Position Paper
Medicines shortages

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- Medicines for Europe aims at ensuring a **patient-centric proactive dialogue** on the availability and access of medicines involving all the stakeholders: payers, regulators and supply chain actors.
- Medicines shortages can be addressed when **multisource alternatives are available**.
- In order to tackle medicines shortages in a multi-source context, Medicines for Europe believes in an approach that **addresses both the root causes of medicines shortages** (**preventing** medicines shortages) and mitigates them once they occur (**mitigating** medicines shortages).

Executive summary

Causes of generic medicine shortages

- **Pressure of costly regulatory/quality procedures and cost-containment measures on generic medicines industry:**

Members of Medicines for Europe are highly committed to quality. To achieve this quality, manufacturers comply with important and stringent regulatory/quality procedures. These procedures are costly and experience has proven that there is an inability of the market to reward the investment on these procedures.
Additionally, the extreme pressure on prices due to **short-term cost containment measures such as tendering**, external reference pricing and payback mechanisms challenge the sustainability of our industry forcing the withdrawal of generic medicines from the market and increasing the risk of medicines shortages.

In order to tackle medicines shortages in a multi-source context, Medicines for Europe believes in an approach that **addresses both the root causes** of medicines shortages (**preventing** medicines shortages) and **mitigates** medicine shortages once they occur.

Recommendations to prevent medicine shortages (addressing the root causes)

- **Ensure market predictability:**
    - A predictable and sustainable pricing and reimbursement environment will increase the number of manufacturers in the market guaranteeing that in case one of the manufacturers cannot supply other manufacturers in the market are able to supply the medicine:
        - Revision and prevention of the application of short-term cost containment measures (e.g. mandated price reductions, internal and external reference pricing, tendering and payback mechanisms) to generic medicines that are undermining the long-term sustainability of manufacturers while increasing the risk of medicines shortages which ultimately affects patient health
    - Prevent disproportionate sanctions that can increase the risk of medicine shortages

- **Improve regulatory efficiency to reduce administrative and cost burden of keeping medicines in the market:**

Rue d'Arlon 50 - 1000 Brussels - Belgium
T: +32 (0)2 736 84 11- F: +32 (0)2 736 74 38
www.medicinesforeurope.com

- Implement flat fee structure for variations
- Optimise the use of Centralised and Decentralised procedures for generic medicines
- Increase flexibility to accept different pack sizes or multi-country packs to address market needs
- Increase use of telematics tool (e.g. FMD, ISO-IDMP, Art. 57, etc.) for communication of changes currently requiring variation submission in large portfolios
- Lower fees/costs for older molecules that still serve a healthcare need

- **Manage available market stock information with non-coercive systems:**
  - Use systems such as European Medicines Verification System that will be in place in 2019 to manage information on medicine shortages throughout the supply chain

Recommendations to mitigate medicine shortages

- **Specific regulatory measures to mitigate imminent medicine shortages:**
  - Flexibility to accept different pack sizes at national level based on Marketing Authorization
  - Flexibility to accept multilingual packages (e.g. eLeaflet as a solution)
  - Efficient Repeat Use Procedure
  - Incentives for medically essential low price products (e.g. lower variation fees/flat fee)

Patient-centric approach to medicines shortages

Medicines for Europe believes in the importance to provide patients timely access to medicines and is committed to provide a safe and continuous supply of medicines as a key public health objective. In this view, Medicines for Europe aims at ensuring a patient-centric proactive dialogue on the availability and access of medicines involving all the stakeholders: payers, regulators and supply chain actors.

Medicines for Europe believes that the medical use of generic medicines should be considered as an opportunity to increase patient access and prevent medicines shortages through increased choice and availability of treatments. Medicines shortages can be addressed when multisource alternatives are available.

Generic medicines have transformed healthcare in Europe by significantly increasing patient access to medicines in an era of rising demands for healthcare services and constrained finances. Over the last ten years, generic medicines have increased access to medicines by over 100% in seven key therapeutic areas without increasing the overall treatment cost.

Drivers of medicines shortages in an off-patent, multi-source sector

Members of Medicines for Europe are highly committed to quality. To achieve this quality, manufacturers comply with stringent regulatory and quality procedures. These procedures are costly and experience has proven that there is an inability of the market to reward the investment on these procedures. Additionally, the extreme pressure on prices due to short-term cost containment measures such as tendering, external reference pricing and payback mechanisms challenge the sustainability of our industry provoking the withdrawal of medicines from the market and increasing the risk of medicines shortages.

In order to tackle medicines shortages in a multi-source context, Medicines for Europe believes in an approach that addresses both the root causes of medicines shortages (preventing medicines shortages) and mitigates them once they occur (mitigating medicines shortages).

Recommendations to prevent shortages

Improve regulatory efficiency

The EU has high regulatory standards in place which need to be complied with before a medicines can be placed on the market. While we encourage these high standards, Medicines for Europe considers that enhancing regulatory efficiency and fit-for-purpose regulatory measures can foster greater access to and availability of medicines. To increase the efficiency and optimise the regulatory processes to reduce the administrative and cost burden of keeping the medicines on the market, we recommend to implement a flat fee structure for variations, optimise the use of Centralised and Decentralised procedures for generic medicines, increase flexibility to accept different pack sizes or multi-country packs to address market needs, increase use of telematics tool (e.g. FMD, ISO-IDMP, Art. 57, etc.) for communication of changes currently requiring variation submission in large portfolios and lower fees/costs for older molecules that still serve a healthcare need.

Ensure market predictability

Generic manufacturing is a competitive business which aims at having efficient operations to minimise costs and offer maximum discounts to payers. To date, the main focus of healthcare policies around generic medicines has been on cutting prices, instead of securing patient access to high-quality medicines. Average price reduction after patent expiry is 50%, increasing further over time up to 80-90%.

Cost-containment measures such as government mandated price reductions, internal and external reference pricing and procurement through tendering, undermine the long-term sustainability of manufacturers while increasing the risk of medicines shortages that ultimately affects patient health. This was also acknowledged by the World Health Organisation (WHO), which stated that *there are more appropriate pricing mechanisms for off-patent medicines than external reference pricing* (WHO HAI 2011 – Project on medicines availability – External reference Pricing). Similarly, most scientific articles reviewing shortages of generic medicines identify cost-containment measures and policies as the underlying root cause[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15].

[1] Alevizakos M, Detsis M, Grigoras CA, et al. The Impact of Shortages on Medication Prices: Implications for Shortage Prevention. Drugs. 2016;76(16):1551-8.
[2] Barlas S. FDA strategies to prevent and respond to drug shortages: finding a better way to predict and prevent company closures. P & T: a peer-reviewed journal for formulary management. 2013;38(5):261-3.;
[3] Birgli. An Evaluation of Medicines Shortages in Europe with a more in-depth review of these in France, Greece, Poland, Spain, and the United Kingdom. Zug: Birgli, 2013. Available from: http://static.correofarmaceutico.com/docs/2013/10/21/evaluation.pdf.
[4] Bogaert P, Prokop A, Bochenek T. Prevention and Management of Medicine Shortages in Belgium, France and from The Perspective of the European Union. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2014;17(7):A412.
[5] De Weerdt E, Simoens S, Casteels M, et al. Toward a European definition for a drug shortage: a qualitative study. Frontiers in pharmacology. 2015;6:253.
[6] Holtorf AP, Rinde H, Maniadakis N. Drug shortages in Europe and the USA: The underlying reasons and consequences. ISPOR 15th Annual European Congress; 10th February 2017; Berlin. Germany: Presented at the ISPOR 15th Annual European Congress (Berlin, 5 November 2012); 2012
[7] Kaposy C. Drugs, money, and power: the Canadian drug shortage. Journal of bioethical inquiry. 2014;11(1):85-9
[8] Kweder SL, Dill S. Drug shortages: the cycle of quantity and quality. Clinical pharmacology and therapeutics. 2013;93(3):245-51.
[9] Markowski ME. Drug Shortages: The Problem of Inadequate Profits. Cambridge, MA: Harvard Law School, 2012. Available from: https://dash.harvard.edu/handle/1/11940215.
[10] McKeever AE, Bloch JR, Bratic A. Drug shortages and the burden of access to care: a critical issue affecting patients with cancer. Clinical journal of oncology nursing. 2013;17(5):490-5.
[11] Pauwels K, Huys I, Casteels M, et al. Drug shortages in European countries: a trade-off between market attractiveness and cost containment? BMC health services research. 2014;14:438.
[12] Pauwels K, Simoens S, Casteels M, et al. Insights into European drug shortages: a survey of hospital pharmacists. PloS one. 2015;10(3):e0119322.
[13] Reed BN, Fox ER, Konig M, et al. The impact of drug shortages on patients with cardiovascular disease: causes, consequences, and a call to action. American heart journal. 2016;175:130-41.
[14] Woodcock J, Wosinska M. Economic and technological drivers of generic sterile injectable drug shortages. Clinical pharmacology and therapeutics. 2013;93(2):170-6.
[15] Yurukoglu AL, E. Ridley D.B. The Role of Government Reimbursement in Drug Shortages. US: Stanford University, 2016. Available from: https://web.stanford.edu/~ayurukog/shortages.pdf.

The most extreme examples of medicines shortages can be found in countries which have disproportionate pharmaceutical pricing policies on generic medicines. In Romania, due to inappropriate cost-containment measures (e.g. clawback tax, external reference pricing, etc.), approximately 2.000 generic medicines have been withdrawn from the market over the last two years alone (annex with links for 'Clawback influence on shortages' and 'Statements of Patient Associations regarding shortages'). As a result, Romania has suffered from chronic shortages of essential but inexpensive medicines such as methotrexate.

Medicines for Europe recommends a predictable and sustainable pricing and reimbursement environment that will increase the number of players in the market to reduce the risk of medicines shortages. This can be achieved with measures that avoid retraction of manufacturers from the market. In particular, to adjust the number of winners of tenders to the market/country characteristics – guaranteeing that multiple players are supplying the market and in case one of the manufacturers cannot supply, other manufacturers in the market are able to supply. Furthermore, disproportionate sanctions should be prevented as they promote retraction of manufacturers from the market and increase the risk of supply. In case there are penalties applied to guarantee supply, these should be proportionate to the revenue of manufacturers and applied in accordance with the contract criteria. In Slovakia, under the umbrella of the Article 81 of Directive 2001/83/EC[16], and to avoid medicines shortages, the government is issuing a legal obligation to manufacturers to supply within 24 hours. In case manufacturers fail to supply, they are subjected to penalties of up to 1 Million Euro. The way in which these penalties are applied (by SKU rather than INN) will lead to disproportionate fines amounting to multiples of generic medicines industry sales which will undermine the sustainability of the pharmaceutical industry and increase the risk of medicines shortages.

Finally, to ensure that the society will continue to benefit from these medicines, it will be important to develop a predictable and sustainable market model. At this moment, generic medicines account for over 56% of the medicines dispensed in Europe at only 22% of the costs, which is only 2-3% of total healthcare budgets.

Address negative healthcare impacts of parallel trade

Parallel exports from Eastern Europe to Western Europe are contributing to availability problems which undermine public health. Slovakia, Czech Republic and Romania are proposing measures to address medicines shortages caused by parallel exports: if a medicine is at risk of experiencing medicines shortages, distributors will have to notify the relevant authorities which will decide whether the medicine can be exported.

[16] Article 81 of Directive 2001/83/EC: EU legislation that imposes legal obligation for the marketing authorisation holder to ensure, within the limits of their responsibilities, a continuous supply.

Recommendations to mitigate shortages

Specific regulatory measures to mitigate imminent shortage

Medicines for Europe encourages the enforcement of already existing regulatory measures to mitigate medicines shortages when they occur.

Such measures would serve two main purposes, namely to allow the concerned manufacturer to resume its activities in compliance with regulatory requirements within a reasonably short timeframe and to encourage other manufacturers producing a therapeutically equivalent medicine to rapidly supply the market.

Mitigating the potential impact of medicines shortages through regulatory discretion measures could consist of various elements such as e.g. in the context of a potential supply disruption, flexibility to accept different pack sizes on national level based on decentralised procedure Marketing Authorisation, harmonisation of pack sizes requirements across EU, incentives for medically essential low cost medicines (e.g. lower variation fees/flat fee). Furthermore, incentives to authorise alternative API supplier(s), simplified way of reporting variations, provide re-packaging flexibility to MAH to address shortages and efficient Repeat Use Procedure would be relevant measures to tackle medicines shortages. These measures are consistent with Medicines for Europe's plea for all possible efficiency gains in the EU regulatory system as outlined in the 42 recommendations of its Regulatory Efficiency report[17].

Beyond regulatory mitigation measures, a more fundamental reflection is needed in order to design a new model aimed at balancing maintenance and regulatory fees for essential medicinal products with limited-to-no commercial attractiveness, and where two or less manufacturers supply the market (higher risk of supply disruption).

Manage available market stock information

In 2019, a European Medicines Verification System (EMVS) will be in place which could support authorities and manufacturers to better manage supply through the management of the information available in the EMVS. We believe that this system constitutes an opportunity to increase transparency in supply chain for supply chain actors, enabling better management of production and supply.

Currently manufacturers have a legal obligation to notify to 28 different competent authorities of supply disruption due to manufacturing and quality issues. Therefore, Medicines for Europe recommends the use of this system as a European harmonised reporting standard of medicines shortages throughout the supply chain. Despite the importance of having in place a proper and controlled communication system, we believe that the notification and aim of the supply chain actors to tackle medicines shortages should not be punished by exorbitant and disproportionate penalties.

[17] http://www.medicinesforeurope.com/wp-content/uploads/2016/03/EGA_Regulatory_Efficiency_Report_2015_low.pdf

Conclusions

In conclusion, Medicines for Europe considers that continuous availability of medicines is a patient-centric shared concern and responsibility of payers, regulators and all supply chain actors. Medicines for Europe believes that preventing and mitigating shortages requires addressing economic causes of shortages, improving regulatory efficiency, more transparency in supply chain and proper and controlled communication.

Medicines for Europe

Medicines for Europe represents the generic, biosimilar and value added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines for Europe, based on 5 important pillars: patients, quality, value, sustainability and partnership. Its members employ 160,000 people at over 350 manufacturing and R&D sites in Europe, and invest up to 17% of their turnover in medical innovation.