European Respiratory Society [1] submission to the EU pharmaceutical strategy roadmap

Executive Summary

On 11 March 2020, the World Health Organization (WHO) declared the novel SARS-CoV-2 coronavirus and associated respiratory disease COVID-19 to be a global pandemic. That pandemic, and particularly the severe acute respiratory disease causing both premature death and chronic lung conditions, has caused an unprecedented worldwide health crisis. The scale of the crisis demonstrates more than ever the importance of EU actions to foster respiratory health such as the pharmaceutical strategy.

Before the pandemic, respiratory diseases represented an enormous and increasing healthcare and economic burden across Europe, with over 600 000 deaths a year and six million hospital admissions with total costs exceeding €380 billion per year [2, 14]. The pandemic has increased this burden and it has shown that the EU must ensure strategic autonomy in active pharmaceutical ingredients and raw materials.

Europe needs high-quality pharmaceutical innovation to improve health and address the needs of patients. A significant problem is the real deficiency of new innovative medicines in the respiratory field, as less than a dozen new classes of medicines have been developed for patients with respiratory disorders over the past 50 years. Therefore, we support revising all relevant EU legislation and incentives frameworks that improve on this issue. Scientific societies, academic research and patients must be central to the strategy. Any regulation proposed should embrace, not hinder, emerging science and technology and digital progress such as Artificial Intelligence (AI).

Key for respiratory patients is that the strategy is bold and ambitious and looks at meaningful ways together with the Member States to improve the accessibility, availability and affordability of medicines. Shortages of medicines are increasingly becoming an issue for patients and there is a need for a common European response to this problem. Specifically, we call for the strategy to:

1. Incentivise scientific societies and academic research to find effective treatments: we need to mitigate the enormous burden of respiratory diseases.
2. Scale up innovation on new classes of medicines this is particularly needed in the respiratory field.
3. Reduce costs: the strategy should examine ways to reduce the costs of drug development.
4. Foster improvements in the regulatory and incentive framework in respect to drug repurposing. Novel indications of ‘old’ therapies is an important way forward.
5. Boost clinical trials in the EU with a strong focus on academic input and independent clinical trials.
6. Accelerate the Health Technology Assessment proposal in order to improve access, affordability and availability of medicines.
7. Review and revise the legislation and on medicines for children (paediatric regulation.)
8. Examine the rare diseases legislation (orphan regulation) and propose improvements.
9. Expand the mandate and resources of the European Medicines Agency.
10. Embrace not hinder the implementation of new health technologies.

1. Incentivise effective treatments: we need to mitigate the enormous burden of respiratory diseases and support scientific societies

While finding effective treatments for Covid-19 is currently a worldwide priority, we must not neglect other respiratory diseases. Globally, respiratory diseases are amongst the leading causes of death, with chronic obstructive pulmonary disease (COPD) now the third and fourth ranked cause of death in Western Europe and worldwide, respectively [3]. Lung cancer has an unacceptably high mortality rate and is the most common cause of death amongst all cancers, accounting for 20% of all cancer deaths in Europe.

Indeed, COPD and lung cancer alone account for >50% of deaths from respiratory disease in Europe, yet there has been little impact of drug therapy on this high mortality for either disease. The only immediate way forward is in establishing early detection (screening) for patients at risk, as early curative treatment is still possible when detected early enough.

Asthma is now one of the most prevalent diseases in Europe and affects people of all ages but, despite effective therapies, many patients are poorly controlled and have a low quality of life [4]. More effective treatments are needed for patients with severe asthma who cannot be controlled with existing therapies. Multidrug-resistant tuberculosis (TB) poses a major threat in Europe with a lack of effective therapies and the risk of transmission amongst deprived populations. Only amongst rarer lung diseases, such as pulmonary hypertension, interstitial lung disease and cystic fibrosis, have there been any advances in drug therapy.

Key to advances in drug therapy involves supporting initiatives of scientific societies. At the European Respiratory Society, we support over twenty clinical research collaborations many of which are exploring the effectiveness of treatments for respiratory diseases. The crisis caused by the pandemic will make it increasingly difficult to fund these collaborations. The pharmaceutical strategy (in connection with the EU4Health funding programme) should explore all possible incentives to support academic research and particularly scientific societies to find effective treatments for the most burdensome diseases where the market has failed.

2. Innovation: the pharmaceutical strategy needs to scale up innovation - this is particularly needed in the respiratory field

There have been very few new classes of drug therapy introduced for the treatment of respiratory disease over the past 50 years. It has proved difficult to find new classes of drug that are even as effective as existing therapies or have a comparable safety record. The best-selling new class of drugs are leukotriene receptor antagonists, but these drugs, although safe, are poorly effective in controlling asthma. Several epithelial growth factor receptor inhibitors are now approved for treatment of lung cancers, but they are effective only in a small minority of patients. The other new drug classes have addressed rare diseases, where there is clearly an unmet need, but these drugs are necessarily very expensive and account for small global sales. Several new classes of drug have been introduced for the treatment of Group 1 pulmonary hypertension, including endothelin

receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase activators and prostanoids.

Recently, drugs have also been approved for cystic fibrosis, but the cystic fibrosis transmembrane conductance regulator potentiator, ivacaftor, is only indicated for the rare G551D mutation, which is found in only 4% of patients with the result that the cost of this drug is around $300 000 per year. New anti-fibrotic drugs (*e.g.* pirfenidone and nintedanib) have also recently been approved for idiopathic pulmonary fibrosis, but the effect of these treatments is small, the side-effects troublesome and the disease rare, with limited survival. It has proved difficult to develop new effective antibiotics, but recently a new drug (bedaquiline) has been approved for the treatment of multidrug-resistant TB, the first new anti-TB treatment for over 40 years [5]. Unfortunately, bedaquiline has frequent, sometimes serious, side-effects and several drug interactions, further limiting its use.

Overall, the track record for drug innovation in respiratory medicine is therefore very disappointing. It is clear that the vast majority of patients with respiratory disease are not being served by the current drug innovation strategy. There is accordingly a severe pressing unmet need to reinvent this process in order to treat extreme burden of respiratory disease. The pharmaceutical strategy must be solutions orientated so that this disappointing landscape can be transformed. We welcome therefore that the Roadmap says that the Strategy 'will seek to address market failures' such as those described above. In the meantime, patient management should have attention (and reimbursement) for better and comprehensive patient management with a place for non) pharmacologic interventions that can often improve patient's health status and coping with their disease.

3. Costs: the strategy should examine ways to reduce the costs of drug development

The costs of drug development are increasing, and it is now estimated that it costs over $1.3 billion to develop each approved drug with costs escalating as the drug progresses further along the development path [6, 7]. The result is that late stage failure during drug development is very expensive and makes it almost impossible for companies to recoup the considerable research and development investment in bringing a drug to market. Reducing attrition, especially late stage attrition, by even a small amount would have a significant impact on the cost of drug development, with complete abolition of attrition reducing the cost of taking a drug to market by almost 80% [8].

Lack of efficacy is now the most common cause of drug attrition and this appears to be a particular problem in respiratory diseases as preclinical animal models are so poorly predictive of the human condition. The duration for drug development is also getting longer with an overall time from drug discovery to registration of >12 years with approximately 6–7 years in clinical development. The cost for developing respiratory drugs is greater and the duration of development longer than for most therapeutic areas [7].

We welcome the Roadmap's intention to review procedures for accelerated development and assessment of medicines for major public health needs and the plan to promote regulatory and

administrative simplification. It should not stop here though and in general the Roadmap should examine ways that EU regulation could help reduce the duration of drug development.

4. Repurposing: the strategy needs to create pathways to facilitate new indications for existing medicines.

An attractive approach to accelerate drug discovery is to repurpose existing drugs by screening them against novel targets [9, 10]. This means that if the drug is already on the market it reduces the problems of side-effects, which are often a greater issue for new chemical entities. Moreover, the pharmacokinetics of these molecules is already established in humans and the time for drug development is markedly shortened. This will therefore significantly reduce the costs associated with bringing the drug to market. An example in the respiratory field is sildenafil, originally marketed for erectile dysfunction and now the most broadly used agent for treating pulmonary hypertension worldwide. Another example is Azithromycine, first used as an acute antibiotic, but now more and more seen in the control of exacerbations in patients with COPD, asthma, after lung transplantation and most recently in the management of COVID-19.

Current pharmaceutical regulations principally focus on the development of new medicines, not new indications for existing medicines, and there is a clear lack of EU and national pathways to facilitate drug repurposing. Making repurposing administratively simpler would be of great benefit to patients and when such cheap drugs are repurposed. Today is it essentially impossible for academics to perform research on this matter and deal with the administrative complexities [11].

The pharmaceutical strategy should focus on repurposing pathways, cut back on the red tape and promote repurposing. This is particularly important as the pharmaceutical industry –where the expertise is in developing trials for regulatory purposes- is not interested in such trials as drugs to be repurposed are often off patent, limiting the economic return on investment in a formal regulatory process.

5. Boost clinical trials

The strategy should seek to boost clinical trials in the EU and this should be in addition to the clinical trials Regulation and should have a strong focus on independent clinical trials. We would also like to see a much stronger emphasis on real life data and observational trials. Authorisation of medicines should take greater account of academic research, which is not currently the case.

We also need more support for pragmatic trials. There is a gap between the market approval of new drugs and real-life clinical practice, which is not currently addressed by the commercial sector. The pharmaceutical strategy should look at ways to facilitate pragmatic trials to show the real-world effectiveness of interventions in broad patient groups that accurately reflect society.

6. Accelerate the Health technology assessment proposal

Bringing a new medicine to market is a risky, slow and difficult challenge. However, even when marketing authorisation is obtained, Health Technology Assessment (HTA) and decisions on drug pricing and reimbursement at a national (or regional) level can often further delay access to medicines for patients. This bottleneck might become even tighter in the future because of the

increasing costs of drugs, particularly biologics. Therefore, a close collaboration is needed among all drug stakeholders for facilitating early access for patients to innovative drugs. The proposal of the Commission on HTA is a step in the right direction. Hopefully, the pharmaceutical strategy can reignite enthusiasm for the HTA proposal, which is moving very slowly through Council at present.

7. Review of the Orphan Regulation

While the Orphan Regulation has had success in stimulating the development of new drugs for rare diseases, it would be beneficial to review it and make some changes. An important characteristic of the Regulation is the fact that only the first applicant working on a specific molecule can receive market exclusivity. This hampers the further development of a number 2 and 3, while it would be important to develop alternatives to the initial medicine [12]. It was hoped this element would stimulate cooperation instead of competition between researchers. Since this cooperation has not taken place, it is time to evaluate this part of the Regulation [12].

An important issue is the fact that once a drug has been registered, little further research is done in this area. For example, a drug developed for cystic fibrosis, focuses on only 8 to 9 possible mutations of the protein involved. However, patients with other mutations will still receive this medicine prescribed off-label by their physician. As a result, there is no incentive left to research the effectiveness of the drug on other mutations.

8. Review of the Paediatrics Regulation

A review is needed to assess whether the incentives are sufficiently strong to stimulate the development of new paediatric medicines. The procedure for obtaining additional market protection could benefit from more coordination and cooperation between developers and researchers. There is also need for the revision of the regulation to support registries of children with chronic diseases to allow rapid assessment of feasibility and recruitment into trials.

We support the resolution of the European Parliament in 2016 that called on the Commission: to consider making changes, including through a legislative revision of the Paediatric Medicines Regulation, that give due consideration to (a) mechanism-of-action-based, rather than only disease-type-based, paediatric development plans, (b) disease and drug prioritisation models that take account of unmet paediatric medical needs and feasibility, (c) earlier and more feasible Paediatric investigation plans (d) incentives that better stimulate research and more effectively serve the needs of the paediatric population, while ensuring there is an evaluation of the research and development costs and full transparency of the clinical results, and (e) strategies to avoid paediatric off-label use where authorised paediatric medicines exist [13].

9. The strategy should empower the European Medicines Agency

Several initiatives such as adaptive licensing, joint scientific advice on HTAs and transparency on clinical trial data have been implemented at the EMA in recent years to support pharmaceutical innovation and reduce the lag time between marketing authorisation and access to market in all European countries of safe, effective and affordable drugs. All these initiatives should be further fostered in the pharmaceutical strategy and where there is a need for greater resources for these efforts the agency should be supported.

The pandemic has shown that the EMA would benefit from an expanded mandate to cover clinical trials in a more comprehensive way, tackle shortages of medicines and it would also make sense for the EMA to cover medical devices like most nationally medicines authorities do.

The strategy should therefore consider expanding the mandate of the European Medicines Agency to facilitate innovation, support clinical trials, cover medical devices and be better able to respond to crises.

10. Embrace not hinder new health technologies

We fully agree with the Roadmap assessment that regulation needs to keep up to date to facilitate and not hamper important scientific and technological advances such as gene and personalised therapies, smart health applications, medical technologies, including AI. The strategy should also be fully aligned with the digital health initiatives such as the European Health Data Space.

References

[1] The European respiratory Society (ERS) is an international organisation that brings together physicians, healthcare professionals, scientists and other experts working in respiratory medicine. It is one of the leading medical organisations in the respiratory field, with a growing membership representing over 160 countries worldwide. Its mission is to promote lung health in order to alleviate suffering from disease and drive standards for respiratory medicine globally. www.ersnet.org

[2] Gibson G J, Loddenkemper R, Sibille Y, et al., eds. The European Lung White Book: Respiratory Health and Disease in Europe. Sheffield, European Respiratory Society, 2013.

[3] Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095–2128

[4] Partridge M R, van der Molen T, Myrseth S E, et al. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC Pulm Med 2006; 6: 13.

[5] Kakkar A K, Dahiya N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. Tuberculosis 2014; 94: 357–362

[6] Wouters O J, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA. DOI: 10.1001/jama.2020.1166

[7] Mestre-Ferrandiz J, Sussex J, Towse A. The R&D cost of a new medicine. London, Office of Health Economics. 2012

[8] Paul S M, Mytelka D S, Dunwiddie C T, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 2010; 9: 203–214

[9] Southan C, Williams A J, Ekins S. Challenges and recommendations for obtaining chemical structures of industry-provided repurposing candidates. Drug Discov Today 2013; 18: 58–70.

[10] Tobinick E L. The value of drug repositioning in the current pharmaceutical market. Drug News Perspect 2009; 22: 119–125.

[11] Vermeersch K, Troosters T, Brusselle G G, Janssens W. Bureaucracy is hampering the success of clinical research. BMJ Opinion 2020; retrieved from: https://blogs.bmj.com/bmj/2020/01/13/bureaucracy-is-hampering-the-success-of-clinical-research/

[12] Ecorys. How well does regulation work? The cases of paediatric medicines, orphan drugs and advanced therapies. Report 2015. Retrieved from: https://www.government.nl/documents/reports/2015/11/09/how-well-does-regulation-work--the-cases-of-paediatric-medicines-orphan-drugs-and-advanced-therapies

[13] European Parliament. European Parliament resolution of 15 December 2016 on the regulation on paediatric medicines (2016/2902(RSP)). 2016. Retrieved from: https://www.europarl.europa.eu/doceo/document/TA-8-2016-0511_EN.html

[14] Barnes P J, Bonini S, Seeger W, Belvisi M G, Ward B, Holmes A. Barriers to new drug development in respiratory disease. European Respiratory Journal 2015 45: 1197-1207; DOI: 10.1183/09031936.00007915