The EuroBiotech Journal
RESEARCH ARTICLE
Pharmaceutical Biotechnology

Early phase value scan for biotechnology innovation

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Abstract

The registration of a medicinal product by EMA or FDA used to be the main driving critical success factor for the future sales of a new medicinal product. The current additional important criteria for reimbursement decisions are cost-effectiveness and budgetary impact, which are taken into consideration in order to make a value for money decision. In order to maximize the chances of obtaining reimbursement at a maximum price, it is very important to have a well thought through strategy at the early onset of the development program in order to proactively cope with the emerging reimbursement hurdles.

This paper aims to provide a pricing, market access and reimbursement strategy, which is based on a strategic scan, sales forecast model, pricing model, and cost-effectiveness model. These models are interacted and linked with a discounted cash flow model in order to optimize the economic value of the company.

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Published online: 9 May 2017
doi:10.24190/ISSN2564-615X/2017/02.08

Introduction

Rational

Registration of a medicinal product by EMA or FDA used to be the main determinant for the future sales forecast of a new medicinal product and would justify a higher valuation of the share of the company, especially for a biotech company with only a limited number of products. Contrary, new emerging requirements from reimbursement authorities and drug policy changes are increasingly going to determine the actual future sales and also the actual post-launch costs. At a central level the demand for cost-effectiveness evaluations and budgetary impact analyses has been increasing, which already resulted in formal extensive dossier requirements in most European countries. In addition, European health authorities have introduced pharmaceutical policy reforms, including business models, like risk sharing agreements, for final decision making on funding new, premium priced, innovative medicinal products.

Current market access hurdles from the last decade

Description

The most important criteria for reimbursement decisions for new innovative drugs are effectiveness, cost-effectiveness and budgetary impact. These criteria are taken into consideration in order to make a value for money decision. A cost-effectiveness analysis provides a cost per QALY, which is the additional cost for a life year gained in perfect health, the so-called quality adjusted life year (QALY). In England, the National Institute of Health and Clinical Excellence (NICE) is using a cost-effectiveness threshold ranging from £20,000 to £30,000 per QALY gained, which means that the English society is willing to pay up to £30,000 per QALY gained for a new, innovative, medicinal product (1). A budgetary impact analysis estimates the impact of a new medicinal product on the annual national healthcare budget.

The requirement for a reimbursement dossier, containing the clinical argumentation as well as the cost-effectiveness analysis and budgetary impact analysis, implies

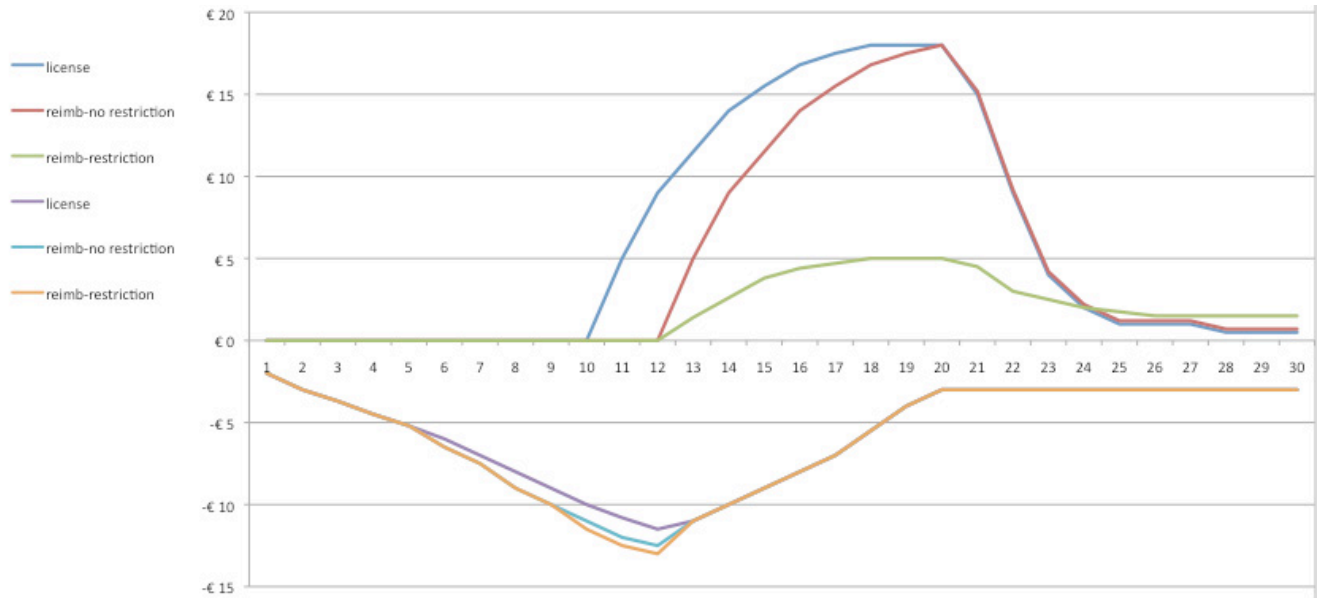

Figure 1. Impact on sales and costs forecast by reimbursement hurdles, including prescribing restrictions.

considerable budgets for constituting such a dossier. However, the reimbursement assessment does not guarantee acceptance of the claim made in the dossier. If the budget impact is considered too high, the prescription of the product may be restricted to a subpopulation. This prescription guideline may result in a considerably niche market, which may only generate 10% to 30% of the total expected sales according to registration (**Fig. 1**).

There is also a probability that the drug will not be reimbursed resulting from a negative assessment. The health authorities may not be convinced of the clinical benefit and/or the cost-effectiveness neither for the total population nor for a subpopulation. In this case, there will be no formal reimbursement under the health insurance system, which means that there will be no sales, except maybe for a very small private market. The huge sunk costs of clinical development and the resulting opportunity costs of not investing this money in another clinical program or financial investment fund become more real possibilities today.

The previous description mainly relates to the central decision making process for outpatient drugs in most countries. It is important to be aware that for inpatient drugs, there may be a country-specific reimbursement and formulary listing system, which may differ from the system for outpatient drugs.

Recent and future market access hurdles

Recently, novel payment approaches, risk-sharing agreements with health insurers are explored to overcome the tension between funding new but expensive technologies and obtaining value for money where traditional coverage is not deemed appropriate. These arrangements between a manufacturer and health insurer can use a variety of mechanisms to address uncertainty about the real performance of technologies in daily practise enabling certain market access. These business models should be considered as agreements concluded by health insurers and pharmaceutical companies to diminish the impact on health insurers' budgets for new innovative drugs. There are various possible arrangements:

- Price-volume agreement (PVA) whereby A penalty is foreseen when a new drug is overshooting a pre-set budget. A penalty can take the form of rebate or payback, lower price for volume above agreed limit, or lower future price.
- Reimbursement is based on the achievement of treatment targets, also called pay-for-performance. In this agreement, the drug is only reimbursed when the individual patient has reached pre-defined treatment target(s).

Strategic planning for global biotechnology

In order to maximize the chances of obtaining reimbursement at maximum price, it is very important to have a well thought through strategy at the early onset of the development program of a new medical product considering the emerging hurdles for market access. The most important issues for reimbursement dossiers are: indication, population, comparator, efficacy and safety, cost-effectiveness and budget impact.

The outcomes of the strategic value scan are determined by the key decision criteria:

- Efficacy and safety: target product profile – clinical data and assumptions
- Budget impact: early sales forecast model
- Price of medicinal product: pricing matrix model
- Cost-effectiveness: cost-effectiveness model
- Financial valuation: discounted cash flow model
- Additional criteria may be included depending on the disease area

The input and outcomes of the strategic value scan, sales forecast model, pricing model, and cost-effectiveness model,

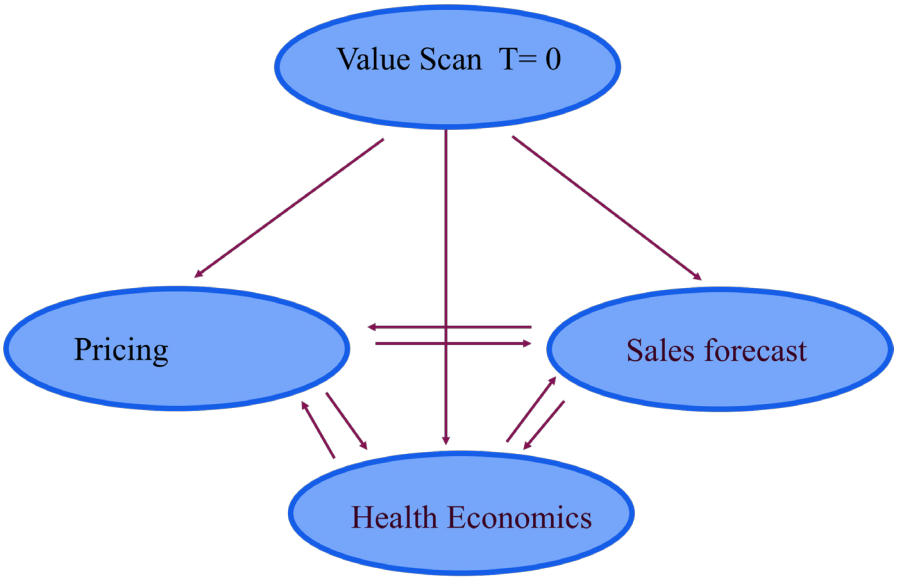

Figure 2. Interaction between pricing, health economics, and sales forecast.

are interacted and executed simultaneously (**Fig. 2**). For example, the price of the new drug resulting from the pricing matrix model can be constrained by the resulting threshold in the cost-effectiveness model.

On the other hand, the input for the cost-effectiveness model and pricing model depends on the position of the new product in the treatment pattern for each scenario and the expected comparators in each position.

In the end the optimal price and positioning of the new product for successful reimbursement, also must fulfil requirements for the investors, who need a minimum return of investment. Therefore, the strategic value scan, sales forecast model, pricing model, and cost-effectiveness model, are directly connected with the discounted cash flow model to optimize the chances of reimbursement, market volume, pricing potential, and economic value.

Early strategic value scan

The objectives of an early strategic value scan for a new innovative medicinal product are:

- To predict the future clinical need and disease pathways at the time of launch.
- To develop various scenarios (e.g. negative, base case and optimistic) for the expected product profile of the new product: e.g. efficacy and safety.
- To predict the position of the new product in the treatment pattern for each scenario and the expected comparators in each position:
  - Positioning: 1-line, 2-line, 3-line treatment
  - Subpopulation: e.g. subpopulation at risk, severe subpopulation
  - Risk of prescription restrictions
- To predict the incremental benefit of the new product versus the relevant expected comparators at each possible position.
- To determine the existence of generics at time of launch and the forthcoming launch of competitive new drugs, which are still in development, but will enter the market before our new product.
- To assess the expected burden of disease at time of launch.
- To assess the opportunities and barriers for registration (FDA, EMEA) and reimbursement of the new drug in the key markets UK, France, Germany, and the US. There may be main differences in market access for outpatient and inpatient drugs. Therefore we consider both outpatient and inpatient market access pathways, if relevant for the new drug.
- To assess the potential risk of payment schedules, which depends on the drug price and prevalence/incidence of patients, for example, pay-for performance for expensive biologicals and price volume arrangements for cheap non-biologicals in broad indications.
- To adapt the design of forthcoming clinical studies from a clinical and market access perspective. For example, health economic data (effectiveness and resource utilisation) may be collected alongside the forthcoming clinical trial, which may be used as input for the health economic models.

The value scan is performed in the key countries in Europe (Germany, UK, France) and US and it provides the needed insight in the product, the indication and the treatment landscape. Next these insights can be applied to the reimbursement rules and regulations in the key markets leading to a strategy on how the biotechnology company can maximize their chances of obtaining reimbursement depending on price and positioning of the new drug. Although most countries require the submission of health economic data, there are differences regarding the appraisal process, including the weight attributed to clinical and economic criteria in the decision-making process. For example, the cost/QALY is of

paramount importance in England, whereas clinical benefit and budget impact are more important in Germany.

The strategic value scan provides guidance on the position of the new product in the treatment pattern for each scenario and the expected comparators in each position. The cost-effectiveness model and pricing model can provide upper limits for the pricing potential for each scenario and the expected comparators in each position. The discounted cash flow model allows the assessment of which scenario (price, positioning) will fulfill the minimal requirements for the financial investors.

Early sales forecast model

The objective of an early sales forecast is to predict the impact of the health economic requirements and the increasing implementation of prescription restrictions on the sales forecast of a new innovative drug. The input for the sales forecast model are the outcomes of the strategic value scan, the pricing model, the cost-effectiveness model, and the discounted cash flow model. The sales forecast model is performed for the key markets with an extrapolation to the global market.

Model design

A sales forecast analysis exploring the revenue implications for a new innovative drug in daily practise after market introduction relies on decision analytic modelling (2). A decision analytic model should as much as possible reflect the expected real life treatment situation for a specific indication at time of launch incorporating predicted treatment patterns with input values (e.g. clinical probabilities, incidence). This model can provide information on the most sensitive parameters for the sales forecast.

Potential number of patients

The potential number of candidates of the target population for a new pharmaceutical depends on epidemiology (prevalence and incidence of the disease), possible prescription restrictions, growth of the target population, off-label use, the expected comparative treatment mix, and diffusion curves.

- Prevalence is the most important parameter in a sales forecast for indications in chronic diseases, where the annual inflow (incidence) equals the annual outflow of patients (e.g. improvement, progression or mortality). Incidence is the most important parameter for diseases with full recovery or death (e.g. infectious diseases) or diseases, like oncology, where the initiation of treatment starts at diagnosis and selection of treatment is based on staging (e.g. adjuvant or advanced treatment).
- The proportion of patients, who are eligible for treatment with the new pharmaceutical, which used to be the registered indication for the new pharmaceutical. Since the last 15 years reimbursement authorities have been increasingly imposing prescription restrictions and consequently reducing the size of the eligible patient population.
- The proportion of eligible patients, which actually is treated with the new pharmaceutical. There may be clinical reasons, especially risk of side effects, warnings and contra indications. The reason may also be more patient related. For example, patients themselves prefer an oral medication, when they have an aversion for a subcutaneous route of administration.
- Performance based/outcome-based models may be used with treatment targets for reimbursement. The product is only reimbursed if treatment targets have been reached per individual patient. The goal a stopping rule is to reduce the budget impact.
- The future expected comparative treatment mix, which includes the existence of generics at time of launch and the forthcoming launch of competitive new drugs, which are still in development, but will enter the market before our new product.
- Diffusion curves or uptake curves over the follow-up period in the sales forecast analysis. These curves reflect the annual proportion of patients switching from each treatment modality of the treatment mix to the new pharmaceutical. The diffusion generally increases from time of launch over the follow-up period in the analysis.
- The potential of off-label use, which means that the new drug may be used outside the registered indication, for example a subpopulation, where the officially registered drugs are not efficacious or lead to intolerable side effects.

Data sources

Data on prevalence and incidence may often be derived from literature, but most other sales forecast analysis can only be derived from expert opinion. The data in a sales forecast model also includes forecasts (annual growth, uptakes curves, substitution effects, changes in prescription restriction and guidelines, future distribution of the available treatment modalities, off-label use). In some cases mathematical methods of extrapolation may be used, for example using data on historical trends, which may allow construction of distribution. In majority, the use of expert opinion is only option for obtaining this type of information.

Analysis

In the analysis, we explore the impact of the various scenarios the sales forecast of a new innovative drug. Premium pricing in a niche market can be an alternative strategy instead of positioning the new drug in the broad market at a lower price. Scenario analyses are performed 1) for the product versus the relevant comparators at each possible position in the treatment pathways, and 2) using different pricing scenarios, and 3) using different uptake scenarios. We assume that incremental clinical benefit for the new product is reflected in the uptake curves and pricing potential. We also assess the impact of the reimbursement criteria on the potential sales by comparing the sales forecast based on registration only with a sales forecast based on prescription restrictions due to reimbursement criteria.

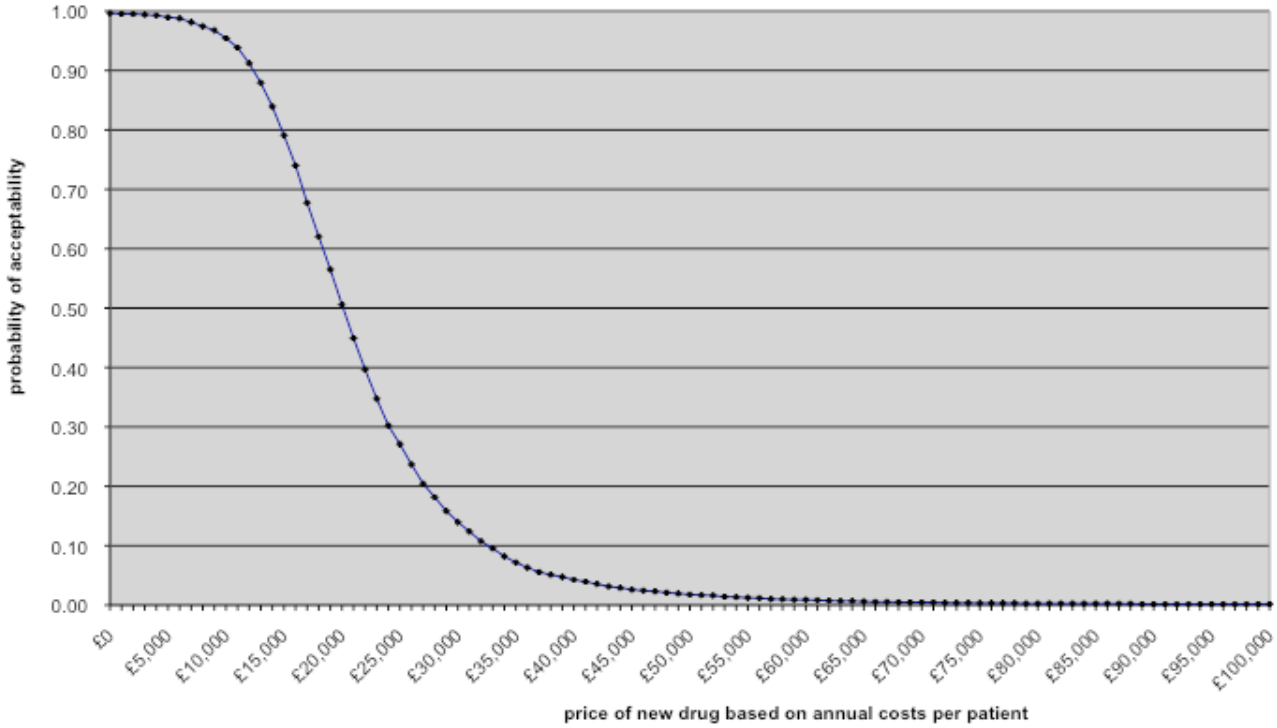

Figure 3. Price-acceptability curve for new product.

Early phase pricing model

Background

Pricing and reimbursement of new pharmaceuticals is currently based on the traditional clinical trial outcomes (efficacy, safety) used for registration, but also cost-effectiveness and budgetary impact. Also, other considerations may be taken into account depending on the specific indication, e.g. equity in the case of rare diseases.

Pricing Matrix Model

A main question is how much the impact is of the various types of data in the pricing and reimbursement process in Europe. The objective of an early pricing study is to quantify this type of uncertainty in order to develop a more solid pricing and reimbursement strategy.

The determination of the pricing potential is based on the analytic hierarch process, as applied in the Pricing Matrix Model, which measures decision makers' preferences for the critical drivers: clinical outcomes (efficacy, safety), cost-effectiveness and budgetary impact. The Pricing Matrix Model is designed to solve complex decision-making problems involving multiple criteria by making judgments about the relative importance of each of these criteria. When the initial price of a new innovative drug with a higher efficacy or better safety, equals the price of standard treatment, the hypothesis is that decision-maker will choose for the new drug, because of its clinical advantages compared with standard therapy. Subsequently the price of the new drug will be increased until the preference will switch to standard therapy, which is the upper price limit for the new drug (3). The price-acceptability curve (**Fig. 3**) shows that there is a probability of 50% that the price of the new product is GBP 23,000 per year, which decreases to 5% for a price of GBP 40,000.

Early phase cost-effectiveness model

Design

The design of an early phase core cost-effectiveness model should incorporate the potential key drivers of a favourable cost-effectiveness for the new product. In addition the model design and the data sources for the model should comply with international health economic guidelines in the study countries.

A core health economic model is constructed using data on the target profile of the new drug, the literature, expert opinion and assumptions. The model allows scenario analyses at possible positions in the treatment pathways (1-line, 2-line) or a subpopulation (e.g. high-risk patients). In addition different pricing scenarios and clinical scenarios (e.g. negative, base case and optimistic) for the expected product profile of the new product (e.g. efficacy and safety) are performed. The scenario analyses are performed for the product versus the expected relevant comparators at each possible position in the treatment pathways. The structure of the model is based on the treatment patterns at time of launch.

The type of model depends on prognosis and disease progression:

- Prognosis: A patient may fully recover without any higher risk for recurrence or other morbidity than the general population (e.g. infection).
- Disease progression: Many diseases will not lead to a complete recovery. There may be: 1) an increased risk for a relapse (e.g. depression), 2) incomplete recovery (e.g.

stroke) or 3) a more continuous chronic character (e.g. Parkinson's disease).

This information is needed to decide on the type of model and its characteristics (need of health states, pathways, follow-up period). Models may be simple decision-analytic trees or they may be complex Markov models. While decision-tree models are appropriate for acute episodes, Markov models are the first choice for health economic analysis of chronic diseases.

This core model will yield information on the effectiveness and cost of care:

- The incidence of clinical events;
- The relevance of different effectiveness;
- The cost structure and main cost drivers;
- The most sensitive clinical and economic parameters;
- Pricing potential of the new drug (break even price in order to have ICER below the threshold (e.g. €80,000 per QALY).

The following components of the design of a clinical study can be based on information derived from the core model: study period, study population, comparators, clinical and economic outcomes, and sample size. The information on the cost drivers will lead to development of an optimal sized case record form (CRF) by collecting more detailed information on most relevant cost drivers. Another key element for a favourable cost-effectiveness is the extrapolation of short-term clinical outcomes resulting from improved efficacy in a RCT to relevant long-term cost-effectiveness outcomes in chronic diseases. Value of information analysis can further refine the trade-off between additional costs in the clinical program and higher probability of reimbursement.

Data sources

The input data for a model consists of probabilities (e.g. response, discontinuation), health care utilisation (e.g. drugs, consultations), prices and tariffs, and QALYs. Data sources for the parameters being used in a model may be clinical trials, literature (e.g. meta-analysis), databases, and official price and tariff lists. The use of expert opinion (Delphi panel) is possible, if there is lack of data in the literature (4, 5). The Delphi panel is usually used for the collection of resource utilisation associated with the local treatment patterns. However, clinical and utility data ideally should be based on actual published data.

Financial Valuation

The future financial performance of a pharmaceutical company is directly related to the future net revenues of its drug portfolio, and therefore a robust assessment of potential sales from forthcoming new drugs is an important predictor of its economic value. For biotech companies with only a limited number of products in the pipeline, the economic value of the company is even more strongly related with the future sales forecast of a new drug. This valuation is based on the Discounted Cash Flow method, which is based on the free cash flows and the required cost of capital. Free cash flow is often defined as the cash flow from operations (or net cash flows from operating activities) minus the cash necessary for capital expenditures. Cash flows from operations represent the sales from the pharmaceuticals, and cash necessary for capital expenditures represents the costs for R&D, production costs and marketing. The sales forecast should definitely include the estimated effects of the new emerging requirements for reimbursement and other pharma policy changes. The cost of capital refers to the opportunity cost of making a specific investment. It is the rate of return that could have been earned by putting the same money into a different investment with equal risk. Thus, the cost of capital is the rate of return required to persuade the investor to make a given investment (6).

The outcomes of the strategic value scan, sales forecast model, pricing model, and cost-effectiveness model can be linked with the Discounted Cash Flow method in order to optimalise the economic value of the biotechnology company taken into considerations the hurdles for reimbursement and market access. Changes in design of a forthcoming clinical trial or positioning of the new product may increase the economic value of the company.

Conclusion

As the valuation of a biotechnology company is directly related to the sales of new products, an appropriate assessment of the potential sales of a forthcoming new medical product is an important predictor of the economic value of the company. This valuation should definitely include the estimated effects of the new emerging requirements for reimbursement and the effects of drug policy changes. This paper provides a pricing, market access and reimbursement strategy, which can be linked with the economic value of the biotechnology company in the early phase development of a new drug.

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