CHAPTER 1: Introduction

1.1. General

It has been said that "a medicine comprises both the drug formulation *plus the information* that a patient receives with it"[1]. This could be said of the prescribing information available for the drug.

Originator products have to prove quality, safety and efficacy prior to licensing, and research provides the basis for prescribing information [1]. Generic products have to prove quality and inter-changeability [1]. Both have a responsibility to ensure the prescribing information for their products remains congruent with current clinical research.

Information regarding the safety and efficacy of a drug reaches the public domain by various means (and to varying extents) via i) company-generated and regulatory authority-approved documents eg. the Summary of Product Characteristics (SPC) in the European Union (which is a lengthy product-specific description prepared through collaboration between the pharmaceutical industry and the Committee for Proprietary Medicinal Products of the centralised European Medicines Evaluation Agency, EMEA) ii) package inserts and patient information leaflets, which may or may not undergo formal review and approval nationally iii) independent and regulatory authority internet websites iv) formularies v) literature databases and vi) regulatory authority publications [1, 2, 3].

Safety and efficacy information should be common to both originator and generic products for any given drug substance. The package insert in scientific language (or the Patient Information Leaflet, which contains the key information in patient-friendly language) may be the only source of appropriate prescribing information available within a specific country or location of a particular healthcare facility, depending on available resources. For this reason it is essential that the key information relating to safety and efficacy should not differ between various brands of the same drug substance, eg. between the originator brand and various generic brands [1, 4]. Similarly, and particularly in today's world of easy access to comprehensive drug information, eg. via the internet, there should be substantial agreement between the texts in various countries to

incorporate best clinical practice, current experience and information from international pharmacovigilance databases [1]. Standardisation of information is vital to providing consistent, comprehensive key summary information for drugs within therapeutic groups and across various brand formulations of the drug.

A literature survey was conducted to obtain a perspective of the experience in a number of countries – this has yielded limited information regarding prescribing information available nationally, and international comparisons, but some commonalities are seen. Some of these studies are discussed below.

An assessment was carried out of manufacturer-provided prescribing information from 37 package inserts for generic brands of atenolol, fluoxetine, ciprofloxacin, metformin and omeprazole manufactured in the Middle East and marketed in Saudi Arabia, versus the British National Formulary (the standard reference selected) and versus the originator product [5]. Substantial disagreement was found between both the generic package inserts and the two comparators. This study recommends that national authorities should implement appropriate measures to remove "misleading and incorrect information in generic package inserts and to incorporate crucial prescribing information that is missing", and that common quality standards be adopted for the region.

Another Middle Eastern study compared ten non-steroidal anti-inflammatory drugs marketed in Saudi Arabia versus their corresponding US labels. Results were substantively similar, ie. Saudi-marketed products generally conveyed limited and incomplete information, and package inserts of the same drug product from various pharmaceutical companies (generics) showed wide variation in the amount of information provided.[6]

A study was carried out in Nigeria in 1983 of drug labelling information contained in national product package inserts compared with similar information in the United States Physicians' Desk Reference (as the standard reference), against the background of the improved drug control regulations introduced at that time in the country. The results indicated in the researcher's opinion, that "most multinational pharmaceutical firms,

especially through their affiliates and subsidiaries, overpromote their drugs for extra indications and mention fewer hazards in their product package inserts than in the United States Physicians' Desk Reference….in product package inserts destined for countries with a literally free drug market." [7]

A small multinational study performed in six European countries investigated the availability of information for marketed pharmaceutical products to doctors and patients, as well as the legal status of the drug compendia published in each country and the implementation of EC Directive 92/27/EEC on labelling and packaging. The study was limited due to difficulties in obtaining package inserts in each of the countries – however, the limited analysis revealed "some differences in the content and presentation of data for doctors and patients." [8]

Some perspective or partial explanation may be provided regarding this widely observed variation in national prescribing information, by a study that was carried out to investigate the differences that exist in the commercial drug compendium monographs available in first world and third world countries. The content of the three first world compendia examined (ie. The Physicians' Desk Reference, ABPI Data Sheet Compendium and the Rote List) was found to be variable, with the Physicians' Desk Reference consistently more comprehensive than either of the other two compendia. In addition, a sample of fifty eight monographs from third world compendia representing five commonly prescribed drugs from the World Health Organisation's Essential Drugs List was selected; the monographs were found to be less comprehensive than those in any of the three first word compendia, and contained approximately 5% inaccurate information. In this study, however, sampled monographs for drugs supplied by multi-national pharmaceutical firms were found to contain the same amount of information as those for drugs supplied by domestic firms (generics).[9]

In the opinion of Dr L Rägo, Quality Assurance and Safety: Medicines, World Health Organisation, "Published studies addressing drug information in general, and readability of patient information have been found, but very little was found specifically addressing

the issue of documenting differences in key aspects of drug information among countries for the same drugs" [1]. Certainly, conflicting information seems to have arisen from the numerous small and/or national studies surveyed.

As a result, in 2003, a systematic, collaborative, international comparative study was carried out by the Drug Information Collaborative Group in association with the Quality Assurance and Safety; Medicines, WHO, to study drug information across various brands of specific drugs in 26 countries (including America – 8 countries, Europe – 8 countries, Africa – 4 countries, Asia & Australasia – 6 countries) [10].

Three widely used drugs were selected from the top 30 drugs in terms of global sales in 2000 (ie. ciprofloxacin, fluoxetine and nifedipine). Written prescribing materials approved by national regulatory authorities were collected where they exist, or where these materials do not undergo national approval, the materials available to health professionals and patients were collected. Material originating from the same company in the various countries was used wherever possible. The reference was the British National Formulary (BNF) due to its world-wide reputation for being a complete, independent, reliable and practice-oriented source of information, widely used around the world as it is easy to obtain and inexpensive.

Results showed that substantial disagreement exists in the materials available to prescribers and patients in different countries, and that even within a single country, disagreement was found in the materials from different brands of the same drug. Only two countries reflected all the BNF indications for ciprofloxacin, three countries for fluoxetine and eleven for nifedipine. Over a third of the sample disagreed in terms of the dosage range recommended by the BNF for nifedipine and fluoxetine. No countries reflected all the major side effects listed in the BNF for ciprofloxacin and fluoxetine and only one country reflected all the BNF side effects for nifedipine. No materials from any of the 26 countries included all the cautions in the BNF – of the 19 cautions in the reference, the worst case was where only one was listed in the package insert from one country. Besides the expected high degree of agreement of materials from the UK

(although never complete), only Italy and USA showed a high proportion of agreement for at least two drugs. Countries reflecting high levels of disagreement in at least some materials analysed included Argentina, Philippines, Mozambique, Poland, Egypt, India, Tunisia and Venezuela. However, a large inter-drug variability was observed, since countries with a high proportion of agreement for one drug showed a low proportion for another. Intra-country comparisons also yielded dissimilar indications, dosages, side-effects and cautions between different brand names of the same drug. [10]

Theoretically, prescribing information is based on an assessment of clinical studies and post-marketing surveillance activities. In the majority of the cases studied, the materials collected related to products of the same mother company, so it could have been assumed that the same basic facts should have been used to make decisions regarding indications, dosage, side-effects and cautions. However, results showed that prescribers and patients are recommended substantially different things in different countries, and the authors believe that this may be due to the fact that national authorities may not conduct a full and systematic assessment of world-wide data before approving prescribing materials. [10]

The role of the national regulatory authority remains key in terms of the contents of their national prescribing information, yet practically many authorities are severely resource-constrained and their task is difficult in the face of the amount of documentation submitted to them. The author of this study [10] concluded that the first vital step is "in recognising the situation and its implications in terms of patient safety, rational drug use and the credibility of regulatory work", and suggests a "simple" measure already in use in some countries could be implemented, namely "requiring that prescribing information for all pharmaceutical equivalents be the same as that approved for a reference drug". [10]

Another suggestion has been made that a new kind of SPC would be more valuable to a prescriber than the current brand-specific one, ie. a composite SPC which would compare the intrinsic properties of the various products within a drug class (eg. angiotensin-converting-enzyme inhibitors), such as the format used by the USPDI (United States Pharmacopoeia Drug Information) [3]. South Africa is one such country to recently adopt

the approach of a composite SPC, and the Medicines Control Council has begun a project of developing "Standardised Package Inserts" (SPI's), which may go some way towards optimising the standardisation of nationally-approved prescribing information.

1.2 Local Scenario

In South Africa, the provision of appropriate, relevant prescribing information to our diverse population is complex both in terms of the key information to be supplied and the method of communication.

Historically and up to the present time, the package insert (which generally uses complex scientific terminology) contains the legislated prescribing information for the product, and must accompany every pack of approved medicines. The text is formally approved by MCC in the pre-approval phase, and alterations are not permitted without approval.

The simplified Patient Information Leaflet (PIL), which uses patient-friendly language, have been legislated in terms of format and content, for some years by the Medicines and Related Substances Control Act 101 of 1965, as amended [11], and in the General Regulations of 2003 to this act [12]. The PIL was intended to replace the scientific package insert at the interface between the healthcare professional and the patient, whilst the scientific package insert was intended to remain the legally-approved source summary of product characteristics for the healthcare professional.

Guidelines for compiling the PIL were published by the Medicines Control Council (MCC) in 2004 [13], using the approved, scientific package insert as the source document. However, resource constraints at the MCC in approving PIL texts submitted by manufacturers, as well as diverse practical problems around the translation (into all eleven official languages), implementation, distribution and version control at the dispenser/patient interface of these materials has to date, resulted in few PIL's being distributed with the medicines and reaching the patient.

As a result, the scientific package insert, which is usually in English and Afrikaans only, currently remains a key source of written prescribing and patient information regarding prescribed medication in South Africa.

The scientific package insert remains the baseline for the future evolution of prescribing information in South Africa, so it is the belief of the author that it is important to establish the extent of variability of package insert information that currently exists locally, so that appropriate policy decisions can be made to regulate such documents in the future. It is thought that significant variability in key information contained in package inserts in South Africa is unlikely between various brands of specific drugs (ie. originator and generic brands) for the following reasons:

i)The MCC rigorously evaluates and controls the content of each individual package insert at the time of licensing every prescription medicine

ii) Historically, all generic products registered by MCC had to carry *identical information* to the originator's package insert (irrespective of possible trademark infringement and subsequent legal action in a few cases) , and

iii) Standard reference texts had to be complied with, eg. Goodman & Gillman, for safety aspects and Martindale for indications and dosage.

However, divergence may take place in the post-registration phase. It is the usual practice of originator companies to update their prescribing information periodically in line with EU and US requirements, based on phase IV clinical trial data, pharmacovigilance activities and ongoing research. This may not be the case with products from non-research-based (generic) companies, and materials from such companies may become outdated, as no regulatory mechanism exists in South Africa to ensure that regular review and updating of all package inserts in the post-registration phase, in fact takes place.

Furthermore, the number of generic products currently being licensed in South Africa is expanding exponentially in line with the National Drugs Policy [14] and the Essential Drugs List of South Africa (EDL) [15], so it is important that controls are implemented pro-actively to prevent potential divergence of key elements in the prescribing information. Parallel importation of products is now provided for in the legislation, as is international tendering [11, 12], and these could potentially result in further divergent materials reaching the South African public, unless appropriately controlled, as the prescribing information from potential source countries may exhibit significant variability, as was found in the WHO study [10].

Against this background, and recognising the need for standardisation of prescribing information across various brands of any given drug/therapeutic class sourced from various countries, the MCC has begun formulating Standardised Package Insert texts (SPI's), which will form the minimum key information to appear on the scientific package insert for a given drug. These are intended to be dynamic documents kept in line with current standard international reference texts, and based on prescribing information available in the international MCC-designated Reference Countries (eg. USA, UK, Canada, EU, Australia), where routine updating of product texts in line with current clinical practice is obligatory.

The SPI's will be the independent reference texts for package inserts in South Africa, in both the registration and post-registration phases. The SPI's will be implemented on an incremental basis both in the pre-registration phase (eg. of new generic brands, and where relevant, for new chemical entities), and in the post-registration phase. The latter would be either during routine industry-initiated package insert updates, or at the five-year product licence renewal period (which has been legislated but is yet to be implemented), or at another period to be determined.

Unfortunately, the policy for development of the SPC's has not been clear. Some have been developed per drug class (eg. ACE inhibitors), while some have been developed for specific active ingredients (eg. Fluoxetine). There has been no differentiation between

texts for different dosage forms (eg. Extended release tablets and paediatric suspensions, ref. the SPI for Clarithromycin), where the safety profiles may differ. Once developed, the texts have not been published for general access by the industry.

1.3 Motivation for the Study

In order to effectively manage a situation, it is necessary to first measure it - it is the belief of the author that a comparison of the key prescribing information in the package inserts currently available for a selection of widely-used drugs, would be a valuable baseline indicator of the actual extent of agreement between:

i) current, local package inserts of generic brands versus the originator brand, and between

ii) the MCC Standardised Package Insert for the specific drug/class, and both the current local originator package insert and the prescribing materials from countries which MCC cites as Reference Countries

This information could serve as an early validation study of the SPI development project, and would assist local regulators in formulating policies to regulate the content of package inserts (and in the future, PIL's).

CHAPTER 2: Aims and Objectives

The provision of consistent, complete and up to date dosing and safety information, both to healthcare professionals and to consumers, is vital to minimize the likelihood of inappropriate prescribing and use of medicines. Local package insert safety texts should not diverge from those in international reference countries or from the outcomes of international clinical research.

The aims of this study were to investigate:

- the consistency of the local prescribing information that is available to the public and to heathcare professionals, when considering originator and generic brands of medicines

and

- how much agreement there is between the Standardised Package Inserts, that are currently being introduced by the Medicines Control Council as the 'gold standard' text for adoption by all brands going forward, when compared with the prescribing information of originator, research-based company plus that available internationally

The objectives of the study were to investigate:

- the variability of key information in the current approved package inserts of the originator product versus generic brands of the same drugs
  and
- the extent of variability between the Standardised Package Insert (SPI), and the approved prescribing information for the originator brand plus that from four, major MCC-designated international reference countries, for the same drug substances

CHAPTER 3: Methodology

3.1 The study sample

Five drugs were selected for assessment, from three major therapeutic classes (ie. antihypertensives, anti-infectives and antidepressants). The drugs selected were enalapril, fluoxetine, ciprofloxacin, amoxyclav (ie. amoxycillin+clavulanic acid) and atenolol.

Inclusion Criteria – for drug selection:

i) The drug should be widely used in South Africa

ii) The drug should be used for treating major diseases, such as those identified by the WHO (eg. infectious diseases, hypertension, etc.) [16]

iii) The originator product plus at least five generic brands should be registered and currently available in South Africa

iv) An MCC Standardised Package Insert text should be available for the drug substance or class, as the reference comparator document

The drug should appear on the Essential Drugs List of South Africa [11], as an additional selection *preference.* i) – iv) are minimum inclusion criteria.

3.2 Methods of Data collection

Local, approved package inserts of registered products were obtained from local retail/state dispensaries.

Internationally approved prescribing information was downloaded from websites of regulatory authorities (eg. EMEA, FDA) or recognised reference sources (eg. BNF, USPDI), or obtained from contacts within the reference country where such approved prescribing information is available without subscription to the website database, i.e. Canada and Australia.

3.3 Structure

The design of this study was adapted from the methodology used in the large international WHO study [6], as it is believed that it permits an objective way of specifying, classifying and comparing drug information both national and international. It provides a suitable statistical model for quantifying degrees of agreement between the various test materials.

Five drugs selected from major therapeutic classes were:

Atenolol	Anti-hypertensive – *β-blocker*
Enalapril	Anti-hypertensive – *ACE inhibitor*
Fluoxetine	Antidepressant – *Serotonin re-uptake inhibitor*
Amoxyclav	Antibiotic – *Penicillin + β-lactamase inhibitor*
Ciprofloxacin	Antibiotic – *Quinolone*

A two-phase model was constructed. The first phase assessed the degree of similarity between originator and generic product package inserts. The second phase assessed the degree of similarity of the MCC SPI versus both the local originator package insert and current prescribing information in the four reference countries (USA, EU, Canada & Australia).

In phase one, Reference Checklist 1 (see Table I, page 15) was constructed, using *all the statements* listed in each of the five local originator package inserts, under Indications, Dosage, Cautions (= contra-indications, warnings and special precautions), Side-effects and Drug Interactions. A manual comparison was made of each of the five generic package inserts, checking whether each of the statements from Reference Checklist 1 was present (x) or not (N). A score-card of variability was compiled for each of the five generic products for each drug (ie. a "5 x 5" comparison).

In phase two, Reference Checklist 2 (see Table II, page 22) was constructed in the same way for the MCC Standardised Package Insert (SPI) for the drug substance/drug class, using *all the statements* listed, under Indications, Dosage, Cautions (= contra-indications,

warnings and special precautions), Side-effects and Drug Interactions in the SPI. The comparators in this case were the local originator's package insert (chosen as a comprehensive comparator because the package insert text is derived from the originator-derived clinical data), and prescribing information for the drug substance/drug class from each of the four reference countries (USA, EU, Canada & Australia). This prescribing information for drug/drug class was obtained directly from the reference country from different sources, and had been approved by the regulatory authorities in the specific country ie:

Reference Country	**Source**
USA	FDA website approved product prescribing information or USPDI website approved prescribing information
EU	EMEA website (approved SPC's) or BNF website approved prescribing information for drug class & drug substance (see "Definitions")
Canada	Package inserts sourced directly from Health Canada
Australia	Package inserts sourced directly from Australia (as MIMS, the TGA-approved prescribing information)

A manual comparison was made of each of the comparator texts, checking whether each of the statements from Reference Checklist 2 was present (x) or not (N). A score-card of variability was compiled for each of the five generic products for each drug (ie. a "5 x 5" comparison). This was also a "5 x 5" comparison.

Statements had to convey the identical meaning to a person with a pharmaceutical/medical background (but the exact wording/terminology could vary) in order to score a (x). At the time that most of the materials evaluated had been approved, the MCC had not yet introduced any requirements to use standardised terminology (eg. the the clinically validated dictionary of medical terminology (MedDRA) for the side-effects section), so some variability in exact wording was accepted, provided the same meaning was conveyed.

Currently available versions of these materials were used, even though the date of publication of many South African package inserts indicated that no recent MCC Council approved updating had taken place (a new date of publication is assigned when MCC Council has given approval to safety and clinical package insert updates). This provided a useful indication of the age of the material in the market (see Definition for Date of Publication, footnotes to Table III, page 32).

All statements categorised under Indications, Dosage, Cautions (contra-indications, warnings and special precautions), Side-effects and Drug Interactions in the originator text (for Reference Checklist 1) or the SPI (for Reference Checklist 2) were included.

All side-effects were included, irrespective of their frequency of occurrence or degree of seriousness, since most texts do not specify this information, and have not historically been required to do so. Side-effects and adverse drug reactions were grouped into one variable named 'side-effects'.

Additional text found in the comparator materials only *was excluded and omitted from the comparisons.*

Table I (Reference Checklist 1) lists the items or statements used within the five sections of the originator package insert (indications, dose, cautions, side-effects and drug interactions)

Table I: Reference Checklist 1 Items for Assessing Agreement of Drug Information Material (derived from Originator Package Inserts)

Drug: Ciprofloxacin **Checklist Parameter: (Total = 122 items)**
Indications: Lower respiratory tract infections: E. coli, Kl. pneumoniae, Ent. cloacae, Pr. mirabilis, Ps. aeruginosa, H influenzae, H. parainfluenzae. Urinary tract infections: E. coli, Kl. pneumoniae, Ent. cloacae, S. marcescens, Pr. mirabilis, P. rettgeri, M. morganii, C. diversus, C. freundii, Ps. aeruginosa, S. epidermidis, S. faecalis. Skin and soft tissue infections: E. coli, Kl. pneumoniae, Ent. cloacae, Pr. mirabilis, Pr. vulgaris, P. stuartii, M. morganii, C. freundii, Ps. aeruginosa, S. aureus, S. epidermidis, S. pyogenes. Gastro-intestinal infections: Infective diarrhoea due to E. coli, C. jejuni, Sh. flexneri, Sh. sonnei. Bone infections: osteomyelitis due to susceptible G-ve organisms. Gonorrhoea. Not effective against Tr. Pallidum. Ps. Aeruginosa infections use aminoglycoside concomitantly. **(8 Items)** **Dosage:** Swallow whole with plenty of liquid. With or without meals. Range = 250 mg - 750 mg twice daily. Duration depends on severity of infection, clinical response & bacteriological findings. Usual duration acute infections = 5-10 days. Severe & complicated infections more prolonged therapy required. Continue treatment for at least 3 days after signs & symptoms have disappeared. Acute uncomplicated cystitis in women = 3 days. Streptococcal infections at least 10 days due to risk of late complications. Lower respiratory tract infections: Mild to moderate 250-500 mg bd. Severe or complicated 750 mg bd. Cystic fibrosis: 750 mg bd (7,5 - 15 mg/kg/day). Urinary tract infections: Acute, uncomplicated cystitis 250 mg bd. Mild to moderate 250 mg bd, severe or complicated 500 mg bd. Skin infections: Mild to moderate 500 mg bd, severe or complicated 750 mg bd. Infectious diarrhoea: 500 mg bd. Bone infections: mild to moderate 500 mg bd, severe or complicated 750 mg bd. Treat for 4-6 weeks or longer. Gonorrhoea: 250 mg stat, single dose. Elderly: As low a dose as possible, depending on severity of illnes & creatinine clearance. I.V. therapy recommended if patient cannot take oral dose or due to severity of illness, or other reasons. Continue thereafter with oral therapy. Impaired Renal or liver function, prolonged half life, dosage adjustment required. Changing renal function/renal impairment & hepatic insufficiency, adjust dose with monitoring of serum levels. Dose adjustment for kidney and/or liver insufficiency (Boxed statement) : i) Creatinine CL $\geq$ 31 ml/min/1.73 m2 $\leq$ 60 ml/min/1.73 m2, max.dose = 1000 mg/day orally or 800 mg/day I.V. ii) Creatinine CL $\leq$ 30 ml/min/1.73 m2, max dose = 500 mg orally or 400 mg/day I.V. iii) Impaired renal function & haemodialysis, max dose = 500 mg orally or 400 mg/day I.V. on dialysis days after dialysis iv) Impaired renal function & CAPD, 50 mg ciprofloxacin I.V. /litre dialysate QID, or oral 500 mg. iv) CAPD patients with peritonitis 500 mg orally QID for v) Liver function disturbances: no dose adjustment vi) Liver & kidney insufficiency [see i) & ii)] **(21 Items)** **Cautions:** (Warnings) History of convulsive disorders - boxed warning. Crystalluria - boxed warning. (Contra-indications) Pregnancy & lactation. Children under 18 years & growing adolescents - boxed warning. Previous hypersensitivity to ciprofloxacin & other quinolones. (Special Precautions) Impaired ability to drive or operate machinery, esp in combination with alcohol. **(6 Items)**

Table I: Reference Checklist 1 Items for Assessing Agreement of Drug Information Material (derived from Originator Package Inserts) (Cont.)

Drug: Ciprofloxacin **Checklist Parameter: (Total = 122 items)**
Side-Effects: Effects on the gastrointestinal tract: Nausea, Diarrhoea, Vomiting, Dyspepsia, Abdominal pain, Flatulence, Anorexia, Oral moniliasis, Pseudomembranous colitis. Effects on Nervous system: Dizziness, Headache, Tiredness, Nervousness, Agitation, Trembling, Insomnia, Peripheral paralgesia, Sweating, Unsteady gait, Convulsions, Increased intracranial pressure, Anxiety states, Nightmares, Confusion, Depression, Hallucinations, Psychotic reactions (may progress to self-endangering behaviour in individual cases), Effects on Sensory Organs: Impaired taste & smell, Visual disturbances (diplopia, colour vision), Tinnitus, Transitory impairment of hearing esp at high frequency, Hypersensitivity reactions: Rashes, Pruritus, Drug fever, Serum-sickness like reactions, Punctate skin haemorrhages (petechiae), Blister formation with haemmorhages (haemorrhagic bullae), small nodules (papules) with crust formation showing vascular involvement (vasculitis), Erythema nodosum, Erythema exudativum multiforme (minor), Stevens-Johnson Syndrome, Lyell Syndrome, Interstitial nephritis, Hepatitis, Hepatic necrosis (very seldom progressing to life-threatening hepatic failure), Anaphylactic /anaphylactoid reactions (eg. Facial, vascular & laryngeal oedema, dyspnoea progressing to life-threatening shock. Effects on cardiovascular system: Tachycardia, Hot flushes, Migraine, Fainting. Other: Joint pain, Hot flushes, Migraine, Fainting, Other: Joint pain, Joint swelling, General feeling of weakness, Muscular pains (imp in pts with myaesthenia gravis), Tendosynovitis, Photo-sensitivity, Transient impairment in kidney function (incl transient kidney failure), Achillotendinitis, Partial or complete rupture of achilles tendon (esp in elderly on prior systemic glucocorticoids), Superinfections with resistant bacteria or yeast-like fungi with long-term or repeated admin. Effects on blood and blood constituents: Eosinophilia, Leucocytopenia, Granulocytopenia, Anaemia, Thrombocytopenia, Leucocytosis, Thrombocytosis, Haemolytic anaemia, Altered prothrombin values, Influence on Laboratory Parameters/Urinary sediment:, Temp ↑ transaminases, Temp ↑ alkaline phosphatase, Cholestatic jaundice esp pts with previous liver damage, Temp ↑ urea, Temp ↑ serum creatinine, Temp ↑ serum bilirubin, Hyperglycaemia, Crystalluria, Haematuria. **(78 Items)** **Drug Interactions:** Incr plasma conc of theophylline and prolonged elimination half life of theophylline, with theophylline, Iron, Antacids containing magnesium, aluminium, calcium or sucralfate (not H2 receptor blockers), CNS stimulation & convulsive seizures with Fenbufen (NSAID), Cyclosporin, increased serum creatinine concentrations, Warfarin (increased effects), Glibenclamide (increased effects), Probenecid (decreased renal secretion of ciprofloxacin and incr serum concentration), Metoclopramide (faster absorption and quicker max plasma concentrations). **(9 Items)**

Table I (Cont.): Reference Checklist 1 Items for Assessing Agreement of Drug Information Material (derived from Originator Package Inserts)

Drug: Fluoxetine **Checklist Parameter: (Total = 91 items)**
Indications: Major depressive episodes (single episodes & recurrent depression with associated anxiety), Bulimia nervosa - decrease binge-eating and purging, Obsessive-compulsive disorder (intrusive, markedly distressing, time consuming or significant functional interference). **(3 Items)** **Dosage:** Oral administration to adults only. Major depressive episode: 20 mg per day, preferably in the morning. Doses above 80 mg per day not recommended. Bulimia nervosa: 60 mg per day. Obsessive-compulsive disorder: 20 - 60 mg per day. With or without food. Tablets swallowed whole or dispersed in 100 ml water. Elderly: Use with caution esp with systemic illness or multiple medication. **(7 Items)** **Cautions**: (Warnings) Rash and possibly allergic phenomena - discontinue fluoxetine. (Contra-indications) Hypersensitivity to any of the ingredients. Severe renal failure (GFR < 10 ml/min). MAOI's during therapy or within 14 days of discontinuing MAOI's. Start MAOI's only 5 weeks after stopping fluoxetine. Pregnancy. Breastfeeding. Children. (Special precautions) Seizures, Avoid in unstable epilepsy, Careful monitoring of patients with controlled epilepsy, Prolonged seizures in pts receiving ECT therapy, Lower or alternate day dosing in significant hepatic dyfunction or mild to moderate renal failure (GFR 10-50 ml/min), Acute cardiac disease - caution due to lack of clinical experience, Loss of body mass, Altered glycaemic control in diabetics - hypoglycaemia during & hyperglycaemia after stopping fluoxetine, Altered platelet function, Abnormal bleeding, Impairment of judgement or skills eg. Caution of impaired ability to perform potentially harmful tasks, eg. Driving & operating machinery, Improvement may be only after 2-3 weeks, therefore supervision of high suicide risk patients is necessary, Observe same precautions for depressive & obsessive-compulsive patients. **(20 Items)** **Side-Effects:** Asthenia, Fever, Palpitations, Vision disturbances, Nausea, Diarrhoea, Dry mouth, Appetite loss, Dyspepsia, Vomiting, Headache, Nervousness, Insomnia, Drowsiness, Anxiety, Tremor, Dizziness, Fatigue, Decreased libido, Seizures, Hypomania or mania, Abnormal dreams, Agitation, Dyspnoea, Pulmonary events incl inflam process with varying histopathology and/or fibrosis, Rash, Urticaria, Serious systemic events poss related to vasculitis, and rarely death, Excessive sweating, Serum sickness, Anaphylactoid reactions, Sexual dysfunction (delayed or inhibited orgasm), Hypothyroidism, Hyponatraemia, Elevated serum transaminase, Aplastic anaemia, Cerebral vascular accident, Confusion, Dyskinesia, Ecchymoses, Eosinophilic pneumonia, Gastro-intestinal haemorrhage, Hyperprolactinaemia, Movement disorders & worsening of pre-existing movement disorders, Neuroleptic malignant syndrome-like events, Pancreatitis, Suicidal ideation, Pancytopenia, Immune-related haemolytic anaemia, Thrombocytopenia, Thrombocytopenic pupura, Vaginal bleeding after withdrawal of the medication, Violent behaviour. **(53 Items)** **Drug Interactions:** MAOI's, CNS active drugs including lithium (increased or decreased lithium levels), 2-fold increase in other anti-dressants blood levels, Adverse events with tryptophan (agitation, restlessness & gastro-intestinal distress), Long elimination half life of fluoxetine & its metabolites wrt pharmacodynamic or pharmacokinetic drug interactions, Diazepam - half life prolonged, Altered plasma concentrations of other plasma protein bound drugs eg. Warfarin, digitoxin, Fluoxetine plasma binding may be altered by other agents. **(8 Items)**

Table I (Cont.): Reference Checklist 1 Items for Assessing Agreement of Drug Information Material (derived from Originator Package Inserts)

Drug: Amoxyclav **Checklist Parameter: (Total = 68 items)**
Indications: Upper respiratory tract infections (caused by amoxycillin-resistant organisms producing β-lactamases sensitive to clavulanic acid) eg. Sinusitis, recurrent otitis media, tonsillitis. Lower respiratory tract infections eg.bronchitis (caused by amoxycillin-resistant β-lactamase-producing E. coli, H. influenzae and H. parainfluenzae), bronchopneumonia. Genito-urinary tract infections (caused by amoxycillin-resistant organisms producing β-lactamases sensitive to clavulanic acid) eg. Cystitis, urethritis, pyelonephritis. Skin and soft tissue infections. Infections caused by amoxycillin-sensitive organisms at the appropriate amoxycillin dosage. **(5 Items)** **Dosage:** Dosage for amoxycillin sensitive organisms is as approved for amoxycillin - clavulanic acid does not contribute to efficacy. Usual adult dose: 1-2 x 375 mg tablets q8h at start of meal. Impaired renal function: serum half life of both components increased in renal failure. Reduce dose or extend dosing interval based on max recommended dose of amoxicillin. Mild renal impairment:(Cr Cl > 30ml/min):no change. Moderate renal impairment: (Cr Cl 10-30 ml/min): 1 tablet q12h. Severe renal impairment: Cr Cl < 10 ml/min: half tablet q12h. Amoxycillin-sensitive organisms - URTI, LRTI, UTI, Skin & Soft Tissue Infections: 1-2 x 375 mg q8h. Amoxycillin-resistant organisms - URTI (otitis media) - H. influenzae, H. parainfluenzae; 2 x 375 mg q8h. LRTI (bronchitis) - H. influenzae, H. parainfluenzae; 2 x 375 mg UTI E. coli, Klebsiella pneumoniae 1-2 x 375 mg q8h; Skin & Soft Tissue Infections: S. aureus: 1- 2 x 375 mg. **(8 Items)** **Cautions:** (Warnings) Serious/occasionally fatal hypersensitivity (anaphylactoid) reactions esp in pts with history of penicillin hypersensitivity and/or history of sensitivity to multiple allergens, Careful inquiry concerning previous hypersensitivity reactions to penicillins, cephalosporins & other allergens before initiating therapy, If allergic reaction occurs, discontinue & institute appropriate therapy - adrenaline, corticosteroids & antihistamines, Transient hepatitis and cholestatic jaundice - use with caution in pts with hepatic dysfunction. (Contra-indications) Allergy to penicillins and cephalosporins. Safety in pregnancy has not been established. Previous history of jaundice/hepatic dysfunction associated with the product. (Special precautions) Periodic assessment of renal, hepatic and haemopoeitic function advisable during prolonged therapy, Not treatment of choice in pts with sore throat or pharyngitis (cause likely to be mononucleosis, due to high incidence of rash with amoxicillin, Caution in lymphatic leukaemia due to susceptibility to amoxycillin-induced skin rashes, Superinfections with mycotic or bacterial pathogens (usually Aerobacter, Pseudomonas or Candida), Severe hepatic dysfunction, use with care - changes in liver function tests, Moderate or severe renal impairment, dosage adjustment required, Amoxycillin is secreted in breast milk. Trace quantities of clavulanate detected in breast milk. No known detrimental effects for breast-fed infant, except risk of sensitisation. **(14 Items)** **Side-Effects:** Most common=diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria, erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness, hot flushes. Hepatic effects: Hepatitis, Cholestatic jaundice, Rise in AST and/or ALT, Effects on the gastrointestinal tract: Gastritis, Stomatitis, Glossitis, Black 'hairy' tongue, Enterocolitis, Mucocutaneous candidiasis, Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), GIT effects reduced by taking at the start of a meal, Hypersensitivity reactions: Skin rashes, Pruritis, Urticaria, Serum sickness-like syndrome, Erythema muliforme, Stevens-Johnson syndrome. Hypersensitivity vasculitis, Bullous exfoliative dermatitis, Toxic epidermal necrolysis, Serious/occasionally fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema, Interstitial nephritis. Haematopoietic and lymphatic: Haemolytic anaemia, Reversible thrombocytopenia, Thrombocytopenic pupura, Eosinophilia, Leucopenia, Agranulocytosis, Thrombocytosis, Prolonged bleeding time & prothrombin time, Central Nervous System effects: Reversible hyperactivity, Dizziness, Headache, Convulsions (impaired renal function or high doses), Miscellaneous: Superficial tooth discolouration. **(36 Items)**

Table I (Cont.): Reference Checklist 1 Items for Assessing Agreement of Drug Information Material (derived from Originator Package Inserts)

Drug: Amoxyclav (Cont.) **Checklist Parameter: (Total = 68 items)**
Drug Interactions: Probenecid decreases renal tubular secretion of amoxycillin (increased & prolonged blood levels) , but does not affect clavulanate excretion, Allopurinol - possible increase in skin rashes (as with ampicillin) but no data available, Alcohol and some beta-lactam antibiotics has precipitated a disulfiram (Antabuse) reaction - therefore avoid alcohol during and for several days after therapy, May reduce efficacy of oral contraceptives (reduced conjugated oestrogens), May lead to selection of resistant strains of organisms - sensitivity testing advisable whenever possible. **(5 Items)**

Table I (Cont.): Reference Checklist 1 Items for Assessing Agreement of Drug Information Material (derived from Originator Package Inserts)

Drug: Atenolol **Checklist Parameter: (Total = 87 items)**
Indications: Management of angina pectoris. Management of hypertension. **(2 Items)** **Dosage:** Angina pectoris: 100 mg per day given once daily or 50 mg bd. Hypertension: 50-100 mg once daily. Compatible with diuretics and other antihypotensive agents. In refractory cases, further reduction in BP achived in combination with other antihypertensive agents. Renal failure. No experience in children. Elderly: reduce dose in elderly. Renal dysfunction: May need to reduce dose. (**8 Items)** **Cautions:** (Warnings): Increased number & duration of angina attacks in Prinzmetal's angina. Aggravation of less severe peripheral arterial circulatory disturbances & severe peripheral vascular disease (peripheral gangrene). Use with caution in first degree heart block. Mask signs of thyrotoxicosis. More severe reaction on repeated challenge in pts with history of anaphylactic reactions to variety of allergens. Significant accumulation in breast milk - caution in nursing women. (Contra-indications): Known hypersensitivity to atenolol, Cardiogenic shock, Second or third degree heart block, Hypotension, Metabolic acidosis (eg. In diabetes), Bradycardia, Severe peripheral arterial circulatory disturbances, Untreated phaeochromocytoma, Sick sinus syndrome, After prolonged fasting, Avoid in cardiac failure unless/until controlled with digitalis or diuretics, Uncontrolled heart failure except hypertrophic obstructive cardiomyopathy, Reversible obstructive airways disease, Reduction in dosage in perioperative period (aggravation of angina pectoris/hypertension) & obscured tachycardia response. (Special precautions): Std doses of bronchodilators will usually reverse increased airway resistence, Pts with phaeochromocytoma require alpha-adrenergic blockers, Masks symptoms of hypoglycaemia, Sexual impotence, Abrupt discontinuation may exacerbate angina pectoris in pts with ischaemic heart disease, Discontinuation must be gradual & pts should limit physical actiity during phase out period, Bradycardia (< 50-55 bpm) indicates further dose increases shd not be made, Severe renal impairment, adjust dosage. Cr Cl 15-35 ml/min/1,73m2, oral dose shd be 50-100 mg every two days. Cr Cl < 15 ml/min/1,73m2, oral dose shd be 25-50mg on alternate days or 100 mg every 4 days. Dialysis pts shd receive 50 mg orally after each dialysis, under hospital supervision, Pregnancy - intra-uterine growth retardation. Weigh benefits against risks, esp first and second trimesters, Administration before birth ot labour - hypotonic, collapsed and hypoglycaemic newborns, Ocassional dizziness or fatigue shd be considered if driving or operating machinery. **(31 Items)** **Side-Effects:** Congestive cardiac failure, Marked bradycardia, Increased intermittent claudication if already present, Cold extremeties, Deterioration of heart failure, heart block and postural hypotension; may be associated with syncope, Raynaud's phenomenon, Confusion, Dizziness, Headache, Mood changes, Nightmares, Overt psychosis, Hallucinations, Sleep disturbances, Depression, Malaise, Dry mouth, Nausea, Vomiting, Diarrhoea, Other GIT disturbances, Elevations in transaminase levels, Hepatic toxicity incl intrahepatic cholestasis, Purpura, Thrombocytopenia, Alopecia, Psoriasiform skin reactions, Exacerbations of psoriasis, Skin rashes, Dry eyes, Paraesthesia, Bronchospasm in pts with bronchial asthma or history of asthmatic complaints, Visual disturbances, Increase in antinuclear antibodies, Fatigue, Adverse reactions more common in pts with renal decompensation. **(36 Items)** **Drug Interactions:** Anaesthetics with negative ionotropic effects and mycardial depression, Hypoglycaemic agents, Phenothiazines, Class I antiarrhythmic agents eg. Disopyramide, Control of dosages & pt response essential with digitalis, Calcium channel blockers with negative ionotropic effects eg verapamil and diltiazem, Dihydropyridines eg nifedipine increase risk of hypotension and cardiac failure in pts with latent cardiac insufficiency, Withdrawal of clonidine exacerbation of rebound hypertension, Concomitant sympathomimetics eg adrenaline, counteract beta-blocker effects, PG-synthetase inhibitors eg ibuprofen and indomethacin decrease hypotensive efect of atenolol. **(10 Items)**

Table I (Cont.): Reference Checklist 1 Items for Assessing Agreement of Drug Information Material (derived from Originator Package Inserts)

Drug: Enalapril **Checklist Parameter: (Total = 118 items)**
Indications: All grades of essential hypertension. Renovascular hypertension. Symptomatic congestive heart failure usually with diuretics and digitalis. Asymptomatic left ventricular dysfunction (eject. Fraction ≤ 35%). **(4 Items)** **Dosage:** Before, during or after food - absorption not affected by food, Essential hypertension - 10 - 20 mg once daily according to degree of hypertension, Renovascular hypertension - 5 mg or less once daily initially. Adjusted to patient needs, Concommitant diuretic therapy - discontinue 2-3 days before ACE inhibitor. 5 mg or less once daily initially. Adjusted to patient needs, Mild renal impairment Cr Cl .> 30 < 80 ml/min = 5 mg/day initially, Moderate renal impairment Cr Cl .≤ 30 > 10 ml/min = 2,5 mg/day initially, Severe renal impairment Cr. Cl. ≤ 10 = 2,5 mg on dialysis days, Heart failure/asymptomatic left ventricular dysfunction = 2.5 mg increased to 20mg/day in single or divided doses, Heart failure; Monitor BP, renal function and serum potassium levels, Heart failure; Reduce dosage of concomitant diuretics. **(10 Items)** **Cautions:** (Warnings): Pregnancy (boxed warning), Foetal and neonatal morbidity & mortality (2nd & 3rd trimester), Disturbance of foetal blood pressure regulatory mechanisms, Oligohydramnios, Craniofacial deformities, Limb contractures, Hypoplastic lung development, Hypotension in newborns, Hyperkalaemia in newborns, Oliguria in newborns, Anuria in newborns after ACE inhibitors in 2nd/3rd trimester, Defective skull ossification, Prematurity and low birth mass, Infant/foetus effects not observed if taken during first trimester. (Contra-indications): Hypersensitivity to product or any of its components, History of angioneurotic oedema with previous ACE inhibitor, Breast feeding. (Special precautions): Symptomatic hypotension, Renal function impairment - reduced and/or less frequent dosing, Hypersensitivity/Angioneurotic oedema, Anaphylactoid reactions during hymenoptera desensitisation, Haemodialysis patients - anaphylactoid reactions, Cough, Surgery/anaesthesia, Serum potassium, Paediatric use - not studied in children. **(26 Items)** **Side-Effects:** Dizziness, Headache, Fatigue, Asthenia, Hypotension, Orthostatic hypotension, Syncope, Nausea, Diarrhoea, Muscle cramps, Rash, Cough, Renal dysfunction, Renal failure, Oliguria, Hypersensitivity/Angioneurotic oedema, Myocardial infarction or CVA, Chest pain, Palpitations, Rhythm disturbances, Angina pectoris, Ileus, Pancreatitis, Hepatic failure, Hepatitis (hepatocellular or cholestatic), Jaundice, Abdominal pain, Vomiting, Dyspepsia, Constipation, Anorexia, Stomatitis, Depression, Confusion, Somnolence/Drowsiness, Insomnia, Nervousness, Paraesthesia, Vertigo, Pulmonary infiltrates, Bronchospasm/asthma, Dyspnoea, Rhinorrhoea, Sore throat, Hoarseness, Diaphoresis, Erythema multiforme, Exfoliative dermatitis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Pemphigus, Pruritis, Urticaria, Alopecia, Impotence, Flushing, Taste alteration, Tinnitus, Glossitis, Blurred vision, Symptom complex (fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, +anti-nuclear antibody, ↑ ESR, eosinophilia, leukocytosis, Rash, Photosensitivity, Other dermatologic manifestations, ↑ Blood urea, ↑ Serum creatinine, ↑ liver enzymes, ↑ Serum bilirubin, Hyperkalaemia, Hyponatraemia, ↓ haemoglobin, ↓ Haematocrit. **(72 Items)** **Drug Interactions:** Other antihypertensives, increased antihypertensive effects, esp. diuretics, Potentiation of hypotensive effects with ß-adrenergic blockers, methyldopa and calcium entry blockers, Ganglionic blocking agents/adrenergic blocking agents, Calcium antagonists - not recommended due to lack of experience, Hyperkalaemia - concomitant potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, ↓ lithium elimination. **(6 Items)**

Table II (Reference Checklist 2) lists the items or statements used within the five sections of the originator package insert (indications, dose, cautions, side-effects and drug interactions).

Table II: Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Ciprofloxacin **Checklist Parameter: (Total = 115 items)**
Indications: Lower respiratory tract infections caused by: Ent. cloacae, E. coli, H. influenzae, H. parainfluenzae, Kl. pneumoniae, Pr. mirabilis, Ps. Aeruginosa. Urinary tract infections caused by: C. diversus, C. freundii, Ent.cloacae, E. coli, Kl. pneumoniae, M. morganii, P. mirabilis, Pr. rettgeri, Ps. aeruginosa, S. marcescens, S. epidermidis, S. faecalis. Skin and soft tissue infections caused by:C. freundii, Ent. cloacae, E. coli, Kl. pneumoniae, M. morganii, P. mirabilis, P. vulgaris, Pr. stuartii, Ps. aeruginosa, S. aureus, S. epidermidis, S. pyogenes. Gastro-intestinal infections: Infective diarrhoea caused by C. jejuni, E. coli, S. flexneri, Sh. Sonnei. Bone infections: Osteomyelitis due to susceptible Gram-negative organisms. Gonorrhoea. **(6 Items)**
Dosage: Treatment of Ps. aeruginosa infections, aminoglycoside to be administered concomitantly. Swallow whole with plenty of liquid. Take with or without meals. Dosage range 250 - 750 mg bd. Duration depends on severity of infection, clinical response & bacteriological cultures. Acute uncomplicated cystitis in women, treatment period 3 days. Generally continue treatment at least 3 days after signs & symptoms of infection disappear. Acute infections, usual duration 5 - 10 days. Severe and complicated infections, more prolonged therapy may be required. Streptococcal infections, treat at least 10 days. Infections of lower respiratory tract: mild to moderate 250 - 500 mg bd, severe or complicated 750 mg bd. Cystic fibrosis: 750 mg bd. Dose range 7.5 - 15 mg/kg/day. Urinary tract infections: Acute, uncomplicated cystitis, 250 mg bd, mild to moderate 250 mg bd, severe or complicated 500 mg bd. Skin infections: mild to moderate, 500 mg bd, severe or complicated 750 mg bd. Infectious diarrhoea: 500 mg bd. Bone infections: mild to moderate 500 mg bd, severe or complicated 750 mg bd. Treatment for 4-6 weeks or longer. Gonorrhoea: single dose 250 mg. Elderly: lowest possible dose. Impaired renal or liver function: prolonged half life therefore adjust dosage. Renal insufficiency: Cr Cl ≥ 31 ml/min/1,73m2 - max 800 mg/day IV; Cr Cl ≤ 30 ml/min/1,73m2 - max 400 mg/day IV; impaired renal function & haemodialysis - as above after dialysis on dialysis days. Renal impairment & CAPD: 50 mg/l of dialysate QID, or 500 mg orally or 2 x 250 mg orally. CAPD patients with peritonitis: 500 mg QID orally. Hepatic impairment: no dose adjustment. **(24 Items)**
Cautions: (Warnings): Use with caution in pts with history of convulsive disorders - boxed warning. Crystalluria - pts to be well hydrated & excessive urinary alkalinity avoided - boxed warning. Treatment of Ps. Aeruginosa infections, use concomitant aminoglycoside. Pregnancy & Lactation: Safety not established. (Contra-indications): History of hypersensitivity to ciprofloxacin, any other quinolones or any of the inactive ingredients. Pregnancy & Lactation. Children under 18 years of age - boxed warning. (Special precautions): Impaired ability to drive motor vehicle or operate machinery, esp in combination with alcohol. **(8 Items)**
Side-Effects: Nausea, Diarrhoea, Vomiting, Dyspepsia, Abdominal pain, Pseudomembranous colitis, Visual disturbances (eg diplopia, colour vision), Tinnitus, Transient impairment of hearing esp high frequencies, Eosinophilia, Leucocytopenia, Granulocytopenia, Anaemia, Thrombocytopenia, Leucocytosis, Thrombocytosis, Haemolytic anaemia, Altered prothrombin values, Skin rashes, Urticaria, Photosensitivity (blisters, sensation of skin burning), Erythema nodosum, Erythema exsudativum multiforme (minor), Stevens-Johnson syndrome, Lyell's syndrome, Punctate skin haemorrhages (petechiae),

Table II (Cont.): Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Ciprofloxacin (Cont.) **Checklist Parameter: (Total = 115 items)**
Haemorrhagic bullae & papules with signs of vascular involvement (vasculitis), Dizziness, Headache, Tiredness, Nervousness, Agitation, Trembling, Insomnia, Peripheral paralgesia, Sweating, Unsteady gait, Convulsions, Increase in intracranial pressure, Anxiety states, Nightmares, Confusion, Hallucinations, Psychotic reactions, Depression, Joint pain, Joint swelling, General feeling of weakness, Myalgia, Tendosynovitis, Achillotendinitis, Partial or complete rupture of achilles tendon, Tachycardia, Flushing, Migraine, Syncope, Crystalluria & haematuria, Interstitial nephritis, Transient renal impairment incl transient renal failure, Anaphylactic/anaphylactoid reactions (eg facial, vascular & laryngeal oedema, dyspnoea progressing to life-threatening shock, Temporary elevations of transaminases, Temporary elevations of alkaline phosphatase, Cholestatic jaundice, Temporary increase in urea, creatinine or hyperbilirubinaemia, Impaired taste and smell, Hyperglycaemia, Hepatic necrosis, Superinfections with resistant bacteria or fungi with long-term or repeated use. **(68 Items)** **Drug Interactions:** Theophylline, increased plasma conc & prolonged half life, Iron, Antacids containing magnesium, aluminium, calcium, sucralfate, but not H2 receptor blockers, NSAID fenbufen, CNS stimulation & seizures, Cyclosporin, due to transient increases in serum creatinine conc., Warfarin, due to warfarin toxicity, Glibenclamide, due to hypoglycaemia, Probenecid, due to increased ciprofloxacin serum concentrations, Metoclopramide, due to accelerated absorption of ciprofloxacin. **(9 Items)**

Table II (Cont.): Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Fluoxetine **Checklist Parameter: (Total = 109 items)**
Indications: Major depressive disorders. Obsessive-compulsive disorder, Bulimia nervosa. **(3 Items)** **Dosage:** Safety/efficay in children not established, Can be given with or without food, Avoid use of alcohol, Lower dose or less frequent dosing in pts with intercurrent illnesses or hepatic impairment, Major depressive disorders: 20 mg daily, preferably in morning, Obsessive-compulsive disorder: 20-60 mg daily, Bulimia nervosa: 60 mg daily, Upward titration over several weeks due to p'kinetic properties, Doses > 80 mg not recommended for any indication, Caution in elderly pts: doses > 20 mg not recommended. **(10 Items)** **Cautions:** (Warnings): Serotonin syndrome with fluoxetine alone or in temporal association with MAOI, Discontinue if pts develop rash or other allergic reactions, Anaphylactoid and serious systemic events involve skin, liver or lung, Worsening of major depressive disorder & suicidal ideation/behavior, may/may not be causal wrt fluoxetine, Observe pts closely for clinical worsening/suicidality at initiation & dose change, Take same precautions taken for major depressive disorder for other psychiatric/non-psychiatric disorders, Observed with antidepressants for major depressive disorder & psychiatric/non-psychiatric indications: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania and mania - may require change to therapeutic regimen, Taper dosage when discontinuing fluoxetine. (Pregnancy & Lactation): Safety in pregnancy & lactation not established. (Contra-indications) Hypersensitivity to fluoxetine or any of the ingredients, Concomitant MAOI's 14 days after disc MAOI, 5 weeks after stopping fluoxetine, Severe renal function impairment (GFR < 10 ml/min). (Special precautions): Close monitoring in first 1-2weeks as improvement may not occur, Close supervision of high risk patients eg. Suicidal tendencies, Same precautions as for pts with obsessive-compulsive disorder, History of seizures due to increased risk of seizures, Discontinue if pt develops a seizure, Avoid in unstable epilepsy, Careful monitoring of pts with controlled epilepsy, Prolonged seizures in ECT, Delayed fluoxetine metabolism in impaired hepatic function, Lower doses/less frequent dosing with significant hepatic impairment, Accumulation of metabolites in renal function impairment, Dose adjustment in mild to moderate renal failure (GFR 10-50 ml/min), Underweight individuals - weight loss, Diabetes mellitus - altered glycaemic control, Abnormal bleeding in pts with history of bleeding disorders, Extrapyramidal symptoms and aggravation of Parkinson's disease in pts with extrapyramidal disorders, Acute cardiac disease - limited clinical experience, Impairment of mental alertness or physical co-ordination eg. Operating machinery, driving motor vehicle, perform potentially hazardous tasks, Withdrawal symptoms - dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, agitation, anxiety, nausea. **(31 Items)** **Side-Effects:** Palpitations, Headache, Nervousness, Anxiety, Drowsiness, Fatigue, Insomnia, Tremor, Asthenia, Dizziness, Abnormal dreams, Agitation, Seizures, Hypomania, Mania, Dyskinesias, Weight loss, Hyponatraemia, Hypothyroidism, Fever, Nausea, Diarrhoea, Dyspepsia, Anorexia, Vomiting, Dry mouth, Decreased libido, Sexual dysfunction (delayed/inhibited orgasm), Raised tranaminase levels, Arthralgia, Myalgia, Visual disturbances, Dyspnoea, Pulmonary inflammation and/or fibrosis, Rash, Urticaria, Prutitus, Excessive sweating, Anaphylactoid reactions, Serum sickness, Aplastic anaemia, Cerebral vascular accident, Confusion, Ecchymoses, Eosinophilic pneumonia, Gastro-intestinal haemorrhage, Hyperprolactinaemia, Neuroleptic malignant syndrome-like events, Pancreatitis, Suicidal ideation, Pancytopenia, Thrombocytopenia, Purpura, Immune-related haemolytic anaemia, Vaginal bleeding after fluoxetine withdrawal, Violent behaviour. **(56 Items)**

Table II (Cont.): Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Fluoxetine (Cont.) **Checklist Parameter: (Total = 109 items)**
Drug Interactions: Long elimination half life fluoxetine & norfluoxetine gives potential for drug interactions for several weeks after discontinuation, MAOI's, Reduce dose of medicines metabolised by CYP P450 CYP2D6 with narrow therapeutic index, fluoxetine inhibits CYP2D6, Lithium incr & decr in serum conc - monitor litium levels, Phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, imipramine, desimipramine - changes in blood levels & poss toxicity, Half life of diazepam prolonged, Tryptophan - agitation, restlessness & GIT distress, Alteration of plasma conc of other protein bound medicines eg. Warfarin, digoxin, Altered anti-coagulant effects & increased bleeding with warfarin. Monitor coagulation when stopping fluoxetine. **(9 Items)**

Table II (Cont.): Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Amoxyclav

Checklist Parameter: (Total = 92 items)

Indications: Upper respiratory tract infections (caused by amoxycillin-resistant organisms producing beta-lactamases sensitive to clavulanic acid): eg sinusitis, recurrent otitis media, tonsillitis. Lower respiratory tract inections (caused by amoxycillin-resistant organisms producing beta-lactamases sensitive to clavulanic acid): eg bronchitis, bronchopneumonia. Genito-urinary tract infections (caused by amoxycillin-resistant organisms producing beta-lactamases sensitive to clavulanic acid) eg cystitis, urethritis, pyelonephritis. Skin and soft tissue infections (caused by amoxycillin-resistant organisms producing beta-lactamases sensitive to clavulanic acid). Infections caused by amoxycillin-sensitive organisms at the appropriate amoxycillin dosage. **(5 Items)**

Dosage: Tablets to be taken immediately before a meal, Infections caused by amoxycillin-sensitive organisms use the approved amoxycillin dosage, Adults: 1 x 375 mg q8h at start of meal, For more severe infections & infections of respiratory tract 1 x 675 mg q8h at start of meal, All tablet strengths contain 125mg clavulanic acid; 2 x 375 mg tablets ≠ 1 x 675 mg tablet and should not be substituted, Amoxycillin-sensitive organisms: URTI, UTI, Skin & Soft Tissue: 1 x 375 mg q8h, Amoxycillin-sensitive organisms: URTI, LRTI, UTI, Skin & Soft Tissue: 1 x 625 mg q8h, Amoxycillin-sensitive organisms: URTI, LRTI, UTI, Skin & Soft Tissue: 1 x 1000 mg q12h, Amoxycillin-resistant organisms: UTI, Skin & Soft Tissue: 1 x 375 mg q8h, Amoxycillin-resistant organisms: URTI, LRTI, UTI, Skin & Soft Tissue: 1 x 625 mg q8h, Amoxycillin-resistant organisms: URTI, LRTI, UTI, Skin & Soft Tissue: 1 x 1000 mg q12h, Impaired renal function: Dose may need to be reduced or interval extended, Mild (Cr Cl > 30 ml/min) - no change, Moderate(Cr Cl 10 - 30 ml/min) - 1 tablet q12h, (Severe (Cr Cl< 10 ml/min) - half tablet q12h, Haemodialysis decreases serum concentrations. Additional dose necessary at end of dialysis. **(16 Items)**

Cautions: (Warnings): Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, Before initiating therapy, careful enquiry about previous hypersensitivity reactions to penicillins, cephalosporins or other allergens shd be made, If allergic reaction occurs, discontinue & institute appropriate therapy, eg adrenaline, oxygen, iv steroids, airway management, Avoid if infectious mononucleosis is suspected due to morbilliform rash associated with amoxicillin, Overgrowth of non-susceptible organisms with prolonged use, Pseudomembranous enterocolitis, Prolongation of prothrombin time - appropiate monitoring in patients receiving anticoagulants, Periodic assessment of organ function, including renal, hepatic and haemopoeitic function advisable in prolonged therapy, Transient hepatitis & cholestatic jaundice - use with caution in hepatic dysfunction. (Pregnancy & Lactation): Safety in pregnancy not established, Amoxycillin distributed in breast milk, may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant. (Contra-indications): Hypersensitivity to penicillins or cephalosporins due to documented cross-sensitivity, Previous history of amoxycillin/clavulanic-associated jaundice/hepatic dysfunction. (Special precautions): Jarisch-Herxheimer reaction when administered to patients with syphilis, Adequate fluid intake and urinary output must be maintained with high doses, Sodium content (esp in high doses) to be considered in pts on sodium-restricted diets, Lignocaine or benzyl alcohol to be used im not iv, Periodic assessments of organ system functions incl renal, hepatic and haemopoeitic function advised during prolonged therapy, Not treatment of choice in sore throat/pharyngitis due to possibility of infectious mononucleosis, Use with caution in lymphatic leukaemia due to susceptibility to amoxycillin-induced skin rashes, Superinfections with mycotic or bacterial pathogens (usually Aerobacter, Pseudomonas or Candida), Changes in liver function - use with caution in pts with severe hepatic dysfunction, Dosage adjustment in moderate or severe renal impairment, Amoxycillin is excreted in human milk - use with caution in nursing women, Use may lead to selection of resistant strains - therefore perform sensitivity testing if possible. **(25 Items)**

Table II (Cont.): Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Amoxyclav (Cont.) **Checklist Parameter: (Total = 92 items)**
Side-Effects: Most frequent: diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria, erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness, hot flushes. Minimise adverse effects esp. nausea & diarrhoea by taking at start of meal, Clavulanate causes GIT symptoms, so if higher concentration of amoxycillin is required, additional amoxycillin should be given separately, Skin rashes, Pruritus, Urticaria, Serum-sickness-like syndrome, Erythema multiforme, Stevens-Johnson syndrome, Hypersensitivity vasculitis, Bullous exfoliative dermatitis, Toxic epidermal necrolysis, Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema, Interstitial nephritis, Nausea, Vomiting, Diarrhoea, Gastritis, Stomatitis, Glossitis, Black "hairy" tongue, Enterocolitis, Mucocutaneous candidiasis, Antibiotic-associated colitis (including pseudomenbranous colitis and haemorrhagic colitis), Hepatitis, Cholestatic jaundice, usually reversible, but death is extremely rare, associated with serious underlying disease or concomitant medication, Rise in AST and/or ALT, Crystalluria, Haemolytic anaemia, Reversible thrombocytopenia, Thrombocytopenic purpura, Eosinophilia, Reversible leucopenia, Agranulocytosis, Slight thrombocytosis, Prolongation of bleeding time and prothrombin time, Reversible hyperactivity, Dizziness, Headache, Convulsions, Superficial tooth discolouration. **(41 Items)** **Drug Interactions:** Probenecid - increased and prolonged blood levels of amoxycillin but not clavulanic acid, Reduced efficacy of oral contraceptives - warn patients accordingly, Allopurinol - increased incidence of skin rashes, Tetracyclines and other bacteriostatic drugs may interfere with amoxycillin bactericidal effects, False positive urine glucose tests if chemical tests are used - use enzymatic glucose oxidase methods. **(5 Items)**

Table II (Cont.): Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Atenolol **Checklist Parameter: (Total = 84 items)**
Indications: Mild to moderate hypertension. Angina pectoris. **(2 Items)** **Dosage:** Children: safety & efficacy not established. Hypertension: 50 - 100 mg once daily as a single dose. Additional doses unlikely to be of benefit in hypertension. Combine with diuretics or other antihypertensive agents for further blood pressure reduction. Angina pectoris: 50 - 100 mg daily as single or divided doses. Elderly: Usual dose for both indications 50 mg once daily. **(5 Items)** **Cautions:** (Warnings): Safety & efficacy in children not established. Thyrotoxicosis - symptoms may be masked. First degree heart block - negative inotropic effect. Modifies tachycardia associated with hypoglycaemia. Pts with phaeochromocytoma treat with α-adrenergic blocker. Asthma, bronchitis, chronic pulmonary disease. Tachycardia responses may be obscured - caution required. Prinzmetal's angina - Increased no & duration of angina attacks. Worsening of peripheral arterial circulatory disturbances & less severe peripheral vascular diseases, due to reduced peripheral circulation. If decision is to withdraw, withdraw at least 48 hours before anaesthesia. Care with ether, cyclopropane & trichloroethylene if atenolol is continued. Adjust dosage in severe renal impairment. Class I antidysrhythmic agents eg. Disopyramide, myocardial depressants & AV conduction inhibitors eg calcium antagonists. Tranfer of pt from clonidine as release of catecholamines may lead to hypertensive crisis. Withdraw atenolol several days before clonidine to prevent rebound hypertension. Combination with verapamil in pts with impaired ventricular function with caution. Do not use combination in pts with conduction abnormalities. Do not give either drug IV within 48 hours of each other. Do not give IV calcium antagonists & anti-arrythmic agents with atenolol. (Pregnancy & Lactation): Safety & efficacy not established. Growth retardation associated with use in pregnancy. Admin before birth & during labour may result in hypotonia, collapse or hypoglycaemia in the newborn. (Contra-indications): Hypersensitivity to atenolol or to any of the ingredients. Second & third degree heart block. Bradycardia < 50 beat/minute. Metabolic acidosis. Severe peripheral arterial circulatory disturbances. Sick sinus syndrome. Untreated phaeochromocytoma. Hypotension. Cardiac failure unless/until controlled with digitalis/diuretics. (Special precautions). Exacerbation of angina pectoris in pts with ischaemic heart disease following abrupt discontinuation. Discontinuation of therapy shd be gradual. Pts shd limit physical activity during phase out period. **(29 Items)** **Side-Effects:** Blood disorders such as thrombocytopenia, Bradycardia, Congestive cardiac failure, Heart block, Fluid retention, Exacerbation of peripheral vascular disease/development of Raynaud's phenomenon, Precipitation of peripheral gangrene, Lassitude, Dizziness, Mild headache, Sleep disorders, Restlessness, Cold extremeties, Hypotension, Paradoxical hypertension, Depression, Paraesthesia, Hallucinations, Psychosis, Nausea, Vomiting, Diarrhoea, Constipation, Mass gain, Stomatitis, Raised liver enzymes, Muscular cramps, Myopathy, Skeletal muscle weakness, Disturbances of vision, Perspiration, Skin rash, Alopecia, Transient hearing loss, Hypersensitivity reactions, Sexual impotence, Bronchoconstriction in pts suffering from asthma, brinchitis and other chronic pulmonary diseases, AE's more common in pts with renal decompensation. **(38 Items)** **Drug Interactions:** Anaesthetic agents - use ones with least negative ionotropic activity. Avoid myocardial drepressant agents. Phenothiazines - life-threatening. Quinidine, procainamide, lignocaine - myocardial depressant. Hypoglycaemic agents - life-threatening. Clonidine - rebound hypertension. Disopyramide - severe bradycardia - life-threatening. Calcium blockers - severe hypotension & cardiac failure in latent cardiac insufficiency. Verapamil - in impaired ventricular function and/or SA or AV conduction abnormalities. Avoid combination in conduction abnormalities. Sympathomimetics eg. Adrenaline/epinephrine. NSAID's eg. Indomethacin & ibuprofen decrease hypotensive effect. **(10 Items)**

Table II (Cont.): Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Enalapril **Checklist Parameter: (Total = 114 items)**
Indications: All grades of essential hypertension. Renovascular hypertension. Symptomatic congestive heart failure usually with diuretics and digitalis. Asymptomatic left ventricular dysfunction (eject. Fraction ≤ 35%). **(4 Items)** **Dosage:** With/without meals, preferably at the same time each day. Initial dose 10-20 mg daily. Usual effective maintenance dose in hypertension 20 mg/day. Maximum dose. Diuretic-treated patients, discontinue diuretics 2-3 days before starting therapy. Subsequent dosage adjustments depend on therapeutic response. Renal impairment, lower dose. Cr Cl 10 -29 ml/min, dose 2.5mg. Renovascular hypertension, reduce dose to 5 mg or less. **(8 Items)** **Cautions:** Warnings: Pregnancy (boxed warning). Cerebrovascular disease or ischaemic heart disease. Volume depleted patients (diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting). Patients at high risk of symptomatic hypotension. Severe autoimmune disease, esp. SLE, other collagen vascular disease or scleroderma. In acute myocardial infarction, patients with renal dysfunction (serum creatinine > 177 micromol/l or proteinuria > 500 mg/24 hours). Persistent hypotension and/or impaired renal function in acute myocardial infarction. Bone marrow depression (increased risk of agranulocytosis and neutropenia). Diabetes mellitus (increased risk of hyperkalaemia and hypoglycaemia). Hyperkalaemia. Renovascular disease or suspected renovascular disease. Renal artery stenosis, bilateral, or in one kidney, or in renal transplant. Renal function impairment (decreased elimination of drug results in increased risk of hyperkalaemia). Anaphylactoid reactions, esp during desensitising protocols eg. Hymenoptera venom). Anaphylactoid reactions in patients exposed to high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulphate absorption. Hypersensitivity/angioedema. Angioedema associated with laryngeal oedema, tongue, glottis or airway obstruction - drug contra-indicated thereafter. Higher rate of angioedema in black patients than in non-black patients. Porpyria use with caution. Safety and efficacy in children not established. Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride may lead to hyperkalaemia, which may be severe. Pregnancy & Lactation: Exposure in 1st trimester - no significant risk to foetus. Exposure after 1st trimester - teratogenicity and severe toxicity - hypotenson, renal failure, anuria, skull hypoplasia, hyperkalaemia, oliguria; oligohydramnios may cause pulmonary hypoplasia, limb contractures, craniofacial deformation. Safety in lactation has not been established. Contra-indications: Sensitivity to product or any of its components. History of angio oedema with previous ACE inhibitor or angiotensin receptor blocker. Hereditary or idiopathic angioedema. Aortic stenosis. Hypertrophic obstructive cardiomyopathy. Severe renal function impairment (creatinine clearance below 30 ml/min). Renal artery stenosis in patients with a single kidney. Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride. Porpyria. Special precautions: Myocardial infarction & CVA's due to severe falls in blood pressure in high risk patients. Monitor therapy when changing dose or adjusting diuretics in volume depleted patients, patients with ischaemic heart disease or cerebrovascular disease. IV 0,9% NaCl & supine position if hypotension occurs. Increased blood urea and serum creatinine in patients without apparent pre-existing vascular disease, esp with a diuretic. Immediate medical attention with signs of facial or extremity etc, due to risk of angioedema. Caution with driving or tasks requiring alertness, due to dizziness. Major surgery or anaesthesia with agents that produce hypotension. **(40 Items)**

Table II (Cont.): Reference Checklist 2 for Assessing Agreement of Drug Information Material (derived from MCC SPI for Drug Substance/Class)

Drug: Enalapril (Cont.) **Checklist Parameter: (Total = 114 items)**
Side-Effects: Decreases in white blood cell count, Decreases in haemoglobin, Decreases in haematocrit, Bone marrow depression, Anaemia, Thrombocytopenia, Agranulocytosis, Haemolytic anaemia, Orthostatic effects (including hypotension, myocardial infarction, cerebrovascular accident, palpitations, tachycardia), Dizziness, Headache, Fatigue, Mood alterations, Mental confusion, Paraesthesia, Vertigo, Sleep disturbances, Hyperkalaemia, Hyponatraemia, Increases in blood urea, Increases in serum creatinine, Diarrhoea, Nausea, Abdominal pain, Indigestion, Dry mouth, Pancreatitis, Vomiting, Taste disturbances, Uraemia, Oliguria, Anuria, Renal dysfunction, Acute renal failure, Impotence, Hepatitis (hepatocellular or cholestatic), Jaundice, Increases in serum bilirubin, Asthenia (weakness/heaviness in leg), Cough, Bronchospasm, Rhinitis, Sinusitis, Urticaria, Diaphoresis, Alopecia, Pruritus, Psoriasis, Pemphigus, Toxic epidermal necrolysis, Stevens-Johnson Syndrome, Erythema multiforme, Hypersensitivity/angioedema of face, Symptom complex: fever, vasculitis, myalgia, arthritis/arthralgia, positive antinuclear antibodies, elevated erythrocyte sedimentation rate, eosinophilia, leucocytosis, Rash, Photosensitivity, Other dermatological manifestations. **(57 Items)** **Drug Interactions:** Diuretics, alcohol and hypotension-producing medications, additive antihypertensive effect, Loop, thiazide or related diuertics - "first dose hypotension", Indomethacin and NSAID's - reduced antihypertensive effect, Potassium supplements or potassium sparing diuretics, Concommitant lithium - increased concentrations of lithium. **(5 Items)**

3.4 Data Analysis

The proportion of checklist items found in each of the materials was calculated for each variable. Statements found in the package inserts that are not included in the reference checklist were not considered. The proportion of the number of checklist items found in the materials against the number of relevant checklist items was first calculated (= "P") and the 95% confidence interval (CI) for the proportions was calculated.

The indicator called the "degree of information agreement" was calculated for Indications, Recommended Dosage (range), Cautions, Side-effects and Drug Interactions for each drug brand or Reference Country.

A "+1" designated the degree of information agreement when the proportion of checklist items found was completely in agreement with the Checklist items or was ≥ to the higher CI
A "0" designated proportions within the CI
A "-1" designated a proportion ≤ the lower CI.

The sum of the individual scores of the five variables (Indications, Recommended Dosage, Cautions, Side-effects and Drug Interactions) was calculated for each of the brands of a given drug or for each Reference Country. These sums were added up as an overall measure of adherence to Checklist 1 or 2.

The results were ranked within a range of maximum (+5) to minimum (-5) agreement.

CHAPTER 4: Results

4.1 Generics versus Originator Product

Table III summarises the source material used in the Checklist 1 comparison, in terms of the originator and five generic companies for each of the five drug substances studied. An indication is given of the range of dates when the MCC council approval was given for the materials (ie. the date of publication).

Table III: Baseline Characteristics of Evaluated Package Inserts from South Africa

Drug Substance	Ciprofloxacin 250, 500, 750 mg	Fluoxetine 20 mg	Amoxyclav 375 mg	Atenolol 50, 100 mg	Enalapril 10, 20 mg
Originator Company	Bayer	Eli Lilly	SmithKline Beecham	Astra-Zeneca	MSD
Generic Companies	Adcock Ingram Arrow Pharma Pharmacare Cipla Life Sciences Ranbaxy	Eli Lilly (own generic) Hexal Pharma Cipla-Medpro Pharmacare Sandoz	Xixia Triomed Adcock Ingram Group Laboratories Ranbaxy	Adcock Ingram Pharmacare Sandoz Hexal Pharma Be-Tabs	Ranbaxy Cipla Life Sciences Pharmacare MC Pharma Hexal Pharma
Published Package Insert Dates*	Range: 7/99 – 7/04	Range: 7/96 – 3/02	Range: 7/90 – 2/05	Range: 1/90 – 2/05	Range: 11/99 – 9/03
	Originator: 1/00 Oldest Generic: 7/99	Originator: 7/96 Oldest Generic: 7/96	Originator: 5/99 Oldest Generic: 10/95	Originator: 1/94 Oldest Generic: 1/90	Originator: 11/94 Oldest Generic: 11/99

Information was drawn from the printed package inserts obtained in the South African market.

* Definition: The Publication Date is allocated initially as the date of registration of a product. Thereafter, updates of safety (and dosage/indications) information attract a new date of publication since they must obtain final approval at a meeting of the full Council at the MCC. Hence, the date of publication of the package insert would indicate when these aspects were last reviewed, either at initial approval or thereafter during the post-registration phase.

Table IV shows the comparison between the information in the originator product and that found in the generic product package inserts, drawn from Appendix B, Raw Data Tables.

Table IV: Originator Product Information Found in the Generic Package Inserts

		Indications	Dosage	Cautions	Side-Effects	Drug Interactions
Ciprofloxacin	No. of originator statements	8	21	6	78	9
(Total = 122 items in Orginator)	Materials: range	6-8	15-20	3-6	71-76	9-9
	Materials: median	8	18	6	75	9
	Brands in full agreement	4	0	3	0	5
Fluoxetine	No. of originator statements	3	7	20	53	8
(Total = 91 items in Originator)	Materials: range	3-3	5-7	12-20	47-53	6-8
	Materials: median	3	6	19	51	8
	Brands in full agreement	5	1	2	2	3
Amoxyclav	No. of originator statements	5	8	14	36	5
(Total = 68 items in Originator)	Materials: range	4-5	6-8	9-14	15-27	2-5
	Materials: median	5	8	13	24	3
	Brands in full agreement	4	4	1	0	2
Atenolol	No. of originator statements	2	8	31	36	10
(Total = 87 items in Originator)	Materials: range	2-2	0-4	11-19	24-24	3-8
	Materials: median	2	2	16	23	7
	Brands in full agreement	5	0	0	0	0
Enalapril	No. of originator statements	4	10	26	72	6
(Total = 118 items in Originator)	Materials: range	4-4	10-10	24-26	70-72	6-6
	Materials: median	4	10	26	71	6
	Brands in full agreement	5	5	4	2	5

Considering MCC's policy over many years, that generic package inserts should be *identical* to the originator package insert for a given drug, it was surprising that there were only 6 occasions (out of a possible 25) when all 5 generic brands were 100% in agreement with the originator section of text (indications, dosage, cautions, side-effects or drug interactions), ie. attracted a score of 5. Conversely, there were 7 occasions (out of a possible 25) where there were no brands in 100% agreement with the originator section of text, ie. a score of 0.

4.2 MCC SPI versus Originator & International Reference Countries

Table V shows the comparison between the information in the SPI and the originator product plus the materials from the four international reference countries, drawn from Appendix B, Raw Data Tables.

Table V: MCC SPI Drug Substance/Class Information Found in the Originator plus International Reference Country Texts

		Indications	Dosage	Cautions	Side-Effects	Drug Interactions
Ciprofloxacin	No. of SPI statements	6	24	8	68	9
(Total = 115	Materials: range	6-6	5-22	2-7	57-66	7-9
items)	Materials: median	6	10	3	66	9
	Countries in full agreement	5	0	0	0	4
Fluoxetine	No. of SPI statements	3	10	31	56	9
(Total = 109	Materials: range	2-3	5-8	16-22	30-51	6-8
items)	Materials: median	3	6	16	39	7
	Countries in full agreement	4	1	0	0	0
Amoxyclav	No. of SPI statements	5	16	25	41	5
(Total = 92 items)	Materials: range	1-5	2-12	11-19	19-40	2-5
	Materials: median	4	6	16	36	3
	Countries in full agreement	2	0	0	0	1
Atenolol	No. of SPI statements	2	5	29	38	10
(Total = 84 items)	Materials: range	1-2	0-3	17-23	23-26	5-8
	Materials: median	1	3	20	23	7
	Countries in full agreement	1	0	0	0	0
Enalapril	No. of SPI statements	4	8	40	57	5
(Total = 114	Materials: range	3-4	2-7	10-25	35-51	3-5
items)	Materials: median	4	4	23	44	4
	Countries in full agreement	3	0	0	0	2

This analysis showed even more marked divergence. There was only 1 occasion (out of a possible 25) when all reference countries were 100% in agreement with the MCC SPI section of text (indications, dosage, cautions, side-effects or drug interactions), ie. a score of 5, and there were 16 occasions (out of a possible 25) where there were no reference countries in 100% agreement with the MCC SPI section of text, ie. a score of 0.

4.3 Degree of Information Agreement – All Materials

Table VI reports the degree of information agreement for checklist 1 (originator) versus the five generic products, and the degree of information agreement for Checklist 2 (MCC SPI) versus the originator product and the international reference country information. The sum of the individual five variables could range from 5 (maximum agreement) to -5 (minimum agreement).

Table VI: Degree of Information Agreement of Assessed Materials versus Reference Checklists 1 & 2

Brand/Country	Indications	Dosage	Cautions	Side-Effects	Drug Interactions	Sum
Ciprofloxacin Checklist 1	P Range= 1.2 – 0.67	P Range= 1.26 – 0.48	P Range= 1.3 – 0.36	P Range= 1.23 – 0.67	P Range= 1.00	
Adcock Ingram (Adco-Ciprin)	1	0	1	0	1	3
Arrow (Ciprol)	0	0	1	0	1	2
Pharmacare (Orpic)	1	0	0	0	1	2
Cipla (Ciploxx)	1	0	0	0	1	2
Ranbaxy (Cifran)	1	0	1	0	1	3
Ciprofloxacin Checklist 2	P Range= 1.00	P Range= 1.1 – 0.14	P Range= 1.1 – 0.14	P Range= 1.26 – 0.60	P Range= 1.2 – 0.72	
Bayer (Ciprobay RSA)	1	0	0	0	1	2
USA	1	0	0	0	1	2
EMEA	1	0	0	0	1	2
Canada	1	0	0	0	0	1
Australia TGA	1	0	0	0	1	2
Fluoxetine Checklist 1	P Range= 1.00	P Range= 1.30 – 0.42	P Range= 1.3 – 0.36	P Range= 1.21 – 0.71	P Range= 1.25 – 0.61	
Eli Lilly (Lilly-Fluoxetine)	1	0	1	1	1	4
Hexal (Prohexal)	1	0	0	0	0	1
Cipla (Nuzak)	1	0	0	0	1	2
Pharmacare (Lorien)	1	1	1	1	1	5
Sandoz (Sandoz-Fluoxetine)	1	0	0	0	0	1

Table VI (Cont.): Degree of Information Agreement of Assessed Materials versus Reference Checklists 1 & 2

Brand/Country	Indications	Dosage	Cautions	Side-Effects	Drug Interactions	Sum
Fluoxetine **Checklist 2**	P Range= 1.24 – 0.62	P Range= 1.21 – 0.02	P Range= 1.22 – 0.0	P Range= 1.28 – 0.16	P Range= 1.28 – 0.28	
Eli Lilly (Prozac RSA)	1	0	0	0	0	1
FDA/USA	1	0	0	0	0	1
EMEA	1	0	0	0	0	1
Canada	1	0	0	0	0	1
Australia (TGA)	0	0	0	0	0	0
Amoxyclav **Checklist 1**	P Range= 1.21 – 0.71	P Range= 1.23 – 0.67	P Range= 1.29 – 0.35	P Range= 1.24 – 0.02	P Range= 1.26 – 0.10	
Xixia (Clamentin 375)	1	1	0	0	1	3
Triomed (Augmaxcil 375)	0	0	0	0	0	0
Adcock Ingram (Adco-Amoclav 375)	1	1	0	0	0	2
Group Laboratories (Clavumox 375)	1	1	0	0	1	3
Ranbaxy (Ranclav 375)	1	1	0	0	0	2
Amoxyclav **Checklist 2**	P Range= 1.28 – 0.16	P Range= 1.01 – 0.21	P Range= 1.23 – 0.01	P Range= 1.26 – 0.32	P Range= 1.28 – 0.00	
Smithkline Beecham (Augmentin RSA)	1	0	0	0	0	1
USPDI	0	0	0	0	1	1
(Augmentin) UK	0	0	0	0	0	0
(Apo-Amoxiclav) Canada	0	0	0	0	0	0
(Augmentin) Australia	1	0	0	0	0	1

Table VI (Cont): Degree of Information Agreement of Assessed Materials versus Reference Checklists 1 & 2

Brand/Country	Indications	Dosage	Cautions	Side-Effects	Drug Interactions	Sum
Atenolol Checklist 1	P Range= 1.00	P Range= 0.84 – 0.28	P Range= 1.1 – 0.14	P Range= 1.23 – 0.03	P Range= 1.22 – 0.02	
Adcock Ingram (Adco-Atenolol)	1	0	0	0	0	1
Pharmacare (Ten-Bloka)	1	0	0	0	0	1
Sandoz (Sandoz-Atenolol	1	0	0	0	0	1
Hexal (Hexa-Blok)	1	0	0	0	0	1
Be-Tabs (B-Blok)	1	0	0	0	0	1
Atenolol Checklist 2	P Range= 1.21 – 0.01	P Range= 1.05 – 0.17	P Range= 1.26 – 0.10	P Range= 1.23 – 0.03	P Range= 1.27 – 0.13	
Astra-Zeneca (Tenormin RSA)	0	0	0	0	0	0
USPDI	0	0	0	0	0	0
BNF	0	0	0	0	0	0
Canada	1	0	0	0	0	1
Australia	0	0	0	0	0	0
Enalapril Checklist 1	P Range= 1.00	P Range= 1.00	P Range= 1.15 – 0.81	P Range= 1.11 – 0.87	P Range= 1.00	
Adcock Ingram (Adco-Enalapril)	1	1	1	0	1	4
Cipla-Medpro (Ciplatec)	1	1	1	0	1	4
Pharmacare (Pharmapress)	1	1	0	0	1	3
MC Pharma (Enap)	1	1	1	1	1	5
Hexal (HR-Enalapril)	1	1	1	1	1	5

Table VI (Cont.): Degree of Information Agreement of Assessed Materials versus Reference Checklists 1 & 2

Enalapril Checklist 2	P Range= 1.27 – 0.53	P Range= 1.12 – 0.12	P Range= 1.13 – 0.09	P Range= 1.30 – 0.24	P Range= 1.28 – 0.40	
Brand/Country	Indications	Dosage	Cautions	Side-Effects	Drug Interactions	Sum
MSD (Renitec RSA)	1	0	0	0	0	1
USPDI (MSD)	1	0	0	0	0	1
EMEA (MSD)	0	0	0	0	1	1
Canada (MSD)	0	0	0	0	1	1
Australia (MSD)	1	0	0	0	0	1
Sum of Agreement vs Checklist 1		Range: 0 - 5			Median: 2	
Sum of Agreement vs Checklist 2		Range: 0 - 2			Median: 1	

It was seen that out of the twenty five generic product package inserts studied, only three demonstrated maximum agreement with the originator product material (Reference Checklist 1), namely one generic fluoxetine product and two generic enalapril products. The range of agreement was 0 – 5 with a median of 2. These findings are similar to those of the WHO international study regarding the national comparisons of materials for different brands of the same drug substance [10] (where eg. the majority of various brands of ciprofloxacin and fluoxetine were in extremely low agreement with the reference regarding side-effects and cautions, and incomplete agreement for indications and dosage; incomplete agreement was also found for various brands of nifedipine across indications, dosage, side-efects and cautions).

In the analysis versus Reference Checklist 2 (the MCC SPI), it was seen that the MCC SPI did not show maximum agreement with any of the originator plus four international reference country materials. The range of agreement was 0 – 2 with a median of 1. These results are also similar to the findings of the WHO international study for the between-country analysis for the same drug substance [10]. The WHO study found a high proportion of overall agreement with the reference for the three drugs studied ie.ciprofloxacin, fluoxetine and nifedipine, for only three countries out of twenty six. Strong disagreement was found overall, for fluoxetine in four countries, and for nifedipine in two countries.

4.4 Discussion of Results

The degree of information agreement was surprisingly low between the originator product and the five generic products that have subsequently been registered by MCC in South Africa, even though it is similar to international experience [5, 10]. Refer to Appendix B, Raw Data Tables for the comparisons of brands of individual drug substances.

It was seen that the dosage information was divergent eg. no generic brands were in complete agreement with the originator package insert for ciprofloxacin and atenolol, and only one brand for fluoxetine.

The nature of the divergence in fluoxetine and ciprofloxacin included:

- omission of instruction to swallow tablets whole or dispersed in 100 ml of water (fluoxetine, three generics, Lilly-fluoxetine, Nuzak and Sandoz-fluoxetine)
- omission of duration of treatment statement (ciprofloxacin, one generic, Ciploxx)
- omission of dosage adjustment statement in impaired hepatic/renal function (ciprofloxacin, three generics, Ciprol, Orpic and Ciploxx)
- omission of dosage for an approved indication (ciprofloxacin, one generic, Ciploxx, omitted the dosage in cystic fibrosis)
- omission of statement regarding use in elderly patients (fluoxetine, one generic, Sandoz-fluoxetine)
- omission of statement restricting use to adults only (fluoxetine, one generic, ProHexal)

One such discrepancy existed for fluoxetine where a statement is omitted from the originator's own generic package insert, namely the instruction to swallow tablets whole or dispersed in 100 ml of water!

The majority of the atenolol generics omitted the following originator statements:

- regarding compatability with diuretics/other antihypertensive medicines (four out of five generics: Adco-atenolol, Ten-Bloka, Sandoz-atenolol and B-Block)
- the recommendation for the addition of other antihypertensive agents in refractory cases (two out of five generics: Ten-Bloka and Sandoz-atenolol)
- the statement regarding use in renal failure (four out of five generics: Adco-atenolol, Ten-Bloka, Sandoz-atenolol and Hexa-Blok)
- the statement regarding lack of experience in children (all five generics: Adco-atenolol, Ten-Bloka, Sandoz-atenolol, Hexa-Blok and B-Blok)
- the statement recommending dosage reduction in elderly patients (all five generics: Adco-atenolol, Ten-Bloka, Sandoz-atenolol, Hexa-Blok and B-Blok), and
- the statement regarding the need to reduce dosage in renal dysfunction (three out of five generics: Adco-atenolol, Sandoz-atenolol and Hexa-Blok)

There were also actual variations in recommended dosage range, eg. in the case of atenolol:

- the originator dose for hypertension is 50 – 100 mg per day, while 4 out of 5 generics stated only 100 mg per day (Adco-atenolol, Ten-Bloka, Sandoz-atenolol and B-Blok)
- the originator dose for angina pectoris is 100 mg once daily or 50 mg twice daily, while two out of five generics stated 50 to 100 mg daily (Sandoz-atenolol and Hexa-Blok)

This is of concern, because the clinical dose-finding and efficacy studies for the drug substance, would presumably relate to the original studies performed during the development of the medicine, and should therefore be consistent across the generic brands. It is unlikely that new efficacy studies would have been performed by generic companies to support altered dosage ranges. It may be possible, particularly in medicines that have been available for many years, that more recent data has lead to a genuine

modification in the recommended dose, in which case the originator should be aware of this and should have updated their own dosing recommendations.

Where the discrepancies were limited to compliance guidance statements (eg. food instructions, duration of therapy, etc.), these omissions may have been oversights, but may still be clinically relevant in terms of pharmacokinetic considerations where food affects drug absorption, or where compliance with the prescribed course of therapy may be affected. Their omission may also be of concern for safety reasons, particularly in special populations such as elderly patients or those with renal or hepatic impairment.

It is also of concern that the safety information on many package inserts has apparently not undergone any updating in line with post-marketing surveillance studies or international database references, as evidenced by dates of publication (see Table III, page 32).

In three out of the five drug substances (see Table III, page 33), the originator package insert had undergone voluntary updating since initial approval (evidenced by the more recent publication dates for their package inserts), yet the generic package inserts had not followed suit, ie. amoxyclav, ciprofloxacin and atenolol. This supports the original assertion that originator and generic products' prescribing information may diverge in the post-registration phase, in the absence of a mandatory requirement by MCC for periodic updating of package inserts. eg.:

- Amoxyclav originator date of publication: 5/99, while the oldest generic product has a date of publication of 10/95.

- Ciprofloxacin originator date of publication: 1/00, while the oldest generic product has a date of publication of 7/99.

- Atenolol originator date of publication: 1/94, while the oldest generic product has a date of publication of 1/90. This indicates that no safety updating has taken place in the generic package insert for seventeen years (or in this case, in the

originator package insert for thirteen years), which is alarming considering the sophisticated pharmacovigilance systems in place internationally, as well as the ready availability of such data on a global basis.

The overall degree of information agreement between the MCC SPI and the originator plus four reference countries, is even more divergent, but is again in agreement with the WHO international study [10], regarding the prescribing information for each drug from different countries. Refer to Appendix B, Raw Data Tables for the drug substances per country comparison.

This situation exists even though the compilation of SPI's is still in an early phase at MCC, and it is of concern since this project aims to introduce the SPI as a standardised, internationally-harmonised SPC-type reference document for the South African market. Information from reference countries would presumably have been checked very recently, probably within the last two years (approximately the time the first SPI's began to become available). It may be possible that new information may have become available to MCC in that time, which is not reflected in the documentation from the international reference countries.

In some individual checklist items that are in complete *disagreement* with the SPI, there is however, substantial *agreement* amongst all four reference countries eg.:

- Enalapril - the MCC SPI (for ACE-inhibitors) has the following contra-indications:
    - Hypertrophic obstructive cardiomyopathy
    - Severe renal function impairment (creatinine clearance below 30 ml/min)
    - Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride, and porpyria

  these contra-indications do not appear in the originator text nor in any of the four reference countries' texts (side-effects versus Checklist 2, P Range = 1.30 – 0.24).

- Enalapril - the MCC SPI includes the following side-effects, which similarly do not appear in any of the comparator country materials:
    - Uraemia
    - Anuria
    - Sinusitis
    - Psoriasis

- Atenolol - the MCC SPI contains the following warnings that do not appear in any of the reference countries or in the originator insert (side-effects versus Checklist 2, P Range = 1.23 – 0.03):
    - Class I antidysrrhythmic agents eg. disopyramide
    - Myocardial depressants & AV conduction inhibitors eg calcium antagonists
    - Transfer of patient from clonidine as release of catecholamines may lead to hypertensive crisis
    - Withdraw atenolol several days before clonidine to prevent rebound hypertension
    - Combination with verapamil in patients with impaired ventricular function, use with caution. Do not use combination in patients with conduction abnormalities. Do not give either drug IV within 48 hours of each other.
    - Do not give IV calcium antagonists & anti-arrhythmic agents with atenolol".

- Atenolol - the MCC SPI contains nine side-effects that are found nowhere in any of the comparator materials (ie. not in originator package insert nor in the four reference countries' prescribing information):
    - Precipitation of peripheral gangrene
    - Lassitude
    - Restlessness
    - Paradoxical hypertension
    - Mass gain

- Stomatitis
- Muscular cramps
- Myopathy
- Transient hearing loss

Similar anomalies have been found between the SPI and reference comparators for fluoxetine and amoxyclav, and to a lesser extent, for ciprofloxacin.

CHAPTER 5: Conclusions and Recommendations

5.1 Conclusions

Existing package inserts of approved products currently available to heathcare professionals and patients in South Africa, show considerable differences between the originator product and subsequent generic brands of the same drug substance.
This may be accounted for to some extent, by the absence of a mandatory requirement for periodic updating or review of package inserts in the post-registration phase.

Regarding the Standardised Package Insert initiative that has been embarked upon by the MCC, this study has shown that there is considerable variation between the SPI's that are available and the texts of the originator product plus four international MCC-designated reference countries, for the same drug substance.

The above findings are of concern in terms of the provision of consistent, complete, internationally-harmonised and up to date dosing and safety information, both to healthcare professionals and to consumers, and inappropriate prescribing may result.

Local package insert safety texts should not diverge from those in international reference countries or from the outcomes of international clinical research. Differences will:

- complicate international post-marketing safety surveillance programmes, as the categorisation and documentation of reported adverse events will be at variance.
- Local clinical trials may be affected in terms of their exclusion criteria, should local contra-indications be at odds with those in the international domain, and the reporting of results may be affected in terms of the categorisation and documentation of reported adverse events.
- There may be serious implications for patients traveling as well as health workers developing therapeutic guidelines and drug utilization reports.

Consideration of these findings appears to lead to the current systems and policies (or shortfalls in these) at the South African regulatory authority, and their key role in remedying the situation.

5.2 Recommendations

The following recommendations are made, based on the findings in this study.

The problem of patently outdated package inserts still being in circulation should be addressed by:

- The introduction of a mandatory updating system, where the time frames are legislated for both the frequency of updating and the time period for the implementation of updated materials following their approval by MCC.

- The date of publication appearing on materials in the market could be an audit point for the MCC to ensure updates are undertaken and implanted on approval.

- The Patient Information Leaflet should have to be updated and implemented in a similar manner - the distribution and translation issues to be appropriately resolved with appropriate urgency.

The following recommendations are made to ensure that all newly registered generic products, and all medicines in the post-registration phase going forward, comply with internationally-congruent and standardised prescribing information:

- The SPI should be retained as the minimum master text against which companies update their package inserts, to be viewed along with the outcomes of new clinical data as it becomes available.

- All existing SPI's as well as all new ones created in future, should undergo rigorous validation to ensure that the texts do in fact, remain strictly in line with international reference country texts, before full implementation of the SPI project.

- The SPI should be reviewed and updated at regular intervals in line with the mandatory requirement for periodic updating or review of package inserts in the post-registration phase.

Other recommendations aimed at improving the quality, usefulness and consistency of package inserts, are made:

- Currently absent from most South African package inserts and SPI's, is additional national or demographically-relevant information (to include SADC countries as a minimum due to the mobility of patients and medicines within the region). Attention must be given to the inclusion of information regarding porphyria, photosensitivity, specific ethnic populations, and administration with antiretroviral and anti-tuberculosis medications. This should be included in the SPI, clearly marked where it differs from reference countries.

- The SPI, as well as the approved package inserts of all originator and generic products should be made readily accessible to the industry and healthcare professionals by the Medicines Control Council. The author believes that a suitable repository for this information would be the Medicine Control Council website (www.mccza.com), as is the case with other regulatory authorities (eg. EMEA website for Europe, FDA website for USA, Health Canada for Canada, etc.). This would be an authoritative resource for the latest prescribing information for any given product. The site would require efficient management to ensure the information remains completely current, and should be resourced by, and under the authority of the MCC, possibly with some contributory funding from the industry.

- Such an SPI and package insert database would be the regulatory source of the scientific package insert, making it unnecessary to include this in the product pack. In the future, only the approved user-friendly Patient Information Leaflet (PIL) would be necessary in the product pack.

In the opinion of the author, the above imperatives are urgent in the South African situation, as exponentially increasing numbers of generic and other products from diverse international sources are reaching the South African market (and other developing countries).

The pressures on available regulatory resources in developing, as well as developed countries are increasing in line with this globalisation, yet it remains the responsibility of regulatory authorities to appropriately regulate the contents of national prescribing information, independent of commercial interests.

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List of Abbreviations

ACE Inhibitor	Angiotensin Converting Enzyme Inhibitor
BNF	British National Formulary, which has a world-wide reputation for being a complete, independent, reliable and practice-oriented source of drug information.
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration (US Regulatory Authority)
International Reference Country	A country where MCC accepts regulatory approvals as substantive evidence in support of South African approvals, and with which MCC aligns itself (ie. USA, UK, European Union, Australia, Canada).
MCC	Medicines Control Council, South African Medicines Regulatory Authority
MedDRA	Medical Dictionary for Regulatory Activities
TGA	Therapeutic Goods Agency (Australia)
PIL	Patient Information Leaflet
SPC	Summary of Product Characteristics
SPI	Standardised Package Insert
USPDI	United States Pharmacopoeia Drug Information
WHO	World Health Organisation
SADC	Southern African Development Community
CI	Confidence Interval
UK	United Kingdom
USA	United States of America

Appendix A

ETHICS WAIVER

Appendix B

COMPARATIVE RAW DATA TABLES