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The American University in Cairo

School of Global Affairs and Public Policy

**GOVERNMENT REGULATORY POLICY TOWARDS THE
BIOPHARMACEUTICAL SECTOR: REGULATORY OUTLOOK ON
BIOSIMILARS IN EGYPT**

A Thesis Submitted to the

Public Policy and Administration Department

in partial fulfillment of the requirements for the degree of

Master of Public Policy

By

Mohamed Atef Abdelhakim Farag

May 2013

The American University in Cairo

School of Global Affairs and Public Policy

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I thank God the most merciful and compassionate for all his gifts in my life

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This is the beginning of a long journey of joy, success, faults, fears and good things to come

Mohamed Abdelhakim
12 May 2013

ABSTRACT

University : The American University in Cairo

Thesis Title : Government Regulatory Policy Towards the Biopharmaceutical Sector:
Regulatory Outlook on Biosimilars in Egypt

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This thesis examines the government regulatory policy towards the pharmaceutical biotechnology sector (Biopharmaceutical), with focus on Similar Biotherapeutic Products (biosimilars). Biosimilars are highly similar but not identical molecules that claim to have similar quality, safety and efficacy of original (innovator/ reference) products. They differ significantly from the chemical based medicines (conventional pharmaceuticals) that the main active substance is usually from a living organism (biological). Such critical products are high on the treatment guidelines recommended for complex diseases with high death and disability burdens. Biosimilars started accessing the Egyptian Market long time before the Government established a proper regulatory structure/pathway to regulate such products. It is expected that Biosimilars will start accessing the Egyptian market with high influx rate during the upcoming years as many originator biopharmaceuticals are losing patent protection between 2013-2020. Such influx requires progressive policy thinking and well-resourced regulatory structures to properly regulate the complex pharmaceutical biotechnology market, ensure protection of public health, prevention of potential regulatory failures and promoting investment in local production for improving access to medicines. The thesis adopts a qualitative methodology using semi structured and in-depth interviews with experts from the concerned governmental regulatory agencies, the biopharmaceutical industry, special interest groups (lobbying bodies), clinicians, civil society and independent researchers. Analytical findings revealed potential for regulatory reforms and policy options were suggested across the three regulatory domains studied (regulatory pathway of biosimilars , pricing policy and intellectual property protection).

Table of Contents

| | |
|--|----|
| ABSTRACT | 3 |
| LIST OF FIGURES..... | 7 |
| LIST OF TABLES..... | 8 |
| LIST OF ABBREVIATIONS | 9 |
| Chapter 1: Introduction | 10 |
| I. Problem statement..... | 18 |
| II. Conceptual framework..... | 19 |
| III. Role of Government in Public Health Protection and Regulation of the medicines market..... | 20 |
| IV. Challenges in regulating biosimilars..... | 21 |
| Chapter 2: Literature Review..... | 24 |
| I. How are Biosimilars different from Generic Medicines..... | 24 |
| II. Biosimilars Economic Value and role in Improving Patient’s Access..... | 25 |
| III. Progress of Biosimilars..... | 26 |
| IV. Biosimilars Regulatory Pathways | 29 |
| V. Comparison of different Regulatory pathways in EU and US..... | 30 |
| A. The EU approach | 30 |
| B. The US approach..... | 31 |
| Chapter 3: Methodology..... | 32 |
| I. Selection of interviewees..... | 34 |
| II. Recruitment strategy | 34 |
| III. Sampling..... | 35 |
| IV. Interviews process | 36 |
| V. Development of the questionnaire tool..... | 38 |
| VI. Direct limitations for this type of research..... | 39 |
| VII. How to solve data limitation problems | 41 |
| VIII. Possible use of resulting findings | 41 |
| Chapter 4: Data Analysis | 42 |
| I. The Regulatory Structure for Biosimilars in Egypt..... | 42 |
| A. The Egyptian Drug Authority (EDA) is the pharmaceutical regulatory body of the Egyptian Ministry of Health (MOH) and it is responsible for..... | 43 |
| B. The Central Administration of Pharmaceutical Affairs (CAPA)..... | 43 |
| C. The National organization for Research and Control of Biologicals (NORCB)..... | 44 |
| D. The Egyptian Pharmacovigilance Center (EPVC) | 45 |
| II. The legal framework | 47 |
| III. The regulatory procedure..... | 48 |
| IV. Requirements to ensure Quality Safety and Efficacy of Biosimilars in the Egyptian Market..... | 49 |
| A. Biological products..... | 49 |
| B. Biosimilar product..... | 50 |
| C. Quality data (Chemistry, Manufacturing and Controls - CMC) | 52 |
| D. Pre-clinical data (toxicology studies in animals) | 52 |
| E. The Antigenicity / Immunogenicity..... | 52 |
| F. Clinical data (comparability head to head clinical studies) | 53 |

| | | |
|-------|--|-----|
| V. | Procedure suggested in draft guidelines for biosimilar registration in Egypt 2013..... | 54 |
| A. | The Final dossier pathway..... | 54 |
| B. | A stepwise pathway..... | 56 |
| C. | Issuing a market authorization (registration) license..... | 58 |
| VI. | The pricing policy and pricing mechanisms..... | 59 |
| VII. | Pricing regulatory structures..... | 60 |
| A. | The pricing committee at CAPA..... | 60 |
| VIII. | Legal framework for pricing in Egypt..... | 60 |
| A. | Ministerial Decree 314/1991..... | 60 |
| B. | The pre-revolution pricing decree (373/2009)..... | 61 |
| C. | The post-revolution pricing decree (499/2012)..... | 63 |
| IX. | The Intellectual Property and Patent Protection in Egypt..... | 66 |
| A. | Global agreements and Free Trade: The TRIPS agreement..... | 66 |
| B. | Integration of TRIPS in the current Egyptian law number 82 for the year 2002..... | 67 |
| C. | TRIPS Plus, data exclusivity and hampering introduction of competition..... | 68 |
| D. | Data exclusivity and concerns of Public safety..... | 70 |
| | Chapter 5: Discussion on Analytical findings..... | 71 |
| I. | Possible Market Failures as a result of the current Government regulation of the Biopharmaceutical sector in Egypt..... | 71 |
| A. | Externalities..... | 72 |
| ➤ | Efficacy risk..... | 73 |
| ➤ | Safety Risk..... | 73 |
| ➤ | Economic risk..... | 73 |
| | The case of the Egyptian Interferon Market Authorization..... | 74 |
| B. | Information Asymmetry and potential hampering of competition: The “Box” system in the market authorization process..... | 83 |
| vi. | To make use of the potential missing opportunity..... | 87 |
| C. | Collective action groups (The pharmacist’s syndicate versus the Industry chamber): politicization of regulations: the new medicines pricing decree (499/2012)..... | 87 |
| | Disadvantages of the new pricing decree..... | 89 |
| | Reflections on the rent seeking behavior and public choice theory in relation to the latest pricing decree 499/2012..... | 96 |
| A. | The stakeholders of the public choice theory..... | 96 |
| B. | Analysis of the dynamics between the latest medicine pricing decree stakeholders..... | 96 |
| | Chapter 6: Conclusion and Policy Options..... | 98 |
| I. | Policy options to ensure quality, safety and efficacy of biopharmaceuticals / Biosimilars in the Egyptian Market..... | 100 |
| A. | Briding the legislative gap on dealing with biosimilars registered as generics..... | 100 |
| B. | Proactively tackling Re-registration requirements..... | 100 |
| C. | Continuing collaboration with stakeholder on draft registration guidelines..... | 101 |
| D. | Strengthening National Regulatory Structures..... | 101 |
| E. | Expediting clinical trials law..... | 102 |
| II. | Policy options to increase Efficiency in the registration process of biosimilars..... | 102 |
| F. | Revisiting the box system..... | 102 |

| | | |
|------|---|-----|
| G. | Increasing scrutiny in pricing committee decision | 102 |
| H. | Commissioning a Regulatory Impact Assessment study by a third party | 102 |
| III. | Policy options to encourage investment in local biosimilars production..... | 103 |
| I. | Subsidizing local biopharmaceutical manufacturers..... | 103 |
| J. | Facilitating technology transfer | 103 |
| K. | Filling the regulatory gap on technology transfer | 104 |
| L. | Intellectual Property Protection Policy | 104 |

LIST OF FIGURES

| | |
|---|----|
| Figure 1: Comparison in structural complexity and size of a biological molecule (monoclonal antibody) and s chemical molecules (Aspirin/ Paracetamol) | 23 |
| Figure 2: Pharmaceuticals versus Biologics: Difference in classification of chemical based pharmaceuticals and Biological products (Biopharmaceuticals) | 24 |
| Figure 3: The Egyptian Drug Authority..... | 42 |
| Figure 4: organizational structure of (CAPA) | 43 |
| Figure 5: Organizational structure (NORCB)..... | 44 |
| Figure 6: Organizational Structure of the Egyptian Pharmacovigilance Center | 45 |
| Figure 7: Recombinant(r) DNA process for generating biopharmaceutical proteins | 50 |
| Figure 8: Registration data required for - Biosimilar (left) and originator or Standalone (right) | 51 |
| Figure 9: Imported biosimilar regulatory pathway in Egypt..... | 55 |
| Figure 10: Proposed regulatory pathway for a locally manufactured biosimilar in Egypt | 57 |
| Figure 11 : Summary of the medicine pricing degree 373/2009 | 61 |
| Figure 12: Summary of the medicine pricing degree 499/2012 - The post 25 th of January revolution pricing decree (499/2012) | 64 |
| Figure 13: Profit margin of different beneficiaries in the medicines supple chain in Egypt according to new pricing decree 499/2012 | 65 |
| Figure 14: Product development life cycle of innovator medicine according to the US FDA | 67 |
| Figure 15: comparison between effects of different IFN type's overtime | 76 |
| Figure 16: Egyptian Government's demand for originator pegylated interferon (Pegasys™ from Roche) prior to registration of the Egyptian interferon (Reiferon Retard™ from Rhein Mina Pharm) | 78 |
| Figure 17: Box System for Generic medicines Market Authorization Application in Egypt..... | 83 |
| Figure 18: Box System for Biosimialrs Market Authorization Application in Egypt..... | 84 |
| Figure 19: Reasons for medicines shortage as reported by the Drug Shortage Unit in CAPA..... | 92 |
| Figure 20 Medicines Shortages during the month of March 2013 in Egypt - Drug Shortage Unit -CAPA | 93 |
| Figure 21: Dynamics of Public choice theory in Egypt's medicines pricing decree | 97 |

LIST OF TABLES

| | |
|---|----|
| Table 1: Major Diseases treated with Biopharmaceutical products..... | 11 |
| Table 2: List of terms given to Biosimilars in different countries | 12 |
| Table 3: List of Biosimilars Manufactured and Registered in Egypt | 13 |
| Table 4: size and complexity of three medicines | 22 |
| Table 5: Examples of currently licensed monoclonal antibodies active substances with potential for biosimilar products to be developed | 28 |
| Table 6: the release date for a regulatory pathway or guidance issued by different National Regulatory Authorities on Biosimilars registration..... | 29 |
| Table 7: Approved Biosimilars in Europe | 30 |
| Table 8: Interviews attempted and conducted..... | 37 |
| Table 9: Registration data required for innovator, generic and a biosimilar | 51 |
| Table 10: Summary of Quality, Safety and Efficacy indicators comparing Pegasys of Roche and Reiferon Retard (Egyptian Pegylated Interferon) | 79 |
| Table 11: Comparison between average profit margins for retail pharmacist across Egypt, UAE and Saudi Arabia | 88 |
| Table 12: Decree 499/2012 retail pharmacy and manufacturer's profit margin distribution for locally manufactured products | 91 |
| Table 13: Table 13: Local producers of biosimilars in Egypt and their area of production focus..... | 95 |

LIST OF ABBREVIATIONS

- API:** Active Pharmaceutical Ingredient
- ANDA:** Abbreviated New Drug Application
- BPCIA:** The Biologics Price Competition and Innovation Act of 2009
- CAPA:** Central Administration for Pharmaceutical Affairs
- CMC:** Chemistry Manufacturing and Control
- EGYPO:** Egyptian Patent Office
- EFTA:** European Free Trade Association
- EMA:** European Medicines Agency
- EASL:** European Association for the study of liver
- EPVC:**The Egyptian Pharmacovigilance Center
- EDA:** Egyptian Drug Authority
- FJP:** Freedom and Justice Party
- IFN:** Interferon
- ICSR:** Individual Case Safety Report
- ICH:** International Conference on Harmonization
- ISO:** International Organization for Standardization
- MAB:** Monoclonal Antibody
- MAH:** Market Authorization Holder
- NORCB:** National Organization for Research and Control of Biologicals
- PEG:** Pegylated
- PK:** Pharmacokinetics
- PD:** Pharmacodynamics
- PSUR:** Periodic Safety Update Report
- QSE:** Quality Safety Efficacy
- SUSARs:** Suspected Unexpected Serious Adverse Reactions
- SVR:** Sustained Virologic Response
- US FDA:** Food and Drug Administration

Chapter 1: Introduction

This thesis is examining the government regulatory policy towards the private pharmaceutical biotechnology (biopharmaceutical) sector with focus on biosimilars. Biosimilars are highly similar but not identical molecules that claim to have the same quality, safety and efficacy of original (innovator/ reference) products. Biosimilars differ significantly from chemical based medicines (conventional pharmaceuticals) in the main active substance (from a living organism - biological origin, it has much complex molecular structures that can never claim to be of identical of original product molecule and consequently any change in the processes of manufacturing or change in production site may have significant impact on quality, safety and efficacy (QSE) of the product and hence on the health of the patient. The continuous advanced progress in scientific development makes it hard to avoid introducing amendments to manufacturing processes for reasons ranging from cutting costs to improving efficiency. This leads to inconsistencies in products attributes between each batch being produced and sometimes these inconsistencies occur within the same batch that needs to be mitigated. The significance for studying such critical products is that they are high on the treatment guidelines recommended for treatment of complex diseases associated with high death and disability burden. Diseases such as hepatitis C virus induced liver inflammation, several types of cancers, diabetes, some hormonal disturbances and a range of other diseases are relying on biopharmaceutical medicines (medicines developed using biotechnological techniques and with active ingredient coming from living organism) Illustration of some examples of disease categories treated using biopharmaceutical medicines (with biosimilars in development) are given in Table 1 below:

Table 1: Major Diseases treated with Biopharmaceutical products

| Disease category | Name of molecule | Innovator producer |
|---|--|---|
| 1. Rheumatoid Arthritis | Etanercept (Enbrel) | Amgen+Pfizer (Joint venture) |
| 2. Anemia due to chronic Kidney disease | Epoetin Alfa (Eprex) | Johnson and Johnson+Amgen (Joint venture) |
| 3. Breast , Stomach, gastroesophageal junction cancers | Trastuzumab (Herceptin) | Roche |
| 4. Leukemia and rheumatoid arthritis | Rituximab (MabThera) | Roche |
| 5. Decrease in immunity due to receiving cancer immunosuppressive treatment | Pegfilgrastim (Neulasta) | Amgen |
| 6. Treatment of hepatitis C induced liver inflammation | Pegylated Interferon alpha 2-a (Pegasys) | Roche |

Due to its high profitability Multinational companies and producers of original reference products are trying to build barriers against market access to biosimilars. Among such efforts is sponsoring legislations that prevents retail pharmacist from switching branded biological products with its biosimilar or forcing pharmacists to consult with physicians prior to doing so. *“Two companies in the US Amgen and Genentech are lobbying to prevent biosimilars from using slogans such as “just like herceptin” or “Better than Rituxan” or “Avastin biosimilar” in their marketing or labels”(Nature Biotechnology,2013).* Companies that produce the innovator product are themselves preparing biosimilars for their own products post patent expiry in collaboration with some generic producers yet claims on superior quality to other rival biosimilars will exist due to their experience in developing the original product. Table 2 below lists the different terms given to biosimilars in different countries.

| Country | Term given for biosimilar |
|---------|---------------------------------------|
| USA | Follow on proteins |
| EMA | Biosimilar |
| WHO | Similar Biological Medicinal Products |
| Canada | Follow on biologics |
| Japan | Subsequent entry proteins |
| India | Biogenerics |
| Saudi | Biosimilars |
| Egypt | Biosimilars |

Table 2: List of terms given to Biosimilars in different countries

Biosimilars started accessing the Egyptian Market almost a decade¹ before the Government established a proper regulatory policy towards such products within the Ministry of Health. Currently around 55 biosimilar products with different concentrations and dosage forms ranging from Insulin's, Interferon's, erythropoietin's and other essential or lifesaving products are manufactured and legally marketed in the Egyptian Market. Table 3 lists the biosimilars manufactured² in Egypt with their registration license date and status

Table 3: List of Biosimilars Manufactured and Registered in Egypt

| <u>Reg. date</u> | <u>License status</u> | <u>Trade name</u> | <u>Composition as mentioned in registration license</u> | <u>Manufacturer name</u> |
|------------------|-----------------------|---------------------------------------|---|-------------------------------------|
| 6/22/2004 | VALID | EPOJET 10000I.u./ml prefilled syringe | RECOMBINANT HUMAN ERYTHROPOIETIN-ALPHA | VACSERA |
| 2/25/2003 | VALID | EPOJET 2000I.u./0.5ml | RECOMBINANT HUMAN ERYTHROPOIETIN-ALPHA | VACSERA |
| 12/7/1999 | VALID | ERYPOIETIN 2000 I.U./vial | ERYTHROPOIETIN | AMOUN PHARMACEUTICAL INDUSTRIES Co. |
| 12/7/1999 | VALID | ERYPOIETIN 4000 I.U./vial | ERYTHROPOIETIN | AMOUN PHARMACEUTICAL INDUSTRIES Co. |
| 4/3/2001 | VALID | LEUCONIL 500µg /vial lyophilized vial | GRANULOCYTE MACROFAGE COLONY STIMULATING FACTOR | EL NILE. |
| 4/3/2001 | VALID | LEUCONIL 300 µg/vial lyophilized vial | GRANULOCYTE MACROFAGE COLONY STIMULATING FACTOR | EL NILE. |
| 4/3/2001 | VALID | LEUCONIL 150 µg/vial lyophilized vial | GRANULOCYTE MACROFAGE COLONY STIMULATING FACTOR | EL NILE. |
| 5/8/2001 | VALID | EGYFERON 1 M.I.U. vial | INTERFERON ALFA-2b | EL NILE. |
| 8/5/2001 | VALID | EGYFERON 3 M.I.U. vial | INTERFERON ALFA-2b | EL NILE. |
| 5/8/2001 | VALID | EGYFERON 5 M.I.U. vial | INTERFERON ALFA-2b | EL NILE. |

¹ Biological products registration list in Egypt- 2013

² Manufacturing may include secondary packaging

| | | | | |
|-----------|-------|----------------------------------|--|---|
| 5/21/2002 | VALID | ERYPOIETIN 3000 I.U. vial | rhu-ERYTHROPOIETIN | AMOUN PHARMACEUTICAL INDUSTRIES Co. |
| 5/21/2002 | VALID | ERYPOIETIN 1000 I.U. vial | rhu-ERYTHROPOIETIN | AMOUN PHARMACEUTICAL INDUSTRIES Co. |
| 6/18/2002 | VALID | INSULIN H BIO R 40I.u.vial | RCOMBINANT HUMAN INSUKIN 40 IU/ML | SEDICO |
| 6/18/2002 | VALID | INSULIN H Bio NPH 40I.u.vial | RCOMBINANT HUMAN INSULIN (40 I.U/ML) /PROTAMINE-SULPHATE(0.14 MG/ML) | SEDICO |
| 2/25/2003 | VALID | EPOJET 4000I.u./0.4ml | RECOMBINANT HUMAN ERYTHROPOIETIN-ALPHA | VACSERA |
| 7/30/2002 | VALID | CHORIONIC 5000 I.U. amp. | HUMAN CHORIONIC GONADOTROPHIN | AMRIYA |
| 7/30/2002 | VALID | AMRIGONE 75I.U. amp. | HUMAN MENOPAUSAL GONADOTROPHIN (FSH+LH) | AMRIYA |
| 7/30/2002 | VALID | FERTILINE 75 I.U. amp. | FOLLITROPIN (RECOMBINANT FSH) | AMRIYA |
| 8/20/2002 | VALID | ERYPOIETIN 10000 I.U. vial | rhu-ERYTHROPOIETIN | AMOUN PHARMACEUTICAL INDUSTRIES Co. |
| 10/1/2002 | VALID | INSULIN H MIX 40I.u./ml vial | HUMAN INSULIN /PROTAMINE-INSULIN HUMAN(HUAMN INSULIN 12 I.U/ml+PROTAMINE-INSULIN HUMAN 28 I.U/ml | SEDICO |
| 7/30/2002 | VALID | CHORIONIC 1000 I.U. amp. | HUMAN CHORIONIC GONADOTROPHIN | AMRIYA |
| 4/29/2003 | VALID | INSULIN H BIO NPH 100I.U.vial | RCOMBINANT HUMAN INSULIN(100 I.U) & PROTAMINE-SULPHATE (0.35 MG) | SEDICO |
| 4/29/2003 | VALID | INSULIN H BIO R 100I.U.vial | RCOMBINANT HUMAN INSULIN 100 IU/ML | SEDICO |
| 4/29/2003 | VALID | INSULIN H MIX 100 I.U.vial | RCOMBINANT HUMAN INSULIN(30 I.U) & RCOMBINANT PROTAMINE- INSULIN HUMAN(70 I.U) | SEDICO |

| | | | | |
|------------|-------|--|---|--------------|
| 6/3/2003 | VALID | REIFERON 3M.I.U. vial S.C/I.M injection | RECOMBINANT INTERFERON ALFA-2a | MINA PHARM |
| 6/3/2003 | VALID | REIFERON 6M.I.U. vial S.C/I.M injection | RECOMBINANT INTERFERON ALFA-2a | MINA PHARM |
| 9/9/2003 | VALID | EPOETIN SEDICO 4000I.u./ml amp. | ALPHA- RECOMBINANT HUMAN ERYTHROPOIETIN | SEDICO |
| 9/9/2003 | VALID | EPOETIN SEDICO 2000I.u./ml amp. | ALPHA- RECOMBINANT HUMAN ERYTHROPOIETIN | SEDICO |
| 11/5/2003 | VALID | EPOFORM 2000I.U/vial | ERYTHROPOIETIN-ALPHA | EIPICO-EGYPT |
| 11/5/2003 | VALID | EPOFORM 4000I.U/vial | ERYTHROPOIETIN-ALPHA | EIPICO-EGYPT |
| 7/2/2002 | Valid | HUMAN INSULIN -MIX VACSERA 30/70 40 I.U./ml vial | INSULIN REGULAR HUMAN 12 IU/ML+HUMAN INSULIN ISOPHANE 28IU/ML | VACSERA |
| 12/14/2004 | VALID | E.P.O. 2000I.U. I.V./S.C.vial | RECOMBINANT ERYTHROPOIETIN-ALPHA | EL NILE. |
| 12/14/2004 | VALID | E.P.O. 3000I.U. I.V./S.C.vial | RECOMBINANT ERYTHROPOIETIN-ALPHA | EL NILE. |
| 12/14/2004 | VALID | E.P.O. 4000I.U. I.V./S.C.vial | RECOMBINANT ERYTHROPOIETIN-ALPHA | EL NILE. |
| 12/28/2004 | VALID | REIFERON RETARD 160mcg/1.2ml vial | PEGYLATED INTERFERON ALPHA 2 a | MINA PHARM |
| 7/5/2005 | VALID | EPOFORM 10000I.U./ml vial | ERYTHROPOIETIN-ALPHA | EIPICO-EGYPT |
| 10/31/2006 | VALID | INSUNIL H NPH 100IU/ml vial. | INSULIN | SEDICO |
| 4/21/2007 | VALID | EPIGONAL amp. | Follicle stimulating hormone (FSH)+luteinizing hormone(LH) | EIPICO-EGYPT |
| 8/14/2007 | VALID | FSH injection 75I.u/1 ml amp of lyophilized powder. | FSH(follicle stimulating hormone) | SEDICO |
| 4/17/2008 | VALID | EPIFASI 5000 I.U.amp. | HUMAN CHORIONIC GONADOTROPHIN | EIPICO-EGYPT |
| 01/04/2005 | VALID | HUMAN INSULIN VACSERA 30/70 (100 I.U) | RECOMBINANT HUMAN INSULIN MIX30/70(100 I.U) | VACSERA |
| 7/2/2002 | Valid | HUMAN INSULIN VACSERA R 40 I.U./ml vial | HUMAN INSULIN REGULAR | VACSERA |

| | | | | |
|------------|-------|--|--|----------|
| 8/10/2004 | VALID | SOMATROPIN 4I.U./vial B.P.2003 | RECOMBINANT HUMAN GROWTH HORMONE | SEDICO |
| 1/18/2007 | VALID | FILGRASTIN 300µg SEDICO LIQUID FOR INJECTION | (RECOMBINANT HUMAN GRANULOCYTE COLONY STIMULATING FACTOR (FILGRASTIN) | SEDICO |
| 11/23/2003 | VALID | ANGIKINASE 100,000 IU VIAL | UROKINASE | SEDICO |
| 11/23/2003 | VALID | ANGIKINASE 250,000IU VIAL | UROKINASE | SEDICO |
| 11/23/2003 | VALID | ANGIKINASE 500,000IU VIAL | UROKINASE | SEDICO |
| 6/18/2002 | VALID | SEDONASE 750,000 IU VIAL | STRPTOKINASE | SEDICO |
| 6/18/2002 | VALID | SEDONASE 1500,000 IU VIAL | STRPTOKINASE | SEDICO |
| 10/17/2006 | VALID | INSULIN H R 100 IU vial | RECOMBINANT HUMAN INSULIN (NEUTRAL) | SEDICO |
| 10/31/2006 | VALID | INSULIN NPH 100 IU vial | RECOMBINANT HUMAN INSULIN 100 I.U VIAL+PROTAMINE SULPHATE 0.24 mg | SEDICO |
| 02/05/2006 | VALID | INSULIN H MIX 100 IU vial | RECOMBINANT HUMAN INSULIN +RECOMBINANT PROTAMINE HUMAN INSULIN 30IU+70 IU/ML | SEDICO |
| 05/02/2006 | VALID | INSULIN H MIX 40 IU vial | RECOMBINANT HUMAN INSULIN +RECOMBINANT PROTAMINE HUMAN INSULIN 12 I.U+28 IU/ML VIAL | SEDICO |
| 7/20/99 | Valid | CHORIONIC GONADOTROPIN 5000 I.U.(U.S.P.22) | CHORIONIC GONADOTROPIN | EL NILE. |
| 6/20/2000 | Valid | CHORIONIC GONADOTROPIN 1500 I.U.(U.S.P.22) | CHORIONIC GONADOTROPIN | EL NILE. |

Due to Biosimilars high profitability, cost, on average, 22 times as much as ordinary drugs (So etal, 2010) it is expected that Biosimilars will access the Egyptian market with a high influx rate specially after the patents for the first group of mono clonal antibodies (MABs) expires. That influx requires progressive policy thinking and well-resourced regulatory structures to properly regulate the complex pharmaceutical biotechnology market and at the same time ensure protection of public health, promote investment in local production for improving access to such critical medicines and creating self-sufficiency.

I. Problem statement

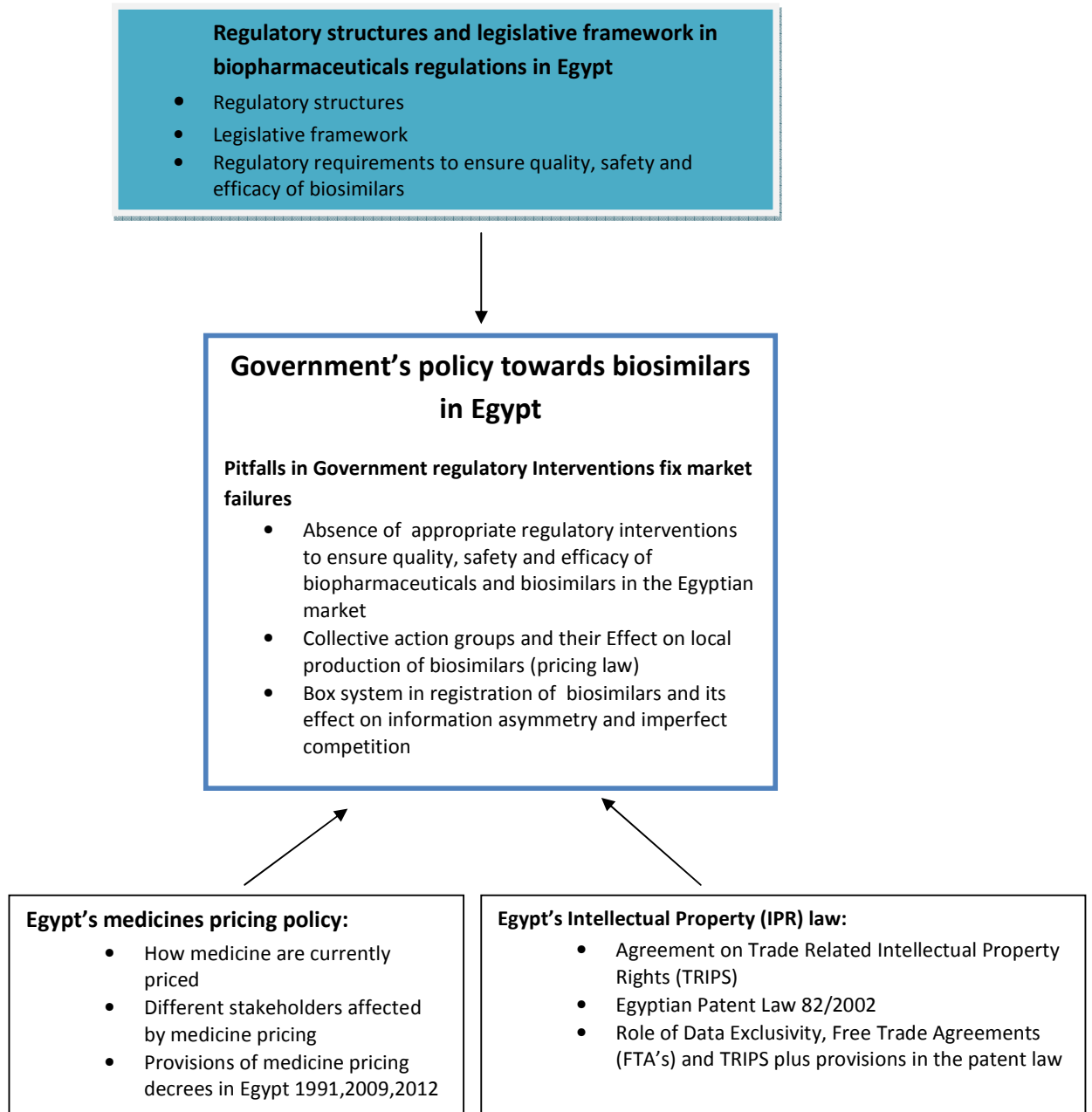
This thesis aims to answer the question of “whether the current government policies for Biosimilars regulation are adequate to ensure protection of public health. In order to answer these question three independent variables will be examined: 1- The regulatory requirements and processes currently in place by the Egyptian government authorities involved in the process of granting market authorization to Biosimilars. 2- The current pricing policy and mechanisms for pricing medicines including biotechnology based medicines and biosimilars. 3- The current regulatory Intellectual Property regime post Egypt’s concession to the agreement on Trade Related Aspects and Intellectual property Rights (TRIPS) in relation to granting patents, patentability criteria and levels of exclusivity granted.

The thesis will also examine implications of the analytical findings from the three independent variables (mentioned above) against the main dependent variable (the role of government in protecting public health of the people. Discussions will touch upon implications of the current regulations on ensuring marketed biosimilar products are of assured quality, safety and efficacy. It will also examine if there are any possible loop holes in such regulatory system that may lead to regulatory failures such as monopolies, information asymmetries, anticompetitive behaviors or externalities that may require possible amendment or change in government regulatory interventions.

The final chapter will set some policy options for the government to consider in improving the processes and bridging any gaps identified during this research. The research is envisaged to contribute to the scarce body of knowledge on government regulation in a new and critical area for the future of the healthcare sector³. This is a qualitative study following semi structured and in-depth interviews to generate data from key experts with knowledge on the subject and from different stakeholders including government agencies, civil society, the local and multinational biopharmaceutical industry.

³ (Europe’s first guidelines to regulate biosimilars was in 2005)

II. Conceptual framework:



III. Role of Government in Public Health Protection and Regulation of the medicines market

Health as a public good and a basic human right will be more on the Egyptian political agenda as one of the main social services that the government should think about how to run and manage in a way that establishes the principles of social justice and equitable access to healthcare services. Healthcare services include healthcare technologies which comprise pharmaceuticals, vaccines, biological and blood products, laboratory, imaging and medical devices or other technologies that intervene in human health and result in its improvement. Medicines are healthcare commodities that can immensely enhance people's lives through its therapeutic value. In other words medicines can add life to years of living rather than adding years to life. The problem stems from the fact that medicines as healthcare commodities that can improve people's life significantly have also other drawbacks due to its side effects. Medicines are not like clothes or chocolates they must have a stringent regulatory system that takes into consideration the three main aspects of quality, safety and efficacy in any consumer product but with special consideration to their risks and tighter regulations that won't hinder access.

IV. Challenges in regulating biosimilars

The advancement in medicines and pharmaceutical technology has resulted in more sophisticated and complex medicines which are more selective, thus less harmful and more effective. Such medicines are usually produced by research and development based pharmaceutical conglomerates which are able to take the risk and finance huge R&D projects to create new molecules. The multinational pharmaceutical companies in order to mitigate the risk have to ensure a proper return of investment (ROI) in the shortest time possible. To ensure ROI, they sometimes price such essential products at exaggerated prices governments usually accept it based on the fact that they have to have the medicines readily available in their public health facilities. Generic medicines stem from the idea that no risk is taken in research and development and thus, original medicines can be copied or reengineered to produce cheaper identical copies. Governments all over the world, especially in the Middle East –and other low/middle income countries have always been pro buying cheaper medicines of assured quality to decrease healthcare budgets. Healthcare budget is already competing with other essentials such as education, food, security and environment which may shift money to any of these domains. The situation is different when it comes to medicines of complex molecules which are usually derived from biological origins and living organisms. The reverse engineering of the products is very hard (almost impossible to produce another identical copy) because it has other variability's than the chemical aspects of normal medicines. This area is undergoing rapid advancement at an unprecedented rate due to its economic significance.

In 2008, 28 percent of sales from the pharmaceutical industry's top 100 products came from biologics; by 2014, that share is expected to rise to 50 % (So etal,2010). These medicines which are considered highly similar of original biological medicines are called biosimilars in this thesis it is referred to as biosimilars. The manufacturing process used to produce a recombinant biological product is much more complex than the process used for synthetic small molecule products. It will usually include numerous extraction, purification and concentration steps that might involve protein denaturation. Each of these steps can influence the

biological activity of the resultant protein (shellekens, 2004). The properties of the product are highly dependent on the production process. A producer of a biosimilar is clearly not in a position to replicate the manufacturing process of the innovator. In addition to the quality data required for all biotechnology products, the companies involved in the developing of biosimilar medicines must additionally submit “comparability data”, usually described as data from a “full comparability exercise” (Mellstedt,2007) .Indeed, manufacturers must characterize, in parallel, both their biosimilar product and the originator reference product. They must demonstrate, with a high degree of certainty, that the quality of the biosimilar medicine is highly similar to the originator/reference medicinal product. A comparability Programme is clearly defined and agreed upon in advance with the National Medicines Regulatory Authority, which defines the set of non-clinical and clinical data that are necessary to sufficiently demonstrate biosimilarity. (EGA, 2011). Table 4 below explains the wide difference in size and complexity by giving examples of three molecules Asprin, Human Growth Hormone and Immunoglobulin Antibody and comparing them to three transportation means: a Bike, a Car and a jet plane.

Table 4: size and complexity of three medicines⁴

| | Small molecule drug | Large molecule drug | Large biologic |
|-------------------|---------------------|---------------------|---|
| Size | Asprin- 21 atoms | hGH- 3000 atoms | IgG antibody- 25,000 atoms |
| Complexity | Bike- 20 lbs | Car- 3000 lbs | F-16 jet- 25,000 lbs (without fuel) |

⁴ <http://biosimilarsource.com/biosimilars.htm>

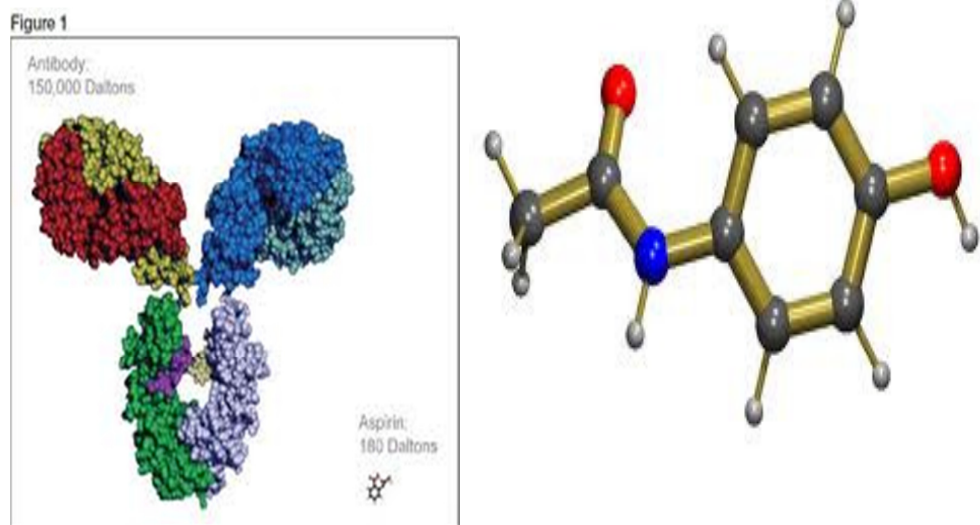


Figure 1: Comparison in structural complexity and size of a biological molecule (monoclonal antibody) and chemical molecules (Aspirin/Paracetamol)⁵

Figure 1 show a stereo-structure of two molecules on the left is a mono-colonal antibody (MAB) which is a biological molecule and on the right is a simple paracetamol (Panadol™) molecule. As both may look the same at hing sight one of the bumps on the MAB structure may be larger than the whole paracetamol molecule. The real difference in size can be shown on the left when a small Aspirin molecule is added beside the MAB

⁵ <http://www.iconplc.com/icon-files/insight-newsletter/Spring10/immunogenicity.html>

Chapter 2: Literature Review

I. How are Biosimilars different from Generic Medicines

According to the European Medicines Agency (EMA): A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorized (the 'biological reference medicine'). The active substance of a biosimilar medicine is similar to the one of the biological reference medicine. Biosimilar and biological reference medicines are used in general at the same dose to treat the same disease. All biopharmaceuticals are inherently variable due to the fact that they are produced from living organisms. This variability exists within batches, from batch to batch, and when production processes are improved or changed or differs between manufacturers. The variability of biopharmaceuticals is greater than that typically observed for conventional pharmaceuticals and applies to originator reference products as well as biosimilars (EMA, 2011)

Figure 2: Pharmaceuticals versus Biologics: Difference in classification of chemical based pharmaceuticals and Biological products (Biopharmaceuticals)

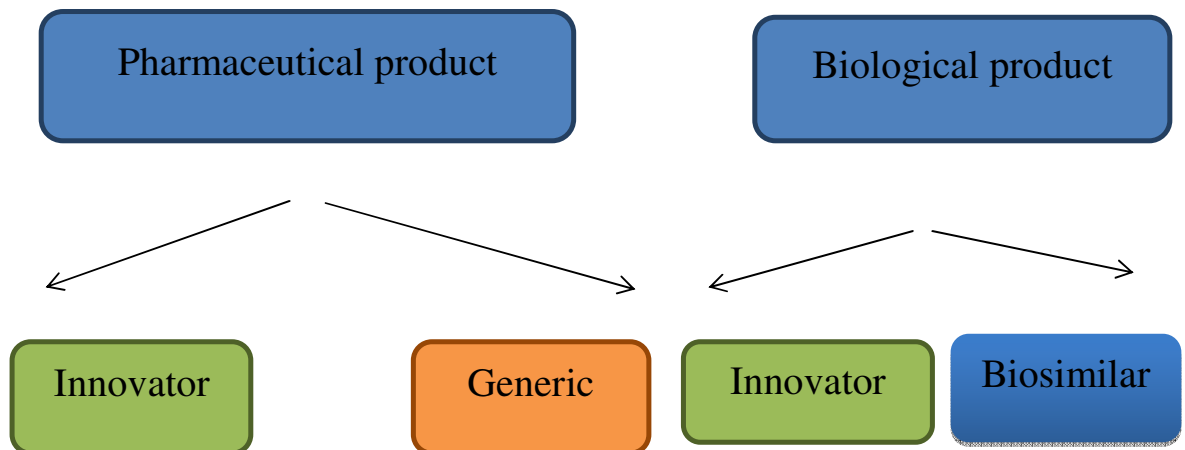


Table 3: Differential indicators for biosimilars and generics: A selection of indicators that are taken in to consideration to differentiate between a biosimilar and a generic in regulation

| | Biosimilar/follow-on proteins | Generic |
|------------------------------|-------------------------------|--------------------|
| Molecular complexity | Complex | Simple |
| Manufacturing | Multi-step process | Simple process |
| Likeness to innovator | Similar | Identical |
| Approval pathway | Abbreviated | Highly abbreviated |

II. Biosimilars Economic Value and role in Improving Patient’s Access

Medicinal products developed through biotechnology constitute an essential part of medicines available to patients today and many medicines in the development pipeline are biotechnology products (EGA, 2011). It is inevitable that “some major biotechnology-derived medicines are, or will soon be, no longer protected by patents. As for all other medicines, when their 20-year patent expires, they will become open to development and manufacture by other companies. This introduces competition in the market which ensures continued patient access to safe, effective, and more affordable, biopharmaceuticals. Without competition the prices of the originator biopharmaceuticals would remain artificially high. Similarly, this competition will serve to stimulate research into new originator medicines. This fact is borne out by the situation in the USA where more than 80% of medicines used are generic medicines and where, at the same time, more new originator medicines are developed than anywhere else in the world” (EGA, 2011).

To give some examples of exorbitantly high prices of branded biopharmaceutical products that are essential for treating diseases such as cancer and arthritis. A breast cancer patients' annual cost for Herceptin is \$37.000. People with rheumatoid arthritis or Crohn's disease spend \$50.000 a year on Humira. And those who take Cerezyme to treat Gaucher disease, a rare inherited enzyme deficiency spend a staggering \$200.000 a year. (SO etal, 2010). Hard evidence exists on the economic gains resulting from interchanging originator biopharmaceutical products with biosimilars “The improved affordability of healthcare that could result from the use of biosimilar medicines is real. As an example, the EPO (Epoetin) biosimilar introduction in Germany resulted in EUR 60m annual savings in the first year of the market. It has been estimated that biosimilars in Germany alone could contribute to 1 billion EUR annual savings from 2017. By 2020 the savings through biosimilars would be more than 8 billion EUR” (EGA, 2011)

III. Progress of Biosimilars

The years 2013-2020 will witness many further developments in relation to biosimilar medicines, and healthcare professionals and healthcare purchasers need to ensure that they are aware of what is happening in this rapidly changing environment (EGA, 2011). One of the most significant new areas is the potential for the development and approval of biosimilar monoclonal antibodies in 2010 in Europe, 6 out of the top 10 leading pharmaceutical products were monoclonal antibodies. It has been estimated that worldwide over 45 monoclonal antibody products are marketed, with total sales in excess of \$40 bln (Shephard,2011). The patent protection on many originator reference biotech products has expired already, and many more will expire over the next few years. As a result most commentators expect a growing number of biosimilar products on the market in the not too distant future. (Table. 7) presents examples of currently licensed monoclonal antibodies active substances with potential for biosimilar products to be developed (Emmreich,2010)

Table 4: 10 Biological drugs to watch for patent expiry in this decade⁶: The table explains the top selling biological drugs with patent protection that is about to expire before 2020

⁶ Nature Biotechnology, Volume 31 Number 4

| Product Name | Producer | Patent Expiry date | Sales | Number of Biosimilars in registered or in development |
|-----------------------------|---------------|--|-------------------|---|
| Aranesp (Darbapoetin Alfa) | Amgen | 2016 in EU and 2024 in US | 2 Billion USD | 2 |
| Enbrel (Etanercept) | Amgen+Pfizer | 2015 in EU and 2019,2023,2028,2029 in US | 7.963 Billion USD | 8 |
| Epogen/Eprex (Epoetin Alfa) | J&J and Amgen | Expired 2004 in EU and 2015 in US | 2.267 Billion USD | 4 |
| Somatropin (Genotropin) | Pfizer | Expired 2008 in EU and April 2013 in US | 832 Million USD | 1 |
| Herceptin (Trastuzumab) | Roche | 2014 in EU and 2019 in US | 6.317 Billion USD | 7 |
| Humira (Adalimumab) | Roche | 2018 EU and 2016 US | 9.265 Billion USD | 4 |
| Neulasta (Pegfilgrastim) | Amgen | August and October 2015 in EU and US | 4.092 Billion USD | 4 |
| Neupogen (filgrastim) | Amgen | Expired 2006 in EU and December 2013 in US | 1.260 Billion USD | 6 |
| Remicade (infliximab) | J&J +Merck&Co | 2014 EU and 2018 US | 8.215 billion USD | 4 |
| Rituxa/MabThera (Rituximab) | Roche | 2013 in EU and 2018 in US | 7.190 Billion USD | 12 |

Table 5: Examples of currently licensed monoclonal antibodies active substances with potential for biosimilar products to be developed

| Trade name | International Non Proprietary Name of active substance | Clinical use (examples) |
|-------------------|---|---|
| Mabthera/Rituxan® | Rituximab | B-cell non-Hodgkin's lymphoma Rheumatoid arthritis |
| Avastin® | Bevacizumab | Colorectal cancer, lung cancer |
| Erbix® | Cetuximab | Colorectal cancer, head and neck cancer |
| Vectibix® | Panitumumab | Colorectal cancer |
| Campath® | Alemtuzumab | B-cell chronic lymphocytic leukaemia (B-CLL) |
| Herceptin® | Trastuzumab | Breast cancer |
| Humira® | Adalimumab | Rheumatoid arthritis, Crohn's disease |
| Remicade® | Infliximab | Rheumatoid arthritis, Crohn's disease, psoriasis |
| Simulect® | Basiliximab | Transplant rejection |
| Zenapax® | Daclizumab | Transplant rejection |
| Xolair® | Omalizumab | Asthma |
| Tysabri® | Natalizumab | Multiple sclerosis |
| Lucentis® | Ranibizumab | Macular degeneration |
| Synagis® | Palivizumab | Respiratory syncytial virus infection |

IV. Biosimilars Regulatory Pathways:

Regulation of biosimilars requires the interplay between several factors: *Reference product*: The product in which the biosimilar will benchmark against and on what basis will it be chosen. Several factors are being weighed when a regulatory pathway to approve biosimilars is designed. *Quality*: The different quality parameters including bioassay, characterization. *Non-clinical data*: Conducting toxicological studies in Animals to know the toxicity profile of the product *Clinical trials*: the types of studies to know the efficacy of the product in human beings and its level of immunogenicity *Pharmacovigilance and risk management*: post-marketing studies to generate safety data. *Data protection*: from innovator may be censored for a period of time after patent expiry to help regain investment and its effect on hampering competition from biosimilars needing to refer to innovator's data in claiming similarity (Frost and Sullivan, 2013). Table 6 below explains the release date for a regulatory pathway or guidance issued by different National Regulatory Authorities on Biosimilars registration.

Table 6: the release date for a regulatory pathway or guidance issued by different National Regulatory Authorities on Biosimilars registration

| Health Authority | Date of guidance release |
|------------------|--------------------------|
| EMA-(Europe) | 2005 |
| WHO | 2009 |
| MHLW (Japan) | 2009 |
| Health Canada | 2010 |
| Korean-FDA | 2010 |
| US-FDA | 2012 |
| Saudi-FDA | 2012 |
| CDSCO (India) | 2012 |
| EDA-(Egypt) | Draft 2012 |

V. Comparison of different Regulatory pathways in EU and US:

A. The EU approach

The EU realized earlier than the whole world the nature of the new regulatory challenge with many applications for similar biologics knocking on its doors. In 2001 they realized that the current pathway for chemical generics market authorization will not provide the required level of knowledge to judge the quality, safety and efficacy for these products to protect safety the union's citizens. The EU medicines regulations are all codified in the EU directive of 2001/83/EC. The first step was to demand safety and efficacy data to support the application in addition to the bioequivalence studies that were conducted for generics. The process involves holding training workshops and consultations with the industry and stakeholders and was transparent. The European Medicines Agency (EMA- responsible for cross EU countries Market Authorization for all therapeutic products) issued a series of guidelines and products later to guide manufacturers on product specific issues. The new pathway was integrated to the 2001/83/EC directive in 2003 and applied to the biotech manufactured medicines and other products like Low Molecular Weight Heparins (LMWH) (Bogaert, 2011).

Table 7: Approved Biosimilars in Europe

| Product Name | Active Substance | Authorization Date | Manufacturer/Company Name |
|-----------------------|------------------|--|---|
| Abseamed | Epoetin alfa | 28 Aug 2007 | Medice Arzneimittel Putter GmbH & Co KG |
| Binocrit | Epoetin alfa | 28 Aug 2007 | Sandoz GmbH |
| Biograstim | Filgrastim | 15 Sep 2008 | CT Arzneimittel GmbH |
| Epoetin alfa Hexal | Epoetin alfa | 28 Aug 2007 | Hexal AG |
| Filgrastim Hexal | Filgrastim | 6 Feb 2009 | Hexal AG |
| Filgrastim Ratiopharm | Filgrastim | 15 Sep 2008 Withdrawn on 20 Apr 2011 | Ratiopharm GmbH |
| Nivestim | Filgrastim | 8 Jun 2010 | Hospira UK Ltd |
| Omnitrope | Somatropin | 12 Apr 2006 | Sandoz GmbH |
| Ratiograstim | Filgrastim | 15 Sep 2008 | Ratiopharm GmbH |
| Retacrit | Epoetin zeta | 18 Dec 2007 | Hospira UK Ltd |
| silapo | Epoetin zeta | 18 Dec 2007 | Stada R & D AG |
| Tevagrastim | Filgrastim | 15 Sep 2007 | Teva Generics GmbH |
| Valtropin | Somatropin | 24 Apr 2006 | BioPartners GmbH |
| Zarzio | Filgrastim | 6 Feb 2009 | Sandoz GmbH |

B. The US approach:

The FDA Act section 505 had two pathways : 1) 505(j) explaining Abbreviated New Drug Application (ANDA) which represents the regulatory pathway of a generic market authorization application requirements and 2) the pathway for follow on proteins described in section 505(b)(2) of the same act. The FDA approved the following follow on proteins through the FDA act:

- Hyaluronidase recombinant human (used in several lifesaving surgical interventions to improve tissue permeability)
- Calcitonin salmon recombinant (treatment of osteoporosis)
- Glucagon recombinant (Raises blood sugar)
- Recombinant somatropin (Growth Hormone)

The US FDA approved the recombinant somatropin based on quality characterization of physiochemical properties to establish that the structure and active ingredient are highly similar to the structure and active ingredient of the reference product. The manufacturer also provided “new” safety data specific to the biosimilar somatropin (omnitrope), vast experience and published literature and comparative efficacy data. In 2010, the US President signed into law a bill governing the regulation of biosimilars. The Biologics Price Competition and Innovation Act of 2009 (BPCIA) permits the licensing of biological products that are shown to be biosimilar to previously licensed reference products.. The law nevertheless does not require the US (FDA) to issue any regulations or guidance to implement its provisions or FDA’s new authorities. (Hordon, 2011).

Chapter 3: Methodology

The general strategy for achieving the study objectives is through information and data collection, analyzing it and inferring some implications then providing some policy options that may help fill any gaps identified from the study findings. This area of study is seldom researched in developing countries due to various reasons the major of which is the lack of democratic regimes which are open for examining, evaluating and disseminating findings of its policies, regulations and government performance in any sector. Hence there is no well-established methodology that was revealed during the literature research on how studies of such nature are being conducted. Due to the nature of information and data to be collected, being mostly either in drawers of government agencies or now with the digital revolution are sometimes on the websites, a qualitative approach is considered the most suitable study type. The reason is that regulations are produced as ink on paper but what is significant is their interpretation, implementation practices and implications of such regulations and policies in real life. This has to be discussed in length with experts in the field and other key informants who may provide insights that reveal what are the real practices and how it is affecting the government role to protect public interests.

This research adopts a qualitative approach that will depend on in depth and semi structured interviews for data collection: interviews with key informants from: **A-**government (Ministry of Health -MoH), central administration of Pharmaceutical affairs (CAPA) (national regulatory authority of the government to regulate the medicines market), National organization for Research and Control of Biologicals (NORCB), the Egyptian patent office (responsible for granting patents for inventions and implementing the international agreements related to Intellectual property protection on medical inventions), Public Procurement and tenders (responsible department in the Ministry of Health which conducts the annual tender to procure medicines. **B-** Industry (biosimilars and biotechnological products producers) both locally manufactured and imported via local or multinational companies, as well as lobbying bodies such as the pharmaceutical industry chamber.

Desk review of Regulatory and legislative information will be collected from government reports and guidelines on registration of biological products in Egypt and other stringent regulatory authorities. Producers and industry chamber will be consulted on the current response to the latest pricing decree by manufacturers in light of the current political changes and economic depression in the country and how it is affecting their ability to produce and fulfill market needs of such crucial products. Views of producers on the role of government in promoting investment in development and production of biotechnology based medicines.

In addition interviews with the representatives from the central administration of pharmaceutical affairs staff. The two competitor companies producing pegylated interferon and supplying MOH (one multinational and other local⁷) will be conducted to validate opinions. The interviews will try to build on the current published literature and the analysis will feed in to the research questions on the ability of the government to protect public health through ensuring quality, safety and efficacy of biological products being granted market authorization in Egypt. It will also analyse the current practices of *registering a biological product for the treatment of hepatitis C virus, versus current regulatory pathways for registration of Biosimilars in developed regulatory authorities (US,EU)*. The thesis also targets academic researchers and clinicians who are working in the field of researching treatments for hepatitis C in Egypt. This section of the thesis is not intended to provide a definitive judgment on any of the two pegylated interferon alfa-2 a in the Egyptian Market but rather to compare the regulatory pathway both products went through to global best practices currently implemented in the field.

⁷ The product (reiferon retard (Pegylated interferon alfa -2a)- later being referred to as the Egyptian interferon) was registered in Egypt in 2004 as a normal generic chemical medicine and not as a biosimilar product

I. Selection of interviewees:

Selection will be based on level of expertise and understanding of the subject of research. The potential to provide valuable data that may not be in public domain and discuss openly sensitive issues as well as shed insights on implications. Since this research is focused on government regulation of the private sector the key informants to be interviewed will be from government and industry as well as some civil society representatives who act as a watch dog and or independent researchers or academics.

II. Recruitment strategy:

A list of expert individuals on the subject with the above knowledge was created using several public sources (professional networking websites as LinkedIn, and literature research). In addition the Principal Investigator has working relations with some governmental organizations who may have some of the required key informants. The principal investigator also participated in an event organized by the central administration of pharmaceutical affairs, registration of biological products section and which gathered industry interested to produce or import biosimilar products in Egypt. The 2 days feedback workshop was aimed at gaining the industry's view points and feedback on the draft guidelines for registration of biosimilar products in Egypt. This was a great opportunity to observe the deliberations between industry and government on the draft regulatory and technical requirements proposed. It was also a very good chance to network and establish contacts with both regulators and industry for the research.

III. Sampling:

The issue of sampling in qualitative research has major debates concerning what is the right sample size. One factor which is significant in qualitative data collection is saturation. In a qualitative framework, research based on interviews often seeks to penetrate social life beyond appearance and manifest meanings. This requires the researcher to be immersed in the research field, to establish continuing, fruitful relationships with respondents and through theoretical contemplation to address the research problem in depth. Therefore a small number of cases (less than 20, say) will facilitate the researcher's close association with the respondents, and enhance the validity of fine-grained, in-depth inquiry in naturalistic (real life) settings (Crouch et al, 2006). Guest, Bunce, and Johnson found with their study that involved 60 interviews theme saturation was achieved after 12 interviews (Guest et al, 2006). The domain studied also is another factor to affect the sample size. In a recent research study by Baker and Edwards of how many qualitative interviews are enough it is mentioned that although many experts agree that saturation is ideal, some give numerical guidance. For example, Adler and Adler advise graduate students to sample between 12 and 60, with 30 being the mean; and Ragin suggests that a glib answer is '20 for an M.A. thesis and 50 for a Ph.D. dissertation' (Baker, S., & Edwards, R. (n.d)). In my research I used purposive non probability sampling which gives the researcher the chance to choose the sample that best fulfills the objectives and need of the research. A sample size of 31 key experts in regulation of the biopharmaceutical sector as well as producers, importers and other stakeholders was aimed at and achieved 55% of which due to various constraints explained in the study limitations section. Number of key informants per section was designed based on the below criteria:

- 1- At least 10 years of knowledge in medicines regulation and 3-5 years of which in regulation of biologicals in Egypt
- 2- At least 10 years of experience in pharmaceutical industry with at least 3-5 years in biopharmaceutical research and development, production, marketing, safety and efficacy

- 3- At least 15 years' experience in policy making position in medicines regulation including procurement and pricing policies
- 4- At least 20 years of experience in clinical research / practice in treatment of hepatitis C and liver diseases in Egypt
- 5- At least 7 years of experience in patent examination and negotiation of Intellectual property Rights agreements at national and international level

IV. Interviews process:

Introductory email messages were sent introducing the Principal Investigator and explaining in brief the research objectives and outcomes. IRB consent forms were attached along with the questionnaire tool. The message included an invitation to be part of the research project and another invitation for discussing any questions or concerns they might have before enrolling in the interview process as explained in the IRB form. A total of 31 attempts was done to conduct the interviews resulted in 17 interviews. All interviews were pre appointed and lasted between 45 minutes to several hours. Interviews were either conducted through a field visit to the government agency concerned or by telephone.

Table 8: Interviews attempted and conducted

| | Number of interviewees attempted | Number of interviewees done |
|--|----------------------------------|-----------------------------|
| Ministry of Health- Procurement of Medicines Department | 1 | 1 |
| Central Administration of Pharmaceutical Affairs(CAPA)- inspection department of biologicals | 1 | 1 |
| Central Administration of Pharmaceutical Affairs - biological registration department | 3 | 1 |
| Egyptian pharmacovigilance center | 1 | 1 |
| Technical office of the Asst. Minister of Health of Pharmaceutical Affairs | 3 | 1 |
| Independent –Senior ex-CAPA | 1 | 1 |
| Rhein-Mina Pharm | 2 | 1 |
| Roche | 3 | 1 |
| Other potential producers or importers | 3 | 1 |
| Pharmaceutical Industry Chamber | 2 | 2 |
| Civil Society (patient’s rights) | 1 | 1 |
| Key Opinion Leader Clinicians using interferon in treating patients with hepatitis C Virus | 4 | 2 |
| Military hospitals | 2 | 0 |
| Egyptian Patent Office/Academy for Scientific Research | 3 | 3 |
| Total | 31 | 17 |

V. Development of the questionnaire tool

A master questionnaire tool was developed including 40 questions divided on two sections by interviewee's type. 1) Questions for Government, 2) Questions for Industry and private sector. Questions under each of the above section were distributed against sub sections of the three main independent variables in question: a) Requirements for quality, safety and efficacy of biosimilar products b) New pricing policy and pricing mechanisms and its relation to availability of biosimilar products c) Intellectual property regime and its relation to access to biosimilar products. I also created another set of subsections representing the dependent variables which I am assuming will be affected by the 3 independent variables , this included open ended questions and in-depth discussions on : i) opinion of the Key Experts on role of government in public health protection based on the current regulations ii) opinion of the Key Experts on any possible market failures (externalities, information asymmetry, collective action, lack of transparency, anticompetitive behavior) and iii) opinion on the role of government in promoting investment in development and local production of biopharmaceuticals.

I wanted to challenge their answers against possible implications that I propose based on what they answered on the independent variables questions set. This helped to validate answers, clarify any misunderstandings between the interviewer and interviewee and to add valuable informed expert's opinion to my discussion chapter. Qualitative data were collected through the semi structured and in-depth interviews using questions from the questionnaire tool. Due to the nature of the topic the data collected was more focused on the philosophy behind the regulations in place, how it compares to global regulations and regulations in stringent regulatory authorities. It also took the form of insights trying to assume positive and negative implications of the current regulations to public health in Egypt and possible loop holes in the regulatory system which may create market failures. The interviewer took notes either on electronic or manual notepads and transcribed after the interview.

VI. Direct limitations for this type of research:

Government or powerful groups (nondemocratic society) restrict free inquiries and keep research limited to safe topics forced to support official Government policies and shy away from politically sensitive topics. Study limitations:

1. I wasn't able to select a randomization sampling technique due to the nature of the topic requiring specific degree of knowledge and expertise, thus this study findings can't be generalized and it doesn't aim to do that.
2. Possible bias from the PI due to prior knowledge of the subject and preconception on the positions of some key experts on the subject due to working relations with some of them.
3. Due to the political and commercial sensitivity of the subject and the data asymmetry being mostly not in the public domain and within closed doors and a lot of gate keepers who control access to the information, data limitations may occur.
4. Some Government officials may have secrecy attitude and fear that infringing their confidentiality may result in negative drawbacks on their careers, especially with the current political turmoil in Egypt.
5. Commercial producers may feel awkward that an external researcher is tackling issues related to one of their products and that results if published may affect their business, they may become reluctant to participate.

6. Breaking the culture of closed doors in governmental intuitions and specially the Ministry of Health is a challenge, being responsible for a social sector that may create and upheaval of public discourse if threatened. Although made clear during my introductory emails that this research is done in my personal capacity as a postgraduate student in the school of Global Affairs and Public Policy at the American University in Cairo and that this research doesn't have any relation to my current professional employer. Being an employee of one of the United Nations agencies working on public health, tackling an issue that is relatively new globally and that affects a significant portion of medicines for diseases with high mortality and morbidity burdens and with no current official regulations in Egypt, created skepticism and resistance among some employees in the biological registration section leading to inability of interviewing some of them despite several attempts.

7. Due to time constraints and the scarcity of key experts who fulfill the above criteria and their very busy schedules made it hard to always find the right time to do the interview face to face and led to conducting the interview over-phone.

VII. How to solve data limitation problems:

Some of the above limitations are unsolvable like 1 and 2. For the rest two main strategies were utilized. The first one is to make the interviewee at ease and explain in depth and transparency the situation with all possible use of the data in the future yet with focus on the confidentiality and protection of the identity of the interviewee. The second solution needed was to find replacements for key interviewees who refused, were reluctant, resisted or shied away from speaking. To solve this I targeted key experts who have been in the same department and moved to another department, left the government recently or retired and thus have no problem in speaking freely and openly, I also tried to be cognizant about possible bias in experts opinions due to internal politics.

VIII. Possible use of resulting findings:

Based on the data collected on the three independent variables the question on whether the current regulatory policy towards Biosimilars is adequate to ensure public health protection. The analysis will then try to draw conclusions and recommend some policy options to the government for improvement of the current regulatory system for biopharmaceutical sector in Egypt.

Chapter 4: Data Analysis

I. The Regulatory Structure for Biosimilars in Egypt:

The World Health Organization conducted a regulatory authority assessment in 2008 which resulted in a report of recommendations to establish an independent autonomous or semi-autonomous regulatory authority in Egypt to regulate the medicines market. The Egyptian Drug Authority (EDA) was established by the Assistant Minister for Pharmaceutical Affairs assigned by the prime minister's decree number 4094 for the year 2008 as a landmark towards restructuring of the regulatory framework for medicines in Egypt. The main aim of establishing the authority was to create an independent body with clear structures and responsibilities that follows standards of the stringent regulatory authorities (US FDA, Canada, Australia, Japan and European Medicines Agency). However the authority remained under the Ministry of Health and with no financial or structural independence. Three main bodies stem from the EDA, namely the Central Administration of Pharmaceutical Affairs (CAPA), the National organization for Research and Control of Biologicals and the National Organization for Drug Control and Research (NODCAR)⁸.



Figure 3: The Egyptian Drug Authority

Photo credits to EDA website (www.eda.mohp.gov.eg)

⁸ Responsible for chemical based medicines thus outside the scope of this research and will not be tackled

A. The Egyptian Drug Authority (EDA) is the pharmaceutical regulatory body of the Egyptian Ministry of Health (MOH) and it is responsible for:

- Protecting people's health by regulating safety and quality of pharmaceutical products.
- Regulation & legislation of pharmacy practice.
- Availability of high quality medicines at affordable prices. (EDA, 2009).

B. The Central Administration of Pharmaceutical Affairs (CAPA):

CAPA is a regulatory body that carries out a range of assessment and monitoring activities for human and veterinary medicines, food supplements, insecticides, medical devices & cosmetics to ensure that they are of an acceptable standard with the aim of ensuring that the community has access to safe , effective affordable & secure products(EDA,2009).

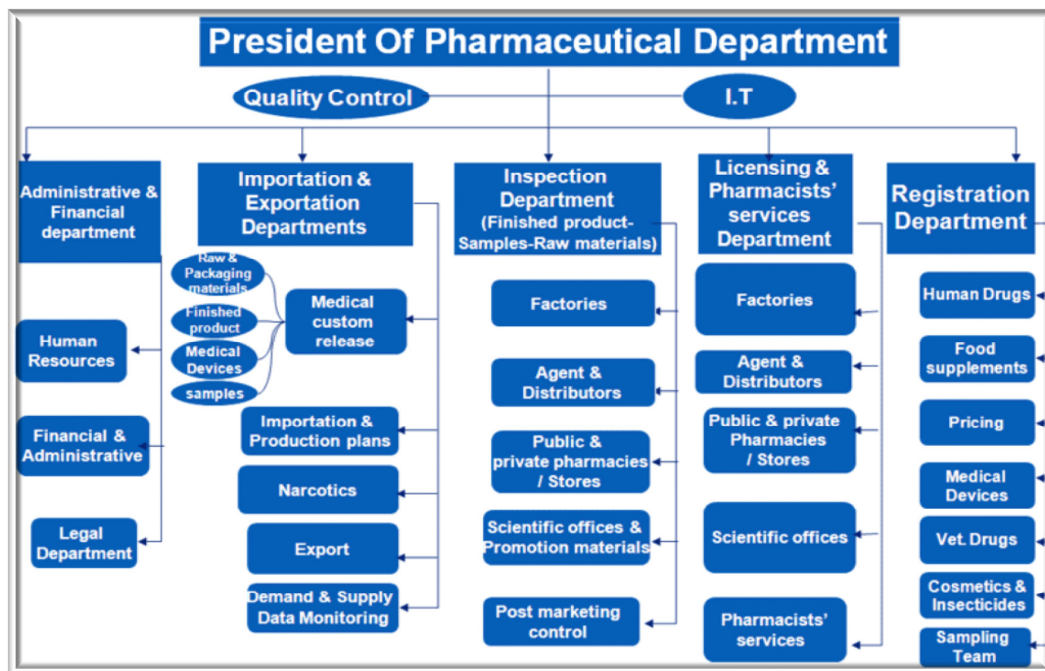


Figure 4: organizational structure of (CAPA)

Photo credits to EDA website (www.eda.mohp.gov.eg)

C. The National organization for Research and Control of Biologicals (NORCB)

The main function of **NORCB** is to ensure the safety, quality and efficacy of all imported and domestic Biologicals in Compliance with WHO requirements & international organization for standardization. One department is in the scope of this research the General Administration for Technical Affairs - clinical trials and lot release. (EDA, 2009).

The National Organization for Research and Control of Biologicals was established in 1995, according to Presidential Decree No. 398/1995, for ensuring Safety, Quality and Efficacy of all used Biological products and Vaccines (locally produced or imported). In 2006, The Ministerial Decrees No. 262/2006 & No.263/2006 were issued to implement the Presidential Decree No. 398/1995, the Board of directors and chairman of NORCB were assigned. The Quality Management System was certified by TUV according to ISO 9001/2000 in October 2008, according to ISO 9001/2008 in January 2010. Three labs of the Organization were accredited by the EGAC according to ISO/IEC 17025/2005 in September 2010. Finally the organization recognized by WHO in October 2010 as a functional National Regulatory Authority (NORCB, 2011).

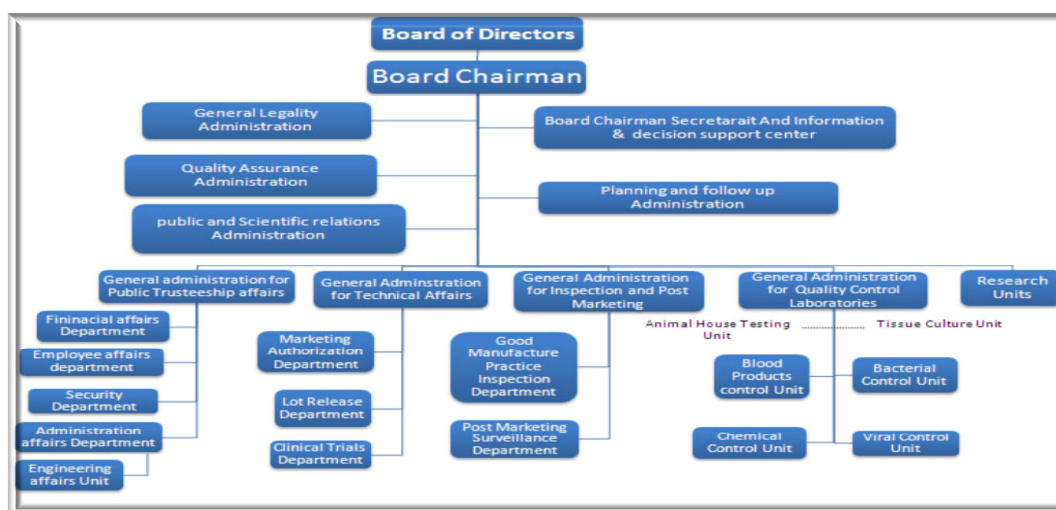


Figure 5: Organizational structure (NORCB)

Photo credits to EDA website(www.eda.mohp.gov.eg)

D. The Egyptian Pharmacovigilance Center (EPVC):

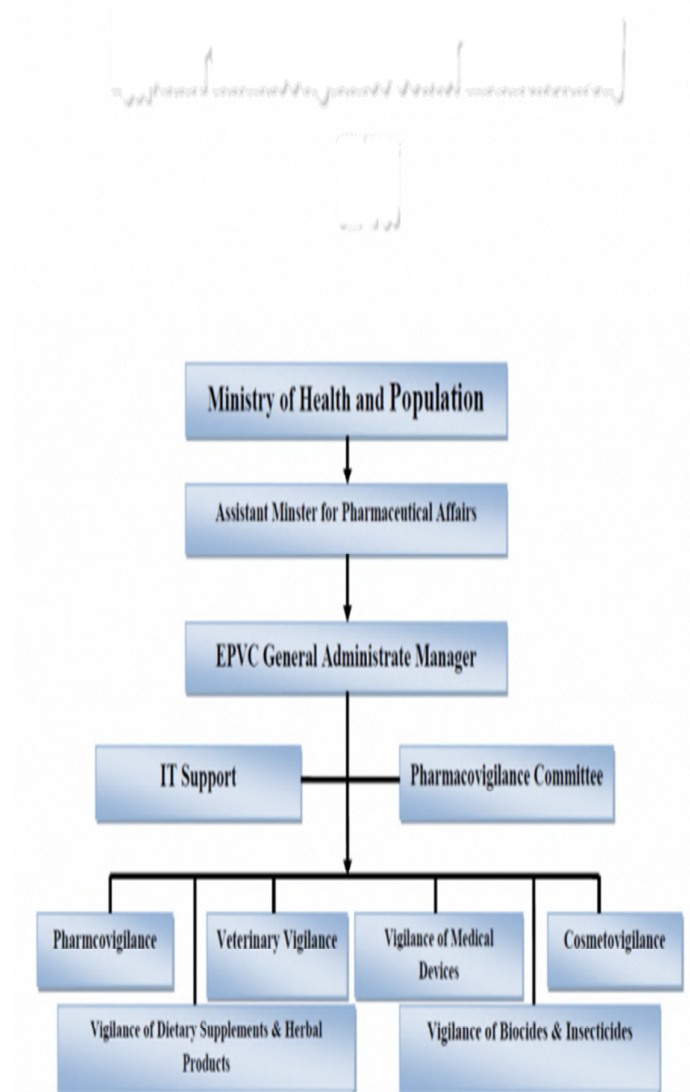


Figure 6: Organizational Structure of the Egyptian Pharmacovigilance Center

Photo credits to EPVC website (www.epvc.mohip.gov.eg)

The center was established by a special decree from the 2008 formed position of Assistant Minister of Pharmaceutical affairs. The decree number 2 for the year 2010 (2/2010)⁹ is applied to both pharmaceutical and biological products and is based on several decrees, the most relevant of which is decree number 397 for the year 1995 related to the establishment of a National Center for Adverse Drug Reactions Monitoring in Egypt. The decree clearly outlines in 11 articles the roles and responsibilities of the government and market authorization holders (MAH) of pharmaceutical or biological products to ensure safety of the products post marketing. It creates the new responsibility of the government to monitor, analyze, assess and take suitable action based on reported adverse events of medicines. Marketing Authorization Holders (MAH) are committed to report in a maximum of 15 days any serious adverse drug reactions resulting from the use of their products to the (CAPA). The MAH should report periodic safety update reports (PSURs) or any phase 4 clinical trial (post marketing studies) data to CAPA. Article 5 in the decree states that PSUR's submission is required at the time of re-registration of the biosimilar product or generic product, and at the time of registration and re-registration for the innovator. The EPVC is entitled to receive any Individual Case Safety Reports (ICSR) about adverse drug events from healthcare professionals (doctors, nurses, pharmacists, etc...), patients or their relatives or any other person for analysis, assessment and entry to the national adverse drug events database. Article 7 of the decree put the responsibility of reporting any Suspected Unexpected Serious Adverse Reactions (SUSARs) which may threaten the life of any volunteer or patient involved in a clinical trial taking place in Egypt on the MAH or Principal Investigator (PI) within 1 day, while other to be submitted within 7 days from happening. Article 8 clarifies the authority of the EPVC to raise a report with its recommendations to the technical committee at CAPA to take any of the following actions: 1) ban importation, 2) ban marketing, 3) suspend marketing and stop manufacturing for a limited duration.

⁹<http://www.eda.mohealth.gov.eg/Download/English%20Decree%20for%20the%20assisstant%20minister.pdf> (Amended in 2012 to decree 368 for the year 2012 (368/2012) with no major changes to the center's mandate) - <http://www.epvc.gov.eg/NewsAttachments/%D9%82%D8%B1%D8%A7%D8%B1%20%D9%88%D8%B2%D8%A7%D8%B1%D9%89%20%D8%A8%D8%B4%D8%A3%D9%86%20%D9%85%D8%B1%D9%83%D8%B2%20%D8%A7%D9%84%D9%8A%D9%82%D8%B8%D8%A9%20%D8%A7%D9%84%D9%85%D8%B5%D8%B1%D9%89%204-7-2012.pdf>

II. The legal framework:

During the interviews it was clear that in Egypt the culture of governmental institutions in functioning is speaking to each other by reference to laws and ministerial decrees. A law would give the regulation a relatively strong power, a ministerial decree has the enforcement power of a law but can always be challenged and changed with another decree without going back to the parliament; a presidential decree is similar to the ministerial decree but with more powers in terms of implementation and continuity. In Egypt regulation of biopharmaceuticals was first mandated in 2009 using the Ministerial decree 297/2009 (for the year 2009). The decree established the rule, procedure for registration of biological products, vaccines, serums and blood derivatives¹⁰. This decree set the guidelines on what is required from manufacturers and importers of biopharmaceuticals to register a biopharmaceutical product in Egypt. Requirements included technical data to present for quality, safety and efficacy as well as other administrative forms to complete or provide about the company and the product in need for registration. However in order to implement such decree functional regulatory structures have to be in place with clear mandate and rights. The two administrative decrees “complementing the ministerial decree” number 3 and 16 for the year 2009 filled this gap by setting the administrative rules for establishing the biological products inspection department and the biological products registration department respectively. This was followed by the presidential decree 244/2009 to iterate the executive functions for the National Organization for Regulation and Control of Biological products (NORCB). The NORCB was established in 1995 by the presidential decree 398 however with no clearly iterated executive functions. NORCB act as the technical arm for the registration department of biological in the Central Administration for Pharmaceutical Affairs (CAPA).

¹⁰ Vaccines, serums and blood derivatives regulations are outside the scope of this research

III. The regulatory procedure:

A. Procedure prior to the 2009 ministerial decree:

Prior to the 2009 ministerial decree which regulates the registration of biological products the requirements for registration of biological products were similar to chemical based medicines. In that sense the requirement for a chemical based generic medicine was to provide proof of quality and for safety and efficacy to rely on the safety and efficacy data from the originator or brand product. In 2008 an amendment which required a proof of therapeutic equivalence to be provided in the generic product's dossier to ensure the efficacy of the generic is within an acceptable range to the originator. Usually between 80-125% of the Area under the curve (AUC) in most guidelines and differs in case the product is of low therapeutic index meaning high toxicity probability, ranges between 95%-115%.

B. Procedure post the 297/2009¹¹ ministerial decree:

This decree differentiated between registration requirements of biological products and chemical based medicines. The decree set the technical requirements of quality, safety and efficacy requirements for both original products and similar biological products. The requirements requested a full dossier data including quality with all the chemistry manufacturing and control data, pre-clinical (toxicological safety studies testing the product in animals) and finally clinical studies to proof efficacy. These guidelines didn't differentiate between original and similar biological products and asked for a complete dossier with full quality, non-clinical and clinical data without explicitly differentiating between reference biological products and biosimilars. The guidelines to interpret this decree have differentiated though between the requirements for locally produced and imported products. Difference however was mainly in administrative requirements for example with the imported products they needed the certificate of pharmaceutical product (CPP) which means that this product is circulating freely in the market of its country of origin or any of the reference countries to Egypt . For locally manufactured products there was a need for the reports of the inspection department on Good Manufacturing Practice while

¹¹ http://www.eda.mohealth.gov.eg/Download/Docs/English_version.PDF

for the imported products if they produced in a reference country then the Egyptian authorities doesn't inspect the facility and they accept the decision of the local authorities in the country of origin.

IV. Requirements to ensure Quality Safety and Efficacy of Biosimilars in the Egyptian Market

A. Biological products:

According to the WHO Technical Report Series, No. 858, 1995, a Biological products are defined as medicinal products made of substances extracted from or produced by living sources whether they are genetically modified living organisms or liquids and tissues extracted from various human or animal sources (WHO TRS,1995) (EDA,2010). Various types of biological therapeutic products exist:

1. Immunological medicinal products: Any medicinal product consisting of vaccines, toxins, serums or allergen products
2. Medicinal products derived from human blood and human plasma
3. Medicinal products developed by means of biotechnological processes (Biopharmaceuticals): Recombinant DNA technology: Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cell.

All the above categories are common in that they are more difficult to characterize or control than chemically synthesized pharmaceuticals due to their complex molecular structure (EDA,2009).

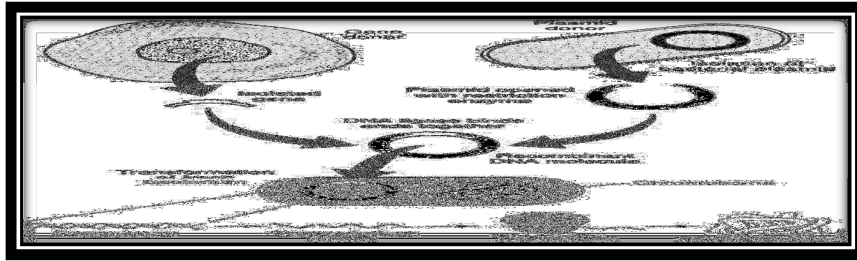


Figure 7: Recombinant(r) DNA process for generating biopharmaceutical proteins

Photo credits: (fhs-bio-wiki.pbworks.com)

B. Biosimilar product:

A biological product (other than blood derived products, recombinant analogues, vaccines and sera) having the same active substance, dosage form, strength and route of administration of a reference biological product and has proven through (a comparability process) that its quality, safety and efficacy are highly similar to a reference biological product when prescribed in a claimed indication. This means that for every biosimilar product claimed there is a reference product. In order for a biosimilar product to claim similarity to a reference product the registration dossier has to include a quality comparability exercise in addition to reduced pre-clinical and clinical comparability studies. The reference product has to be marketed in Egypt or has been marketed for at least 4 years (well established) in the markets of any of the reference countries for Egypt (mainly Western Europe, USA, Canada, Australia and Japan). One reference product will be used for the three types of comparability (quality, pre-clinical and clinical). Figure 8 below illustrates how much data need to be generated for demonstrating quality, safety and efficacy of a biosimilar versus a stand-alone or an innovator (reference) product while Table 9: illustrates the data required to be submitted by a company to apply for a registration license for its product type (Innovator , chemical Generic, biosimilar)¹².

¹² PowerPoint presentation by the biological registration department – CAPA – Feedback workshop on draft guidelines for biosimilars registration in Egypt 24-5 February 2013, Cairo, Egypt.

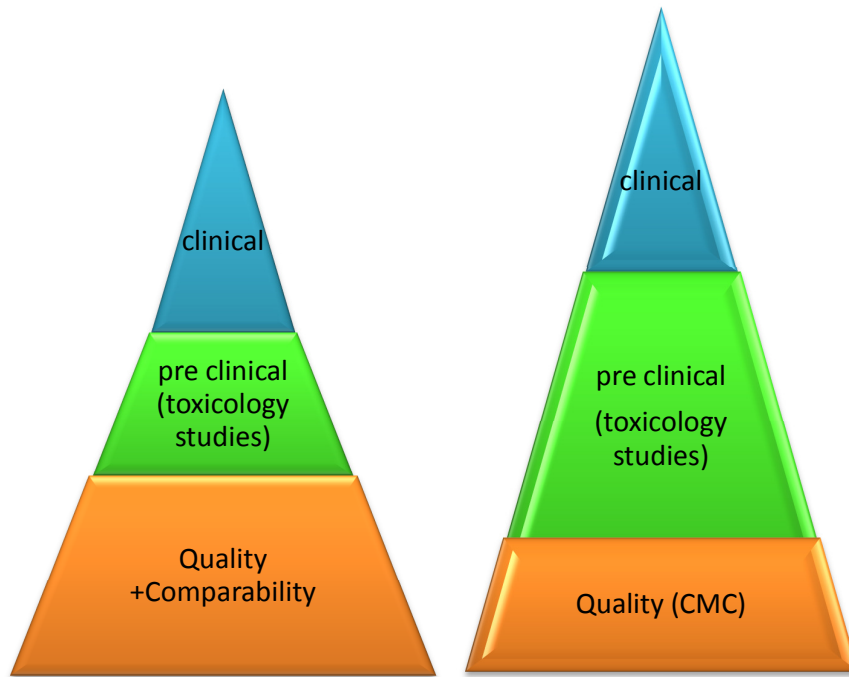


Figure 8: Registration data required for - Biosimilar (left) and originator or Standalone¹³ (right)

Table 9: Registration data required for innovator, generic and a biosimilar

| Regulatory attribute | Type of product | | |
|----------------------|--|----------------------|--|
| | Innovator | Generic | Biosimilar |
| Quality | Full quality dossier | Full quality dossier | Full quality dossier plus Comparability exercise |
| Non-clinical | Full non-clinical Dossier | No data Required | Comparative in vitro studies Comparative PK and/or PK/PD Comparative repeat-dose Toxicity, other studies. |
| Clinical | Full clinical dossier Data from Phase I, II and III studies | BE study | Comparative Phase I (PK/PD) And Phase III (Safety and Efficacy) Studies |

¹³ Are new molecular entities from the same class of the original product yet doesn't claim similarity.

C. Quality data (Chemistry, Manufacturing and Controls - CMC) :

The biosimilar approach require complete quality data including data on analytical techniques methods used in analysis and their validation, results of analysis, for the raw material (active substance), inactive substances (additional material with no therapeutic value) and finished product (final product) in addition manufacturing process in step wise presentation, in process controls and stability data for both active and finished product. In addition to that data on packaging materials used has to be included. The comparative characterization studies This is the basic concept which needs to be established prior to moving to the non-clinical/pre-clinical and the clinical studies. In this comparative exercise analytical validated methods should be used to characterize the following in both the biosimilar and the reference product: 1- physiochemical properties, 2-impurity and contamination, 3- structural characterization and 4-biological action assays.

D. Pre-clinical data (toxicology studies in animals):

The most important factor in these studies is the repeat dose toxicity studies at least one study of long duration with toxico- kinetic measurements taken should be conducted.

E. The Antigenicity / Immunogenicity:

Means the possibility of the medicine inducing antigenic response in the patient, leading its immune system to produce a reaction (antibodies) against its own body which may lead to death in a very short interval. This is actually one of the main differences between biological and chemical medicines and considered significant factor in granting market authorization to a biosimilar product. Although animal immunogenic studies may not accurately predict immune response in humans, antibody measurement can be a clear factor in determining immunogenicity and should be included in the repeat dose toxicity study. Other studies may include the following: Single-Dose Toxicity, Repeat-Dose Toxicity, Genotoxicity, Carcinogenicity, Reproductive and Developmental Toxicity, Local Tolerance Fertility and Embryonic Development, Embryo-Fetal Development, Pre- and Post-natal Development & Maternal Function, Offspring, Juvenile, Second & Third-Generation Studies, Local Tolerance.

F. Clinical data (comparability head to head clinical studies)¹⁴:

The clinical comparability exercise is a step wise procedure it starts with studies to know the effect of the body on the ingested biosimilar (pharmacokinetic studies -PK), studies to determine the effect of the biosimilar on some biomarkers (pharmacodynamics studies - PD) then it move to the efficacy trials and finally clinical safety trials (safety in humans).

- **PK studies:** Absorption, Distribution, Metabolism and Elimination (ADME) are the main parameters for investigation. A range of acceptance for each parameter demonstrating similarity versus the reference product should be pre-determined by the manufacturer, justified and documented in the study protocol. Due to the lack in acceptance criteria for biological in the literature. The acceptance range for chemical based medicines of 80%-125% may be applied.
- **PD studies:** specific markers in the body should be selected and monitored for the effect of the reference and biosimilar products. PD markers like reticulocyte count in case of erythropoietin for example can be used as substitute for clinical effectiveness if therapy induced changes can affect clinical outcomes.
- **Efficacy trials:** preferably double blinded or at least observer blind.
- **Clinical safety:** pre-market authorization data should be obtained from an adequate number of patients to provide a comprehensive safety profile. Adverse events observed if any should be compared in terms of type, severity, and frequency. The focus should be on immunogenicity data and it is essential to do a pre and post marketing immunogenicity studies.
- **Risk Management (RMP) and Product Pharmacovigilance Plan:** should be presented to the Egyptian pharmacovigilance Center. It should include post marketing immunogenicity study at the time of submission of the market authorization application. If at any of the above steps significant difference between the biosimilar product and the reference product are detected, this should be investigated and if there is no justification for such differences not related to the product's performance of quality, safety and efficacy the product may not be accepted as a biosimilar and a Standalone (asks for full product

¹⁴ Power point presentation by Dr Heba Khalil , NORCB on clinical requirements for Biosimilars

quality, safety and efficacy data not in comparison to a reference product) application may be considered.

V. Procedure suggested in draft guidelines for biosimilar registration in Egypt 2013:

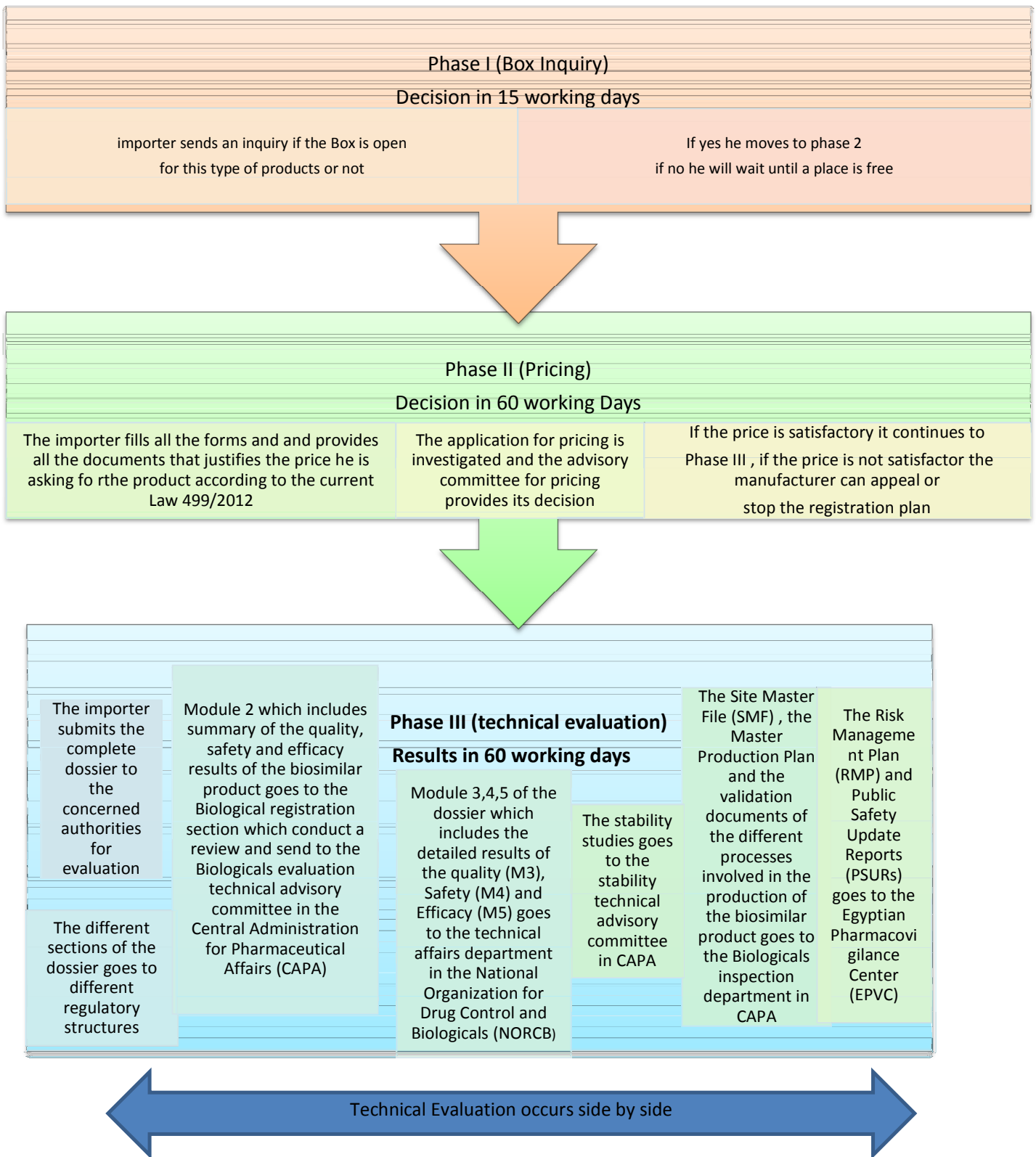
Two regulatory pathways can be adopted for registration of biosimilars in Egypt:

A. The Final dossier pathway:

This is for finished biosimilar products imported in its finished form or for a biosimilar product that is developed, manufactured, and filled under the control of the regulatory authority of the country of origin and only labeling and secondary packaging takes place in Egypt¹⁵. In this case the dossier for the finished product only is assessed in Egypt. Figures 9 and 10 explain the step wise regulatory pathway which an imported and a locally manufactured biosimilar pass through to gain registration license in Egypt according to the latest draft biosimilar guidelines issued by CAPA biological registration section.

¹⁵ placing the vial or main product container in to the cartoon box “secondary package”

Figure 9: Imported biosimilar regulatory pathway in Egypt



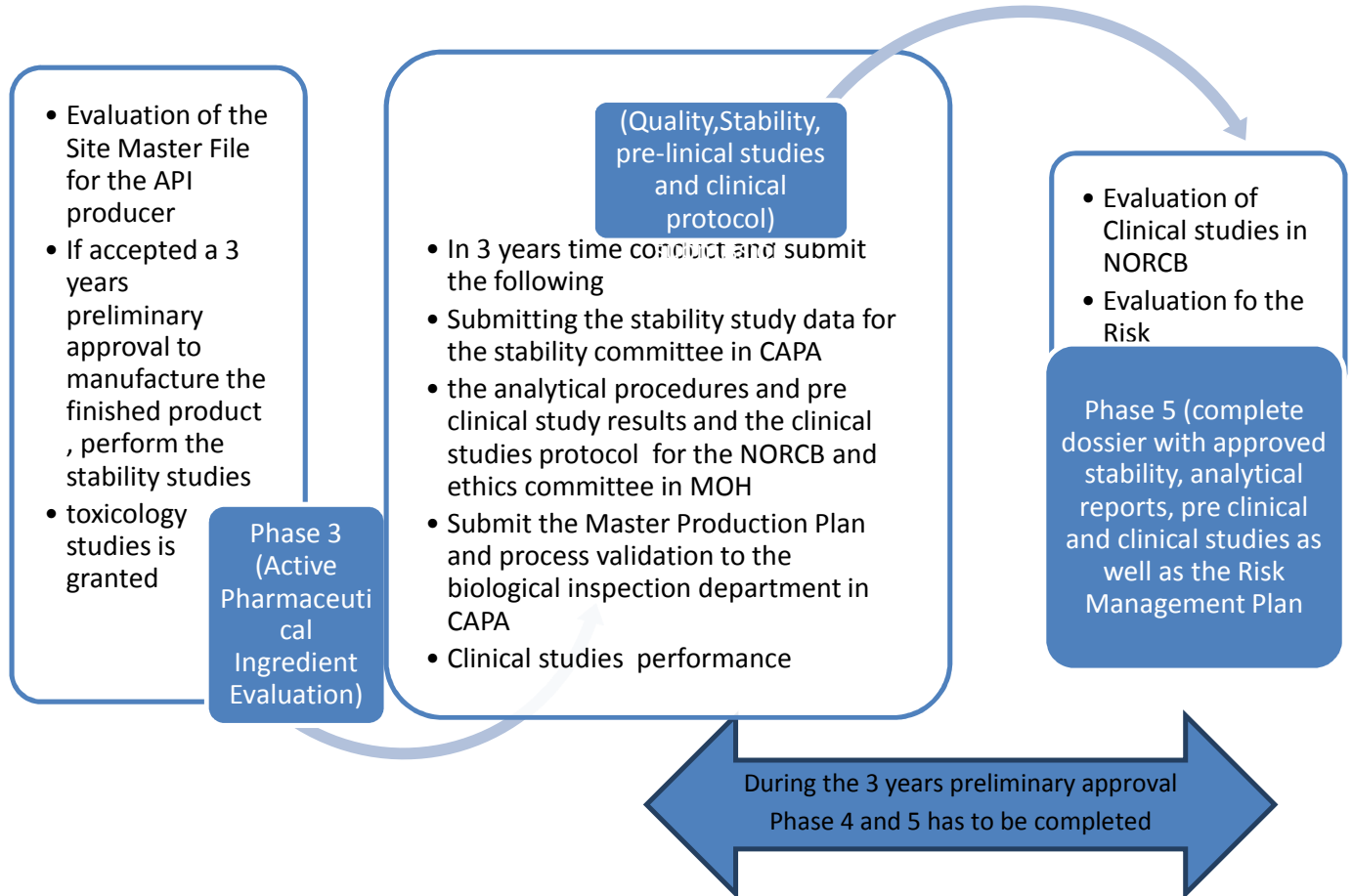
B. A stepwise pathway:

This is pertaining to biosimilar products *developed and manufactured in Egypt* or in the case of a manufacturer importing the final product in the form of bulk and doing the primary packaging (adding the injection powder or solution in to the glass vial). In this case the development and registration process goes in parallel.

The box approval and the pricing steps are cross cutting with the final dossier procedure mentioned above. However it should be noted that for the Box approval to be granted there has to be less than 12 similar products of the production in question. 6 of which are imported and 6 are locally produced. So in case the product is locally produced and the 6 slots for locally produced products are filled the company has to park its product application on a waiting list until a slot is available and can't compete for the slots of the imported products and vice versa.

In the production of biological products *the product is the process* and hence the Egyptian regulatory authority has to evaluate the different phases of development and manufacturing in a step wise approach to ensure the product is being manufactured according to Good Manufacturing Practices and to ensure its process will render a product with high probability to produce acceptable results when it undergoes the comparability studies in quality, safety and efficacy. The regulatory pathway for the locally produced biosimilars post the box and pricing phases:

Figure 10: Proposed regulatory pathway for a locally manufactured biosimilar in Egypt¹⁶



¹⁶ Phase 1 and 2 are the same as the imported biosimilars pathway hence omitted for layout issues

C. Issuing a market authorization (registration) license:

Reports from the different working parties involved in phase III technical evaluation (CAPA, NORCB and EPVC) are presented to the technical advisory committee on biological registration and a decision is made within 60 working days based on the results of whether to grant or refuse the marketing authorization. The total duration expected for granting or rejecting a marketing authorization request for an imported biosimilar product is 39 weeks and for a locally manufactured product excluding on how much time the manufacturer will use from the 3 years grace period given to conduct all the quality, safety and efficacy studies 52 weeks. The final stage is the re-registration when the company reapplies for its expired market authorization in 10 years.

VI. The pricing policy and pricing mechanisms

Medicine pricing is an essential element of medicines regulatory policy. As it was explained in the different regulatory pathways for biosimilars, pricing agreement comes before technical evaluation which gives a strong perception of it being a “rate limiting step” that affects if the product will continue in its registration process or it will stop. Pricing becomes even important when it comes to biological products of sometimes sophisticated biotechnology industrial development techniques and of high risk of unpredictable behavior of the product due to its origin coming from a living organism and complex structure. Biologicals are often of higher price tier than chemical medicines due to the above mentioned reasons but also due to the fact that many of them are treating either complex disease, orphan diseases or are lifesaving products. Since the pricing issue is often charged with push and pull and exercising of pressure tools between the government and the company. Biosimilars coming to governments as a safe haven to reduce costs of sometimes exorbitantly expensive branded biological, especially now with the Egyptian government planning to implement universal health coverage and designing their health services package which will be covered under the mandatory social or tax based insurance scheme¹⁷.

Based on epidemiological studies, essential medicines for diseases that affect the majority of the population would presumably include a lot of biological and potentially biosimilars in the upcoming years. Egypt has some of the highest rates for several types of cancers globally amongst are the breast cancer, hepatitis C which can progress to develop liver cancer, diabetes. All of these are treated with medicines from biological origin; such medicines are expected to be purchased in the package for reimbursable health services under the new health insurance law. Tackling how medicines at large are priced in Egypt would give a proxy indicator of how products of relatively higher price tier may be affected in terms of patient’s access to these products. The government of Egypt set the rules and procedures for pricing medicines for human use and based on such procedure the company and the pricing committee undergoes the negotiation process to reach an agreement on what may be a fair price.

¹⁷ Presentation by Dr. Mohamed Moustafa Minister of Health and Population , Sharm EL Sheikh, April 2013

VII. Pricing regulatory structures:

A. The pricing committee at CAPA:

The main regulatory structure in place is the pricing committee which is responsible for reviewing the pricing application and documents provided by the manufacturer. The pricing committee is composed of seven representatives, three from: The Ministry of health (focus on therapeutic return or value to patients), The ministry of trade (focus on industrial development) and The ministry of supplies (focus on achieving lowest possible price). In addition some university professors from different technical backgrounds in the pharmaceutical field for any consultations related to the therapeutic value of such products. The selection of the committee members is not based on clear publically available criteria and is assigned by the head of the CAPA. Decisions made by the pricing committee shall be endorsed by the Minister of Health.

VIII. Legal framework for pricing in Egypt

A. Ministerial Decree 314/1991:

This was the first decree that clarified the way medicines are being priced and the different price components. It used the cost plus pricing mechanism. The cost plus mechanism that used to be in place depended on a fixed profit margin on local and imported products that the governments assigns and is added to the total the company declares as costs of developing the product until it is ready for sale to the first point in the supply chain. Due to various disadvantages of such system including claims that the invoices presented by the companies to justify the total costs are unverifiable and hence presents a window for maximizing profits based on false invoices. The process was also claimed to be cumbersome and consuming for both the manufacturer who tries to collect invoices for every expense used in producing and marketing the product and also for the assessor who faces a huge pile of documents to go through and verify within a limited time frame.

B. The pre-revolution pricing decree (373/2009):

The decree number 373/2009 was issued in 2009 by the Minister Hatem El Gabaly. The decree shifted the way medicines has been priced in Egypt from “cost plus” to a new mechanism known as reference pricing or “external” reference pricing. The main idea of the reference pricing system is to overcome the cost plus verification process by linking the final price of the product to the same product’s price in a list of countries. If the product is an originator then the price will be 10% less than the lowest price from the reference list. If the product is a biosimilar the price will be 30% less than the price of the locally registered brand. The decree caused a hype amongst many of the human rights and patients’ rights groups as it was considered a bold step liberating in a way the prices of medicines by linking them to international prices¹⁸. The Minister mentioned in the last article in the decree that an evaluation study to be conducted one year post the implementation of the decree to evaluate the impact of such policy on medicines prices however nothing was reported by the ministry of health if the study was done and what were the results.

Figure 11 : Summary of the medicine pricing degree 373/2009

¹⁸ a court case was filed by the Egyptian Initiative for Personal rights which was lost in its final round and the decree was considered constitutional and legal by the administrative judiciary authority

Originator (Brand product)

- 10% less than the lowest price in the reference list of countries
- With the introduction fo the first biosimilar the originator's price is reduced by 2% for each year the originator was present solely in the market.
- The reference list include the 27 member states of the EU, GCC(excluding Qatar), Argentina, Algeria, Canada,Japan,Jordan,Iran,Lebanon, Sudan, Turkey, India, Philipines, Morocco)
- For products manufactured using high tech (biotech or other sophsicated technology) a comparative pharmaco-economic study to be submitted.

Generic / Biosimilar

- 30% less then the originator's price if the product was manufactured in a facility that passed the inspection for Good Manufacturing Practices (GMP) from US FDA, European Medicines Agency (EMA), Japan,, Australia or WHO Prequalificaion or any country memembr in the International Conference on Harmonization (ICH)
- 40% less from manufacturing facilities locally approved by the Egyptian Drug Authority only
- 60% less from local companies which has no manufacturing facility but manufactures in other local facilities via contracts (toll manufacturing)

Profit Margin of retail pharmacist/ others

- remains the same from the law number 314 for the year 1991
- retail pharmacist's margin 10-12% in imported products and 18-20% in locally manufactured products
- the consumer price is evaluated every 3 years for products priced according to this law or in case there is a drastic change of the currency exchange rate by 15% + or - according to the central bank of Egypt Currency Exchange Rate.
- Manufacturing facilities are given a grace period until 2020 to improve their manufacturing and operational quality standards to meet the US FDA, EMA Japan or WHO prequalification or ICH member countries .

C. The post-revolution pricing decree (499/2012)¹⁹:

The new decree which took place after the 25th of January revolution by Dr Fouad Al Nawawi the latest Minister of Health prior to Dr. Ahmed Mostafa (Minister of Health) in Hesham Kandil's government. The decree didn't have a radical shift in the way medicines are priced, it kept the same external reference pricing model. It however changed the distribution of the profit margins for the different beneficiaries in the medicine's supply chain. Any price has three main beneficiaries 1) producing company or importing company, 2) distributor or wholesaler (may be more than one involved) and 3) the retail pharmacist. The new decree will price the brand product according to the lowest price in the reference list of countries. The first 5 generic products the price will be 35% to 40% less than the locally priced brand. Each generic after that till the 11th generic (cap) will be 10% less than the previous generic. The new decree mentioned that it cancels the old decree 373/2009. Article 6 of the decree detailed the change in profit margin distribution between the beneficiaries. It included the creation of two categories of products either local or imported. For the imported the division is between products of price less than 500 LE and products of more than 500 LE. The locally manufactured are products either on or off the National Essential Medicines List and subsidized products. Figure (13) below outlines the changes in profit margins for the different beneficiaries as per the current pricing law number 499/2012. Before going in to Table (2) outlining the different terminologies of price components is considered crucial. The Ex – Factory price is the price of the product in the factory, CIF is called the Cost, Fright and insurance which is how much it cost the company to get the product in to the port of the importing country. Then we have the distributor or whole sale's price markup(s) ,the retailer's markup and finally tariffs, taxes and customs²⁰.

¹⁹ <http://www.eda.mohealth.gov.eg/Download/Docs/499.pdf>

²⁰ Tariffs, taxes and customs vary from product to product according to importance, global best practices is to remove any of these inflation factors to medicine prices to improve accessibility. In Egypt tariffs, customs and taxes are applied to all medicines except medicines for chronic diseases

Figure 12: Summary of the medicine pricing degree 499/2012 - The post 25th of January revolution pricing decree (499/2012)

| Originator (Brand product) | Generic / Biosimilar | Profit Margin of retail pharmacist/ others |
|---|--|--|
| <ul style="list-style-type: none"> •equal to the lowest consumer price identified in the list of reference countries in case the brand price is identified in more than 5 countries •In case the price is identified in less than 5 countries the above may apply or a comparative study between the originators from different classes for the same therapeutic effect •The reference list (only guiding not obligatory) include the 27 member states of the EU, GCC(excluding Qatar), Argentina, Algeria, Canada,Japan,Jordan,Iran,Lebanon, Sudan, Turkey, India, Philipines, Morocco) however CAPA has the right to review the price in any other country in the world and take its price in to consideration. •For products manufactured using high tech (biotech or other sophsiticated technology) a comparative pharmacoeconomic study to be submitted and CAPA has the right to take a lower price if identified before granting the pricing decision | <ul style="list-style-type: none"> •Generic: •35% less then the originator's price for the first 5 generics •40% less for the rest of generics (6 products) •In case of products manufactured using high technology such as biotechnology (biosimilars): •30% less than originator price in case the product was manufactured in a reference country (ICH country) with a cap on price not to exceed the price of the same product in the country of origin or any of the countries it is marketed in •35% less in case it was manufactured in a non reference country with a cap on price not to exceed the price of the same product in the country of origin or any of the countries where it is marketed | <ul style="list-style-type: none"> •Profit margins are detailed in Figure(13) below •the consumer price is reviewed in case there is a drastic change of the currency exchange rate by 15% + or - according to the central bank of Egypt Currency Exchange Rate OR •In case the company propose a price review for 5% of the total of its products per year •For the already priced originators, the CAPA has the right to review the price of the originator post the pricing decision in any of the countries in the world and incase found its price less than in Egypt it is priced accordingt o the new lowest price and what applies to generics prices. •Margins for retail pharmacist will continue to grow by 1% each year for already priced products until it reaches the new margin •In case a company stopped its manufacturing of a product and imported it instead the retail pharmacist will continue to have the 30% margin instead of moving to the imported margins category (18-22.9%) and the difference will be borne by the manufacturer |

Figure 13: Profit margin of different beneficiaries in the medicines supply chain in Egypt according to new pricing decree 499/2012²¹

| Scenario /price for beneficiary | Local Manufacturer / importer Profit Margin EX factory price or (CIF) | Distributor Profit Margin From CIF price | Retail pharmacist profit margin in Egypt from distributor's price |
|---|---|--|---|
| For imported products with consumer price less than 500 LE: | 6.4% | 8.8% | 22.9% |
| | | 6.4 from consumer price | 18% from consumer price |
| For Imported products with consumer price more than 500 LE | 6.4% | 6.4% | 18.5% |
| | | 4.8% from consumer price | 15% from consumer price |
| | | A cap of 150 EGP is exercised and in case more the difference is deducted from consumer's price for the benefit of patient | A cap of 450 EGP is exercised a difference is deducted from consumer's price for the benefit of patient |
| locally produced, filled or packaged and labeled (Bulk) products outside the essential medicines list | 25% | 8.8% | 30% + (4.5% of CIF price=4.13% of distributor) as cash payment incentive = 34.13% 25% from consumer's price = 29.13% |
| products from the National Essential Medicines (local or imported) | 15% | 7.86% | 25% |
| Subsidized products by the government (local or imported) | NA | 4% | 10% |

²¹ <http://www.eda.mohealth.gov.eg/Download/Docs/499.pdf>

IX. The Intellectual Property and Patent Protection in Egypt

A. Global agreements and Free Trade: The TRIPS agreement

Intellectual property and access to medicines or commodities of therapeutic value have a long history of debate. The debate between access to medicines and protection of commercial interests and incentivizing innovation has passed through various leaps through modern history. The latest of which is considered a radical shift when the agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) was ratified by the majority of world countries to comprise the new world order of intellectual property protection. The TRIPS agreement obliges signatories (member countries of the WTO) to integrate measures to grant patent protection and exclusivity from third party exploitation of a patented invention. Medicines being a commodity that affects health is still produced by an entity where return of investment is considered a priority on its shareholders' agenda and will try to exert all efforts to protect it from competition to increase profits. One new molecule is a result of long years of investment in research and development by pharmaceutical companies. The development process of one medicine is outlined in figure (14). The percentage of Investigational New Drug (IND) applications that pass through the preclinical testing, Phase I, II, III process and is accepted for FDA review process is 2 from each 10 new molecules. The process itself takes between 12-17 years and the time of filing a patent application is usually at the time of filing an IND meaning 9-13 years from the 20 years patent protection are already consumed before even the product is in the market. These entities by corporate law have the right to maximize profit and increase shareholders value. Having only one company producing a life-saving commodity not only introduces monopolistic power but also has profound impact on the public health, security and economy. Consequently developing countries lobbied the WTO for trade negotiation rounds with a development focus that took place in Doha, namely the Doha rounds. Articles to protect public health were weaved in to the agreement to ensure protection of intellectual property will not affect public health protection.

Figure 14: Product development life cycle of innovator medicine according to the US FDA²²

| | Pre Clinical Testing | | Phase I | Phase II | Phase III | | FDA | Approval |
|------------------------------|---------------------------------------|----------|------------------------------|--|--|----------|----------------|--|
| Years | 3.5 | | 1 - 2 | 2 - 4 | 4 - 6 | | 1.5 | Total = 12 - 17 |
| Test Population | Laboratory and Animal Studies | FILE IND | 20 to 100 Healthy Volunteers | 100 – 300 Patient Volunteers | 1,000 to 3,000 Patient Volunteers | FILE NDA | Review Process | Post Marketing Safety Monitoring |
| Purpose | Assess Safety and Biological Activity | | Determine Safety and Dosage | Evaluate Effectiveness. Look for Side Effects. | Verify Effectiveness, Monitor Adverse Reactions from Long-Term Use | | | Large Scale Manufacturing ----- Distribution ----- Education |
| % of all new drugs that pass | | | 70% of INDs | 30% of INDs | 27% of INDs | | | 20% of INDs |

B. Integration of TRIPS in the current Egyptian law number 82 for the year 2002²³

Egypt was a signatory of the TRIPS agreement in 1995 and joined the World Trade Organization in 1996. By signing the agreement countries are obliged to make their laws and regulations complying with the TRIPS agreement article or in other words “TRIPS compliant”. Historically the Egyptian law granted patents only for pharmaceutical processes but not products so for example if the pharmaceutical manufacturer developed a process which increase or enhance a specific product, system or another process the patent is given over the process itself but not on the final product. This law for the year 1949 granted patents for processes for 10 years and for 15 years for products other than medicines. (*The trips agreement and Egypt’s responsibility to protect the right to health.* 2005, January)

This was replaced in 2002 by law number 82 for the year 2002 (82/2002) , however Egypt had a grace period till 2005 till it starts granting patents to medicines. The Egyptian Patent office (EGYPO) is the entity responsible for receiving, assessing and making decision on patent applications filed in Egypt (Egypt as other

²² Power point presentation by Roche Medical department

²³ http://www.wipo.int/wipolex/en/text.jsp?file_id=126540

countries doesn't recognize patents granted in other territories, to be granted patent for your product protection you have to file a local application). Until April 2009, The EGYPO, has 30 legal examiners, 115 technical examiners and 30 pharmaceutical examiners. The EGYPO received 2800 applications in the mail box until January 2005, 80% of which were for pharmaceutical products (UNDP, 2009). Patents are granted by the EGPO if the subject application fulfills three criteria: 1- *Inventive step* 2- *Novelty*, 3- *Industrial application*. Patents in the new law are granted for 20 years however the new law although TRIPS compliant has several articles which ensures protection of public health and public interest and prevention of the abuse in exclusive exploitation of the patent or failing to utilize such exploitation by not being able to industrially produce the product in these case the government has the right to issue non voluntary license to a third party to produce the same patented product. Such freedom is called TRIPS flexibilities which resulted from the Doha declaration²⁴.

C. TRIPS Plus, data exclusivity and hampering introduction of competition

A new movement of handling free trade outside the WTO circles are the bilateral trade agreements, the most famous of which is the US Free Trade Agreements (FTA's) in such agreements the US and another country agree on specific measures to take in terms of economic reform in order to liberate trade in goods and services between the two countries with what may result in economic prosperity and welfare. The EU now runs its own free trade agreements which also follow suit the US model. The problem with these agreements is the requirements for the developing country have to comply with in order to prove economic readiness for the developed country. A new type of obligations and strict measures on intellectual property protection resulted from such negotiations when the US and EU try to protect the interests of their corporates by requesting inclusion of highly restrictive intellectual property protection articles in the agreement annexes or what is called *TRIPS plus*. Egypt has gone through FTA negotiations with the US during the time of Rashid Mohamed Rashid ²⁵in 2005 but never commenced due to resistance from the Egyptian side. The Egyptian Government signed only one FTA with the European Free Trade Association countries (EFTA) in 2006. The negotiation rounds

²⁴ http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm

²⁵ Minister of Trade in Ahmed Nazif government

included pressures from the Swiss side on Egypt to include an annex that including TRIPS plus articles. The annex would have included articles on granting extensions on patents for more than 20 years, patenting enantiomers or same form of the drug with different stereotyped and for different indication of the same molecule. Egypt signed the agreement with EFT countries without signing on the TRIPS plus annex on pharmaceuticals with the current head of the Egyptian patent office heading the Egyptian delegation's final rounds of negotiations. One of the major TRIPS plus requirements is what is called Data exclusivity (DE). DE in a nutshell is the preventing the generic or biosimilar producer from utilizing or referring to the safety and efficacy data from the animal and clinical studies conducted by the reference product or innovator.

Development of one new molecule may cost a company around 1 billion USD in research, high throughput screening, identification of potential leads and then trying these leads in animals, going to Phase I, II and III clinical trials in humans. The concept of a chemical generic or a biosimilar that provide a cheaper alternative and relies on the innovator's clinical and non-clinical data in safety and efficacy profiles the cost is reduced to 2-3 million USD in Generics and 75-250 million during a 7-8 years' time in case of biosimilars (Sandoz, 2013). In case this safety and efficacy data can't be utilized, this will hamper the development of cheaper alternatives –after- patent expiry and creates a backdoor for patent extension. Currently the US grants 5 years DE while Europe grants 11 years DE. The Egyptian patent law currently includes no articles or provisions on data exclusivity however article **56-60** details the protection measures for undisclosed information or confidential information of commercial value.

The law provides a maximum of 5 years protection to such information or until they are no longer of commercial value whichever comes sooner. It also provides a window to the protection of public interest when it mentions in article 56 of the same law that in case the government find disclosure of such information is in favor of protection of public interest this is not considered infringement of the patent's rights. The case of Biosimilars although the head to head clinical comparability may reduce the amount of clinical data dependence on originator the earlier stages of non-clinical testing to generate safety data requires access to no-

clinical and animal studies by the reference product (originator) for safety proof of concept.

D. Data censorship and concerns of Public safety

Another reason it is important data exclusivity may jeopardize public interest is the safety of the product. For the past few years several products has been in the market for many years and suddenly withdrawn by their companies at the end of their life cycle due to reports on possible life threatening side effects. Examples of this are Vioxx™ of Merck &Co and Avandia™ of Glaxo Smith Kline (GSK). Regulatory authorities like the US FDA and EMA have fallen under public scrutiny because the question then was if these products have been stringently assessed by such well-resourced regulatory authorities how come such fatal side effects were not reported in the data submitted by the companies at the time of registration.

Since November 2010, the EMA has released nearly 2 million pages of detailed clinical trial information - an approach it says reflects growing public demands for more openness to ensure that drug makers cannot conceal adverse drug effects. The EMA said it intended to appeal the interim ruling by the European Union's general court preventing it from releasing documents until a final decision is given. The EMA plans to step up transparency further by establishing a process for the release of full clinical trial data, which will come into force on January 1, 2014."The European Medicines Agency is committed to proactive publication of clinical trial data, once the marketing-authorization process has ended. We are not here to decide if we publish clinical trial data, but how," said Mario Rasi EMA Director General. (Bryant, 2013).

Chapter 5: Discussion and Analytical findings

I. Possible Market Failures as a result of the current Government regulation of the Biopharmaceutical sector in Egypt:

In perfect markets the allocation of resources is done in a way that maximizes the welfare of citizens, to ensure goods and services that consumers demand are produced efficiently and to encourage innovation and broader consumer choice. Market failures mean a situation when a market is left to itself and doesn't allocate resources efficiently, and where such situation exists there is potential for government to intervene to improve outcomes for business, environment, community and the economy (New South Wales Government, 2012). Different types of market failures exist including positive and negative externalities, free riding on public goods, market powers (monopoly, oligopoly) and information asymmetry. Sometimes when governments intervene to regulate a sector, market failures arise as a result of such government intervention, leading to what is called government regulatory failures. Nevertheless just like medicines every regulation has its side effect. Market gains have to be weighed against Market failures to examine the cost benefit ratio and when Government intervenes it should be according to regulations to avoid using public office for personal gains. Research findings from the interviews with the experts on the three independent variables, (registration process of biosimilars, pricing policy and intellectual property regime in Egypt) were analyzed. The below section is on the possible failures which may arise from government regulation of Biosimilars. Studying possible failures arising from government regulations is significant because not only it reduce the markets efficiency and public welfare but also it leads to loss of public trust , public scrutiny and political unrest.

A. Externalities:

May be positive or negative and in case positive it represents an external benefit and in case of negative it represents an external cost. In the case of regulations of biopharmaceutical sector in Egypt regulations did not exist until 2009. More than 50 locally produced biological products (aside from vaccines, plasma derivatives and blood products) hit the Egyptian market, some of which are biosimilars some are standalone the common thing among them is that they were registered and currently in the market without adequate proof of quality, safety and efficacy according to international standards or the standards of developed regulatory agencies of the International Conference on Harmonization (ICH) to regulate biosimilars. Absence of the required regulations (the current guidelines for biosimilars are still in draft format) resulted in negative externalities when companies producing biosimilars or biologicals of the same therapeutic category using different processes , expression system or formulation techniques (standalone) take advantage of the regulations' absence and register their products as generics "chemical generics" following a *legally legitimate*. The regulatory requirements until the 2009 decree didn't oblige manufacturers to provide the required quality, safety and efficacy data relevant for registration of a product from a biological origin or do the comparability exercise on quality, safety and efficacy. The only requirements was to conduct what is called a bioequivalence study (testing the medicines in a small number of volunteers for a short period of time) .The main external cost on the society (externality) is the risk of public health compromise from these products which we can't be judged as of lower quality, safety or efficacy than their reference products but there is a potential that such incomplete regulatory requirements may pose specific risks:

➤ **Efficacy risk**

The current biosimilars in the Egyptian market didn't provide enough data as currently required by the draft biosimilars guidelines prepared by CAPA. Data needed was head to head comparability exercise with the reference product efficacy. Doing a bioequivalence study doesn't provide such evidence.

➤ **Safety Risk**

Culture of reporting adverse drug events is still in its early stages (The EPVC only started in 2010) with the Egyptian pharmacovigilance center doing a lot of efforts to stimulate a reporting culture among health care professionals and users of medicines. So even if there is a risk management plan for these companies and a pharmacovigilance officer in charge as the demand side the supply side (being the consumers and healthcare professionals) has a long way to go. Currently the center has around 400 reports on adverse events from the whole of Egypt and no restriction was issued on any biological product as from 2010-2012²⁶(EPVC, 2013).

➤ **Economic risk**

Such products are although of lower cost than originators they used for the treatment of complex or life threatening diseases such as hormonal deficiencies, liver inflammation and cancers. Such diseases require long terms treatment courses , if the quality, safety and efficacy of such products are not properly assessed they may lead to prolonged illness and with the current out of pocket payment on health according to WHO is standing at around 50% in Egypt²⁷ they may incur catastrophic expenditure to cover a single treatment course.

One case which is worth presenting is the case of the pegylated interferon alpha – 2 a used for the treatment of hepatitis C virus induced liver inflammation. The case directly touches upon the research dimensions. It is however worth noting that the objective of using this case is not to prove or disprove the government decision on registering the Egyptian interferon in 2004 and including it under the health insurance reimbursement list. Having the chance through this research to interview senior level executives from the producing firms, some clinicians and

²⁶ <http://www.epvc.gov.eg/NewsAttachments/Restrictions%20and%20Withdrawals.pdf>

²⁷ WHO National Health Accounts estimate the expenditure on medicines in Egypt in 2008 to be between 60% from total health expenditure

government regulators provided a chance to analyze the situation and suggest what would be a possible way forward for this dilemma.

The case of the Egyptian Interferon Market Authorization

i. Hepatitis C virus in Egypt: Public Policy relevance of the problem:

Globally, approximately 150 million people are infected with hepatitis C (HCV) and it is estimated that 350,000 people die each year from HCV-related liver disease (WHO, 2012). Egypt has among the highest rates of HCV in the world at 22% (Wiktor, S., 2013), meaning almost one in every 4.5 people may be infected with hepatitis C virus in Egypt's population of around 90 million people. In some studies it was mentioned that 500,000 new cases of hepatitis C virus are reported every year (WHO GAR, 2009). These figures are alarming and should be taken seriously by the post-revolutionary government of Egypt. The public policy relevance of the problem is hence, unquestionable, government and politicians should design and implement policies to combat such diseases that are evidence based and which would achieve the target objectives set to develop the country.

ii. Socioeconomic impact of the problem:

The effects of such disease burden are immense in terms of the economic power wasted via lost working days, workforce, hospitalizations and unnecessary expansion of healthcare budget. The treatment costs are increasingly posing a problem in countries like Egypt where until this moment there is no clear public health insurance policy communicated by the government. The health insurance system set up by the government in mid-nineties proved unsuccessful in terms of equity (leaving out agriculture workers and other workers in the informal sector) and quality of service rendering many beneficiaries unsatisfied. The government in 2009-2010 began to develop a draft law for health insurance that would achieve the principles of universal health coverage based on equity and health as a human right principle. Therapy for hepatitis C is extremely expensive, making it largely unaffordable. The availability of full or part government funding for treatment of hepatitis C depends heavily on the income status of a country: such funding is available in 83% of high income, 77% of middle income, and 33% of low income countries respectively (MSF Access Campaign, 2013). The above situation has very

much affected ability to access medicines in the country. In the case of hepatitis C treatment the treatment options were all imported as it remained under the patent so no cheaper versions were available.

iii. Hepatitis C Virus Induced Liver Inflammation treatment:

The treatment of hepatitis C virus have developed along the course of years since its discovery in 1989 into complex protein based molecules that are able to stimulate the immune system to attack the virus while at the same time be more selective and thus reduce the treatment course side effects. The current treatment of choice for the virus is called (Pegylated interferon alpha 2 –a or b). The product has been produced globally by two companies Roche from Switzerland and Schering Plough from the USA (now part of Merck pharmaceuticals global). Until 2004 there were no medicines within the biosimilar/standalone for hepatitis C treatment in the Egyptian Market until a joint venture between a German biotechnology company namely “Rhein biogenetics” and an Egyptian company “Mina Pharm” managed to produce the pegylated interferon for the treatment of hepatitis C and registered it in the Egyptian Ministry of Health. The product named (reiferon retard) was priced at a third of the two other competitors, The rationale for treatment of chronic hepatitis is to reduce inflammation, prevent progression to fibrosis, cirrhosis, and finally hepatocellular carcinoma (cancer of liver cells) through the eradication of the virus in chronically infected patients.

iv. Addition of polyethylene glycol (PEG) moiety to protein may result in:

- Prolonged plasma half-life
- Reduced clearance
- Less immunogenicity

v. Characteristics of pegylated proteins depend on:

- Structure of PEG moiety (e.g., size, branching, linkage bond strength)
- Site(s) of attachment to parent compound

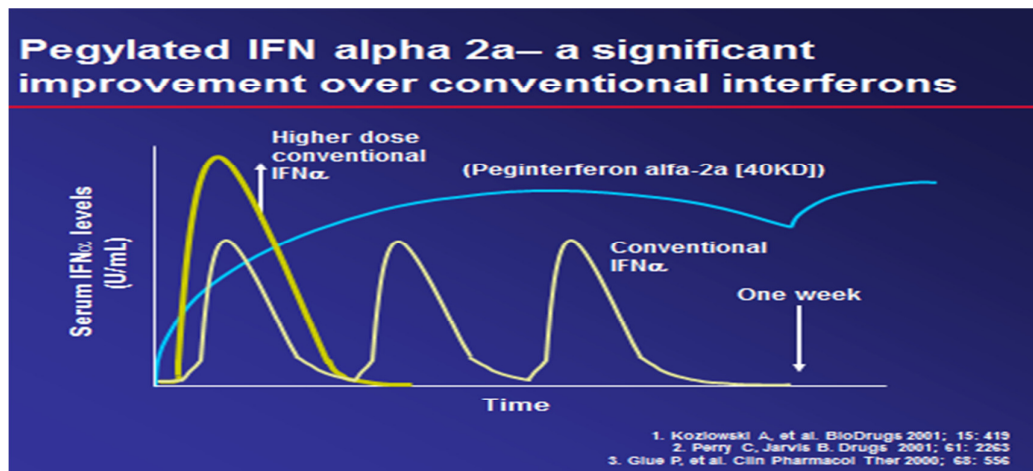


Figure 15: comparison between effects of different IFN type's overtime²⁸

vi. The EASL Clinical Practice Guideline on Management of hepatitis C virus infection:

- The combination of pegylated IFN-a and ribavirin is the approved Standard of Care (SoC) for chronic hepatitis C.
- Two pegylated IFN-a molecules, pegylated IFN-a2a (180 µg once per week) and pegylated IFN-a2b (1.5 µg/kg once per week), can be used in combination with ribavirin²⁹.
- No other types or Pegylated Interferon are mentioned in the international practice guidelines

vii. The debate on interferon's for treatment of hepatitis C patients in Egypt:

There is a heated debate that started in 2011 on the Egyptian interferon in Egypt with two points of view one advocating to withdraw the product until further assessment based on the right regulations to ensure safety, efficacy and quality and the other is pro the product as it provides a safe haven for the government to provide low cost treatment for a growing number of hepatitis C patients and it proved effective in maintaining a Sustained Virological Response (SVR).

The Egyptian interferon is also a new window for local production of biological products using technology transfer. The Egyptian government was and is still facing a challenge to provide affordable treatment to HCV patients using the

²⁸ PowerPoint presentation by Roche Egypt Medical department

²⁹ http://www.who.int/selection_medicines/committees/expert/19/applications/Pegyinterferon_6_4_3_A_Ad.pdf

treatments for HCV, due to budget constraints. The current annual MOH procurement value for pegylated interferon is almost 3 million Egyptian pounds from the Egyptian interferon excluding the health insurance procurement tender value which represents as quoted from an ex CAPA director “a total of 700 million EGP” for hepatitis C treatment in Egypt. The value for treatment of hepatitis C allocated by the government through MOH, liver institutes and the Health Insurance Organization tenders is 25% of the total annual budget available for procurement of all types of medicines by the MOH (2011-2012 tender value stood at 2.8 billion Egyptian pounds)³⁰.

The decision to register Reiferon retard relieved such high burden from a price of more than 1000 EGP for one prefilled injection to be used for a 48 treatment course to 217 EGP for the Reiferon retard representing 1/5th of the originator’s price at that time. However the price of 1000 EGP was in private sector (retail pharmacies) and a series of negotiations between the producing company (Roche) and the government resulted in a lower price of 250 Egyptian pounds for the Swiss interferon imported as bulk , only labeled and undergoes secondary packaging in an Egyptian manufacturer named *Memphis pharma* (new trade name *Pegferon*). The agreement with the government encouraged the inclusion of the Roche’s product in the MOH tender however the health insurance organization didn’t approve Pegferon’s inclusion in its reimbursement list. As per Roche: a request was done to establish a record for patients receiving/reimbursed for pegylated interferon from the health insurance to monitor their SVR and clinical success rate but it was rejected by the health insurance organization and no reason was given for this refusal.

³⁰ Total Pharmaceutical Expenditure in 2008 stood at 8.3 billion EGP as per the last round of National Health Accounts in Egypt

viii. The Argument of Roche Producer of the originator PEG-IFN (Pegasys™):

As a research based company that invests in high risk research to produce innovative medicines, the company was not in favor of a competitive product to take part of its market share. The WHO 19th expert committee for selection and use of essential medicines received a request in 2013 for inclusion of the pegylated interferon alpha-2-a and b on its essential medicines list³¹. The application included that there are currently few biosimilars however none are registered in a stringent regulatory authority of ICH country and due the absence of a WHO prequalification system for such products it is very hard to ensure there quality, safety and efficacy at an international standard (Witkor, 2013). The Roche product Pegasys when launched in Egypt was the market leader, the government had no choice of procuring it with an inelastic price demand. It was the only pegylated interferon on the health insurance list. The Egyptian interferon when introduced in 2004 raised the concerns of Roche and hence Roche started to negotiate with the government reduction in the price of its imported product that went down from 1000+ EGP→ 600+ EGP→ 400+ EGP until an agreement was reached on the second brand for Roche (local secondary packaging) and reducing the price to 250 EGP to be competitive with the Egyptian interferon.

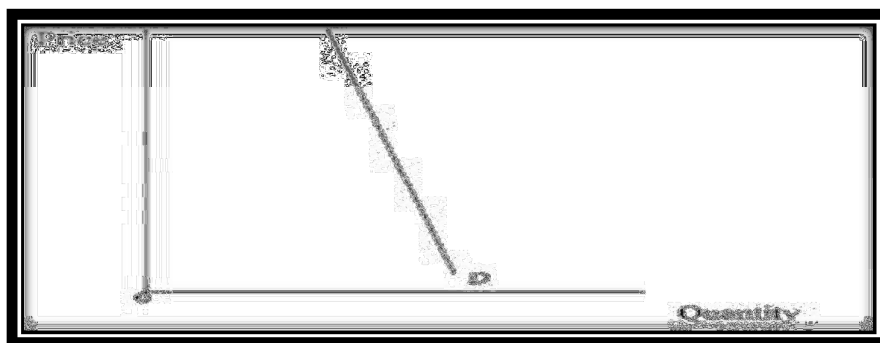


Figure 16: Egyptian Government’s demand for originator pegylated interferon (Pegasys™ from Roche) prior to registration of the Egyptian interferon (Reiferon Retard™ from Rhein Mina Pharm)

The company in parallel started to question the therapeutic value, safety and efficacy profiles of the Reiferon retard. The below table 10 compares both products.

³¹ The WHO Essential Medicines List (EML) stands as a guide for countries to select the most essential medicines in their national procurement decisions

Table 10: Summary of indicators comparing Pegasys and Reiferon Retard (Egyptian Pegylated Interferon)

| | Subject | Pegasys® | Reiferon Retard® |
|--------------------------------|--|--|---|
| Indicator | Drug Class | Biological Drug | Stand Alone Follower |
| Clinical Program | Number of trials on the clinical trial registry (clinicaltrials.gov) | Over 400 | 2 |
| | Pre-clinical safety data | present | unknown |
| | Data from Phases I, II, and III of the drug development process | Available | NA |
| | Post marketing surveillance data | Available | PV system in the company |
| Published Data | Number of published articles on patients with hepatitis c | 2145, all were published in academic journals | 2 articles published in academic journals |
| | Level of Evidence Available | Systematic Reviews, Randomized Controlled Trials, Cohort Studies | One study was Non Randomized, Open Label, Single Arm |
| Registration / Approval Status | FDA Approval Status | Approved for the management of chronic hepatitis c since 2002 | Not approved |
| | EMA Approval | Approved for the management of chronic hepatitis c since 2002 | Not approved |
| | GMP (Good Manufacturing Practice) | According to the European Commission Standards | Local facility has EDA approval and German Rhein Biogenetics has German regulatory authority approval |
| | Registration status | 51 countries | Egypt Only and currently negotiation with some other countries |

ix. The argument of Rhein-Mina Pharm producer of the Egyptian Interferon (Reiferon Retard™):

The Joint Egyptian – German venture that represents a leap in biopharmaceutical production in Egypt have a direct and straight forward argument on the allegations of its competitor. That is the product although was registered as a chemical generic it has been in the market for more than 8 years now and is proven to be effective. Evidence on this has been published in 2 clinical studies done by Egyptian clinicians on Egyptian patients of geno type -4 (special viral geno type where majority of Egyptian patients are infected with)³². The company considers the product *a Stand Alone* follower rather than a biosimilar due to the origin of the bacteria (expression system were the recombinant gene is ingested and protein is produced) is different than the originator³³ also because of the pegylation process and attachment technique are different. The product also still represents a more economic option than the Roche product.

x. Proposed way out of the dilemma:

At the time of renewal of the market authorization license (registration). Two scenarios may exist to apply the biological assessment on the Reiferon retard to ensure its quality, safety and efficacy. The decision will depend on how the Egyptian regulatory authority will define Reiferon retard. The author is of the opinion that Reiferon Retard should be treated as a Stand-alone follower and not a biosimilar due to reasons mentioned above.

³² Number of subjects in the clinical studies for Pegasys done on Egyptian patients of geno-type 4 hepatitis C virus were 140 subjects in two studies done by Thakeb et al and ANRS 1211 while two other studies by shobokshi etal and Diago etal with 60 and 49 subjects were conducted in Saudi Arabia and Germany respectively on geno type 4. 100 subjects for Reiferon retard first study done by Esmat etal : “Evaluation of a novel Pegylated-Interferon alpha 2 a (Reiferon-Retard®) in Egyptian Patients with Chronic Hepatitis C – Genotype 4” and 107 for the second study done by Taha etal , named “ efficacy and safety of the novel Pegylated-Interferon alpha 2 a (Reiferon-Retard®) in Egyptian Patients with Chronic Hepatitis C – Genotype 4”

³³ Originator uses E.coli and Reiferon Retard use Hansensula strain

➤ **Reiferon Retard as a Stand Alone:**

The product will have to provide a full dossier based on the guidelines set in decree 297 for the year 2009, including full quality CMC, safety and efficacy data. As Reiferon Retard in this case will not rely on the reference product safety and efficacy data, hence the abridged pathway of biosimilars will not apply. This situation may represent a huge investment by the manufacturer in nonclinical and clinical studies. The product is currently the only pegylated inteferon on the health insurance list and hence will cause disruption in healthcare budget if withdrawn or suspended until the new safety and efficacy studies are finished, data assessed and a decision is made. The disruption may be caused by the fact that when Roche is the sole supplier a price review may be requested which may lead to an increase in the product's price that may overburden an already exhausted medicines procurement budget. Shortages may occur and patients treated with interferon may develop a "breakthrough",³⁴ due to disruption in the treatment course (unavailability at some weeks as many patients attend to the public healthcare center weekly to get the injectable shot). To avoid such scenario the government may: A- keep Reiferon retard in the market and reimbursement list while conducting the requested studies by the government 2-In case the government decides to withdraw or suspend the market authorization until the data is supplied , the government may consider signing an agreement with Roche for supply with legally binding terms which won't allow for a price review for the period Roche's product is solely in the health insurance reimbursement list, MOH and liver institutes lists while the reiferon retard is undergoing its safety and efficacy trials. In case the Reiferon retard failed to show acceptable safety and efficacy data, the agreement may be reviewed to allow for price change based on the pre-set pricing policy of the government.

³⁴ A term given when an increase in the virus in the blood occurs during the treatment course, possibly due to interruption of the treatment course

➤ **Reiferon retard as a Biosimilar:**

1. In this situation the product will rely on Roche's Pegasys™ safety and efficacy data but will have to develop a complete comparability exercise on quality attributes including complete characterization of Reiferon Retard physiochemical, purity, structural and biological action versus Pegasys's data. In case the quality exercise shows acceptable similarity the safety and efficacy data levels will then be conducted.

In both cases depending on how developed the pharmacovigilance system of the company, the individual and periodic safety reports available (ICSR and PSUR's) on Reiferon Retard and the possible risks identified by the reference product (Pegasys) Risk Management Plan (RMP) are to be assessed. This includes Phase IV (post marketing) studies. In addition warning boxes on any possible safety issues may be added to the package and package insert to further minimize the risks.

B. Information Asymmetry and potential hampering of competition: The “Box” system in the market authorization process:

The first step in the registration process of any medicines in Egypt is an application for checking if there is an empty slot in the 12 available slots of the “Similar Box”. The box system as it stands is the tap which control how many similar versions of the same medicines the government is authorizing for marketing in the national market.

Currently it allows the first originator product and then 11 generics one imported and the 10 has to be locally manufactured to encourage local manufacturing in Egypt. In case of products produced using advanced technology like rDNA and other Biotechnology techniques, the current situation is 1 originator and 5 imported and 6 locally manufactured. Reasons being , these products are produced by 10-14 local manufacturers which are still developing limited capacity in terms of technology development or transfer. Since the market needs are much higher than local supply a wider importation window was set at 5 biosimilars or biogenerics. The box system was heavily criticized from many of my interviewees as its only merit is that it reduces the work burden on CAPA because it limits the number of application from a specific class of products and hence the number of required quality, safety and efficacy assessments needed to be done by the government agency.

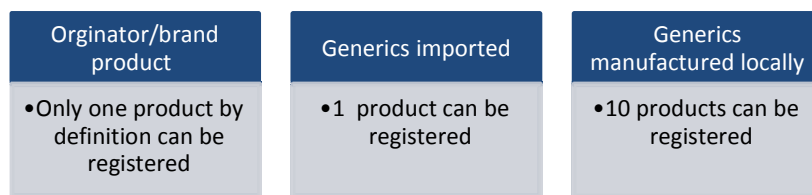


Figure 17: Box System for Generic medicines Market Authorization Application in Egypt



Figure 18: Box System for Biosimilars Market Authorization Application in Egypt

The main regulatory failure that might arise from this system is lack of transparency and inefficiency in this system that may lead to anticompetitive behavior, imperfect competition and increase the potential for lower quality products. To elaborate more the below examples are given:

- i. **Scenario 1:** *Company A* has sent an application to CAPA for inquiry on availability of a slot in the “similar box” the box had 2 slots empty and *Company A* was informed by CAPA on the availability of a slot for registration of company A’s biosimilar. *Company A* owner also owner of another company named *Company B* which produces the same biosimilar under another trade name and in another facility. The owner of *Company A* knows someone in CAPA who has access to the “similar box” and can pass through the information about the availability of a final slot for this product. Meanwhile *Company C* which is a local manufacturer wants to invest in this area and now wanting to apply for registration of the product a 3rd biosimilar of the same product. The owner of *Company A and B* knew about the plans of *Company C* and want to deter such potential competition so he applies for the final slot under *Company B* due to his access to the censored Box data. Now the box of similar is full and blocked the registration of *Company C*. *Company C* applied *only one day after* *Company B* occupied the last empty slot in the box and inquired about the availability and received a negative reply that the box is full and he has to park his application on a waiting list until a slot is empty. This hypothetical scenario may or may not happen in reality. The importance of a system which is available in the public domain may reduce the vulnerability of

such anticompetitive practices. An online system displaying the situation of slots for each product without mentioning the names of the applying companies to keep commercial confidentiality is an option CAPA may want to take in to consideration.

- ii. Scenario 2:** Under the newly proposed draft guidelines for biosimilars in Egypt - explained in the data analysis section- a company after occupying a place in one of the eleven slots available in the box (5 imported-6 locally manufactured) has 3 years to complete its studies and then the studies are assessed for an acceptance/rejection decision. This implies that for the companies that the faster you apply the less risk you face because you won't lose anything by occupying a slot in the box system and blocking others and in case study results reveals positive the company may continue in its application and if failed its occupation to the slot in the box did not cost it anything aside from the registration fees³⁵. The inefficiency arises from the fact that this area of biosimilars is an area where Egypt needs to start promoting local investment and manufacturing to strengthen access to these affordable medicines. Now back to example 1 in case the last two slots available are being competed against with three companies **A, B and C. Company A and B** applied before company C which has a much more success prospects and stronger profile in terms of quality (already exporting to US and Europe from the same facility) and investment capital than **company A or B. Company A and B** spent 2 years generating their quality and safety data and only company A's biosimilar showed positive similarity profile of quality, safety and efficacy while company B's biosimilar had serious safety issues with few patients developing immunogenetic reactions during immunogenicity study. Company B's product was rejected and now a slot is open company C can now apply but after 2 years lag time were the investor (company C owner) changed his mind about investing in biosimilars as the current regulations is not encouraging investors by limiting the number of applicants to marketing authorization.

³⁵ Currently set at 100 EGP for local manufacturer

iii. Information asymmetry and its effect on product quality: The issue of lack of transparency and asymmetric information has a significant effect on product's quality. There is always a probability that some very good players who can produce quality products are present yet not knowing this information and hence the consumer is affected because the information is distributed in a manner where not all potential players are informed and hence the probability of missing the best quality products remains a significant result of information asymmetry.

iv. Possible solution:

CAPA may consider removing the Box system for Biosimilars/biopharmaceuticals due to the following reasons:

1. It limits competition which increases supply and may reduce prices leading to improved access
2. It is not encouraging local investors in an area Egypt has to focus its efforts to promote local investment and attract foreign direct investment

v. *The box system may be a funding source to build inspector's capacity*

The main argument of the government is that “*if we open the box with no cap or limit we will get until may be 55 generics or similar of the same medicine*” (quoting one of my interviewees from CAPA). Each generic follows a 10 % decrease in price than the previous one. The argument is that the 13th or 14th generic with the presumably very low market price given to the company in order to compromise that low price versus costs, the company will be manufacturing using raw material and active ingredients imported from a manufacturer of unacceptable quality standards. The argument is easily refuted that CAPA may conduct Good Manufacturing Practices (GMP) Inspection Audits to the Active Ingredient (Drug Substance) manufacturer usually in India and China (representing 80% of global supply) to assess their level of GMP compliance.

vi. To make use of the potential missing opportunity

The other argument is that the current inspector's capacity can't inspect Active substance producer and can only inspect finished product producer (FPP). If the box system is to continue, the government may consider opening extra slots with a higher registration fee that is pooled in a fund for regulatory capacity building to train CAPA inspectors on auditing Active Ingredient Manufacturers and hence developing an asset that may remain in house for years and can later transfer the knowledge to others, while increasing competition, reducing price, improving access without compromising on quality. Meanwhile regulatory collaboration paying a nominal fee outsourcing or semi-sourcing out the assessment of the active ingredient's master file or its GMP inspection with a more developed regulatory authority like in Saudi Arabia or Jordan or making use of other bilateral or multilateral agencies like WHO, US FDA or EMA can ensure the quality of the products and serve to transfer knowledge between the Egyptian authority and more developed regulatory systems.

C. Collective action groups (The pharmacist's syndicate versus the Industry chamber): politicization of regulations: the new medicines pricing decree (499/2012)

The latest pricing decree which was out in June 2012 created a wide hype among stakeholders in the healthcare sector. Price being a major driver for patient's access should be fair to all parties involved producer, user and payer. The pricing law as explained in the data analysis section changed the profit margins for pharmacists to be one of the highest in the region. A comparative table below shows the profit margins prior to the 499 decree, post the decree in Egypt compared to margins in wealthy countries such as Saudi Arabia and UAE.

Table 11: Comparison between average profit margins for retail pharmacist across Egypt, UAE and Saudi Arabia³⁶

| Margin for beneficiary per country | Retail pharmacist profit margin in (314/1991) and (373/2009) decrees | Retail pharmacist profit margin in Egypt (499/2012) decree | Retail pharmacist profit margin in UAE (decree 834/2008) ³⁷ | Retail pharmacist profit margin in KSA (Saudi Pricing Policy) |
|--|--|--|--|---|
| For imported products | 10-12% | 20.7% | 19.75 % | 15% ³⁸ |
| locally produced, filled or packaged and labeled (Bulk) products | 18-20% | 21.6% | 21% | 15% |

➤ *Advantages of the new pricing decree 499/2012*

Aside from being favored by all retail pharmacists and owners of retail pharmacies, the new decree has a public health advantage by setting a cap of 450 EGP in profit margin for the retail pharmacist which is exercised by deducting the difference from consumer's price for the benefit of patient. So in case a product is proposed for the pricing committee as 3500 EGP consumer price setting the retail pharmacist's margin at 525 EGP. The consumer price is deducted till it reaches the 450 EGP maximum which translates to 3000 EGP patient's price making a 500 EGP deduction from consumer's price. However this is only applicable for imported medicines more than 500 EGP.

³⁶ Margins were listed in different countries legal documents as % of different prices (distributor's price or CIF/ex-factory price) and expressed for different categories (imported/local, chronic medicines/antibiotics, etc...). For comparison purpose: The proposed table rounded all figures to one denominator (retail pharmacist margin as % of distributor's price)

³⁷ <http://www.tamimi.com/en/publication/publications/section-3/june/prices-discounts-on-drugs.html>

³⁸ The tier System in Saudi Arabia Pharmacy Profit for local products (SR50 or less 20% , Greater than SR50 – SR200 15% , More than SR200 10%): <http://212.100.220.58/NR/rdonlyres/DE3C597F-9499-47D5-9A32-1D6E82AF0152/0/SaudiPricingGuidelinesandTheProposedNewSystem.pdf>

➤ **Disadvantages of the new pricing decree:**

1. Increasing barriers for investment in local production of biosimilars:

The new decree was faced by a huge hype from the manufacturer's side especially local manufacturers because the increase in the retail pharmacist profit margin was cut from the manufacturer's margin. The syndicate of pharmacists was the main lobbying body behind this decree. The syndicate lobbied the minister of health Dr. Fouad Al Nawawi and provided reports showing that manufacturing companies in Egypt achieve profits between 20-30% according to the manufacturer's reports in the stock markets. The retail pharmacists are facing increasing prices of all other basic commodities in Egypt and their salaries are low due to the very low profit margins given under the previous law. Manufacturers on the other hand disagree with this and interviewing a senior executive of the industry chamber he mentioned that with the current spike in USD dollars exchange rate many - quoting him *"Devaluation reached 30% and they are getting the USD for 8.30 EGP from the black market"* - manufacturers now are facing a problem that they are not able to achieve "break-even" for many of their products leading them to either stop its production as they are losing or not abiding by the new decree by continuing with the old system . This lead the MOH to send inspectors for the first time to check manufacturers compliance and auditing price receipts selling to distributors and retail pharmacies. The production of biosimilars is a complex process compared to production of generics in terms of the time needed (2-5 years), risk imposed (variable behavior among batches may lead to rejection of batches and loss of money), monetary investment (number of studies needed and comparability exercise with reference product). Such decree will not encourage local producers to continue investing in these life-saving drugs and critical industry, they will rather shift to less risky and easier business to generate quick profits. The decree has to create balance and deal with the biopharmaceutical industry outside the scope of such decree to provide and advantage of producers in this area.

2. The decree doesn't provide pricing incentive for improving quality:

In the pre revolution decree of Hatem El Gabaly the decree provided 10% preferential pricing incentive for generics produced in manufacturing facilities which passed the quality inspections (GMP, etc..) of the US FDA, European Medicines Agency (EMA), Japan or WHO or any other country member in the ICH consortium. The new decree didn't mention anything on this article and cancelled the old decree hence cancelled this 10% preferential pricing for manufacturers who provide evidence for quality operations meeting international standards. The decree however mentioned the biosimilars (referred to in the decree as hi tech generics) imported from ICH countries will get a 35% reduction while those imported from non-reference will get 40% reduction in price than originator. The decree didn't mention about locally manufactured , in case assuming the high tech locally manufactured are equivalent to the non-reference countries imported the price incentive will still be less than the 373 decree standing at 65% of the originator's price while the 373 decree provided a 70% of the originator's price, difference of 5%.

3. Distribution of pharmacist profit margin is not encouraging local production of essential medicines:

Essential medicine list includes the medicines which are based on national public health needs representing the public health needs for the majority of the population. These medicines are crucial to be present in all public health facilities at least. The profit from locally produced was deducted by 7-12% from manufacturer to retail pharmacist. For essential medicines products which are crucial for the majority of the population the profit margin of the manufacturer was reduced between 5-15% to the retail pharmacist.

Table 12: Decree 499/2012 retail pharmacy and manufacturer’s profit margin distribution for locally manufactured products

| Production type | Manufacturer’s margin | Retail pharmacist’s margin |
|---|------------------------------|--|
| locally produced, filled or packaged and labeled (Bulk) products outside the essential medicines list | 25% | 30% (encouraging for pharmacist but not good for manufacturers) |
| Products from the National Essential Medicines local or imported) | 15% (not encouraging) | 25% (encouraging for dispensing and discouraging for production) increase over the previous by 7% so may negatively affect production of Essential medicines |

4. Shortages in medicines as a result of the 499/2012 pricing decree:

The government is currently facing implications of the latest pricing decree as more than 500 types of medicines are in shortage due to various reasons. CAPA setup a medicines shortage unit in order to respond to such crisis, with the objective of investigating and reporting medicines shortages and its reasons and facilitating possible solutions. Quoting one of my interviewees working for the drug shortage unit in CAPA *“around 25% of drug shortages can be attributed to the new pricing decree. We conduct interviews with manufacturers who stopped producing the medicines in short and many of which relate such stoppage to the impossibility of reaching breakeven with the new pricing decree”*. From the biopharmaceutical/biosimilars which faced shortage as a result of the current pricing decree is Human chorionic gonadotropin hormone produced by EIPICO which is the sole producer. The other categories included almost all categories of medicines with varying shortage levels. Figure (19) shows the reasons for shortage as reported by the medicines shortage unit in CAPA.

Reason for Shortages Statistics from the monthly drug shortages report by CAPA (Feb 2012)

- Low price (new pricing decree)
- export oriented manufacturer(priority to export markets)
- sole manufacturer's drug product
- closed production line
- Financial problems
- Unexpected Increases in Demand and late NODCAR report
- late re-registration or variation problems
- import approvals delay

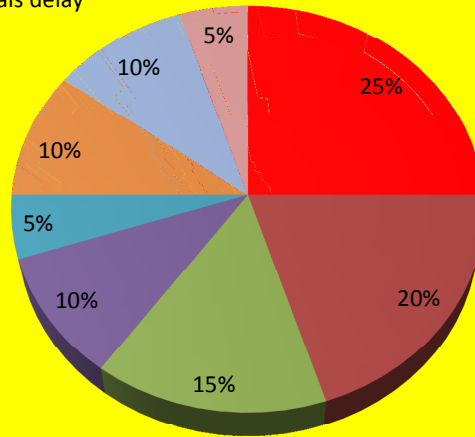
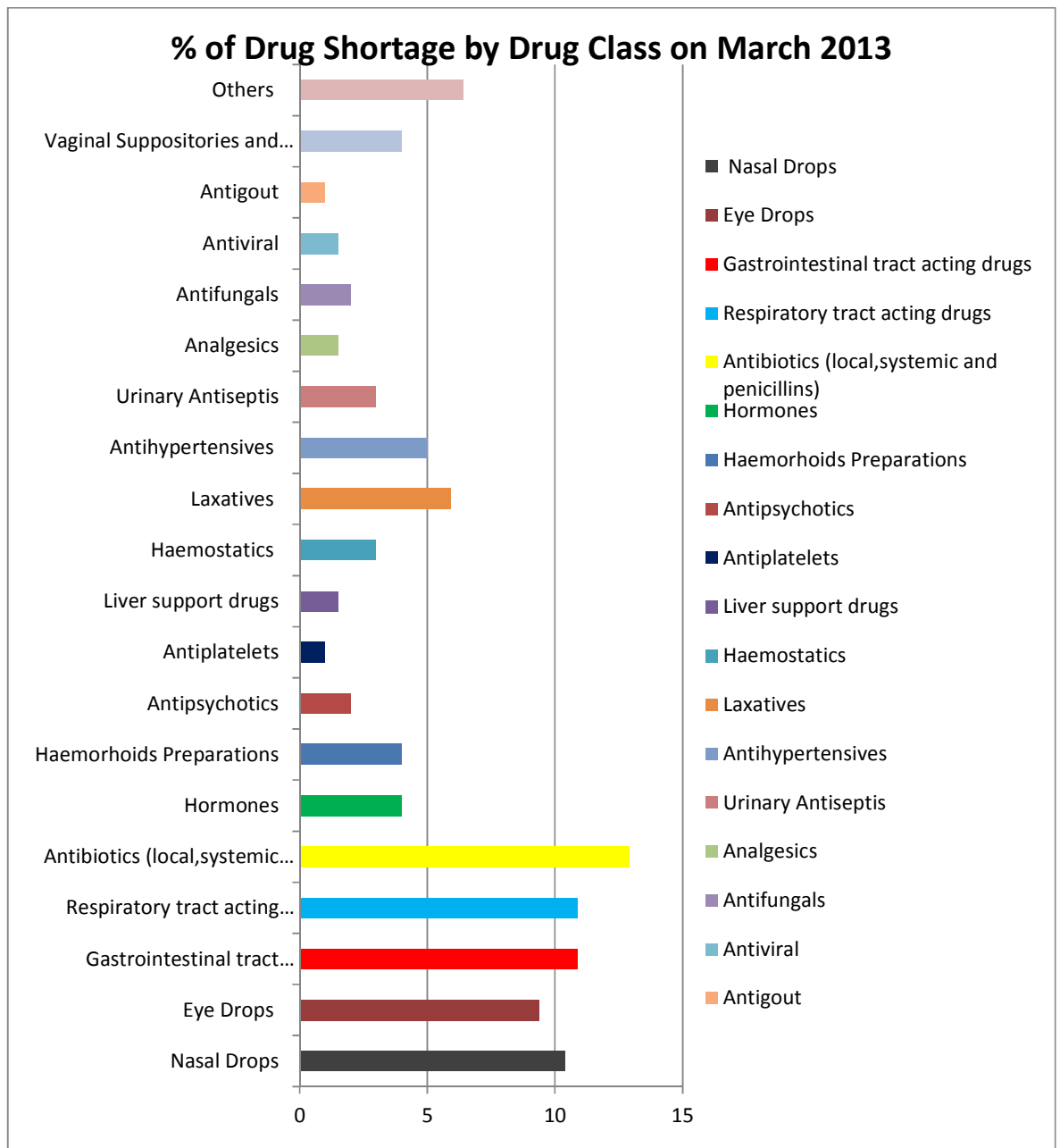


Figure 19: Reasons for medicines shortage as reported by the Drug Shortage Unit in CAPA



**Figure 20 Medicines Shortages during the month of March 2013 in Egypt -
Drug Shortage Unit -CAPA**

Several meetings took place between the two lobbying bodies and the regulatory body (CAPA/MOH) to reach a consensus. The presidential authority realizing the size and magnitude of the problem ordered the central bank to instruct local public and private banks to provide hard currency (USD) to pharmaceutical industry needs and to facilitate the importation process of raw materials.

The government also is trying to respond to the shortages of life saving medicines by opening the box for registration of these medicines and providing facilitated importation and fast track registration procedure for such medicines.

This may solve the problem in short term however on long run, the local production may be negatively affected. Putting in to consideration that local production in Egypt depends on 130 manufacturers which supply the market with 82% of its needs , quoting a senior executive in the Egyptian pharmaceutical industry chamber *"56% of needs are produced by multinationals -18% of which are imported and 38% locally produced, 4% from holding companies or government companies the rest 40% come from private local manufacturer"* is facing significant losses while the government become more and more dependent on imported products. From these 130 only 10 are producing biotechnology based biopharmaceuticals between 30-40 products (including heparins, epoetins, insulins, hormones, GSF'S, interferons, etc..) are currently registered or under registration from a total of 344 registered biopharmaceuticals representing between 10%-12% of market needs.

The pricing decree until these lines is under discussion by various stakeholders within CAPA including the pricing committee with the possibility of reviewing it to stop the current problems to increase the number of local manufacturers focused on this area.

Table 13: Table 13: Local producers of biosimilars in Egypt and their area of production focus

| Manufacturer's name | Area of biopharmaceutical/ biosimilar production (including bulk filling , labeling and packaging final bulk) focus |
|--|---|
| 1. (EGYVAC) and affiliated company of the Holding Company for Biological Products and Vaccines (VACSERA) | <i>Vaccines, Insulin, antitoxins, antivenoms, urokinase</i> |
| 2. Egyptian International Pharmaceutical Industries Co. (EIPICO) | <i>Human Growth Hormones, menopausal chorionic gonadotropin (FSH+LH),erythropoietin</i> |
| 3. Rhein Minapharm Co. | <i>r DNA technology producing: Pegylated Interferons, anti inflammatory proteins, Human Pituitary hormones</i> |
| 4. Sedico | <i>Insulins, streptokinase, urokinase,filgrastim</i> |
| 5. Eli Lilly/Egypt | <i>Insulins</i> |
| 6. ACAPI | <i>Interferon alfa</i> |
| 7. El-Nile Co. | <i>Erythropoietin, interferon alpha-2a,2-b,granulocyte colony stimulating factor(G-CSF), Human Chorionic Gonadotropin</i> |
| 8. CID | <i>Heparin</i> |
| 9. Amoun | <i>Erythropeitin,heparin,</i> |
| 10. Otsuka | <i>Interferon Alfa</i> |
| 11. ACDIMA | <i>Interferon Alpha-2a, Streptokinase</i> |
| 12. Amriya | <i>Fellotropin, HCGonadotropin,Human menopausal Gonadotropin (HMG)</i> |
| 13. Marcyrl | <i>Urofollitropin (FSH)</i> |
| 14. Alexandria | <i>Heparin</i> |

Reflections on the rent seeking behavior and public choice theory in relation to the latest pricing decree 499/2012:

Nobel Prize winning economist Michel Buchnan sat the foundation of the Public choice theory and its players. The idea in a nutshell is that elected government politicians, government officials are taking their decisions which may affect the public based on several other factors than the public's interests amongst is the pressure from lobby groups and special interest groups who may be rent seeking trying to shape the regulatory framework to benefit their own interests. In other words, public choice is an application of neoclassical economic tools (self-interest and utility maximization) to explain political behavior (P.O.Lee, n.d).

A. The stakeholders of the public choice theory: has been exemplary fitting in the pricing decree 499/2012: 1) Government represented by the Minister of health 2) special interest group represented by the syndicate of pharmacists and The pharmaceutical industry chamber which is another special interest group seeking rent 3)the patients access to medicines is the public interest.

B. Analysis of the dynamics between the latest medicine pricing decree stakeholders: The new pricing decree came up after almost one and half year of the revolution, the economic situation was getting worse due to the post revolution economic recovery phase, military rule and lack of interest from foreign direct investors in Egypt. The freedom and justice party won majority of the parliament which was later dissolved and majority of the seats on executive boards of most professional syndicates. The Syndicate of pharmacists was no difference with a board composed of almost 85% from the FJP³⁹. The programme of the syndicate promised the long sought after request of increasing profit margins for pharmacists to improve their economic standards being one of the highest educated/respected strata in the Egyptian society. Many youth groups within the syndicate waived to the syndicates that in case promises made weren't fulfilled the current board will be thrown away in the buildup of the post-revolutionary *Categorical demands* hype made by several professional sects including (doctors, teachers, transportation authority workers, etc...). The situation in Egypt was absolutely far away from bearing any policy that would increase medicine prices on consumers (i.e.: patients). The presidency elections were ongoing and a FJP candidate has a 50% chances for

³⁹ Voting majority

winning so the other player represented by the Minister of health was also seeking self-interests in remaining in the post elections government (reason for such assumption is that the decree was signed after the presidency elections were announced by the winning of the FJP candidate-current president of Egypt – Dr. Mohamed Morsi). The decree unfortunately was not well received by the manufacturing sector and the industry lobby reacted aggressively by not abiding by the decree and by stopping the production for some essential medicines also seeking their self-interests trying to pressure the new government to change the law to the old margins or increase prices. Unfortunately the public interest was not taken into consideration where patients are now suffering shortage in accessing some medicines and in the near future the industrial capacity of Egypt in this strategic sector may be jeopardized due to many manufacturers stopping production, selling their facilities or production lines and facing financial difficulties.

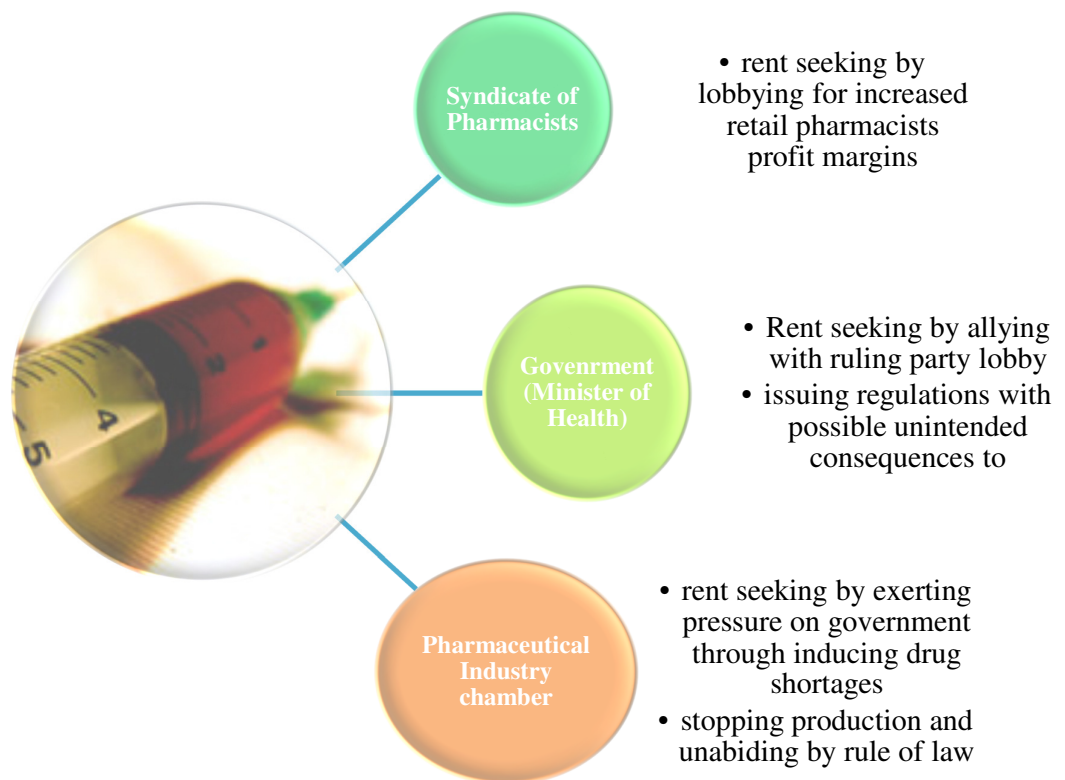


Figure 21: Dynamics of Public choice theory in Egypt's medicines pricing decree

Photo credits: policyinnovations.org

Chapter 6: Conclusion and Policy

Options:

This study aimed at examining the current regulatory policy in Egypt pertaining to regulation of the biopharmaceutical sector and with emphasize on the regulations of biosimilars as a key component of this sector. The government regulatory interventions are usually in place to dispel market inefficiencies, failures and restores balance. Despite being a highly regulated sector little attention is given to studying the government interventions and possible failures of such interventions in the medicines sector in general and the biopharmaceutical sector in particular.

The government of Egypt is faced with a challenge to regulate biosimilars after many of which have been approved in the country as generics and thus not following international standards in assessment of the QSE of such critical lifesaving products. Legislative and regulatory gaps exist on how to deal with this negative externality of similar copies of biologicals which has been registered prior to the 2009 decree as chemical medicines and being marketed freely. The process of registration itself proved to have potential for improvement in terms of curbing process's vulnerability for anticompetitive behavior, improving transparency and increasing efficiency of operations.

The intellectual property protection regime in Egypt is welcoming to local producers. The law number 82/2002 complies with the TRIPS agreement and provide patent protection for medicines for 20 years from the date of filing yet it possess many articles which represents flexibilities for the government to revoke, invoke or issue licenses voluntarily and compulsory to local producers if public health is at danger. The Minister of health has special power to cancel granted patents by the EPO for 60 days post granting the patent for public interest's protection reasons providing less risk for local producers to venture in to producing biosimilars backed by a supportive IP protection legal framework.

The area of local production is potentially hampered by the latest pricing decree 499/2012. The decree redistributed profit margins between retail pharmacists

and producers leading to unintended consequences of drug shortages, financial implications on producers and potential closure of production lines of some manufacturers. The study finally examined the dynamics of the latest pricing decree in the context of one of the theories of modern political economics namely the public choice theory. The potential for rent seeking behavior by different self-interest group and government on the expense of public interest is something that leads to regulatory inefficiencies in fixing market failures.

The area of production of medicines using advanced biotechnological technique is currently at its primary stages in Egypt with a very small number of local producers of few items, mainly overlapping. This area has potential for growth if the government adopted complementary policies that promote innovation, facilitating south-south or north-south technology transfer and providing preferential financial incentives for investors in this area.

The below policy options are set for consideration by the government in order to maximize efficiency of regulatory interventions pertaining to the biopharmaceutical sector and particularly to biosimilars:

I. Policy options to ensure quality, safety and efficacy of biopharmaceuticals / Biosimilars in the Egyptian Market

A. Bridging the legislative gap on dealing with biosimilars registered as generics prior to the 297/2009 decree:

A ministerial decree has to be issued to fill the current legislative gap on how to deal with biosimilars or standalone biopharmaceuticals registered as generics prior to the 297/2009 ministerial decree and current draft guidelines that regulates biosimilars.

B. Proactively tackling re-registration requirements:

This has to be managed on case by case basis on what quality, safety and efficacy data the product provided in the initial registration phase and what data needs to be generated and studies to be done in order to provide proof of safety, efficacy and quality. Considering the culture of reporting on adverse events in Egypt being in its early stages (EPVC established in late 2010) anecdotal evidence may be taken in to consideration for the quality, efficacy and safety profiles of the products during the (10 years primary registration period) spent in the market however studies following regulatory procedure according to international standards and requirements to ensure quality, safety and efficacy have to take place based on assessment of the product risks and benefits. The depth and extent of such studies also will be dealt with according to the new requirements and depending on the current quality, safety and efficacy data available on the product. The regulatory structures involve (CAPA Biological registration, inspection departments and concerned NORCB departments) should start educating companies with products with about to expire registration license and whom are close to applying for re-registration on what is the type of QSE data needed from them and put a time frame on generating such data through studies supervised by the responsible regulatory structures.

C. Continuing collaboration with stakeholder on draft registration guidelines:

The current draft guidelines on regulations of biosimilars represents a positive step towards being proactive in tackling an upcoming regulatory challenge. The government is encouraged to continue the progressive regulatory thinking by meeting with manufacturers in feedback workshops and finalize the current version in a format agreed upon by majority of stakeholders. However there is an eminent need to back MOH with the required senior expertise in such meetings to avoid the pressure exerted by industry experts on mid-level government employees who usually run those meetings on behalf of CAPA.

D. Strengthening National Regulatory Structures:

The government should consider the fact that the presence of a legal and policy regulatory structures in place without the required qualifications and the right caliber is jeopardizing Public Health. Scientific expertise and nurturing regulatory talent is the main asset of regulatory authorities. The current recruitment system is dependent on an annual supply of around 200 pharmacists who should be employed as part of the government policy for compulsory service. A competency based model for recruitment should be adopted rather than compulsory service distribution to retain the best regulatory talents. Recruitment on project basis may be adopted and salary scales has to be revised to fit with inflation and market rates. Currently the salary of employees is composed of (fixed 30% and a variable of 70%)which put them in a status of stress as the variable component can be removed any month due to the worsening economic condition, this affects their ability conduct their regulatory functions and may also affect public health outcomes. In order to achieve this level of autonomy has to be revisited and the Egyptian Drug Authority has to be autonomous on reality rather than on paper. Currently 45% of the funds (revenue pool for licensing and registration) money goes to NRMA and the rest to MOH 35% and the ministry of finance 20% while they don't contribute with any significant CAPA/NORCB operational costs.

E. Expediting clinical trials law:

With the new biosimilars draft guidelines requiring companies to conduct their clinical trials is another legislative gap that exists implying the lack of a legal cover for the currently proposed regulations to conduct clinical trials in Egypt. Many of the industry representatives interviewed voiced out their concern that the absence of such law will drive them to conduct the trials outside the country which impose significant costs. Such costs are unnecessary when a national law exists and may be factored in to pricing decisions leading to increase in biosimilars prices. The current draft law being under discussion has to be expedited for assessment as soon as a new parliament is elected.

II. Policy options to increase efficiency in the registration process of biosimilars:

A. Revisiting the box system

The government may consider making it public for chemical based medicines and removing it for the local producers to encourage investment in local production.

B. Increasing scrutiny in pricing committee decision

The government may consider addition of a permanent member to the current pricing committee representing civil society groups interested in patient's rights and access to medicines.

C. Commissioning a Regulatory Impact Assessment study by a third party

To assess the impact of the latest pricing decree one year after its promulgation on price of medicines, shortage and effect on local production and review the percentages to reach a mid-way between the retail pharmacists and producers.

III. Policy options to encourage investment in local production of Biosimilars:

A. Subsidizing local biopharmaceutical manufacturers:

Medicines are not a normal commodity they are inelastic in demand and this may lead to catastrophic health expenditures with a very high out of pocket payment level like in Egypt. Hence the government should focus on development of a strong base of local industry that is able to manufacture biosimilars for life saving and critical diseases at an affordable cost. The government may start thinking strategically about subsidizing local producers of biosimilars falling on the essential medicines list (like interferons, human albumin, etc.). Egypt has an opportunity with its reasonable foundation of manufacturers currently producing biosimilars. The opportunity exists to collaborate and develop joint ventures with some of the early adopters (India, Korea, China, Iran, Cuba, Argentina, etc...) to develop molecules that are about to lose patent protection and worth a total of **50 billion USD** in annual sales (GEN, 2013)⁴⁰. **Subsidies may take the forms of** financial and other incentives such as interest-free loans, preferential pricing over imported, free land, etc... The current practices of providing preferential treatment to local manufacturers at tenders should continue by providing lower fee for participation, giving favourable pricing (imported has to be at least 15% less than local). In addition tariffs and customs mark-ups may be further reduced. Currently a sales tax of 5% applies to different medicines categories (aside from the chronic and non-communicable disease medicines).

B. Facilitating technology transfer:

Currently few of the producing biotech companies develop their own technology, some are dependent on technology transfer agreements with foreign manufacturers others are just filling or labeling the vials. Currently the government is not promoting technology transfer or making enough effort to be an attractive option to investors. This area due to its strategic considerations may need clear government policy and constant efforts to transmit the message to the private sector and facilitate

⁴⁰ <http://www.genengnews.com/insight-and-intelligenceand153/biosimilars-10-drugs-to-watch/77899804/>

their investment, quoting an ex senior director of a governmental entity and currently CEO of one pharmaceutical manufacturer , *“this area should be highly adopted on the Egyptian political agenda , it touches upon medicines that may affect national security especially in transfer of technology to produce life-saving products and vaccines”*. The easier way to start is by looking south to Latin America or Asia with several main players like India, Iran and Cuba⁴¹.

C. Bridging the regulatory gap on technology transfer:

The government still doesn't have guidelines for technology transfer were it may consider embarking on its development if it will open arms for investors to do it, it should know how and what it will regulate in it This is currently misleading and deterring to many investors considering to venture in to this area.

IV. Policy options to preserve the TRIPS flexibilities in the current patent protection policy:

The government of Egypt should realize that it is not yet hit with the effect of patents on access to medicines. This is simply because most medicines currently on patent were registered and in use prior to the 2005 promulgation of the patent law and due to the very flexible articles in the Egyptian patent law, many multinational companies were reluctant to file patent application in Egypt with around 161 patents filed. It is interesting to compare this figure with other developing countries. According to a South Center study in Argentina, 951 pharmaceutical patents were granted in 2000–2007; in Brazil, 278 patents were granted in 2003-2008; in Colombia 439 in 2004–2008; in India 2347 in 2005–2008; and in South Africa, 2442 patents were registered in 2008 (Iskander,2012). However for all the new innovations post 2010 and this is mainly in the biopharmaceutical sector, the government will face aggressive pressure from countries of multinational corporations to introduce measures to increase patent protection like Data Exclusivity and otherTRIPS plus measures and even the current article on TRIPS flexibilities⁴² may be challenged as being non-TRIPS compliant due to their unclear wording and sometimes ambiguity on how they are

⁴¹ government dedicated 80 acres compound for toxicological studies and testing of biotech products in animals

⁴² Articles 17 and 24

implemented. The government should send only qualified negotiators to negotiation rounds of bilateral or regional trade agreements. Quoting a senior executive of the Egyptian Patent Office “ *In Free Trade Agreement rounds, if negotiators don’t have the required qualifications and understanding of the subject, signing a simple annex may be very easy , nevertheless implications will be devastating, leading to reduced access to affordable medicines, hampering local production and jeopardizing public health*”.

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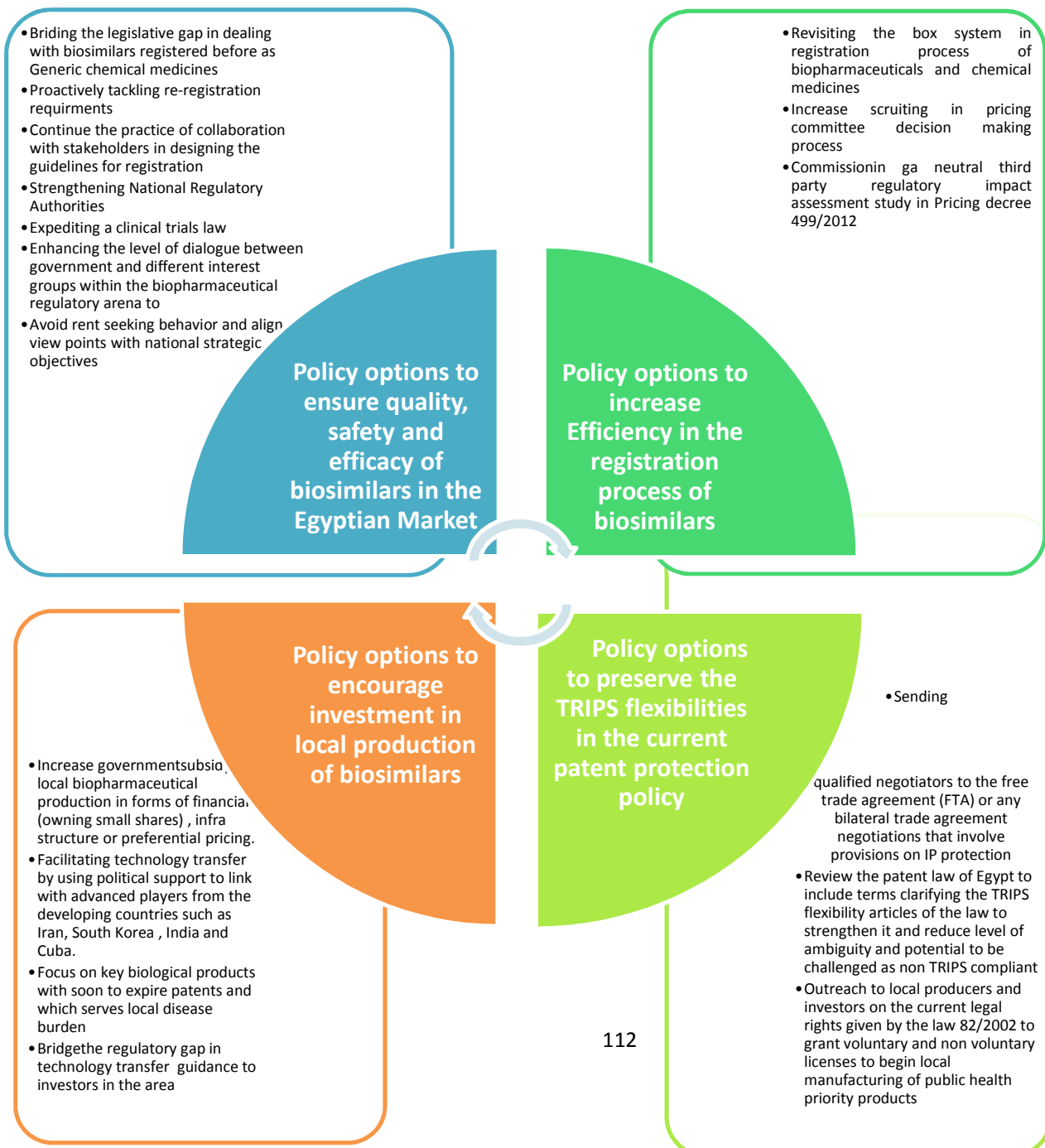
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Appendix -1

Proposed conceptual Model for resolving the identified gaps in the Egyptian government's regulation of the Biopharmaceutical sector



Appendix -2

Questionnaire for Expert interviewees

Regulatory framework:

- 1- Please list the Decrees on regulations , pricing and clinical trials of Biosimilar products
- 2- How many Biological products are registered? What about those registered before 2009
- 3- How many are biosimilars or non-vaccines or blood products?
- 4- How many are locally manufactured?
- 5- How do you perceive the process of registration of biological products prior to 2009 decree on establishing a biological registration department in terms of ensuring quality, safety and efficacy?
- 6- How do you compare it to Global Best Practices
- 7- How many biosimilars are under application for registration (from the time of 2009 guidelines-present)?
- 8- Were their registration deferred until the final guidelines are ratified?
- 9- How do you ensure GMP compliance if you don't inspect source of Active Pharmaceutical Ingredient? Adequacy versus SRA guidelines?

Challenges in Regulating biosimilars

- 10- What are the general challenges in regulating such market in Egypt?
- 11- How do you plan to deal with products registered before 2009 to reduce risk on the society from such products?
- 12- If registration status review at time of re-registration is the envisaged solution. When product suspension happen at time of re-registration, do you expect the process will continue? How do you think this will affect patient's access?

Pharmacovigilance/Adverse Drug Events Reporting:

13- When was the National system for tracking adverse drug events established in Egypt?

14- How many reports were received? Were any reports related to biological products?

15- How many companies have a system to track adverse events from products in the market and when was it established?

Reimbursement/ Health Insurance:

16- Which hepatitis C interferons are on the list of the formulary for reimbursement by Health Insurance?

Procurement:

17- How are medicines procured for public institutions in Egypt? How much is the annual procurement budget for medicines? How much of it is for biological?

18- How much is for Hepatitis C virus interferon treatment?

Special interest Groups:

19- How do you perceive the role of the chamber of industry lobby in affecting the current pricing law?

Pricing related questions:

20- How are medicines priced and why are biological products of higher price tags than normal chemical based products?

21- Do you plan to include value based pricing in your future pricing policy? Do you think the registration committee has the scientific capacity to assess pharmacoeconomic studies to establish a price to the value of product?

22- Are there any taxes levied on raw materials in preparation of medicines or biosimilars?

23- Are there any taxes levied on the final finished products

IP related questions:

24- How do you ensure bio-similar products submitted for registration are not infringing patents? Do you cooperate with EPO? Please elaborate on such cooperation

25- Do you have cases for patent disputes of medicinal or biological products in Egypt? If yes how many in 2012-2013?

26- What is the normal legal route taken in case of a dispute?

27- Is data exclusivity part of the Egyptian Patent Law? When was last amendment? If not do you think it is envisioned for being integrated to the patent law?

- 28- What do you think the role of data exclusivity will play on the number of biosimilar products?
- 29- Do you have other information which you want to add and you think are useful in my research ?

Market Failures: Do you feel the current regulatory policy for biosimilars allow for any possible loopholes for any form of market failures as below

- A. Externalities: positive or negative
- B. Information Asymmetry
- C. Monopolies

For industry:

- 30- How do you perceive the market for biosimilars in Egypt in the next 5 years?
Market Growth and profitability?
- 31- How many companies do you think will plan to introduce biosimilars to the Egyptian market?
- 32- How do you perceive the registration process in Egypt for biologicals in particular?
- 33- Do you think there is a level of information asymmetry in the regulatory process of biosimilars in Egypt?
- 34- How do you perceive the licensing procedure for investors in the area of biological or biotechnological production?
- 35- Are there any taxes levied on raw materials in preparation of medicines or biosimilars?
- 36- Are there any taxes levied on the final finished product?
- 37- How about other government policies in the field of R&D promotion for such products?