
Lizheng Shi, PhD, MS Pharm,1 Meredith Hodges, MPH,2 Michael Drummond, PhD,3 Jeonghoon Ahn, PhD,4 Shu Chuen Li, PhD,5 Shanlian Hu, MD,6 Federico Augustovski, MD,7 Joel W. Hay, PhD,4 Jim Smeeding, RPh, MBA8

1School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, USA; 2School of Pharmacy, The University of Texas at Austin, Austin, TX, USA; 3Centre for Health Economics, University of York, Heslington, York, UK; 4Department of Pharmaceutical Economics and Policy, University of Southern California, Los Angeles, CA, USA; 5School of Biomedical Sciences, University of Newcastle, Callaghan, NSW, Australia; 6School of Public Health, Fudan University, Shanghai, China; 7Institute for Clinical Effectiveness and Health Policy (IEC5), Buenos Aires, Argentina; 8JestaRx Group, Dallas, TX, USA

ABSTRACT

Objective: The pharmacoeconomic guidelines available in the literature or promulgated in many countries are either vague or silent about how drug costs should be established or measured so an international comparison of cost-effectiveness analysis (CEA) results can be made. The objective of this report is to provide guidance and recommendations on how drug costs should be measured for CEs done from an internationally comparative perspective.

Methods: Members of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices—Use of Drug Costs for Cost Effectiveness Analysis (Drug Cost Task Force [DCTF]) subgroup from several countries were experienced developers or users of CEA models, and worked in academia, industry, and as advisors to governments. They solicited comments on drafts from a core group of 174 external reviewers and more broadly, from the members of the ISPOR at the ISPOR 12th Annual International meeting and via the ISPOR Web site.

Results: Drug units should be standardized in terms of volume of active ingredient, regardless of packaging and dosing strength variations across countries. Drug costs should be measured in local currency per unit of active ingredient and should be converted to other currencies using sensitivity analyses of purchasing power parities (PPP) and exchange rates, whichever is more appropriate. When using drug prices from different years, consumer price indices for the local currency should be applied before the PPP and/or exchange rate conversion.

Conclusion: CEA researchers conducting international pharmacoeconomic analysis should tailor the appropriate measure of drug costs to the international perspective, to maintain clarity and transparency on drug cost measurement in the context of international drug comparisons and report the sensitivity of CEA results to reasonable cost conversions.

Keywords: drug cost, health technology assessment, pharmacoeconomics.

Background to the Task Force

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices—Use of Drug Costs for Cost Effectiveness Analysis (DCTF) was recommended by the ISPOR Health Science Policy Council on December 13, 2004 and was approved by the ISPOR Board of Directors on May 15, 2005. Because how drug costs should be measured for cost-effectiveness analyses (CEAs) depend on the perspectives, five Task Force subgroups were created to develop drug costs standards from the societal, managed care, US government, industry, and international perspective. This report is part VI: an international perspective (one of six reports from this ISPOR Task Force on Good Research Practices—Use of Drug Costs for Cost Effectiveness Analysis [DCTF]). The other reports (part I: issues and recommendations; part II: a societal perspective; part III: a managed care perspective; part IV: US government perspective; and part V: industry perspective) are also published in this issue of Value in Health (volume 13, issue 1). This DCTF subgroup met to develop core assumptions and an outline before preparing a draft report. The Task Force subgroups held open forums and/or group leader breakfast meetings at the ISPOR Annual International Meetings and European Congresses. The draft report was circulated to 174 Task Force primary reviewers (who were self-identified from a broad range of perspectives). After this review, a new draft was prepared and made accessible for broader review by all ISPOR members. Comments for these reports by Task Force primary reviewers and ISPOR membership are published at the ISPOR Web site. All opinions reflect those of the authors and not necessarily their affiliations.

We aim to review pharmaceutical price and cost issues of our subgroups’ designated perspective (i.e., ex-US perspective). As such, we will review current practices from literature articles, including the Organization for Economic Cooperation and Development and developing countries, which usually have very little presence in the research and development (R&D) of new chemical entities. In recent years, considerable attention has been focused on pharmaceutical prices in emerging markets [1]. Therefore, in addition to the literature search, a panel of experts (J. Ahn, F. Augustovski, S. Hu, and S. Li) from South Korea, Argentina, China, and Australia, respectively, has provided input on two questions: 1) How are drug prices set in your respective country? and 2) What are the sources of drug cost estimates used in pharmacoeconomic studies in your respective country and what are the key issues?

Introduction

Since the early 1990s when Australia proposed guidelines requiring CEA of new pharmaceutical products, there has been an increase in the number of pharmacoeconomic studies performed [2]. One of the important parameters of these studies is drug
costs, including both the cost of the study drug and its comparators. In addition, the cost of concomitant drugs used to treat adverse events can be an important component of the evaluation. Unlike other parameters, there have been few studies on how drug costs are estimated. Nevertheless, there have been many methodological questions proposed concerning these studies, for example, whether the methods are consistent across studies and theoretically correct.

The costs of drug regimens involve not only the estimation of the drug price but also the impact of any wholesale discounts, pharmacy costs, and assumptions about wastage (owing to package or vial size). This becomes a major problem when international comparisons are performed because these values differ across countries, and many countries do not have the same drug compounds, dose sizes, strengths, or packaging.

There is also an increase in theoretical literature often linked to discussions about patent protection that suggests market prices for drugs are not good approximations for social opportunity costs (the theoretically correct estimate of cost to be used in economic evaluations undertaken from the societal perspective). Issues of importing price controls, parallel trade, and the globalization of the pharmaceutical market make these pricing issues even more relevant. For example, four different methodological approaches to pharmaceutical price regulation were found in the European Union countries, including fixed pricing, cost-effectiveness pricing, profit controls, and reference pricing [3]. Another study looking at pricing issues showed the potential cost savings to Ireland if an alternative pricing mechanism was used [4].

For years, in countries around the world, such as Australia, the Netherlands, and Canada, pharmacoeconomic studies have been used by governments to set domestic prices or to evaluate alternative regulatory systems [5]. With an increase in the use of economic evaluations by governments around the world, there is an urgency and need to develop a standard for drug costs in pharmacoeconomic studies from the international perspective.

Argentina

Unlike their neighbor Brazil [6], there is no formal drug price regulation in Argentina, and sale prices are set according to market rules. The country does not currently have cross-referencing pricing mechanisms. Nevertheless, there are several mechanisms that regulate drug prices. Regarding national reference pricing, around 200 essential drugs are included on the formulary for the Social Health Insurance Package (PMO). This formulary is regulated by the Superintendency of Health [7]. Also, generic prescribing is strongly enforced by a congress law passed in 2004 [8,9]. One of the problems with drug prices is that not all prescription drug costs are available through publicly available sources (Manual Farmacéutico, Kairos, IMS). High-cost drugs are handled by direct selling, escape price controls, and monitoring (some examples are imatinib, saquinavir, bevacizumab, sorafenib) [10]. A recent proposal by the Superintendency of Health created a drug observatory of the National Health Insurance (NHII) System [11]. During recent years, agreements between the government and industry involved reducing the price of more than 200 drugs and regulating gradual price increases over time. Nevertheless, there is no clear evidence that these agreements are being honored [10].

Until 2005, pharmacoeconomic evidence was recommended to include new drugs in the Social Health Insurance Package (PMO), but this is not true anymore. Nevertheless, currently, pharmacoeconomic evidence is informally considered by many stakeholders in the macro-level and meso-levels [12]. Main sources of drug costs for the public sector come from publicly available data from manufacturers’ bids. Nevertheless, in the case of evaluations from the social insurance or private HMO perspectives, costs are estimated by different payers, or otherwise, from available sales price sources (Manual Farmacéutico, Kairos, IMS), and a variable rebate is applied according to the sector. Also, there is an independent and publicly available Health Care Costs Database in Argentina for researchers performing economic evaluations [13].

Australia

In the Australian health-care system, drugs that have been approved for marketing, after going through the evaluation process for efficacy, safety, and quality by the Therapeutic Goods Administration, would usually apply for inclusion in the Pharmaceutical Benefits Scheme (PBS) funded by the Commonwealth Government at the earliest opportunity. The inclusion of a drug into the PBS qualifies the drug to be reimbursed by the Commonwealth Government for its use in the community and private hospital settings. The recommendation for inclusion is made to the minister of health through an independent expert committee, the Pharmaceutical Benefits Advisory Committee (PBAC). After a positive recommendation by the PBAC, the price of the drug is determined by negotiations between the Pharmaceutical Benefits Pricing Authority (PBPA) and the sponsor company [14]. Since 1993, it is mandatory that the inclusion of a new drug into the PBS is cost-effective when compared with existing drugs in the scheme. It is only after the recommendation by the PBAC of acceptable cost-effectiveness that the reimbursement price of the drug is negotiated between the sponsor company and the PBPA. In the assessment of cost-effectiveness, the cost of the new drug used by the PBAC is based on that supplied by the sponsor company. The cost of the drug is usually the uniform price as requested by the global headquarters of the sponsor company to be supplied internationally. Sometimes, this may pose a problem as the proposed price may not be considered to be cost-effective in comparison with existing drugs for the same indication available in the PBS, but the sponsor company is reluctant or unable to reach a reduced price with PBPA. This may sometimes result in the drug not being included or delay of inclusion of the drug in the PBS.

China

Before 2000, drug prices were set by local price authorities. Afterward, the power of price setting moved upward to the national planning committee, now called the State Development and Reform Commission (SDRC) [15,16]. In recent years, the Chinese government implemented a series of regulations and legislations to control drug prices, such as pharmaceutical law, decree of drug price administration, government pricing methods for drugs, etc. In the past 10 years, the scope of price control in terms of the number of drugs widened from 1500 items to 2400 items. Although these drugs represent only 20% of the total medicines on the market, they make up approximately 60% of the total pharmaceutical expenditure in China.

To make drug pricing more scientific and transparent, and promote the equity of competition, the SDRC announced a method for drug differential pricing and price ratios in 2005. A drug’s differential price and price ratio comparison is defined as the price difference between forms, strengths, and packages of the same medicine, which is influenced by average production cost, production technique, the efficiency and effectiveness of
clinical application, the convenience and treatment cost, etc. All price reductions or adjustments by the government have followed this policy. All chemical drugs in the same International Nonproprietary Names (INN) should be classified as one drug [17]. The World Health Organization (WHO) collaborates closely with INN experts and national nomenclature committees to select a single name of worldwide acceptability for each active substance that is to be marketed as a pharmaceutical. The INN facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name.

In February of 2007, the SDRC published “Working Guidelines for Pharmaceutical Pricing”; it requires at least two pricing professionals doing an in-depth study on the drug cost to the pharmaceutical manufacturers and exchanging views with pharmaceutical manufacturers. If needed, public hearings should be organized by the discipline and supervision authority. The basic data on pricing, suggestions, and recommendations for price adjustments are presented during the hearings. Sometimes, these hearings are open to the media, which allows for feedback from the public. In February of 2007, the SDRC also formulated the working rules on medical services and pharmaceuticals price. It was pointed out that all prices set for medical services or pharmaceuticals should go through the following five steps: 1) cost investigation and audit; 2) market price investigation; 3) regional coordination; 4) expert review and confirmation; and finally, 5) public hearing on the issues of price. The following criteria could make pharmaceutical companies to apply some drugs to go through a separated pricing mechanism; it will be based on quality, efficacy, safety, good clinical practice evidence, and opinion from expert's consultation.

In April of 2007, the China State Council (administration branch of central government) expressed its determination to further investigate and monitor the cost of medicines, improve the pricing method, and expand the number of price control drugs, specifically targeting prescription drugs [18].

For some medicines or new medicines without set prices, manufacturers have the right to set their own prices, and then report those prices to the provincial government. The Provincial Price Bureau sets temporary prices in the record and reports them to the central government. Most foreign pharmaceutical companies factor into the drug cost the expense of the sales team, rebates, commissions, and promotions, thereby raising the ex-manufacturer price. Another pricing behavior is that the manufacturers widen the gap between the wholesale price and real business price to the tenders, leaving an attractive profit to the tenders.

In pharmacoeconomic studies in China’s hospitals with a fee-for-service payment system, drug costs, as part of direct medical costs, are usually estimated based on acquisition (transaction) costs (i.e., the retail price of pharmaceuticals in hospitals), which include the wholesale price plus a 15% to 25% markup and rebates from pharmaceutical companies. The key issues of cost estimation in pharmacoeconomic studies in China are that some literature articles only consider acquisition (transaction) costs of drugs rather than total direct medical costs [19].

South Korea

In the Republic of Korea (South Korea), the NHI program is a compulsory insurance plan for the whole population, except for the lowest income households (1.8 million people, 3.6% of the Korean population) who are covered by the Medical Aid program. The two health insurance programs provide the same benefit package with fee-for-service type reimbursements for hospital, physician, and pharmacy services [20]. The Health Insurance Review Agency (HIRA) reviews all the claims and decides the reimbursement amount, including the maximum allowable cost (MAC) for all the pharmaceuticals (both Western and traditional medicines) listed by the NHL. The MAC is negotiated with manufacturers based on the adjusted average price of seven foreign countries (United States, UK, France, Japan, Germany, Italy, and Switzerland). Then, the MAC is regularly reviewed, but especially for any drug significantly exceeding expected volume or any drug with a MAC significantly higher than the weighted average of the surveyed acquisition cost (13 hospitals and 67 pharmacies were surveyed in 2007). Because MAC is publicly available from the HIRA Web site (in Korean) [21], most Korean researchers use the published MAC as the drug cost for their pharmacoeconomic studies, which are rapidly growing in Korea as a result of the positive list system (PLS) started in 2007, i.e., for any new drug, CEA is required to be listed to the NHL [22]. There are a couple of issues in using drug cost data from Korea, including high generic drug prices and uncovered off-label use. According to the recent Guidelines for Determining and Adjusting New Medical Technologies (2006-123), the MAC of the first to the fifth generic can be 68% of the original drug price (which is lowered to 80% of the original price as soon as the first generic drug enters the market) and each following generic drug can have 90% of the cheapest generic MAC previously available, e.g., the sixth generic can have 61.2% of the original drug price, the seventh generic can have 55.08% of the original drug price, and so on. In addition, in Korea, any off-label use (including on-label use exceeding dosage recommendation) of pharmaceuticals is not eligible for reimbursement, and it is technically illegal to charge any noneligible item as an out-of-pocket expense without a special approval from the minister of health and welfare (though this illegal practice exists). Hence, the Korean Ministry of Health and Welfare has recently announced a plan to legalize the off-label use of pharmaceuticals if the providers’ Institutional Review Board approves the off-label use and reports to the HIRA within 10 days [23]. Nevertheless, any off-label use is the patients’ out-of-pocket expense. Therefore, the HIRA is able to monitor such use nationally each year and can eventually convert it to an eligible coverage.

Western Europe

There are three main approaches to setting drug prices in Western Europe, international reference pricing, reference-based reimbursement (clustering), and value-based approaches. Under international reference pricing, prices are set in relation to existing prices in several selected “reference” countries. This approach is popular in Southern Europe (e.g., Spain, Italy) because they are not normally the first countries to introduce new drugs, so there are often existing prices to compare with. Normally, the jurisdictions concerned base its prices on the average of those in the reference countries, or they request a small discount on existing prices. The main issues arising under this approach are: 1) the choice of reference countries; and 2) the approach used for currency conversions outside the Eurozone. Essentially, international reference pricing emphasizes those countries that are first to introduce new products and their approach to setting prices.

Under reference-based reimbursement (clustering), similar drugs are grouped and one price (i.e., reimbursement level) is set for the group. Manufacturers are free to set their own price, but they almost always gravitate to the reference price for fear of losing market share as a result of higher co-pays. In most of the countries operating such schemes, the approach is limited to
drugs that are chemically equivalent, but in The Netherlands and Germany, it has been extended to products that are deemed to be “therapeutically” equivalent. The concept of equivalence may or may not extend beyond a drug class.

In Germany, reference-based reimbursement becomes a possibility when the first drug in a given class becomes generic. A recent example is statins, where all were given a reference price similar to the generic simvastatin, which was based on an evaluation conducted by the Institute for Quality and Efficiency in Healthcare. As a result, one of the newer statins, rosuvastatin, was not launched in Germany as soon as in comparable countries. In The Netherlands, a new drug is placed in an existing cluster unless the manufacturer claims that the product has attributes that would justify a premium price. In these situations, an economic evaluation is requested to support the claim. The main issues arising under reference-based reimbursement are: 1) how the judgments are made for therapeutic clustering (how similar do drugs have to be); and 2) how is the price established for the first drug in a new cluster.

Finally, a number of approaches for assessing the cost-effectiveness of drugs exist in Europe, although they have varying degrees of transparency. Probably, the most transparent schemes are those existing in Sweden and the UK. In these jurisdictions, although the manufacturer is free to set the price of an individual drug, the price of drugs is linked to cost-effectiveness to the extent that the new product needs to demonstrate “adequate” cost-effectiveness at the price the manufacturer wishes to charge. Other countries operating similar schemes, although not necessarily for all new products, include Belgium, Denmark, Finland, and Portugal. Cost-effectiveness assessments are also undertaken in these countries, although other factors may enter into the final pricing decision.

In addition, although not based on explicit assessments of cost-effectiveness, the approach to pricing and reimbursement in France awards a premium to drugs that are considered innovative, and on occasion, companies may be asked to conduct post-marketing studies to demonstrate some of the benefits that are claimed at the time of launch. Nevertheless, the extent to which the agreements reached are truly value based or closer to simple price-volume agreements is a matter for debate.

**Literature**

Currently, an increase in the number of pharmacoeconomic studies being performed has been seen, but only a few of these articles discuss how drug costs are estimated. These articles include cost-benefit analyses, cost-utility analyses, CEAs, and those concentrating on drug price controls. An article by Francis Pang states that there are a number of economic evaluations that have not been published because of “compounds being terminated in development, lengthy timetables for the implementation of clinical trial programs, and commercial strategic issues.” When Pang’s article was published in 2002, there were only 14 published empirical articles analyzing multinational pharmacoeconomic studies [24]. The pharmacoeconomic field continues to grow, which may lead to an increase in the number of articles discussing price estimation in the future.

Currently, many of the studies published concentrate on the United States and the European Union, but articles are rarely found that look at other areas of the world. Reinharz et al. [25] points out several obstacles of doing pharmacoeconomic research in underdeveloped areas, such as Latin America. When estimating costs in Latin America, specifically in Mexico and Brazil, Reinharz found that management data were unsuitable to provide valid information on costs and production. This article illustrates the need for pharmacoeconomic research in other areas of the world.

**Currently Used Measures for Drug Cost**

In the articles that discuss how costs are estimated, there are several measures currently used, but one of the main ones is purchasing power parities (PPPs) [5]. Nevertheless, there appears to be limitations associated with each method. Providing international drug price comparisons is difficult because every country has its own pharmaceutical market basket [26]. Because of this variability of medications between countries, Danzon and Kim [5] proposed three measures that can be applied to different strengths and doses of medications. These measures include, the number of IMS standard units, the number of grams (kg) of active ingredient, and the pack size of a drug. One of the limitations found with these measurements is that they do not look at the differences between generic and brand products. Another widely used measure to estimate drug costs is the defined daily dose, which is defined as the number of grams for either a normal dose or recommended dose. This measurement was originally recommended for use in multinational studies by the WHO [27] because it provides a common measurement among countries that otherwise are different. Nevertheless, this measure does not adjust for duration of treatment. In a study completed for the productivity report in Australia [28], price comparisons were performed at the manufacturer level, using IMS health data, which included mostly wholesale to retailer prices. Thus, there are many measures used to estimate drug costs when performing international studies, but each one has limitations that need to be considered.

As part of the work of this Task Force, the European subgroup reviewed the methods for estimating drug costs in 57 economic evaluations conducted in Denmark, Finland, Ireland, Norway, and the UK. It was found that practice fell far short of the ideal, with a substantial number of evaluations failing to report the source of the drug costs, the route of administration, the cost year, or whether the estimates took account of pharmacy charges, sales taxes, wastage, or drug monitoring costs [29].

**Controversies**

Several controversies exist regarding drug costs in international economic evaluations, but the main ones are generalizability and validity. In this case, generalizability is defined as the extent to which the results in an evaluation are generalized from one setting to another. It is not unusual for costs from one country in a multinational trial to be used as a proxy for costs in other countries [4]. This can result in biases on costs used and the population examined, so a question that needs to be asked is if the price levels are stable from one population to another [23]. Barbieri et al found that the key factor affecting the variation of results from country to country seems to be whether resource use is allowed to vary across countries [30]. Other generalizability issues include, but are not limited to, the populations being compared in terms of economic status and health insurance.

In addition to generalizability, validity is also a very controversial topic in drug cost comparisons. The most discussed threat to validity is the lack of representative samples used in pharmacoeconomic analyses [4,24,25]. Danzon and Kim [5] point out that generics are excluded in many of the analyses that estimate costs, even though in some countries, generics constitute about a third of pharmaceutical sales. Reinharz et al. [25] indicate that validity problems in underdeveloped countries are due to poor quality and accessibility of data. Another threat to validity is the
comparison drugs used for analysis because comparisons involving cost data also bring up the issue of exchange rate conversions because they fluctuate daily [4]. Indeed, because pharmacoeconomic studies estimate the incremental cost-effectiveness of the new drug as compared with existing ones, the estimates can be greatly influenced by differences in the prices of the older drugs across countries, many of which are the result of exchange rate fluctuations. That is, while these drugs may have been priced at a similar level in all countries at the time of launch, changes in the relative value of currencies since that time may mean that prices differ if converted at today’s relative values.

**Discussion and Recommendations**

The application of economic evaluation in drug pricing and reimbursement is variable. An evaluation across nations reveals that rank by price level does not correlate with rank for pharmaceutical expenditures per capita, as expenditures are a function of differences in medical practice patterns and in social, political, and economic values [31]. Therefore, economic evaluation alone cannot set a price for a medicine, because a decision has to be made about the proportion of added value going to society and the proportion going to the pharmaceutical company as a reward for innovation [32]. Although beyond the scope of this article, it would be interesting to assess whether countries with a large stake in pharmaceutical R&D typically allow higher prices for drugs than those countries that do not experience this investment.

Differential pricing, based on Ramsey pricing principles, is the second best efficient way of paying for the global joint cost of pharmaceutical R&D [33]. Danzon further argued that achieving appropriate and sustainable price differences will require higher income countries to forgo trying to “import” low drug prices for low-income countries, through parallel trade and external referencing. The WHO advocates both differential pricing and price transparency. Nevertheless, price transparency may jeopardize the well meaning of increased access to pharmaceuticals in developing countries [5]. International price comparisons, which can differ in various sectors and suppliers in some developing countries, can refer to some readily available/published sources (i.e., the Management Science for Health international drug price indicators [34] and WHO/Health Action International manual [35]).

Variation of currency exchange rate may also influence the methods to account for drug cost in pharmacoeconomic studies. When the CEA analysis uses the exchange rate within a country, the expected exchange rate fluctuations have a similar effect on all drugs sourced from the same country, which would probably mean that the drug costs vary together in a similar magnitude. This can be tested with a sensitivity analysis using different multipliers for the drug costs. Nevertheless, the total costs in a CEA involving international comparison would usually depend on more than just drug costs, and the drug and other costs may be differentially affected by exchange rate fluctuations. To prevent the large fluctuations of exchange rates, the PPP calculation/conversion is suggested as an alternative sensitivity analysis. Nevertheless, researchers should be aware of the limitations of using the PPP, which resulted from the strictest assumptions that the real value placed on goods and services are homogeneous across countries and goods markets are perfect (i.e., international shipment of goods able to take place freely, instantaneously, and without cost).

Finally, as mentioned above, in several European countries, most notably The Netherlands (through the Health Care Insurance Board), Sweden (through the Dental and Pharmaceutical Benefits Agency), and England (through the National Institute for Health and Clinical Excellence), there has been a trend toward value-based pricing. The first step has been to conduct pharmacoeconomic studies to establish the value of new drugs and, by implication, to assess whether there is any justification for a price premium over and above existing drugs for the conditions concerned. Currently, drug costs included in pharmacoeconomic studies are based on the price proposed by the manufacturer. Nevertheless, in the future, it is possible that the pharmacoeconomic studies form the basis for price negotiations. In England, the suggestion is that a value-based price could be established for each indication in which the drug is used, with a higher price being allowed for those indications where more value is added [36].

**Task Force Recommendations**

In summary, a few points regarding drug cost need to be considered in conducting pharmacoeconomic analysis or international drug comparison:

- Drug units should be standardized in terms of volume of active ingredient, regardless of package and dosing strength variations across countries.
- Drug costs should be measured in local currency per unit of active ingredient and should be converted to other currencies using sensitivity analyses of PPP and exchange rate, whichever is more appropriate.
- When using drug prices from different years, the consumer price index for the local currency should be applied before the PPP and/or exchange rate conversion.
- A modified social perspective should be employed where drug costs should reflect the best pricing available to the government or other large third-party payers in the country.
- Drug costs should be kept as transparent as possible.
- The type of drug pricing (value-based, reference pricing, market pricing, MAC, etc.) should be clearly identified in the pharmacoeconomic application.
- ISPOR should maintain a Web site indicating how drug prices are determined in each country and region, to be updated periodically by the ISPOR Task Force on Good Research Practices—Use of Drug Costs for Cost Effectiveness Analysis (DCTF).

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Drug Cost Estimate in Countries outside of the United States


