A STUDY OF VALUE TRANSITIONS IN THE BASAL INSULIN REGIMEN FOR TREATMENT OF TYPE 2 DIABETES
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Thesis presented to Escola de Administração de Empresas de São Paulo of Fundação Getulio Vargas, as a requirement to obtain the title of Master in International Management (MPGI).

Knowledge Field: Pharmaceutical management

Adviser: Prof. Dr. Antonio Gelis Filho

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Approval Date

___/___/_____

Committee members:

Prof. Dr. Antonio Gelis Filho

Prof. Dr. Servio Tulio Prado Jr.

Prof. Dr. Ricardo Ratner Rochman
Gludsted, Emil Brohl
86f.

Orientador: Antonio Gelis Filho.
Dissertação (MPGI) - Escola de Administração de Empresas de São Paulo.


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Type 2 diabetes is a progressive disease projected to grow tremendously in prevalence. Basal insulin analogues used to be the most efficacious treatment and last step in therapeutic intensification. Today, demographic, economic and epidemiologic transitions have placed pressure on healthcare systems and payers’ budgets. Three imminent threats require the basal insulin regimen to rethink how value can be addressed in the market: mounting institutional pricing pressure, biosimilar competition and, new innovative anti-diabetic drug classes with the potential to delay insulinization. Products aspiring to compete in the basal insulin regimen must avoid commoditization and steer clear of new threats. This paper identifies seven strategies and tactics to successfully address value in the diabetes market and particularly in the basal insulin regimen: 1) cost-based advantage and price competition; 2) value-based pricing; 3) risk-sharing agreements; 4) redifferentiation and post-approval evidence generation; 5) combination products carrying complementary mechanisms of action; 6) treating comorbidities and adjacent diseases; and, 7) indicating for patient sub-populations.

KEY WORDS: VALUE, DIABETES, INSULIN, GLARGINE, PHARMACEUTICAL, DIFFERENTIATION, BIOSIMILAR, PRICE, RISK-SHARING
RESUMO

A diabetes tipo 2 é uma doença progressiva cuja projecção é crescer tremendamente em prevalência. Análogos de insulina basal eram considerados o tratamento mais eficaz, e utilizados em último instância durante a intensificação terapêutica. Hoje, transições demográficas, econômicas e epidemiológicas tem colocado pressão nos sistemas de saúde e no orçamento dos usuários. Três iminentes ameaças levam o regime de insulina basal à necessidade de repensar a maneira como seu valor é apresentado ao mercado: crescente pressão institucional sobre os preços, competição de biosimilares e novas classes medicamentos inovadores anti-diabetes com o potencial de atrasar a insulinização. Produtos que buscam competir no regime de insulina basal devem evitar a comoditização e esquivar-se de novas ameaças. Este trabalho identifica sete estratégias e táticas para apresentar de maneira bem sucedida valor no mercado de diabetes e particularmente no regime de insulina basal: 1) vantagem baseada em custo e competição por preço; 2) precificação baseada em valor; 3) acordos de compartilhamento de riscos; 4) re-diferenciação e geração de evidencias pós-aprovação; 5) produtos combinados que apresentam mecanismos complementares de ação; 6) tratamento de co-morbidades e doenças adjacentes; e, 7) indicação para pacientes de determinados sub-grupos da população.

PALAVRAS CHAVE: VALOR, DIABETES, INSULINA, GLARGINA, FARMA-CÊUTICOS, DIFERENCIAÇÃO, BIOSIMILAR, PREÇO, COMPARTILHAMENTO DE RISCOS
“Nowadays people know the price of everything and the value of nothing”

- Oscar Wilde
# Table of contents

Introduction .................................................................................................................. 12

Methodology ................................................................................................................ 13
  Delimitations .......................................................................................................... 13
  Limitations .............................................................................................................. 14

Research question ........................................................................................................ 14

The Underpinnings of Value Theory ......................................................................... 15
  The emergence of perception, management and power in value theory ..................... 17

An account of pharmaceutical value ............................................................................ 19
  The clinical value of pharmaceuticals ...................................................................... 21
  The pharmacoeconomic value of pharmaceuticals ...................................................... 22
  The societal value of pharmaceuticals ..................................................................... 23
  The value under innovative pharmaceuticals ......................................................... 24

Diabetes Mellitus .......................................................................................................... 26
  Etiology and epidemiology ....................................................................................... 26
  Medical complications and health expenditures ..................................................... 28
  Disease prevention and treatment .......................................................................... 29

The Insulin Market ...................................................................................................... 32
  Insulin typology ....................................................................................................... 32

Basal insulin analogue products ................................................................................ 35
  Insulin glargine U-100 ............................................................................................ 36
  Insulin detemir ......................................................................................................... 37
  Insulin glargine U-300 ............................................................................................ 38
  Insulin degludec ....................................................................................................... 38

Insulin manufacturers .................................................................................................. 39

Insulin business models and value levers ................................................................. 42

Threats to The Basal Analogue Regimen .................................................................... 45

Mounting pricing pressure in the institutional market ................................................. 45
  Private formulary payers trawl the market for discounts ........................................... 46

Biosimilar competition ............................................................................................... 50

Innovative drug classes delaying insulinization ....................................................... 54
Cardiovascular benefit and its role in the treatment paradigm ........................................... 57

Analysis ........................................................................................................................................ 61

A revised value definition for basal insulin analogues ................................................................. 62

Tactical and strategic recommendations for addressing product value ....................................... 63

1. Cost-based advantage, price competition and market imperfections ........................................ 64
2. Value-based pricing .................................................................................................................. 65
3. Risk-sharing agreements .......................................................................................................... 67
4. Redifferentiation and new evidence generation ........................................................................ 68
5. Developing combination drugs ............................................................................................... 70
6. Treating adjacent diseases and comorbidities ........................................................................ 71
7. Indicating for patient subpopulations ..................................................................................... 72

Conclusion ..................................................................................................................................... 74

References ...................................................................................................................................... 77

Appendices .................................................................................................................................... 85
Tables and figures

FIGURE 01: Historical Evolution of the Axiology

FIGURE 02: Connections Between Axiology and Pharmaceutical Value

FIGURE 03: Trends in Prevalence of Diabetes, 1980-2014, by WHO Region

TABLE 04: Total Diabetics, Prevalence and Diabetes-Related Health Expenditure 2015 and Forecasted 2040, by IDF Region

FIGURE 05: T2DM Treatment Intensification (left) and Distribution of Patients and Value across Treatment Classes (right)

FIGURE 06: Pathophysiologic Mechanisms for Whom Failure Leads to Hyperglycemia in T2DM Patients

FIGURE 07: Therapeutic Regimes for Glycemic Management in T2DM Patients

TABLE 08: Pharmacologic Agents for Glycemic Control in T2DM Patients

FIGURE 09: Insulin Time-Action Profiles (left) and Global Insulin Volume Market by Segment (right)

FIGURE 10: Percentage of Analogue Insulin Sales by Income Level

FIGURE 11: Weekly US New-to-Brand Rx Volume Market Share

TABLE 12: Top-10 Insulin Manufactures by Product Registrations and Revenue

FIGURE 13: Global Insulin Market (left) and Global Insulin Volume Market Share (right)

FIGURE 14: Global All-Diabetes Value Market Share

TABLE 15: Business Models and Value Levers

FIGURE 16: US Pharmacy Benefit Manager Coverage Market Share

FIGURE 17: Manufacturer Rebates for Medicare Part D Drugs

FIGURE 18: Illustrative Price Evolution in the Basal Insulin Analogue Space

FIGURE 19: Biosimilar Market Share and DOT Price for EPO and GH

TABLE 20: Biosimilar Impact on Price and Usage in Epoetins

TABLE 21: Products in the Basal Insulin Regimen after Biosimilar Entrance

FIGURE 22: GLP-1 Total Prescription Market Share in the US

FIGURE 23: Semaglutide and Cardiovascular Outcome in T2DM Patients

FIGURE 24: Value-Based Pricing Model

FIGURE 25: Eight Niches and the Products Most Likely to Win

FIGURE 26: Seven Ways of Addressing Value in the Market for Basal Analogue Insulin for the Treatment of T2DM
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMR</td>
<td>Amélioration du Service Médical Rendu</td>
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<tr>
<td>BNDES</td>
<td>The Brazilian Development Bank</td>
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<tr>
<td>CAD</td>
<td>Canadian Dollar</td>
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<tr>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies in Health</td>
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<tr>
<td>CAGR</td>
<td>Compact annual growth rate</td>
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<tr>
<td>CGRP</td>
<td>Calcitonin gene-related peptide</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>DOT</td>
<td>Days of treatment</td>
</tr>
<tr>
<td>DPP-4</td>
<td>Dipeptidyl peptidase-4</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EPO</td>
<td>Epoteins</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>FDA</td>
<td>U.S. Food &amp; Drug Administration</td>
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<tr>
<td>FDC</td>
<td>Fixed-dose combination</td>
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<tr>
<td>GH</td>
<td>Growth hormone</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycated hemoglobin</td>
</tr>
<tr>
<td>HHS</td>
<td>US Department of Health and Human Services</td>
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<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
</tr>
<tr>
<td>MERCOSUR</td>
<td>Mercado Común del Sur</td>
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<tr>
<td>MS</td>
<td>Market share</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<tr>
<td>NPH</td>
<td>Neutral Protamine Hagedorn</td>
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<tr>
<td>OAD</td>
<td>Oral anti-diabetic</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<tr>
<td>OOP</td>
<td>Out-of-pocket</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
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<tr>
<td>Part D</td>
<td>Medicare Prescription Drug Coverage</td>
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<tr>
<td>PD-1</td>
<td>Programmed cell death protein 1</td>
</tr>
<tr>
<td>PK/PD</td>
<td>Pharmacokinetics / Pharmacodynamics</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
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<tr>
<td>Rx</td>
<td>Prescription</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>Sodium/glucose cotransporter 2</td>
</tr>
<tr>
<td>SU</td>
<td>Sulfonylurea</td>
</tr>
<tr>
<td>T1DM</td>
<td>Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>tMU</td>
<td>Total million units</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USD</td>
<td>United States Dollar</td>
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<tr>
<td>VBP</td>
<td>Value based pricing</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction
The diabetic prevalence is expected to reach 642 million in 2040, more than 10 percent of total worldwide population. That same year diabetes-related health expenditure will amount to $802 billion USD but still come in 35 percentage points short compared with the prevalence growth. Already today, more than 100 million people rely on insulin therapy and the market is projected to carve out $53 billion USD in 2022, with the analogue segment looking at the lion’s share. For two decades the diabetes market has been shining glazed for the better part of insulin manufacturers – now it seems the sugarcoating is cracking.

Historically patients were treated with Metformin and SU before being moved on to insulin therapy. Basal insulin analogues constituted the most efficacious treatment and last step in therapeutic intensification. Due to proprietary protection analogues enjoyed market exclusivity and high prices. Today, demographic, economic and epidemiologic transitions are placing pressure on healthcare systems and payer budgets. At the same time, patients and healthcare professionals demand new innovative technologies to significantly enhance the value of diabetes treatment.

Three imminent threats require the basal insulin regimen to rethink how value can be addressed in the market. Those are: an institutional pricing pressure, biosimilar competition and, new innovative anti-diabetic drug classes with the potential to delay insulinization. In the classic model, individual patient outcomes lead to cost-beneficial pricing. Under the new market requirements, insulin manufacturers must redefine how and to whom they address the value of their products and transit to a selling place where it offers a competitive edge against rival products that tap into the regimen by leaps and bounds.

In this paper I set out to identify strategic and tactical ways to address value in the dynamic market for basal insulin analogues. In doing so I will simultaneously deal with the value of new and innovative drug classes as well as older products in the home stretch of their life cycle. First I outline my methodological choices and limitations. Thereafter follows a literature review, which highlights the chronological underpinnings of value theory. On page 15 I introduce diabetes and on page 21 I present the insulin market, business models and levers that are important to my analysis. Next I embark on the three threats to the basal insulin analogue regimen. That should give the reader an elaborate idea about why it is
relevant to identify new ways of addressing value. Finally to finish, I shed light on and summarize each of my findings throughout the concluding sections of the paper.

Methodology
This paper is an exploratory study of the value transitions in the basal insulin regimen for treatment of type 2 diabetes. It uses a mix of qualitative and quantitative data but rely in its full length on secondary research including meta-analysis and the author’s own interpretation of ready available raw records. The sources include academic journals, periodicals, industry news, publications, empirical studies, global and industry statistics, legal documents, medical reviews or analyses and company announcements. A total of 120 sources were identified as reliable and valid through research in libraries, databases or Internet search engines. The sources are evenly apportioned between academic and professional backgrounds.

The paper investigates of the broader context of value and as such does not offer an absolute quantification. It attempts to synthesize an answer to the research question bearing in mind that several alternative solutions may be similarly beneficial. The diabetes market is in constant movement and therefore it is imperative to stay constantly updated, dynamic and ready for change. During the span of writing this thesis, major events in the market emerged that required alterations. Some of those are: the discontinuation of major products; regulatory delays on approval processes; label updates on at least one basal insulin analogue; cardiovascular outcome data published; pharmacy benefit manager exclusion lists for 2017 published; and, biosimilar regulation passed in several countries including Brazil. The paper tries to capture all changes up until the fourth quarter of 2016.

Delimitations
I acknowledge that analyzing value in a pharmaceutical context require vast medical expertise. Due to my professional and academic background in international management I rely on medical meta-analyses and conclusions derived from sources by authors with the proper scientific qualifications. I have attempted to translate data of medical nature into managerial content because I recognize that that process is essential to the pharmaceutical business realm.

For the purpose of the study I also have had to limit the scope entirely to the type 2 diabetes market. That decisions is grounded in the fact that type 2 diabetes, contrarily to
type 1 diabetes, is a lifestyle disease characterized by intensification of treatment. In an intensification paradigm there is a higher likelihood for disruptive competitors and therefore the challenge for basal insulin seems bigger and more relevant to address. For future research, it will be interesting to study the impact of value transitions in type 2 diabetes on the type 1 diabetes market.

Limitations
Garthwaite and Duggan looked for empirical evidence on the value of pharmaceuticals. They concluded among other things that the sheer number of treatments often makes it difficult to estimate the effect of medications on overall health (2010). In diabetes, as you are about to see, that is particularly true. The amount of comorbid and adjacent conditions and health states for which there are treatments and the way patients transition from one state to another provides a difficult foundation for value assessment.

Overcoming this obstacle requires research to focus only on the value of one product in one single patient subpopulation. However in doing so the comparative effectiveness research that has become so important for addressing value in the new market ceases to exist. Limitations from the medical field also count study biases. I have been cautious to not include sources that were explicitly aimed at positioning products before competitors and sponsored for that purpose by the manufacturer.

Finally good granular market data is a scarce resource because the most specific market reports are very expensive and the literature publically available usually focuses only on the larger diabetes markets in high-income countries. Wirtz (2016) have highlighted the same obstacle to her recent work on profiling the insulin market.

Research question
The state of the insulin market and the imminent threats outlined in the introduction calls for change in the strategic or tactical approach of insulin makers and payers. Ultimately those factors have led me to the following research question:

How can product value be successfully addressed in the market for basal analogue insulin for the treatment of type-2 diabetes mellitus?

To answer this question I found that it is essential first to study fully the underpinnings of value theory because they have laid the groundwork for today’s understanding of value as a concept. Therefore the following pages of this paper review the literature on value theory.
The Underpinnings of Value Theory

Our pursuit for an understanding of the value concept dates all the way back to Aristotle who held that the source of value was based on need; he was also the first to distinguish between value in use and value in exchange (Fogarty, 1996). We, however, start in the late 16th and 17th century when an array of intellectuals first articulated their puzzlement around the idea of what determines the value of things. Davanzati (1588) introduced utility and scarcity in his Lecture On Money, while about a century later William Petty stated that the determinants of value were deduced as the factors of production – land and labour. Richard Cantillon, influenced by the French agrarians, supported the work of Petty but saw land as the only determining factor of production (Fogarty, 1996).

In Scotland 1705, John Law elaborated on the work of another British philosopher, John Locke. In Money and Trade Considered, Law refines Locke’s value definition by stating that “the prices of goods are not according to the quantity in proportion to the vent, but in proportion to the demand” (1705; in Fogarty, 1996). It was also Law who first outlined the infamous water-diamond paradox in his Essay on a Land Bank (Law & Murphy, 1994).

These early thoughts on value were substantially normative (Fogarty, 1996) and it was not until Francois Quesnay advanced his beliefs through the Physiocratic School that value theory really gained traction in the literature (Rea, 2000-2003). Quesnay (1758) published the Tableau Economique, which seeks to uphold that all value ultimately derives from the production of food. As agriculture taps into the life-giving force of nature, only there is it possible to generate a surplus in excess of the labour effort put into the production (Quesnay, 1758; in Rea, 2000-2003).

During mercantilist times, the general idea that value has a lot to do with money was a popular fallacy (Rea, 2000-2003). Until today, money and value are associated and play pivotal roles in economic theory. Nonetheless, history has taught us that money and value are not one of a kind. Adam Smith paved the road to an enhanced understanding of the value concept with his 1776 seminal text, The Wealth of Nations. Smith argued that the relative value of things is determined by the costs of production: land, stock and labour, with a large emphasis on the latter (Smith, 1776; Rea, 2000-2003).

In Rea’s (2000-2003) reflections on Smith’s theory (1776) of value, we understand that seeking to explain [as Smith does] price in terms of costs of production is a vulnerable
approach on the grounds that it cannot justify how all prices and price changes come about. Smith is largely recognized as one of the leading forces behind classical economic theory and, although his notions exhibit shortcomings, much of the succeeding literature on value has its underpinnings in Smith’s work.

The most prominent texts based on Smith’s theory are those of David Ricardo and Karl Marx. Ricardo perfected Smith’s theory by stating that in “possessing utility, commodities derive their exchangeable value from two sources: from their scarcity and from the quantity of labour required to obtain them” (Ricardo, 1871 in Fogarty, 1996). Some years later Marx pronounced his support for Smith and Ricardo’s labour theory of value by asserting that the value of “all commodities are only definite masses of congealed labour time” (Marx, 1867 in Fogarty, 1996).

Intrinsic theories were at the heart of value discourse in most literature until Jeremy Bentham spearheaded a new paradigm in 1780. In his Introduction to the Principles of Morals and Legislation he reasoned, any act resulting in happiness must be considered morally correct. All human acts result in either pleasure or pain; if the sum contributes more to pleasure than pain, it is good (Rea, 2000-2003). Bentham’s subjective theory of value, or utilitarianism, has become essential to our contemporary understanding of the value concept.

It is not immediately obvious why the particular relationships between product and price are what they are (Rea, 2000-2003). As such, Ruskin issued a critique of the economic concept of value much in line with Bentham’s hypothesis. In Unto This Last (1860) Ruskin’s central point was that real value depends on the moral sign attached to it. Despite of greatly advanced notions on value, early utilitarianism failed to understand a key distinction of two concepts: total utility and marginal utility (Rea, 2000-2003).

The first explicit theories on marginal utility were offered by William F. Lloyd in his Lecture on the Notion of Value as distinguished Not Only from Utility, but also from Value in Exchange (1833) and Nassau W. Senior who claimed that marginal utilities were the ultimate determinants of demand in An Outline of the Science of Political Economy (1836). Nonetheless, it was three other scholars, Jevons, Menger and Walras, who led the marginal revolution.

In A General Mathematical Theory of Political Economy (1863) Jevons explains us how it is possible that goods that are essential to life can be cheaper than goods that are
not. Menger developed the axiom that rational consumers have to choose among numerous goods in order to maximize total utility (1871). Finally, Walras presents a theory in *Éléments d’économie politique pure* (1826), which seeks to explain that the marginal adjustments made by individual consumers do in fact affect economies beyond that of the decision-maker.

In 1890, Alfred Marshal became the first to combine intrinsic and utilitarian theories of value. In *Principles of Economics*, Marshall identified that the value of a thing (in this case the price) was determined by both subjective demand and cost of production, that is supply. His beliefs laid the groundwork for neo-classical economics and the bedrocks of today’s value literature.

**FIGURE 01: Historical Evolution of the Axiology**

The emergence of perception, management and power in value theory

There is a plethora of writings on value theory in contemporary literature, however value remains loosely defined. Semantics are embracing on the concept of perceived value to adjust for the point that real value is in fact context-dependent (Zeithaml 1988; Holbrook,
1994, 1999, in Sanchez-Fernandez & Iniesta-Bonillo, 2007). From a medical viewpoint, for example, some patients might value the relief of hypoglycemia when other place larger concerns on weight gains associated with insulinization. Moreover there has been a paradigm shift from the study of value theory to the study of value management.

Sanchez-Fernandez and Iniesta-Bonillo provide an excellent review of research on the concept of perceived value (2007). Their work runs the gamut from dynamic value models that consider the effects of expectations, desires and perceptions of performance (Spreng et. al., 1993) to Monroe’s prolific research stream with origins in price studies and focus on the price-quality relationship (1979; 1990).

Perceived value is defined as the outcome of an evaluative judgment (Lapierre et. al., 1999). We notice the application of this definition when payers or regulatory agencies review drugs. It is the result of the consumer’s overall assessment of the utility of a product based on perceptions of what is received and what is given (Zeithaml 1988; Payne & Holt, 2001). Finally it is described as a cognitive trade-off between perceptions of quality and sacrifice (Dodds et. al., 1991).

The most influential studies of perceived value in its original conception are those of Monroe and Zeithaml (Sanchez-Fernandez & Iniesta-Bonillo, 2007). They display a consensus that additional to price, a full appreciation of the [value] concept includes considerations of time, effort and search involved in the overall sacrifice made by the consumer (Monroe 1990, Zeithaml 1988).

Studies seeking to understand the value in customer-seller relationships (Oh, 2003; Lindgren & Wynstra, 2005, Thaler, 1985) and the impact of consumer’s internal reference price (Grewel et. al., 1998; Thaler, 1985) also constitutes a significant portion of the perceived value research reviewed by Sanchez-Fernandez and Iniesta-Bonillo.

In the modern realm of management it is no longer just a question about defining value but also a matter of seizing value. As you cannot seize something that is undefined the two issues are usually addressed together (Gummerus, 2013; Karababa & Kjeldgaard, 2013). Gummerus (2013) suggests that we distinguish between value creation processes and value outcomes in today’s research.

An important application of management has been its use in value creation (See Brandenburger & Stuart, 1996). Gnechi provides an excellent and very simple vision of how to create value in over-supplied markets. “Companies should define their own supply so
that they can propose performance that is superior to that guaranteed by competitors”. Furthermore, value can be created only by “understanding how customers’ needs intersect with the company’s capabilities and also with the products of the competitors” (2009). The pharmaceutical discourse is currently centered on the notion of unmet need, confirming Gnecchi’s theory. In Karaba and Kjeldgaard’s recent work about socio-cultural perspectives on value in marketing we are also told that value is co-created by companies and customers (2013).

Finally Nitzan and Bichler (2009) propose an original theory of value that seems to demonstrate why pharmaceutical companies must rethink how they address value in a post-exclusivity market. In *Capital as Power: A Study of Order and Creorder* the authors argue for a power theory of value when the power of private ownership is exercised through prices\(^1\). Their argument however is subject to a catch-22, as power stems from the ability to deploy monopoly prices and the ability to set prices is based on the possessed degree of market power.

**An account of pharmaceutical value**

Accounting for the value of pharmaceuticals is semantically different from discussing general axiology; nonetheless we can observe parallel movements in the theoretical paradigms (see figure 02). Pharmaceutical manufacturers identify drug value from attributes like efficacy or the cost-benefit implications for overall treatment. Other institutions are more inclined to consider longevity and quality of life as important determinants. Differences in perception of the value of pharmaceuticals exist widely between manufacturers, payers, health authorities, physicians and patients (Deloitte Center for Health Solutions, 2012).

The U.S. Food & Drug Administration (FDA) deems prescription pharmaceuticals valuable if the “drug’s benefits outweigh its known risks for its proposed use”. The benefits are established through a multidisciplinary review, however the FDA notes, “no matter how much data are available [they] often have to make a judgment call” (2016).

In Holbrook’s typology of consumer value we identify the differences between extrinsic and intrinsic value; between self-oriented and other-oriented value and; between

\(^1\)“In capitalism, power is the governing principle as rooted in the centrality of private ownership. Private ownership is wholly and only an act of institutionalized exclusion, and institutionalized exclusion is a matter of organized power” (Nitzan & Bichler, 2009, p.228).
active and reactive value (Holbrook 1999, in Loane, Webster & D’Alessandro, 2014). Similarly the value of pharmaceuticals can be categorized under direct value, being the ability to improve mortality, tolerability and to mitigate other complications (in Holbrook: extrinsic; self-oriented; reactive) and indirect value, such as helping patients live normal productive lives free from the incapacitating effects of illness, particularly chronic conditions (in Holbrook: Intrinsic; self- and other-oriented; active) (Foundation for Managed Care Pharmacy, 2014).

Historically value was focused on individual patient outcomes, meaning one drug’s efficacy leading to cost-effective pricing of that particular drug. Fiminska (2014) reasons that today, “value must be addressed on a community level with evidence demonstrating how the drug will impact our system and its management”. Fiminska stresses the importance of a holistic assessment of drug benefits and risks, the necessity to improve healthcare system efficiency by addressing an unmet need and public affordability.

Regardless of outcome measure, drugs are approved only when considered safe and to varying degree value adding. For decades, pharmaceuticals were evaluated on the basis of their impact on biomarkers rather than considering the overall health outcome for patients. “If a drug lowered blood sugar it was approved for the treatment of diabetes”, says LaMattina (2013).

Several regimens that have comfortably been used in medical practice are now being shown to have questionable value (LaMattina, 2013). That is because too often the value of pharmaceuticals is determined solely on absolute commercial grounds before shareholders. The Foundation for Managed Care Pharmacy epitomizes this mistake by stating that adding value to health care means delivering a fair return on investment (2001).

Instead, value of pharmaceuticals should be relative to some alternative because only by prescribing incremental value over other treatment options can we justify premium price (Deloitte Center for Health Solutions, 2012). This notion is perfectly aligned with the marginal utility theory of value (see figure 02). For patients, the marginal value is particularly imperceptible (Castano, 2014). Paris and Belloni (2013) define the pharmaceutical customer value as either the customer’s maximum willingness-to-pay or best alternative plus the value of any differentiating features. However, even when the patient wants to pay for added benefits it is not obvious to him or her how to assess the short-term clinical outcomes that yield those benefits (Castano, 2014).
**FIGURE 02: Connections Between Axiology and Pharmaceutical Value**

The clinical value of pharmaceuticals

There is broad consensus that clinical trials are useful for demonstrating absolute value of pharmaceuticals. Yet, trials provide no evidence on the relative or marginal value of a drug because they are primarily designed to show non-inferiority to placebo (Garthwaite & Duggan, 2010). LaMattina (2013) argues that studies of value must result in greater confidence that a new drug will provide long-term health benefits in order to be successful.

Estimating the efficacy of medications relative to existing treatments is a rather untested methodology (Garthwaite & Duggan, 2010). Nevertheless, comparative effectiveness research is gaining importance, which might boost supply. As such, Milne, Cohen, Felix and Chakravarthy showed that payers are using comparative effectiveness evidence for most types of post-approval decisions such as pricing. Pharmaceuticals can also acquire marginal value over existing treatment options as post-approval evidence
generation potentially triggers indication extensions, formulary exclusivity or establish superiority claims (2015). The problem in addressing value of pharmaceuticals in a clinical matter is that the industry’s mind-set remains supply-sided. According to Castano, “in other industries that are driven by consumers’ search for value for money the design of value start[s] from the consumer’s need, expectations and preferences i.e. manufacturers have a consumer-driven mind-set” (2014). Indeed, Lexchin found that industry-funded research is four times more likely to produce positive outcomes compared to research backed by any other source of funding. Biases are commonly introduced though the choice of comparator agents, dosage administration, conflict of interest and seeding trials (2011) as well as extensive use of preliminary data (Fries and Krishman, 2004; in Lexchin 2011).

The pharmacoeconomic value of pharmaceuticals
Economic evaluation of pharmaceuticals is a widely adopted methodology by institutional payers. It is used to inform pricing and reimbursement decisions and explicitly considers incremental utility for patients as the determining factor of value. Health authorities favoring economic evaluation usually conduct a cost-utility ratio analysis to quantify the value of a drug. In doing so, they take into account patient preferences or utility derived from different health states. The most common measure of outcome in cost-utility analyses is the quality-adjusted life year (QALY), which captures both gains from reduced morbidity (quality of life) and mortality (quantity of life) in a single metric (Paris & Belloni, 2012).

The Canadian Agency for Drugs and Technologies in Health (CADTH) used a cost utility analysis to rule out formulary inclusion of Sitagliptin, an oral anti-diabetic agent, in 2008. The CADTH requested a pharmacoeconomic drug review pitting Sitagliptin against

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2 See Novo Nordisk, 2016a, for example of application to the FDA to include clinical post-approval trial data (SWITCH-2) in the label of insulin degludec, Tresiba.
3 One QALY is equal to one year in perfect health.
established treatment options. The analysis found that Sitagliptin was only associated with greater benefits and lower incremental costs against Rosiglitazone 8mg (-$362 per QALY).

Versus other comparator presentations weighted by their share of claims, Sitagliptin boasted an incremental cost of $9,225 per QALY (Canadian Agency for Drugs and Technologies in Health, 2008).

As evident from our Sitagliptin case, usually the choice of comparator is critical. Relative efficacy, effectiveness and added therapeutic value of a drug depend heavily on the intervention it is compared with (Paris & belloni, 2012). The United Kingdom’s (UK) National Institute for Health and Care Excellence (NICE) takes a different approach. NICE asserts that the additional cost to produce one QALY must not exceed a certain threshold for the new drug to be considered for reimbursement. This threshold represents the marginal value of the mix of established treatment options and currently is set at £30,000 per QALY for routine evaluations (Moreno & Ray, 2016).

The societal value of pharmaceuticals

The utilization of pharmaceuticals can impact society on many levels. Estimating the totality of extrinsic value is difficult; isolating the individual effects and evaluating them is seemingly a better option. The OECD recognizes that extrinsic value is context-dependent and recommends EU countries to only pay for drugs in relation to the value they bring to the country’s own health system and society (Paris & Belloni, 2012).

Countries like Norway and Sweden have opted for a social perspective to evaluate pharmaceuticals. Paris and Belloni (2012) argue that in principle it could have a large impact on prices paid and society but in practice there is little evidence. Castano (2014) points to the fact that societies that recognize a universal right to healthcare (e.g. Sweden and Norway) isolate the individual’s willingness-to-pay from the actual medical care received. In those systems there is a risk of moral hazard whereby the marginal benefit of the drug can be far lower than its marginal cost.

Pharmaceuticals that treat chronic conditions such as diabetes have the ability to generate a myriad of non-health benefits. Garthwaite and Duggan (2010) found significant empirical evidence showing that increased pharmaceutical utilization results in lower crime rates, increased productivity and labor force participation. Another extrinsic benefit of pharmaceuticals is the effect of increased drug spending on expenditures of other medical
services. The rationale is that effective\(^4\) pharmaceuticals should lower the spending on other more expensive treatments.

To maximize societal value many institutions are increasingly exploring value-based pricing. These schemes identify the price that ensures that expected health benefit of pharmaceuticals exceed the health predicted to be displaced elsewhere in the system due to costs (Claxton, 2007; in Paris & Belloni, 2012). Indeed Miller and Frelch (2000) analyzed country health expenditure and found that higher levels of spending on new pharmaceuticals were positively correlated to increases in life expectancy. A large number of studies have also generated supportive evidence that increased utilization of new pharmaceuticals (implying increased expenditure) leads to a significant increase in overall life expectancy and reductions in hospital\(^5\) and other non-drug spending (Shaw, Horace & Vogel, 2005; Lichtenberg, 1996, 2004; Cremieux et al., 2005; in Garthwaite & Duggan, 2010).

**The value under innovative pharmaceuticals**

There is a growing financial pressure on payers from demographic and epidemiologic transitions but mostly as a consequence of new medical technologies that generate small incremental benefits (Castano, 2014; Newhouse, 1992 and Smith et al, 2009 in Garthwaite & Duggan 2010; Foundation for Managed Care Pharmacy, 2001). This trend poses the question whether new pharmaceuticals are worth their cost. Several stakeholders argue that they are: these include patients who generally perceive meaningful health improvements (Garthwaite & Duggan, 2010) and the industry, which justifies value on clinical (Foundation for Managed Care Pharmacy, 2001) and economic grounds (Moreno & Ray, 2016).

Milne et al. says “calculations of budgetary impact are related to affordability, not to comparative effectiveness of value” (2015). Hence, little is known about the added value under innovation that new drugs can inject into the healthcare system. The OECD analyzed how countries refer to value when deciding on reimbursement of new medicines and found that there is no consensus on how to assess particular value under innovation. Furthermore, they found no evidence that innovation beyond clinical efficacy was considered in practice to inform reimbursement decisions (Paris and Belloni, 2012).

\(^4\) Effective refers to the impact on the health system and its management (adapted from Fiminska, 2014)

\(^5\) Lichtenberg (1996) estimated that an increase in utilization of drugs of $1 is associated with $3.65 decrease in hospital expenditure (in Garthwaite & Duggan, 2010)
If a new pharmaceutical in France is evaluated to bring major (ASMR I) or significant (ASMR II) improvements it is entitled to a price premium. Similarly, Germany does not cluster new pharmaceuticals in reference price groups and entitle a price premium if the drug brings some additional benefit to the health system. The degree of added benefit is established in a negotiation process (Paris & Belloni, 2012).

Correspondingly, Japan applies a defined range of price premium entitlements according to the usefulness of the new drug. If the new drug is indicated for pediatric use it entitles a 5-20 percent price premium. If the new drug is categorized as innovative over the comparator, it is granted a 70-120 percent premium. Countries like Sweden, Norway and the UK make use of cost-effectiveness ratios to assess the level of innovativeness. The basis of this evaluation is the amount of QALYs gained in addition to comparators (Paris & Belloni, 2012).

Moreno and Ray published an elaborate critique of the use of QALY in assessing the value of innovation. They argue that the conventional approach of cost-effectiveness analysis using QALYs as the final outcome measure tends to underestimate the value of innovative drugs by disregarding the off-patent price and incidence patients. In doing so, the model is prevented from capturing benefits to future patients and future savings from off-patent prices. The drop in the price of a pharmaceutical stemming from generic entry represents a significant transfer of value from the manufacturer to the health authority (2016).
Diabetes Mellitus

In the following pages I will provide an introduction to Diabetes Mellitus. First the etiological and epidemiological particularities are accounted for. Next, I outline the medical complications associated with Diabetes Mellitus and shed light on the economic magnitude of the condition. In particular the diabetes-related health expenditures are described. Finally I present the prevention and treatment options currently used for disease management. Here, a focus on therapeutic regimens and specific agents’ mechanism of action provides the basis for discussion.

Etiology and epidemiology

Diabetes Mellitus (hereinafter diabetes) is a chronic disease that occurs when the pancreas fails to effectively produce insulin or when the body cannot make good use of the insulin it produces. Insulin is a hormone, which allows glucose to enter the body’s cells where it is converted into energy. Without sufficient insulin, the resulting accumulation of glucose in the blood leads to hyperglycemia. There are two major types of diabetes:

- **Type 1 diabetes (T1DM)**, also known as insulin dependent or juvenile-onset diabetes, is the result of an autoimmune reaction causing the pancreas to produce no or very little concentrations of insulin. T1DM usually develops at a young age and requires daily insulin injections to survive (International Diabetes Federation, 2016; World Health Organization, 2016b).

- **Type 2 diabetes (T2DM)** is typically the result of poor dietary habits and a sedentary lifestyle. Moreover there is a substantial discussion about the effect of genes on the development of T2DM. The disease occurs when the pancreas does not produce enough insulin (relative insulin deficiency) or if the body does not make effective use of the insulin it produces (insulin resistance). T2DM is a progressive chronic condition in which insulin levels decline over time because of decreasing amounts of beta cells and their diminished secretory capacity. Beta cell failure results among other things from exposure to chronically elevated levels of blood glucose also known as glucotoxicity (Ismail-Beigi, 2012; International Diabetes Federation, 2016).

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6 Other specific and minor types of diabetes also exist, e.g. gestational diabetes
According to the World Health Organization (WHO) and the International Diabetes Federation (IDF), global prevalence of diabetes among adults over 18 years has risen from 4.7 percent to 8.8 percent over the last 35 years. Last year the estimated worldwide amount of diabetics was 415 million and that number is expected to grow with 9 million every year until 2040 (International Diabetes Federation, 2016; World Health Organization, 2016b). Moreover, it is said that 46.5 percent of adults with diabetes remain undiagnosed. Figure 03 shows the historical trend of diabetes prevalence by WHO region and table 04 summarizes the 2015 and forecasted 2040 prevalence, total diabetics as well as diabetes-related health expenditure by IDF region.

**FIGURE 03: Trends in Prevalence of Diabetes, 1980-2014, by WHO Region**

The normal glycemic target range is 6.0 – 6.5 percent, hence the diagnosis of T2DM is based on a glycated hemoglobin (HbA1c) level of 6.5 percent or more. Hemoglobin is a protein within red blood cells, which carries oxygen and glucose in the blood; by joining to glucose, hemoglobin becomes glycated. Physicians use HbA1c as a measure to diagnose diabetes because it provides us with a picture of average glucose levels over a longer period of time. T2DM can also be diagnosed by looking at a 2-hour plasma glucose level (>200mg/dL) or the fasting plasma glucose level (>126mg/dL) (Ismail-Beigi, 2012).
Medical complications and health expenditures

Diabetes is a global concern that has been on the rise more rapidly within low- and middle-income countries. It is estimated that 87-91 percent of all people with diabetes in high-income countries suffer from T2DM. T2DM is a more common condition than T1DM as it is fuelled by cultural and social changes in lifestyle and consumption, ageing populations and increased urbanization. T2DM affects health status and life span substantially and carries significant societal costs. The condition is the leading cause of blindness, kidney failure, and lower-limb amputation. Other complications count diabetic foot, oral health, nerve damage and cardiovascular disease (World Health Organization, 2016b; International Diabetes Federation, 2015; Ismail-Beigi, 2012).

**TABLE 04: Total Diabetics, Prevalence and Diabetes-Related Health Expenditure 2015 and Forecasted 2040, by IDF Region**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>North America &amp; Caribbean</td>
<td>44.3 mil.</td>
<td>60.5 mil.</td>
<td>12.9 %</td>
<td>14.7 %</td>
<td>$348 bn.</td>
<td>$390 bn.</td>
</tr>
<tr>
<td>South &amp; Cent. America</td>
<td>29.6 mil.</td>
<td>48.8 mil.</td>
<td>9.4 %</td>
<td>11.9 %</td>
<td>$34.6 bn.</td>
<td>$55.6 bn.</td>
</tr>
<tr>
<td>Europe</td>
<td>59.8 mil.</td>
<td>71.1 mil.</td>
<td>9.1 %</td>
<td>10.7 %</td>
<td>$156 bn.</td>
<td>$174 bn.</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>35.4 mil.</td>
<td>72.1 mil.</td>
<td>9.1 %</td>
<td>11.4 %</td>
<td>$17.1 bn.</td>
<td>$31 bn.</td>
</tr>
<tr>
<td>Africa</td>
<td>14.2 mil.</td>
<td>34.2 mil.</td>
<td>3.2 %</td>
<td>3.7 %</td>
<td>$3.4 bn.</td>
<td>$5.5 bn.</td>
</tr>
<tr>
<td>South East Asia</td>
<td>78.3 mil.</td>
<td>140.2 mil.</td>
<td>8.5 %</td>
<td>10.7 %</td>
<td>$7.3 bn.</td>
<td>$12.9 bn.</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>153.2 mil.</td>
<td>214.8 mil.</td>
<td>9.3 %</td>
<td>11.9 %</td>
<td>$106 bn.</td>
<td>$133 bn.</td>
</tr>
<tr>
<td>Total World</td>
<td>415 mil.</td>
<td>642 mil.</td>
<td>8.8 %</td>
<td>10.4 %</td>
<td>$673 bn.</td>
<td>$802 bn.</td>
</tr>
</tbody>
</table>

**Source:** International Diabetes Federation, 2015

The economic burden of diabetes is massive. In 2015, 12 percent of global health expenditure was used on diabetes; that accounts to $673 billion. Although the diabetic population is expected to increase by 54 percent during the next 25 years, the diabetes-related health spending is only projected to rise another 19 percent (International Diabetes Federation, 2015). With that kind of investment gap, society must put pressure on its health
care systems. Major cost drivers are hospitalization and outpatient care, however another contributing factor is the rising prices for medications, particularly for analogue insulin (World Health Organization, 2016a).

While an estimated $1,622 USD to $2,886 USD was spent per person with diabetes last year, low-income countries generally pay much larger out-of-pocket shares of health expenditure than do middle- and high-income countries. IDF reports that in Latin America, for instance, it is not unusual to pay 40-60 percent of the medical expenses out-of-pocket (2015). To cope with this issue in the short run, the WHO suggests diabetes management to integrate with management of other non-communicable diseases; or maybe even with tuberculosis and HIV/AIDS; to improve efficiency and outcomes (2016a).

**Disease prevention and treatment**

Ismail-Beigi (2012) provides us with an excellent introduction to glycemic management of T2DM. Where T1DM is almost always treated with insulin injections, T2DM prevention and treatment offers a great variety of regimen options. In embryonic stages of T2DM, lifestyle modification including diet control and exercise intensification is recommended. When pharmacological therapy is needed, metformin becomes the cornerstone of T2DM management.

**FIGURE 05: T2DM Treatment Intensification (left) and Distribution of Patients and Value across Treatment Classes (right)**

T2DM is a progressive disease (see page 15) and multiple therapeutic agents are available when metformin alone becomes insufficient. The problematic is that very little evidence exist to unilaterally support the choice of any second-line agent over another. Hyperglycemia is caused by the failure in one or more of the mechanisms outlined in figure 06. Each therapeutic agent is said to have a mechanism of action, targeting one of the
causes for hyperglycemia. For example, metformin improves insulin sensitivity by reducing hepatic glucose production whereas DPP-4 inhibits the degradation of GLP-1 thereby increasing insulin levels. Ismail-Beigi (2012) notes that considering agents with complementary mechanisms of actions is the logical strategy for improving T2DM management. Table 08 summarizes all the currently relevant agents and figure 07 illustrates in which order they are commonly administered.

**FIGURE 06:** Pathophysiologic Mechanisms for Whom Failure Leads to Hyperglycemia in T2DM Patients

**FIGURE 07:** Therapeutic Regimes for Glycemic Management in T2DM Patients

SOURCE: ADAPTED FROM ISMAIL-BEIGI, 2012

SOURCE: AUTHOR’S OWN INTERPRETATION
### TABLE 08: Pharmacologic Agents for Glycemic Control in T2DM Patients

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Expected reduction in HbA1C (%)</th>
<th>Mechanism of action</th>
<th>Pharmalogic function</th>
<th>Side-effects</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide (Metformin)</td>
<td>1.0 - 2.0</td>
<td>Reduce hepatic glucose production</td>
<td>Improve insulin sensitivity</td>
<td>Gastrointestinal</td>
<td>Low (generic)</td>
</tr>
<tr>
<td>Sulfonylurea (SU)</td>
<td>1.0 - 1.5</td>
<td>Stimulate insulin release by closure of specific potassium channels on beta cells</td>
<td>Increase insulin levels</td>
<td>Modest weight gain and hypoglycemia</td>
<td>Low (generic)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>0.5 - 1.4</td>
<td>Enhance insulin sensitivity in peripheral tissues and reduce hepatic glucose production</td>
<td>Improve insulin sensitivity</td>
<td>Increased risk of myocardial infarction</td>
<td>High</td>
</tr>
<tr>
<td>DPP-4</td>
<td>0.5 - 0.8</td>
<td>Inhibit the degradation of GLP-1 and results in elevated levels of circulating GLP-1</td>
<td>Increase insulin levels</td>
<td>No weight effect; CV risk; joint pain; allergy</td>
<td>High</td>
</tr>
<tr>
<td>SGLT-2*</td>
<td>0.5 - 1.0</td>
<td>Selectively and reversibly inhibit natrium-glucose cotransporter-2 in the proximal tubule, thereby preventing glucose reabsorption.</td>
<td>Reducing plasma-glucose</td>
<td>Weight loss; CV safety (38%); vaginitis; decreased bone density</td>
<td>High</td>
</tr>
<tr>
<td>GLP-1</td>
<td>0.5 - 1.5</td>
<td>Increase blood glucagon-like-peptide 1 activity or levels and stimulate insulin secretion while inhibiting glucagon secretion.</td>
<td>Increase insulin levels</td>
<td>Delayed gastric emptying and appetite suppression, resulting in weight loss; CV risk unkown</td>
<td>High</td>
</tr>
<tr>
<td>Human insulin (NPH)</td>
<td>1.0 - 2.5</td>
<td>Stimulate glucose uptake by responsive tissues and decreases hepatic glucose production</td>
<td>Increase insulin levels</td>
<td>Weight gain and hypoglycemia</td>
<td>Low (generic)</td>
</tr>
<tr>
<td>Insulin analogue</td>
<td>1.0 - 2.5</td>
<td>Stimulate glucose uptake by responsive tissues and decreases hepatic glucose production</td>
<td>Increase insulin levels</td>
<td>Weight gain and hypoglycemia</td>
<td>High**</td>
</tr>
<tr>
<td>Fixed-dose combinations</td>
<td>1.0 - 2.5</td>
<td>GLP-1/Insulin combination</td>
<td>Increase insulin levels</td>
<td>GLP-1/Insulin combination</td>
<td>High</td>
</tr>
</tbody>
</table>

* Source: Christiansen, 2016
** The price of insulin analogues is currently undergoing a period of transformation as insulin glargine has gone off-patent in 2015.

Source: Adapted from Ismail-Beigi, 2012
The Insulin Market
The global insulin market was valued at approximately $20.8 billion USD and grew at a rate of 12.9 percent in sales in 2012 (Wirtz, 2016). It is estimated to reach $53 billion USD in 2022, boasting a 10-year CAGR of 9.8 percent. Insulin analogs are expected to comprise revenue of over $45 billion USD already in 2020 (Grand View Research, 2015) and the insulin delivery device market is expected to add another $12.8 billion USD, taking the total insulin and delivery device market to astonishing $65 billion USD (Mordor Intelligence, 2016).

Approximately 100 million people around the world need insulin (Wirtz, 2016). Still insulin is generally added to the therapeutic regime much later than medically indicated (Ismail-Beigi, 2012). The T2DM market is driving global growth because of dietary and lifestyle changes leading to increased incidence (Thermalin Diabetes, 2016). However the lack of access to affordable insulin remains a key barrier to effective treatment (World Health Organization, 2016a). According to Wirtz, insulinization rates ranged from 2.4 percent in Taiwan to 23.5 percent in the US (2016). This hefty gap suggests that there is a geographic disparity of access to insulin or widely varying prescribing trends. Indeed the WHO claims that insulin is only generally available in a minority of low-income countries (2016a).

In the following sections I will clarify general insulin typology, including the difference between human and analogue insulin as well as between basal and bolus insulin. Next an overview of the most important products will be provided for. Importance is based on the potential impact on the market meaning certain products will already be firmly established whereas others might be new with a significant potential to make a future impact. Finally I will elucidate how the market is comprised in terms of manufacturers and other stakeholders including the business models that exist hereof.

Insulin typology
Insulin is a hormone that allows glucose to enter the body’s cells where it is converted into energy. When insulin is naturally produced in the pancreas it is said to be endogenous and when it is manufactured in a laboratory it is called exogenous insulin. The body needs two different types of insulin regardless of its origin: basal and bolus. Basal insulin is released gradually at all times to keep blood glucose controlled between meals and over night. Bolus
insulin is a rapid and short-acting response to mealtime increases in blood glucose due to carbohydrates intake. The routine dose of basal insulin is 0.2 – 0.4 international units (IU) per kilogram body weight per day whereas pre-meal bolus insulin dose should seek to match the immediate carbohydrate intake (Hieronymus & Geil, 2006; Monnier, Colette & Owens, 2013).

Within the exogenous category of insulin, that is central to our analysis, numerous types exist. Foremost, it is important to understand the distinction between human and analogue insulin. Human insulin can be fast-acting (also known as regular), intermediate-acting (also known as Neutral Protamine Hagedorn) or premixed (Wirtz, 2016). Regular fast-acting human insulin falls under the bolus category while intermediate-acting represents the basal class. To produce the current versions of basal human insulin, Neutral Protamine Hagedorn (hereinafter NPH), protamine is added to recombinant synthesized human insulin.

**FIGURE 09: Insulin Time-Action Profiles (left) and Global Insulin Volume Market by Segment (right)**

Basal human insulin peak time-action values are reached during an interval of four to eight hours after injection (Monnier, Colette & Owens, 2016) and NPH shows a pronounced peak effect, increasing the risk of nocturnal hypoglycemia significantly. Moreover NPH fails to replicate the physiological profile and is associated with high intra-patient variability and requires multiple dosage administrations per day; as a result NPH insulin is generally less expensive than analogues (Singh & Gangopadhyay, 2014; Wirtz, 2016). Thermalin Diabetes argues that “the (NPH, red.) segment is declining as [it] is moving to the end of its life cycle, being displaced by the more effective but slightly more expensive insulin analogues” (2016).
Insulin analogues are similar to human insulin but have an altered amino acid sequence. This provides the chemical properties needed for improved glycemic control and lower frequency of hypoglycemic events. Basal analogues as such have a longer duration of action (thereof long-acting) with a peak time-action profile within the duration of four and 16 hours and less intra-patient variability. Basal long-acting analogues do not demonstrate a significant decrease in HbA1c levels versus NPH; studies report similar NPH and analogue drops (Wirtz, 2016; Sing & Gangopadhyay, 2014; Monnier, Colette & Owens, 2013; Rotenstein, Ran, Shivers, Yarschoan & Close, 2012).

White (2016) raises a common concern regarding the switch from NPH to basal analogue insulin. While the reduction in hypoglycemic events stemming from analogue administration may affect both willingness to titrate and patient adherence there is a large risk of dosing errors. This is because NPH usually is sold in U-500 concentrations (500 IU/mL) whereas the most common analogue comes in a U-100 formulation (100 IU/mL). Confusing the two formulations in administration of insulin injections can result in severe or fatal hyper- and hypoglycemic events.

In recent years, new innovative formulations of basal analogue insulin have been developed to provide an even longer duration of action and especially to address the unmet need of dealing with nocturnal hypoglycemia (White, 2016; Sing & Gangopadhyay, 2014). These formulations are dubbed ultra-long-acting and include molecules such as insulin degludec and insulin glargine U-300 (see page 27). Despite great innovations however, the WHO is yet to include any analogue preparations in the list of essential medicines because its systematic review did not find evidence of cost-benefit against NPH (World Health Organization, 2016a).

The role of basal insulin, particularly, is increasing in the management of Diabetes therapy (Sing & Gangopahay, 2014). Analogues are expected to yield revenues of over $45 billion USD by 2020, mainly on the account of switch from NPH. The magnitude of analogues is founded in the T2DM market which is expected to contribute with approximately 85 percent of the before mentioned revenue. Moreover, the new innovative ultra-long-acting formulations are anticipated to be the most lucrative products with a likely CAGR of over 15 percent until 2020 (Grand View Research, 2015). A proportionally large number of analogues are approved in high-income countries compared to lower-income countries. The disparity may be explained by purchasing power, as analogues are
substantially more costly than NPH (Wirtz, 2016). Figure 10 shows the percentage of analogue insulin sales in the basal segment in high- and middle-income countries.

**FIGURE 10: Percentage of Analogue Insulin Sales by Income Level**

Basal insulin analogue products

Treatment of T2DM with products from the basal insulin analogue regimen is associated with an overall reduction in diabetes-related complications. These analogues generate a surplus of QALYs relative to NPH; however only on rare occasions do the medical improvements yield a positive cost-benefit outcome. Clinical benefits and indirect cost-savings simply do not appear to offset the increased acquisition cost of basal analogue insulin products (Cameron & Bennett, 2009). In the clinical and pharmacoeconomic evaluation of basal insulin, the comparator agent is critical for the outcome. The reference comparator preparation is often chosen from similar medications, which have been relevant to the market for numerous years and are used globally on routine basis. In the basal insulin regimen most products are compared to NPH or insulin glargine (Monnier, Colette & Owens, 2013).

Another critical factor in the evaluation of basal insulin is the methodology for determining utility scores (ultimately expressed in detrimental or incremental QALYs). A widely used instrument is the EuroQol-5D, which consists of the five dimensions: mobility, self-care, usual activities, pain and anxiety. Furthermore it is now being discussed and increasingly accepted that fear of hypoglycemia should have a chronic detrimental impact on the health-related quality of life (Cameron & Bennett, 2009). Cameron & Bennett
concludes that routine use of basal insulin analogues increments the cost to institutional payers, however when the fear of hypoglycemia is incorporated in the model, the gap between incremental cost and the cost-effective threshold shrinks (2009).

In the succeeding sections I will describe the most relevant molecules available in the basal insulin analogue market. Particularly I will comment on the pharmacokinetic (PK) and pharmacodynamics (PD) profiles as well as cost-effectiveness studies of insulin glargine U-100, insulin glargine U-300, insulin glargine biosimilars, insulin detemir and insulin degludec. The PK/PD profile and cost-benefit outcomes are important to insulin manufacturers as they represent competitive marketing claims and inform label indications. It is by virtue of these claims and indications that the manufacturers are able to differentiate their products from one to another.

**Insulin glargine U-100**

In 2000, the FDA and the European Medicines Agency (EMA) approved the first long-acting basal insulin analogue for the treatment of T1DM and T2DM. The molecule insulin glargine is developed and manufactured in a U-100 preparation by French drug maker Sanofi-Aventis (hereinafter Sanofi). None of the pre-approval studies investigating insulin glargine were designed to look for hard endpoints, as it was not required by the regulatory agencies. In fact insulin glargine showed no superiority with respect to HbA1c reduction over NPH; nevertheless, post-approval studies and meta-analysis were able to demonstrate significant benefits in reducing hypoglycemia (Sing & Gangopadhyay, 2014).

Since 2000, studies have consistently shown that insulin glargine do not reduce HbA1c levels versus NPH. However it is a fact that the PK/PD features of the glargine molecule boast a less pronounced peak time-action profile and less intra-patient variability than NPH. More importantly insulin glargine was labeled as a long-acting analogue, meaning that the prolonged duration requires only one injection per day (Wirtz, 2016). Finally the U-100 formulation of insulin glargine shows neutral effect on cardiovascular outcome and cancer (White, 2016); but only after the manufacturer responded to speculations with a 6-year interventional, randomized, open label study to evaluate the effects of insulin glargine

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7 Cameron & Bennett, 2009, consider insulin detemir and insulin glargine with an on-patent price. In 2015 the patent of insulin glargine expired resulting in market-wide price decreases, which mathematically generates a higher level of cost-effectiveness than expressed in the analysis.

8 Real world evidence has shown that although insulin glargine (and detemir) were labelled as long-acting once-daily insulin, they often require two injections for optimal control.
in reducing cardiovascular mortality and morbidity (Clinical.Trials.gov identifier NCT00069784).

This seminal insulin glargine study was dubbed ORIGIN and has become a fundamental factor in today’s insulin market. Sanofi markets insulin glargine U-100 under the trade name Lantus. In 2015 the molecule lost market exclusivity as the patent expired; since then, biosimilar products can enter the market and make free use of the ORIGIN study. Biosimilar products are generic versions of complex biological molecules developed by companies other than the reference product’s patent owner. Although manufacturers of biosimilars use techniques for production similar to those of the reference product the two products are unlikely to be bio-identical in their molecular characteristics and clinical profiles. Biosimilar products are important because their manufacturers do not bear full-scale research and clinical trial costs which usually results in cheaper products compared to the originator (Rotenstein, et al., 2012). Biosimilar competition and its impact on the basal analogue market are covered in-depth on page 39.

**Insulin detemir**

Danish pharmaceutical manufacturer, Novo Nordisk, launched insulin detemir, the second-to-market basal analogue, in 2004. Insulin detemir is remarkable similar to insulin glargine U-100 in terms of its PK/PD profile. In pre-approval trials, comparison to NPH showed no superiority in terms of HbA1c reduction, however post-approval studies demonstrated an improved effect on nocturnal hypoglycemic events and a prolonged duration of action (Singh & Gangopaghay, 2014; Wirtz, 2016). Insulin detemir is marketed under the trade name Levemir.

A Canadian cost-effective analysis of insulin analogues found that the incremental cost per QALY was more than three times higher for insulin detemir compared to insulin glargine. Both analogues failed to dominate NPH even after fear of hypoglycemia was included in the model (Cameron & Bennett, 2009). The low cost-effectiveness of insulin detemir versus insulin glargine could be explained by detemir’s time-to-market disadvantage, possibly resulting in larger glargine market share leading to economies of scale and lower cost of goods sold. A lower price by definition will always be more effective at generating QALYs for money.
**Insulin glargine U-300**

In response to the imminent threat from glargine U-100 biosimilars, Sanofi launched a new and improved insulin glargine formulation, insulin glargine U-300, in 2015. The new formulation, marketed as Toujeo, contains three times more international units per mL than insulin glargine U-100. It is associated with a more stable PK profile than the U-100 formulation and has a confirmed ultra-long duration of action. Improvements are also demonstrated on nocturnal and severe hypoglycemia and insulin glargine U-300 causes less weight gain than does the original intermediate and long-acting insulin (White, 2016).

An increasing problem in the diabetes patient population is growing obesity rates. Excess weight and T2DM are closely related conditions as they are both driven by the same sedentary lifestyle behavior. Obese patients with T2DM require large dosages of insulin because titration is body-weight dependent. As insulin glargine U-300 is three times more concentrated than earlier basal analogues it is convenient for obese patients who tries to avoid dispensing large volumes and the consequential injection site discomfort (White, 2016). Finally, White (2016) notes that insulin glargine “U-300 is likely to benefit people at high risk of hypoglycemia, allows for once-daily dosing, alleviate adherence issues related to rigid dosing schedules and people requiring large-dose insulin injections”.

**Insulin degludec**

Novo Nordisk also developed an ultra-long acting basal insulin analogue but contrary to Sanofi’s second glargine product, Insulin degludec as it is called, is an innovative new molecule. Insulin degludec is marketed as Tresiba since 2013 when it was EMA approved although it only snagged FDA’s approval in late 2015. The product is a U-200 formulation with its duration of action found to be more than 42 hours. Insulin degludec was compared in head-to-head pre-approval studies to both insulin glargine and Novo Nordisk’s own insulin detemir. The studies and following meta-analyses showed significant benefits in the control of nocturnal hypoglycemia, however they were heavily criticized for induced bias because insulin degludec was always administered with the main meal whereas insulin glargine U-100 could be administered at any time of the day as per its label (Singh & Gangopadhyay, 2014).

Insulin degludec is innovative in the way that it draws its long duration and stable profile from the combination of the properties of insulin glargine and insulin detemir.
Cost-effectiveness analyses of insulin degludec conclude that the product adds beneficial value for the cost for a T2DM patient subpopulation suffering from recurrent hypoglycemia (Singh & Gangopadhyay). Overall cost-benefit analyses of the entire diabetes spectrum are lacking however it might be a deliberate manufacturer decision to only position insulin degludec with a high cost before a small subpopulation with an unmet need. Insulin degludec is also used in fixed-dose combination preparations (FDC) with Novo Nordisk’s GLP-1 analogue liraglutide and bolus insulin aspart. The two products, respectively marketed as Xultophy and Ryzodeg, are expected to have major impact on the treatment paradigm. I cover FDCs more in-depth on page 59.

**FIGURE 11: Weekly US New-to-Brand Rx Volume Market Share**

![Weekly US New-to-Brand Rx Volume Market Share](image)

**Insulin manufacturers**

Roughly 100 million people around the world need insulin and yet only three companies largely supply the entire market (Wirtz, 2016; World Health Organization, 2016a). In terms of revenue shares, Novo Nordisk, Sanofi and Eli Lilly capture 93 percent of the total bolus and basal, human and analogue insulin market. Only a handful of other companies are supplying insulin on a multinational basis\(^9\) and the vast majority of these rely on the NPH market.

Wirtz (2016) identified a total of 42 insulin manufacturers worldwide, most however only supply NPH and solely to their country of origin. A few NPH specialists such as Indian Wockhardt and Biocon or Mexican Pisa are also developing a biosimilar of insulin glargine U-100. Table 12 shows the revenue market share of top-10 insulin manufacturers by products

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\(^9\) Supplying insulin to two or more countries.
registered globally. Since only seven remaining percent of the market is divided among approximately 39 manufactures, their exact share remains unknown.

**TABLE 12: Top-10 Insulin Manufactures by Product Registrations and Revenue**

<table>
<thead>
<tr>
<th>Company</th>
<th>Country</th>
<th>Products registered in % of countries</th>
<th>Revenue market share</th>
<th>Main Insulin product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novo Nordisk</td>
<td>Denmark</td>
<td>91.7%</td>
<td>41%</td>
<td>Levemir; Tresiba; Ryzodeg; Xultophy; human insulin</td>
</tr>
<tr>
<td>Sanofi</td>
<td>France</td>
<td>83.5%</td>
<td>32%</td>
<td>Lantus; Toujeo; Soliqua; Apidra; Insuman</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>United States</td>
<td>77.7%</td>
<td>20%</td>
<td>Humalog; Humilin; Abasaglar</td>
</tr>
<tr>
<td>Bioton</td>
<td>Poland</td>
<td>21.5%</td>
<td>Unknown</td>
<td>Human insulin</td>
</tr>
<tr>
<td>Wockhardt</td>
<td>India</td>
<td>14.0%</td>
<td>Unknown</td>
<td>Glaritus; Human insulin</td>
</tr>
<tr>
<td>Biocon</td>
<td>India</td>
<td>14.0%</td>
<td>Unknown</td>
<td>Galactus; human insulin</td>
</tr>
<tr>
<td>Julphar</td>
<td>UAE</td>
<td>10.7%</td>
<td>Unknown</td>
<td>Human insulin</td>
</tr>
<tr>
<td>Tonghua Dongbao</td>
<td>China</td>
<td>5.8%</td>
<td>Unknown</td>
<td>Human insulin</td>
</tr>
<tr>
<td>Pisa</td>
<td>Mexico</td>
<td>4.1%</td>
<td>Unknown</td>
<td>Galactus; human insulin</td>
</tr>
<tr>
<td>Polfa Tarchomin</td>
<td>Poland</td>
<td>2.5%</td>
<td>Unknown</td>
<td>Human insulin</td>
</tr>
</tbody>
</table>

**Source:** Adapted from Wirtz, 2016

In the following paragraphs I will comment on the three large insulin manufacturers, Novo Nordisk, Sanofi and Eli Lilly. I will also introduce the role of other major pharmaceutical companies in the market for anti-diabetes medication, because some agents supplied by these companies are becoming increasingly important and relevant for a paradigm change.

In 2014, Danish-based diabetes specialist **Novo Nordisk** came in on an overall first in terms of diabetes-related global sales with reported $11.3 billion USD. In fact, today, Novo Nordisk relies more on its GLP-1 agonist\(^{10}\), liraglutide (trade name Victoza) than it does on insulin; however both human insulin as well as analogues constitute the historic legacy and significant portions of the bottom line. Novo Nordisk has been at the forefront of insulin development since the early 20\(^{th}\) century and currently produces more insulin than any other company in the world. Since the company boasts a large assortment of patented innovative drugs, particularly GLP-1 and insulin analogues, they have enjoyed exclusivity and premium prices for many years (Wasserman, 2015; Rotenstein et al., 2015).

Novo Nordisk’s portfolio consists of human insulin, the basal analogues Levemir and Tresiba as well as insulin aspart, a bolus analogue for meal-time or combination therapy. Novo Nordisk’s in-house research and development have crafted some powerful innovative

\(^{10}\) Considering long-term sustainability of the total diabetes portfolio (Stovall, 2016: Staton, 2016a)
products that are currently launching or in pipeline for imminent launch. Among these are the basal-bolus FDC Ryzodeg and basal-GLP-1 Xultophy. The GLP-1 segment in particular looks promising as Novo Nordisk is reporting late phase trials of Semaglutide, a once-weekly GLP-1 and promising performance with liraglutide for obesity, marketed as Saxenda. Novo Nordisk is also looking at developing an oral GLP-1 and had its eyes on oral insulin; the latter could have proven to be the Holy Grail of diabetes treatment had it not been discontinued due to a lack of commercial viability in late 2016 (Wasserman, 2015; Adams, 2016).

**Sanofi**, a French pharmaceutical involved in a plethora of therapeutic areas, dominates the basal insulin analogue market. The company racked in $10.7 billion USD in diabetes sales in 2014, driven mainly by its multiple blockbuster Lantus (Wasserman, 2015). Lantus sold more than four times that of its closest competitor in the drug class, Levemir. However after losing product exclusivity in 2015, Lantus has come under pressure from biosimilars and new innovative technologies.

**FIGURE 13: Global Insulin Market (left) and Global Insulin Volume Market Share (right)**

Sanofi is the only company out of the big three, which does not have a significant participation in the human insulin market. Important products in Sanofi’s portfolio count Toujeo, Apidra, Amaryl, and newcomer FDC Soliqua. Imminent product launch options are scarce for Sanofi but the company has recently in-licensed a second GLP-1 agonist and a SGLT-2 inhibitor and is working on a bolus insulin lispro biosimilar to compete in the rapid-acting insulin market (Rotenstein et al., 2012; Sanofi, 2016).

American-based insulin pioneer **Eli Lilly** did not market a basal insulin analogue until the Lantus patent expired. Most of Eli Lilly’s insulin business is in the human segment.
however, the company’s insulin glargine U-100 biosimilar, basaglar (among other names), is predicted to be a massive headache for Sanofi and Novo Nordisk’s basal analogue revenues (Rottenstein et al., 2015). Eli Lilly also demonstrates strong participation in the GLP-1 market with Trulicity, in the SGLT-2 market with Jardiance, in the DPP-4 market with Tradjenta and recently launched the highly innovative SGLT-2/DPP-4 combination Glyxambi. In 2014, Eli Lilly reported roughly $4.5 billion USD in diabetes revenues (Wasserman, 2015) but many of the abovementioned formulations are fresh launches so the revenue could be positively impacted in the years to come.

**FIGURE 14: Global All-Diabetes Value Market Share**

*The top-10 companies* producing pharmaceuticals for diabetes reported a total of $62 billion USD in global sales in 2014. Subtracting the $26.5 billion USD captured by the three big insulin manufacturers leaves $35.5 billion USD for the remaining seven companies – the number is remarkably more substantial because most of the competing drug regimens are comprised by so called oral anti-diabetic (OAD) pills with a generally lower cost of production and price than injectable biologics like insulin.

The leader company in the non-insulin segment is Merck who relies on its Januvia franchise for diabetes. Merck brought in $7.4 billion USD in diabetes sales in 2014 (Wasserman, 2015). Other significant companies are Novartis, AstraZeneca and Boeringer Ingelheim. The latter, in particularly has proved a strong ally through several partnerships with Eli Lilly including the development of Basaglar and Glyxambi.

**Insulin business models and value levers**

To purchase insulin in the private market you must have a prescription issued by a medical professional. Usually the private market is out-of-pocket however several co-pay models
exist around the world. Due to physicians’ influence, the prescription is generally considered as the primary lever for purchase. Other levers are perceived discounts, education and patient services. Oftentimes, the physician and the patient perceive value differently, meaning that levers should be applied on a very individual basis. For example, the physician might think that a company sponsored patient support program is invading the space of his or her medical profession whereas the patient may in fact value additional support.

In 2009, generic products accounted for 75 percent of all prescriptions in the US. This number is likely to be even higher in low- and middle-income countries. It is a fact that physicians should be fairly aware of their patients’ purchasing power and as such, they also have an economic responsibility towards patients. Biosimilars work for insulin just like generics do for synthetic drug classes. They have the potential to reduce treatment costs by expanding competition, even increasing accessibility to insulin in markets that are underserved (Rotenstein et al., 2012).

**TABLE 15: Business Models and Value Levers**

<table>
<thead>
<tr>
<th>Business model</th>
<th>Private (OOP)</th>
<th>Formulary reimbursement</th>
<th>Private tender</th>
<th>Public tender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lever</td>
<td>Prescription</td>
<td>Access(^{11})</td>
<td>Price</td>
<td>Price</td>
</tr>
<tr>
<td>Other levers</td>
<td>Discount</td>
<td>Prescription</td>
<td>Prescription</td>
<td>Prescription</td>
</tr>
<tr>
<td></td>
<td>Education</td>
<td>Education Co-pay</td>
<td>Education</td>
<td>Education</td>
</tr>
<tr>
<td></td>
<td>Services</td>
<td></td>
<td>Services</td>
<td></td>
</tr>
</tbody>
</table>

\(^{11}\) Market access is a multidisciplinary organizational area whose primary objective is to demonstrate the value of pharmaceuticals by using complex economic models, clinical data or real-world evidence and reimbursement insight to justify the proposed price point before an institutional payer.

The institutional market is much more complex than the private. Sometimes we do not distinct between public and institutional, but I consider public to be any purchase undertaken by a public entity such as the ministry of health or an institution governing public health insurance plans. It is easier to address the institutional market as a whole including the public segment. By institutional I mean any purchase undertaken by a non-private person counting health maintenance organizations, public entities, insurance companies, pharmacy benefit managers and others.

Tendering constitutes are significant portion of the institutional insulin business. Private tenders are often decentralized tenders issued by private institutions like pharmacy
benefit managers, hospitals or other health maintenance organizations. Public tenders are usually centralized and organized by the main health authority of a national government. For tenders in general, price is the single most important lever. Only on a few occasions, prescription and education plays a role, mainly for the smaller decentralized tenders intrigued by the value from underlying services of the product.

In government tenders particularly, insulin biosimilars are predicted to be very strong. That is because governments’ decisions about insulin purchasing, tendering practices and price can have an enormous impact on public budgets. In a stressed economic environment governments must seek to uphold the value of healthcare and cut costs significantly. If prices do not fall, the cost tends to be transferred to the patient (World Health Organization, 2016a).

The last sort of major business model is found in the reimbursed market. Here, inclusion in formulary lists is imperative as it determines where in the therapeutic value chain your product will be utilized and paid for. Companies fight for the highest position on formularies and protocols (also known as tiers) and the decision to fund insulin analogues seems to depend on how much the institution is willing to pay per QALY gained and the availability of financial resources (Cameron & Bennett, 2009). Wirtz notes that with very few exceptions all countries list human bolus insulin and NPH (2016).

In recent years, as the financial crisis have raged, many payers encourage the use of NPH by placing these products in a favorable high-tier formulary position (Rotenstein et al., 2012). A similar pattern is expected for the introduction of biosimilars – in fact major US pharmacy benefit managers such as CVS and United Health already announced the substitution of Lantus with Eli Lilly’s insulin glargine biosimilar Basaglar by early 2017 (Staton, 2016c).

For an institutional payer looking to determine value of insulin the primary lever seems to be QALYs for money (i.e. cost-benefit). It is therefore unlikely that long and ultra-long acting basal insulin analogues will be considered an efficient investment for early treatment of T2DM in the future (Staton, 2015h). However, the reimbursed market offers favorable conditions for formulary placement of basal analogues in sub-populations with unmet need (usually nocturnal hypoglycemia) that suffer from inadequate control with NPH (Cameron & Bennett, 2009).
Threats to The Basal Analogue Regimen

Today’s economic, demographic and epidemiological transitions have placed alarming pressure on the basal insulin regimen (Castano, 2014). Three factors in particular require imminent attention: 1) a mounting pricing pressure in the institutional market, 2) biosimilar competition and, 3) innovative drug classes delaying insulinization with stepped-up cardiovascular benefit evidence. To compete in this new landscape it is important to have a deep understanding of the impacts brought about by these three factors. In the following sections I detail and discuss each of he major threats to the basal insulin analogue regimen.

Mounting pricing pressure in the institutional market

Garber highlights that “expanding use of biologics has severely impacted budgets for pharmaceutical products in every major area of medical therapeutics” (2015). Fact is that healthcare spending relative to gross domestic product continues to grow and pharmaceutical costs can expect to come under increased scrutiny from governments pressured to balance their budgets (Hunt, Manson & Morgan, 2011). Payers must now move beyond price control (Rodriquez, 2015) as patients and physicians push to accelerate access to new costly medicines “despite often significant uncertainty surrounding their health benefits” (Adamski, Godman, Ofierska-Sujkowska, Osinska, Herzholz, Wendykowska, Laius, Jan, Sermet, Zara, Kalaba, Gustafsson, Garuoliene, Haycox, Garattini & Gustafsson, 2010).

Several factors have caused the pharmaceutical industry to find itself in a time where its profit margins are substantially lower than they were just a few years ago (Hunt Manson & Morgan, 2011); and older drug categories like basal insulin are taking the bigger squeeze (Staton, 2015h). Out-of-pocket spending on medication is high, particularly in developing countries, and eventually governments and private payers have to fund novel drugs (Rodriquez, 2015). To do so, regulators and payers are raising the bar to market access with respect to demonstrating value for money, allowing few or no price increases and barring follow-on products that bring irrelevant incremental value (Hunt, Manson & Morgan, 2015).

Moreno and Ray (2016) ask the question: how should value be shared between manufacturer and society? In Latin America, governments have initiated numerous initiatives to cut prices and transfer as much value to society as possible. In Brazil and Colombia, extensive international reference pricing schemes were implemented recently. The Brazilian government applies the lowest of 11 reference prices for new products and in
Colombia all essential medicines are adjusted biannually according to the third quartile of a large reference price basket. In the latter case some products saw price drops up to 90 percent upon implementation in 2012 (Rodriquez, 2015).

Another great example of cost saving schemes is the Pan American Health Organization’s (PAHO) annual vaccine tender who joins the demand of multiple countries to obtain a lower price from manufacturers. Since PAHO’s umbrella organization WHO now places high priority on non-communicable chronic diseases it is not unlikely to see anti-diabetic drugs be next in line for large intergovernmental tenders. Finally, last year, MERCOSUR ministers of health agreed to pursue pooled purchasing of pharmaceuticals to gain greater bargaining power in the future (Rodriquez, 2015). Interestingly bundled rebates are generally discouraged by managed care organizations in the US as the schemes impede transparency (Adamski et al., 2010).

In Europe other mechanisms have been put in place to limit budget impact of new expensive biologics like insulin analogues. The primary effort is on improving transparency in classifying new drugs as innovative and linking that degree of innovativeness to pricing decisions (Adamski et al., 2010). Moreno and Ray found that “a major hurdle to reaching consensus around the measurement of innovation is the lack of a standardized definition of innovation itself” (2016). Newer reimbursement arrangements also seek to circumvent off-label prescribing and utilization outside of the patient sub-population in which the drug’s value is greatest (Adamski et al., 2010).

Private formulary payers trawl the market for discounts
It is not only governments who face overheated healthcare budgets; private institutional payers are on the lookout for cost savings too (Deloitte Center for Health Care Solutions, 2012). The pharmaceutical industry is facing three major hurdles with respect to private payers.

I. Payers, in particular large pharmacy benefit managers, trade discounts and rebates for formulary top-tier placement and seem willing to extend indications in exchange for lower prices as long as there is a clear evidence base (Paris & Belloni, 2012; Staton, 2016a). Because of pressure from payers to deliver this evidence on value as a prerequisite for reimbursement, manufacturers face delayed launches (Milne et al., 2015).
II. Payers are growing more aggressive in pitting products from competitive drug classes against one another for discounts and insulin have been remarkably vulnerable to exclusions (Staton, 2016b; Staton, 2015g). In the bolus segment, for example, Eli Lilly’s Humalog and Novo Nordisk’s Novolog are being played out against each other for exclusive coverage with approximately 50 percent of the US health plans choosing one over the other (Staton, 2015h).

III. Even if new insulin products and other anti-diabetes medications prove to carry significant health improvements they will be paid for only after CGRPs, Alzheimer’s treatment, PD-1s and other immunotherapies for cancer. Innovative drug categories are expected to consume large pieces of payer budgets, leaving little room for diabetes products (Staton, 2015h).

**FIGURE 16: US Pharmacy Benefit Manager Coverage Market Share**

Getting access to payers has become a real headache for manufacturers who are now looking desperately to demonstrate value from their offerings. In the US, large pharmacy benefit managers such as CVS Health and Express Scripts have recently announced their formulary lists for next year. Express Scripts is not listing Novo Nordisk’s Victoza (GLP-1), Levemir and Tresiba (basal insulin analogues) as well as GlaxoSmithKline’s Tanzeum (GLP-1). Instead the retailer decided to chase exclusive coverage agreements with Eli Lilly’s GLP-1 Trulicity and Sanofi’s insulin franchise Lantus and Toujeo (Staton, 2016abc; Helfand, 2016c). The latter two products could however see their formulary spot slip as Express Scripts says, “it might change its basal insulin lineup to reflect anticipated product launches”; assumingly, that is a reference to Eli Lilly’s insulin glargine U-100 biosimilar Basaglar (in Staton, 2016c).
CVS Health and UnitedHealth, respectively the second and third largest pharmacy benefit manager in the US, also dropped a massive bomb on the diabetes market when they announced their 2017 formulary exclusions of the all-time diabetes bestseller Lantus. Bernstein analyst Ronny Gal says, “it is a big deal by any measure”. As such, “in diabetes therapy it is the largest commercial product ever excluded from a formulary”. CVS Health also excluded Lantus follow-on insulin glargine U-300, Toujeo, adding to the downturn of Sanofi. Both Sanofi’s products are being replaced by Eli Lilly’s insulin glargine biosimilar Basaglar (in Staton, 2016cg).

On an overall manufacturer-wide basis, Novo Nordisk still has the best position in the US with Levemir boasting preferred coverage on the majority of plans. In comparison, Lantus has best-tier placement in 86 percent of the plans while Victoza, Bydureon and Byetta claims 70 percent, 86 percent and 70 percent respectively (Staton 2015h). Since Express Scripts barred out multiple Novo Nordisk drugs for 2017 the Danish drugmaker revealed it have had to trade discounts for formulary placement elsewhere; those negotiations have yielded net prices moderately lower than this year’s average (Adams, 2016).

**FIGURE 17: Manufacturer Rebates for Medicare Part D Drugs**

In Medicare Part D plans a few diabetes medications take part of the top-10 list. These plans accounts for more than 30 percent of diabetes coverage in the US and their rebates have been increasing massively in the past 10 years (see figure 17). Lantus and Januvia are the two most prescribed Part D diabetes products. Today they both have new
direct competitors in their respective drug classes and the US department of Health and Human Services (HHS) who manages Part D negotiations should use that fact to win discounts. The HHS is notoriously known for offering the most restrictive coverage and tends to exclude particular brands completely rather than craft tiered co-pay arrangements (Staton, 2015ah; Funk, 2016).

Staton notes that despite aggressive moves from payers and little pricing freedom, general coverage remains high (2015h). Novo Nordisk initially projected a 2016 profit growth of nine percent but due to stepped up competition and pricing pressure from US payers that number was quickly bumped down with 1-3 percentage points (Adams, 2016). The two major players in the basal insulin analogue space, Novo Nordisk and Sanofi, have chosen different pricing strategies for this year’s negotiations. For the long-acting established analogues, Levemir and Lantus, prices are expected to be flat. However, while Novo Nordisk priced Tresiba with a moderate premium over Levemir, Sanofi chose to go for parity price between Lantus and Toujeo (Staton, 2015ch). See figure 18 for a summary of the relative price levels and potential evolution in the basal insulin regimen.

**FIGURE 18: Illustrative Price Evolution in the Basal Insulin Analogue Space**

![Image of Figure 18 showing the relative price levels and potential evolution in the basal insulin analogue space](image)

**SOURCE: AUTHOR’S OWN INTERPRETATION BASED ON PUBLIC STATEMENTS**

Staton emphasizes that analysts expected both Toujeo and Tresiba to be priced lower in order to gain market share from the older products quickly; this would have shielded the businesses from biosimilar entrance. Instead, Novo Nordisk is relying on “early adoption by smaller more permissive plans and on its ability to persuade other payers of Tresiba’s worth”
It is likely that Sanofi paired up the list price of Toujeo and Lantus only to allow more net price flexibility on Lantus thereby creating a Toujeo premium and competing with glargine U-100 biosimilars at the same time. Finally, the hope is that recently launched ultra-long-acting insulin analogues offer sufficient benefits over their older peers to justify premiums. However, when biosimilars enter the market at a price of minus 15 percent, basal insulin analogues could see net prices decline because the innovations of their prolonged time-action profile new drugs does not offset payers wish to cut costs (Staton, 2015dh).

**Biosimilar competition**

We have seen how governments and other institutional payers are taking steps to engineer low prices for costly biologics. One of the most effective ways to do so is by increasing competition within a specific drug class. Here, in particular, health authorities around the world have started to appraise generic products of biologics, so called biosimilars. Regulatory agencies have established special pathways for approval of biosimilar products and the latest result of those efforts was the replacement of Lantus with Basaglar on several of the major pharmacy benefit manager formularies (Garcia-Nares, Leyva-Carmona, Perez-Xochipa & Chiquete, 2015; Staton, 2016c; Adamski et al., 2010).

Guidelines for the approval of generic synthetic oral agents have little applicability to biologic products and thus with the recent patent expiration of several molecules problems arose. Registration of similar biologics has generally been treated as new chemical compounds, which requires safety and efficacy trials prior to approval. Today a fast-track approval process is in place in most countries mainly as a result of the much needed price competition in the biologics space (Garber, 2015). Biosimilar products are allowed to utilize the clinical studies of an originator product meaning that the ORIGIN study of Lantus is now available to all glargine U-100 preparations enabling extrapolation of indications, safety and efficacy.

Biosimilar products are complex molecules and thus it is highly unlikely that they will be bio-identical to the originator. The concern is that minor structural modifications can produce major differences in the PD/PK profile for insulin. Sanofi who used to enjoy exclusivity can emphasize that glargine U-100 biosimilars are not automatically interchangeable with Lantus (Garber, 2015). Indeed the first case of a hypersensitivity reaction to an insulin glargine biosimilar was documented last year. A 51-year old woman
with T2DM was switched from Lantus to a biosimilar preparation and admitted to a third level hospital as a result of her reaction. When the patient was later switched back to Lantus she could resume her insulin regimen as normal (Garcia-Nares et al., 2015).

IMS Health (2016) confirms that the rational behind introducing biosimilars is to increase price competition. The proliferation of competition does not only affect the price of directly comparable products but the entire drug class. In the basal insulin regimen it is evident that the introduction of glargine U-100 biosimilars have had an impact on the price of drugs like insulin detemir and degludec. IMS Health studied the relationship between biosimilar market share and price. They found that there is little correlation, asserting that high savings can be achieved even at low biosimilar uptake. That is because the originator product and drug class will have to reduce prices too. Figure 19 shows the correlation between biosimilar market share and average day of treatment (DOT) price in the Epoetins (EPO) and growth hormone (GH) markets.

**FIGURE 19: Biosimilar Market Share and DOT Price for EPO and GH**

Moreno and Ray (2016) argues that the introduction of biosimilars to healthcare systems relying on cost-effective analysis distorts competitive pricing. As off-patent technologies are inexpensive and therefore highly efficient at generating QALYs, the cost-effective analysis does not reward the effort to foster innovation reflected in research and development expenses. Traditional cost-effective analyses make the assumption that a drug’s price remains unchanged throughout its life-cycle; thus, the time to patent expiry and the expected off patent price should be factored in, according to the authors. Accounting for a low off-patent price will allow manufacturers to capture a higher on-patent price.
As we have seen earlier in this paper, access to insulin is major problem for T2DM patients in developing and especially undeveloped countries. Lower prices should by definition increase access to medicine, however according to IMS Health (2016), different levels of price elasticity exist for pharmaceuticals across countries and social classes. In the Epoetin example price per DOT decreased with the introduction of biosimilars for all countries but while volumes increased in countries with historically low usage the opposite happened in countries with historically high usage (see table 20).

When pharmaceutical markets become commoditized because of generic or biosimilar entrance, the existing products must adapt to the new environment. Originators’ behavior tends to move in a multitude of different directions. IMS Health (2016) reported that the most common responses to biosimilar entrance were:

I. The originator’s manufacturer launches a new innovative longer-acting product, adding incremental value at no price premium compared to the originator. This can potentially change the paradigm and thus usage pattern. Sanofi’s response to its loss of glargine U-100 was to launch Toujeo, an added-value glargine U-300, at parity price.

II. The originator significantly reduces price levels. This approach is aligned with Moreno and Ray’s (2016) new cost-effective analysis proposition.

III. The originator’s manufacturer starts to develop and produce biosimilars itself.

**TABLE 20: Biosimilar Impact on Price and Usage in Epoetins**

<table>
<thead>
<tr>
<th>Epotins</th>
<th>Price per DOT in 2015 vs Year before biosimilar entrance</th>
<th>Volume DOT in 2015 vs Year before biosimilar entrance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low historical usage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>-36%</td>
<td>460%</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>-46%</td>
<td>120%</td>
</tr>
<tr>
<td>Poland</td>
<td>-49%</td>
<td>186%</td>
</tr>
<tr>
<td><strong>High historical usage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>-18%</td>
<td>-32%</td>
</tr>
<tr>
<td>Austria</td>
<td>-36%</td>
<td>-28%</td>
</tr>
<tr>
<td>Germany</td>
<td>-45%</td>
<td>-25%</td>
</tr>
</tbody>
</table>

**SOURCE: ADAPTED FROM IMS HEALTH, 2016**
**TABLE 21: Products in the Basal Insulin Regimen after Biosimilar Entrance**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Molecule</th>
<th>Product</th>
<th>Manufacturer</th>
<th>Reference product</th>
<th>Biosimilar</th>
<th>Innovation</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono</td>
<td>Insulin Glargine</td>
<td>Lantus</td>
<td>Sanofi</td>
<td>○</td>
<td></td>
<td></td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toujeo</td>
<td>Sanofi</td>
<td></td>
<td></td>
<td>●</td>
<td>Ultra-long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abasaglar</td>
<td>Eli Lilly / Boehringer Ingelheim</td>
<td></td>
<td></td>
<td>●</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Galactus</td>
<td>Biocon/Mylan</td>
<td></td>
<td></td>
<td>●</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MK1293 / SB9</td>
<td>Samsung Bioepsis / Merck</td>
<td></td>
<td></td>
<td>●</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Basalin</td>
<td>Gan&amp;Lee</td>
<td></td>
<td></td>
<td>●</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N/a</td>
<td>Geropharm</td>
<td></td>
<td></td>
<td>●</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Basugine</td>
<td>LG Life Sciences</td>
<td></td>
<td></td>
<td>●</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PB (MDT)-3030</td>
<td>Paras Biopharmaceuticals</td>
<td></td>
<td></td>
<td>●</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glaritus</td>
<td>Wockhardt</td>
<td></td>
<td></td>
<td>●</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td>Insulin Degludec</td>
<td>Tresiba</td>
<td>Novo Nordisk</td>
<td></td>
<td>●</td>
<td></td>
<td>Ultra-long-acting</td>
</tr>
<tr>
<td></td>
<td>Insulin Detemir</td>
<td>Levemir</td>
<td>Novo Nordisk</td>
<td>○</td>
<td></td>
<td></td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td>Insulin Human</td>
<td>NPH</td>
<td>Multiple</td>
<td>○</td>
<td></td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td>Premix</td>
<td>Glargine/Lispro</td>
<td>BioChaperone</td>
<td>Adocia</td>
<td></td>
<td>●</td>
<td></td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td>Degludec/Aspart</td>
<td>Ryzodeg</td>
<td>Novo Nordisk</td>
<td></td>
<td>●</td>
<td></td>
<td>Long-acting</td>
</tr>
<tr>
<td>FDC</td>
<td>iGlarLixi</td>
<td>Soliqua</td>
<td>Sanofi</td>
<td></td>
<td>●</td>
<td></td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td>iDegLira</td>
<td>Xultophy</td>
<td>Novo Nordisk</td>
<td></td>
<td>●</td>
<td></td>
<td>Ultra-long-acting</td>
</tr>
</tbody>
</table>

○ = original products  ● = innovative (new) products
As insulin glargine, the best selling insulin analogue ever, reached its patent cliff in 2015 several companies prepared to enter the market with biosimilar products. In table 21, nine of the major glargine biosimilars are identified and it becomes clear that the market size in terms of players has doubled, intensifying price and value competition. The most promising new competitor is Eli Lilly and Boehringer Ingelheim’s Basaglar. Due to Eli Lilly’s strong existing portfolio in the diabetes market, the companies’ large manufacturing capabilities and extensive sales forces, Basaglar could cause real pain to Sanofi and Novo Nordisk’s analogue franchises. Staton (2015d) proclaimed that Basaglar would make inroads at 15 percent discount compared to Lantus. However, persuading health care professionals that an insulin biosimilar is easily substitutable for Lantus is a difficult proposition. In Norway, the government has taken radical steps to prove the worth to physicians by carrying out its own head-to-head studies.

Another insulin glargine U-100 biosimilar is Merck and Samsung’s MK-1293. Merck reported recently that MK-1293 matched Lantus at both efficacy (HbA1c reduction) and safety in two separate phase III studies (Staton, 2016e). Gan & Lee, a leading Chinese biotechnology company also is cooking up a glargine biosimilar. In many countries Gan & Lee relies on local partnerships to push their product. In Brazil for example, the company joined forces with Biomm who has strong public BNDES support and an already-signed public-private-partnership on the production of NPH (Ministério da Saúde, 2013).

Finally, Biocon, a large Indian insulin manufacturer initially bets on emerging markets for its glargine formulation. However, the company is building a $250 million USD production site in Malaysia to serve the large Japanese market in collaboration with Fujifilm. The two partners are hoping that the Japanese success will establish enough credibility and validity to obtain regulatory approvals in the US and Europe (MacRae, 2016).

**Innovative drug classes delaying insulinization**

Bernstein analyst Tim Anderson says that paradigm shifts in primary care takes time and that we are not simply going to see a massive switch of T2DM patients from one class of agents to another (Helfand, 2015a). However, the diabetes landscape is becoming ultracompetitive and it is reasonable to believe that all stakeholders will evaluate anything, which benefits or hurts a specific drug class, closely (Palmer, 2015a). Already in 2002, Silvio Izneuchi found that no less than five different oral drug classes were equally efficacious in
lowering HbA1c (in Garthwaite & Duggan, 2010). Since Izneuchi’s study a plethora of new innovative agents have joined the marketplace and expanded the options for intensification between Metformin and insulin.

In 2006, the first *dipeptidyl peptidase 4 (DPP-4)* inhibitor, Sitagliptin, was approved by the FDA. Sitagliptin is sold under the trade name Januvia by Merck and have been joined by several other DPP-4s such as saxagliptin, alogliptin and linagliptin marketed respectively as Onglyza (AstraZenica), Nesina (Takeda) and Tradjenta (Boehringer Ingelheim) alone or in FDC with Metformin (Ingelfinger & Rosen 2016; Palmer, 2015a). Evercore analyst, Mark Schoenebaum, notes that the DPP-4 class is generally well-tolerated, neutral on weight and has been considered safe for most parts. However the FDA has added warnings to the entire DPP-4 class’ label about the risk of pancreatitis and allergic reactions as well as hypoglycemia when used for combination therapy. Last year the FDA added another cautionary language: DPP-4 drugs can cause severe and disabling joint pain (Palmer, 2015a; Staton, 2015e).

Brown, Grima and Sauriol (2014) examined the cost-effectiveness of insulin glargine versus Januvia in the Canadian healthcare system. The study found that treatment with insulin glargine resulted in cost-savings of $1,434 CAD and a gain of 0.08 QALY per patient. Insulin glargine also brought cost savings of one percent for cardiovascular disease-related complications and five percent for renal-related complications. Nevertheless, it is difficult establish clear and unbiased evidence that one agent is superior to the other on a cost-effective basis. As such, a different study also submitted to the CADTH, implied that the DPP-4 class dominated insulin glargine on second-line therapy for T2DM patients. This study pooled dug classes, assuming that all drugs in the same class carry equal efficacy.

*Glucagon-like peptide 1 (GLP-1)* agents for T2DM have been around since 2005, when the FDA approved twice-daily exenatide marketed as Byetta. Still, it was not until 2009 that the drug class made its mark on the diabetes stage. Novo Nordisk’s liraglutide, trade name Victoza, was approved that year and quickly emerged as the dominant product in the class. Today Victoza has reached blockbuster status but despite growing sales it is losing market share to Eli Lilly’s Trulicity (Meek, 2014; Adams, 2016; Staton, 2016a). See figure 22 for an overview of the GLP-1 market shares in the US.
In T2DM, GLP-1 agents are typically adopted before insulin as an add-on to Metformin although the biologic preparation must be injected like insulin (Staton, 2015f). Because of the earlier adoption and potential impact on comorbid conditions (see page 60), GLP-1s have become a very attractive commercial area to enter. The current competition in the GLP-1 field focuses on prolonged time-action and therefore a range of formulations exists for twice-daily, once-daily and once-weekly administration.

**FIGURE 22: GLP-1 Total Prescription Market Share in the US**

The most prominent molecules in addition to liraglutide are dulaglutide (Trulicity), albiglutide (Tanzeum by GlaxoSmithKline) and lixisenatide (Adlyxin by Sanofi) but several of the companies behind have continuous development of their GLP-1 portfolio (Ingelfinger & Rosen, 2016). Novo Nordisk, for example, is developing semaglutide, a once-weekly version of Victoza, and announced that they will submit for regulatory approval already this year, much earlier than Victoza stands to lose its patent (Novo Nordisk, 2016).

Victoza boasts evidence of cardiovascular benefit but other agents from rival classes also cut heart risk (Adams, 2016). Therefore Novo Nordisk moved quickly to announce that its follow on GLP-1 semaglutide was superior to both AstraZenica’s GLP-1 Bydureon and Merck’s DPP-4, Januvia (Helfand, 2016c). Novo Nordisk is likewise preparing for a head-to-head study of semaglutide versus Eli Lilly and Boehringer Ingelheim’s empagliflozin, also known as Jardiance (Staton, 2016a). Finally the Danish drugmaker is seeking more differentiation from the drug class itself by pursuing the first oral GLP-1 currently entering expanded phase III trials in the PIONEER program (Palmer, 2015b; Staton 2016a).

The last and most recent breed from the herd of anti-diabetes drug classes is the sodium/glucose cotransporter 2 (SGLT-2). Only three SGLT-2 molecules were approved so
far; still Evercore ISI analyst Schoenebaum expects to see the new drug class overtake DPP-4 within just six years. The three molecules, canagliflozin (Invokana), dapagliflozin (Farxiga) and empagliflozin (Jardiance), are considered the biggest competitive threat to insulin and GLP-1 products (in Helfand, 2015a; Ingelfinger & Rosen, 2016) because they are orally administered and therefore have the ability to delay progression to injectable treatments (Sagonowski, 2016).

In the US, Invokana dominates formulary coverage due to Johnson & Johnson’s extensive rebate schemes. As such, Invokana was approved in 2013 and reached blockbuster status already two years later (Helfand, 2015a; Palmer, 2015a). In Europe, NICE recently recommended all three SGLT-2 agents for preferred second-line regimen as an add-on after Metformin and SU. NICE’s backing carries substantial gravity as many other European health authorities inform their coverage based on the UK’s assessments (Sagonowski, 2016).

In 2015 the SGLT-2 class took the biggest hit since its first approval. The FDA added a warning for the risk of bone fractures and concerns about decreased bone density to the class’ label (Palmer, 2015a). Nonetheless, the SGLT-2 products continue to prosper and recently triggered talks about a paradigm shift in diabetes therapy. The first ever diabetes medication to generate evidence of cardiovascular benefit became Eli Lilly’s Jardiance. Although the Jardiance data is expected to be seen as a class effect, AstraZenica already launched two phase IIIb studies to “define the potential role” of its own SGLT-2 Farxiga (Helfand, 2016a).

Cardiovascular benefit and its role in the treatment paradigm
Roughly 50 percent of T2DM-related deaths worldwide are due to cardiovascular complications. Decreasing the risk of cardiovascular disease is an essential part of diabetes management but until 2015 no anti-diabetes product showed evidence of cardiovascular benefit (Staton, 2015g). Regulatory guidance recently adopted the pre-approval requirement of demonstrating cardiovascular safety (Main, Marso, Consoli, Eliaschewitz, Jodar, Leiter, Lingvay, Rosentock, Seufert, Warren, Woo, Hansen, Holst, Petterson, & Vilsbøll. 2016). Safety ultimately means neutral effect, however having a drug that can go beyond safety and treat cardiovascular disease have caught the attention of several manufacturers. Cardiovascular benefit is a big claim to carry and manufacturers who own it
are likely to push for use of their products earlier in the treatment paradigm (Palmer, 2015a; Stovall, 2016).

Insulin is generally considered to have a neutral effect on cardiovascular disease and, as it is commonplace by now, the class does not win out on it. Most DPP-4 molecules failed to prove cardiovascular safety however they reached market before the new regulatory guidance was implemented. As such, saxagliptin was studied in the SAVOR-TIMI 53 (ClinicalTrials.gov Identifier: NCT01107886) trial while alogliptin underwent the EXAMINE (ClinicalTrials.gov Identifier: NCT00968708) study (Ingelfinger & Rosen, 2016); some even suggested added events of hospitalization due to heart failure from these drugs. Staton (2015e) notes that Merck’s Januvia may be the best positioned DPP-4 on the cardiovascular side as the molecule, sitagliptin, showed no additional heart risk in its 2008 to 2015 TECOS (ClinicalTrials.gov Identifier: NCT00790205) trial. Analysts expect that the TECOS data could lift Januvia sales by around 10 percent by 2020.

The SGLT-2, Jardiance, manufactured by Eli Lilly and Boehringer Ingelheim was the first anti-diabetes product to generate evidence of cardiovascular benefit. For Jardiance, and in most other cardiovascular studies, the main endpoints were reduced risk of heart attack, stroke and death from cardiovascular disease. The Jardiance trial dubbed EMPA-REG OUTCOME (ClinicalTrials.gov Identifier: NCT01131676) studied 7,000 T2DM patients and found that the combined risk of the main endpoints reduced by 14 percent with empagliflozin therapy (Staton, 2015g).

Looking more closely at the data, Jardiance cut the risk of death from cardiovascular disease by 38 percent and all cause mortality by 32 percent. Helfand believes that this kind of data has the potential to inform guideline changes that bring Jardiance and its SGLT-2 class peers much earlier in lines of therapy. The Jardiance data possibly will be considered a class effect, however, Jardiance’s sales representatives will be able to air it more easily before doctors and if health care professionals want to practice evidence based medicine they should be prescribing Jardiance (2015a). Staton (2015e) and Evercore ISI analyst Schoenebaum also insist that the Jardiance data will sway the medical community to prescribe SGLT-2s, and in particular Jardiance, in front of DPP-4s more eagerly.

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12 Eli Lilly and Boehringer Ingelheim have submitted an application to the FDA for including the EMPA-REG OUTCOME data in Jardiance’s label (Staton, 2016a)
While Eli Lilly and Boehringer Ingelheim pursue additional Jardiance indications outside the diabetes space other SGLT-2 manufacturers are embarking on their own cardiovascular outcome trials. AstraZeneca for example won’t be able to match Jardiance until 2019 the earliest (ClinicalTrials.gov Identifier: NCT02653482) and the Merck/Pfizer collaboration around ertugliflozin is only now looking to enroll 8,000 T2DM to their trial (ClinicalTrials.gov Identifier: NCT01986881). The latter study actually had to expand its endpoints in the light of Jardiance data to “properly power it to measure a cardiovascular benefit” explains Staton (2016f).

Finally the GLP-1 segment appears to come in strong on the cardiovascular benefit. Liraglutide was studied in the LEADER trial (ClinicalTrials.gov Identifier: NCT01179048) and fleshed out results in early 2016. Treatment of T2DM with Victoza reduced the risk of combined cardiovascular death and nonfatal myocardial infarction by 13 percent compared to placebo (Marso et al., 2016). Although no GLP-1 before liraglutide proved cardiovascular benefit, Novo Nordisk’s own follow-on, semaglutide has already topped the LEADER study. In the cardiovascular safety, pre-approval, SUSTAIN-6 (ClinicalTrials.gov Identifier: NCT01720446) trial, Novo Nordisk hypothesized that semaglutide would be non-inferior to placebo for the primary composite outcome of cardiovascular disease endpoints. Semaglutide hit the primary outcome and more: patients on the GLP-1 saw a reduced risk of 26 percent versus those treated with placebo (Marso et al., 2016).

Although semaglutide was the second GLP-1 to have cardiovascular benefit evidence it is the first anti-diabetic pipeline agent to have it before submitting for regulatory approval. Likewise, semaglutide will only be the fourth weekly GLP-1 to market but Novo Nordisk’s strong evidence will be useful in early payer negotiations and might have the potential to swipe away competition entirely (Slowey, 2016; Staton, 2016a). The reduced risk of the composite outcome in SUSTAIN-6 was primarily driven by a 39 percent decrease in the rate of non-fatal stroke and a 26 percent decrease in nonfatal myocardial infarction (see figure 23). Main et al. (2016) notes that the cardiovascular death endpoint probably needed more time to separate out and as such Novo Nordisk is already planning for a larger and longer cardiovascular outcome trial post approval (Slowey, 2016).
FIGURE 23: Semaglutide and Cardiovascular Outcome in T2DM Patients.

SOURCE: MAI ET AL., 2016; SUSTAIN-6
Analysis

The basal insulin analogues have relied on a blockbuster model for years (Lexchin, 2011). T2DM patients intensified treatment after Metformin and SU by moving on to NPH and later Lantus or Levemir. Very little competition with the ability to disrupt this patient journey existed until the arrival of DPP-4. In fact, only with the entrance of GLP-1 and SGLT-2 agents did the insulin analogues start to feel the pressure on their regimen. Historically the analogue products were able to sell themselves in any business model on the basis of individual patient outcomes leading to a cost-beneficial price point. Lantus and Levemir could freely speak to all of their clinical benefits without focusing on the stronger messages because competition could never match their attributes’ aggregated efficacy. Now, the tide has changed: a plethora of novel competing products and economic pressures have flushed in tougher requirements from payers about the value of anti-diabetes treatment.

In the contemporary marketplace, a product must provide evidence for its impact on a community level and on the effectiveness of the healthcare system and its management. Selling irrelevant incremental value or failing to generate value in a societal context means not selling at all. Tender opportunities are largely captured by the lowest-bidder: in the insulin regimen that will almost certainly be NPH or glargine biosimilar products (see figure 18). In the private market, competing means spending money on promotion and product detailing to physicians. With less certainty of success this is a costly and fierce place to invest for the insulin manufacturers who doesn’t boast a biosimilar.

Finally, the formulary reimbursement market appears to offer the best inroads to success if you are able to demonstrate premium value. Institutional payers are in principle ready to pay a premium or to allow incremental costs for an innovation that proves its worth for a patient sub-population with unmet needs (Paris & Belloni, 2012). They are also at the forefront of adopting innovative payment schemes that lower the pressure on budgets and ensure a high level of therapeutic value with reduced financial risk. It does seem however, for now, that the emergence of biosimilars and early oral drug classes will pose a large challenge, even in the formulary reimbursement market. A revised value definition and way of addressing that value is needed for the basal insulin analogues to find their potential role and compete in the market.
A revised value definition for basal insulin analogues

Value exists in numerous forms throughout the insulin market, as we have learned. Loane et al. (2014) identified quality of life as the value experienced by consumers of pharmaceuticals – the patient. Zeithaml (1988) on the other hand suggest that we define value in four distinct ways: 1) value as low price, 2) value as whatever the consumer wants in a product, 3) value as the quality obtained for the price and 4) value as what the consumer gets for what he or she gives. Unfortunately, Zeithaml’s approach doesn’t allow us to identify specific value for a product at each point of the chain.

Khalifa (2004) proposes a solution: a three-fold integrative model that looks at perceived value in exchange (a cost-benefit model), as customer build-up (on the benefit side of the value equation) and as customer dynamics (to reflect how the customer evaluates a supplier’s offer). In this respect we can identify value in the objective form through a quantitative cost-effectiveness analysis and in the subjective form from both the patient’s and the payer’s perspective.

In her work on creating a perfect value proposition, Fiminska (2014) notes that in times of austerity measures, where affordability is more important than mere clinical value, creating a value proposition that payers cannot say no to is critical. Castano (2014) emphasizes that the pharmaceutical industry should embrace on a more consumer-driven mindset to anticipate and meet the patients’ needs, expectations and preferences in the short term. Competing for patients or contracts with payers leads to value destruction at both manufacturer and payer level and as such it is imperative to design a business model in which value is defined from the payer and ultimately patient’s perspective.

In this respect and in the light of the new market landscape, basal insulin analogue value is context dependent. It is greatest in the sub-patient population for whom the specific insulin serves an unmet need. It is demonstrated in absolute terms by its clinical efficacy and ability to impact systems, their management and expenditures on other pharmaceuticals or healthcare processes. In relative terms, compared to competing agents, value is determined by the cost-effectiveness, usually expressed in the price of incremental QALYs. There is no one size fits all for value propositions in the insulin regimen. Each product owns different features and will be able to bring different types of value. However no insulin can bring all at once. Finally value should be designed from a patient perspective.
Tactical and strategic recommendations for addressing product value

Undifferentiated products now characterize the diabetes market. The old blockbuster model allowed few products to highlight all their features at the same time. Today, if everyone says the same, two factors make a difference: price and promotional spending. None of these are good for profits so it becomes clear that insulin manufacturers must make the perceived difference of their products relevant to the market. Rodríguez (2015) stresses that to get access to payers and keep products relevant, value is the name of the game. The value proposition is the reason why an offering is worth paying for. In quantitative terms it represents the holistic utility payers receive from the product less the price paid. Fiminska (2014) specified that a value proposition should be aspirational and that it is important to define unmet needs early in the product development.

Boudler, Porsborg-Smith and Reeves (2016) from The Boston Consulting Group air their concern that at the onset of commoditization, “businesses may be wholly unprepared” and “fail to respond with anywhere near the required boldness or speed”. To successfully embrace commoditization companies wanting to compete must establish themselves on the basis of one of three factors:

I. cost-based advantage;
II. advantage based on exploitation of market imperfections; or
III. advantage based on product redifferentiation.

Many businesses instinctively pursue redifferentiation of their product. In the insulin regimen we have seen Sanofi and Novo Nordisk do exactly that with their follow-on products Toujeo and Tresiba who respectively are expected to replace Lantus and Levemir. Nonetheless, there are large potentials for tapping in to the cost-based and arbitrage-based advantage models.

Against the backdrop of Boudler, Porsborg-Smith and Reeves’ framework I have identified seven specific tactics and strategies for addressing value in the basal insulin regimen. In the following subsections I will embark on each of them, outlining their advantages and disadvantages and their applicability to different business models. I will also seek to tie each tactic or strategy to the value typology outlined in figure 01 and figure 02. Finally I comment on the nexus between axiology and certain tactics or strategies to demonstrate the importance of understanding value theory in depth before designing value propositions.
1. Cost-based advantage, price competition and market imperfections

Competing on price generates societal, or extrinsic, and pharmacoeconomic value because low prices mean less budget pressure and effective generation of QALYs for money. Lantus is on a slowdown over the next few years and Sanofi is counting on its ability to convert patients to Toujeo. That is because biosimilar products of insulin glargine entered the market last years when the molecule lost its patent. Biosimilars are making inroads at around 15 percent discount compared to Lantus and they have no or little costs associated to development or clinical trials. Rea (2000-2003) taught us that money, price and value are not one of a kind, however in some parts of the insulin business that does not hold true. Tender business and other models driven solely by price are expected to boost biosimilar penetration and the manufacturers investing in that space stands to benefit from their low operating costs and exploitation of arbitrary arrangements.

Joining forces with native players who can give biopharmaceutical manufacturers a local competitive edge is a commonly used tactic. We saw how the Biomm example put Gan & Lee right at the heart of a flourishing Brazilian insulin market. Pil and Holweg (2006) confirms that because of the “constant tension between opportunity and threat, companies need to explore opportunities for managing risks, gaining additional influence over customer demand and generating new ways to create customer value”. However, depending on commoditization and arbitrage likely will limit the window of opportunity as other competitors follow suit. Boudler, Porsborg-Smith and Reeves argue that the potential is particularly limited when the production process itself is commoditizing.

The glargine molecule is becoming commoditized but the production process is not. That means biosimilars and Lantus will not de jure be interchangeable – payers can only consider them per se. Ultimately, due to the downward pricing pressure, it seems that Lantus and the glargine biosimilars could replace NPH as the preferred first-line insulin. However, from a mathematical perspective market concentration is bad and therefore the real question is: can the increase in sales volume from NPH replacement compensate for the loss of sales value from price erosion? Other arbitrary models include confidential contracts that provide discounts while maintaining list price, price-volume agreements, and patient access strategies (Neumann, Chambers, Simon & Meckley, 2011).
2. Value-based pricing
Bentham made his mark in axiology by stating that any act resulting in happiness must be considered morally correct. As such, the happiness, or value, that pharmaceuticals bring is expressed in QALYs and the incremental utility in incremental QALYs. The problem in this model is that the amount of happiness expressed in QALYs derived from a medication must be established prior to administration because it should be translated into prices. What if the treatment finally does not provide the happiness that was expected? Solving this problem has become one of the most sought-after goals in the pharmaceutical realm. The answer ahead of us could be value-based pricing.

**FIGURE 24: Value-Based Pricing Model**

![Value-Based Pricing Model Diagram](source: Adapted from Deloitte Center for Health Solutions, 2012)

Paris and Belloni (2012) argue that value-based pricing can offer better value for money to payers and that its design provides clear signals to manufacturers that they will be rewarded if their product addresses the priorities of the payer. The aim of value-based pricing models is to reduce uncertainty around cost-effectiveness by linking the price paid to the performance of the product rather than to the volume. See figure 24 for illustration of how value-based pricing models work. Finally, the Deloitte Center for Health Solutions says a successful value-based pricing arrangement is incumbent upon a clear definition of when the pharmaceutical works or does not work (2012).
According to Moreno and Ray (2016), stakeholders participating in price negotiations still articulate the level of innovativeness qualitatively. The Deloitte Center for Health Solutions confirms that developing consensus around value metrics and price thresholds may be the biggest hurdle for implementing value-based pricing. It lists four particular difficulties (2012):

I. Evaluation requires large-scale real world data prior to model implementation so changes from the baseline can be assessed.

II. It is necessary to determine how to measure value if a medication is indicated for combination therapy and not mono therapy.

III. Value-based pricing will be conducted over a certain time span, which may be a problem if patients transition between health plans before the outcome is achieved.

IV. For manufacturers who do not meet the value metrics, having fixed costs could challenge the viability of the value-based model.

In conclusion, payers are in principle ready to pay a premium for an innovative drug however establishing a clear link between innovation and price seems difficult (Paris & Belloni, 2012).

A few players in the diabetes market have already attempted to establish value-based pricing models. Merck implemented a pay-for-performance pricing scheme for Januvia (Deloitte Center for health Solutions, 2012) and Novartis tested a model with their Entresto drug for chronic heart failure. In the latter example, Novartis offered an initial discount under the agreement that the insurer would pay more if Entresto cut the need for further hospital visits compared to older medications (Miller, 2015).

In an interview with Novartis’ and Roche’s CEOs, Miller (2015) found that abandoning the pay-per-pill approach might push up immediate pharmaceutical spending but is likely to reduce overall medical bills. The two CEOs do not believe that the conventional model is sustainable any longer and stressed that when budget pressures are high enough payers will move towards aligning value with price. For the moment, the largest concerns besides finding good value metrics are insufficient electronic patient record infrastructure, medical privacy and resistance by doctors who fear added bureaucracy (Miller, 2015).
3. Risk-sharing agreements
Risk-sharing agreements appear similar to value-based pricing and arguably value-based pricing does share financial risks between payer and manufacturer (Neumann et al., 2011). However many more risk-sharing models exist that does not tie price to performance metrics. Spreng et al., (1993) worked on the effects of expectations, desires and perceptions of performance when estimating value. Risk-sharing agreements have the ability to align expectations and eliminate the perception-induced risk in transactions.

Adamski et al. (2010) refers to risk-sharing agreements as schemes concluded by payers and manufacturers to diminish the impact on payer’s budgets brought about by uncertainty and the need to work within finite funds. Sweeney et al. (1999) pointed out that perceived risk is a significant mediator of the quality-value relationship that was so extensively studied by Monroe. As such it will make sense for manufacturers to incur the cost of risk sharing when there is a promising but underdeveloped evidence base and the prospect of resolving uncertainty with new evidence is favorable (Neumann et al., 2011). In the insulin regimen, this could be an attractive option for the new ultra-long acting analogues, Toujeo and Tresiba who hope to gain traction in the patient sub-populations who suffer from severe or nocturnal hypoglycemia.

Although risk-sharing agreements are widely cited in the literature for their potential to push a paradigm shift, Neumann et al. (2011) notes that the enthusiasm has been premature. Risk-sharing agreements are unanimously supported with regard to products with unclear clinical and pharmacoeconomic outcomes at launch (Milne et al., 2015); still experience in the field mainly demonstrates how hard these agreements are to implement (Neumann, et al., 2011). Adamski et al., (2010) stresses that there are only a limited number of situations where risk-sharing should be considered including those where objective schemes, competent assessment staff and proper electronic patient record infrastructure are easily put in place.

In the diabetes field, the Italian health authority first adopted risk-sharing schemes for exenatide, sitagliptin and vidagliptin. The details of the contracts remain undisclosed, but it is known that the Italian government reimburses fully these drugs until further real-world re-evaluation of the level of innovativeness can be conducted (Adamski et al., 2010). The anti-diabetes drug manufacturers could look towards other therapeutic fields for inspiration. In the UK, Novartis entered into agreement with the NHS, following concerns
about the budget impact of Lucentis, an agent against macular degeneration. Novartis allowed NHS to restrict the reimbursement to 14 injections, paying for the drug itself if more was needed. Johnson & Johnson also has deals with the NHS to pay for the initial period of treatment for patients who do not respond to their drugs.

Finally Merck entered into agreement with Cigna, a US health insurance company, to provide rebates for Januvia and Janumet when there is an increase in the percentage of patients who reach HbA1c targets taking any OAD. The rebates increase further if the percentage of patients who are adherent to Merck’s products increases. The objective behind giving rebates even when patients are not using Januvia or Janumet is that, as most patients require multiple OADs to achieve HbA1c targets, the arrangement allows Merck to maintain a favorable tier-two formulary position (Neumann et al., 2011).

4. Redifferentiation and new evidence generation
According to Boudler, Porsborg-Smith and Reeves (2016), product redifferentiation can be a highly effective way to confront commoditization. The idea is to overhaul the product’s characteristics and value proposition. Sanofi launched a class-book example on product redifferentiation with Toujeo, a more powerful and concentrated version of insulin glargine. Although redifferentiation is an attractive option, manufacturers must manage their aspirations: successful redifferentiation depends on the manufacturer’s ability to create a premium product that provides value for money.

New differentiated products are challenged by their own value because they are often introduced to the market at high costs. As a result they must provide significant benefits in order to be considered cost-effective (Garthwaite & Duggan, 2010). We heard from LaPierre et al. (1999) that perceived value is defined as the outcome of an evaluative judgment. The FDA backed up this statement in expressing that they often had to make a judgment call on the evaluation of new health technologies. Health authorities and payers are thirsty for enhanced transparency and real-world data generation could be the answer.

Meeting the demand for value proof of new products require much more data than the pharmaceutical industry routinely produced (Milne et al., 2015). Moreover, the outcome studies in demand are pragmatic and observational, conducted in a real world setting (Cziraky & Pollock, 2015). Milne et al., (2015) found that:
“uncertainty remains as to how the industry and payers use post-approval studies to guide decision-making with regard to pricing and reimbursement. Correspondingly there is uncertainty regarding whether the industry’s investment [...] will have a positive return in terms of market access”.

The increase in budgets for generating evidence for payer decisions has been 12 percent on average since 2012 (Milne et al., 2015). It is not unusual, nowadays, that outcome studies last 3-6 years, require 10,000-25,000 patients and cost up to $500 million USD. Despite the uncertainty and costs, payers and manufacturers are expected to engage in more post-launch data collection to determine whether differentiated pharmaceuticals are working or not (LaMattina, 2013; Neumann et al., 2011).

Real-world evidence provides societal or extrinsic value because it ensures that the medications paid for have a significant impact on the society in which they were tested. Moreover, differentiated products, by definition must provide clinical value and value under innovation. One of the trial designs that are most effective in establishing differentiation is a head-to-head study. In head-to-head studies, two products are compared directly on a single set of value metrics. Instead of proving non-inferiority to placebo, manufacturers aim to establish superiority claims. Fiminska highlight that other new evidence standards count hard endpoints instead of surrogate markers and effects in patient subgroups (2014).

A few years ago the FDA published an interesting announcement: a new class of low-density lipoprotein lowering drugs, PCSK-9 inhibitors, might not need pre-approval outcome studies. Still the manufacturers, Sanofi included, conducted extensive trials because cholesterol guidelines would not incentivize payers to embrace PCSK-9s unless backed by data showing reduced rate of heart attacks versus statins. LaMattina (2013) stresses that payers will take the same stance in other therapeutic areas where existing treatment options are already deemed sufficient, such as diabetes.

In the diabetes fields Novo Nordisk have recently submitted post-approval data to the FDA in an application to update the label of Tresiba with confirmed effect on fewer episodes of nocturnal hypoglycemia (Novo Nordisk, 2016a). This is a deliberate attempt to differentiate Tresiba from competition and if accepted it is likely to give the product a competitive marketing edge. Finally, Boudler, Porsborg-Smith and Reeves (2016) list five circumstances in which the redifferentiation strategy is particularly challenging:
I. When the production process is mature
II. When the pricing transparency is high
III. When the industry’s value chain has already been deconstructed
IV. When there are diminishing marginal returns on incremental increases in marketing spending
V. When there are cost-effective substitutes for the product

Bearing these circumstances in mind it is clear that redifferentiation of basal insulin analogues is not an easy path however there may be opportunities in patient sub-populations as you will see on page 61.

5. Developing combination drugs
Several diabetes associations have issued guidelines recommending that if HbA1c targets are not reached with basal insulin, treatment should be intensified through combination therapy (Aroda, Rosenstock, Wysham, Unger, Bellido, Gonzalez-Galvez, Takami, Guo, Niemoeller, Souhami & Bergenstal, 2016). Therefore manufacturers of insulin are growing increasingly interested in the two-drug approach. Multiple companies are currently developing SGLT-2/DPP-4 products like Glyxambi or Insulin/GLP-1 biologic fixed dose combinations like Xultophy. Moreover, AstraZenica became the first to initiate the test of a GLP-1/SGLT-2 cocktail, in its DURATION-8 trial, this year (Helfand, 2016b).

The complementary effects of insulin and GLP-1 and the potential for mitigating barriers to their individual use has put that mix, specifically, at the heart of combination drug discourse. GLP-1 has an effect in post-prandial plasma glucose and weight loss while long- or ultra long-acting basal insulin impacts fasting plasma glucose and nocturnal hypoglycemia (Aroda et al., 2016). The combination drug strategy is mainly contributing with added clinical value in that respect.

Although the FDA advisory committee has just approved Xultophy and backed Soliqua in a 12 to 2 vote¹³ payers are reluctant to give combination products favorable placement on formularies. In the Xultophy and Soliqua clash, Leerink Partners analyst Seamus Fernandez expects the Sanofi product to receive a slightly narrower label than its counterpart. Fernandez estimated peak sales of about $5 billion USD for Xultophy and $1.5 billion USD for Soliqua, however pricing is considered a major obstacle. Bernstein analyst

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¹³ Final FDA decision expected in December 2016 for both Xultophy and Soliqua
Ronny Gal argues that the combination products will be priced up to 36 percent higher than their individual components alone (Staton, 2016d).

6. Treating adjacent diseases and comorbidities
Castano said the pharmaceutical industry should start to explore opportunities from a consumer-driven perspective (2014). Today’s problem for manufacturers is that there are too many players treating to the same target: HbA1c. An aggressive strategy is to expand the treatment of diabetes to target adjacent diseases and comorbidities. As T2DM is a lifestyle disease a large number of comorbid conditions often accompany the normal symptoms. Cameron and Bennett explained us that the use of HbA1c alone as a surrogate marker is already considered invalid to forecast clinical outcomes because it does not take into account the impact on for example cardiovascular disease.

Novo Nordisk is the only diabetes company who has explicitly expanded the franchise in other areas of adjacent diseases (Novo Nordisk, 2016). A few years back, liraglutide won FDA approval for the treatment of obesity (trade name Saxenda) and the follow on GLP-1, semaglutide, already boasts cardiovascular benefit data prior to regulatory submission. As outlined earlier in this paper, Novo Nordisk has announced that they expect to run a larger cardiovascular outcome study for semaglutide and has its hopes up that payers will be convinced of advantages in therapies external to the immediate disease area (Slowey, 2016).

The objective in treating adjacent diseases and comorbidities is that payers start to think outside diabetes and into the potential benefits of wider areas like cardiovascular disease or metabolic syndrome and realize that savings can come from these areas too. Novo Nordisk also tests its GLP-1 agents in fatty liver disease, which is closely linked to obesity and diabetes. The medical community already considers fatty liver disease an unmet needs area and the market is estimated at a flashy $35 billion USD (Staton, 2015b).

Moving into adjacent diseases and comorbidities both serves unmet needs and has the potential to improve healthcare system management by shifting costs. Furthermore, as it is untested territory, the approach is highly effective in generating value under innovation, clinical value and pharmacoeconomic value at the single cost of research and development including data generation.
7. Indicating for patient subpopulations
New drugs are becoming more and more niched (Rodriquez, 2015). In diabetes it is not a matter of ceasing properties, it is a question of differentiation. By niching your product in narrow patient subpopulations with unmet needs the value of your product can be demonstrated more easily and with higher guarantee – the only problem: your potential market shrinks. Zeithaml (1988) said that value is context dependent and that is particularly true in diabetes. T2DM patients struggle with different problems and will value any medication according to its ability to improve the patient’s own condition and health state.

In Gncchi (2009) it was proposed that companies should define their own supply in over-supplied markets like the newly commoditized insulin regimen. Only in doing so can insulin manufacturers provide performance that is superior to that guaranteed by competitors. The value in a niche is created by identifying where patients’ unmet needs intersect with the products attributes and also with that of the competitors. For T2DM patients I have identified eight needs. Any insulin, or other anti-diabetes agent for that matter, should focus its value proposition on speaking only to one of those needs. If the product boasts an attribute, like lowering weight or reducing the rate of nocturnal hypoglycemia, place efforts on highlighting that particular product attribute in a patient subpopulation that is looking specifically for it.

**FIGURE 25: Eight Niches and the Products Most Likely to Win**

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Price</th>
<th>Administration</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All</td>
<td>• NPH</td>
<td>• SGLT-2</td>
<td>• Lantus</td>
</tr>
<tr>
<td></td>
<td>• Biosimilars</td>
<td>• DPP-4</td>
<td>• Levemir</td>
</tr>
<tr>
<td></td>
<td>• Lantus</td>
<td></td>
<td>• Biosimilars</td>
</tr>
<tr>
<td>Pediatric</td>
<td>High-dosage</td>
<td>Weight &amp;</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>• Levemir</td>
<td>• Toujeo</td>
<td>Comorbidities</td>
<td>• Tresiba</td>
</tr>
<tr>
<td>• Lantus</td>
<td></td>
<td>• GLP-1</td>
<td>• Toujeo</td>
</tr>
<tr>
<td>• Biosimilars</td>
<td></td>
<td>• SGLT-2</td>
<td></td>
</tr>
</tbody>
</table>

**SOURCE: AUTHOR’S OWN INTERPRETATION**
According to the author’s own interpretation, GLP-1 and SGLT-2 agents are in the best position to meet the weight-comorbidity niche. High-dosage issues seem to be best served by insulin glargine U-300 as it comes in a higher concentration. Coping with severe or nocturnal hypoglycemia is likely to be won by insulin degludec who is currently waiting for FDA’s notch to update Tresiba’s label for that exact attribute. Lantus, the all-time bestseller, provides good and stable insulin adherence and Levemir claim pediatric indication down to two years. Price on the other hand is likely to fall out in the favor of NPH or glargine biosimilars unless Sanofi chose to compete with Lantus in that area. Administration refers to the preference for oral agents over injections and will certainly be snagged by SGLT-2 products in the future. Finally products that target HbA1c are undergoing commoditization and targeting that patient population will not fall in favor of any one agent over another.
Conclusion

Type 2 diabetes is a progressive disease projected to grow tremendously in prevalence across the board. Historically patients were treated with Metformin and SU before being moved on to insulin therapy. Basal insulin analogues constituted the most efficacious treatment and last step in therapeutic intensification. Due to proprietary protection, insulin glargine and insulin detemir enjoyed market exclusivity and high prices for many years. Today, demographic, economic and epidemiologic transitions have placed increasing pressures on healthcare systems and payers’ budgets.

Three imminent threats require the basal insulin regimen to rethink how value can successfully be addressed in the market. First, the institutional pricing pressure carves out higher rebates and discounts than ever before. Second, the loss of Lantus’ patent allows biosimilar products to enter with unprecedented low prices for insulin analogues. These copycats are expected to take the lion’s share of price driven business opportunities in the future. Third and finally, new innovative anti-diabetic drug classes with the potential to delay insulinization are being launched in leaps and bounds.

As I came into the home stretch of this paper it became clear to me that manufacturers wanting to compete on product value in or with the basal insulin regimen must do whatever they can to avoid commoditization. Value is a context dependent subjective evaluation of what is received less what is given. How product value can successfully be addressed in the market must be redefined for each product or drug class and I have identified seven strategies and tactics to do so.

First, cost-based advantage and price competition generate high societal value because it alleviates budget pressures and expand accessibility to insulin. Second, value-based pricing provides societal and pharmacoeconomic value by eliminating the uncertainty about product efficacy. Third, risk-sharing agreements enhance transaction transparency and lower concerns about potential budget impact thereby injecting societal value to the system. Fourth, redifferentiation adds value under innovation as well as clinical and societal value, because to be successful, the level of innovativeness of the new attributes must counterweigh incremental cost. Fifth, developing combination products brings clinical value as it allows for complementary mechanisms of action. Sixth, treating comorbidities and adjacent diseases contribute with all types of value as does the seventh, indicating for patient sub-populations. The two latter exhibit great opportunities to serve unmet needs
**FIGURE 26: Seven Ways of Addressing Value in the Market for Basal Analogue Insulin for the Treatment of T2DM**

<table>
<thead>
<tr>
<th>#</th>
<th>Tactic/strategy</th>
<th>Strength</th>
<th>Weakness</th>
<th>Business model</th>
<th>Value type</th>
<th>Sources</th>
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<td>1</td>
<td>Cost-based advantage, price competition and market imperfections</td>
<td>Product price and operating costs</td>
<td>Dependency on commoditized markets. Likely limited window of opportunity</td>
<td>Tenders Private Reimbursement</td>
<td>Societal (extrinsic) Pharmacoeconomic</td>
<td>Boudler, Porsborg-Smith &amp; Reeves, 2016 Pil &amp; Holweg, 2006 Neumann et al., 2011</td>
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<tr>
<td>3</td>
<td>Risk-sharing agreements</td>
<td>Enhancing transparency</td>
<td>Contracting difficulty</td>
<td>Reimbursement</td>
<td>Societal (extrinsic)</td>
<td>Neumann et al., 2011 Adamski et al., 2010 Milne et al., 2015</td>
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<tr>
<td>5</td>
<td>Developing combination drugs</td>
<td>Differentiating and complementing mechanisms of action</td>
<td>Product price and cannibalization</td>
<td>Reimbursement Private</td>
<td>Clinical</td>
<td>Helfand, 2016b Aroda et al., 2016 Staton, 2016d</td>
</tr>
<tr>
<td>6</td>
<td>Treating comorbidities and adjacent diseases</td>
<td>Serving unmet needs and improving system management</td>
<td>Cost of evidence generation</td>
<td>Reimbursement Private</td>
<td>Societal (extrinsic) Clinical Innovation Pharmacoeconomic</td>
<td>Staton, 2015bf Slowey, 2016</td>
</tr>
<tr>
<td>7</td>
<td>Indicating for patient subpopulations (niching)</td>
<td>Serving unmet needs and improving system management</td>
<td>Risk of study-bias</td>
<td>Reimbursement Private</td>
<td>Societal (extrinsic) Clinical Innovation Pharmacoeconomic</td>
<td>Rodriguez, 2015 Gncchi, 2009</td>
</tr>
</tbody>
</table>

**SOURCE: AUTHOR'S OWN INTERPRETATION**
and hence can improve healthcare system management. See figure 26 for a full summary of the seven tactics and strategies outlined in the preceding sections.
References


Aroda, V. R; Rosenstock, J; Wysham, C; Unger, J; Bellido, D; Gonzalez-Galvez, G; Takami, A; Guo, H; Niemoeller, E; Souhami, E. & Bergenstal, R. M. (2016). Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care*. Published ahead of printing by the American Diabetes Association. DOI: 10.2337/dc16-1495


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### APPENDIX 1: List of major molecules and brands studied in this paper

<table>
<thead>
<tr>
<th>Class</th>
<th>Molecule</th>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Status (FDA)</th>
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<td>DPP-4</td>
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<td>Nesina</td>
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<td>N/a</td>
<td>Merck/Pfizer</td>
<td>Phase III</td>
<td>VERTIS-SITA</td>
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*Biosimilar product

### APPENDIX 2: List of major manufacturers studied in this paper

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<th>Website</th>
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