Quality of the Combined Oral Contraceptive pill (0.15mg levonorgestrel and 0.03mg ethinylestradiol) in the private retail pharmacies of Nyeri Town, Kenya. Results from a postmarket quality study

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Research submitted in partial fulfillment of the award of M.Sc. in Pharmacy Administration and Pharmacy Policy Specialising in Regulatory Sciences

University of the Western Cape in partnership with Hibernia College

2015
Abstract

Background: The effectiveness of the combined oral contraceptive pill as a family planning method is dependent on its quality. The quality of medicines on the healthcare market is established through postmarket quality studies.

Methods: The quality of the combined oral contraceptive pill was established through the collection of samples from 17 (62%) private retail pharmacies in the Nyeri town of Kenya. Their quality was then determined through the assay of content of levonorgestrel and ethinylestradiol and the levonorgestrel dissolution test at the National Quality Control Laboratory.

Findings: 13 of the 17 pharmacies were licensed with the Pharmacy and Poisons Board while 4 were unlicensed. Femiplan® was available in all the 17 pharmacies while Microgynon® was available in only 4 pharmacies. 17 samples of Femiplan® and 4 samples of Microgynon® were collected. None of the samples was counterfeit or falsely labeled. All the samples passed the assay of content of levonorgestrel and ethinylestradiol and the levonorgestrel dissolution test.

Conclusion: Notwithstanding the fact this study provides a snapshot in time, it is reasonable to conclude that the combined oral contraceptive pill (0.15mg levonorgestrel and 0.03mg ethinylestradiol) in the Nyeri town of Kenya private retail pharmacies is of the right quality with respect to the quality tests of assay of content of levonorgestrel and ethinylestradiol and the levonorgestrel dissolution test.
Declaration

I declare that this thesis that I now submit for assessment on the programme of study leading to the award of Master of Science in Pharmacy Administration and Pharmacy Policy Specialising in Regulatory Sciences has not been submitted as an exercise for a degree at this or any other university. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work.

I agree to deposit this thesis in the University of the Western Cape and Hibernia College institutional repositories or allow their libraries to do so on my behalf, subject to South Africa’s and Irish Copyright Legislation and the University of the Western Cape and Hibernia College libraries conditions of use and acknowledgement.

Signed. **TOM MWANGI KAUKI**  
Dated. **30TH JULY 2015.**
Acknowledgements

This project could not have been finished without the support of others. In the first instance, I would like to thank Professor Peter Eagles, University of the Western Cape and Miriam O'Donoghue, Hibernia College for their guidance and support throughout the project. I am also grateful to my wife Esther Muthoni Mburu for her support and encouragement throughout the whole course.
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1. Introduction

Pharmaceutical services in Kenya are provided through the private and public sector (Ministry of Medical Services – Kenya 2010, p. 17). As of June 2015 there were 38 pharmaceutical manufacturers, approximately 250 wholesale pharmacies, 5,000 retail pharmacies and 12,000 medicines registered in Kenya (Ministry of Medical Services – Kenya and World Health Organization 2010, p. 17). Public sector pharmaceutical services are provided through the Ministries of Health located at the National Government and the 47 County Governments (Ministry of Medical Services 2008). The Kenya Medical Supplies Agency, the Pharmacy and Poisons Board and the National Quality Control Laboratory are government agencies established for public sector medical supplies, medicines regulation and medicines quality testing respectively (Kenya Medical Supplies Agency 2015; National Quality Control Laboratory 2015).

It is the responsibility of governments to promote and protect public health by ensuring that the medicines on the healthcare market are not of poor quality. A medicine is deemed to be of poor quality if it fails to meet the pharmacopoeial specifications it claims to comply with (Shakoor, Taylor and Behrens 1997; Kaur et al 2008; Hadi et al 2010). A poor quality medicine can have the wrong ingredients, inadequate amounts of the right ingredients, excess amounts of the right ingredients or the right ingredients in the right quantities but with a poor dissolution profile (Almuzaini, Choonara and Sammons 2013).


The quality of medicines on the healthcare market is established through postmarket quality studies. Due to financial constraints, it is impossible for medicines regulatory authorities to collect samples of all medicines on the healthcare market at a given time and test their quality and therefore they adopt a risk and impact on public health approach in determining which medicines to sample.

75% of all women in Kenya using contraceptives opt for hormonal contraceptives with 32% of them going for combined oral contraceptives (Republic of Kenya, Division of Reproductive Health 2009, p. 69). The combined oral contraceptive pill (0.15mg levonorgestrel and 0.03mg

The purpose of this project was to establish the quality of the combined oral contraceptive pill (0.15mg levonorgestrel and 0.03mg ethinylestradiol) in the private retail pharmacies of Nyeri Town, Kenya. This was with respect to the quality tests of assay of content of active pharmaceutical ingredients and dissolution.

2. Literature review

2.1. Medicines. Not your ordinary consumer product

Medicines are not your ordinary consumer product owing to the asymmetry of information about medicines which exists between prescribers and consumers (Brundtland 1999; Rago and Santos 2008, p.66). Consumers find themselves not in a position to make decisions about when to use medicines, which medicines to use, how to use medicines and to weigh the potential benefits of medicines against their risks (Brundtland 1999; Rago and Santos 2008, p.66). Healthcare professionals also do experience difficulties in making informed decisions on all aspects of medicines unless specially trained (Nikiema 2014).

Therefore, medicines needs to be regulated with an aim of protecting and promoting public health and this is achieved through the following mutually reinforcing activities: the assessment of quality, safety and efficacy of medicines during market authorisation and postmarket, the licensing of manufacture, import, export, distribution and promotion of medicines, the inspection and surveillance of manufacturers, importers, wholesalers and retailers of medicines and last but not least the provision of independent medicines information to healthcare workers and the general public (World Health Organization 2003; Rago and Santos 2008, p.67).

2.2. Medicines regulation. Historical perspectives

Human beings have been taking medicines since history began (Penn 1979). The regulation of medicines is also not of recent origin. The ancient Egyptians had a flourishing medical profession in which physicians administered their medicines in accordance with a written law called the sacred book (Penn 1979). The Hippocratic Oath which originated after the 5th Century BC enjoined the physician then and now against the giving of ‘pharmacon oudeni’ meaning lethal drug (Penn 1979; National Institutes of Health, National Library of Medicine, History of Medicine Division 2012). The medieval Muslim countries, in the early part of the 9th century, established the office of the hisba headed by the muhtasib as the official responsible for enforcing public health regulations (Levey 1963). The muhtasib had specific instructions to inspect the drugs of the syrup makers while cautioning them not to flout medicines related public health regulations (Levey 1963).
Unfortunate events have played a significant role in the evolution of medicines regulatory frameworks (Rago and Santoso 2008, p.65). The enactment of the Federal Food, Drug and Cosmetic Act in the United States of America was hastened following the 1937 sulfanilamide disaster in which more than 100 people died after consuming an elixir sulfanilamide laced with diethylene glycol as the solvent (Bowie and McKenzie 1972; Ballentine 1981; Rago and Santoso 2008, p.65). The thalidomide tragedy also had a major role in catalysing developments within the medicines regulatory frameworks (Rago and Santoso 2008, p.65-66). Thalidomide, a sedative and hypnotic drug, widely used as a morning sickness treatment between 1958 and 1960, resulted in an estimated 10,000 babies being born with phocomelia worldwide (Rago and Santoso 2008, p.66; Tantibanchachai 2014). In 1963 the Australian Government formed the Australian Drug Evaluation Committee to evaluate the safety of medicines before they are offered for sale to its citizens in response to the thalidomide tragedy (Therapeutic Goods Administration 2014). The Drug Amendments of 1962 were enacted requiring that the United States Food and Drug Administration approve all new drug applications following demonstration of safety and efficacy (Rago and Santoso 2008, p.66; Tantibanchachai 2014). In the United Kingdom the Committee on the Safety of Medicines was established in 1963 following the thalidomide tragedy (Rago and Santoso 2008, p.66).

Regrettably, unfortunate events are still catalysing developments in the medicine regulatory frameworks. In November 2013, President Barrack Obama signed into law the Compounding Quality Act to regulate the compounding of human drugs following the death of 64 people from meningitis contracted after receiving a fungi-contaminated methylprednisolone acetate injection produced by a Massachusetts-based compounding pharmacy (Gaffney 2013; The Lancet 2013 Dennis 2014; Outterson 2014; United States Food and Drug Administration 2014).

2.3. Modern medicines regulatory frameworks

Modern medicine regulatory frameworks are laid down by legislation to be enforced by government agencies known as medicines regulatory authorities. Medicines regulatory authorities regulate the trade in medicines (human, veterinary and herbal) and a host of other products such as nutraceuticals, medical devices, in vitro diagnostics, food, cosmetics and tobacco products as provided for by legislation (Food and Drugs Authority Ghana 2014; Medicines and Healthcare Products Regulatory Agency 2014; Medicines Control Council 2014; Pharmacy and Poisons Board 2014; Therapeutic Goods Administration 2014; United States Food and Drug Administration 2014). The Pharmacy and Poisons Board of Kenya also regulates the practice of pharmacy. This is in contrast to other countries such as South Africa where we have the Medicines Control Council for medicines regulation and the South African Pharmacy Council for pharmacy practice regulation (Medicines Control Council 2014; South African Pharmacy Council 2014).
The most important function of medicines regulatory authorities is to ensure that the medicines on the healthcare market are not compromised with respect to quality, safety and efficacy. The quality of a medicine is of special significance since its compromise subsequently compromises the safety and/or efficacy of the medicine. Keoluangkhot and colleagues describe the case of an adult in Laos with uncomplicated malaria who failed to improve clinically following treatment with an artemether injection whose artemether content was 74% of the manufacturer’s label claim, a clear case of quality failures compromising the efficacy of medicines (Keoluangkhot et al 2008). The poor quality isosorbide mononitrate contaminated with a heavy dose of the antimalarial pyrimethamine supplied to patients in Pakistan in the year 2012 had a compromised safety evidenced by the death of 120 patients who used it (Arie 2012; The Lancet 2013).

2.4. What is a poor quality medicine?

Before we delve further into matters ‘quality of medicines’ it is important that we gain an understanding of what is meant by the quality of a medicine. A medicine is deemed to be of poor quality when it fails to meet the pharmacopoeial specifications it claims to comply with (Shakoor, Taylor and Behrens 1997; Kaur et al 2008; Hadi et al 2010). A poor quality medicine can have the wrong ingredients, inadequate amounts of the right ingredients, excessive amounts of the right ingredients or the right ingredients in the right quantities but with a poor dissolution profile (Almuzaini, Choonara and Sammons 2013).

Poor quality medicines can be genuine medicines produced by authorized manufacturers in which case they are referred to as substandard or out of specification medicines (Bate, Mooney and Milligan 2012; European Directorate for the Quality of Medicines and Healthcare of the Council of Europe2013; World Health Organization 2012). They can also be medicines that are illegally manufactured and fraudulently mislabeled with respect to identity or source in which case then they are referred to as counterfeit medicines (Bate, Mooney and Milligan 2012; World Health Organization 2012).

2.5. Poor quality medicines. Historical perspectives

Human beings have been taking medicines since history began and poor quality medicines are perhaps as old as the medicines themselves (Penn 1979; World Health Organization 1999; Newton et al 2006; Rago and Santoso 2008, p.64). Dead flies adulterating the ointment of the apothecary, a person who prepares and sells medicines, appears as a comment in the Bible (Ecclesiastes 10:1, King James Version; Oxford Dictionaries 2014). The 17th century witnessed the deliberate adulteration of the cinchona bark, the first effective treatment for malaria, with other astringent barks precipitated by the huge demand of the cinchona bark in the then malaria endemic Europe (Newton et al 2006; Cambridge University Library 2014).

Our concern for the quality of medicines is also not of recent origin with the concepts for assuring the quality of medicines having evolved gradually over time (World Health
Organization 1999; Newton et al 2006; Rago and Santoso 2008, p.64). The first century AD, witnessed the Greek physician Pedanius Dioscorides advising on the dangers of adulterated medicines (World Health Organization 1999). The *Materia Medica* of Dioscorides highlighted some organoleptic tests for the detection of adulterated medicines (Penn 1979). The fine clay ‘terra sigillata’ used from early Greek times for the treatment of wounds was made into round cakes and stamped with designs alluding to its authenticity and quality (Penn 1979). In the medieval Muslim countries we had the muhtasib, official in charge of enforcing public health regulations, vested with powers to inspect the shops of the syrup makers (Levey 1963). The development of obligatory pharmacopoeial standards dates back to the 16th century and the 1498 New Compound Dispensatory issued by the Florentine guild of physicians and pharmacists for the apothecaries of Florence is regarded as the first official pharmacopoeia of a specific political unit in Europe (Penn 1979).

### 2.6. Need for the concern for quality of medicines

The agenda of assuring the quality of medicines on the healthcare market should zealously be pursued by governments due to the following reasons. Firstly, the use of poor quality medicines can result in therapeutic failure with a subsequent increase in morbidity and mortality (World Health Organization 2003; Newton et al 2006; Keoluangkhot et al 2008; World Health Organization 2012). Secondly, the use of poor quality antimicrobials leads to development of resistance and this is especially undesirable among the sub-Saharan Africa high public health priority diseases specifically malaria, tuberculosis and the Acquired Immune Deficiency Syndrome (World Health Organization 2003; Alfadl et al 2006; Newton et al 2006). Thirdly, the detection of poor quality medicines on the healthcare market leads to erosion of public confidence in healthcare systems which can compromise the uptake of high public health priority healthcare services such as immunization (World Health Organization 2003; Newton et al 2006; World Health Organization 2012). Fourthly, it is a waste of resources to spend money on poor quality medicines whether individually or by governments (World Health Organization 2003; Alfadl et al 2006). Fifthly, the use of poor quality medicines leads to spurious reporting of resistance which can lead to unwarranted alterations of treatment protocols (Newton et al 2006). Lastly, it is an exercise in futility to translate evidence on drug treatment outcomes into treatment policy when the medicines actually used have inferior efficacy due to poor quality compared to the medicines originally tested during clinical trials or bioequivalence studies (Newton et al 2006; Newton et al 2009).

### 2.7. Poor quality medicines. Now and recently

Since the 17th century adulteration of the cinchona bark, the world is still grappling with the problem of poor quality medicines notwithstanding the modern medicine regulatory frameworks. An Institute of Medicine of the National Academies report estimated that in the year 2011 substandard or falsified medicines were sold in at least 124 countries worldwide (Institute of Medicine of the National Academies 2011).
Poor quality medicines are a problem for both the high and low income countries affecting both the expensive brands and cheap generics (World Health Organization 2012). Poor quality medicines have being witnessed in the medicines for the treatment of life-threatening conditions such as tuberculosis, medicines for the treatment of neglected tropical diseases such as visceral leishmaniasis and even in cheap generic versions of painkillers and antihistamines (Senior 2008; Dorlo et al 2012; World Health Organization 2012; Division of Malaria Control, Pharmacy and Poisons Board and National Quality Control Laboratory 2013). The problem of poor quality medicines appears to burden the low income countries more compared to the high income countries (Institute of Medicine of the National Academies 2013; The Lancet Editorial 2013).

The world is still witnessing deaths occasioned by the use of medicines laced with diethylene glycol as the solvent and to mention a few: 7 deaths in South Africa in 1969, 14 deaths in India in 1986, 5 deaths in Spain in 1987, 85 deaths in Haiti in 1995, 33 deaths in India in 1998, 12 deaths in China in 2008 and 57 deaths in Nigeria in 2008 (Bowie and McKenzie 1972; Singh et al 2001; Sosa et al 2014). 81 people died in the United States of America during the 2007-2008 heparin crises after using a heparin batch contaminated with oversulfated chondroitin sulfate (Briones 2008; Harris 2008). Avastin without active pharmaceutical ingredient was detected in the United States of America in the year 2012 (World Health Organization 2012). In June 2014, the United States Food and Drug Administration instituted a product recall of metoprolol succinate 100mg manufactured by Wockhardt Limited, India and metoprolol succinate 25mg manufactured by Dr. Reddy's Laboratories Limited, India after the two products failed dissolution tests, one of the basic tests of medicines quality (United States Food and Drug Administration 2014).

In August 2008, health authorities in South Africa withdrew from the healthcare market two brands of antituberculosis medicines after World Health Organization accredited quality control tests indicated inadequate concentrations of rifampicin and isoniazid (Senior 2008). The lack of a substantial financial incentive in the market for medicines for Neglected Tropical Diseases has also not protected these medicines from poor quality batches (Dorlo et al 2012). In 2008, a generic miltefosine without the active pharmaceutical ingredient emerged in Bangladesh for use in the national leishmaniasis elimination programme (Senior 2008; Dorlo et al 2012).

2.8. Reasons for the availability of poor quality medicines

There are various reasons for the availability of poor quality medicines on the healthcare market. The first one is the failure of medicine manufacturers to adhere to Good Manufacturing Practices (Bate, Mooney and Milligan 2012). The second reason is the pharmaceutical manufacturers’ use of poor quality pharmaceutical raw materials (Shakoor, Taylor and Behrens 1997). The third reason is the degradation of finished pharmaceutical products and pharmaceutical raw materials due to poor storage practices coupled with the high temperatures and humid conditions that
prevail in the tropical countries (Shakoor, Taylor and Behrens 1997; Taylor et al 2001). Lastly, we have the unscrupulous businessmen who guided by criminal greed engage in the production of poor quality medicines facilitated by lack of legislation criminalizing the production and marketing of poor quality medicines and if existent the failure of enforcement by government authorities and if enforced light penalties being imposed by the judiciary on the culprits (Newton et al 2006 and Onwujekwe et al 2009).

2.9. Measures for ridding the healthcare market of poor quality medicines

There are various measures which medicine regulatory authorities can adopt to rid the healthcare market of poor quality medicines. The first one is the implementation of a robust marketing authorisation process encompassing a thorough evaluation of the quality data as presented on the Common Technical Document. The second measure is the conduct of regular and thorough inspection of pharmaceutical manufacturers to ensure that the manufacture of active pharmaceutical ingredients and finished pharmaceutical products adheres to Good Manufacturing Practices.

The third measure entails the routine inspection of medicines distribution outlets in order to ensure that the medicines offered for sale are registered and that medicines distributors adheres to Good Distribution Practices by having for instance a system for batch tracing in case of poor quality medicinal product recall. The fourth measure entails having a paper and online based platform through which healthcare providers and the general public can report incidents of poor quality medicines. An example is the Pharmacy and Poisons Board poor quality medicinal product reporting form, also called the pink form, through which healthcare workers and the general public alert the Pharmacy and Poisons Board of any incidents of poor quality medicines (Pharmacy and Poisons Board 2014). The last and very important measure entails the conduct of regular postmarket quality studies.

2.10. Postmarket quality studies

Postmarket quality studies entail the collection of medicines samples within a given geographical area and subjecting them to quality tests mainly the assay of content of active pharmaceutical ingredient(s) and dissolution. Postmarket quality studies can be conducted on a routine basis, following a complaint of a poor quality medicine or through sentinel site monitoring which entails the monitoring of the quality of medicines at a given site over a certain period of time.

The benchmark for the postmarket quality of a medicine lies in its compliance with the laid down pharmacopoeial specifications it claims to comply with (Taylor et al 2001). A pharmacopoeia is an official book of medicines quality standards and the term is derived from the Greek word pharmaco-poios meaning drug-maker (United States Pharmacopeial Convention 2000; Rago and Santoso 2008, p.64; Rago and Santoso 2008, p.72). A pharmacopoeia is legally binding and contains the recommended quality specifications for the analysis and determination of medicinal
substances, specific dosage forms, excipients and finished pharmaceutical products (Rago and Santoso 2008, p.72). Quality specifications are composed of appropriate tests for confirming the identity and purity of medicinal products, ascertaining the amount of active pharmaceutical ingredients and the performance characteristics of medicinal products (Rago and Santoso 2008, p.72). The **assay of content of active pharmaceutical ingredient(s)** and the **dissolution test** are two quality specifications which find application in postmarket quality studies (Shakoor, Taylor and Behrens 1997; Taylor et al 2001; Laroche et al 2005; Alfadl, Abdoon, Elamin and Elnabi 2006; Kaur et al 2008; Onwujekwe et al 2009; Hadi et al 2010; Bate, Mooney and Milligan 2012; Evans et al 2012; Boateng 2013).

Postmarket quality studies are also conducted by researchers affiliated to academic institutions and organizations such as the World Health Organization. The Promoting the Quality of Medicines program funded by the United States Agency for International Development and implemented by the United States Pharmacopeial Convention assists medicines regulatory authorities in the conduct of postmarket quality studies through financing and provision of technical assistance (Ghana Food and Drug Authority and The Promoting the Quality of Medicines Program 2013; United States Pharmacopeial Convention 2014).

The Medicines Information and Pharmacovigilance Directorate of the Pharmacy and Poisons Board is the unit responsible for the conduct of postmarket quality studies in Kenya. This unit has for instance been monitoring the quality of antimalarials since the year 2011 with the results indicating that a significant proportion of antimalarials in the Kenyan healthcare market are of poor quality (Division of Malaria Control, Pharmacy and Poisons Board, National Quality Control Laboratory and The Promoting the Quality of Medicines Program 2011; Division of Malaria Control, Pharmacy and Poisons Board, National Quality Control Laboratory and The Promoting the Quality of Medicines Program 2012; Division of Malaria Control, Pharmacy and Poisons Board, National Quality Control Laboratory and The Promoting the Quality of Medicines Program 2013).
Table 1: Antimalarials postmarket quality studies results. Kenya

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples collected</td>
<td>536</td>
<td>499</td>
<td>545</td>
</tr>
<tr>
<td><strong>Percentage</strong> of samples <strong>registered</strong> with the Pharmacy and Poisons Board</td>
<td>94</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>Samples analysed using minilab in the field – Level 1</td>
<td>519</td>
<td>496</td>
<td>514</td>
</tr>
<tr>
<td><strong>Percentage</strong> of samples that <strong>passed</strong> Level 1 minilab testing</td>
<td>92</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Samples analysed using minilab at the National Quality Control Laboratory – Level 2</td>
<td>80</td>
<td>65</td>
<td>71</td>
</tr>
<tr>
<td><strong>Percentage</strong> of samples that <strong>passed</strong> Level 2 minilab testing</td>
<td>76</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Samples analysed using compendial methods at the National Quality Control Laboratory – Level 3</td>
<td>44</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td><strong>Percentage</strong> of samples that <strong>passed</strong> Level 3 compendial testing</td>
<td>84</td>
<td>76</td>
<td>90</td>
</tr>
</tbody>
</table>

The average results are 5% failure at Level 1 minilab testing, 11% failure at level 2 minilab testing and 16% failure at level 3 for compendial testing.

The Ghana Food and Drug Authority over the months of August and September 2012 assessed the postmarket quality of uterotonics (oxytocin injection, ergometrine injection and ergometrine tablets) in the Ghanaian healthcare market and found that a significant proportion of them failed the assay of content of active pharmaceutical ingredient (Ghana Food and Drug Authority and The Promoting the Quality of Medicines Program 2013).

Table 2: Uterotonics postmarket quality study results. Ghana

<table>
<thead>
<tr>
<th>MEDICINE</th>
<th>Oxytocin injection</th>
<th>Ergometrine injection</th>
<th>Ergometrine tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAMETERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samples collected</td>
<td>185</td>
<td>103</td>
<td>15</td>
</tr>
<tr>
<td>Samples subjected to the assay of content of active pharmaceutical ingredient</td>
<td>169</td>
<td>99</td>
<td>11</td>
</tr>
<tr>
<td><strong>Percentage</strong> of samples which <strong>failed</strong> the assay of content of active pharmaceutical ingredient</td>
<td>56</td>
<td>74</td>
<td>100</td>
</tr>
</tbody>
</table>
The Medicines and Healthcare Products Regulatory Agency, United Kingdom’s medicines regulatory authority, regularly identifies high risk medicines in need of postmarket quality surveillance based on criteria such as patient exposure, product stability and impact and likelihood of risk (Medicines and Healthcare Products Regulatory Agency 2014). The postmarket quality of these medicines is then surveyed on a one-off basis or continually sampled from pharmacies for authentication using a variety of analytical quality testing techniques (Medicines and Healthcare Products Regulatory Agency 2014).

In the European Union, postmarket quality surveillance of centrally authorized and mutually recognized medicines is done by the General European Official Medicines Control Laboratory Network on behalf of the European Directorate for the Quality of Medicines and Healthcare (European Directorate for the Quality of Medicines and Healthcare of the Council of Europe 2013). 20-25 Official Medicine Control Laboratories from 15-20 Member States participate in the scheme every year and the scheme results indicate a high level of quality is present in the medicines that are in use within the European Union since out of specification parameters have so far been found in only 2% of the medicines subjected to the surveillance programme (European Directorate for the Quality of Medicines and Healthcare of the Council of Europe 2013).

Postmarket quality studies published in various journals point toward a significant proportion of medicines circulating in the healthcare market of the low income countries been of poor quality. 1912 antimalarials and antibiotics samples were collected from 11 African cities (Accra, Addis Ababa, Cairo, Dar es Salaam, Kampala, Kigali, Lagos, Luanda, Lubumbashi, Lusaka and Nairobi), 3 Indian cities (Delhi, Chennai and Kolkata) and 5 middle income countries cities (Sao Paolo, Moscow, Bangkok, Istanbul and Beijing) in 2012 and subjected to quality tests (Bate, Mooney and Milligan 2012). 3.8% of them failed quality tests performed with the Global Pharma Health Fund e.V. Minilab and 5.2% failing product authentication by Raman spectrometer (Bate, Mooney and Milligan 2012). 58% of 77 samples of antimalarials sampled in Guyana over the period of June and August 2009 failed quality control tests (Evans et al 2012). 18% of 104 antibiotic samples collected from pharmacies in Indonesia in the year 2010 failed quality control tests (Hade et al 2010). Out of 713 samples of isoniazid and rifampicin purchased at community pharmacies in 19 cities of 17 countries, 65 (9.1%) had insufficient active pharmaceutical ingredient with the failure rate being 9.1% in Africa, 10.1% in India and 3.9% in other middle-income countries (Bate et al 2013; Binagwaho et al 2013).

Postmarket quality studies conducted in the low income countries have tended to focus more on antimicrobials most probably due to the high burden of infectious and communicable diseases. A search of medical literature on EMBASE, MEDLINE, Google Scholar, PubMed and International Pharmaceutical Abstracts for postmarket quality studies on combined oral contraceptives yielded no results. It is imperative that postmarket quality studies are conducted to
establish the quality of the combined oral contraceptives circulating in the Kenyan healthcare market.

2.11. Combined oral contraceptives

Contraception, also referred to as birth control, entails the use of various medical devices, drugs, sexual practices or surgical procedures to prevent pregnancy (Nordqvist 2012; The State of Queensland 2014). Contraception is achieved either by prevention of fertilization of the female egg by the male sperm or by prevention of implantation of the fertilized egg in the uterus (Kimathi, Micheni and Muriithi 2002, p.87).

There are various methods of contraception available in Kenya and these include: the natural family planning method also called periodic abstinence or fertility awareness method, the barrier methods such as the male condom, female condom, diaphragm and sponges, the surgical contraception method through tubal ligation for women and vasectomy for men, the intrauterine contraceptive devices which can be copper based or hormonal and lastly we have the hormonal contraceptives administered as combined oral contraceptives, progestogen only contraceptives, intramuscular shots and implants or delivered through the transdermal patch, the vaginal ring and the hormonal intrauterine contraceptive device (Kimathi, Micheni and Muriithi 2002, p. 91-92; Crouch 2009, p. 489-490; Republic of Kenya, Division of Reproductive Health 2009 p. 21).

Hormonal contraceptives can either be progestogen-only or combined hormonal contraceptives (Amin et al 2012, p. 514). The progestogen-only contraceptives are classified into oral progestogen only contraceptives, intra-uterine progestogen-only devices and the parenteral progestogen-only contraceptives which are administered through deep intramuscular injections or as subcutaneous implants (Crouch 2009, p. 493, Amin et al 2012, p. 521; McEvoy et al, 2013, p. 3118). The combined hormonal contraceptives combine an oestrogen and a progestogen and are administered through the combined oral contraceptive pill, the vaginal contraceptive ring or the transdermal contraceptive patch (Amin et al 2012, p. 515; McEvoy et al 2013, p. 3103).

Majority of the combined oral contraceptive pills contain ethinylestradiol as the oestrogen component with the progestogen component being one of the following progestogens: levonorgestrel, norgestrel, ethynodiol, desogestrel, gestodene, drospirenone, norethisterone, norethindrone, norgestimate or dienogest (Amin et al 2012, p. 519-520; McEvoy et al 2013, p. 3116-3117). The readily available brands of the combined oral contraceptive pills in Kenya are composed of 0.15mg levonorgestrel and 0.03mg ethinylestradiol. The combined oral contraceptive pills can also be monophasic or phasic (Amin et al 2012, p. 515; McEvoy et al 2013, p. 3104). The monophasic ones contain a fixed amount of an oestrogen and a progestogen in each of the active tablets in a cycle while the phasic ones contain varying amounts of the two hormones in a cycle and in that case they can be biphasic, triphasic or estrophasic (Amin et al 2012, p. 515; McEvoy 2013, p. 3104).
The combined oral contraceptive pills achieve their contraceptive effect through an interplay of several factors with the most important being the inhibition of ovulation and the thickening of the cervical mucus thus providing a physical barrier to spermatozoa (Crouch 2009, p. 491; Bayer Pharma AG 2011; McEvoy et al 2013, p. 3114). They also make the endometrium too thin for implantation (Crouch 2009, p. 491). The inhibition of ovulation is through suppression of the hypothalamic-pituitary system with the oestrogen component suppressing secretion of the follicle-stimulating hormone and the progestogen component inhibiting the preovulatory rise of the luteinizing hormone (McEvoy 2013, p. 3114).

It is the responsibility of governments to ensure that the medicines and medical devices employed as methods of contraception are not quality compromised since this has an impact on their effectiveness as methods of contraception. Contraception is the platform through which we practice family planning (World Health Organization 2014). Family planning enables us to bring forth life when it is wanted, expected and welcome (Kimathi, Micheni and Muriithi 2002, p 87; Crouch 2009, p. 488). In addition, a woman’s ability to utilize contraception to space and limit her pregnancies has a direct impact on her health and the outcome of each pregnancy (World Health Organization 2014). Family planning plays a central role in the achievement of the Millenium Development Goals reiterated by the 2005 revision of the Millenium Development Goal number 5 through addition of Target 5.B on attainment of universal access to reproductive health under which we have two direct family planning indicators namely: the contraceptive prevalence rate and the unmet need for family planning (Republic of Kenya, Division of Reproductive Health 2009 p. 1; United Nations 2014). Family planning is an essential priority component in the Kenya Essential Package for Health and the Kenya National Reproductive Health Policy 2009-2015 (Crouch 2009, p. 488; Republic of Kenya, Division of Reproductive Health 2010, p. 2).

A particular method of contraception for which governments should be concerned about its postmarket quality is the **combined oral contraceptive pill containing 0.15mg levonorgestrel and 0.03mg ethinylestradiol**. This is due to the following reasons. Firstly, a significant number of women in Kenya use the combined oral contraceptive pill as a family planning method. Nearly 75% of all women in Kenya using contraceptives opt for hormonal contraceptives with 32% of them going for the combined oral contraceptive pill (Republic of Kenya, Division of Reproductive Health 2010, p.69). Secondly, the combined oral contraceptive pill (0.15mg levonorgestrel and 0.03mg ethinylestradiol) is listed as an essential medicine in the 2013 World Health Organization Essential Medicines List and the 2010 Kenya Essential Medicines List (Republic of Kenya, Ministry of Medical Services and Ministry of Public Health and Sanitation 2010; World Health Organization 2013). Thirdly, every Kenyan has a right under the Constitution of Kenya to access the highest attainable standards of healthcare. This includes the right to access family planning methods which are of the right quality. Lastly, the combined oral contraceptive pill is also used in emergency contraception and has non-contraception uses such

In Kenya various healthcare providers are engaged in the provision of the combined oral contraceptive pill as a family planning method with one of the main providers being the private retail pharmacies where it is sold without prescription (Republic of Kenya, Division of Reproductive Health 2010, p.21).

3. Methodology

3.1. Background.

Medicines regulatory authorities conduct postmarket quality studies either on a routine basis, following a poor quality medicinal product complaint or through sentinel site monitoring. Sentinel site monitoring entails the monitoring of the quality of a medicine in a given site over a certain period of time. Postmarket quality studies entail the collection of medicines samples from the healthcare market which are then subjected to pharmacopoeial based quality tests mainly the assay of content of active pharmaceutical ingredients and the dissolution test.

Informed decisions on the minimum number of samples to be collected in postmarket quality studies so as to be representative for a given geographical area are hindered by a lack of reliable data on the prevalence of poor quality medicines and on the proportion of pharmacies selling poor quality medicines. This is especially so for combined oral contraceptives where a search of medical literature revealed not a single postmarket quality study on the combined oral contraceptive pill (0.15mg levonorgestrel and 0.03mg ethinylestradiol).

The Pharmacy and Poisons Board employs two methods in the collection of samples during postmarket quality studies. The first one entails the collection of samples from a randomly selected list of pharmacies in a given geographical area. The second one is through the convenience sampling method which is potentially flawed by bias since the sample collectors target the more geographically accessible pharmacies. The covert (simulation-client) and overt methods of sample purchase are applied as the case may be.

After consultation with the Pharmacy and Poisons Board, it was decided that samples be collected from the private retail pharmacies only as this was part of a study been conducted by the Pharmacy and Poisons Board targeting a wider range of reproductive health medicinal products available in the private and public pharmaceutical sectors of Kenya. This explains why samples were not collected from the public sector as had been stated in the research proposal.
The readily available brands of the combined oral contraceptive pill (0.15mg levonorgestrel and 0.03mg ethinylerstradiol) in the private pharmaceutical sector of Kenya are Femiplan® and Microgynon®. This project therefore focused on these 2 brands.

3.2. Geographical area of study

The geographical area of focus in this project was the Nyeri town of Kenya. Nyeri town is the headquarters of Nyeri County. Nyeri is one of the 47 counties in Kenya.

3.3. Selection of private retail pharmacies for sample collection

All the 27 private retail pharmacies in Nyeri town were mapped by noting down their names and locations. The Pharmacy and Poisons Board was consulted on their licensure status and it was established that 23 are licensed while 4 are unlicensed. The 4 unlicensed premises were selected for sample collection and from the remaining 23 pharmacies 13 were randomly selected for sample collection. A total of 17 private retail pharmacies were therefore selected for sample collection representing 62% of the total number of private retail pharmacies in Nyeri town.

3.4. Samples collection

A sample was defined as that number of tablets bearing the same proprietary name, with similar content and strength of active pharmaceutical ingredients, bearing the same batch number and procured from a given pharmacy. Collection of samples was done on the 28th and 29th of August, 2014 through the covert/simulation-client method. Two covert shoppers were engaged to pose as customers. The typical user of the combined oral contraceptive pill as a family planning method is a female aged 20-40 years and the 2 covert shoppers fitted this profile. 1 covert shopper was engaged in the purchase of Femiplan® pills and the other one for the purchase of Microgynon® pills. The covert shoppers were trained on what to say while making the purchases and were also under instruction to purchase 3 cycles of either Femiplan® or Microgynon® as the case may be. 3 cycles provided 63 tablets of the combined oral contraceptive pill.

Sample coding and filling of the sample collection form was done immediately the covert shopper left a given retail pharmacy and before the next purchase was done. The sample collection forms were dated and indicated the name and location of the pharmacy concerned and the following details regarding the sample: proprietary name, name and strengths of active pharmaceutical ingredients, quantity collected, batch number, date of manufacture, expiry date, name and address of the manufacturer as indicated on the pack and lastly the name and address of the marketing authorisation holder as indicated on the pack. The nomenclature used to code the samples was COC/xxx/yyy with COC being combined oral contraceptive abbreviated, xxx being the facility code incremental from 001 as the pharmacies are visited and samples collected and yyy being the sample number also incremental from 001 as the samples are collected and coded.
3.5. Samples submission to the Pharmacy and Poisons Board

All the samples were checked to confirm that they had more than 6 months left to their expiry date. The samples were then digitally photographed using a Sony Digital Still Camera model number DSC-W350 and all the pertinent sample details tabulated in a Microsoft Office Excel 97-2003 worksheet. All the samples package colour and writings were visually inspected for obvious signs of counterfeiting. The samples were retained in their point-of-purchase packaging, sealed in individual plastic bags, packed in a carton and stored in a lockable cabinet at room temperature prior to transport to the Pharmacy and Poisons Board.

A form for submitting samples to the Pharmacy and Poisons Board was duly filled indicating the following sample details: sample code, facility name, brand name, stated manufactured by, batch number, expiry date and the quantity. The samples were delivered and received at the Pharmacy and Poisons Board on 21 September 2014.

3.6. Samples submission to the National Quality Control Laboratory

A sample analysis request form was filled for each of the samples requesting for identification, assay and dissolution tests for levonorgestrel and ethinylestradiol. The samples were submitted to the National Quality Control Laboratory on 16 October 2014.

3.7. Assay of the content of levonorgestrel and ethinylestradiol

The average of the 10 individual results obtained in the test for uniformity of content was used in the assay.

The test for uniformity of content was conducted through the High Performance Liquid Chromatography method in accordance with the British Pharmacopoeia 2012 Volume V Appendix XII C. The internal standard method was applied using the following stock solutions: Solution A containing 0.0625% weight/volume of levonorgestrel British Pharmacopoeia Chemical Reference Substance, Solution B containing 0.025% weight/volume of ethinylestradiol British Pharmacopoeia Chemical Reference Substance, Solution C containing 0.020% weight/volume of 2-hydroxylbiphenyl (internal standard) and Solution D from dilution of 1 milliliter of Solution C to 20 milliliter with the solvent mixture.

Solutions for the chromatography were then prepared as follows: Solution 1 by mixing the volumes of solutions A and B as specified in the compendia with 5 milliliter of solution C and diluting to 100 milliliter with a mixture of 40 volumes of water and 60 volumes of acetonitrile and Solution 2 by adding 4 milliliter of solution D to one tablet and heating at 60 degrees centigrade in an ultrasonic bath for 25 minutes and then shaking for a repeat ultrasound treatment. This was then cooled and the clear supernatant fluid used.
The chromatographic procedure was then carried out using a stainless steel column (15 centimetres by 4.6 millimetres) packed with octadecylsilyl silica gel (5 micrometre), a mixture of 49 volumes of acetonitrile and 51 volumes of water as the mobile phase with a flow rate of 1.5 millilitres per minute and a detection wavelength of 215 nanometres.

The content of levonorgestrel and ethinylestradiol in each tablet was calculated using the declared content of levonorgestrel in the British Pharmacopoeia Levonorgestrel Chemical Reference Substance and the declared content of ethinylestradiol in the British Pharmacopoeia Ethinylestradiol Chemical Reference Substance.

The specification for levonorgestrel and ethinylestradiol was 90.0 - 110.0 % of the label claim.

3.8. Levonorgestrel dissolution test

Poor manufacturing practices, degradation due to poor storage and the use of incorrect excipients results in medicines with poor dissolution and a subsequent compromised bioavailability.

The ethinylestradiol dissolution analysis was not done due to lack of a spectrofluorometric detector. Levonorgestrel dissolution analysis utilizes an Ultraviolet 247 nanometres detector which was available.

The levonorgestrel dissolution test was carried out through the High Performance Liquid Chromatography method with compendia adopted from the United States Pharmacopoeia 37 National Formulary 32 Volume 3 page 3542. The medium consisted of polysorbate 80 (5 micrograms/gram) in water with acetonitrile and water (6:4) as the mobile phase. The United States Pharmacopoeia Levonorgestrel Reference Standard solution was prepared in medium having known concentrations that would be obtained by dissolving 1 tablet in 500 millilitres of the medium. The sample solution was prepared by withdrawing 15 millilitres portions of liquid from each vessel and passing through a polyvinylidene filter and discarding the first 10 millilitre of the filtrate. The chromatographic system consisted of a column of 4 millimeters with a flow rate of 1 milliliter per minute and an injection size of 100 microliters.

The percentage of levonorgestrel dissolved was calculated using the below formulae

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{CS}{CU} \right) \times 100
\]

\[
r_U = \text{peak response of the corresponding analyte from the Sample solution}
\]

\[
r_S = \text{peak response from the corresponding analyte from the Standard solution}
\]

\[
CS = \text{concentration of the appropriate United States Pharmacopoeia Reference Standard in the Standard solution (micrograms/milliliter)}
\]

\[
CU = \text{nominal concentration of the corresponding analyte in the Sample solution (micrograms/milliliter)}
\]
The tolerance limit for levonorgestrel was that not less than 65% of the labeled amount of levonorgestrel should be dissolved.

4. FINDINGS, ANALYSIS AND DISCUSSION

4.1. Pharmacies, samples availability and registration status

There were 27 private retail pharmacies in Nyeri town at the time of sample collection. 23 were licensed with the Pharmacy and Poisons Board while 4 were unlicensed. 17 (62%) pharmacies were selected and visited for sample collection. Femiplan® was available in all the 17 pharmacies while Microgynon® was available in 4 pharmacies. 17 samples of Femiplan® and 4 samples of Microgynon® were collected giving a total of 21 samples. 20 of the samples had 63 hormone-containing tablets each while 1 sample had 42 hormone-containing tablets. Femiplan® and Microgynon® are registered with the Pharmacy and Poisons Board.

4.2. Pertinent sample descriptors

1 cycle of Microgynon® consisted of 21 hormone-containing beige coated tablets and 7 hormone-free brown coated tablets while that of Femiplan® consisted of 21 hormone-containing yellow tablets and 7 hormone-free brown tablets.

The hormone-free tablets contained 75mg of ferrous fumarate.
Table 3: Pertinent sample descriptors (N = 21)

<table>
<thead>
<tr>
<th>SAMPLE CODE</th>
<th>BATCH NUMBER</th>
<th>EXPIRY DATE</th>
<th>SAMPLE SIZE (TABLETS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COC/001/001</td>
<td>FN306</td>
<td>Feb 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/002/002</td>
<td>FN301</td>
<td>Dec 2017</td>
<td>63</td>
</tr>
<tr>
<td>COC/003/003</td>
<td>FN204</td>
<td>Nov 2017</td>
<td>63</td>
</tr>
<tr>
<td>COC/004/004</td>
<td>FN304</td>
<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/005/005</td>
<td>FN301</td>
<td>Dec 2017</td>
<td>63</td>
</tr>
<tr>
<td>COC/006/006</td>
<td>FN304</td>
<td>Jan 2018</td>
<td>42</td>
</tr>
<tr>
<td>COC/007/007</td>
<td>FN303</td>
<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/008/008</td>
<td>FN304</td>
<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/009/009</td>
<td>FN304</td>
<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/010/010</td>
<td>FN302</td>
<td>Dec 2017</td>
<td>63</td>
</tr>
<tr>
<td>COC/011/011</td>
<td>FN304</td>
<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
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<td>Feb 2018</td>
<td>63</td>
</tr>
<tr>
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<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/014/014</td>
<td>FN303</td>
<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/015/015</td>
<td>FN304</td>
<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/005/016</td>
<td>32375A</td>
<td>Mar 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/008/017</td>
<td>32375A</td>
<td>Mar 2018</td>
<td>63</td>
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<tr>
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<td>FN304</td>
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<td>63</td>
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<td>381A</td>
<td>Mar 2017</td>
<td>63</td>
</tr>
<tr>
<td>COC/016/020</td>
<td>FN304</td>
<td>Jan 2018</td>
<td>63</td>
</tr>
<tr>
<td>COC/012/021</td>
<td>32375A</td>
<td>Mar 2018</td>
<td>63</td>
</tr>
</tbody>
</table>

4.3. Visual inspection of the samples

A visual inspection of the samples did not reveal any counterfeit or falsely labeled batches.
4.4. Assay and dissolution test results

The label claim for Femiplan® and Microgynon® was 0.15mg levonorgestrel and 0.03mg ethinylestradiol. Femiplan® label claim specified the British Pharmacopoeia while that for Microgynon® was not specific on the pharmacopoeia.

Levonorgestrel and ethinylestradiol assay was done in accordance with the British Pharmacopoeia while the levonorgestrel dissolution test was adopted from the United States Pharmacopoeia. Both pharmacopoeias are recognized in Kenya for testing the quality of medicines.

All the samples passed the identification test, the assay of content of levonorgestrel and ethinylestradiol and the levonorgestrel dissolution test. **NOTE** - The ethinylestradiol dissolution test was not conducted due to the laboratory lacking a spectrofluorometric detector for the liquid chromatographic system.
Table 4: Results of assay of content of levonorgestrel and ethinylestradiol and the levonorgestrel dissolution test (N = 21)

<table>
<thead>
<tr>
<th>Sample code</th>
<th>Assay</th>
<th>Dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levonorgestrel determination (%)</td>
<td>Ethinylestradiol determination (%)</td>
</tr>
<tr>
<td>COC/001/001</td>
<td>97.2</td>
<td>97.2</td>
</tr>
<tr>
<td>COC/002/002</td>
<td>96.9</td>
<td>105.7</td>
</tr>
<tr>
<td>COC/003/003</td>
<td>95.2</td>
<td>94.0</td>
</tr>
<tr>
<td>COC/004/004</td>
<td>98.3</td>
<td>99.6</td>
</tr>
<tr>
<td>COC/005/005</td>
<td>97.1</td>
<td>97.3</td>
</tr>
<tr>
<td>COC/006/006</td>
<td>103.9</td>
<td>104.1</td>
</tr>
<tr>
<td>COC/007/007</td>
<td>97.2</td>
<td>98.5</td>
</tr>
<tr>
<td>COC/008/008</td>
<td>97.9</td>
<td>98.5</td>
</tr>
<tr>
<td>COC/009/009</td>
<td>96.8</td>
<td>96.9</td>
</tr>
<tr>
<td>COC/010/010</td>
<td>97.1</td>
<td>99.8</td>
</tr>
<tr>
<td>COC/011/011</td>
<td>97.4</td>
<td>98.7</td>
</tr>
<tr>
<td>COC/012/012</td>
<td>97.9</td>
<td>100.2</td>
</tr>
<tr>
<td>COC/013/013</td>
<td>97.6</td>
<td>98.8</td>
</tr>
<tr>
<td>COC/014/014</td>
<td>102.2</td>
<td>101.2</td>
</tr>
<tr>
<td>COC/015/015</td>
<td>96.7</td>
<td>96.9</td>
</tr>
<tr>
<td>COC/005/016</td>
<td>103.1</td>
<td>101.4</td>
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<tr>
<td>COC/008/017</td>
<td>104.5</td>
<td>101.1</td>
</tr>
<tr>
<td>COC/017/018</td>
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<tr>
<td>COC/002/019</td>
<td>102.0</td>
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</tr>
<tr>
<td>COC/016/020</td>
<td>105.8</td>
<td>103.5</td>
</tr>
<tr>
<td>COC/012/021</td>
<td>103.8</td>
<td>100.2</td>
</tr>
</tbody>
</table>
NOTE: For 3 samples, the laboratory reported that they were insufficient samples to carry out an out of specification investigation for the test of uniformity of content for ethinylestradiol (sample COC/002/002, COC/006/006 and COC/010/010) and levonorgestrel (sample COC/006/006). These did not impact on the assay since as earlier stated the assay was determined from the average of the 10 individual results obtained in the test for uniformity of content.

4.5 Discussion

Due to financial constraints, it is virtually impossible for a medicines regulatory authority to conduct laboratory quality tests an all samples of medicinal products available in the healthcare market. Therefore, a likelihood of risk and impact on public health approach is adopted in determining which medicinal products to routinely sample and test for quality.

The aim of this research project was to establish the quality of the combined oral contraceptive pill (0.15mg levonorgestrel and 0.03mg ethinylestradiol) in the private retail pharmacies of Nyeri town, Kenya. This was as part of a larger study by the Pharmacy and Poisons Board covering a wider range of reproductive healthcare products circulating in the private and public pharmaceutical sector of Kenya. The quality determination was to be pegged on the quality tests of assay and dissolution for levonorgestrel and ethinylestradiol.

This research project reports positive results. None of the samples was found to be counterfeit and they all passed the levonorgestrel and ethinylestradiol assay and the levonorgestrel dissolution test. Regrettably, it was not possible to characterize the quality of the samples with respect to the ethinylestradiol dissolution test due to a technical hitch at the laboratory occasioned by the lack of a spectrofluorometric detector in the liquid chromatographic system which indicates some capacity issues at the National Quality Control Laboratory.

These positive results indicate that the manufacturers of the concerned sample brands adhere to Good Manufacturing Practices and that the products are handled and stored well throughout the distribution chain. Poor manufacturing and distribution practices have been identified as causes of substandard medicines in the healthcare market (World Health Organization 2015). There are no studies in literature on the postmarket quality of combined oral contraceptives in Kenya for comparison purposes. Therefore, this and the wider study to be reported by the Pharmacy and Poisons Board would be useful for comparing with future studies.

This project was not without limitations and it is imperative that we appreciate them as we draw our conclusions. Firstly, the quality of the combined oral contraceptive pills was not characterized with respect to the ethinylestradiol dissolution test. Secondly, a cross-sectional study such as this research project provides a snapshot in time about the quality of medicines on the healthcare market. Thirdly, the Marketing Authorisation Holders of the sample brands were not contacted to authenticate the samples. Authentication relied wholly on the visual inspection of the samples by the researcher. Fourthly, lack of previous studies on the postmarket quality of
combined oral contraceptive pills in the Kenyan private retail pharmaceutical sector was a hindrance to the determination of appropriate sample sizes. Lastly, the number of tablets available per sample was not sufficient enough to have samples reserved for retesting. This was due to the limited number of tablets a mystery shopper could purchase without arousing suspicion. This is one of the limitations of using the covert as opposed to the overt method in the purchase of samples.

5. Conclusions and recommendations

Considering that none of the samples was counterfeit and that they all passed the levonorgestrel and ethinylestradiol assay and the levonorgestrel dissolution test, it is reasonable to conclude that the combined oral contraceptive pill (0.15mg levonorgestrel and 0.03mg ethinylestradiol) circulating in the Nyeri town of Kenya private retail pharmacies is of the right quality. This conclusion is drawn only with regard to the quality tests of levonorgestrel and ethinylestradiol assay and the levonorgestrel dissolution analysis. The ethinylestradiol dissolution analysis was not conducted.

There are various recommendations which can be made from this research project. Firstly, postmarket quality studies on reproductive healthcare products including but not limited to combined oral contraceptive pills should routinely be conducted by the Pharmacy and Poisons Board covering both the private and public pharmaceutical sectors. In consideration of the financial burden of analysis, a criterion of likelihood of risk and impact on public health would be useful in determining which medicines to sample. Secondly, the Ministry of Health Government of Kenya needs to consider how it can subsidize the cost of analysis at the National Quality Control Laboratory. It cost approximately 7,500 United States Dollars to analyse the 21 samples in this research project. This huge cost of analysis is the main impediment to the conduct of postmarket quality studies on a routine basis by the Pharmacy and Poisons Board.

Thirdly, for three of the samples (sample codes COC/002/002, COC/006/006 and COC/010/010) which the laboratory reported that they were insufficient samples to conduct a uniformity of dosage unit out of specification investigation, it is recommended that those samples with those specific batch numbers be overtly purchased from the market and submitted for analysis at the National Quality Control Laboratory. Fourthly, the National Quality Control Laboratory needs to be equipped with a spectrofluorometric detector in the High Performance Liquid Chromatography system. Lastly, all the unlicensed private retail pharmacies in Nyeri town should be closed down and criminal sanctions be imposed on the owners.
6. Bibliography


Bayer Pharma AG (2011) Microgynon® Fe summary of product characteristics, 7 July.


European Directorate for the Quality of Medicines and Healthcare of the Council of Europe (2013) History, benefits and results of testing mutual recognition/decentralized procedure products, July [Online]. Available at: https://www.edqm.eu/en/MPDPCP_Post_Marketing_Surveillance_Scheme-686.html?aMotsCles=a%3A1%3A%7Bs%3A0%3A%22%22%3Ba%3A1%3A%7Bi%3A0%3Bs%3A4%3A%22omcl%22%3B%7D%7D (Accessed: 31 October 2014).


7. Appendices

7.1. Research proposal

Title
An assessment of the quality of Combined Oral Contraceptive pills containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg in the Nyeri Town of Kenya pharmaceuticals market.

Introduction

It is the ultimate responsibility of drug regulatory authorities to ensure that pharmaceuticals in the healthcare market are of the right quality. In this regard, various strategies are adopted by drug regulatory authorities in this quest and they include among others implementing a robust initial marketing authorisation regime, conducting regular Good Manufacturing Practices audits of pharmaceutical manufacturers, conducting regular Good Distribution Practices audits of pharmaceutical distributors and lastly conducting regular postmarket surveillance of pharmaceuticals in the pharmaceuticals market in order to single out the poor quality pharmaceutical products with or without a market authorisation.

A class of pharmaceutical products deserving of postmarket surveillance in spite of the limited resources that the drug regulatory authorities in the developing countries such as Kenya have is the Combined Oral Contraceptive pill containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg. This is due to the following factors. Firstly, in Kenya nearly 75% of all women using modern contraceptives choose hormonal methods with 32% opting for the Combined Oral Contraceptive pill (Republic of Kenya 2010). Secondly, the Combined Oral Contraceptive containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg is listed as an essential drug in the Kenya Essential Medicines List which makes it readily available in both the public and private healthcare markets (Republic of Kenya 2010). Lastly, Combined Oral Contraceptives containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg have other health benefits apart from family planning and are prescribed for dysmenorrhea, irregular cycles, emergency contraception and premenstrual mood syndrome (Republic of Kenya 2010).

Pursuant to the foregoing, the researcher is seeking approval of his research proposal which will entail an assessment of the quality of sampled Combined Oral Contraceptives containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg in the Nyeri town of Kenya pharmaceutical market. The assessment of quality will be through assay and dissolution tests and the proposed site of analysis will be the National Quality Control Laboratory in Kenya.
Methodology

Nyeri town in Kenya is home to 26 identified distribution points for the Combined Oral Contraceptives containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg and these include 3 public hospitals, 1 private hospital, 2 wholesale dealers in pharmaceuticals, 3 private medical centres and 17 retail pharmaceutical outlets.

In this regard, this research will entail collection of samples of Combined Oral Contraceptives containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg at the following 13 sampling sites / distribution points: 3 public hospitals, 2 wholesale dealers in pharmaceuticals, 1 private hospital, 3 private medical centres and 4 retail pharmaceutical outlets.

It is envisaged that a sample will consist of a minimum of 100 tablets and a sample will be regarded as distinct based on the batch/lot number. The researcher targets a total of 12 samples as a minimum. It is worth noting, and this has a bearing on the determination of the sample size, that there are 3 brands of Combined Oral Contraceptives containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg which are registered with the Pharmacy and Poisons Board and thus authorized to be in the Kenyan market.

The samples will be subjected to quality tests specifically assay and dissolution tests at the National Quality Control Laboratory. The National Quality Control Laboratory is mandated by the Pharmacy and Poisons Act (2002) of the Laws of Kenya as a testing facility for pharmaceuticals.

Ethical considerations

This research does not entail the collection of samples from research participants so there is no ethical approval issues envisaged. The researcher will foot the bill for the cost of analyzing the samples the National Quality Control Laboratory. The results of the research will be forwarded to the Pharmacy and Poisons Board of Kenya, the Division of Reproductive Health Ministry of Health, the Director of Health Nyeri County and lastly the owners of the pharmaceutical outlets where the Combined Oral Contraceptive pills containing Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg will be sampled from.
7.2. Sample collection form

**RESEARCH PROJECT TITLE.**
An assessment of the quality of the Combined Oral Contraceptive pill - Ethinylestradiol 0.03mg and Levonorgestrel 0.15mg in the Nyeri Town of Kenya pharmaceuticals market.

**SAMPLE COLLECTION FORM.**

1. Date ..........................
2. Name and address of health facility
   ..............................................................................................................................
   P.O. Box ........................................ Postal code .........................................................
   Physical location ............................................................... ............................................
3. Facility code ..........................
4. Sample code ..........................
5. Sample brand name .......................................................... ...........................................
6. Sample active pharmaceutical ingredients including strength
   ..............................................................................................................................
7. Dosage form ..........................
8. Sample quantity collected .......................................................... ...........................................
9. Batch number ..........................
10. Date of manufacture .......................................................... ...........................................
11. Expiry date ..........................
12. Name and address of the manufacturer (as indicated on the pack).
   ..............................................................................................................................
13. Country of origin of the product (as indicated on the pack).
   ..............................................................................................................................
14. Name and address of the marketing authorisation holder.
   ..............................................................................................................................

Sample collection done and witnessed by.

<table>
<thead>
<tr>
<th>S/N</th>
<th>NAME</th>
<th>DESIGNATION</th>
<th>SIGNATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.3. Sample photos

Sample code: COC/001/001
Sample code: COC/003/003
Sample code: COC/004/004
Sample code: COC/005/005
Sample code: COC/006/006
Sample code: COC/007/007
Sample code: COC/008/008
Sample code: COC/009/009
Sample code: COC/010/010
Sample code: COC/012/012
Sample code: COC/013/013
Sample code: COC/014/014
Sample code: COC/005/016
Sample code: COC/008/017
Sample code: COC/017/018
Sample code: COC/002/019
Sample code: COC/016/020
Sample code: COC/012/021
### 7.4. Certificates of analysis

Sample code: COC/001/001
## Sample code: COC/002/002

### Republic of Kenya

**National Quality Control Laboratory**

Hospital Road, 9th Complex, Box 29726, 00202 Nairobi - Kenya

Telephone: 2726493, 2726-090, 3544526-00, Fax: 2718073

Email: info@nqcl.go.ke Website: www.nqcl.go.ke

---

### CERTIFICATE OF ANALYSIS

**Certificate No:** CAN/2014/1057

**Product:** FEMIPLAN™ TABLETS

**Date Received:** 16.11.2014

**Batch No.:** 176201

**Mfg. Date:** Jan 2013

**Exp. Date:** Dec 2016

**Client Ref No.:** COC/002/002

**Manufacturer:** FAMY Care Ltd.

**Address:** 1608/1609, G.I.D.C., Sarigam – 396 155, Valsad, Gujarat, INDIA

**Client:** Pharmacy and Poisons Board, P.O. Box 25663 - 00506, Nairobi, KENYA

**Tests Requested:** Uniformity of Dosage Unit, Identification, Dissolution, Assay

---

### RESULTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Compendia</th>
<th>Specification</th>
<th>Determined</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>B.P. 2012 Vol V App XIC</td>
<td>Not more than 1 unit is less than 85% or greater than 115% of the average tablet content. Acceptance Value of the 10 dosage units is ± 5%</td>
<td>Levonorgestrel: AV ± 7</td>
<td>Complies</td>
</tr>
<tr>
<td>Identification</td>
<td>HPLC</td>
<td>B.P. 2012 Vol III Page 2807</td>
<td>Retention time of the Major Peak in the sample preparation corresponds to that in the standard preparation</td>
<td>Levonorgestrel: Super-imposable peak at RT Value: 6.4 ± 10% min. present in the sample preparation</td>
<td>Complies</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>Adopted U.S.P. 37 N.F. 32 Vol. 3 Page 5562</td>
<td>No tablet less than 65%</td>
<td>Levonorgestrel: 95.7% (n=3, RSD=2.8%)</td>
<td>Complies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B.P. 2012 Vol III Page 2807</td>
<td>No tablet less than 75%</td>
<td>Ferrous Fumarate: 97.7% (n=6, RSD=5%)</td>
<td>Complies</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>B.P. 2012 Vol III Page 2807</td>
<td>90.0 - 110.0%</td>
<td>Levonorgestrel: 96.6% (n=10, RSD=3.5%)</td>
<td>Complies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B.P. 2012 Vol III Page 2806</td>
<td>90.0 - 105.0%</td>
<td>Ferrous Fumarate: 96.0% (n=3, RSD=6.5%)</td>
<td>Complies</td>
</tr>
</tbody>
</table>

---

### CONCLUSION

The results comply with the specifications for the Identification, Dissolution, and Assay tests performed. However, there were insufficient samples to carry out an out of specification investigation for the Uniformity of Dosage Unit test for Ethinyloestradiol.

**Analyst:** MR. M. SANGALE |
**Date:** 31/12/2014

**Analyst:** DR. G. WANG’ANG’A |
**Date:** 31/12/2014

**Analyst:** DR. M. KWENA |
**Date:** 31/12/2014

**Director:** DR. H. K. CHEPKWONY |
**Date:** 31/12/2014

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### RESULTS

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPENDIA</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
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</tr>
</tbody>
</table>

### CONCLUSION

The product complies with the specifications for the tests performed.

ANALYST:  MR. M. SANGALP  
DATE:  31/12/2014

ANALYST:  DR. O. WANGANDA  
DATE:  31/12/2014

ANALYST:  DR. M. AWUHA  
DATE:  31/12/2014

DIRECTOR:  DR. K. CHWITINDO  
DATE:  31/12/2014
**CERTIFICATE OF ANALYSIS**

**PRODUCT:** PEMIPLAN TABLETS

**LABEL CLAIM:** Each sugar coated yellow pill contains: Levonorgestrel R.P. 0.15 mg, Ethinyloestradiol R.P. 0.03 mg. Each sugar coated brown pill contains: Etonogestrel R.P. 75 mg, Etynyl Estradiol 24.55 mg (as ethinyl estradiol) of (fenretic iron)

**PRESENTATIONS:** Cream coloured (2 pills) & brown coloured (7 pills), circular shaped, biconvex tablets plain on both faces packed in a blister strip of 28 tablets contained in a printed box.

**MANUFACTURER:** FAMY Care Ltd.

**ADDRESS:** 1609/5009, GIDC, Surat - 395 105, Valach, Gujarat, INDIA

**CLIENT:** Pharmacy and Poisons Board, P.O. Box 2760 - 0000, Nairobi, KENYA

**TEST(S) REQUESTED:** Uniformity of Dosage Unit, Identification, Dissolution and Assay.

<table>
<thead>
<tr>
<th>Test/Method</th>
<th>Compliance</th>
<th>Specification</th>
<th>Determined</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>R.P. 2012 (Vol 32) Page 286</td>
<td>No more than 2% in less than 6% or greater than 10% of the average tablet weight</td>
<td>Levonorgestrel: ( \bar{x} = 0.15 )</td>
</tr>
<tr>
<td>Identification</td>
<td>HPLC</td>
<td>R.P. 282 Vol 11, Page 289</td>
<td>N.B. The Main peak in the sample preparation corresponds to that in the standard preparation</td>
<td>Levonorgestrel: Super-imposable peak at RT Volatile: 6.4±1.0 min, present in the sample preparation</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>USP 37 NF 32 Vol 3 Page 284</td>
<td>No tablet less than 65%</td>
<td>Levonorgestrel: 97.6% (n=15, SD=2.9)</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>R.P. 282 Vol 11, Page 289</td>
<td>90.0±10.0%</td>
<td>Levonorgestrel: 98.5% (n=15, SD=2.2)</td>
</tr>
<tr>
<td></td>
<td>Titrations</td>
<td>R.P. 282 Vol 11, Page 289</td>
<td>90.0±10.0%</td>
<td>Female Fumarate: 97.1% (n=15, SD=1.1)</td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product complies with the specifications for the test performed.

**ANALYST:** MRS. M. SANGALE

**ANALYST:** DR. C. WANGANJA

**ANALYST:** DR. M. KIVONGA

**DIRECTOR:** DR. H. K. KIMWISO
**SAMPLE CODE:** COC/005/005

---

**CERTIFICATE OF ANALYSIS**

**PRODUCT:** PLAN TABLETS

**DATE RECEIVED:** 19-06-2014

**REF. NO:** NQA2341-1059

---

**LABEL CLAIM:**
- Each sugar-coated yellow pill contains: 
  - Levonorgestrel: 0.15 mg.
  - Ethynyl estradiol: 0.03 mg.

**PRESENTATION:**
- Cream coloured (2 pills) & brown coloured (7 pills), circular shaped, biconvex tablets, plain on both faces packed in a blister strip of 9 tablets contained in a printed box.

**MANUFACTURER:** FAMO Care Ltd.

**ADDRESS:**
- 1605/4600, G.I.D.C., Surat - 395125,
- Valsad, Gujarat,
- IN24A.

**CLIENT:**
- Pharmacy and Poisons Board,
- P.O. Box 27635 - 00106,
- Nairobi, KENYA.

**TESTS REQUESTED:**
- Underside of Dosage Unit: Identification, Dissolution and Assay.

---

### RESULTS

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPONENT</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uniformity of Dosage Unit</strong></td>
<td>HPLC</td>
<td>LEV</td>
<td>Min. 20 &amp; max. 25 mg, or greater than 10% of the average/dissolution as a dissolution test</td>
<td>Levonorgestrel; ( A^+ = 5 )</td>
<td>COMPULCE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EST</td>
<td></td>
<td>Ethynyl estradiol; ( A^+ = 5 )</td>
<td>COMPULCE</td>
</tr>
<tr>
<td><strong>Identification</strong></td>
<td>HPLC</td>
<td>LEV</td>
<td>R.P. 2015 Vol. XIII Page 3805</td>
<td>Levonorgestrel; Super insoluble peak at R.U. Value 6.2 ± 1.5%, present in the sample preparation</td>
<td>COMPULCE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EST</td>
<td>R.P. 2015 Vol. III Page 798</td>
<td>Ethynyl estradiol; Super insoluble peak at R.U. Value 4.3 ± 1.5%, present in the sample preparation</td>
<td>COMPULCE</td>
</tr>
<tr>
<td><strong>Dissolution</strong></td>
<td>HPLC</td>
<td>LEV</td>
<td>USP NF 32 Vol. 3 Page 1842</td>
<td>No tablet less than 85% Levonorgestrel; 97.9% (N=3; 95.0-99.9%)</td>
<td>COMPULSE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EST</td>
<td>R.P. 2015 Vol. III Page 798</td>
<td>No tablet less than 75% Ethynyl estradiol; 97.9% (N=3; 95.0-99.9%)</td>
<td>COMPULSE</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>HPLC</td>
<td>LEV</td>
<td>R.P. 2015 Vol. XIII Page 3805</td>
<td>Levonorgestrel; 97.1% (N=3; RSD=4.6%)</td>
<td>COMPULSE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EST</td>
<td></td>
<td>Ethynyl estradiol; 97.1% (RSD=4.7%)</td>
<td>COMPULSE</td>
</tr>
</tbody>
</table>

---

**CONCLUSION:**

The product complies with the specifications for the tests performed.

**ANALYST:**
- M.E. M. SANGALE
  - 31/12/2014
- D.G. WANGANGA
  - 31/12/2014
- D.M. KENNA
  - 31/12/2014

**DIRECTOR:**
- D.H.K. CHIRINOSONI
  - 31/12/2014
### RESULTS

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPRENDIA</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>B.P. 2012 Vol V, App X and XIII</td>
<td>Not more than 1 tablet is less than 67% or greater than 115% of the average weight at content. Acceptance Value of the 10 dosage units ≤ 15</td>
<td>Levonorgestrel: AV = 25</td>
<td>Cone Investigation Needed</td>
</tr>
<tr>
<td>Identification</td>
<td>HPLC</td>
<td>B.P. 2012 Vol III Page 2967</td>
<td>Retention time of the major peak in the assay sample preparation corresponds to that in the assay standard preparation</td>
<td>Levonorgestrel: Super-impossible peak at RT 5.2 ± 10 min. present in both the assay sample and standard preparations</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>Adopted U.S.P. 37, N.F. 32 Vol. 3 Page 3542</td>
<td>No tablet less than 65%</td>
<td>Levonorgestrel: 95.5% (n=6, RSD=1.3%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Titration</td>
<td>HPLC</td>
<td>B.P. 2012 Vol III Page 2816</td>
<td>No tablet less than 75%</td>
<td>Ferrous Fumarate: 95.5% (n=6, RSD=1.3%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>B.P. 2012 Vol III Page 2967</td>
<td>90.0 ± 110.0%</td>
<td>Levonorgestrel: 95.5% (n=10, RSD=8.2%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethinylestradiol: 94.1% (n=10, RSD=1.1%)</td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product complies with the specifications for the Identification, Dissolution and Assay tests performed. However, there were insufficient samples to carry out an Out of Specification investigation for the Uniformity of Dosage Unit test.

**ANALYST:**
- MK. C. ROTICH: DATE: 16/02/2015
- DR. G. WANG'ANG'A: DATE: 16/02/2015
- DR. N. MWAURA: DATE: 16/02/2015
- DR. H. K. CHEPKWONY: DATE: 16/02/2015

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Sample code: COC/006/006
**CERTIFICATE OF ANALYSIS**

**PRODUCT:** Tempran Tablets  
**REF. NO.:** NDQA2014I0064  
**DATE RECEIVED:** 23-02-2014  
**LAB. CLAIMS:** Each tablet contains: Levomepromazine B.P. 0.15 mg, Ethysalbital B.P. 0.65 mg. Each sugar coated brown pill contains Ferrum Fumarata B.P. 75 mg, Ragirol (Magnesio to 24.572 mg of Ferrous Iron)

**PRESENTATION:** Cream coloured (21 pills) & brown coloured (1 pill), circular shaped, bisected tablets placed on both faces packed in a blister strip of 22 tablets contained in a printed box.

**MANUFACTURER:** PAND Care Ltd.

**EXP. DATE:** 22-03-2018

**CLIENT:** Pharmacy and Poisons Board, P.O. Box 25603 - 0060.

**CLIENT REF. NO.:** COC1007/007

**TESTS REQUESTED:** Uniformity of Dosage Unit, Identification, Dissolution and Assay.

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPONENTS</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>R.P. 2012 Vol. III Page 520</td>
<td>Not more than 2 tablets at less than 95%, not more than 1 tablet at less than 90%</td>
<td>Levomepromazine; AV = 100.3%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>R.P. 2012 Vol. III Page 520</td>
<td>RT of the peak (Rt) in the sample preparation correspond to that in the standard preparation</td>
<td>Levomepromazine; Super-imposable peaks at Rt Value: 6.5 ± 0.5 min present in the sample preparation</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>TNCY 1 17 N.F. 12 Vol. 7 Page 342</td>
<td>No tablet less than 60%</td>
<td>Levomepromazine; 60%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Titration</td>
<td>R.P. 366 Vol. III Page 206</td>
<td>No tablet less than 75%</td>
<td>Levomepromazine; 91.1%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>R.P. 2012 Vol. III Page 520</td>
<td>900 ± 150%</td>
<td>Levomepromazine; 92.5% (n=10 STUDY)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Assay</td>
<td>Titration</td>
<td>R.P. 366 Vol. III Page 206</td>
<td>900 ± 150%</td>
<td>Ferrum Fumarata: 100.1%</td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product complies with the specifications for the tests performed.

**ANALYST:** MR. M. SANGE  
**DATE:** 30/12/2014

**ANALYST:** DR. G. WANGANGA  
**DATE:** 30/12/2014

**ANALYST:** DR. M. KIONGA  
**DATE:** 30/12/2014

**DIRECTOR:** DR. H. K. CHIRCHONY  
**DATE:** 30/12/2014

*Quality Medicines Board*
**CERTIFICATE OF ANALYSIS**

**PRODUCT:** 
FEMPLAN TABLETS

**REF NO:** 
NAQ/2014/1054

**DATE RECEIVED:** 
10/7/2014

**LABEL CLAIM:** 
Each sugar coated yellow pill contains: Levonorgestrel B.P. 0.15 mg. Ethinylovrediol B.P. 0.05 mg. Each sugar coated brown pill contains: Ferrous Fumarate B.P. 75 mg., Rigosomine 24.375 mg.

**PRESENTATION:** 
Cabinet enclosed (21 pills) & brown coloured (7 pills, circular shaped, hexagonal tablets plain on both faces packed in a blister strip of 28 tablets contained in a printed box.

**MANUFACTURER:** 
RAND Care Ltd.

**CLIENT:** 
Pharmacy and Poison Board, P.O. Box 27663 - 0000.

**ADDRESS:** 
1608/1609, G.D.C. Siliguri - 315 155, Vardha, Gujarat, INDIA.

**TESTS REQUESTED:** 
University of Doseage Unit; Identification, Dosage Unit and Assay.

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPARISON</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Doseage Unit</td>
<td>HPLC</td>
<td>USP 37 NF 32 Vol II, Page 1032</td>
<td>No tablet less than 65%</td>
<td>Levonorgestrel: 90.1% (n=6, RSD=1.5%)</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>USP 37 NF 32 Vol II, Page 288</td>
<td>No tablet less than 75%</td>
<td>Levonorgestrel: 92.5% (n=5, RSD=2.1%)</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>USP 37 NF 32 Vol II, Page 299</td>
<td>90.0 - 101.0%</td>
<td>Levonorgestrel: 93.5% (n=10, RSD=2.5%)</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>USP 37 NF 32 Vol II, Page 299</td>
<td>90.0 - 101.0%</td>
<td>Ethinylovrediol: 98.9% (n=10, RSD=3.3%)</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Ferrous Fumarate</td>
<td>HPLC</td>
<td>USP 37 NF 32 Vol II, Page 288</td>
<td>90.0 - 101.0%</td>
<td>Ferrous Fumarate: 98.2% (n=3, RSD=1.4%)</td>
<td>COMPLETED</td>
</tr>
</tbody>
</table>

**CONCLUSION:** 
The product complies with the specifications for the tests performed.

**ANALYST:** 
MI M. SANGALE

**ANALYST:** 
DR. G. MANGATIA

**ANALYST:** 
MI M. MISHRA

**DIRECTOR:** 
DG B.E. CHEPJOGA

**DATE:** 
31/12/2014
**CERTIFICATE OF ANALYSIS**

**PRODUCT:** FEMPLAN TABLETS

**REF. NO.:** NDQA00910058

**DATE RECEIVED:** 25-07-2014

**LABEL CLAIM:** Each sugar coated yellow pill contains: Levonorgestrel B.P. 0.15 mg. Ethinyloestradiol B.P. 0.05 mg. Each sugar coated brown pill contains: Ferrous Fumarate B.P. 75 mg. (Equivalent to 24.25 mg of Ferrous Sulphate)

**PRESENTATION:** Cream coloured (21 pills) & brown coloured (7 pills), circular shaped, biconvex tablets placed on both faces packed in a blister strip of 28 tablets contained in a printed box.

**MANUFACTURER:** Famy Care Ltd.

**ADDRESS:** 1004/1006, G.I.D.C. Sanijana - 396 155, Valsad, Gujarat, INDIA

**CLIENT E/R NO.:** Pharmacy and Poisons Board, P.O. Box 27568 - 00208, Nairobi, KENYA

**RESULTS:**

<table>
<thead>
<tr>
<th>TEST DESCRIPTION</th>
<th>METHOD</th>
<th>COMPOUNDS</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlabelled of Dosage Unit</td>
<td>HPLC</td>
<td>R.P. 1924 M.A</td>
<td>80±10%</td>
<td>Levonorgestrel</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethinyloestradiol</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Value of the sample within ±15%</td>
<td></td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>U.S. 37 NF 52</td>
<td>No tablet less than 95%</td>
<td>Levonorgestrel: 97.3% (n=5, SD=3.2%)</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NBP 296</td>
<td>No tablet less than 73%</td>
<td>Ferrous Fumarate: 94.1% (n=5, SD=1.3%)</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Titration</td>
<td>N.B. 2022 Vol. III Page 298</td>
<td>0.0 - 1800%</td>
<td>Levonorgestrel: 92.6% (n=5, SD=1.8%)</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethinyloestradiol: 96.9% (n=5, SD=2.1%)</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Titration</td>
<td>N.B. 2022 Vol. III Page 386</td>
<td>90.0 - 105.0%</td>
<td>Ferrous Fumarate: 97.4% (n=5, SD=1.4%)</td>
<td>Completed</td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product complies with the specifications for the tests performed.

**ANALYST:** MR. M. SANGALE

**DATE:** 31/12/2014

**ANALYST:** DR. R. M. WANGANGA

**DATE:** 31/12/2014

**ANALYST:** DR. M. SWENA

**DATE:** 31/12/2014

**DIRECTOR:** DR. H. K. CHEGWIN

**DATE:** 31/12/2014
**CERTIFICATE OF ANALYSIS**

**CERTIFICATE No:** CAN/2014/1069

**PRODUCT:** FEMIPLAN + TABLETS

**LABEL CLAIM:**
- Each sugar coated yellow pill contains: Levonorgestrel B.P. 0.15 mg.
- Ethinyloestradiol B.P. 0.03 mg. Each sugar coated brown pill contains:
- Ferrous Fumarate B.P. 75 mg. (Equivalent to 24.375 mg of Ferrous iron)

**PRESENTATION:**
- Cream coloured (21 pills) & Brown coloured (7 pills), circular shaped, biconvex tablets plain on both faces packed in a blister strip of 28 tablets contained in a printed box.

**MANUFACTURER:** FAMCI Care Ltd.

**ADDRESS:** 1608/1609, G.I.D.C., Surigam - 390 155, Vadodara, Gujarat, INDIA.

**CLIENT:** Pharmacy and Poisons Board, P.O. Box 27663-00500, Nairobi, KENYA.

**TEST(S) REQUESTED:** Uniformity of Dosage Unit, Identification, Dissolution, Assay by Uniformity of Content and Titration

**RESULTS**

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPENDIA</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>B.P. 2012 Vol. 9 App. XII C</td>
<td>Not more than 5 unit is less than 15% or greater than 115% of the average tablet content. Acceptance Value of the 10 dosage units in 5 units</td>
<td>Levonorgestrel: AV = 7</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Identification</td>
<td>HPLC</td>
<td>B.P. 2012 Vol III Page 2987</td>
<td>RT of the Major Peak in the sample preparation corresponds to that in the standard preparation</td>
<td>Ethinyloestradiol: AV = 18</td>
<td>Of INVESTIGATION NEEDED</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>Adopted U.S.P. 32 N.F. Vol. 3 Page 3542</td>
<td>No tablet less than 65%</td>
<td>Levonorgestrel: 97.2% (n=6, RSD=1.5%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Titration</td>
<td>B.P. 2012 Vol. III Page 2816</td>
<td>No tablet less than 75%</td>
<td>Ferrous Fumarate: 95.4% (n=6, RSD=0.0)</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>B.P. 2012 Vol III Page 2987</td>
<td>90.0 - 110.0%</td>
<td>Levonorgestrel: 97.1% (n=10, RSD=2.6%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Titration</td>
<td>B.P. 2012 Vol. III Page 2816</td>
<td>90.0 - 105.0%</td>
<td>Ferrous Fumarate: 97.2% (n=3, RSD=1.1%)</td>
<td>COMPLIES</td>
<td></td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product complies with the specifications for the Identification, Dissolution and Assay tests performed. However, there were insufficient samples to carry out an out of specification investigation for the Uniformity of Dosage Unit test for Ethinyloestradiol.

**ANALYST:** MR. M. SANGALE       **DATE:** 31/12/2014

**ANALYST:** DR. G. WANG'ANG'A    **DATE:** 31/12/2014

**ANALYST:** DR. M. KWAENA        **DATE:** 31/12/2014

**DIRECTOR:** DR. H. K. CHEPKONYO **DATE:** 31/12/2014

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### Certificate of Analysis

**Product:** TIMIPLAN TABLETS  
**Ref. No.:** NIAQA20141064  
**Date Received:** 4th Oct 2014  
**Presentation:** Each sugar coated yellow pill contains: Levomepromazine B.P. 15 mg, Ethenzamide B.P. 45 mg, Each sugar coated brown pill contains: Ferrous Fumarate B.P. 75 mg (equivalent to 24.35 mg of Ferrous Iron)  
**Manufacturing:** FAMY Care Ltd.  
**Address:** 500, 501, D.D. Gaurav, - 360 155, Vadodra, Gujarat, INOIA  
**Client:** Pharmacy and Poisons Board  
**Sample Code:** COC/011/011

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Compendia</th>
<th>Specification</th>
<th>Determined</th>
<th>Remarks</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tartrazine</td>
<td>HPLC</td>
<td>R.P. 2008 Vol. Y</td>
<td></td>
<td></td>
<td></td>
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<td>2461</td>
<td></td>
<td></td>
<td></td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Resorcinol</td>
<td>HPLC</td>
<td>R.P. 2008 Vol. Y</td>
<td></td>
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<td></td>
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<td>2461</td>
<td></td>
<td></td>
<td></td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Melamine</td>
<td>HPLC</td>
<td>R.P. 2008 Vol. Y</td>
<td></td>
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<td>2461</td>
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<td>COMPLIES</td>
</tr>
<tr>
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<td>2461</td>
<td></td>
<td></td>
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<td>COMPLIES</td>
</tr>
<tr>
<td>Iodine</td>
<td>HPLC</td>
<td>R.P. 2008 Vol. Y</td>
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<td></td>
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<td>2461</td>
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<td></td>
<td></td>
<td>COMPLIES</td>
</tr>
<tr>
<td>Moisture</td>
<td>HPLC</td>
<td>R.P. 2008 Vol. Y</td>
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<td></td>
<td>2461</td>
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<td></td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2461</td>
<td></td>
<td></td>
<td></td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

**Conclusion:** The product complies with the specifications for the tests performed.

**Analyst:** Mr. M. K. RANGAL  
**Date:** 01/02/2014  
**Director:** Dr. H. K. CHIRIMONY  
**Date:** 01/02/2014
### CERTIFICATE OF ANALYSIS

**Sample Code:** COC/012/012

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>REF. NO.</th>
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<tbody>
<tr>
<td>FEMPLAN TABLETS</td>
<td>NXQ2391410360</td>
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<table>
<thead>
<tr>
<th>DATE RECEIVED</th>
<th>DATE</th>
<th>ADDRESS</th>
<th>MANUFACTURER</th>
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<tbody>
<tr>
<td>04/02/2014</td>
<td></td>
<td>1600/1609, G.D.C.Surujun - 396 155, Valsad, Gujarat, INDIA.</td>
<td>FAMO Care Ltd.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLIENT</th>
<th>TESTS REQUESTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy and Poisons Board</td>
<td>Uniformity of Dose Unit, Identification, Dissolution and Assay.</td>
</tr>
</tbody>
</table>

#### RESULTS

<table>
<thead>
<tr>
<th>METHOD</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dose Unit</td>
<td>No tablet less than 60%</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td>Dissolution</td>
<td>No tablet less than 75%</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>90.0 - 101.0%</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td>Titration</td>
<td>95.5%</td>
<td>COMPLIES</td>
<td></td>
</tr>
</tbody>
</table>

#### CONCLUSION

The product complies with the specifications for the tests performed.

**ANALYST:** M.M. SANCHEZ

**DATE:** 03/15/2014

**ANALYST:** DR. M. K. CHIHANGA

**DATE:** 03/25/2014

**ANALYST:** DR. M. K. CHIHANGA

**DATE:** 03/25/2014

**DIRECTOR:** DR. M. K. CHIHANGA

**DATE:** 03/25/2014
**CERTIFICATE OF ANALYSIS**

**PRODUCT:** FEMPLAN TABLETS

**LABEL CLAIM:** Each tablet contains: Levonorgestrel 0.15 mg. Ethinyl Estradiol 0.05 mg. Each tablet contains: Ferrum Pteratum 35 mg, Raphani Semen 2.625 mg, of Ferrous Iodo)

**PRESENTATION:** Cream colored (21 pills) in brown colored (7 pills, circular shaped, bisected tablets plain on both faces packed in a blister strip of 28 tablets contained in a printed box.

**MANUFACTURER:** FANG Can Ltd.

**ADDRESS:** 1606/1609, G.D.C., Sarjani - 396 155, Valsad, Gujarat, INDIA

**DATE RECEIVED:** 9-8-2014

**REF NO:** NDQA/2014/0001

**DATE:** 26-3-2014

**CLIENT:** Pharmacy and Poisons Board, P.O. Box 27963 - 00020, Nairobi, KENYA

**TESTS REQUESTED:** Uniformity of Dosage Unit, Identification, Dissolution and Assay

### RESULTS

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPONENTS</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>Levonorgestrel</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dihyestradiol</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td>Identification</td>
<td>HPLC</td>
<td>Levonorgestrel</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dihyestradiol</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>Ferrum Pteratum</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raphani Semen</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>Levonorgestrel</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dihyestradiol</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>Ferrum Pteratum</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raphani Semen</td>
<td>90.9 ± 0.2 %</td>
<td>COMPLIES</td>
<td></td>
</tr>
</tbody>
</table>

### CONCLUSION

The product complies with the specifications for the tests performed.

**ANALYST:** MR. C. KOTISH
**DATE:** 31/12/2014

**ANALYST:** DR. G. MANGINGA
**DATE:** 31/12/2014

**ANALYST:** DR. M. KWINGA
**DATE:** 31/12/2014

**DIRECTOR:** DR. H. K. CHAPRON
**DATE:** 31/12/2014
# Certificate of Analysis

**Product:** Femplana Tablets  
**Ref. No.:** NAQ/2014/1050

**Date Received:** 13-06-2014

**Label Claim:** Each sugar coated yellow pill contains: Levonorgestrel 0.15 mg, Ethinyl Estradiol 0.03 mg, Each sugar coated brown pill contains: Ferrous Fumarate 75 mg (Equivalent to 24.575 mg of Ferrous Iron)

**Presentation:** Round coloured (7 pills) & brown coloured (7 pills), circular shaped,诵ives tablet plain on both faces packed in a blister strip of 28 tablets contained in a printed box

**Exp. Date:** 08/08/2016

**Address:** 1600/1600, G.I.D.C. Sarigam - 396 155, Vadodara, Gujarat, INDA

**Client:** Pharmacy and Poisons Board, P.O. Box 2966 - 00600, Nairobi, KENYA

**Test(s) requested:** Uniformity of Dosage Unit, Identification, Dissolution and Assay.

## Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Compendia</th>
<th>Specification</th>
<th>Determined</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>USP 37 NF 32, Vol. 2 Page 862</td>
<td>No tablet less than 65%</td>
<td>96.7%</td>
<td>COC/015/1015</td>
</tr>
<tr>
<td>Identification</td>
<td>HPLC</td>
<td>USP 37 NF 32, Vol. 2 Page 862</td>
<td>Rf of the Major peak in the sample preparation corresponds to that in the standard preparation</td>
<td>96.7%</td>
<td>COC/015/1015</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>USP 37 NF 32, Vol. 2 Page 862</td>
<td>No tablet less than 75%</td>
<td>95.5%</td>
<td>COC/015/1015</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>USP 37 NF 32, Vol. 2 Page 862</td>
<td>90.0 – 110.0%</td>
<td>98.0%</td>
<td>COC/015/1015</td>
</tr>
<tr>
<td>Titrates</td>
<td>HPLC</td>
<td>USP 37 NF 32, Vol. 2 Page 862</td>
<td>Potassium Iodide</td>
<td>9.8%</td>
<td>COC/015/1015</td>
</tr>
</tbody>
</table>

## Conclusion

The product complies with the specifications for the tests performed.

**Analyser:** M. M. Kibengo  
**Date:** 10/12/2015
CERTIFICATE OF ANALYSIS

Certificate No: CAN/2014/1088

Sample Code: COC/005/016

RESULTS

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>Not more than 5% to pass or not less than 95% of the nominal tablet content. Acceptance Value of the 10 tablets is 95.9 ± 3.5</td>
<td>Levogramspeak AV = 4</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Identification</td>
<td>HPLC</td>
<td>RT of the major peak in the sample preparation corresponds to that on the standard preparation</td>
<td>Levogramspeak RT (t) = 12.3 ± 3.5%</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>No solid less than 5%</td>
<td>Levogramspeak FPF = 92.9% (n=10, RSD = 1.3%)</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Titation</td>
<td>HPLC</td>
<td>No solid less than 75%</td>
<td>Levogramspeak P = 92.9% (n=10, RSD = 1.3%)</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>90.0 - 105.0%</td>
<td>Levogramspeak AV = 55.1% (n=10, RSD = 1.3%)</td>
<td>COMPLETED</td>
</tr>
<tr>
<td>Titation</td>
<td>HPLC</td>
<td>90.0 - 105.0%</td>
<td>Levogramspeak P = 92.9% (n=10, RSD = 1.3%)</td>
<td>COMPLETED</td>
</tr>
</tbody>
</table>

CONCLUSION: The product complies with the specifications for the tests performed.

ANALYST: MR. E. BOTICH          DATE: 31/12/2014
ANALYST: DG. G. WANGANG'A      DATE: 31/12/2014
ANALYST: DG. H. KWENA         DATE: 31/12/2014
DIRECTOR: DR. H. K. CHEPKONGA  DATE: 31/12/2014
Sample Code: COC/008/017

CERTIFICATE OF ANALYSIS

CERTIFICATE No CAN/2014/1079

PRODUCT:

MICROCYNON Forte Tablets

REF. NO.: NDQA201410806

LABEL CLAIMS:
1 beige coloured tablet contains Levomepromazine 0.15 mg.
1 brown coloured tablet contains Ferrous fumarate 75 mg.

PRESENTATION:
Beige coloured (25 tablets) & Brown coloured (7 tablets), circular shaped. Stacks tablets, pack on both sides packed in a blister strip of 32 tablets contained in a printed box.

MANUFACTURER:
Bayer Schering Pharma AG

ADDRESS:
1542 Berlin, GERMANY

CLIENT:
Pharmacy and Poisons Board
P.O. Box 27660 - 00506, Nairobi, KENYA.

TESTS REQUESTED:
Uniformity of Dosage Unit, Identification, Dissolution and Assay

RESULTS:

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPARISON</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>B.F. 2012 Vol III Page 56</td>
<td>AV = 7</td>
<td>COMPLETE</td>
</tr>
<tr>
<td>Strength of Dosage Unit</td>
<td>HPLC</td>
<td>B.F. 2012 Vol III Page 2007</td>
<td>AV = 3</td>
<td>COMPLETE</td>
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<tr>
<td>Levomepromazine</td>
<td></td>
<td></td>
<td>Levomepromazine</td>
<td>COMPLETE</td>
</tr>
<tr>
<td>Weighted average</td>
<td></td>
<td></td>
<td>Weighted average</td>
<td>COMPLETE</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>Advanced U.G.F. P.R. 7 Page 38</td>
<td>98.5%</td>
<td>COMPLETE</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>B.F. 2012 Vol III Page 288</td>
<td>99.0 - 99.5%</td>
<td>COMPLETE</td>
</tr>
<tr>
<td>Titration</td>
<td>Titration</td>
<td>B.F. 2012 Vol III Page 288</td>
<td>97.8%</td>
<td>COMPLETE</td>
</tr>
</tbody>
</table>

CONCLUSION:
The product complies with the specifications for the tests performed.

ANALYST: MR. C. ROTICH          DATE: 31/12/2014
ANALYST: DR. C. WANGANG'A      DATE: 31/12/2014
ANALYST: DR. M. KIVINA        DATE: 31/12/2014
DIRECTOR: DR. H. K. CHEPLIONG     DATE: 31/12/2014
Sample Code: COC/017/018

<table>
<thead>
<tr>
<th>TEST(S) REQUESTED:</th>
<th>Uniformity of Dosage Unit, Identification, Dissolution and Assay</th>
</tr>
</thead>
</table>

<p>| TABLE: | UNIVERSITY OF DURBAN-WESTERN CAPE |</p>
<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPOUNDS</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>R.P. 2013 Vol. III</td>
<td>Page 206</td>
<td>No tablet less than 65%</td>
<td>Levoglucosan: 94.4% (95.00 ± 2.35%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R.P. 2013 Vol. III</td>
<td>Page 205</td>
<td>No tablet less than 75%</td>
<td>Levoglucosan: 95.0% (95.00 ± 2.35%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R.P. 2013 Vol. III</td>
<td>Page 205</td>
<td>95.0% – 105.0%</td>
<td>Levoglucosan: 101.2% (95.00 ± 5.00%)</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>USP 37 NF Vol. XI</td>
<td>Page 3432</td>
<td></td>
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<td></td>
<td></td>
<td>USP 37 NF Vol. XI</td>
<td>Page 2806</td>
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<tr>
<td></td>
<td></td>
<td>USP 37 NF Vol. XI</td>
<td>Page 2805</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>R.P. 2013 Vol. III</td>
<td>Page 205</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CONCLUSION: The product complies with the specifications for the test performed.
# Certificate of Analysis

**Sample Code:** COC/002/019

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>MICRONON TABLETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATE RECEIVED</td>
<td>18/11/2014</td>
</tr>
<tr>
<td>Batches</td>
<td>18/1/5</td>
</tr>
<tr>
<td>M/C DATE</td>
<td>Apr 2012</td>
</tr>
<tr>
<td>MANUFACTURER</td>
<td>BAYER Schering Pharma AG</td>
</tr>
<tr>
<td>ADDRESS</td>
<td>NaN2 Berlin, GERMANY</td>
</tr>
<tr>
<td>DATE ISSUED</td>
<td>18/11/2014</td>
</tr>
</tbody>
</table>

**Client:** Pharmacy and Poisons Board, P.O. Box 27043, 00200, Nairobi, KENYA.

**Test Requested:** Uniformity of Dosage Unit, Identification, Dissolution and Assay.

## Results

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPONENTS</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>B.P. 2012 Vol. III Page 2907</td>
<td>NT</td>
<td>0.0%</td>
<td>COMPLETE</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>B.P. 2012 Vol. III Page 2907</td>
<td>NT</td>
<td>100.0%</td>
<td>COMPLETE</td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
<td>B.P. 2012 Vol. III Page 2015</td>
<td>NT</td>
<td>95.1%</td>
<td>COMPLETE</td>
</tr>
</tbody>
</table>

**Conclusion:** The product complies with the specifications for the tests performed.
**CERTIFICATE OF ANALYSIS**

**PRODUCT**: FEMIPLAN TABLETS

**REF. NO.**: NDQA20110069

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPARAISON</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uniformity of Dosage Unit</strong></td>
<td>HPLC</td>
<td>USP 22  Vol. III, Page 336</td>
<td>No tablet less than 95%</td>
<td>105.9%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No tablet less than 105%</td>
<td>105.9%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td><strong>Dissolution</strong></td>
<td>HPLC</td>
<td>USP 37  Vol. II, Page 330</td>
<td>No tablet less than 45%</td>
<td>45.3%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No tablet less than 75%</td>
<td>75.2%</td>
<td>COMPLIES</td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
<td></td>
<td></td>
<td>Phial contents should be in good condition, clear &amp; free from foreign matter.</td>
<td>COMPLIES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>COMPLIES</td>
<td></td>
</tr>
</tbody>
</table>

**CONCLUSION**: The product complies with the specifications for the test performed.

**ANALYST**: Dr. G. Wang'a
**DATE**: 31/12/2014

**ANALYST**: Dr. M. Kinyoza
**DATE**: 31/12/2014

**DIRECTOR**: Dr. H. K. Chilowono
**DATE**: 31/12/2014
**CERTIFICATE OF ANALYSIS**

**PRODUCT:** MICROGYNON® 28 TABLETS

**DATE RECEIVED:** 03/03/2014

**LABEL CLAIMS:** 1. Beige coloured tablet contains Levonorgestrel 0.15 mg, Ethinyl oestradiol 0.03 mg, 1 brown coloured tablet contains Ferrous fumarate 0.3 mg.

**PRESENTATION:** Beige coloured (28 tablets) & Brown coloured (7 tablets), circular, shaped, biconvex tablets, plain on both faces packed in a blister strip of 28 tablets contained in a printed box.

**MANUFACTURER:** BAYER Schering Pharma AG.

**ADDRESS:** EDK Lydia, GERMANY

**CLIENT:** Pharmacy and Poisons Board, P.O. Box 27660 - 00106, Nairobi, KENYA

**TESTS REQUESTED:** Uniformity of Dosage Unit, Identification, Dissolution and Assay

**RESULTS:**

<table>
<thead>
<tr>
<th>TEST</th>
<th>METHOD</th>
<th>COMPONENTS</th>
<th>SPECIFICATION</th>
<th>DETERMINED</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of Dosage Unit</td>
<td>HPLC</td>
<td>Levonorgestrel</td>
<td>Not more than 5% is less than 85% of the average labelled content. Acceptance Value of the hi-range form is 85%</td>
<td>Levonorgestrel AV = 15</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethinyl oestradiol</td>
<td></td>
<td>Ethinyl oestradiol AV = 11</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td>HPLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution</td>
<td>HPLC</td>
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</tr>
<tr>
<td></td>
<td>Titration</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC</td>
<td>Levonorgestrel</td>
<td></td>
<td>Levonorgestrel 105.1% (avg 103.4 ± 0.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrous fumarate</td>
<td></td>
<td>Ferrous fumarate 96.3% (avg 95.2 ± 1.5%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Titration</td>
<td>Levonorgestrel</td>
<td></td>
<td>Levonorgestrel 105.1% (avg 103.4 ± 0.9%)</td>
<td>COMPLIES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrous fumarate</td>
<td></td>
<td>Ferrous fumarate 96.3% (avg 95.2 ± 1.5%)</td>
<td>COMPLIES</td>
</tr>
</tbody>
</table>

**CONCLUSION:** The product complies with the specifications for the tests performed.

**ANALYST:** Dr. C. Mwangi

**DATE:** 31/12/2014

**ANALYST:** Dr. G. Wangang A

**DATE:** 31/12/2014

**ANALYST:** Dr. M. Kivina

**DATE:** 31/12/2014

**DIRECTOR:** Dr. H. E. Chepyogon

**DATE:** 31/12/2014