisations. In the past years, new quality regulations have been issued and information technology has been applied to the medication distribution process. However, unit dose distribution (distribution of doses for individual patients per intake, directly from the central pharmacy to the patient on the ward) has not been introduced widely.

From findings in international literature, estimates of the prevalence of medication errors and their clinical outcomes have been made. Non-optimal distribution techniques could be associated with medication errors leading to an excess length of stay of 4.6 days in 4.35% of all hospital admissions.[193][194][195][196][197] It is estimated that this prevalence could be reduced by 2/3 by introducing unit dose distribution systems. An estimate of mortality of "drug misadventures" (the sum of mortality by adverse reactions to correctly taken medicines + mortality by medication errors) ranged from 0.09 to 0.24 per 100 admissions.[198]

In the hospital setting, groups of nurses are responsible for dispensing incisive medication to rapidly changing patient populations, with unstable medication regimens, in a complex and stressful environment, while using suboptimal distribution techniques. Medication information support for nurses and patients (e.g. by the provision of patient package inserts) is virtually non-existent.

4.6 The quality of patient package inserts in Belgium revisited

note This work was carried out in the context of a Master thesis by Pieter Paul Clompen.[199]

Objective of this study
To conclude the series of descriptive studies, we wanted to perform a small assessment of the quality of Belgian patient package inserts in 2000, 16 years after Belgian legislation was first published and 8 years after the European legislation.

> ***Setting:*** *Belgium, the European country that pioneered the legal enforcement of readability in drug information.*
> ***Time frame:*** *2000*
> ***Design:*** *A descriptive study by linguistic computer analysis and direct observation.*
> ***Material:*** *A quota sample of 18 inserts (in Dutch) from 5 therapeutic classes.*
> ***Method:*** *The inserts were evaluated as to readability by computer analysis and by direct observation for legibility, design, comprehensiveness and consistency.*

Results
There was considerable variability in length. Half of the inserts (N=80) were between 500 and 699 words long (one third shorter: between 300 and 499; one quarter longer: between 700 and 1299 words per insert). The number of sentences was 40 and 49 in half of the inserts (in one third shorter between 20 to 39; in one quarter longer between 50 and 79 sentences per insert).

In half of the inserts the average sentence was 14 to 15 words long (12 to 13 words in one third; 16 to 19 words in one quarter). One half of inserts had less than 2 punctuation marks per sentence and the other half 2 or more.

The proportion of medical jargon words of total words was less then 3% in one half of the inserts and 3% or more (up to 5%) in the other half. Only two inserts had less than 1% medical jargon words.

Six inserts (one third) failed the readability test (described above) and 12 (two thirds) succeeded.

Legibility was assessed by measuring the height of the letters (the *x-height*) and the space between lines (*line space*). Only 8 of the 18 inserts had sufficient x-height (minimum 1.4 mm, according to the European Guideline on the Readability of the label and the package leaflet of medicinal products for human use[95] and none had sufficient line space (minimum 3 mm). Line space was even less than 2.5 mm in 8 inserts.

Design was rather dull in most inserts. Colour was used in only four inserts (with contrast problems in one). There was disturbing use of capital letters in one insert. Eight inserts did not use structured lists for enumerations (e.g. of side- effects). In only one insert, punctuation for structured lists was used as recommended by the guideline (introduction by colon, line end by semicolon and group end by full stop). Inserts for products with the same active ingredients had different lists of side-effects and indications.

Discussion and conclusion

During the nineties, there was little improvement in the quality of patient package inserts. Many companies continue to produce unattractive documents, barely complying with the minimum requirements. Other companies make an effort to produce an acceptable insert within the boundaries of regulatory constraints. None of the inserts testified to innovative, creative design. Regulatory authorities failed to enforce legislation, to ensure quality of communication and consistency in information across different brands of the same medicine.

Part III

Intervention studies on the impact of written drug information

Tu vivras de projets qui ne feront qu'attendre.
Jacques Brel

In Part II we have focused on the evaluation of a particular drug information programme, namely the introduction of patient package inserts (PPIs) in Belgium between 1988 and 1992. We conducted a number of descriptive studies in different settings and with different constituencies. We tried to monitor a few changes in patient behaviour at the level of the general (Belgian) population by means of uncontrolled pre-post studies.

In Part III we will focus on interventional studies, aimed to generate a better understanding of the impact of written drug information.

In Chapter 1 of Part III, we will start with a conceptual reflection on the relationship between written drug information and patient compliance, triggered by recent improvement in the measurement of patient compliance with electronic monitoring, a new and much more precise method.

In Chapter 2, we will describe the results of a comparative randomised clinical trial of atenolol versus lisinopril in the treatment of essential hypertension, with a nested design for additional testing of two different information strategies (PPI versus no information). This will provide a preliminary exploration of how the impact of drug information on patient compliance could be examined.

In Chapter 3, the results of an experimental psychological study with human volunteers is described, exploring the effect of the addition to the PPI of a small section on the benefits of the medicine.

In Chapter 4, we report on an additional randomised clinical study by Van haecht on the impact of a patient package insert (PPI) versus a technical insert (TI) on the risk perception of patients using Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for small accidents with joints (wrist, shoulder, ankle or knee). It is presented extensively here, because it was a key study in our research programme. In addition, we will briefly report on the design of a placebo controlled randomised trial, which was not completed. This trial compared the impact of atenolol versus placebo in essential hypertension, on patient compliance and reported side-effects, with a secondary nested randomization of PPI versus TI. The findings of the experimental studies presented in Part III will be discussed in Part IV.

Chapter 1
Written drug information and patient compliance

Originally published as: Vander Stichele RH. Promises of a measurement breakthrough. In: Metry JM, Meyer UA (Eds). Drug Regimen Compliance. Issues in clinical trials and patient management. New York: John Wiley and Sons, 1999. (see facsimile 4 in Annex 1)

Nothing is so firmly believed as that which we least know.
Michel de Montaigne

1.1 Motives for this review

In 1996, I was invited by the editors of the book mentioned above to write a chapter in the field of drug information and report on my experiences with electronic monitoring of patient compliance. During the 1988 conference on patient package insert in Ghent, Belgium, I had the privilege to meet Prof. John Urquhart, invited to the conference to speak about models of risk communication. Prof. Urquhart introduced me to the developments on the scene of compliance measurement. He showed me a new device to measure daily drug intake by electronic monitoring, the Medication Event Monitoring System (MEMS). After seeing the first results of observations of real life patient behaviour, the importance of this new instrument was clear to me. I had been following the compliance literature for years and had taught on the subject to medical students and general practitioners. I grasped the importance of this development for the issue of written drug information and embarked on writing a review of the methods to measure compliance in clinical trials.[200]

In 1990, I had the opportunity to participate in a trial where the MEMS technology was used (see chapter 2 of Part III), and later I was involved in the design and analysis of the results of a number of other trials with electronic monitoring.

Below is an overview of relevant concepts.

1.2 Relevant concepts developed in this review

We will only present a short description of the concepts developed in this qualitative review.

1.2.1 Stagnation in compliance research due to lack of precise measurement

In this review of 1999, the field of patient compliance is described as a stagnating research field, with few original contributions, hampered by the lack of precise measurement techniques. In the eighties and nineties, the number of qualitative reviews far exceeded that of original publications (by one to ten; see fig.1 in facsimile), indicating slowing progress, repetition and stagnation.

1.2.2 A breakthrough in measurement technique

The advent of electronic monitoring has thoroughly changed the research field of patient compliance. The MEMS device resembles an ordinary cylindrical pill container with a somewhat oversized cap. In the cap, microelectronic circuit was concealed, able to record the date and time of the opening and closing of the box. This circuitry consisted of a clock, a micro switch, a memory and an output device. Each time the cap was removed to open the pill box, the micro switch was triggered. A time and date reading is then fed into the memory. Later, these readings can be retrieved by placing the cap over an output reader and transferring it to computers for further analysis by special software.

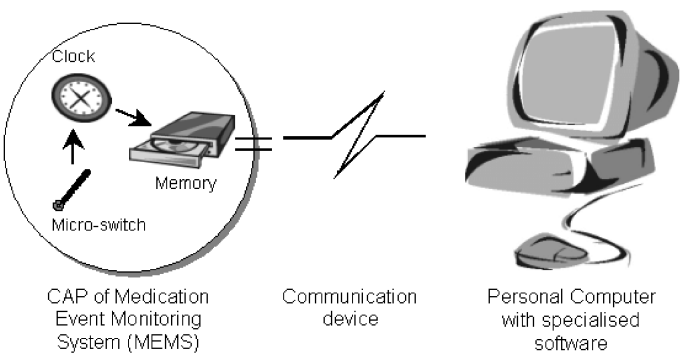

Figure 1: Principal elements of electronic monitoring devices.

The arrival of electronic monitoring was considered a breakthrough in measurement. What was fundamental in this innovation was the ability to identify and time stamp the occurrences of dose omissions.

Prof. Urquhart, inventor, developer and advocate of this novel measurement technique, has also proposed a taxonomy for the interpretation of the data stemming from MEMS.[201] For the initial decision to start the prescribed treatment, he suggested the term “adherence” (here meaning acceptance of treatment). It is a yes-or-no decision.

note The decision not to start the medicinal treatment can be taken after consultation and before going to the pharmacist[201], before picking up the ordered medication at the pharmacist's,[202] or at home, after the purchase of the medication.

The term "execution" for the middle part of patient compliance. Here, we look at the congruence between two time series: the time series as prescribed by the physician and the time series as taken by the patient. Finally, after some time, patient compliance can come to a final stop. The proposal here was to use the label "(dis)continuation". Again, this is a yes-or-no decision. The term "persistence" applied to the time which elapsed between the start of the treatment and its final discontinuation.

note **Patient compliance, adherence or concordance?**
Confusion patient compliance is well reflected in the sometimes harsh discussions on the terminology. "Patient compliance" is the oldest term. Haynes defined it as "the extent to which a person's behaviour (in terms of taking medicines, following diets, and or making life style changes) coincides with medical or health advice".[203]
In reaction to judgemental use of the term, a new label, i.e. "adherence", was proposed: it implies "a more active, voluntary collaborative involvement ... in a mutually acceptable course of behaviour to produce a desired preventative or therapeutic result".[204] More recently, yet another term, "concordance", has been adopted by some researchers in the field,[205] to underline the move to patient empowerment in the physician-patient relationship. Although the latter trend may have its advantages, the more pragmatic viewpoint on this labelling issueis to stick to the MeSH keyword "patient compliance", which was introduced in 1975 and is still used today. Search strategies in MEDLINE using the terms "compliance" (without the prefix "patient"), "adherence", and "concordance" yield smaller recall and much less precision, because irrelevant articles on lung diseases, blood diseases and statistical issues turn up in publication listings. One could not agree more with Myers and Midence when they state: "If clinicians and researchers cannot agree on suitable terminology on the topic they are investigating, how are they going to agree on anything else?".[167]

With the new and precise method of electronic monitoring, the stages of patient compliance can be unravelled and researchers can look at the details of the actual regimen and its deviation from the regimen prescribed (see Fig. 1. in facsimile 5) with sometimes frightening precision. In the other chapters of the book in which this review was published, ample testimony was given of the promises of this new technique, with the fascinating results of more then 50 peer-reviewed publications of studies with MEMS in the previous decade.

In our chapter, we examine which impact more precise measurement of compliance could have on the development of new insights with regard to risk assessment and to risk communication by means of patient package inserts.

1.2.3 Non-compliance and the clinical setting

In observational studies of compliance, the distribution of compliance (the percentage of patients taking x% of prescribed dosages) is similar across different clinical settings.[206]

However, results of *intervention studies* on modifying compliance obtained in a particular clinical setting should not be generalised too easily to other clinical settings.

Indeed, the clinical setting is determined both by the characteristics of the disease and by the characteristics of the medicinal treatment. By proposing the term "disease-drug dyad", we want to stress that there is an unbreakable bond between the two elements in the patient's perception which determines the specificity of the clinical situation. Important characteristics of the disease are:

- whether the disease is acute or chronic
- whether the disease is symptomatic or asymptomatic (not perceivable by the patient)

Important characteristics of the medicinal treatment are:

- whether the treatment is complicated by frequent minor but perceivable side-effects
- whether the treatment is associated with serious risk
- whether the treatment prevents, cures or only alleviates the disease
- whether the treatment is vulnerable to (short) interruptions in the regimen.

We will first enumerate some examples of these disease-drug dyads and then look at their characteristics.

Table 4: Disease-drug dyads

DISEASE	DRUG
Curable cancer	Hair-loss-inducing oncology treatment
Hypertension	Beta-blockers
Acute bronchitis	Antibiotics
AIDS	Experimental treatment
Tuberculosis	Streptomycine
Depression	Amitryptilline
Asthma	Inhaled steroids

Let us explain in more detail some of these examples.

A patient who has suffered from severe headache for 2 months may be confronted with the bad news that she/he has cancer. The good news is that it is a curable form of cancer, but again there is bad news: to get cured, she/he will have to take a drug that will cause hair loss (be it temporary).

To his/her astonishment, a patient who felt in perfectly good shape is told that he/she suffers from severe hypertension, and starts taking beta-blockers, which make him/her feel "old and cold".

A patient with acute bronchitis is given antibiotics, which he/she stops after three days because of heartburn and because he/she is feeling somewhat better. He/she is in good shape again, six days after the onset of the illness.

A patient with severe depression finally gives up resistance to getting proper treatment, feels even worse after one week of taking amitryptilline, because of dryness of the mouth, dizziness and constipation. He/she was not told that these embarrassing but mild side-effects would probably subside after two weeks, nor that it would take at least two weeks before he/she would feel less depressed.

A patient who has lived a merry life until now is confronted with the diagnosis of AIDS and presented with a complex experimental treatment, which entails unknown efficacy, is potentially riddled with dangerous serious side-effects, and has a high probability of less dangerous, but inconvenient minor side-effects. The treatment must be followed meticulously; otherwise, the theoretical chance of getting better is lost.

In the fifties, a patient with severe tuberculosis, a disease without efficacious treatment at that time, was given the opportunity to start a treatment with streptomycine; at the same time, he was informed that this might cause permanent deafness.

The mother of a young adolescent child with asthma, characterised by frequent severe attacks of wheezing, is told that she should administer a high dose of inhaled steroids to her child every day, in the midst of his/her growth spurt.

These are just a few examples to illustrate the difficult choices people have to make, often in difficult conditions, with very little precise information or too much or conflicting information. And yet, they have to make judgements and decisions to act (or not to act).

With these examples, we also want to illustrate that the characteristics of disease and treatment are intricately related and mould together in the patient's mental perception of the risks and benefits of a treatment for a disease in a specific clinical situation.

1.2.4 Non-compliance and benefit/risk perception of treatment

We can distinguish different types of (non-)compliance:

- the (perfect) complier
- the partial complier
- the overuser
- the erratic user
- the partial dropout
- the dropout.

The complier follows the treatment as directed, either because the doctor told him/her to do so, or because he/she really wants it that way. The partial complier intends to follow the treatment as directed, but occasionally forgets a dose (a dose omission) or takes a drug holiday (a period of 3 consecutive days where no dose is taken); he/she regularly presents at control visits and may not mention non-compliance, unless prompted to do so in a non-obtrusive way. The overuser abuses the drug and systematically takes more than directed. The erratic user may alternate drug holidays and periods of frantic overuse. The partial dropout alternates short periods of use with prolonged drug holidays. The dropout has stopped taking the drug altogether.

The complier may benefit fully from the treatment and minimise its risks. The partial complier will not benefit fully from the drug; in some cases even minor deviations of the treatment schedule will jeopardize efficacy; in addition, interruption of the treatment may cause additional risks to which regular drug takers are not subjected; ending a series of regular intake may cause withdrawal effects. Starting a new series of intake after a drug holiday may cause strong first dose effects, which is not without danger for the patient. The overuser will be exposed to the risks of overdose and addiction. The erratic user will combine the worst of two worlds: more risk and less benefit. The partial dropout will have little gain from his treatment, but will still be exposed to its risks. The dropout will no longer be subjected to any risk from the treatment but not benefit from its action anymore either.

For each of the six types of non-compliance, we have indicated the risk of the treatment with a grading scale (absent risk, acceptable risk, moderately augmented risk, strongly augmented risk). We did the same for the benefit of the treatment (optimal, suboptimal, doubtful, absent). By combining the two approaches, a categorical classification into six types of non-compliance is constructed, based on alterations in the risk/benefit ratio of the treatment.

Not all of these types of non-compliance may be prevalent in all clinical situations. Erratic users are seldom found among users of antihypertensives, but can be found among users of inhaled bronchodilators for asthma or benzodiazepine users for chronic fear syndromes.

Another important point to make is that the distinction between compliers and partial compliers cannot be defined by a simple rule that is valid for all clinical situations (e.g. less than 80% of the doses taken). Whether a particular number of dose omissions causes deterioration of treatment efficacy or side-effects, depends on the pharmacodynamic and pharmacokinetic properties of the drug itself. Patients with a transplanted heart or kidney must scrupulously take their immunosuppressive medication, since even a short interruption of therapy is a risk factor for acute rejection, organ loss or even death. Patients on long acting antihypertensives (reserpine, amlodipine, perendopril) may skip their treatment for more than one day without having their blood pressure run up again. The moment when the coverage of a drug subsides, depends on the drug. When a dose is omitted, the normal prescribed dosing interval is prolonged. When the actual dosing interval between the last dose in a regular

sequence of doses and the first dose in a new sequence of doses is longer than the duration of the action of the drug, a period of absence of therapeutic coverage starts (from the moment of the waning drug action to (and some time after) the moment of the first dose of the new series of doses).

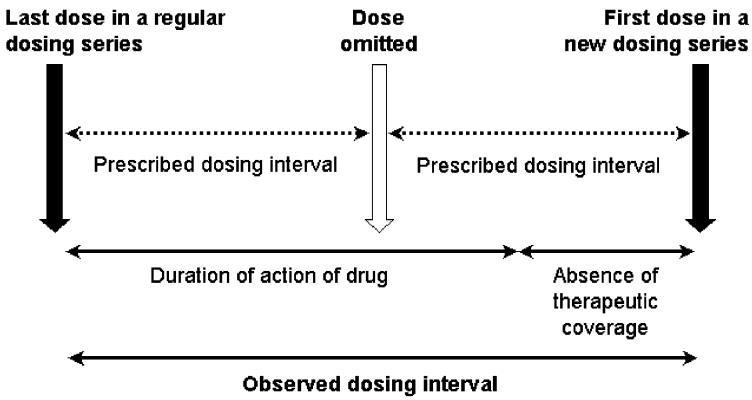

Figure 2: Duration of drug action, dosing interval, therapeutic coverage

In every clinical situation, where clinicians and researchers try to improve compliance, the distinction between punctual and partial compliance must be set a priori, by taking into account the pharmacokinetic and pharmacodynamic properties of the drug itself. Only electronic monitoring provides enough detailed information about dosing intervals and other aspects of non-compliance, to allocate patients to these classes of non-compliance htat have been defined a priori.

1.2.5 Model for studying the impact of written drug information on compliance

To study how written drug information may influence compliance, we needed to establish a pathway, and an array of possible intermediate and confounding variables. In this exercise, we will make abstraction of procedural information (information on how and when to take the medicine) and compliance problems caused by patients not knowing how to execute the treatment schedule correctly. We will focus on the impact of written drug information on patients' perception of the risks and the benefits of the treatment on patients' decision to start or continue a treatment.

We started by making a graph of what was well-known from the compliance literature (see fig. 2 in facsimile 4 of Annex 1).

For a drug to have an effect, it must be taken. So, in between the drug and its effects stands patient compliance as one important intermediate variable,

sometimes considered the most prevalent and important source of variability in drug effect.[207]

The effect of the drug may influence patient compliance in a variety of ways. A good effect can motivate the patient to continue treatment, but if symptoms of the disease disappear, the patient may lose the motivation to continue treatment (as often happens in treatment with antibiotics). The effect of diuretic agents (forcing the patient to urinate frequently and abundantly in the hours after the morning intake) may hinder activities of daily life and may be a cause for postponing intake on special days. Patients may also engage in stop-and-start experiments "to check from time to time whether the treatment still works".

Drugs not only have effects but also side-effects. The occurrence of side-effects may cause a change in the subjective benefit/risk perception of the patient, which may lead to non-compliance, as patients may immediately withdraw from therapy or engage in stop-and-start experiments "to check whether the side-effect is related to the drug".

Dose omissions (whether intentional or caused by forgetfulness) can reduce the beneficial effect of the drug treatment on the disease for which the drug is indicated. Dose omissions may cause withdrawal phenomena which will be interpreted by patients as side-effects. In addition, upon resumption of dosing, first-dose effects may occur. Hence, because a number of patients regularly engage in drug holidays, the objective balance between the benefit and the risk of drug, susceptible to withdrawal phenomena and first-dose effects, may alter. If these phenomena are perceived by the patient, the (subjective) perception of the risk of the treatment might be acutely distorted, leading to further deterioration of patient compliance.

The question is now how drug information (either verbal or written) can impact on these phenomena. Here, the assumption is that the decision to comply with therapy (start or continue) will be influenced by the benefit/risk perception of a particular patient in a specific clinical condition.

This benefit/risk perception may be shaped by prior experiences and general knowledge about drugs through education, and it will be changed by specific information provided prior to the first intake. It will also be changed (and possibly dramatically so) by personal experience of effects or side-effects during intake, at which time information can again be consulted to interpret bodily symptoms.

1.2.6 Designs for testing the impact of written drug information on compliance

In the following chapters we will present trial designs to test active groups and controlled groups in a randomised way for the differential impact of written drug information in various shapes. One can test written drug information versus no information. This design may be ethically difficult in clinical

situations, where there is an ethical duty of informed consent. More often, two (or more) different types of written drug information will be tested. One can test the impact of linguistic differences, graphical differences, differences in communication style, differences in the extent of risk information and differences in the extent of benefit information. It is hazardous to mix more than one of these aspects in one trial.

In clinical psychology studies, one can work with human volunteers who are not exposed to the drug (but to a clinical scenario) and are then exposed to different forms of written drug information. In the clinical situation, the intervention is composed of two elements, namely the drug under study and the written drug information that goes with it.

The design can be made more complicated, by testing different types of written drug information and by testing the intake of an active drug versus placebo or versus an active comparator.

In the nested design of the comparator being aplacebo, the content of the information provided to the placebo group can be identical to that in the active group (although twice nested into different styles of information, but with identical content).

If the clinical trial tests an active product versus another active product, then we are confronted with a problem of differential exposure and a difficulty of unblinding of allocation. Different drugs may have different side-effect profiles when applied to the same indication. Suppose we limit the content of the written drug information for patients exposed to drug A to the side-effects of drug A (albeit in two different styles) and also limit the content of the written drug information for the comparator drug to the side-effects of the comparator drug. By doing so, our intervention would not only introduce two different drugs and two different styles of written drug information, but also two different contents of written drug information. This would certainly confound our appreciation of the impact of the difference in style in written drug information. For the clever physicians and patients participating in the trial it would, furthermore, introduce a technique to escape the blinding of allocation of the two drugs. By studying the informed consent messages and the written drug information provided (regardless of its style) it would be possible to discover to which drug the patient was allocated. This would of course invalidate the results of the trial.

In the study presented in the next chapter, we provide a solution to this problem. We decided to merge all information elements with regard to side-effects of drug A and of drug B into one text. This hybrid text was then rewritten in the two different styles to be tested, while maintaining the content common to both drugs.

An example of such a hybrid insert, combining content information on atenolol and on lisinopril (in the patient package insert version) is given in Fig. 1 of Facsimile 5. A similar, but more sophisticated, version is given in Fig. 3 of Facsimile 4. The exposure to two different medicines remains blinded, as the content of the information is completely identical for all

patients, although the style of the information is not. This approach solves the dilemma between blinding and correct information.

1.3 Further discussion in the context of this thesis

Since the advent of electronic monitoring, theoretical insights into the problem of patient compliance have deepened. The importance of staging patient compliance in phases (adherence, execution, discontinuation) becomes more and more underpinned with empirical data. We have used this staging approach to make decisions on where to focus our research.

Scholars in clinical psychology had effectively warned us not to expect too much from this piece of Bible-type paper, in terms of motivational support in the action and maintenance stages of medication taking behaviour. In these stages, social support and control, cueing, and human motivational efforts are needed to support the patient in his/her initial steps and in developing routines.

In the later stages, however, the concept of benefit/risk perception remains of some importance, and might be more dynamic than static. Experiences of effect and side-effect during the initial try-out or during routine drug intake might affect and change benefit/risk perception and induce changes in compliance and ultimately less or more discontinuation. We simply do not know whether this latter mechanism or rather a gradual motivational slip of routine procedures by a lack of cueing is the most common cause of partial compliance and dropout.

The study presented in Chapter 2 of Part III was an attempt to explore the magnitude of potential differences in execution of treatment between different drug classes for chronic therapy of hypertension, with and without patient information.

In the study presented in Chapter 3 of Part III, we decided to focus on the initial phase (adherence) as the most important target for our research, and more specifically on the processes of benefit/risk perception as perceived by the patient in that phase.

Chapter 2
Measuring patient compliance with electronic monitoring: lisinopril versus atenolol in essential hypertension

Originally published as: Vander Stichele RH. Thomson M, Verkoelen K, Droussin AM. Measuring patient compliance with electronic monitoring: lisinopril versus atenolol in essential hypertension. Post Marketing Surveillance 1992;6:77-90. (see facsimile 5 in Annex 1)

Motives for this study

As early as 1990, the Belgian branch of the pharmaceutical company Merck, Sharp and Dohme invited me to participate in the early phases of preparation for a *phase IV trial* of a new product against hypertension from a new pharmaceutical class (an *ACE-inhibitor*, named lisinopril). The product had just been registered by the Belgian authorities. Hence, the basic evaluation of the available data from sophisticated pre-registration studies on efficacy and safety were evaluated with a positive initial result, as the product was allowed to be launched into the market.

At that moment, companies like to conduct additional post marketing studies for various reasons. One reason may be to familiarise opinion leaders with the new product or "to get the product into the pen" of prescribers. Getting more information on safety under natural conditions is another possible motive. The company might also want to compare the new product with the main competitor drug.

When I was called on board to consult the company, the decision had already been taken to conduct a relatively small comparative trial, to test lisinopril versus atenolol, a *beta-blocker agent*, a classic product for use in hypertension. I was interested in this comparison, because beta-blockers are first-line agents for the prevention of the clinical consequences of hypertension (in principle a condition without symptoms). Many patients experience no side-effects under atenolol, but a substantial number of patients report experiencing a feeling of cold hands and tiredness. Beta-blockers also cause a drop of the heart rate (which physicians may notice). These medications also restrain the normal quickening of the heart beats when a patient performs physical exercise, hence reducing the ability of patients to exercise. Atenolol might be considered as a drug with noticeable effects. This means that the patient and/or the physician is capable of observing the effects of the drug on the body in some cases. Lisinopril was not known at that time to have this peculiarity (although it was soon to be discovered, that ACE-inhibitors may cause an annoying cough in 1 in 20 patients).

I agreed to participate in the conduct of this study (as affiliated to the General Practitioners Research Institute and not to the Heymans Institute of

Pharmacology), when the company agreed to use electronic monitoring (the MEMS-device) in this study. To me and to the company, it was first hand experience with this new instrument to measure patient compliance, at that time a new, expensive and somewhat fragile device, considered a gadget by some. Furthermore, the company accepted my proposals to change the research protocol and raise the sample size, to add a dimension of testing the impact of patient package inserts to the study.

Setting
Post Marketing Surveillance General practice in Belgium, a western European country.

Objective of the study
To compare two antihypertensive medications (lisinopril, an ACE-inhibitor and atenolol, a beta-blocker) for side-effects and patient compliance and to investigate the impact of a patient package insert (PPI) on patient compliance.

Timeframe
Autumn 1990.

Design
This study was a randomised, open, comparative trial with one week of washout and 8 weeks of active treatment in two trial groups (without and with PPI), while each group was randomised further to either lisinopril or atenolol. The splitting into two trial groups was performed by group randomization: fate allocated each participating general practitioner to either a group where all GPs gave all their patients the study medication with a patient package insert, or a group where no participants got a PPI. This procedure was chosen to reduce confusion among GPs. Each participating GP, however, had to agree in advance to participate, regardless of the outcome of this allocation. The allocation within each of these trial groups to either lisinopril or atenolol was performed as follows: each physician received 6 medication packages, 3 with 60 tablets of atenolol 100 mg and 3 with 60 tablets of lisinopril 20 mg. GPs were not blinded to this allocation (they could see the difference between tablets), but were given a block randomization scheme (a random sequence of even and odd numbers in a envelope) to let fate decide which patient would get what, together with a firm request to follow the scheme.

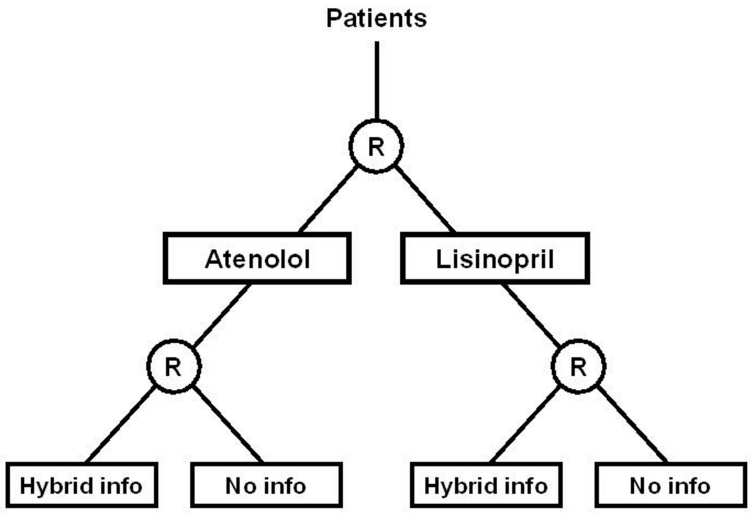

Figure 3: Research design of the atenolol versus lisinopril study

R = randomisation
Hybrid info: a patient package insert with information about typical side-effects of the two drugs

Visits for blood pressure measurement and adverse events report writing were planned on the first day, after one week of washout, 4 weeks later and again 4 weeks later for final evaluation.

The tablets were distributed, prepacked in the MEMS device (a plastic pill container with a screwable cap, containing electronic circuits to record opening and closing times of the cap). The MEMS devise was itself placed within an outer carton package (containing either a PPI or not), according to the allocation. MEMS devices were supposed to be operational during the 8 weeks of the trial, to be retrieved for further analysis at the end of the trial.

The PPI was a hybrid of the official insert of both atenolol and lisinopril, blended into one text, and then transformed into an understandable text, without loss of information (see Facsimile 5 in Annex 1).

We wanted to have a least 32 patients in each of the four subgroups, a minimum to have some power in the analysis.

Participants

We invited 26 GPs to recruit 6 patients each, for a target total of 156 patients. Patients had to be older than 21 and younger then 65 years and to have mild to moderate hypertension not treated yet or treated with a drug that did not control the blood pressure or was not well tolerated. Patients should not have been treated before or have contraindications for beta-blockers or ACE-inhibitors, and should not have additional severe health problems. So, this was to be a selection of uncomplicated hypertension patients, mainly on diuretics, with one or other reason to switch to a new antihypertensive agent.

Methods

We asked the GPs to record pulse rate and blood pressure at each visit, with a standardised procedure, more stringent than in every day practice, as is the custom in research projects.

At each visit, the physician inquired about all adverse events in the past period with an open question (not a questionnaire), and recorded whether or not he/she considered the event to be a side-effect of the medication.

The use of the MEMS device to measure patient compliance (see Chapter 1 of Part II for illustration) was not concealed from the patients and was part of the informed consent procedure. Patients were asked to return the MEMS at the end of the study. A description of what kind of information can be extracted from this device is given in Fig. 1 of Facsimile 5 in Annex 1). The MEMS data were used to classify patients in three categories, relevant for hypertension treatment:

- punctual complier
- partial complier
- dropout.

According to the nature of the data (percentages or averages), the appropriate statistical tests were used to test relevant differences in a conservative way for significance.

Ethical issues

The protocol of the trial was submitted to the Ethical Commission of the Flemish Research Institute, a certified board to supervise clinical medical research. Informed consent was given orally on the nature, aim and conduct of the study and on the use of the compliance monitoring device.

Results

Eight of the 26 physicians did not recruit a single patient (6 in the PPI trial group, 2 in the non PPI group). The remaining 18 GPs provided data for 74 patients (a median of 4 patients recruited per participating physician). Three patients (each from a different physician) were excluded because the GPs did not comply with the stipulations of the protocol for letting in or keeping out patients. Retrospectively, the data from another 3 patients, all from the same physician, were excluded from the analysis, because we discovered that the data was fake (see below for explanation).

Hence, we retained 68 patients for analysis. All were white Caucasians, between 23 and 65 years old, 53 years on average, with two more female than male patients. Six patients (one on lisinopril and 5 on atenolol) were recruited for intolerance to previous treatment, 15 were not previously on treatment (5 on lisinopril, 10 on atenolol) 44 were recruited because of low control of blood pressure, and 3 for a combination of reasons.

Thirty-two patients were randomised to lisinopril (13 with a PPI) and 36 to atenolol (18 with a PPI). There was no significant difference between the patients allocated to atenolol or lisinopril with regard to sex, height, and weight. There was a significant difference in age, as in the 60+ group only 6 of the 25 patients were on atenolol. Analysis revealed that 3 physicians had not respected the allocation procedure and had only put younger patients on atenolol.

Of these 68 patients, 18 did not complete the trial. Fifteen of them discontinued the trial and notified their physicians. Three others were identified as dropouts only later, after the analysis of the compliance date in the MEMS device. One of these patients experienced an abnormal slowing of the heart rate (*bradycardia*) and heart pounding (*arrhythmia*), notified his physician (who did not withdraw the patient), stopped taking the drug without notifying the investigator, but attended the visits till the end of the trial; two other patients did not take any medications in the first 28 days of the trial but started intake after the second visit.

Among the 18 dropouts, 13 experienced an adverse event; among the 50 patients who completed the trial, 7 experienced adverse events (a statistically significant difference).

Among the 38 patients on atenolol, 11 patients experienced 16 adverse events (11 of which were side-effects to the drug, according to the physician), and 8 dropped out. Among the 32 patients on lisinopril, 9 experienced 11 adverse events (4 probable side-effects) and 5 patients dropped out.

Among the 20 patients experiencing adverse effects, 10 had received a PPI and 10 not. Seven of these 10 patients with adverse effects and with a PPI dropped out, one was a punctual complier, 2 were partial compliers. Six of the 10 patients with adverse effects, but without a PPI dropped out, and 4 remained punctual compliers.

During the trial, the mean heart rate in the lisinopril group remained 80 beats per minute, while in the atenolol group the mean rate dropped to 68 beats per minute, again a statistically significant and clinically relevant difference.

The drop in blood pressure was equal in both groups, with one in six patients not responding.

Of the 50 patients who completed the trial, 4 patients failed to return the MEMS device. Hence, we had compliance data from 46 patients, of whom 36 did not miss one day of dosing, and hence were punctual compliers. In the lisinopril group, 91% of the patients were punctual compliers, in the atenolol group 65% were punctual (a significant difference).

In Table 2 of Facsimile 5 in Annex 1, a detailed breakdown is given of the number of adverse events occurring in punctual compliers, partial compliers and dropouts, depending on their allocation to lisinopril or atenolol or to the PPI group or to the group without PPI. The highest number of dropouts (n=5) was found in the group of patients receiving a PPI, but the numbers were too small even to attempt statistical analysis.

We were able to show at what time of day most patients performed their once daily intake (see Fig. 2 of Facsimile 5 in Annex 1). On weekdays the average hour of intake was 07.30 a.m., on Saturday 09.00 a.m., and on Sunday 09.30 a.m. Drug holidays started slightly more often in the weekend.

Short overview of the discussion and conclusions in the original publication

The first objective of this study was to compare two antihypertensive medications in a general practice setting. We did not need to perform this study to know that both medications lower the blood pressure and that atenolol lowers the heart rate. Because this study was performed in general practice, we experienced a number of problems: failure to reach recruitment targets, a few protocol violations, one case of physician fraud, a relatively high rate of adverse reactions and dropout, some missing data in the case report forms, a few recording devices not returned. This all contributed to a loss in empirical power, beyond the level where a clear answer to the second objective (is there an impact of the PPI on compliance?) was possible. In addition, the procedure for random allocation was not followed by 3 physicians, choosing younger patients for atenolol, introducing selection bias. Finally, in studies involving beta-blockers, there is always the element of observer bias, as physicians who are supposed to be blinded to the allocation can observe the lower heart rate in patients.

This was a company-driven trial in post marketing and maybe not conducted with all the rigour one could expect in a premarketing trial. In addition, we could have chosen a stronger randomization procedure in the design. Nevertheless, the continuing logistic support of the company (also when things were not running exactly as planned) helped much to finalise this project. In retrospect, not enough precautions were taken to assure blinding. The main drive for occasional breaking of the blinding by a limited number of physicians was probably the reluctance of physicians to prescribe beta-blockers to elderly (also documented in other studies), while those physicians may not have grasped the negative consequences for the analysis of the data.

The problems we encountered prevented us to reach firm conclusions with regard to the objectives. Even the significant findings must be looked at critically, because of the possibility of bias and confounding by age. However, there are interesting lessons to be learned from the problems observed, interesting descriptive results, and interesting experiences in the light of subsequent research.

This study tells us something about the reality of research in general practice. Eight GPs agreed to participate, but did not recruit. Maybe it was too difficult to say "no" to a pressing demand to participate. Maybe, the allocation to the PPI group led to investigator dropout despite prior agreement on this issue. The reluctance of GPs to prescribe beta-blockers in the elderly is well known, although the rationale may be questioned. Many GPs only occasionally participate in trials, are not trained in the rigour of procedures,

and often do the work on top of a busy schedule. So, we take the opportunity here to thank the investigators of this study for their efforts.

In this study, electronic monitoring played a crucial role in the detection of one of the first documented cases of investigators' fraud. The fraud was discovered because the recordings of the time of dosing in all the patients of this particular physician consistently showed unusual opening times between 10.00h and 11.00h in the morning and no recordings on Saturday and Sunday (the weekend). We soon realised that these were fake patients, that the physician had filled in the case report forms himself and manipulated the medication vials (without fully understanding the concept of timing).

This potential for audit and quality control in clinical trial of this technique, designed to measure patient compliance, was unexpected. Equally unexpected was the finding that a detection procedure for fraud is necessary, even among physicians who participate on a voluntary basis.

This study was one of the earliest clinical trials with the MEMS device, and it illustrated its power for describing the different aspects of compliance, some of them unattainable by other methods. It was possible to study in detail the variation in the length of the time interval between the all the doses one patient has taken during the study (the mean dosing interval). It was possible to look for intervals that exceeded 24 hours by more than 6 hours. This was then used to explore the consequences of different ways to separate punctual from partial compliers (see Table 3 of Facsimile 5 in Annex 1).

Unfortunately, we did not get far in the analysis of the impact of PPIs in this study. There was a small trend towards more adverse events and dropout and more compliance problems in the atenolol group with PPIs. After taking a critical look at the available data, it was clear that the numbers were too small, the power was too low, and the potential of bias too big to make any conclusion.

Further discussion in the context of this thesis

We realised that in new trials on this subject, a design testing the impact of PPI would no longer be feasible. From the early nineties on, medical ethics committees, supervising the conduct and protocols of clinical trials, rightly started to stress the importance of written informed consent and would no longer accept a trial where some of the patients were withheld information in one way or another.

It was frustrating to realize that our thorough analysis of the compliance data could not lead to firm conclusions. "Looking at the data" was, however, a tremendous experience, which shaped our thinking about future trial design and typology of different classes of patient compliance. We could not refrain from proposing a hypothesis for a future study: *In clinical trials, involving drugs with noticeable signs and symptoms of drug action or with noticeable signs of fading drug action or a high frequency of minor side-effects, it can be hypothesised that patient compliance and the perception and attribution of adverse reactions will probably be influenced by written drug information,*

resulting in differential occurrence of dosing irregularity, drug holidays or dropout.

The next logical step was to test the hypothesis formulated in the previous study in a bigger trial, which was better designed and more rigorously conducted. Our interest was sharpened to design a decisive new trial. In Chapter 4 of Part II, we will describe a study by our colleague Van haecht from 1990, focusing on an intermediate step, and one other attempt in 1992 to come up with more definitive answers. Before that, and somewhat against the chronology, we will discuss a study from 1998, published in 2002. That study focuses on the benefit side of the benefit/risk perception of medication by the patient.

Chapter 3
Impact of benefit messages in patient package inserts on subjective drug perception

Originally published as: Vander Stichele RH, Vandierendonck A, De Vooght G, Reynvoet B, Lammertyn J. Impact of benefit messages in patient package inserts on subjective drug perception. Drug Information Journal 2002;36:201-208 (see Facsimile 6 in Annex 1).

Shannon's Observation:
Nothing is so frustrating as a bad situation
that is beginning to improve.

note Because precedence is given to first author publications, this study from 1998 is presented here prior to the studies from the first half of the nineties, described in chapter 4 of Part II. Readers who prefer to read the studies chronologically are advised to read that chapter first.

Motives for this study

In 1996, after an interruption of a few years, we resumed our interest for patients package inserts, triggered by two students in experimental psychology from our university. The proposal was to conduct a study now focusing on benefit perception, rather than on risk perception. There were several motives for this.

First, we realised that our previous research was predominantly focused on risk perception, and that it was time to look at the insert from the opposite, more positive side.

Secondly, we realised that the content of the patient package insert is of course predominantly risk information. The section of the side-effects is the largest section, and there are sections on contraindications, special warnings and what to do in case of overdose. The amount of space allotted to explain what the drug is for is limited, in fact, to the name of the drug, the list of its indications and the pharmaceutical class to which the drug belongs. That can hardly be considered a coherent, ample and convincing description of the benefits of the drug.

In the literature on the impact of doctor-patient interaction, there is some evidence that a doctor who explains the nature of the disease to the patient, how the drug works and how it will affect the illness will obtain patient satisfaction and compliance to a large extent.[208][209][210][211] This led to the hypothesis that a similar message in the patient package insert will lead to a similar result.

In the late eighties I had reviewed several thousands of drafts of patient package inserts for the Belgian Registration Commission. It was my experience that the registration authorities were reluctant to permit paragraphs on the positive side of the medication. The PPI was considered an authoritative

document. It was not conceivable to permit messages with a promotional hint into the texts. Furthermore, it would require too many resources from the regulatory authorities to check these passages, discuss them with the company and enforce compliance to the ban on promotional messages in the package insert. This attitude was confirmed in 1996 in a series of in-depth interviews with regulators in the Belgian Pharmaceutical Inspectorate and medical managers and regulatory affairs managers from the industry.

Yet, during our proofreading, we noticed that most of the drafts of the PPIs were not of good quality. Our review was limited to flagging jargon words and overly complex sentences. It was not for us to edit the communication style of these texts, which was, in our opinion, mediocre most of the time.

In chapter 1 of Part I, we mentioned the paradox that before the transition of technical inserts to patients package inserts in 1988, the majority of a representative sample of the Belgian population read and appreciated the technical inserts, despite the fact that they were basically unintelligible. Maybe lay people read technical inserts in the way that one listens to a Gregorian chant or a Latin Mass. Enveloped and enchanted but hardly grasping the meaning of things.

We realised that taking away jargon and long sentences, without changing the communication style and the content, may lead to a more direct and unbalanced confrontation with risk information, which can be frightening, even when (or especially when) partly understood.

After long debate with the Department of Experimental Psychology of Ghent University, we decided to go for a "what if" approach, and to test the impact of a well-written, easy to understand patient package insert, which included a small paragraph on benefit hidden in the text. We discussed the protocol of the study and drew up a budget for adequate logistic support to permit the department of clinical psychology to conduct the study. Once there was an agreement, I contacted Willem Amery, Vice-president Pharmacovigilance at the Janssens Research Foundation, with a request for an unconditional grant. A contract was signed and the study was launched.

Setting

The study was conducted in Flanders, the Dutch speaking part of Belgium, among members of community associations for women, among female relatives of psychology students, and among caregivers (partners or family members) of psychotic patients, recruited through a self-help group.

Objective of the study

To evaluate the effect of the insertion of benefit information into a patient package insert on patients' knowledge and subjective benefit/risk perception.

Time frame
Data were collected from the autumn of 1997 to the spring of 1998.

Design
A randomised controlled clinical psychology experiment with human volunteers.

Methods
We decided on the following basic approach:

1. to work with human volunteers to whom a scenario would be read and not with patients actually experiencing the disease (for pragmatic reasons)
2. to conduct an experiment where the participants would be randomised into three groups:
   – a group without an insert (the control group) (CON-group)
   – a group with a normal patient package insert (PPI-group)
   – a group with a benefit paragraph added to the normal patient package insert (BEN-group)
3. to carry out the same experiment three times, each time placing the patient into a different clinical condition.

In each of the three experiments an identical procedure was followed. We set out to recruit 90 volunteers (called subjects hereafter). Subjects were given a briefing on the nature of the study before being asked for informed consent. Subjects were read an introductory script to familiarise themselves with the clinical context of the experiment. This means they were told a story of someone experiencing an illness. Subjects were then asked to imagine that this story was their own story, that they went to see a doctor, and that a prescription was issued, and that they were now back home with the prescribed medicine. Subjects were then randomised (with a machine producing numbers by chance) to one of three conditions:

- the CON-group was given another reading task, for a similar length of time
- the PPI-group had time (5 to 15 minutes) to read the normal insert
- the BEN-group got equal time to read the insert with the benefit paragraph.

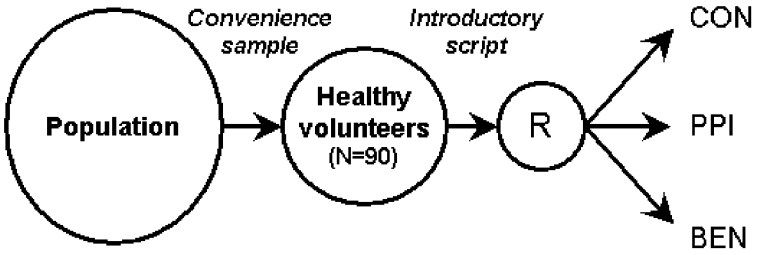

Figure 4: Research design of the benefit study

R = randomisation
CON = control group
PPI = Normal patient package insert group
BEN = patient package insert with a benefit message

Subjects could not speak to each other or have group discussions during the experiment. We used the text of the commercially available inserts, in 12 point type (big enough to be readable). For the products used in this study, these texts were of good quality, written for comprehension by readers with a low educational level (people who went to school till the age of 16). The scenario and the text of the benefit paragraph (60 to 80 words long) for each of the three experiments can be seen in Fig. 1. of facsimile 6 in Annex 1).

When reading time was over, the inserts and the control reading text were collected, and the volunteers were given a data collection booklet with measurement tests:

1. A knowledge test was taken. The test consisted of 20 simple questions, edited for readers with a low educational level, to be answered with YES or NO or DON'T KNOW, with one point for each correct answer. The minimum possible score was zero and the maximum possible score 20 points. Of the 20 questions, 16 related to the correct usage of the medicine and the risk messages, and 4 to the experimental benefit messages.
2. A test of how subjects perceived the risk and the benefit of the drug was taken. Subjects were presented with a statement: "The benefits of this medicine are greater than its risks" and then asked to indicate whether they strongly disagreed, moderately disagreed, took a neutral stand, moderately agreed or strongly disagreed.

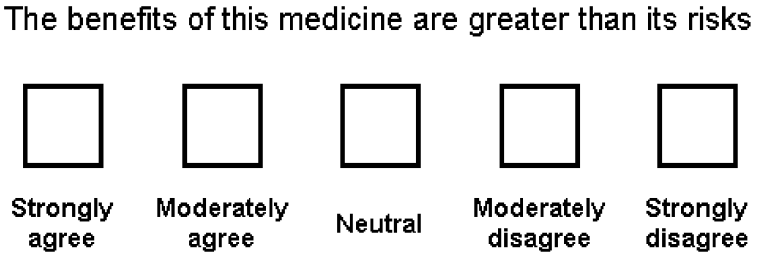

Figure 5: 5-point Likert scale to measure benefit/risk perception

Participants

The same experiment was repeated three times, each time with different subjects and placing them into a different clinical condition.

- In Experiment 1, the clinical condition was the use of the drug cisapride (CIS) for benign disturbances of the stomach and the bowels. The benefit paragraph focused on explaining drug action. Tests were taken in small groups of 10 to 30 subjects. The subjects were adult women from community organisations.
- In Experiment 2, volunteers were asked to imagine the use itraconazol (ITR) for infection by molds (fungus) of the toe nail. The subjects were relatives (mostly mothers) of psychology students. The benefit action focused on monitoring signs of healing. Tests were taken individually.
- In Experiment 3, the clinical condition was the use of risperidone (RIS) in chronic psychotic patients. The subjects were caregivers (partners or family members) of psychotic patients, recruited through a self-help group (SIMILES). The benefit paragraph focused on the relation between the disease and drug action. Tests were taken individually or in small groups of 10 to 30 patients.

We aimed at a sample size of 3 times 30 subjects per experiment. We used the appropriate tests for results in points (knowledge) and in percentages (% agreeing with the statement). We estimated in advance that differences of 20% points between subgroups could be considered a relevant difference, big enough to matter in clinical conditions. We chose the statistical power in such a way that we were reasonably sure (95% sure) that if the result was positive, this result could be trusted. In case the result was negative, we would be less sure (80%) that we had not missed a true difference.

Ethical issues

The participating organisations agreed to the study and all subjects gave informed consent orally after an oral briefing. The design was discussed with a member of a medical ethical committee, but not formally submitted for approval, as no test medications were given nor incisive tests performed. All subjects were debriefed after the test.

Results

In the 3 experiments, we recruited respectively 89, 102, and 83 subjects. All were female in experiments 1 and 2, and in experiment 3, 60% were female. In the second experiment, two-thirds of the subjects were highly educated (relatives of psychology students), while only one-third was highly educated in the other experiments. In the third experiment, 35% of volunteers (caregivers of psychotic patients) were familiar with the drug under study (risperdon) and they were older than the subjects in the other groups. There were no dropouts after randomization.

In all three experiments, the control group who had not received written drug information, performed pretty badly on the knowledge test (the control caregivers in experiment 3 did somewhat better). The two experimental groups that did receive an insert did equally well in all three experiments (although both under 10 points out of 20 in experiment 1).

Table 5: Median of correct answers on 20 simple questions on the medication

EXPERIMENTAL GROUP	CON	PPI	BEN
EXP 1 (CIS)	2	8	9
EXP 2 (ITR)	5	15	16
EXP 3 (RIS)	8	15	14

In Fig. 3 of facsimile 6 in Annex 1, more detailed information is given about the range of these results in each subgroup.

In the next table, the results are given for the appraisal of benefit and risk by the patients.

Table 6: Percentage of subjects agreeing with the statement: "the benefits of this medicine are greater than its risks"

EXPERIMENTAL GROUP	CON	PPI	BEN
EXP 1 (CIS)	36	31	62
EXP 2 (ITR)	62	41	64
EXP 3 (RIS)	84	54	70

In the group confronted with benign stomach and bowel problems (Exp. 1), the appraisal of both control (CON) and PPI subgroups was significantly lower than the score of the subgroup with the benefit message (BEN).

In the group confronted with the toe nail infection situation (Exp. 2), and among the caregivers of psychotic patients (Exp. 23), the PPI subgroup scored significantly lower than the control subgroup (CON) and the subgroup with the benefit message (BEN). In Fig. 4 of Facsimile 6 a more detailed and graphical representation of these results is given.

In summary, the results were fairly consistent in the three experimental groups:

- The 3 control subgroups had consistently worryingly bad results on the knowledge test, consistently worse than in the two intervention subgroups
- Benefit perception in the control subgroups was high (except in experiment 1, and very high in experiment 3)

- Benefit perception in the PPI subgroups was rather low in all three experiments, and always significantly lower than CON and BEN (except CON in experiment 1)
- Benefit perception in the BEN subgroups (with a benefit paragraph in their insert) was high again and significantly higher than in the PPI subgroups, consistently in the three scenarios.

The significant differences were higher than 20 percent points (16% for CON/BEN in experiment 3), and hence clinically relevant.

Short overview of the discussion and conclusions in the original publication

This was an experimental study in clinical psychology, not a clinical study with patients. One must be careful not to make generalizations for the entire population or even for patients suffering from the conditions studied here. Our selection of volunteers was not intended to represent the general population. We deliberately sought female subjects, because we wanted subjects with a keen interest in drug information. We knew women play the role of gatekeeper for the other members of their families (see Chapter 1 of Part II). Furthermore, it was convenient for us to address and get access to these groups of volunteers through community social organisations (that is why this is called a convenience sample). This selection procedure may affect our possibilities to generalise the results, but it did not affect the internal validity of the study. Indeed, once the group was selected, the division into three subgroups was left to chance (randomization). Each subject in the convenience sample had an equal chance of ending up in any of the three subgroups. Therefore, conclusions from these results are valid, but must be limited at least to persons (women) with a keen interest in medication.

We have chosen three clinical conditions to conduct our experiments, rather pragmatically by taking medications from one single company. First of all, this company had a reputation for producing good quality patient package inserts. Secondly, in doing so, we were able to choose an interesting mix of clinical situations. In experiment 1, we had a benign, acute, self-limiting disease, causing clear and not very frightening symptoms, to be treated by medication without frightening side-effects; in experiment 2, it was a chronic disease of a more cosmetic nature, to be treated with a drug, with the potential to cause severe liver problems (although these seldom occur); in the third experiment, we were dealing with serious, chronic mental illness, for which a drug with troublesome side-effects has to be taken.

It is possible that subjects in experiment 1 with cisapride considered the situation as not serious enough to be treated with medicines. Subjects in experiment 3 might have had a positive bias toward the unavoidable need for the medication, given their familiarity with the situation (caregivers) and, to some extent, with risperdon.

We were surprised by the strong and consistent results:

- The effects on knowledge were obvious, expected and interpreted as a confirmation of the design and the quality of conduct of the study. We

knew from the literature that uninformed subjects know little about medication and that written drug information has an impact on knowledge (see the general discussion for a review)
- It came as a surprise that the (rather uninformed) subjects from the control subgroup apparently had a positive bias toward the benefits and risks of medicines in general, given their high scores (at least for experiments 2 and 3)
- In the subgroups confronted with the PPI, the benefit/risk balance was clearly typed to the negative side, as at least half of the subjects did not consider the benefits greater than the risk
- In the BEN subgroups (confronted with the benefit message in the insert), however, more than 60% of subjects perceived greater benefit for the medicine. This means a positive ratio between benefit and risk was maintained.

In both the subgroups confronted with the inserts, a real information transfer had occurred, including information about risk items. In the BEN subgroups, this transfer of knowledge seemed not have been detrimental to the benefit/risk perception. In the PPI group, the benefit/risk balance was less favourable.

The consistency of the results in the 3 experiments with diverse clinical situations strengthens the credibility of the findings.

Based on the findings, we formulated a hypothesis for further research: *adding a section of benefit information within the patient package insert helps to integrate increased knowledge about medication into a more balanced benefit/risk perception.* More research is needed to confirm (or reject) this hypothesis, and to explore its clinical relevance, for example with regard to the impact on patient compliance.

Further discussion in the context of this thesis

With this study completed, it was possible to end the research project on a positive note. The manuscript was submitted in 2001 and published early in 2002. By that time, there was accumulating evidence that cisapride occasionally caused serious trouble with the rhythm of the heart (QT-prolongation and torsades de pointes) when taken in combination with a host of other drugs. This illustrates that it is necessary to survey the safety profile of drugs constantly, even when they are already on the market. Reports on adverse events are collected and evaluated. They may lead to retraction or restriction of drugs, to changes in labelling, to different drug choices by the physician and, ultimately, to a change in the perception of the risk and the benefit of the drug by the patient.[212][213]

Chapter 4
Other interventional research

4.1 Impact of patient package inserts for pain killers in uncomplicated strains of joints and muscles

Originally published as: Van haecht CHM, Vander Stichele RH, De Backer G, Bogaert MG. Impact of Patient Package Inserts on Patients' satisfaction, adverse drug reactions and risk perception: the case of NSAIDs for post-traumatic pain relief. Patient Educ Couns 1991;17:205:215.

Motives for this study

This study was the central study of the doctoral thesis by Dr. Chris Van haecht. We report the study here, because it was conducted during the PPI Evaluation Programme, because of the experimental nature of the study, and because of its focus on risk perception and report of adverse drug reactions.

The study focused on the use of Non Steroidal Anti-Inflammatory Drugs (NSAIDs). These are medicines which relieve pain and reduce swelling in strained joints or muscles. Patients in discomfort (pain, difficulty using the affected joints or muscles) can use these medicines for temporary relief of symptoms, which will usually subside with or without medicines in a maximum of 5 days. Patients are not obliged to take such medicines. If they do, they can stop taking the medicines at the first sign of side-effects. However, the use of these medications causes serious complications in a small percentage of patients, such as bleeding ulcers in the stomach.

Hence the clinical situation chosen here was better suited to the study of risk perception than to the study of patient compliance.

Objective of the study

To measure the impact of a patient package insert (PPI) versus a technical insert (TI) with a non steroidal anti-inflammatory drug (NSAID) on:

- patient satisfaction with medication information
- reporting of side-effects
- benefit/risk perception.

Setting

Patients consulting in general practice in the Dutch-speaking part of Belgium.

Time-frame

March 1989 to February 1990.

Design
A randomised, controlled, clinical trial testing a patient package insert (PPI) versus a technical insert (TI).

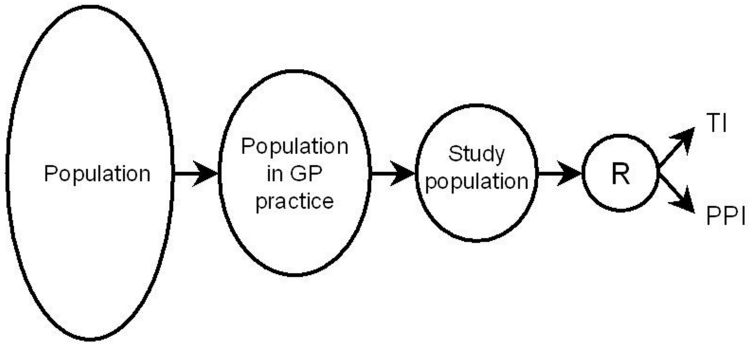

Figure 6: Research design of the NSAID study

R = randomisation
TI = technical insert
PPI = patient package insert

Participants
Patients with minor injuries (strains of joints or muscles) to whom the general practitioner (GP) would routinely prescribe NSAIDs were included. The following were excluded: children (less than 14 years of age), pregnant women, patients with contraindications for NSAIDs, and patients who had taken NSAIDS in the past 6 months. Forty-two GPs were asked to select 10 patients each in a period of maximum 6 months.

Method
The GPs were instructed to inform the patients about the symptomatic nature of the treatment, and to ask the patients to stop treatment when complaints disappeared or in case of adverse drug reactions. Patients were instructed to return for a control visit one week later. Patients were not informed about the existence of two types of package inserts.

The study medication was the NSAID pirprofen (Rengasil) from Ciba-Geigy. It was distributed by the physician during the first consultation, in packages of 30 capsules of 300 mg, normally to be taken three times a day.

The study medication was distributed to the GPs in blocks of 10 numbered packages. Each set contained 5 packages with a patient package insert (PPI) inside, and 5 with a technical insert (Ti) inside, in an order determined by chance. The GP was not aware of the type of insert inside the packages.

The inserts used were those approved by the Belgian health authorities (the PPI was approved in January 1989) without any linguistic or graphical change.

The overall look of the insert was identical, including the small character size (point 9). The main differences between PPI and TI were:

- shorter sentences
- replacement of medical jargon by lay terminology (e.g. loss of appetite, tendency to vomit, stomach ache and stomach ulcer replaced anorexia, nausea, epigastric pain and ulcus ventriculi)
- lay terminology in the subheadings, turned into questions.

At the second control visit, leftover medication was returned to the physician for a pill count and the patients were asked to fill in a self-administered questionnaire, immediately after the visit and return it directly to the researchers in a closed, prestamped envelope. Inserts were not retrieved by the doctor.

In the questionnaire, patient satisfaction was assessed by confronting the patient with nine statements, to be scored on 5 point Likert scales (from "strongly disagree" to "strongly agree"). Benefit/risk perception was evaluated by two separate scales (unlabelled semantic differential scale with seven grades). Each individual score on the benefit scale was to be subtracted from each individual score on the risk scale, to attempt to construct a composite measurement of benefit/risk perception.

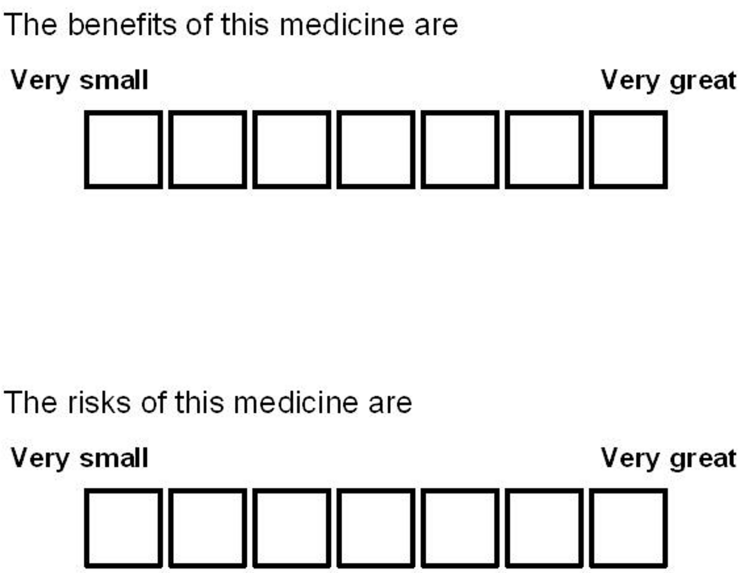

Figure 7: Unlabelled 7-point scales to measure benefit perception and risk perception

Patients were also asked to scale (with another seven grade scale) the influence of their physician, their family, their own opinion and the insert on the decision to take the medicine.

Percentages were compared with the Chi-square test. The results of the scores on the seven grade scales were considered to be ordinal variables. This

takes into account that a score of 4 is bigger than a score of 5, but does not assume that the difference between 1, 2, 3, 4, 5, 6 and 7 is equal). When the comparisons were between two groups (e.g. PPI versus TI), the Wilcoxon-Mann-Whitney test was used to make the distinction between significant and insignificant differences. In case the comparisons were between three groups (e.g. patients not reading the insert, patients reading the insert superficially, patients reading the insert thoroughly), the Kruskal-Wallis test was used. Differences between medians of groups of 1 point or more on the seven grade scale were considered relevant.

At the return visit all spontaneously mentioned reports of presumed side-effects were recorded. In addition the patients were asked whether or not this side-effect made them stop taking the drug. In the questionnaire, 10 common health problems were listed. Patients ware asked to tick the health problems which they experienced any day during the last week, and to indicate whether they felt the occurrence of these health problems was related to the taking of the drug.

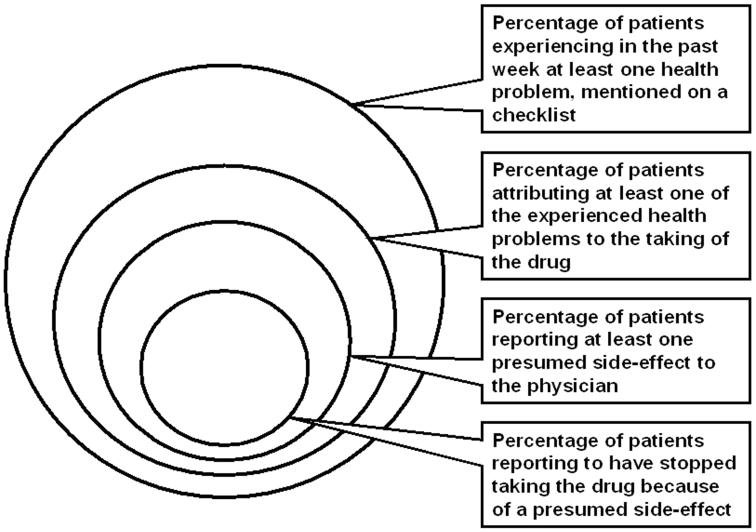

Figure 8: Gradation in 4 methods to assess the frequency of health problems

Ethical issues

The study protocol was approved by the Ethics Committee of the Ghent University Medical School. All patients were asked for oral consent to participate in the study.

Results

A total of 366 patients was included in the study. Thirteen% did not show up at the control visit or did not return the questionnaire. Between the respondents and the drop-outs there were no significant differences in sex and age, type of injury or type of insert. Further analysis is based on a sample of

317 patients (156 allocated to the TI group and 161 allocated to the PPI group).

The average age of patients was 36 years (SD 15 years, range 14 to 82y). Fifty-five % were male. Fifty % had a schooling age of 14 years, 32% of 18 years, and 18% a higher educational level. Patients suffered from an injury to the foot or ankle, hand or wrist, knee, in the back, mostly from a direct hit (contusion) or from a bad movement (distortion). Forty-three % were also prescribed a topical treatment and 3% another oral drug.

Only 29% of the patients stated that they had not read the insert; 43% read the insert superficially and 28% thoroughly (no difference between PPI and TI group). The insert was read by 61% of the lower educated and 84% of the higher educated patients(P>.001).

Overall satisfaction with the insert among the 225 readers (108 allocated to the TI group and 117 allocated to the PPI group) was quite high (median 6 on a scale from 1 to 7) and independent of the type of insert. The PPI was judged more understandable than the TI (6 versus 4) and less vague (2 versus 4).

The median benefit perception was 5, whether the insert was (superficially) read or not. TI readers scored a median of 6 and PPI readers of 5 (Wilcoxon P = 0.0451).

Median risk perception was 1 for non readers, 2 for superficially reading patients, and 3 for thoroughly reading patients (Kruskal-Wallis P = 0.0072). It was 2 for TI readers and 3 for PPI readers (NS).

The median span between the median benefit score and the median risk score was 3 scale points in the TI group and 2 scale points in the PPI group (Wilcoxon P = 0.0163).

Readers of the insert scored the influence of the physician at 6, with non-readers at 7 (Kruskal-Wallis P = 0.0494). Patients who had read the insert thoroughly scored their own opinion at 4 and the influence of the package insert at 3, while non-readers and superficially reading patients scored resp. 2 and 1 (Wilcoxon P resp. 0.0162 and 0.0001). The score for the influence of family was 1 in all reading groups.

In total, 53% of patients checked one of the health problems on the questionnaire, and 42% attributed such a problem to the drug. Thirty-three % spontaneously reported a problem to the physician and 13% mentioned that the problem had been a reason to stop taking the drug. The problems mentioned were predominantly problems with the bowels and the stomach.

Nearly all patients reported discontinuation of treatment after 5 days.

Women reported 1.5 problems on the checklist and attributed 0.9 problems to the medication, while men reported 0.9 problems ($P < 0.01$), and attributed 0.6 problems ($P < 0.05$). There were no associations with age or educational level.

The data were split according to package insert readership.

Table 7: Reporting of health problems and side-effects by patients with an injury of joints or muscles, according to insert readership

LABEL	Non-readers (N=92)	Superficial readers (N=136)	Thorough readers (N=89)	Chi-square P
% of patients experiencing a health problem	41%	55%	61%	P=0.025
% attributing the health problem to the drug	28%	48%	48%	p=0.005
% of patients spontaneously reporting to the physician	16%	37%	42%	P=0.001
% reporting that they have stopped the drug	5%	17%	14%	P=0.035

In addition a breakdown was made according to the type of insert.

Table 8: Reporting of health problems and side-effects by patients with an injury of joints or muscles, according to the type of insert (TI versus PPI)

LABEL	Patient package insert readers (PPI) (N=117)	Technical insert readers (TI) (N=108)	Chi-square P
% of patients experiencing a health problem	61%	53%	NS
% attributing the health problem to the drug	53%	43%	NS
% of patients spontaneously reporting to the physician	46%	31%	P=0.034
% of patients reporting that they have stopped the drug	21%	11%	NS

Discussion and conclusion

In the clinical context of this study (non-serious injuries of joints and muscles), slightly fewer patients read the insert (thoroughly) , as compared to the level of readership in previous studies reported in Part I. There were no differences in readership according to the type of insert.

This study is one of the few which tests two types of inserts randomly. As the differences between the two types of insert in this study were small and limited to linguistic change, it was remarkable that relevant and significant differences were found in benefit/risk perception and in the perception of health problems and side-effects.

Although more patients who had read the insert perceived the PPI as more understandable and less vague, the overall satisfaction was high, with no difference between types of insert; both PPI and TI scored 6 on a scale from 1 to 7. This paradox might be explained by the hypothesis that with regard to satisfaction, the very fact of giving information is more important than the content of that information.

Readers of the PPI scored the benefits of the drug lower and the risks higher than readers of the TI. The question is whether this effect is troublesome or not. Especially with NSAIDs, one might say that the patients obtained a more reasonable perception of the drugs' benefit and risk by reading an understandable insert.

In this study, a clear link was established between reading of an insert and perceiving health problems. It would be wrong to interpret this as proof for the popular belief that reading the side-effect section of a package insert suggests side-effects to patients, who will then promptly experience these side-effects. One could say that reading the insert makes patients more aware of signals given by the body, whether these are related to taking the medication or not.

In addition, the health problems experienced were more often associated with the medication. In this attribution process, the patient makes a mental link between the health problem experienced and the medication. In this study, we had no possibility to check whether this attribution process was correct or not.

It was also clear that patients reported health problems more often, when they have read the insert, especially if they had read it thoroughly and if the insert was a PPI. Again, one can look at this phenomenon in two ways. On the one hand, it can be considered a waste of resources and needless harassment of physicians, if this increased reporting is interpreted as exaggerated sensibility, incorrect attribution or sheer suggestion of side-effects. On the other hand, one can welcome more dialogue between the patient and the physician about the safety profile of the medicine. Anyway, this study does not permit evaluation of the correctness of the attribution process by patients.

The percentage of patients naming side-effects as a reason to stop treatment was clearly higher among readers of inserts. There was a trend toward more cessation under PPIs, but this was not significant (the study may be underpowered). Again, this can be interpreted in different ways. One might say that written drug information has a detrimental effect on patient compliance. However, one may also welcome all interventions that make people stop taking a potentially dangerous comfort medicine such as NSAIDs earlier (at the first sign of a potential problem, or as soon as one feels better). The method for recording the duration of drug intake in this study was patient self-reporting. The validity of this method was considered too doubtful to engage in an analysis.

This study concluded that in the setting of an optional, symptomatic treatment of a self-limiting disease (injury to joint and muscles), reading

written drug information has an impact on both patients' perception (less benefit and more risk perception; more health problems experienced and attributed) and on patients' behaviour (more spontaneous reporting of health problems and more cessation of therapy because of perceived side-effects). Reading a patient package insert (as opposed to reading a technical insert) was associated with a higher percentage of patients reporting health problems to the physician.

Further discussion in the context of this thesis

The results of this study were both thrilling and frustrating. Thrilling because a clear effect of reading understandable written drug information was shown on patients' perception and behaviour. The results were frustrating because they did not allow to evaluate correctness of attribution process and the (non)existence of suggestion effects.

Ciba-Geigy participated in this study by providing the packages and inserts of the product pirprofen (trade name Rengasil). One might say the company took some risk by involving its product in a trial focusing on risk perception and using self-administered questionnaires with a list of possible health problems. Such a technique yields high rates of presumed side-effects, which can be easily misinterpreted. Anyway, a few months after the end of the study, pirprofen was withdrawn from the market. The reason was probably that the product did not fit the companies' portfolio well, with other more successful NSAIDs on the forefront.

The study by Van haecht was also an incentive for us to look for ways to go beyond the improvement of only the linguistic quality of inserts. Making inserts more understandable by shortening the sentences and getting rid of medical jargon reveals more clearly that the content of the insert is unbalanced with an excess of risk information. If improving readability does not coincide with improvement in communication of risk and benefit information, then potentially detrimental effects of written drug information could be enhanced. This insight was the main trigger for setting up the study on benefit messages, reported in Chapter 3 in Part III.

4.2 A tale of a halted study

I can live with despair, but it is the hope I cannot stand.
John Cleese, in "Clockwise"

Motives for this study

In 1992, we were given the opportunity to write a protocol for a trial that would take this research field one step further, incorporating new methods and answering some key questions. We received a research grant from a charity fund, after our proposal was selected by the Federal Fund for Scientific

Research. It was a 100,000 EUR grant, and we considered this amount sufficient to set up a clinical trial in General Practice. In the following paragraphs, we will describe the protocol of the study, in order to explain the aims and the ambitions of the study. Results will not be presented, because the study was aborted, as we failed to recruit enough valid cases. We report on this unfortunate outcome to illustrate that failure is not uncommon in scientific work, to explain the design of this study, and to reflect on the experience gained.

Description of the study

The aim of the study was to explore the effect of complete, understandable written drug information about a beta-blocking agent, used in the treatment of essential hypertension on:

- patient compliance
- the attribution of health problems to the medication
- spontaneous reporting of side-effects
- benefit/risk perception.

The study was a randomised placebo controlled clinical trial comparing atenolol 100 mg once daily (and a lay language patient package insert) with placebo once daily (with the same patient package insert) to be conducted in general practice.

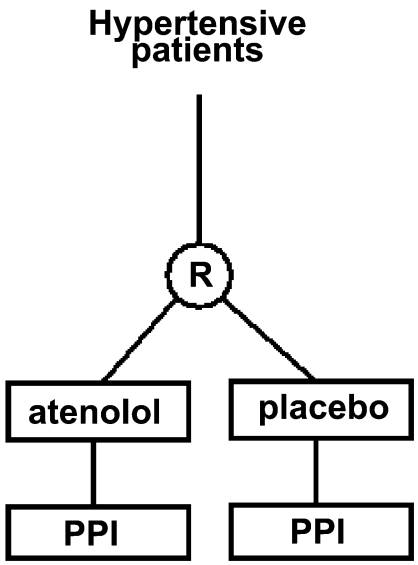

Figure 9: Research design of the halted atenolol versus placebo study

R = randomisation
PPI = patient package insert

We asked 15 general practitioners to recruit 8 patients each for a total of 120 patients, to be randomised into two groups of 60 patients, and to be followed for 3 months in 4 visits at D0 (start), D14 (two weeks), D42 (six weeks) and D83 (twelve weeks). Patients needed to be between 20 and 70 years of age, presenting mild to moderate, uncomplicated essential hypertension, either newly detected, or switched from previous therapy because of non-response or intolerance. Patients should be able to answer a simple self-administered questionnaire and to self-administer their medication.

We excluded patients with:

- serious problems of the hearth, liver, gut or kidney
- dementia
- treatment with beta-blocking agents in the preceding year
- shortage of the mineral potassium in the blood (hypokalemia)
- pregnant women, lactating women, women wishing to become pregnant and women taking oral contraceptives
- contraindications for beta-blocking agents
- co-medication that could interact with beta-blockers.

Patient compliance in this study was to be measured by electronic monitoring, using the Medication Event Monitoring System (MEMS, Aprex, USA).

Spontaneously mentioned side-effects were to be recorded. Side-effects mentioned as a reason for stopping the therapy were also recorded.

At the third visit, on day 42 (six weeks after the start of the study) a questionnaire was given to the patient, to be filled in and collected at the last visit. Patients were asked to tick a list of potential health problems experienced during the last month, and to note whether, in their opinion, the health problems were related to taking the medication. There were 10 potential health problems on this list. Five of them were symptoms possibly attributable to atenolol (because in other trials it was documented that these symptoms occurred more frequently than placebo).

For the measurement of benefit/risk perception in this study, we again used the technique of the two unlabelled semantic differential scales, one for benefit perception, one for risk perception (see above).

Blood pressure was to be measured with the stricter procedure for clinical trials. The pulse rate was to be determined at each visit.

We designed the study to test the hypothesis that the rate of punctual compliance was equal in the atenolol group and the placebo group (the null hypothesis).

The study protocol was approved by the Ethics Committee of the Ghent University Academic Hospital. Patients were given full information on the aims of the study, and were informed of the use of placebo and electronic compliance monitoring. Investigators were to give written confirmation that oral informed consent was obtained from each patient. Patients were informed

that they could withdraw from the study, at any given moment, for whatever reason, without repercussions for their further treatment.

Start and halt of the study

We originally planned a study duration of 9 months to give time to each participating general practitioner to recruit 8 patients. After 4 months, it became clear that most participating GPs would not reach their recruitment targets and that the study would fail.

Discussion of the reasons for failure

There was a clear discrepancy between the demands of the protocol and the severe inclusion and exclusion criteria, on the one hand, and the capability and motivation of participating GPs to recruit patients, on the other hand.

The exclusion criteria were harsh, logistic support and rewards for GPs for the extra work limited.

Last, but not least, there was the placebo-controlled nature of the study, which might have made it more difficult for patients to agree to participate, for GPs to accept to participate in the trial, and for GPs to be motivated to try to convince patients to enlist in the trial.

Looking back, a design with an active comparator instead of placebo would have been more suitable. We chose not to go for an active comparator, because possible differences might in effect have been more subtle and more difficult to detect with relatively small sample sizes.

One could put it bluntly and say: we gambled and lost. It is more appropriate to say that designing scientific studies involving patients is difficult. Trade-offs have to be made between rigour, concern for the safety of the patients and willingness to achieve trustworthy results.

Further discussion in the context of this thesis

This study was originally planned as the closing study of this research programme. It would have enabled us to continue the work of Van haecht, reported in Chapter IV of Part III, with regard to the experience, attribution and reporting of health problems during chronic drug intake. It was a disappointment when the study failed, and for some years there was little impetus to continue research on this subject. Luckily, in the late nineties, we were able to conduct a less ambitious and more modest experimental psychology trial, reported in Chapter 3 of Part III, as a worthy closure of the programme.

Part IV

General discussion and conclusions

Science must be explained as simply as possible but not simpler.
Albert Einstein

In the final part of this thesis, we will first provide a round-up of the descriptive studies in Part II regarding the Belgian Patient Package Insert Evaluation Programme. We will list the main findings of the intervention studies from Part III and briefly discuss the results in connection to other findings in the literature. We will then group the hypotheses for further research resulting from this work. In addition, we will list a number of recommendations for future developments with regard to patient package inserts. In the final conclusions we will focus on the two main themes of this thesis, namely the acceptance by the public of patient package inserts (PPIs) and their impact on benefit/risk perception by the patient.

1 Discussion of Part II

1.1 Round-up of the descriptive studies in the Belgian Patient Package Insert Evaluation Programme

These studies can be grouped into:

- descriptive studies describing the attitude of relevant parties:
  - patients
  - physicians
  - regulatory affairs managers.
- consecutive pre-post studies, providing time series information on the progression and the impact of the introduction of patient package inserts on a national scale:
  - Two repeated population surveys
  - Two repeated registration studies in general practice.

In addition, a number of descriptive studies were conducted describing the provision of drug information to specific patient groups (socially active elderly living at home, frail elderly at home, elderly in subacute geriatric wards, elderly in homes for the aged, and adolescents). Finally, we described the

medication distribution system in nursing homes and in hospital care in Belgium.

From a methodological point of view, the studies presented here have their limitations. Most studies are exploratory and descriptive, primarily on quota samples, often making abstraction of the time line of the implementation of PPIs in Belgium. Choices have been made between covering a broad range of specific populations on the one hand, and precision by large sample sizes, intense recruitment and non-response management, on the other hand, sometimes at the expense of generalizability of the conclusions. The pre-post studies (or more accurately pre-during studies) are merely two consecutive cross-sectional unpaired measurements, and not (quasi)-experimental studies or even controlled studies. The interest of this research resides perhaps more in the diversified approach of different settings and actors. The results provide a broad perspective on the background of giving drug information in health care, and some hints about the possible impact of a shift from Technical Inserts to Patient Package Inserts on a national scale. Our aim was to exploit this natural experiment as much as possible, to evaluate the introduction of PPIs in Belgium, and, more generally, to provide more insight in the way patients deal with medication and medication information.

It was our ambition to measure the impact of the implementation of a health policy programme, namely the introduction of patient package inserts on a national scale in Belgium between 1988 and 1992. We will comment on the quality of the implementation of the programme, on the quality of the Belgian inserts and on the impact of the programme in Belgium.

1.2 Evaluation of the impact of the Belgian PPI Programme

We demonstrated by a non-paired, pre-post population survey that there was no significant difference between the proportion of patients (9 in 10) stating they read the insert, before the change and half way through the change. The percentage of people stating they read the insert was somewhat smaller in lower versus higher educated patients, but still high. We consider this as proof that there was no decrease of the readership of inserts in Belgium. We also demonstrated that patients in Belgium were not aware of the transition. We established that acceptance by the public of technical inserts was high before the introduction of PPIs, and high beyond the possibility of improvement. The measurement of satisfaction was not repeated, hence the possibility of a reduction in the general level of satisfaction was not excluded.

The transition from technical inserts to patient package inserts was limited in scope (only linguistic simplification) but complete in implementation. By the end of 1992, all inserts were replaced. This transition has gone by unnoticed, without protest from the health care providers or complaints from the general public, as monitored by our surveys of the physicians and the population. Consumer associations, however, expressed their disappointment in the quality of the inserts.

The comparison of the results from the two consecutive clinical general practice registration studies (one in spring 1989 and one in spring 1990) are of interest. We observed a limited but relevant impact of the PPI on patients reporting possibly drug-related health problems. We observed a small increase in the percentage of patients spontaneously reporting health problems to their GPs in a follow-up visit for hypertension (from 29% to 43%), no change in percentage of patients reporting a health problem after prompting (around 70%), and a slight increase in percentage of patients attributing these prompted health problems to the medication currently taken (from 21% to 35%). This increase was observed in higher educated patients as well as in lower educated patients. There was also a hint that the increase might be associated with the introduction of the PPIs.

This may have been a temporary effect, an artifact caused by the increasing percentage of higher educated people in the population. It may also be an indication that PPIs do have small impact but on a massive scale in reporting minor ailments from medication usage. If among the population the reporting of health problems possibly related to drugs increases, this may be a blessing or a curse. It may mean more unnecessary work for health care workers. But it may also lead to greater awareness and prompter detection of adverse effects, and a swifter reaction. A key issue is whether a patient experiencing a relevant health problem, while taking medication, will attribute this health care problem correctly to the drug taken. This aspect has not been studied in this work.

When the introduction of PPIs in Belgium was well under way, our research focus and the remaining funds available for evaluation research were diverted to more fundamental and experimental research on the impact of written drug information on patient behaviour, described in Part III. It was clear by then that the political drive to implement high quality patient package inserts had waned. Readability control was again taken up by pharmacological experts. As the Belgian Pharmaceutical Inspectorate did not have a document management system, it was not able to control the consistency of the different drafts, even for products with the same active ingredient.

A public information campaign, drawing attention to the existence of PPIs, was not conducted. In 1995, the European Medicines Evaluation Agency (EMEA) became operational, and many new products were evaluated centrally (including the evaluation of the user leaflet). Interest in the subject further subsided.

Because of the requirement to have an insert in the three official languages (Dutch, French, German), companies continued to be confronted by too much text to be printed on sheets that were too small, a problem often resolved at the expense of type size, making the inserts barely legible. By 1992, it was clear that the transition to patient package inserts in Belgium was going to be a minor operation, limited to making the texts of the inserts more readable by using shorter sentences and by reducing medical jargon. However, graphical

design remained dull, with very few companies experimenting with colour and emphasis. The disparity among inserts for similar drugs has not decreased. Belgian inserts are of variable length and quality. Moreover, the content of inserts for similar drugs is not always consistent. Some companies, for example, managed to slip a small benefit section in the approved text of their inserts.

1.3 Integration with the literature about acceptance of written drug information by patients

To review the literature on acceptance of written drug information we will address the following topics:

- do patients read PPIs when it is provided?
- do patients emotionally accept PPIs in the drug distribution system?

1.3.1 Do patients read patient package inserts?

There are a number of studies from European countries where inserts are routinely provided in the distribution process. These studies date from before the era of the introduction of patient package inserts. So the readership data provided here pertain to readership of technical inserts. In Italy, in a 1990 survey of almost 7000 respondents, recruited through community pharmacists, 80% stated they usually read the insert of their medicines.[214] In Germany also, readership was high in a study of 315 patients, where 96% said they regularly read the insert (of which three quarters in full, and one quarter only certain sections).[215] A Swiss survey (German and French speaking parts) showed that 67% of respondents stated that they always read the insert, 20% sometimes, and 13% never.[216] In another Swiss observational study (N=102), 56% of the patients had read the package leaflets of antihypertensive and anti-infective drugs in full, 26% in part and 18% not at all.[217]

Rupf in Switzerland also took advantage of the gradual change from TI to PPI in the drug distribution system in the late eighties, to set up an observational study, with focus on readership.[218] He found that 79% of the 47 patients who received a PPI read it in full, versus 35% of the 55 patients who received a TI (P less than 0.001, stratified by age).

For Belgium, a number of studies were presented in this thesis, confirming the high levels of readership for technical inserts and patient package inserts. This level remained steady during and after the introduction of patient package inserts.

In our studies, readership levels were a bit lower in the elderly, the poorly educated, and the chronically ill (with strong intercorrelation between these demographic variables). Readership levels were somewhat lower in clinical

studies than in population surveys. High readership was confirmed in observational and interventional research (see Chapter 4 of Part III).

It is clear that changing from a drug distribution system with technical inserts to a drug distribution system with patient package inserts does not affect the high levels of readership of this document.

In systems where PPIs are not part of the drug distribution system, one needs to address the question whether a PPI was distributed before one can ask whether the insert was read.

In the US, an exceptional twelve year series rate of 4 cross-sectional telephone surveys was conducted to assess the reception of voluntary provided drug information on a nation-wide scale with subjects who retained a new prescription at the retail pharmacy during the past 4 weeks (for themselves or for a family member), in 1982, 1984, 1992, and 1994.[219] The percentage of patients reporting to have received any written information from physicians increased only slightly (from 5% to 15%). However, there was a gradual increase of penetration of written drug information dispensed by pharmacists, from 16% in 1982 to 59% in 1994. High reading levels of written drug information were noted, similar to the levels in Europe. A slight increase was noted in the frequency of spontaneous verbal counselling, both by physicians (focused more on side-effects and precautionary information) and by pharmacists (more on instructions and precautionary information). The number of patients asking questions remained very low (less than 10%).

This can be seen as a remarkable result of the efforts of pharmacists associations, legislation (OBRA 1990) and voluntarism from private initiatives.[220][221][222][223]

In a recent assessment of the implementation and quality of written information with new prescriptions in community pharmacies in the US, based on trained actors, the percentage of patients receiving written drug information was 87%. However, the length and quality of the leaflets varied greatly and the majority of leaflets did not include adequate information about contraindications, precautions, and how to avoid harm.[224]

The controversy about the voluntary or mandatory approach[58][225][113] is not over. It remains unlikely that the goals of full distribution of information, fulfilling minimum requirements will be reached by voluntary efforts only.

From the UK, where the introduction of PPIs was slow, there are two studies with contrasting results. In a 1999 study, when mandatory leaflets were still a novelty, one fifth of patients failed to notice the leaflet. Of those who recalled receiving a leaflet, only two fifths read some of it and one fifth all of it.[226] The other study is a qualitative study with ethnographic interviews and focus groups, where patients indicated that they rarely use information leaflets (of OTC products), only when the medication was new or when a side-effect was experienced.[227] We have no direct explanation for these diverging results, except to see them as an artifact of the turmoil in a changing distribution system, with which patients have not yet become familiarised.

1.3.2 Do patients accept PPIs in the drug distribution system?

There are numerous anecdotal reports, showing dissatisfaction with technical inserts (TI) and even with PPIs, because the information presented was too complex, too extensive, not extensive enough, difficult to read, difficult to understand, difficult to remember, causing fear, causing confusion. Surprisingly, this does not seem to affect the overall appreciation of the provision of written information.

Most of the studies on readership described above also investigated satisfaction with communication. Van haecht reviewed an impressive array of studies showing that the introduction of a PPI contributes to a feeling of satisfaction among patients, efforts to produce a more understandable insert are appreciated, and the patient package insert (PPI) is considered to be useful.[38]

In Italy, a large scale prospective study was conducted studying the acceptability of TIs and experimental PPIs of 3 OTC products and 2 prescription drugs, in the wake of the upcoming European regulations.[214] The study found higher satisfaction for the PPI than for the TI with regard to accessibility of content and ease of understanding the contraindications of drug use.

There are indications that too much zeal in trying to lower readability levels of PPIs may lead to dissatisfaction among readers, judging the text as uninteresting and childish.[228]

Emotional reactions to risk information may hinder information transfer and reduce acceptance of the PPI. Our studies indicate that fear arousal by reading inserts, even with ill-designed inserts, was limited to less than one third of the patients.

Confusion (a state of cognitive disarray with a strong emotional undertone) may arise from conflicting information between messages from physicians, pharmacists and inserts, or from information overload. Confusion may be more prevalent when the text is incomprehensible. In Rupf's study, 93% of the patients reading a TI felt somewhat confused, compared to 27% reading a PPI.

In the randomised control trial on NSAIDs, reported in Chapter 4 of Part III, there was no difference in overall (high) levels of satisfaction between the TI group and the PPI group.

It is, however, unlikely that PPIs will relieve dissatisfaction caused by the absence of agendas or insufficient discussion of treatment options.[49] However, we found convincing arguments in our studies and in the literature that providing written drug information is perceived positively by the majority of patients, as the majority of patients desire drug information, but do not often get it from health care providers or recall having received it. This satisfaction with written drug communication will probably reinforce pre-existing satisfaction with physician-patient interaction during the consultation. PPIs may relieve frequently occurring dissatisfaction caused by

unfulfilled information needs, once the drug treatment option is considered and accepted.

2 Discussion of Part III

Benefit and risk of treatment are concepts with vast connotations. The literature on the subject is extensive and it is easy to get lost. We will stick to the discussion of empirical data about the impact of an intervention (the patient package insert) on subjective cognition (benefit/risk perception of medication).

2.1 Round-up of the interventional studies on benefit/risk perception

We worked on new designs to introduce written drug information in the context of clinical trials, without jeopardizing concealment of allocation. We acquired some experience with electronic monitoring of patient compliance and with finding new ways for expressing these data. We tested two different scales to evaluate benefit/risk perception by patients. We worked with self-administered questionnaires to explore the process by which patients are experiencing, reporting, and attributing health problems possibly related to their medication.

This work on measurement instruments was exploratory, as it was considered premature to engage in formal validation procedures.

The publications of Part III can be grouped as:

- a qualitative review of the impact of written drug information on patient compliance from a conceptual point of view
- two ill-fated attempts to explore the impact of written drug information on antihypertensives:
  - atenolol versus lisinopril, presented in Chapter 2 of Part III, where the blinding of allocation was biased, and hence the results could not be considered as conclusive
  - the halted atenolol versus placebo study, briefly discussed in Chapter 4.2 of Part III, without results
- two intervention studies with conclusive results
  - a clinical trial of two type of inserts for NSAIDS for pain in acute injury, presented in Chapter 4.1 of part III
  - a clinical psychology study on benefit messages, presented in Chapter 3 of Part III.

We will limit ourselves in this discussion to the empirical results of the two conclusive interventional studies.

2.2 Results of the two conclusive studies

We will first list the main findings of these studies separately, and then confront our findings with other studies on this subject.

2.2.1 Results of the NSAID study by Van haecht

First, we would like to stress the clinical setting in which these results were obtained, namely the short treatment of joint or muscle injury. The main conclusions are as follows:

- insert readership is independent of the type of insert
- highly educated patients are more likely to read inserts
- overall satisfaction with inserts is high, independent of the type of insert
- the PPI was judged to be more understandable and less vague than the TI
- benefit of medicines is rated high by patients, whether or not they read inserts
- reading the PPI reduced the positive benefit perception somewhat and sharpened the risk perception somewhat
- reading inserts resulted in a higher rate of experiencing health problems, a higher rate of attribution and a higher rate of stopping therapy because of presumed side-effects
- reading a PPI resulted in higher rates of spontaneous reporting of health problems.

2.2.2 Results of the benefit study

As for the results of the benefit study, we would like to stress the fact that this is a study in human volunteers and not in patients. The study fount that:

- people who are not presented with written drug information have a positive prejudice toward the benefit of medicines, but know little about their risks
- reading an insert increases knowledge about the medicine
- among readers of a PPI without benefit information, the percentage of readers with a positive benefit/risk perception was lower than among controls
- among readers of a PPI with benefit information, the percentage of readers with a positive benefit/risk perception was not lower than among controls.

2.3 Integration with the literature on benefit/risk perception by patients

A number of reviews and conceptual articles have been devoted to the cognitive processes of medical decision-making by patients, general risk information,[229][230][231] information on the risk of treatment,[232] and drug information.[233][234][235][236][237][238][239][240]

In addition, researchers have pointed to the detrimental effects of information overload and fear arousal on the limited ability of most patient to process risk information.[236][241]

The seminal paper on cognitive processes in response to written drug information is by Morris and Aikin. In this article an analogy is drawn between how the brain processes risk information and how the body processes drugs.[233]

Direct measurement techniques of how people perceive the risk and benefit of drug treatment are scarce and riddled with methodological problems. Examples of such research can be found in studies focusing on public perception of pharmaceutical risk among other environmental and medical risks[242][243][123][124] and on differences in risk perception between different drug classes.[244]

In pharmacoeconomic research, "willingness to pay" techniques and standard gambling techniques are used to assess patients' perceptions of drug value.[245] This can also be seen as an attempt to measure subjective benefit/risk assessment by the patient.

In two studies presented in Part III of this thesis, scales were presented for direct assessment of either risk or benefit, or a composite measurement of benefit/risk weighing. It has been argued that it is impossible to dissect benefit and risk perception processes in the mind, and that one should only look for composite measurements of benefit/risk perception.[246] However, in most intervention studies, the effect of risk communication is most often measured by behavioural results, such as patient choices between two possible treatments or patient compliance, and not by a direct measure of benefit/risk perception.

In a recent systematic review of one-to-one risk communication interventions in health care, the focus was predominantly on oral communication and on behavioural change.[225]

The study by Van haecht (presented in Chapter 4.1 of Part III) is a rare example of a clinical study with direct measurement of benefit/risk perception of drugs.

In the field of benefit communication, research is even scarcer and limited to experimental psychology studies. Misselbrook and Armstrong reviewed patients' perceptions of the benefit of treatment in reaction to different numerical expressions of reduction of the risk of illness.[247] In our experimental study, presented in Chapter 3 of Part III, we ascertained a potential impact of a short paragraph (approximately 80 words) in the PPI

(approximately 800 words) about the benefit of the medicine on the benefit/risk perception of human volunteers.

For a thorough proposal for a research agenda to improve our understanding of the cognitive aspects of benefit/risk perception, we refer to Lilja.[248]

3 Suggestions for further research

A researcher may reflect on the results of other authors, on the relevant theoretical frameworks, on the experience with new measurement tools and on the interpretation of one's own results. This leads to hypotheses for further research, to be tested in new studies, and consequently confirmed or refuted. From the work presented here, we have derived a number of hypotheses, which we will list below.

- The characteristics of disease and treatment are intricately related and mould together, when patients create mental perceptions of risks and benefits of a treatment for a disease in a specific clinical situation.
- The results of intervention studies on modifying compliance, obtained in a particular clinical setting, should not be generalised too easily to other clinical settings.
- Deciding to start a medicinal treatment (after reading the insert), will result in new experiences, which will change the nature of the stimuli that lead to the coping action. Changes in disease representation and in the emotional status from before the coping action have also been observed, and these changes will form the basis of the appraisal of the coping action.
- In clinical trials involving drugs with noticeable signs and symptoms of drug action or with noticeable signs of fading drug action or a high frequency of minor side-effects, it can be hypothesised that patient compliance and the perception and attribution of adverse reactions will probably be influenced by written drug information, resulting in differential occurrence of dosing irregularity, drug holidays or dropout.
- Making inserts more understandable by shortening sentences and getting rid of medical jargon reveals more clearly that the content of the insert is unbalanced, with an excess of risk information. If improving readability does not coincide with improvement in communication of risk and benefit information, then potentially beneficial effects of written drug information will be reduced.
- Adding a section of benefit information within the patient package insert helps to integrate increased knowledge about medication into a more balanced benefit/risk perception.

By focusing on acceptance and benefit/risk perception, we have selectively addressed positive aspects of the impact of the PPI. For a full appraisal of the impact of the PPI, the behavioural effects of the PPI need to be addressed. The following topics merit further research into the effect of the PPI on:

- effect on attribution and reporting of health problems
- patient compliance
- other behavioural aspects
  - avoiding medication errors
  - reacting adequately to side-effects
  - observing precautions outcome.

4 Recommendations for future developments with regard to patient package inserts

Patient package inserts have become an established part of the drug distribution system in the European countries and in a host of other countries. Given the strong tendency to international harmonization in pharmaceutical regulations, it is more likely that PPIs will eventually also be generally introduced in the US and in Japan, rather than abolished in Europe. Continued interest in enhancing the quality of this traditional printed medium is warranted, even more so in the light of the general penetration of information technology.

4.1 Improving the quality of the scientific data sheet to produce better PPIs

Reducing information overload is an important endeavour in high quality risk communication. Hence, it is crucial to be able to discriminate between noise, signals, events and reactions in relation to a specific drug. Hopefully, advances in pharmacovigilance and scientific risk assessment will help to strike a better balance between information overload and relevant risk information in the future.

More systematic reporting of pharmacokinetic and pharmacodynamic data may make it easier to assess the clinically relevant items to be transposed to patient information. Proposals for a standardised assessment of the quality of the technical clinical pharmacology information in drug labelling for professionals have been made.[249] Two potentially important information items are often underreported in technical drug labelling.[249] Firstly, information on the mechanism of action of the active ingredient may be useful. Secondly, information on the clinical consequences of interrupting drug dosing may be important.[250] A good example of the latter can be found in the US

patient package inserts for oral contraceptives, which carry an item "What to do if you miss a pill?".[251]

All claims of efficacy in drug labelling have to be accepted by the regulatory authorities. However, lists of possible indications may be accompanied by a grading of the level of evidence in support of such claims. Such grading scales have been developed for professional guidelines, and may also be used in drug labelling. Moreover, where available, references can be made to meta-analytic synthesis of effect sizes.

More controversial is the addition of information about the decrease in effects size in various patterns of non-compliance. A historical example of this can be found in the labelling of the lipid lowering drug colestyramine.[252] One may argue that more effort is needed to provide enough numerical data about effectiveness of drugs in everyday practice (in contrast with efficacy data from clinical trials) to underpin benefit messages about the merits of full compliance.

It is possible that with growing maturation of health outcome research, quality of life research and pharmaco-economics, these new forms of benefit information will find their way into drug labelling and ultimately into patient drug information.[253][254]

4.2 Solving liability issues as impediments to high quality communication

Fear of liability has been a strong incentive for full risk disclosure in drug labelling for professionals.

European legislation on drug labelling in 1992 clearly stipulated that risk information should be conveyed in patient package inserts. It sets the stage for full but balanced risk disclosure, making overt legal prudence superfluous. In the European courts with the Napoleontic legal tradition and in the UK courts with a Common Law tradition, liability claims for adverse reactions to medicines have seldom been introduced or sustained.[255] In the absence of no-fault compensation systems, this situation is only acceptable if high quality risk information is provided to the public.[256]

In the USA, where liability claims are harsh reality for manufacturers, the line of defence has been the "learned intermediary" doctrine. In this line of reasoning, companies cannot be sued for harm caused by medicines to patients, as long as the company has fully informed the physician and the pharmacist (the learned intermediaries), who will then inform the patient. This situation had two consequences. Firstly, drug labelling for professionals tends to be excessively exhaustive. Secondly, the USA pharmaceutical industry has not embraced the concept of the patient package insert, as it would undermine their liability defence. However, there is ample evidence that health care providers (the learned intermediaries) do not routinely engage in elaborate activities of providing risk information about medicine. Hence, this legal

doctrine is far from being evidence-based. It has been criticised as an inadequate system for informing patients about the medicines they use.[257] The approach will be difficult to sustain, with increasing switches from prescription to over-the-counter status,[258] increasing penetration of direct-to-consumer advertising for prescription drugs,[259][260][261][262][263] the advent of other forms of manufacturer-affiliated communication in the information age,[264] and attempts at coalition forming between the industry, patient educators[265] and patient advocacy groups.[266]

It is time for the legislators to make the necessary adaptations to legal doctrines, so that the liability impediments to the production of a high quality tool in drug information can be lifted.

4.3 Avoiding inconsistency between patient package inserts

A weak spot of patient package inserts is the lack of consistency in length, content or structure between the different patient package inserts of medicinal products with the same active ingredient. This is the inevitable consequence of the final authorship of this document by the manufacturer. In times of frequent shifts from original brand to generic and from generic to generic, this may be confusing for patients.[267]

Inconsistencies may be generated by diverging company policies, but also by inconsequent or incompetent regulatory control. Sometimes, economic policies of primary or secondary patent protection are involved.[268]

Reviewers in the regulatory agencies should have the tools to compare PPIs from different medicines with the same active substances, and if possible with a generic template for frequently used active substances.

Some guidance in the translation of technical terms into popular terms would be welcome, as diverging attempts to simplify medical jargon may result in a Babel-like confusion. This is especially true for the names of pharmaceutical groups, necessary for consistent cross-referencing, e.g. in the sections on drug-drug interaction.

With regard to the risk of taking the drug during pregnancy and breast feeding, international bodies have proposed a range of specific formulations, reflecting the current state of knowledge about the risk of each active substance.[269]

4.4 Investing more expertise in the production and testing of PPIs

4.4.1 A multidisciplinary approach to the production of PPIs

More and more pharmaceutical companies have realised the importance of a well written PPI for the image of their product at all levels. Other companies

still view the task of writing PPIs as a necessary bureaucratic nuisance, which can be left to the local regulatory affairs manager, assisted by a lawyer.

Writing a good PPI involves the collaboration of the medical and marketing director, and the involvement of linguistic experts, communication specialists, psychologists, specialists of instructional manuals, and experts in graphical and functional design. Typographical expertise is critical for documents, where the pressure to use small print is high.[270] Use of pictograms is a tricky issue, that should be left to experts.[271]

The functionality of the text can be greatly enhanced by involving users (patients) from the early conceptual phases to the completion of the document.[272][273][274]

Multinational companies will need to elaborate document management systems to oversee different versions of one PPI, to ensure a house style in the PPIs of their drugs, and to coordinate translations and regulatory adaptations for the PPIs of their drugs in different countries.

4.4.2 Testing PPIs

Readability testing by means of computer programmes is an often forgotten means of quality control in the production process.[275] The popular general purpose word processors nowadays have this function built in, but adaptation to the specific domain of written drug information is necessary. This can be achieved by constructing controlled vocabularies.

However information technologies cannot be a substitute to user testing. There are simple ways and more sophisticated ways to put drafts to a panel of users.[128][276] The EMEA has recommended one particular method of user testing, putting perhaps too much emphasis on one of the possible approaches.[96] Nevertheless this is a breakthrough: it was accepted that results of user tests could be brought into the discussion between a company and the regulatory authorities.

In the previous decade, a number of formalised measurement techniques have been developed for user tests, focusing on user satisfaction,[277] the effect on self-efficacy,[278] and on the overall assessment of design quality.[279] Some techniques focus on the suitability of the text to sustain shared-decision making,[280][281] but as stated previously, this might be a little bit outside the scope of the PPI, which we regard as an instrument for informed compliance (or non-compliance), rather than an instrument for informed choice between different treatment options.

More attention should be given to an integration of testing and appraisal of the PPI in the regulatory approval process. No company wants to risk delay in registration due to a dispute over the wording of a paragraph in the PPI. The rush to registration may be so hectic that there is little time for multidisciplinary discussions and user testing in the production of a PPI. Hence, a proposal could be to acknowledge the preliminary character of the PPI added to the registration dossier. While price and registration discussions

are conducted, the PPI could be further improved and tested, with another submission of a final PPI, six to twelve months after registration.

4.5 Linking up with new media for patient drug information

Besides the patient package insert, there are many other forms of written drug information. Written drug information can be handed out by physicians or pharmacists, in preprinted forms or generated on the spot by printing machines, connected electronically to a collection of drug monographs. Numerous drug books with general information on drug taking and essential information on the popular medicines are published in many countries.[282][283] For numerous ailments, specific leaflets, pamphlets or brochures have been written, focusing on self-management, treatment options, shared decision making, or drug taking compliance.

The attraction and impact of the content of printed media can be enhanced by taking it into the realm of multimedia. Television, video[284] and computers may display a richer and more appealing array of messages, but remain in their simple form examples of uni-directional mass communication, requiring more technical and educational skills and generally more money. Internet technology has provided cheaper production of programmes, cheaper distribution and almost global connectivity. Drug information can now be provided through the Internet on kiosk screens or PC terminals, in the physician's surgery or in the pharmacy,[285] or in the privacy of the patient's home.

A striking feature of these electronic media is the ability to react to the consumer's input (interactivity), so that the user can navigate through the information and decide to what extent he/she wants to be informed.[286] Moreover, the content and style of the information can be adapted to the users' characteristics (individualization), such as sex, age, native language, educational level, and even coping style in risk information seeking.[287][288][289]

However, these fascinating developments will only supplement and not substitute the face-to-face dialogue with the health care professional, neither will they, in my opinion, obviate the need for the presence of a PPI in drug packages.

4.6 Integrating Evidence Based Medicine in PPIs

Traditionally, the source of information for the PPI is the pharmaceutical company, but the content is approved by the regulatory authority, in collaboration with the national centre for pharmacovigilance, in many countries united into one institution. This makes the PPI an authoritative source for the patients. The experts of regulatory authorities advise on whether or not a new product can be marketed and which indication,

contraindications and side-effects are to be listed in the PPI. Usually, there are yes-or-no discussions on whether a specific item should be listed or not, with occasionally fierce fighting over the subtle wording.

In the final text, there is little room to refer to the original evidence for the decisions to list or not to list a particular indication or side-effect. The original studies are often not referenced, neither is there referral to the quantitative details of these studies. Statements in the PPI are seldomly accompanied by the level of evidence, in contrast to what is often the case in more elaborated practice guidelines.[290]

One solution could be to build bridges of information between the PPI and national Drug Information Centres (DICs), closely linked to the registration authorities. Such centres exist in many countries, with the aim of providing independent drug information to health professionals, and increasingly to patients.[291]

A number of these DICs have brought their drug bulletins and formularies to the Internet, and have gained experience in communicating with their audience through this new medium. By inserting a link to the Drug Information Centre in the Patient Package Insert, access to more elaborate and more generic evidence-based information on indications and side-effects of specific products can be provided. It will be a challenge to integrate the difficult notions of evidence-based medicine and the desire to provide understandable information on the complex issues of risk and benefit of medicines,[292] Examples,[293][294][295] recommendations[296] and quality criteria[297] are beginning to emerge. Moreover, gateways should be available to more general information sources supporting shared decision-making (e.g. the Cochrane Collaboration Consumer website),[298][299] with clear criteria to rate the quality of health related websites.[300][301][302][303]

4.7 Intensifying the interaction between "learned intermediaries" and the PPI

Health care providers in primary care (physicians and pharmacists) have traditionally taken a rather negative attitude to the provision of written drug information in the form of PPIs. The associations of pharmacists in the US and also in Europe, however, have increasingly been engaged in a number of health education projects, including written (or multimedia) drug information.

There is little communication between physicians and pharmacists,[304] and hence, there is poor coordination between information given by the physician, the pharmacist and the PPI. Very little research has been done on the effects of a positive reinforcement of the messages in PPIs by health professionals and about using the PPI as an instrument for communication between health care providers and patients.[305][306]

Hopefully, more physicians will realize that good communication with the patient, supported by relevant information, is important to achieve rational

and effective prescribing.[307] Moreover, the information gap between patients and professional health care professionals has been closing since the advent of the World Wide Web, as patients increasingly have access to the information sources for professionals.[308][309]

Health care professionals should adopt a more positive attitude towards PPIs, and accept that they have an important supportive role in the flow of drug information toward the patient. Physicians and pharmacists should adapt to better educated patients with better drug information sources, such as the PPI and the World Wide Web. On the one hand, persuading patients to continue chronic drug therapy with inconvenient side-effects will be increasingly difficult. On the other hand, it will be more difficult to persuade patients to start necessary treatment with inconvenient side-effects. In the former situation, physicians will be forced to reconsider their choice of therapeutic groups. The latter situation is an appeal to the art of convincing patients to do what is necessary, despite inconveniences.

4.8 Embedding PPIs in health education and public health policy

Health education has become an established part of public health in many sectors of health care and prevention. With regard to pharmaceuticals, regulatory health authorities should realize that "educating prescribers as well as patients may be a critical ingredient to an evolving and still imperfect framework of drug policy".[310]

In 1996 the World Health Organisation organised a global survey on the activities of nations in the area of public education in rational drug use.[311] The study concluded that there is a well evidenced and compelling need for public education in the appropriate use of drugs, with potential benefits for the individual, the community and the policy-makers. The study found that in most national drug policy documents, public education on drug use is included as a core element. Nevertheless, a lack of commitment to systematic and structured public education in rational drug use was observed in developed as well as in developing countries.

Recommendations can be found in the literature for both epidemiological approaches to target drug information[312] and to design health education interventions,[313][314] which can be adapted to the subject of pharmaceuticals.

In Europe, there has been a clear policy on the role of written drug information in the distribution of medicinal packages with the introduction of mandatory patient package inserts in 1992. The implementation of this legislation, however, has been lagging.

In many countries, the government has supported Drug Information Centres, producing independent drug information for professionals but increasingly also for patients

Some countries have fully supported the Evidence-Based-Medicine (EBM) movement and provided logistic support for the production and dissemination of the EBM information products. In the near future, we could witness open access for health professionals as well as for patients to high quality independent drug information services through electronic libraries.[315]

The continued physical provision of high quality written drug information in the form of PPIs (preferably with links to the independent sources of information) can only strengthen these new developments. This mix of interventions will put education about pharmaceuticals at the core of drug and health policy.

5 Final Conclusions

Patient package inserts are an essential part of modern drug distribution systems and a tool for patient education and health policy. Routinely provided inserts are read by the vast majority of patients and have a positive impact on patient satisfaction, regardless of their quality.
A drug distribution system with patient package inserts has been accepted and welcomed by the population.

High quality patient package inserts have a proven positive impact on knowledge about drugs in those patients who read the insert. The effects on readership, satisfaction, and on knowledge alone may warrant their automatic provision, each time a medicinal product is dispensed, with or without prescription, in spite of the slightly higher distribution costs. These are strong arguments for the universal application of the European system of mandatory and comprehensible patient package inserts. Additional claims of positive behavioural effects of PPIs on patient compliance have barely been demonstrated. The evidence is limited for an impact of current PPIs on the reduction of medication errors and off-label use, on the observance of precautions, and on the stimulation of adequate reactions when side-effects occur.

Benefit/risk perception is an important cognitive concept for understanding patients' mental processing of written drug information in patient package inserts. Direct measurement of benefit/risk perception with more validated tools is necessary for an improved comprehension of the relation between benefit/risk perception and behaviour. This may be crucial to our ability to design (and retest) better patient package inserts, to help patients make informed and shared decisions about adherence to drug treatment, and to assist them in the proper and safe continuation of treatment. One instrumental aspect of writing better PPIs may be the introduction of an elaborate benefit section. By combining benefit messages and risk messages in the patient package insert, improved transfer of information and a more balanced benefit/risk perception may be achieved.

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