



INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

IGBA Reactive Statement on “Analysis of the costs of production of medicines in the WHO Model List of Essential Medicines”

The International Generic and Biosimilar Medicines Association (IGBA) appreciates the opportunity to provide its comments on the “*Analysis of the costs of production of medicines in the WHO Model List of Essential Medicines*” dated January 2017.

IGBA would like to highlight several concerns related to the methodology used in the paper. Further we will provide a case for why we disagree with the thesis of the paper – that price reductions of generic medicines will lead to more sustainable healthcare systems. Finally, IGBA uses this opportunity to make several recommendations for action to support a sustainable global pharmaceutical market for continued patient access to safe, effective and high quality medicines.

1. Comments on the methodology of the paper

The analysis presented in the WHO paper “*Analysis of the costs of production of medicines in the WHO Model List of Essential Medicines*” fails to represent the true cost of manufacturing and selling medicines in highly regulated markets. The analysis exclusively includes costs of goods and does not account for all the other mandated activities the pharmaceutical industry is obliged to comply with, such as development, quality assurance, pharmacovigilance, distribution, legal, regulatory and capital costs. The article only takes into account costs of excipients, costs of APIs, direct labour and manufacturing costs related to the conversion of these ingredients to the finished products, and some indirect manufacture-related overhead costs such as minimum compliance with environmental or quality standards.

Moreover the paper presents an average of manufacturing costs and fails to recognize the large variability in costs associated with the manufacture of different medicinal products. Factors such as the type of medicinal product, the product portfolio of manufacturers, the required capacity of the manufacturing line, batch sizes and total volume of certain products are important to take into account to determine the real manufacturing cost. In addition, the analysis only considers the manufacturing position in India and other countries likely able to manufacture at an even lower cost (i.e. China). While we acknowledge that India and China are cost competitive for the production of many APIs, there are still API manufacturers in a number of other regions. For example, for many of the more complex generic and biosimilar medicines, we still observe significant production in Europe, U.S. and Japan, where the manufacturing costs are claimed to be significantly higher than in India or China. We therefore question why the WHO appears to suggest via this article that all API production should move to India, China, or other jurisdictions. We believe it is not the role of the organization to make recommendations on industrial policy.



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The analysis fails to sufficiently acknowledge the variability in regulatory standards across the different regions of the world. Highly regulated markets apply much higher standards of GMP than less regulated markets, requiring additional costs for ongoing compliance. The article notes that investment is required to upgrade a manufacturing facility to comply with GMP standards, but unrealistically assumes that costs to set up and comply with GMP are captured within the \$0.01/tablet conversion cost. For example, the Indian drugs regulator has only recently announced that WHO GMP would be applied to all manufacturers across India. This policy is expected to lead to the closure of thousands of manufacturing companies in India as they will not be able to invest in the necessary upgrades to meet this requirement.

Since the paper recommends using cost as a basis for price of the medicines in scope, not only the manufacturing costs but all relevant overhead costs need to be taken into account. Below is a list of important contributing costs that the paper fails to include in the analysis:

- Development costs: The development of a new generic medicine involves several bioequivalence trials. These trials together with several other development costs including formulation development, analytical method development, stability studies, etc. are an important contributor to the total cost of a generic product. Though the paper notes the existence of these development costs, it does not include an estimate of these costs in the analysis and furthermore does not establish this lack of development cost as a significant limitation. Due to the fact that there is no global development for generic medicines, companies are required to conduct multiple trials to meet different national requirements. For example, a generic medicine approved in the EU is required to fulfil different requirements to be approved in Switzerland. If the WHO is concerned with the cost of medicines, tackling this issue of disharmonized requirements would go a long way to improving the situation.
- Regulatory costs: The marketing of a generic product can only be accomplished after the submission and approval of a Marketing Authorization Application (MAA) dossier to the relevant competent authority. As the paper notes, the establishment of such a dossier is very resource intensive, particularly in highly-regulated markets. The paper does not, however, include regulatory costs required to file a dossier in its calculation. The analysis also fails to acknowledge the differences in regulatory standards globally. Navigating this global patchwork of regulation has significant impact on the cost of manufacturing, dossier submission, post-marketing surveillance, etc.

Moreover, after the approval of the MAA dossier, the Marketing application has to be maintained, an activity that involves the submission of numerous variations and renewals on an annual basis, which contribute significantly to costs required to keep the product on the market. 75% of the European regulatory fees paid by companies are for maintenance costs, which amount to over 20 million Euros per year. A single manufacturer can have more than 20,000 MAA to maintain in Europe alone, and the number of variations and their subsequent fees have increased by 45% over the last 5 years. Highly regulated markets have significantly higher maintenance costs than less regulated markets.



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In addition, manufacturers increasingly face costs associated with other government mandated programs. For example, in Europe, the falsified medicines directive will cost manufacturers at least €1 billion to upgrade manufacturing lines with barcode printers. In the US, the GDUFA I fees (2013 – 2017) were \$300 million/year (inflation adjusted year over year), and now, under GDUFA II (2018 – 2022) fees will be \$493 million/year (inflation adjusted year over year).

IGBA believes that WHO must be aware that increasing regulatory costs are significant for this industry. Any manufacturers selling medicines in these highly regulated markets will bear the cost of these increasing regulatory requirements regardless of manufacturing location; it is naïve to include only Indian taxes as an additional cost in the analysis, with no discussion of regulatory cost. The lack of inclusion of regulatory costs in this analysis is a significant limitation not acknowledged by the authors, and constrains the application of this paper's results to a real-world setting.

- Quality Assurance (QA) costs: The pharmaceutical industry is a globalized industry that relies on supply chains that are often very complex. To keep oversight of these supply chains and to guarantee the quality of the products manufactured throughout the supply chain, global QA and global auditing of the various supply chains is very important and contributes to costs. The paper only includes material cost of building a quality laboratory, not the costs associated with ongoing global oversight.
- Pharmacovigilance Costs: The regulations relating to Pharmacovigilance are becoming more arduous and stringent, and consequently more costly, with expensive skilled staff and IT systems required. Authorities impose these conditions on manufacturers to ensure patient safety. Dossiers have to be maintained and updated by highly skilled staff to further promote patient safety, adding additional costs. The paper does not acknowledge the cost burden associated with increasing pharmacovigilance requirements.
- Distribution costs – The paper explicitly removes distribution costs from the COGS calculation with no discussion of why this decision is made (see section 7.2.3). The regulations relating to supply chain management are becoming more laborious and rigid, and consequently more costly, with expensive skilled staff and IT systems required. Authorities impose these conditions on manufacturers to ensure patient safety.
- Legal costs: The analysis also fails to consider legal costs. In a highly competitive market, where generic companies operate, very rarely a generic company enters the market without undertaking litigation – or defending themselves from litigation (usually patent issues) before courts. Especially for the generic sector, these costs are particularly relevant and represent a significant burden.
- Cost of capital: Although capital costs for the establishment of a medicine manufacturing facility were considered in the investigations of the report, the concept of cost of capital was ignored. Except for government operated pharmaceutical plants, investors expect a return when they invest in a manufacturing concern. In basic terms, cost of capital is the return on funds to investors, both shareholders and lenders require as a reward for their investment. Without profit expectations very little investment would be applied to pharmaceutical manufacturing.



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If a comparison between cost and price is to be made, it is critical that all above aspects be taken into consideration. We recognize that this is a complex exercise, but the lack of inclusion of costs central to medicines production in areas such as development, regulatory and legal undermines the credibility of the analysis. If it is not possible to accurately reflect true costs of production including these aspects, we recommend reconsidering whether proceeding with this assessment is appropriate.

IGBA would also like to note that the analysis reports a few pricing cases that occurred in the UK, Italy and the US. These are cases where there have been alleged breaches of competition laws. These cases cannot as such be considered as a benchmark of the activities of generic medicines developers in the debate on prices of medicines.

The price-price comparisons referenced in the report are incorrect. The author makes erroneous claims in the price comparisons due to lack of consideration of the difference between list and net prices. In the case of the cancer drugs cited for the UK market, the author is referring to list prices. The net prices for those drugs – which are significantly lower than the figures stated by the author – are publicly available because these drugs are purchased through hospital tenders. IGBA is surprised that the study takes these wrong figures into consideration. The net prices hospitals pay for these medicines are available on this website: <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>

Moreover, there is a huge difference in healthcare systems around the globe, so when the study calculates the price of a drug in a country it should be specific and take into consideration prices and volume of consumption of the said product in the public and private sectors. The price of a product cannot be taken as an absolute number. In fact, some countries have a reimbursement system, others do not. For instance there is a huge difference between Algeria, Lebanon, Turkey and Jordan. Indeed, to calculate a price of a drug in Jordan, for example, a weighted price should take into consideration volume and price in tenders and in the private sector.

The article contains no understanding of the generic business model or the lifecycle of generic products which determine the sustainability of the industry. The generic industry cannot follow a “cost of goods plus” model because there is no monopoly position by a single manufacturer. The industry is driven by competition throughout the lifecycle. Generic companies typically earn their returns at launch by taking market share from originator companies through price competition. Price erosion is highest at this phase of market entry (typically 40-60% to reference). At a second phase, generic competition leads to more price competition between generic manufacturers. As prices reach very low levels over time, the number of manufacturers decline and prices tend to stabilize (leading to another 20-30% erosion). If prices go too low (as is often the case in Europe due to cost-containment measures), markets become overly reliant on one or two manufacturers (leading to erosion by another 10-20%). This leads to stock outs and increasingly to shortages. The key learning is that generic profitability and price erosion for payers are closely associated with competition at entry of the first generic. Instead of focusing on academic exercises to determine cost of goods sold with no grounding in market reality, it would be helpful if WHO looked into how the generic industry business model works and the impact of healthy market competition on



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medicines prices. The researchers used 'furosemide' in South Africa as an example of their argument. It is notable that furosemide has been discontinued by Sunpharma (Be Tabs) in this territory as it was being sold at a loss.

The Australian Government has recognised the link between the price paid for generic medicines and their ongoing supply. Through discussions under a Strategy Agreement between the Australian Government and the Generic and Biosimilar Medicines Association, an analysis was conducted by the Department of Health, looking at a selection of generic medicines including a number on the WHO EML. To support the ongoing supply of medicines to Australian patients, price increases were applied to around 60 medicines in December 2016.

2. Price reductions of generic medicines will not lead to a more sustainable healthcare systems

Not only is the methodology of the analysis incorrect, but also the design of the scope. As a consequence its findings are misleading to healthcare policy makers and decision makers and may lead to catastrophic results on public health should the application of this methodology lead to further price erosions, threatening the sustainability of the generic industry, and subsequently access to medicines.

IGBA fails to understand the argument according to which lowering prices of generic medicines would ultimately lower prices of originator products. Over the last several years, mandatory price cuts on generic medicines have been strongly applied in almost all regulated markets, while prices of new chemical entities have increased significantly. Since generic medicines only contribute to 2-3% of the healthcare budget, cutting prices of this group of medicines that provides the majority of essential medicines to patients is useless.

Rather than cutting prices of generic medicines, healthcare policies should stimulate uptake of generic medicines in order to take advantage of the efficiency that these products produce. The generic medicines sector is the only one bringing sustainability to pharmaceuticals through competition. In fact, the major challenge our industry faces is to bring competition to specialty markets where the capital investment costs and the risks are much higher than conventional generic medicines. The lower biosimilar costs of biotechnology products for the EU-US market alone are anticipated to be around \$100 billion/year. This is more than the combined EU-US generic medicines market at current prices. The focus should therefore be where the real sustainability problem lies.

Price cuts in several European countries have also led to unsustainable business dynamics, withdrawal of medicines from the market and ultimately shortages of these medicines. Moreover, driving prices of generic medicines down to unprofitable levels can create a market environment where not only generic producers are forced to withdraw from the market, but where there is also no HTA efficiency, with subsequent reduced innovation.



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3. Recommendations towards a sustainable health care system

The IGBA would like to put forward a few ideas deemed relevant to optimise costs of medicines and that encourages the WHO to support:

- Stimulating generic and biosimilar medicines competition via uptake measures and removal of barriers, allowing competition to start on day 1 after patent expiry
- Advancing global development of complex generic and biosimilar medicines
- Harmonising and simplifying registration and MAA maintenance requirements of Medicines Regulatory Authorities
- Sharing of information between Medicines Regulatory Authorities
- Supporting mutual recognition of Good Manufacturing Practices (GMP) inspections
- Ensuring balanced IP/regulatory incentives
- Supporting the introduction of a manufacturing/export waiver during the patent term extension period in Europe
- Stressing the importance of stringent patent examination and quality of patents more generally to reduce frivolous litigation
- Improving regulatory efficiency to minimize disproportionate burden on generics, including through tools to reduce duplication such as introduction of e-leaflets and multi-country packs

IGBA remains ready to constructively cooperate with the WHO and all the relevant actors in order to increase access to high quality medicines and better healthcare outcomes globally.