Collaboration for Innovation

The Urgent Need for New Antibiotics

ReAct policy seminar, Brussels, 23 May 2011

ReAct
Action on Antibiotic Resistance

Collaboration for Innovation – The Urgent Need for New Antibiotics

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Executive summary

A policy seminar specifically focusing on the urgent need to develop new antibiotics was organised by the international network ReAct – Action on Antibiotic Resistance (www.reactgroup.org) on May 23rd, 2011 in Brussels. The seminar gathered close to 50 key actors from the EU commission, member states, EU and government agencies, WHO, academia, the pharmaceutical industry, civil society and others.

The seminar aimed to contribute directly to the EU strategy against antimicrobial resistance (AMR) and its potential impacts which is currently under development and planned to be published in November 2011, as well as to the EU Commission's comprehensive action plan including concrete proposals concerning incentives to develop new effective antibiotics, to be presented in 2012.

Rather than only focusing on incentives to stimulate the private sector, the seminar aimed to broaden the framework and also explore a number of fundamental questions: How difficult is it to discover new antibiotics? What are the scientific bottlenecks? What forms of collaboration are essential to make breakthroughs?

In addition to an agreement on the need for a radically new business model that delinks revenues from sales, there was broad agreement that the challenges around innovation require new forms of collaboration and sharing of knowledge.

The following points summarise ReAct's understanding of the key messages from the seminar.

The world is facing a serious crisis of antibiotic resistance

- Resistance results in huge health and economic burdens worldwide
- We cannot keep (mis)using antibiotics the way we have for the last 70 years

Intervention from the public sector is justified and necessary

- We must ensure innovation of new antibiotics accessible for all in real need
- The distribution of such a new antibiotic must be controlled, marketing restricted and rational use be enforced. Innovation and use must be driven by medical need and prioritized according to a stringent analysis of the global magnitudes and trends of antibiotic resistance
- We need new approaches to innovation and a radically different business model
- There are major scientific challenges that need to be solved to discover new antibiotics
- New collaborative models for innovation are needed
- Neither big or small pharmaceutical companies, nor academia will manage the challenge in isolation

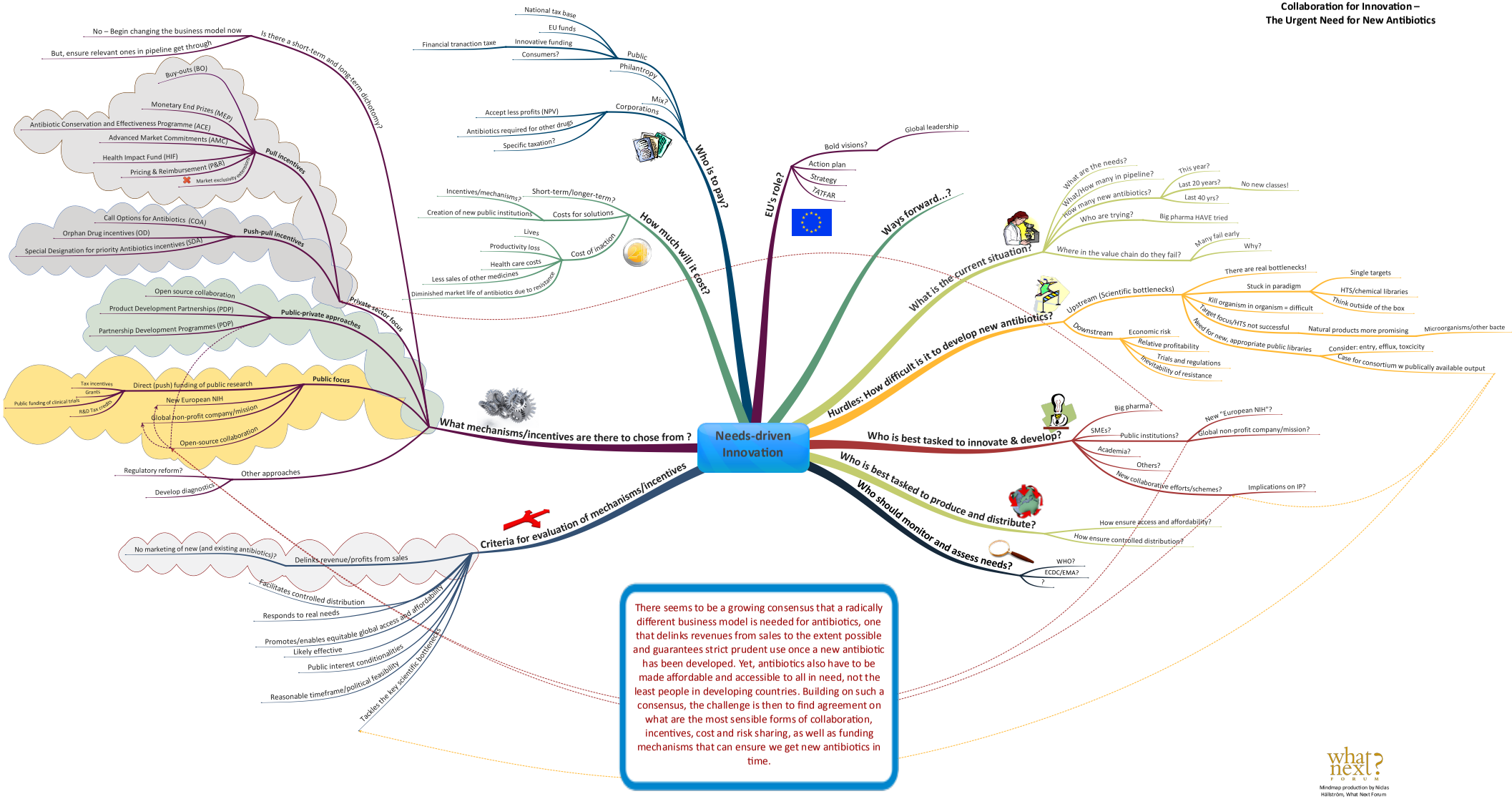
Next steps

- Ask appropriate scientific questions and think in innovative ways
- Mobilise globally to solve the very real and significant scientific challenges
- Explore and create new, open collaborative models, platforms and/or facilities that regard antibiotic innovation as a public interest mission requiring unprecedented pooling of resources and expertise
    - Involve the pharmaceutical industry – through its expertise, its chemical compound libraries and experiences from past mistakes and successes – in public interest efforts and knowledge sharing
- Critically investigate what incentives, mechanisms and combinations of these are most likely to result in priority antibiotics
- Ensure that any choice of incentives, mechanisms or institution-building promote:
    - Delinking return of investment from sales
    - Controlled use and distribution
    - Equitable global access and affordability

ReAct

ReAct Policy Seminar
Brussels, 23 May 2011

Collaboration for Innovation – The Urgent Need for New Antibiotics



There seems to be a growing consensus that a radically different business model is needed for antibiotics, one that delinks revenues from sales to the extent possible and guarantees strict prudent use once a new antibiotic has been developed. Yet, antibiotics also have to be made affordable and accessible to all in need, not the least people in developing countries. Building on such a consensus, the challenge is then to find agreement on what are the most sensible forms of collaboration, incentives, cost and risk sharing, as well as funding mechanisms that can ensure we get new antibiotics in time.

what next? FORUM
Mindmap production by Niclas Hällström, What Next Forum

Background

About ReAct

ReAct – Action on Antibiotic Resistance (www.reactgroup.org), links a wide range of individuals, organizations and networks around the world taking concerted action to respond to antibiotic resistance. ReAct´s vision is that current and future generations will have access to effective prevention and treatment of bacterial infections as part of their right to health. ReAct is based at Uppsala University in Sweden and has an international secretariat with representatives from different parts of the world holding various key functions within the organization. One focus of ReAct is to catalyse processes to find new ways to reinvigorate the innovation of antibiotics. Other areas of work are to increase the visibility of antibiotic resistance, to support the development and implementation of national platforms for a coordinated response to tackle antibiotic resistance, to stimulate evidence generation and to promote rational use of antibiotics.

ReAct does not accept membership or funding from companies or institutions whose support might create a real or perceived conflict of interest.

About the ”Antibiotic innovation” policy process

In order to kick-start the policy discussions for how to incentivize research and development of new antibiotics, Sweden initiated an expert conference during its Presidency of the European Union in 2009. ReAct was part of the organizing and scientific committee preparing the conference. The results of the conference entitled “Innovative Incentives for Effective Antibacterials” led to a set of conclusions by the European Health Ministers, which included a call to the EU Commission to develop a comprehensive action plan including concrete proposals concerning incentives to develop new effective antibiotics. This plan will include, among a number of other important issues, concrete proposals concerning incentives to develop new effective antibiotics. In addition, in November 2011, and in conjunction with the Antibiotic Awareness Day, the Commission is planning to present a broad strategy addressing all sources of antimicrobial resistance (AMR) and their potential impacts. It will address public health, food safety, consumer safety, environment, animal health and welfare as well as non-therapeutic use of antimicrobial substances.

Moreover, during the Swedish EU Presidency, a transatlantic taskforce (EU and US) on antimicrobial resistance (TATFAR) was established which addresses strategies for improving the pipeline of new antimicrobial drugs and diagnostic devices, and maintaining existing drugs on the market. The other two focus areas for TATFAR address appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, and prevention of drug resistant infections. The TATFAR report was published in September, 2011[1].

[1] See http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/210911_TATFAR_Report.pdf

To keep the momentum of these discussions and developments and to further deepen the dialogue on the need for new antibiotics, ReAct arranged a global conference in Uppsala, Sweden in September 2010 on "The Global Need for Effective Antibiotics – Moving Towards Concerted Action". The conference gathered 200 participants from around the world, representing 45 countries and many leading stakeholders – civil society organizations, academia, pharmaceutical industry, governments, and supranational organizations. The messages from the Uppsala Conference included:

- A shared conviction that antibiotic resistance is indeed a global problem. Like global warming, it requires joint action, not least by governmental alliances.
- A clear statement from the pharmaceutical industry that return of investment on R&D of new antibiotics will have to be delinked from market sales in order to limit the misuse of antibiotics and that novel antibiotics will be made globally accessible and affordable. This requires a new business model where private and public sectors cooperate.
- A strong recommendation to all stakeholders to speed up the efforts to limit unnecessary use of antibiotics, while at the same time making these medicines affordable and accessible in low income countries.
- A commitment to improve the monitoring of antibiotic resistance across the world, through shared data and increased efforts. A global network of surveillance will require common methods, and is crucial for both prudent use and needs driven development of new agents.

The seminar "Collaboration for Innovation"

In order to contribute directly to the broad EU strategy on AMR and action plan on innovative incentives to develop new effective antibiotics, ReAct was encouraged to organise a seminar in Brussels in late May 2011. ReAct prepared a multi-stakeholder seminar with almost 50 participants from the EU, member states, government agencies, WHO, academia, pharmaceutical industry, civil society and others (see list of participants in appendix).

Rather than narrowly focusing on incentives, ReAct aimed to broaden the framework and posed the following basic questions: How difficult is it to discover new antibiotics? What are the scientific bottlenecks? What forms of collaboration are essential to make breakthroughs?

A number of presenters were asked to prepare input to the seminar to cover scientific bottlenecks, issues around collaboration, as well as assessments of incentives. The aim was to engage all participants in an open exploration and joint framing of the area to guide further work. While seeking common understanding on the overriding conclusions that a radically new business model is necessary and that new antibiotics must be used prudently – while access and affordability for those in need are ensured – the seminar did not seek consensus at the detailed level.

This report

We thank Niclas Hällström, What Next Forum, for moderating the meeting and drafting this report which is an attempt to capture the key conclusions, agreements and viewpoints that were presented in the meeting and in the background documents. The report does not claim to be comprehensive but presents the conclusions, interpretations and perspectives of ReAct as organiser of the seminar. It is thus not a consensus document that has been agreed on by all presenters and participants. Efforts have however been made to provide a fair and balanced document that will hopefully inform the EU process in a positive way, and stimulate further debate, discussion and action in this important area.

Meeting report – Highlights and conclusions

A public health crisis

- The world faces a tremendous health crisis due to antibiotic resistance. This crisis has several dimensions, all equally important to address:
    - The severe overuse of existing antibiotics which greatly accelerates resistance
    - The lack of access to affordable and effective antibiotics for poor people and populations in need
    - The lack of innovation and development of new antibiotics
- This crisis has a very real time dimension: The world may soon face a situation with a multitude of serious and lethal bacteria resistant to every kind of antibiotics – taking us back to the pre-antibiotic era.
- Drastic changes in current patterns of antibiotic use as well as new approaches to innovation must take place *now* in order to prevent a full-out crisis within the next 5-10 years.

The cost of inaction is astronomical

- In addition to the health dimension with severe threats to the modern health care system and millions of deaths, there are severe economic costs. Already today an estimated 2 million EU citizens contract hospital-acquired infections. According to one study, in one year, 25,000 deaths only in the EU were attributable to a subset of antibiotic-resistant bacteria with societal costs estimated at 1.5 billion Euros per year[2]. In total, the health and economic costs are significantly higher and threaten to explode within only a few years.
- Taking a macroeconomic approach, Smith *et al.* calculated that, assuming a MRSA level of 40 percent in a given society, the real gross domestic product (GDP) would fall between 0.4 to 1.6 percent[3]. For the EU this would translate to between 49 and 196 billion Euros (based on 2010 Eurostat figures for GDP at market prices).
- A full-out crisis of antibiotic resistance would likely lead to a severe economic crisis for EU, and would undermine third world development. Implications for

[2] The Bacterial Challenge: time to react. Technical Report. ECDC/EMA (2009)

[3] Smith et al, Journal of Health Economics 24 (2005), 1055-1075

international security and international relations, including travel and migration, would be severe.

- The costs of inaction would soon become astronomical, which thus motivates considerable public investments in solutions *now* – especially considering the long lag times for pharmaceutical drug development.
- Yet, given limited public funds and a difficult economic situation for most governments, the relative costs for different approaches to spur innovation and development of new antibiotics must be considered carefully. However, if a costly intervention is deemed to be the most effective and likely to deliver results, it should be justifiable given the longer-term savings of both lives and public funds.
- While the seminar only touched on possible financial sources, this is an important aspect to discuss further. Apart from direct EU and member state budgetary support there are also possibilities to explore a number of innovative global funding mechanisms, including for example revenues from Financial Transaction Taxes and use of IMF Special Drawing Rights[4].

We need to monitor and assess needs for innovation, and use of antibiotics

- Innovation must be medically needs-driven and based on prioritisation of what types of antibiotics are needed.
- There needs to be clearer mandates for, as well as coordination efforts between the public institutions that should monitor and assess priority needs.
- In this context, the EMA and the ECDC may need a clearer mandate and more resources to monitor both antibiotic use, resistance magnitudes and trends, and the current innovation pipeline as a basis for assessing what types of new antibiotics that are most needed. In a global context, WHO should strengthen its capacity considerably, with the added task of monitoring access and needs in developing countries.
- Assessment efforts need to be broad-based and involve all stakeholders, including civil society.

[4] There are currently discussions around possible innovative financing mechanisms internationally. Financial Transaction Taxes would be imposed on e.g. currency trading and/or other financial assets with the dual aims of discouraging financial speculation while raising revenue that could be used for various public goods, such as climate financing and health. The transformation of IMF Special Drawing Rights have been proposed for generating funds for e.g. climate finance for developing countries.

We need to prioritise and ensure the innovation of new diagnostic tools

- With quick, reliable and affordable diagnostics, the overuse and misuse of antibiotics can be reduced significantly. Diagnostics are cost-effective even at relatively high unit costs: any decreased number of days at an intensive care unit and avoided antibiotic resistance translates into substantial savings for the public sector.
- A major challenge to overcome as far as diagnostics are concerned is their lack of speed: ideally, diagnostic tools should provide such rapid results that they can guide whether to prescribe antibiotics in connection with the patient-physician interaction.
- Accurate and fast diagnostic tools would also enable identification of patients for clinical trials, thereby speeding up the development process.

A crisis of innovation

- There is a severe lack of new antibiotics being developed.
- Over the last 40 years, only two antibiotics belonging to new classes have been marketed. However, those two antibiotic classes were discovered before 1987.
- There are very few candidates in the advanced stages of the drug development chain. Given the time lag in drug development, innovation efforts must be speeded up *immediately*.
- In the last few years, most of the large research-oriented pharmaceutical companies have abandoned the area of antibiotics.

Contrary to what is commonly thought, this crisis [of innovation in the pharmaceutical industry] is not attributable to a shortage of funding or to overly cautious regulators. Instead, the industry R&D model, which for the last 15 years has strived to minimize risk through the disciplined application of strict processes, has become increasingly unable to deliver breakthroughs.

Bernard Munos, InnoThink Center for Research in Biomedical Innovation

It is difficult to discover new antibiotics

- It is a misconception that the pharmaceutical industry has focused on development of variations of existing antibiotics (”me-too” drugs). On the contrary, vigorous efforts to screen for and design novel antibacterials have been made by the pharmaceutical industry until recently, however with little success.
- Part of the problem has been a paradigm shift within both industry and academia to focus on ”rational” drug development with an emphasis on single targets and high-throughput screening of large chemical compound libraries.

- At the same time, the very particular aspect of ”targeting an organism (bacterium) inside another organism (the human host)” that characterises antibiotics has not been given enough attention. There needs to be much more focus on the substantial biological challenges to ensure that potential antibiotics can enter the bacteria, that they are not immediately pumped out (”efflux”), and that they are only toxic to the bacteria.
- In addition, the issue of resistance potential has not been given enough attention and has likely not been assessed correctly in drug development of antibiotics, despite being a fundamentally important factor. If new drugs are prone to be made ineffective due to rapidly arising resistance they are of limited or no value.
- Most of the novel classes of antibiotics that have been discovered emanate from natural products, and are mostly a result of unpredictable, ”chance” empirical discovery (often in multidisciplinary settings), not ”rational” target-oriented linear innovation.

> ***It is easy to kill bacteria. It is hard to kill bacteria in ways that will affect only the desired spectrum of bacteria without toxicity to the host...***
> ***Chemical collections in use are not well designed for finding molecules that can enter and stay in bacteria.***
>
> **Lynn Silver, LL Silver Consulting**

The appropriate scientific questions have to be asked

- One must ask how to overcome key obstacles to antibacterial discovery. Important questions and approaches (further developed in a short review paper prepared for the meeting[5]) include:
    - How can chemical sources and molecular libraries be improved?
        - Remove toxic, detergent, reactive compounds from libraries
        - Define physiochemical characteristics specifying bacterial entry and efflux
        - Revive natural product screening
    - How can one pursue targets with low resistance potential?
        - Focus more efforts on ”multi-targets”
        - Develop methodologies for modelling and preventing risks of resistance for single-enzyme inhibitors
    - How can one – with better chemicals – return to empirical discovery drawing on a common pool of knowledge and molecules?
    - How can one formulate commonly shared knowledge and methodologies on how to evaluate potential antibiotics?

[5] See http://www.reactgroup.org/uploads/publications/react-publications/Scientific-obstacles-to-discovery-of-novel-antibacterials_Silver.pdf

- There is a need to urgently organise a meeting of key scientists to share essential knowledge, to reignite antibiotic discovery and to examine scientific challenges such as drug entry into bacteria. Key questions need to be identified and answered, and should guide both industry, academia and research funders. The meeting should also consider the kinds of research environments and collaborations needed to most effectively tackle these questions.

The key message – a new business model

- There is a need for a new and different "business model" for antibiotics, one that aims to delink revenues from sales and guarantees strict prudent use once a new antibiotic has been developed.
- Yet, antibiotics also have to be made affordable and accessible to all in need, not the least to people in developing countries.
- Building on such consensus, the challenge is then to find agreement on what are the most sensible institutions, incentives, cost and risk sharing, and funding mechanisms to ensure that new antibiotics are developed in time.
- The EU commission is strongly recommended to emphasise the need for a new business model in its strategy and action plan.

> ***The industry is concerned that any new incentive structure should not rely on a business model driven by maximising product sales for success, since this does not align well with the stewardship of antibiotic resources. The way forward lies in a business model for new antibiotics in which the industry is incentivised to promote appropriate use rather than over-use.***
>
> **European Federation of Pharmaceutical Industries and Associations (EFPIA)**

New forms of collaboration and sharing of knowledge are essential

- The pharmaceutical industry has down-sized interdisciplinary innovation environments in which risk-accepting, long-term experimentation was favoured. It has therefore to a considerable extent lost in capacity to discover new antibiotics.
- There is very little publicly accessible knowledge of industry's past failures in drug development; yet this is essential knowledge in order to avoid duplication of errors and to gain enhanced understanding.
- There is also potential to improve the relevance of academic research in this area. Considerable public research funding has been directed to single-target-oriented research programs, while there is significant need to tackle the broader set of scientific questions mentioned above.
- New breakthroughs in antibiotic innovation and development require unprecedented pooling and sharing of knowledge, creative research environments, as well as asking the right kinds of questions.

- Development of new antibiotics is an essential public good; innovation efforts should to a large extent be seen in the perspective of a global mission to pool and draw on all available knowledge, and to fully share experiences of both failures and successes. It is important to more effectively engage both academic researchers, small and medium enterprises (SMEs) as well as developing country companies in this global effort.

> ***To escape marginalization, and reclaim its role as one of the great contributors to human welfare, the pharmaceutical industry must change its course, and re-engage in high-risk translational research on a large scale. It must do so by joining hands with numerous partners to create broad portfolios of potential breakthroughs, and pay for this shift of resources to early discovery by embracing efficient open innovation models, restricting clinical research to genuine breakthroughs and de-funding other projects.***
>
> **Bernard Munos**

- Methodologies and understanding of e.g. drug entry into bacterial cells must be accessible and widely shared public knowledge.
- Criteria for how to systematically evaluate potential new antibiotics need to be revised e.g. with regard to resistance potential.
- New forms of open access collaborations are crucial, and a follow-up seminar on open-source approaches for innovation of antibiotics should be considered as soon as possible.
- Collaborative innovation platforms in the form of networks are essential drivers of innovation and are effective. They are more prone to risk-taking and development of unconventional creative environments for unpredictable, breakthrough research. They also tend to carry relatively low costs compared to other incentives and large institutions.
- There are several examples in other areas (both pharmaceutical drug development and other fields) to draw experiences from. Such efforts can be purely public, or be built on collaboration between the public and the pharmaceutical drug industry (for details see background paper prepared for the meeting describing possibilities to use open innovation in antibiotics research[6]).
- The EU commission should highlight the importance of supporting new, collaborative, open source efforts for pooling essential knowledge and methodologies for antibiotic drug development.
- New approaches to intellectual property (IP) regimes that places the public interest first and facilitates collaboration for innovation as well as global affordability and accessibility for those in need should be explored. The EU commission could facilitate such a process and include an overview of already existing ideas and initiatives that could be relevant for antibiotics.

[6] http://www.reactgroup.org/uploads/publications/react-publications/Using-Open-Innovation-to-Tackle-the-Dearth-of-Antibiotics_Munos.pdf

Appropriate incentives and platforms must be developed and put in place

- It is essential to first understand the scientific challenges and the needs for collaboration for innovation, in order to make the most sensible and effective choices regarding incentives and creation of new mechanisms and platforms to address innovation of antibiotics.
- It is also important to evaluate any incentive, mechanism or proposals for new platforms in relation to a number of essential criteria. These include whether they:
    - are likely effective to generate breakthrough innovation and new antibiotics
    - aim to delink revenues from sales
    - support controlled distribution
    - respond to urgent health needs
    - promote or enable equitable global access and affordability
    - are politically feasible, including e.g. a reasonable cost to the public tax payers
    - have a reasonable timeframe
    - are in the interest of the public common good

It has often been assumed that the pharmaceutical industry would be the prime mover, and that the key challenge then is to incentivise the industry to prioritise antibiotics relative to other more profitable drugs. In such cases so called ”pull” and ”push/pull” mechanisms make sense as primary policy interventions[7]. If, on the other hand, individual pharmaceutical companies are unlikely to be successful on their own, pure pull and push/pull incentives will not be effective, and constitute a waste of public resources and loss of valuable time.

Consider, if Big Pharma (and biotechs) have been largely unsuccessful in finding novel antibacterials to develop…
Will that be reversed by increasing financial incentives or revising regulatory policy?

Lynn Silver

[7] A *pull* mechanism offers a reward that is granted only after a product has been fully developed, such as a monetary prize or an advanced commitment to purchase the product if successfully invented. A *push-pull* mechanism also includes some “push” elements, i.e direct support for research.

- Depending on one's views of the above, different approaches can be formulated:
    - A private sector focus with pull or push/pull incentives funded by the public sector
    - Primarily public sector focused approaches
    - Public-private collaborative approaches

Private sector focus

- Most of the private sector focused "pull" and "push-pull" incentives build on a competitive framework, where companies are supposed to be incentivised to pursue innovation in isolation and in competition with each other, with little or no motivation for collaboration.
- However, other private sector directed efforts could stimulate enhanced private sector focus on collaboration and pooling of knowledge, either within industry exclusively (e.g. patent pools) or in partnership with public entities (see below). Such approaches should be explored and evaluated further.
- If society opts to pursue pull and push-pull mechanisms to stimulate increased efforts by industry, it is essential that public interest conditionalities are ensured (e.g. to ensure possibilities for differentiated pricing, controlled use, marketing rules etc.).
- There is much uncertainty on what is the relative profitability (relative Net Present Value (NPV)) of different medicines and what level of incentive is needed to change priorities within industry. There are also different views on what levels of publicly funded incentives can be justified for attracting industry to pursue a global public good such as new antibiotics.
- An overview of several pull and push-pull incentives is available in a background paper prepared for this seminar[8] which does not make specific recommendations, but rather aims to facilitate the comparison of different incentives based on a number of criteria.
- Market exclusivity extensions are not included in the report (only as part of e.g. orphan drug legislation packages). "Market exclusivity" as an incentive does not fulfil the requirement of delinking of revenue from sales. Transferable market exclusivity extensions also shift the burden onto other patient groups, and are thus highly controversial. *The EU commission and other public institutions are advised not to pursue these types of incentives*.
- Each incentive has advantages and disadvantages, and differ depending on the interests of each actor. Only some of them have previously been fully applied in drug development. When evaluating incentives, key criteria such as their ability to support conservation efforts, to delink revenues from sales, and to facilitate affordability and access in developing countries should be considered in addition to the incentives' probability of stimulating innovation.

[8] See http://www.reactgroup.org/uploads/publications/react-publications/Exploring-Responses-to-the-need-for-new-antibiotics_Morel.pdf

- It is also important to note that industry is not homogeneous. Different parts of the industry—small and medium enterprises (SMEs), large multinational companies, developing country firms, generic firms, biotech start-ups etc. – respond to incentives differently.

Primarily public sector focused approaches

- A range of purely public initiatives to drive innovation can be considered. Such initiatives can either be pursued in parallel to private sector incentives, or as a substitute for these.
- Increased direct funding for public academic research can be increased – under condition that the most appropriate scientific questions are formulated (see above).
- Ambitious network-based initiatives such as the Open-Source Drug Discovery Initiative in India can be set up specifically for antibiotic innovation[9].
- Interdisciplinary research centres that physically gather excellence can be set up at universities. These can in turn be connected to both each other and to open-source initiatives, thus constituting particular nodes of expertise.
- The idea of entirely new kinds of facilities should be considered and explored. Granted the magnitude and urgency of the crisis, and the need for broad-based collaboration, a European or global ”mission” may be established as a non-profit facility with the explicit task of developing new antibiotics. Such an endeavour could pool researchers and expertise from both academia and the private sector to form new interdisciplinary research environments. Industry would provide experts and chemicals as in kind contributions, while getting other benefits in return[10].
- Similar to the above idea, the prospects for a European Platform on Antibiotic Resistance should be explored. Such a platform could: function as a watchdog to assess needs and what is currently in the research pipeline, fund translational research among academic laboratories, support open-access research and publicly accessible molecule libraries, offer grants and fellowships, coordinate a patent pool for e.g. fixed-dose combinations, fund and facilitate major collaborative efforts such as Public Private Partnerships and other innovative institutional schemes. It could also involve the establishment of interdisciplinary research environments for drug development in priority areas, similar to the NIH National Center for Advancing Translational Sciences (NCATS), which could pool expertise from both the public and the private sectors.
- EU should facilitate further exploration and assessment of the merits and possibilities to support the formation of different public sector initiatives, including assessments of costs in relation to other approaches.

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[9] See http://www.osdd.net

[10] This kind of approach is further elaborated on by among others Carl Nathan, see e.g.“Aligning pharmaceutical innovation with medical need”, *Nature Medicine,* Vol 13, No 3 2007.

Public-private collaborative approaches

- In order to facilitate broad collaboration and pooling of experts, chemical resources and knowledge, new forms of public-private collaborations may be set up. Such schemes and consortia can be formed in many different ways and at different scales.
- Public-Private Partnerships such as the Drugs for Neglected Diseases Initiative (DNDi)[11] and Medicines for Malaria Venture (MMV)[12] can be set up specifically for antibiotic innovation. MMV has a budget of $55 million per year, 42 employees, involves 130 partners (pharma and biotech) and has received 712 project ideas. Of the 47 investigated ideas one has already resulted in one approved drug and two are currently subjected to regulatory review. The DNDi has already brought several products to market, including several combination drugs.
- Efforts such as the Structural Genomics Consortium (SGC) is currently taking shape, where corporations and academic researchers participate in a public-private partnership to determine the three-dimensional structures of proteins of medical relevance, which are then placed in the public domain without restrictions[13].
- Further exploration and a workshop on new public/private platforms should be conducted.
- In the EU there is currently a pre-competitive collaborative programme between industry and the EU Commission, the Innovative Medicines Initiative (IMI)[14]. So far limited attention has been devoted to antibiotics.
- The current IMI should investigate means to contribute to antibiotic development within its remaining work period. The design of the IMI's second phase should specifically consider a substantial component directed to innovation of new antibiotics and explore means to involve a broader set of stakeholders in its design.

Views on the different approaches

There are different views on what the balance should be between the different approaches above.

Some argue against large public initiatives and take the view that private companies are the central actors for innovation, and that existing public-private initiatives such as the IMI (Innovative Medicines Initiative) are more or less sufficient. Others, acknowledging the failure of the current pharmaceutical system of innovation to deliver antibiotics, argue that industry has limited capacity (but an important role to play) in broad and truly innovative antibiotics research and that new and unconventional approaches are needed. In turn, there are different views on whether

[11] See http://www.dndi.org/

[12] See http://www.mmv.org

[13] See http://www.thesgc.org

[14] See http://www.imi.europa.eu/

public initiatives should be primarily decentralised networks or if they should be larger physical facilities, or a combination of both.

Some also make the point that there are different roles for different actors depending on where one looks in the drug development chain. While research and discovery may justify more efforts on collaboration and sharing of knowledge, some argue that industry is and should be the key actor in the development, testing and distribution of new antibiotics. Others argue that there are good reasons from innovation, cost and public interest points of view to ensure public control of most of the drug development chain.

It is possible to imagine various combinations of approaches, mechanisms and platforms. Regardless of the solution chosen, all phases of the drug development chain must be characterized by a willingness to collaborate and to share essential knowledge.

Current regulations for approval of new antibiotics should be reviewed and possibly reformed

- It is important to review current regulatory frameworks for approval of new antibiotics, in order to facilitate the innovation/development process, while ensuring patient safety. This could possibly result in a new regulatory framework for “special designation for priority antibiotics”.
- Antibiotics often require considerable phase III trials because efficacy and safety of new drug candidates need to be proven for several diseases (“indications”). This prolongs the time for approval and adds costs. Reviews of reformed regulations for possible streamlining should be considered, for example alternative methodologies for clinical trials, the use of pharmacokinetic and pharmacodynamic modelling, and conditional approval mechanisms.

We must ensure controlled use of future antibiotics

- Irrespective of what kinds of mechanisms, incentives and institutions that are chosen to drive innovation, any new antibiotic must be distributed and used in a controlled manner.
- It is essential to formulate an agreement where all key actors agree on the principles of controlled use while respecting the need for access to affordable antibiotics for everyone in need.
- Agreements, policies and legislation ensuring responsible, if any, marketing of new (and possibly also existing) antibiotics should be pursued.

Concluding remarks

Managing the resistance problem requires political action and awareness of decision makers to promote research and implementation of global strategies for action. Antibiotics must be viewed as a global public good and a fundamentally changed view of how to collaborate to overcome the lack of research and development of new antibiotics is urgently needed. Facing the global challenge of antibiotic resistance, clearly new business models for bringing novel antibiotics to market will be needed. The ongoing pandemic spread of resistant bacteria illustrates that the problem can only be addressed through international cooperation and thus that any new strategy to manage antibiotic resistance must take into consideration issues of global access and affordability. ReAct strongly believes that for current and future generations to have access to effective prevention and treatment of bacterial infections as part of their right to health, all of us need to act now.

Appendix 1: Seminar agenda

Moderator: Niclas Hällström, *What Next Forum*

Introductions:

- Welcome & Introduction (Otto Cars, *ReAct*)
- Meeting objectives & Overview (Niclas Hällström, *What Next Forum*)

Setting the Scene:

- The antibiotic resistance crisis (Otto Cars, *ReAct*)
  Q & A
- EU policy processes (Nabil Safrany*, EU Commission, DG SANCO*)
  Q & A
- How difficult is it to discover new antibiotics? (Lynn Silver, *LL Silver Consulting*)
  Q & A

Coffee Break

- The role of diagnostics in the management of antibiotic resistance (Anna Zorzet, *ReAct* & Isabelle Caniaux, *bioMerieux*)
  Q & A
- Views on roles and responsibilities of the pharmaceutical industry (Richard Bergström, *EFPIA*)
  Q & A

Lunch

Mechanisms & Incentives:

- Welcome back & Introduction to the section (Niclas Hällström, *What Next Forum*)
- Exploring responses to the lack of new antibiotics: how do different incentives compare? (Chantal Morel, *London School of Economics*)
  Q & A
- Views on the possibilities for open source collaboration (Bernard Munos, *InnoThink Center for Research in Biomedical Innovation*)
  Q & A

General discussion and ways forward:

- Reflections by Tido von Schoen-Angerer (*MSF/Access to Essential Medicines Campaign*)
- Reflections by Kris Weerasuriya (*WHO, Geneva*)

Coffee Break

- General discussion and conclusions

Appendix 2: List of participants

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Appendix 3: List of commissioned background documents

Scientific Obstacles to Discovery of Novel Antibacterials

Lynn Silver, LL Silver Consulting

http://www.reactgroup.org/uploads/publications/react-publications/Scientific-obstacles-to-discovery-of-novel-antibacterials_Silver.pdf

Using Open Innovation to Tackle the Dearth of Antibiotics

Bernard Munos, InnoThink Center for Research in Biomedical Innovation

http://www.reactgroup.org/uploads/publications/react-publications/Using-Open-Innovation-to-Tackle-the-Dearth-of-Antibiotics_Munos.pdf

Exploring responses to the need for new antibiotics: How do different incentives compare?

Chantal Morel, London School of Economics

http://www.reactgroup.org/uploads/publications/react-publications/Exploring-Responses-to-the-need-for-new-antibiotics_Morel.pdf

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