Objectives of the Meeting

Technical Consultation on Innovative Models for New Antibiotics’ Development and Preservation

Zafar Mirza
13 May 2014
WHO, Geneva

Health Systems and Innovation (HIS) Cluster
"If current trends continue unabated, the future is easy to predict. Some experts say we are moving back to the pre-antibiotic era. No. This will be a post-antibiotic era. In terms of new replacement antibiotics, the pipeline is virtually dry, especially for gram-negative bacteria. The cupboard is nearly bare."

"A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child’s scratched knee could once again kill."

Keynote address at the conference on Combating antimicrobial resistance: time for action, Copenhagen, Denmark, 14 March 2012
What you need to know
WHO’s first global report on antimicrobial resistance, with a focus on antibiotic resistance, reveals that it is no longer a prediction for the future. Antibiotic resistance – when bacteria change and antibiotics fail – is happening right now, across the world.

The report is the most comprehensive picture to date, with data provided by 114 countries.

Looking at 7 common bacteria that cause serious diseases from bloodstream infections to gonorrhoea.

High levels of resistance found in all regions of the world.

Significant gaps exist in tracking of antibiotic resistance.

Over the last 30 years, no major new types of antibiotics have been developed.
**Recommendations for intervention**

6.1 Encourage cooperation between industry, government bodies and academic institutions in the search for new drugs and vaccines.

6.2 Encourage drug development programmes which seek to optimize treatment regimens with regard to safety, efficacy and the risk of selecting resistant organisms.

6.3 Provide incentives for industry to invest in the research and development of new antimicrobials.
The evolving threat of antimicrobial resistance
Options for action

Chapter 6.
Fostering innovation to combat antimicrobial resistance

*Penicillins were the first beta-lactams. This class included cephalosporins and carbapenems, developed in the 1960s and 1980s, respectively.
Source: Reproduced with data from [1]. Modified with permission from Thomson Reuters (Professional) Ltd.
CEWG on R&D for Antibiotics

2012

• "A serious market failure"

• "the spread of resistance to antibiotics is detrimental to public health and necessitates further R&D which is insufficiently incentivised and scientifically challenging."

• "a particular cause for concern currently is the low level of investment in R&D on antibiotics."
Combating antimicrobial resistance, including antibiotic resistance (EB134.R13)

• URGES MEMBER STATES:

(8) to encourage and support research and development, including by academia and through new collaborative and financial models, to combat antimicrobial resistance and promote responsible use of antimicrobials, develop practical and feasible approaches for extending the lifespan of antimicrobial drugs and encourage the development of novel diagnostics and antimicrobial drugs;

• REQUESTS THE DIRECTOR GENERAL:

(5) to develop a draft global action plan to combat antimicrobial resistance, including antibiotic resistance, which addresses the need to ensure that all countries,…;

…. (f) foster innovation and research and development for new tools;
The Context of this Technical Consultation

- WHO's ongoing work in the follow-up of CEWG report on exploring innovative approaches for financing and coordination for R&D for those health technologies which suffer from market failure.

Objectives of this Technical Consultation

1. To be informed by the state-of-the-art thinking and proposed models for financing, developing and preserving new antibiotics.

2. To have critical review of these models by the leading experts.

3. To present WHO current thinking on R&D and preservation of new antibiotics.

4. To enrich and improve WHO proposed model through discussions with the leading experts.
The Innovative Medicines Initiative: ND4BB models of collaboration

Angela Wittelsberger, PhD
IMI Scientific Officer
IMI offers a new ecosystem involving all stakeholders to deliver sustainable healthcare

Calls 1-8 → 46 projects → > 6000 researchers

61% of projects reported some form of PATIENT INVOLVEMENT

REGULATORS ON BOARD OF 12 PROJECTS

50% of projects have REGULATORY AUTHORITIES representatives in Scientific Advisory Boards

IMI’s New Drugs For Bad Bugs (ND4BB) programme

- Increasing the efficiency of clinical trials by creating clinical investigator and laboratory networks
  **COMBACTE**

- Advancing basic research through public-private collaboration
- Learnings and best practices by sharing data and information

**Topic 1: COMBACTE**
- a) Enabling Clinical Collaboration and refining clinical trial design
- b) Clinical Development of GSK1322322
- c) Clinical Development of MEDI4893

**Topic 2: TRANSLOCATION**
- Research penetration and efflux Gram-negatives Data Hub and Learning from R&D experience

**Topic 3: ENABLE**
- Discovery & development of new drugs combating Gram-negative

**Topic 4:**
- Driving re-investment in R&D and Responsible use of Antibiotics

**Topic 5:**
- Clinical development of antibacterial agents for Gram-negative antibiotic resistant

**Topic 6:**
- Systemic molecules against HAIs due to clinically challenging Gram-negative pathogens

**Topic 7:**
- Inhaled Antibacterials in CF and non-CF BE

ENABLE: €81.85 million, started Feb 2014, runs 6 years
Led by GSK and Uppsala University

Drug Discovery Platform

Supporting multiple programmes

Portfolio Management Committee

Controls Progression decisions

Open Calls to attract best programmes

Programmes with novel molecules

Supported by Drug Discovery Platform

Hit-to-lead (8)

Lead-to-Candidate (3)

Candidate-to-Phase 1 (1-2)

Phase 1 clinical trial (1-2)

IMI’s New Drugs For Bad Bugs (ND4BB) programme

- Increasing the efficiency of clinical trials by creating clinical investigator and laboratory networks
  
  **COMBACTE**
  
  **Topic 1**: 
  a) Enabling Clinical Collaboration and refining clinical trial design
  b) Clinical Development of GSK1322322
  c) Clinical Development of MEDI4893
  
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  TRANSLOCATION
  Research penetration and efflux Gram-negatives Data Hub and Learning from R&D experience
  
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  ENABLE
  Discovery & development of new drugs combating Gram-negative
  
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  **Topic 7**: 
  Inhaled Antibacterials in CF and non-CF

- Advancing basic research through public-private collaboration
- Learnings and best practices by sharing data and information

**Unique collaborative model of drug discovery**

**ENABLE**

**Providing a neutral trusted platform to bring stakeholders together and to align public and private interests**

ND4BB Topic 4

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Driving re-investment in R&D and responsible use of antibiotics

Overall objective

To develop options for a new sustainable economic model of antibiotic R&D and responsible use of antibiotics

- New commercial models
- Shared understanding of responsible use of antibiotics
- Quantification of the economic burden of resistance
- Definition of clinical impact of emerging MDR pathogens
- Quantification of the value of a new antibiotic

Testing and validation of options (legal, political, regulatory feasibility; geographical differences; medical practice; impact on new programmes in development)

Challenge

Involvement of all stakeholders: public health, Government/payers, clinical societies, Academia, Industry
Thank you
The Diagnosis

- Chronically underfunded basic research
  - Limited technological developments
  - No disruptive therapeutic innovation

- Pharmaceutical company disengagement
  - In a resource-limited environment, businesses have chosen other areas
  - Critically thin pipeline against emerging resistant pathogens

- Commercial model doesn’t work
  - Investor returns not competitive
  - Doesn’t promote antibiotic preservation
Solve the Antibiotic Crisis

- **Bridge the funding gap**
  - Public/private partnership to secure funding for existing programmes
  - e.g. IMI, BARDA

- **Create favourable regulatory environment**
  - Make it possible for antibiotics in the pipeline to be developed
  - Great progress on that in the past 2-3 years, let’s keep it going

- **Provide economic incentives for the developers**
  - e.g. extended exclusivity, price guarantee, volume-delinked commercial models
Create a Sustainable Model

• **Re-engage pharma (private)**
  • Skills, tools and track record in drug discovery and development
  • Very significant private funding available

• **Step-increase in basic research funding (public)**
  • Focus on knowledge generation and disruptive innovation
  • Encourage knowledge sharing and partnership with pharma/biotech
  • Governments, NP organisations, International Funds etc.

• **Target drugs to patients and pathogens**
  • Only prescribe new drugs to patients who need them
  • Greater effectiveness & durability, slower resistance
  • Incentive : pricing commensurate with volume
A call to action

• Devise novel funding mechanisms for basic research in antibacterials
  • Country (e.g. NIH), regional (e.g. IMI) or global coordination (WHO?)
  • Fresh funding or re-direct investment from other disease areas
  • Objective is to **double** basic research funding over the next 5 years

• Develop incentives to promote development of disruptive treatments
  • Regulatory approval paths, IP, premium pricing
  • Attract fresh private investment & create competition for first/best in class

• Promote development and adoption of targeted drugs and rapid diagnostics
  • Dedicated regulatory paths & funding for technology development
  • Evolve medical practice, encourage or enforce adoption
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Antibiotic Health Impact Fund
A proposal for a delinked system that rewards innovation into new antibiotics while also enabling access for those in the greatest need

Thomas Pogge, PhD
President, Incentives for Global Health
Rewarding innovative antibiotics

Developers of new antibiotics are offered annual rewards based on the drug’s health impact (H) and preservation of its global efficacy (E) – on condition that, for human uses, the drug is sold at or below cost in all LMICs.

This delinkage deal is voluntary but economically compelling; hence it strengthens incentives to develop new antibiotics.

Better access to antibiotics would cut down on the hundreds of thousands of annual deaths, mainly children in low-income settings, due to susceptible bacterial infections.

Registered innovators would want to reduce low-value uses of their product (where expected loss in E is not justified by gain in H plus any price mark-up).

- High volume of use of fluoroquinolones and carbapenems in India have created widespread resistance there
Designing the rewards

H rewards are sensitive to the number of patients served and to the health gain the drug brings to each patient relative to the treatment s/he would otherwise have had.

E rewards are sensitive to the percentage of susceptible patients and to the health gain the drug brings to the average susceptible patient relative to no treatment at all.

Rewards could be restricted to fixed terms (10+ y), perhaps longer for E than for H. Such reward periods could extend beyond the patent period, even if generics enter the market.

The reward scheme should be complemented by efforts in basic research, vaccinations, surveillance, diagnostics, infection control, general antibiotic stewardship and other public health measures focused on infectious diseases.
Financing and Administration

An intergovernmental agency for infectious diseases would control use and licensing of all antibiotics and administer the aHIF reward scheme and the supplementary efforts. This agency could be financed through user fees on (i) all non-human uses of any antibiotics worldwide, and (ii) all human uses of any including generic antibiotics in HICs. With OECD human antibiotics expenditures at $30+ billion, $3 billion could easy be raised from (ii). Annual rewards of $2.4 billion would attract a robust stream of antibiotic product registrations, sustaining ca. seven aHIF antibiotics in the range of $200-500m annually.

In HICs, the price of aHIF-registered antibiotics could be left to the innovator or else be limited to cost plus the user fee.
Chatham House Working Group on New Business Models for Antibiotics

John-Arne Røttingen, Division Director
Division of Infectious Diseases Control
Norwegian Institute of Public Health
Associate Fellow, Chatham House Centre for Global Health Security
Professor of Health Policy, University of Oslo
Visiting Professor of Global Health, Harvard School of Public Health

Technical Consultation on Innovative Models for New Antibiotics’ Development and Preservation
WHO, May 13 2014
Chatham House Working Group process

- September 2013: Draft background paper, by Kevin Outterson
- October 2013: Roundtable discussion
- January 2013: Constituted a working group
- March 2014: Inception paper for working group, by Kevin Outterson, Unni Gopinathan, Chris Hoyle
- Fall 2014
  - 2nd working paper
  - 2nd Roundtable
Six features of “Delinkage” business models

• Structuring the innovation reward
• Geographic scope
• Product scope
• Financing mechanisms
• Ownership of the intellectual property
• Control of marketing and utilization
Six features of Delinkage business models

- **Structuring the innovation reward**
  - Timing (development phase, post authorization)
  - Size/valuation approach (e.g. health impact or broader)
  - Multiple/single payments
  - Insurance model, service level agreements

- **Geographic scope**
- **Product scope**
- **Financing mechanisms**
- **Ownership of the intellectual property**
- **Control of marketing and utilization**
Six features of Delinkage business models

• Structuring the innovation reward
• Geographic scope
  • Single country, regional, global, or a select group of countries based on interest
  • Scalability – framework agreement?
  • Coordination – global body?
• Product scope
• Financing mechanisms
• Ownership of the intellectual property
• Control of marketing and utilization
Six features of Delinkage business models

• Structuring the innovation reward
• Geographic scope
• Product scope
  • Pathogen or product?
  • All anti-infective technologies (including vaccines & diagnostics)?
  • All antimicrobials, only systemic antibiotics, or just highly effective new antibiotics?
• Financing mechanisms
• Ownership of the intellectual property
• Control of marketing and utilization
Six features of Delinkage business models

- Structuring the innovation reward
- Geographic scope
- Product scope
- **Financing mechanisms**
  - Pooling or individual countries
  - Innovative financing
  - General taxation or health insurance payers
  - Refundable tax credits
  - User fees (Pigouvian taxes) on agricultural and human antibiotic sales
- Ownership of the intellectual property
- Control of marketing and utilization
Six features of Delinkage business models

• Structuring the innovation reward
• Geographic scope
• Product scope
• Financing mechanisms
• **Ownership of the intellectual property**
  • Private, public, private-public partnership
  • Third party patent pool
  • “Exclusivity in perpetuity“
  • Control of generic entry
• Control of marketing and utilization
Six features of Delinkage business models

- Structuring the innovation reward
- Geographic scope
- Product scope
- Financing mechanisms
- Ownership of the intellectual property
- Control of marketing and utilization
  - Restrictions on sales and trade
  - Requirements for prescriptions
  - Strong regulations (e.g. like narcotics)
  - Transparency and accountability on marketing efforts and detailed data on sales
  - Extraterritorial control/access in LICs
Driving Re-Investment In R&D And Responsible Use Of Antibiotics (ND4BB, IMI)
Thank you
Antibiotic Innovation Funding Mechanism

Features:

● The creation of new financial innovation incentives that are delinked from drug prices.
● The elimination of perverse incentives for drug developers to promote inappropriate or low value use of drugs, particularly where there are significant negative impacts on the conservation of the antibiotic resources.
● The creation of economic incentives to induce the open sharing of knowledge, data, materials, and technology relevant to the development of new products.
● The competitive production of generic supplies of products at affordable prices.
● The transfer of technology to drug manufacturers in developing countries.
● Opportunities for researchers, institutions and both small and large businesses to participate as suppliers of innovations, in both developed and developing countries.
● A sustainable system of financing for open source development of new antibiotics.
Stage 1

- Create a governance structure, open bank accounts, negotiate contracts with WHO (or some other entity) to provide secretariat services, and with the Medicines Patent Pool (or some other entity) to manage the licenses.
- First round of voluntary financial commitments.
- Adopt initial policies on licensing, conservation objectives, innovation priorities.
- Adopt policy on use of competitive intermediaries to manage grants and interim prizes.
- Offer and later award initial grants.
- Consultation with experts and stakeholders on innovation inducement prize designs.
- Design initial prizes, including both end product prize, open source dividend, and at least one interim results prize.
Stage 2

- Create the user fee or tax on antibiotic drugs.
- Identify global revenue targets.
- Identify conservation objectives.
- Make recommendations and share best practices as regards norms for scaling fees and taxes to achieve conservation and other social objectives, particularly as regards low value uses of drugs with significant negative externalities, and differential prices to accommodate differences of incomes between and within countries.
BARDA Partnering Model

• BARDA partners with companies to develop new antibiotics
  — Phase I-Phase III clinical development, toxicology, clinical pharmacology, CMC, etc.
• This provides non-dilutive funding to companies
  — Consistently observed companies use our partnership to leverage further financing in public/private markets
• Model shifts risk to government partner, not developer/investor
• Provide technical guidance and support as part of our collaboration
  — Benefit from observing multiple antibiotic development programs concurrently
### Current Portfolio of Antibacterial Products

#### BARDA’s BSA Supported Product Pipeline

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Compound</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achaogen</td>
<td>Plazomicin (ACHN-490)</td>
<td>Next-generation aminoglycoside: Broad Spectrum Plague, Tularemia and carbapenem resistant Enterobacteriaceae (CRE)</td>
</tr>
<tr>
<td>CUBRC/Tetraphase</td>
<td>Eravacycline (TP-434)</td>
<td>A novel fully synthetic tetracycline: Broad Spectrum Plague, Tularemia and Multi-drug resistant (MDR) infections (clAI)</td>
</tr>
<tr>
<td>Cempra</td>
<td>Solithromycin (CEM-101)</td>
<td>Next-generation fluoroketolide: Broad Spectrum Anthrax, Tularemia and community-acquired bacterial pneumonia (CABP)</td>
</tr>
<tr>
<td>Basilea</td>
<td>BAL30072</td>
<td>A novel sulfactam: Broad Spectrum MDR Gram negative infections</td>
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<tr>
<td>Rempex</td>
<td>Carbavance™ (meropenem/RPX7009)</td>
<td>Carbapenem/β-lactamase inhibitor: Broad Spectrum CRE, complicated urinary tract infections (cUTI), hospital-acquired pneumonia/ventilator-associated pneumonia (HAP)/VAP)</td>
</tr>
<tr>
<td>GSK</td>
<td>A portfolio approach</td>
<td>Broad Spectrum Antibiotic Portfolio A partnership to fund multiple compounds to combat antibiotic resistance at various stages of development</td>
</tr>
</tbody>
</table>

Disclaimer: The above projects are supported by BARDA’s BSA Program utilizing non-dilutive funding via a contract and/or agreement. The stage of development is approximate as of January 2014 (please refer to the sponsors site for updated information). The table represents the compounds most advanced commercial indication being pursued under either a US or International regulatory authority.
BARDA Portfolio Partnership

• May 2013 BARDA established a 5 year $200M partnership with GSK
• Utilizes a mechanism with the USG known as Other Transactional Agreement
• Principles of these agreement include:
  — Flexibility
  — Cost Sharing
  — Joint Strategic Oversight
• This model of partnering could be expanded to further entice companies to re-engage in antibacterial drug development
Concerns with Other Models

• Need for pricing reform-can the market do it through higher pricing for narrow indications?

• Institutional licenses
  — Tracking of use a requirement
  — Does not move us away from a unit sold model

• Advanced Market Commitments
  — Sustainability
  — Changing a market to be reliant on subsidization
  — Shifting risk back to developer
A potential solution for AMR R&D

Emiliano Rial Verde
McKinsey & Company

Technical Consultation on Innovative Models for New Antibiotics’ Development and Preservation
May 13, 2014
**What a potential solution might want to achieve**

<table>
<thead>
<tr>
<th>What it should do</th>
<th>Why?</th>
<th>Grad. programs size (relative)</th>
<th>Market size (USD b)</th>
<th>Non-prescription sales (%)</th>
<th>Resistant enterobacteria isolates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster basic microbiology research</td>
<td>Current underinvestment</td>
<td></td>
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<tr>
<td>De-risk investment/increase return</td>
<td>Shrinking market</td>
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<tr>
<td>Ease regulatory approval</td>
<td>Superiority discourages alternatives</td>
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<tr>
<td>Encourage appropriate use</td>
<td>Current overuse</td>
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<tr>
<td>Support access</td>
<td>Developing world problem</td>
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**Grad. programs size (relative)**

- Neuro. Microb.
  - 100
  - 68

**Market size (USD b)**

- 2008: 15.5
- 2013: 12.6

**Non-prescription sales (%)**

- Italy: 19.0
- Brazil: 46.0
- Nigeria: 100.0

**Resistant enterobacteria isolates (%)**

- Brazil: 35.0
- India: 41.0
- China: 83.0

*“Superiority [...] vs. standard of care [...] to command premium pricing is a [...] challenge” – Opinion leader*
The AMR Fund operating model

- Portfolio mgmt.
  - Proposals
  - Funds
  - Academia
  - Shares
  - Reviews
  - CROs
  - Pharma
  - Manufact.
What this proposal does not answer

1. Post-LOE period resulting in unregulated manufacturing and volume-based sales models
2. Revenue stream sustainability if all funders expect monetary returns—cannot be entirely private
3. Regulatory reform
4. What else?
Current WHO model for development / preservation of new antibiotics
13 May 2014

Marie-Paule KIENY, ADG/HIS
Some assumptions

- Innovators should be rewarded, within reason
- No additional profit should be provided for higher volume sales
- Discovery and innovation takes place mostly in the academia and small companies rather than large companies
- LMICs, and in particular emerging countries, have enormous untapped innovation capacity
- PDPs have been able to drive the development of new drugs
- Some "generics" companies have high technical capacity
- Self-regulation by manufacturers and users unlikely, esp due to over-the-counter LMIC markets and "counterfeit" medicines
- (some) companies would work "on contract" provided the offer is sufficiently attractive
- Preservation will require GLOBAL arrangements
- New antibiotics should be a Global Public Good
- Access should be ensures without regard to ability to pay
## SWOT analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
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<tbody>
<tr>
<td>- Delinkage model</td>
<td>- May need UN-level agreement</td>
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<tr>
<td>- Ensures both incentivization of R&amp;D AND preservation</td>
<td>- Need for global IP management arrangements to ensure Exclusivity in perpetuity and compulsory licenses</td>
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<tr>
<td>- Access and affordability for ALL countries</td>
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<tr>
<td>- Transparency</td>
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<td>- Strong global governance</td>
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<tr>
<td>- Operations overseen by competent agent</td>
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<tr>
<td>- Clinical trials financed by consortium</td>
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<tr>
<td>- Incentives on Products and/or Pathogens possible</td>
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<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
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<tr>
<td>- Leverage science in LMIC in addition to HIC</td>
<td>- Lack of political leadership (shared responsibility)</td>
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<tr>
<td>- Engage LMIC manufacturers</td>
<td>- Insufficient financial investment</td>
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<tr>
<td>- Exploration of natural compounds in LMIC</td>
<td>- &quot;Classification&quot; could make access in LIC challenging (as for opioids)</td>
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<tr>
<td>- Will use both Push and Pull financial mechanisms: prizes, grants, pooled fund</td>
<td>- Push-back from animal sector</td>
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<tr>
<td>- Multinational companies willing to support delinkage models</td>
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<tr>
<td>- Potential for simultaneous worldwide registration</td>
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<tr>
<td>- Sharing of safety information and global arrangements on safety claims</td>
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<tr>
<td>- Development of POC Dx in conjunction with Abx</td>
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