INDEPENDENT REVIEW ON ANTI-MICROBIAL RESISTANCE (AMR)

REGULATION-INNOVATION INTERACTIONS IN THE DEVELOPMENT OF ANTIMICROBIAL DRUGS AND DIAGNOSTICS:

AN EVALUATION OF DRUG AND IVD INDUSTRY VIEWS

Jack Scannell

SUPPLEMENTARY REPORT 2

Jack Scannell, Visiting Fellow,
Innogen Institute,
Science, Technology and Innovation Studies,
University of Edinburgh,
Old Surgeons Hall,
High School Yards,
Edinburgh EH1 1LZ
www.innogen.ac.uk
jack.scannell@ed.ac.uk
jack.scannell@www.casmi.org.uk

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Summary

The antimicrobial resistance (AMR) problem is the consequence of brisk bacterial evolution in the face of slow biomedical progress. This report ignores the biological, behavioural, and commercial factors that influence the evolution of bacteria. It focuses instead on the regulatory factors that influence the pace of drug and diagnostic innovation.

The dearth of substantially novel antibacterial drugs over the last ~30 years follows from four factors: First, the economic exhaustion of traditional methods for antibiotic discovery, based largely on the fermentation broths and extracts of soil-derived microorganisms (Silver, 2011) (Balz, 2007); second, the failure between the mid-1990s and early 2000s of industrialised drug discovery based on genomics and high-throughput screening to discover attractive looking broad spectrum candidates (Payne, *et al*., 2007), despite turning up a few potential narrow-spectrum agents; third, regulatory guidelines that made certain clinical trials very difficult, particularly for narrow spectrum drugs (Rex, *et al*., 2013) (IDSA, 2011) (Coates, Halls, & Hu, 2011); and fourth, only mediocre profit potential (Sertkaya, *et al*., 2014). In short, substantially novel drugs that might have been discoverable appeared neither developable nor sellable.

Our interviews suggest that novel antimicrobials are developable once more, although some frustrating differences remain between the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the US. Clinical trials used to be a major barrier to innovation. It was as if the FDA had placed such an emphasis of experimental purity that trials for certain indications were unethical and impractical to run (IDSA, 2011) (Coates, Halls, & Hu, 2011). However, the FDA and the EMA now guide the industry towards trials that are pragmatic. Some statistical hurdles have been lowered slightly, which means smaller trials. Trial recruitment criteria have become more permissive, which means it is easier to enrol patients. Another regulatory innovation is pathogen-specific approval for serious infections with few good treatment options. For the first time, this allows trials to pool patients with infections at different anatomical locations (e.g., pneumonias, wounds, urinary tract, etc.) but which share a common infectious agent. This will have an important enabling effect on clinical trials (Rex, *et al*., 2013).

We have estimated the R&D costs of pathogen-specific vs. conventional approval. Estimates of average R&D cost per approved drug following the conventional route, including the cost of failed projects and the time cost of money[1], are a hefty $1.6bn to $2.2bn[2]. These estimates are based on our analysis of recent work commissioned by the US Department of Health and Human Services (Sertkaya, *et al*., 2014). It is plausible that the average R&D spend per pathogen-specific drug approved via the new pathways would be around two thirds less ("only" $752m). However, these kinds of R&D cost estimates are **extremely** sensitive to failure rate assumptions. Failure rates are, in turn, extremely sensitive to the quality of preclinical drug candidates, to their novelty (Porges, Shi, & Pancratov, 2014), to regulation, and to the diagnostic tools that are available to enrich trials for patients whose pathogens are likely to be sensitive to the drug in hand. Thus a $2.2bn figure may be accurate, or may even be an under-estimate, for attempts to bring highly novel broad spectrum agents to market using 1995-2005 drug discovery technology and a standard regulatory path. However, it is probably too high for narrow spectrum agents that address serious infections using today's regulatory routes. Nor will it apply to new drugs that are more modest modifications of existing agents, nor to drugs that are designed to block bacterial resistance mechanisms to other

[1] We have followed Paul *et al*. (2010) and Sertkaya *et al*. (2014) and assumed an 11% real cost of capital for the entire R&D process. This is higher than drug companies' average cost of capital implied by the current nominal 9% to 9.5% cost of equity for major drug companies (Scannell, Hinds, & Evans, submitted). Drug companies generally have low debt, so their cost of equity is close to their average cost of capital. However, some authorities apply a much higher cost of capital to earlier stages of R&D (Cockburn & Lerner, 2006). If instead of 11%, we assumed a real cost of capital of 9% or 8%, the range of cost estimates would fall to $1.4bn & $1.9bn, and to $1.3bn & $1.76bn respectively.

[2] Expressed in real 2012 dollars. Note also that these costs are viewed from the point of launch. The out of pocket costs, not adjusting for the time cost of money, are $843m to $975m. These become $1.6bn to $2.2bn at the point of launch because the cost of capital is 11% per year, the R&D process takes 10 to 12 years, and much of the money is spent early in the process on failed projects.

antibiotics, nor perhaps to novel combinations of existing drugs. Thus neither our cost analysis nor anyone else's provides a definitive answer. Consensus among analysts, investors, and drug companies on the average success-weighted cost of an R&D project starting today is unachievable. Different players will make different assessments based on the specific details of the opportunities they see and they will invest, or not, accordingly.

The consensus among our interviewees is that the major brakes on drug innovation are now commercial:

- *"The major external uncertainty is how – and how much – the company will get paid* [if our] *drugs come to market. This is the question that makes the investors scratch their heads more than any other."*
- *"There is still no consensus among the* [big] *drug companies on whether they should be involved in antimicrobials or not. Some firms (e.g., Roche?) seem to be positioning themselves now for the day that the commercial route finally becomes clear. Other firms (e.g., AstraZeneca? Biota?)* [seem to be] *either getting out of antimicrobials and/or waiting until the commercialisation route is clear."*

Their view is that within the plausible ranges of R&D cost, the potential for future profit is generally too small to justify major investment. Most antibacterial drugs are sold into markets in which the drug industry has relatively low pricing power (unlike, for example, cancer drugs or orphan drugs, which can be very expensive), in which patients receive only short courses of treatment, and where novel drugs will be held back for use only as a last resort.

Following our interviews and analyses, we suggest several initiatives that may stimulate innovation. Given the short duration of this project and the interim nature of this report, our recommendations are tentative.

First, the complete convergence of FDA and EMA guidelines on developing antimicrobial drugs. Convergence might happen indication by indication, or else could start with drugs for patients with serious infections and few alternative treatment options. Perhaps the agencies could also provide joint scientific advice. Perhaps the mechanisms established via the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) programme could help to achieve this objective[3].

Second, public sector support for diagnostics as an economic complement to private sector drug R&D. Better pathogen identification could make drug R&D much less expensive. If one can double the proportion of patients recruited into a trial whose pathogens are sensitive to drug X, one can, in principle, reduce the size of the trial by a factor of four. However, for some indications this requires rapid microbiological diagnosis that is impractical today. In the long run, better diagnostics will also create new drug niches, particularly for narrow spectrum drugs. Furthermore, diagnostic R&D appears to be between 10 times and 100 times less expensive than drug R&D. However, diagnostics are less profitable than drugs, and adoption and reimbursement are problematic. This discourages private sector investment.

There may be a case, therefore, for substantial public sector support for the diagnostic technologies and microbiological services that are most likely to reduce the size and cost of individual drug trials and their aggregate failure rates? It would be helpful to create a number of centres in the UK and/or at a European level that develop and validate diagnostic technologies and microbiology workflows, and specialize in running clinical trials for antimicrobial drugs.

It also seems appropriate to suggest that public sector institutions such as the NHS, the Health Protection Agency, and European agencies, would be well placed to work as infection sample collectors and repositories, and could collaborate with private sector test developers. A lack of low

[3] While it is conceivable that guidelines on clinical trial design, conduct, endpoints, etc., can be unified we would expect that legislative and regulatory barriers would prevent unified regulatory scrutiny of the final dossier and would prevent unified approval. In other words, unified trial guidance will produce trials that still feed into two separate regulatory jurisdictions; one at the FDA and one at the EMA.

cost access to samples of infected and non-infected material is a major barrier to R&D for diagnostic tests.

Third, pre-competitive preclinical development. This is a speculative suggestion, much of which may be funded already. A great deal of unglamorous but important work in drug R&D relates to preclinical development, dealing with regulatory requirements for toxicology and safety. This also deals with some animal models of disease, with drug absorption, metabolism, excretion, potential drug-drug interactions, options for routes of administration and formulation, etc. Preclinical development is much easier for therapies for which there is long commercial and regulatory experience. However, for new therapeutic technologies such as bacteriophages or transcription factor traps, there are no existing standards and many uncertainties. The public sector and agencies such as the MRC and Wellcome Trust could, as part of translational research programmes, fund pre-competitive preclinical work of the kind that is a necessary prelude to regulatory scrutiny.

Fourth, linking future financial incentives with EMA and FDA regulation. Some of the properties that would be desirable in new antimicrobials may have little commercial value in conventional drug markets, for example mechanistic novelty or in-vitro evidence that microbial resistance evolves slowly or not at all. These properties have implications for the design of incentives and for regulation, presuming that the FDA and EMA would adjudicate on the mechanistic novelty and on the rate of evolution of microbial resistance before incentives payments were made.

The US already has a nascent incentive system for new antimicrobials which operates via the FDA. The FDA Safety and Innovation Act of 2012 provides for 5 years of 'orphan-like' market exclusivity to certain antimicrobial drug candidates[4] that are awarded Qualified Infectious Disease Product (QIDP) status. In 2 years, the FDA has awarded QIDP status to around 40 antibiotics in clinical development (Woodcock, 2014). The QIDP designation has no direct parallel in Europe. Thus the FDA is already sending commercial signals to the industry on where to direct antimicrobial investment in a way that the EMA is not.

We have two additional proposals related to AMR policy development.

1. More work should be done to understand why some companies are investing in drug development today. There are several recent reviews on the molecular, pharmacological, and antimicrobial properties of drugs in the R&D pipeline (e.g. de Souza Mendes & de Souza Antunes, 2013; Coates *et al.,* 2011). However, there do not appear to be any analyses of the likely investment or commercial case for the observed pattern of activity. It is important to characterise the clinical and late-preclinical pipeline of antimicrobial drugs from a commercial perspective, to understand why certain projects are attracting investment today, to assess the extent to which they address the AMR problem, and to understand what this means for the design of future incentives.
2. A secretariat could be established that collates and publishes on a timely basis data that are currently scattered but are likely to be of use to a wide range of people working on the AMR problem. As an example, it would be useful if those engaged in AMR policy work were able to obtain structured information on drug pipeline status. This could then be compared, over time, with changes in regulation, technology, or financial incentives. So, for example, have the GAIN provisions and QIDP status in the US been correlated with an increase in clinical trial activity? How many agents are reformulations or combinations of existing products? How many are new drug classes? What is the mix of broad spectrum vs. narrow spectrum agents? How does the pattern of pipeline activity and progress match the perceived medical need? Where are the venture capital firms putting their money? What kind of deals are the big drug companies doing? High level epidemiological data on patterns

[4] https://www.federalregister.gov/articles/2014/06/05/2014-13023/establishing-a-list-of-qualifying-pathogens-under-the-food-and-drug-administration-safety-and

of AMR might also be useful to a wide range of people (although it is clear such data are limited).

As a final observation, there was a sense of technological optimism with respect to the AMR problem in rich countries with good health systems, but something bordering on pessimism for poor countries with weak health systems. It seems reasonable to hope that the drug industry, with suitable incentives, will produce a range of novel drugs, but that many will have narrower patterns of antimicrobial activity than in the past. These will be useful for patients with access to microbiology services that can match drugs with target organisms. In contrast, poor patients in poor countries face a thornier set of problems: The AMR problem is often worse; narrow spectrum drugs are of little use without microbiology services; novel broad spectrum drugs are more difficult to discover and bring to market; and there are few novel broad spectrum drugs in the pipeline. Furthermore, any novel broad spectrum drugs that do emerge will be obvious targets for the most intense stewardship.

1. The Impact of EU and US Regulatory Systems on Drug Innovation[5]

Unreasonable clinical trial requirements used to be seen by the industry and others as a major barrier to antibacterial drug innovation (Coates, Halls, & Hu, 2011) (Rex, *et al*., 2013). For example, the Infectious Disease Society of America argued that certain FDA guidelines circa 2010 would have placed experimental purity over clinical pragmatism to such an extent that it would have been both impractical and unethical to recruit patients into the trials that the FDA required (e.g., Box 1, below (IDSA, 2011) (IDSA, 2014)).

Box 1. Example of a Shift from Impractical to Practical FDA guidance

Former (2010) FDA guidance for HABP/VABP (IDSA, 2011)
FDA requires *"the prior use of antibacterial drugs effective against bacteria that cause HABP/VABP should be avoided in a non-inferiority [NI] trial because such treatments will reduce the difference between treatment arms and potentially bias conclusions about treatment effects"*
Infectious Diseases Society of America (IDSA) complains that this makes studies for this indication infeasible since the requirement eliminates nearly all members of this hospitalised and typically seriously ill patient group.
FDA requires no active antibacterial therapy of any kind within 24 hours of enrolment.
IDSA complains that this would be unethical and impractical, as the priority should be to treat patients first and then enrol them into the trial. It would make it impossible to get informed consent, particularly from severely ill / incapacitated VABP patients
Current (2014) guidance for HABP/VABP (IDSA, 2014) (FDA, 2014)
FDA acknowledges that a *"a complete ban on all patients who have received prior antibacterial therapy could. . . have adverse consequences"* and allows the enrolment of patients who have received up to 24 hours of therapy in the previous 72 hours before enrolment.
IDSA states that *"We view this new draft as a considerable improvement and appreciate FDA's consideration of our earlier input. Specifically, we appreciate the allowance of 24 hours of prior antibacterial drug therapy before enrolment, the addition of a second primary endpoint based on survival and no diseases-related conditions, the clarification that a sponsor's choice of comparator drug should reflect the current standards of care as defined by IDSA and other authoritative scientific bodies, and the elimination of patient reported outcomes (PROs) as appropriate measurements"*

Other perceived problems were shifting targets, statistical hurdles that demanded very large trials, and paradoxical situations where no trial design appeared satisfactory, as noted by Coates, Halls, & Hu (2011):

- *"… the FDA in the USA, having agreed to the protocol for telavancin hospital acquired pneumonia (HABP)/ventilator-associated pneumonia (VABP) studies with clinical response as the primary endpoint, the agency requested additional data and analyses to support an evaluation of all-cause mortality as the primary efficacy endpoint. As a result, the company may have to conduct new studies. Initial applications for dalbavancin and iclaprim have also been rejected by the FDA."* [It is usually much harder to show a statistically robust survival effect than a statistically robust clinical response to a drug. This is for two reasons. First, deaths are rarer events than drug responses and statistical power depends on the number of events that the trial collects. Second, deaths depend on a range of factors, not just the drug. This reduces the signal to noise ratio, which also requires larger trials. Of course, death rate provides the most valid measure of whether the drug really worked.]

[5] In what follows, we illustrate some points with comments from our interviews. These comments are based on notes we made during interviews, and not on transcripts from recorded conversations. Therefore, it is possible that we have not always captured the detail or the intention of the interviewees.

- *"The requirement of the FDA for a smaller non-inferiority margin and to restrict nosocomial pneumonia trials to VAP is unlikely to result in new agents for multidrug resistant (MDR) gram-negative pneumonia. For a non-inferiority margin of 7%, the cost of a HABP/VABP study would total $600 million and take 8–10 years for enrolment, even using hundreds of centres. This would double if the trial were to be VAP only."* [The point about non-inferiority margins is technical but important. For non-intuitive statistical reasons, trials to show that one drug is *probably no worse than* another drug can be relatively large and expensive when compared with trials that are designed to prove that one drug is *probably better than* something else. Furthermore, it takes roughly twice as many patients to show that something is "probably no more than 7% worse than something else" (as required by the FDA in the example above) than to prove that something is "probably no more than 10% worse than something else" (as required by the FDA for HABP/VABP today).]
- *"Further regulatory difficulties are envisaged that will discourage the development of MDR-gram-negative antibiotics. With no standard therapy, non-inferiority studies are not possible; historical controls are considered irrelevant and superiority studies are not ethical as patients cannot be randomized to ineffective therapy for infections with high mortality."* [The point here is that the likely trial requirements appear to be mutually exclusive.]

2 More Reasonable Regulatory Guidelines

The FDA and the EMA now guide the industry towards trial designs that appear reasonably deliverable. For example, there have been changes in the details of statistical requirements (e.g., wider non-inferiority margins in some cases) which mean smaller trials; there have been changes in recruitment criteria (e.g., patients can have received prior antibiotics in some cases) which make enrolment easier. There has also been particular movement for new drugs that might help patients who suffer from infections for which there are few treatment options. Consequently, none of our interviewees in the drug or biotechnology industry identified regulation as the primary problem today:

- *"In broad terms, the regulatory environment has improved over the last 5 years. Regulation no longer appears to be a major barrier. However, the devil is in the detail…."*
- *"The FDA and EMA have put in a lot of work.* [Regulation] *is not regarded as a major bottleneck.* [We have] *nothing yet in the clinic, but we could probably access the patients, testing, etc. to run the trials* [we need] *to today, if* [we] *had to.*
- *"… the regulatory environment has moved and is moving in the right direction, mainly as a result of the GAIN* [provisions] *in the US. The FDA and EMA have also converged to an extent."*

The consensus among the interviewees was that the primary barrier today is a lack of clear financial incentives for R&D investment.

The regulatory improvements are recent. In 2013 and 2014, the FDA issued a range of guidelines and draft guidelines for the development of drugs for several important classes of infection: Community-acquired bacterial pneumonia (FDA, 2014); hospital-acquired and ventilator-associated bacterial pneumonia (FDA, 2014); uncomplicated gonorrhoea (FDA, 2014); acute bacterial skin and skin structure infections (FDA, 2013); and for more general therapies for patients with unmet need with respect to serious bacterial infections in general (FDA, 2013) (FDA, 2014). These guidelines followed from the GAIN[6] provisions of the FDA Safety and Innovation Act of 2012. The new guidelines provide detailed practical advice on the design and conduct of preclinical studies and clinical trials that are likely to be required to obtain regulatory approval. The EMA has also issued new guidance (European Medicines Agency, 2011) (European Medicines

[6] GAIN means "Generating New Antibiotics Now". A legislative attempt called the GAIN Act was subsumed within the Food and Drug Administration Innovation and Safety Act of 2012. For an overview, see: The Pew Charitable Trust (2013); Woodcock (2014).

Agency, 2013) that is similar in both scope and direction. Both the FDA and EMA propose to allow considerable flexibility in the development paths and labelling for drugs that may treat severely ill patients with few good treatment options.

The kind of flexibility that the FDA and EMA propose is illustrated in the table below (Rex, *et al*., 2013). **We are not suggesting that this framework has been adopted in a formal sense by the regulatory agencies.** However, the classification in the table is congruent with US regulations (Rex, *et al*., 2013) and can be mapped onto the current guidance from both the FDA and EMA. It also provides a clear and concise way to describe the range of development paths that now exist.

The table shows four "tiers" of approval. Tier A corresponds to the conventional standards under which most antibiotics have been approved in recent years (but reflecting the more reasonable standards with respect to recruitment, statistical requirements, etc., that we discussed above) and under which some drugs will continue to be approved. For Tier A, the clinical trial programme is structured to support approval for use of *"drug X"* in *"infection Y"* (e.g., community acquired pneumonia; skin and skin structure infection; etc.).

The sponsor must run specific clinical trials that show that drug X has a positive risk-benefit profile in each infection for which the drug can be marketed. Thus, if drug X were to be used in community-acquired and hospital-acquired pneumonias, then two sets of trials would be required; one set for pneumonia in the community and the other set for pneumonia in hospitals.

Tier C represents an important regulatory change. This is a pathogen-specific approval (e.g., MRSA; highly resistant gram positive anaerobes; etc.) based on more tentative evidence from infections across a range on anatomical locations. Here, the drug sponsor can pool within a single clinical trial patients with different loci of infection (e.g., pneumonias, sepsis, wound infections) but who share a common pathogen. Thus the clinical trials may show a positive risk-benefit profile against the pathogen without proving definitively that the drug has a positive risk-benefit profile for each specific kind of infection caused by the pathogen[7]. This has an important enabling effect on clinical trials. Many pathogens, particularly those that are highly resistant to existing antibiotics, are relatively rare. This makes clinical trial recruitment extremely difficult if all ~1000 patients have to have hospital-acquired pneumonia, or of all ~1000 patients have to have acute skin and skin structure infections (Rex, *et al*., 2013).

Some of the practical differences between a Tier C clinical trial programme and a more conventional Tier A programme are illustrated in Table 2 (below). We consider the cost implications later.

Tier D, approval without any human efficacy trials, is also a something of a regulatory innovation. This can occur when human efficacy trials would be unethical or otherwise unfeasible. There is already at least one example of Tier D-type approval. In 2012, the FDA approved raxibacumab, a monoclonal antibody for the treatment of inhalation anthrax[8]. We consider the potential cost of a Tier D programme below.

Tier B would apply to a drug that had robust efficacy data for pneumonias, for example, but more tentative efficacy data in a range of other infections. It is something of a hybrid between Tiers A and C.

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[7] This is a more permissive approach by the regulator. We understand that, for example, there have been cases where drugs have had positive trials in one indication (e.g., hospital-acquired bacterial pneumonia) but negative trials in an apparently similar indication (e.g., ventilator-associated bacterial pneumonia).

[8]The FDA had previously granted the drug fast track designation, priority review, and orphan drug status. The drug's efficacy data came from one primate study, and three rabbit studies. There were no human efficacy studies. There were, however, studies in around 330 healthy volunteers, looking at tolerability and at pharmacokinetics (FDA, 2012). Raxibacumab is destined for a US stockpile of agents to combat potential bioterrorism. Its production was commissioned by the Biomedical Advanced Research and Development Authority (BARDA). Raxibacumab was developed by Human Genome Sciences (since acquired by GSK) and the contract has been worth around $350m.

Table 1. Tiered Regulatory Framework for Antibacterial Agents, (from Rex, *et al*., 2013)

Typical efficacy data requirements	How the drug would be marketed (Note – our **emphasis** below)
Tier A. Two standard Phase 3 trials of drug X in infection Y. Additional indications for drug X can be added after single Phase 3 studies	Drug X is indicated for treatment of infection Y when proven or strongly suspected to be caused by drug X-susceptible strains of [list of pathogens]
Tier B. One standard Phase 3 trial of drug X in infection Y, plus small prospective studies and descriptive data focused on the tier C pathogen(s) in a range of standard infections	Drug X is indicated for treatment of infection Y and [list of studied infections from tier C database] when proven or strongly suspected to be caused by drug X-susceptible strains of [list of pathogens]. **Because data for drug X in these infections are limited, drug X should be used only if other alternatives are known or suspected to be less suitable**
Tier C. Small prospective studies for drug X and descriptive data focused on the tier C pathogen(s) in a range of standard infections	Drug X is indicated for treatment of [list of studied infections from tier C database] when proven or strongly suspected to be caused by drug X-susceptible strains of [list of pathogens]. **Because data for drug X in these infections are limited, drug X should be used only if other alternatives are known or suspected to be less suitable**
Tier D. Animal studies	Drug X is indicated for the emergency treatment of infection Y caused by susceptible strains of organism Z. **Drug X should not be used for infection Y unless other options are unavailable**

Antibacterial agents can also qualify for a range of programmes that have been developed over the years at the FDA and EMA to expedite or otherwise encourage the development of drugs that address important medical needs. These include FDA[9] programmes such as Breakthrough Therapy designation, Accelerated Approval, Priority Review, Fast Track Designation, or Orphan Drug designation (FDA, 2014) and new EMA initiatives such as Adaptive Licensing[10] (European Medicines Agency, 2014).

Therefore, for conventional small molecule drugs and biologics (e.g., monoclonal antibodies), few industry participants now see the regulatory path as unduly onerous. However, few if any drugs have yet negotiated the entire FDA or EMA processes under the new guidelines; only raxibacumab perhaps. There is therefore optimism about, rather than practical experience of, the new regulatory approaches.

[9]Some mechanisms expedite regulatory scrutiny whose parameters are otherwise unchanged (e.g., Priority Review). Some may reduce the pre-launch clinical trial requirements (e.g., Accelerated Approval may provide for initial approval on the basis of surrogate endpoints, while longer trials are conducted to confirm that there are real benefits. Approval can be withdrawn if real benefits fail to materialize). Others (e.g., Fast Track and Breakthrough Therapy designation) increase the degree of collaboration between the FDA and the sponsoring drug company with respect to the design and conduct of the clinical programme.

[10]Adaptive Licensing is being piloted by the EMA. It is a more gradual form of market introduction that may offer expedited marketing to high-need patient populations, and then broader use as evidence on the balance between risk and benefit accumulates (Baird, *et al*., 2013) (Eichler, *et al*., 2012) (Eichler, *et al*., 2014) (Woodcock, 2012).

Table 2. Illustration of Possible Differences between Tier A and Tier C Development

Trial process	Tier A illustration: Conventional HABP/VABP based on (FDA, 2014)	Tier C example: Narrow Spectrum Drug for Pseudomonas aeruginosa based on (Rex, *et al*., 2013)
Duration of clin. phases	70-80 months (Sertkaya, *et al*., 2014)	40-50 months
Clinical trial process	Sequential Phase I, II, and III trials Phase III: Perhaps a single trial but only if the agent has shown activity in another infectious disease indication in an independent trial. Trial should be randomized and double-blind. The expectation is that it will be a non-inferiority trial against the current standard of care. Ideally the investigational drug would be broad spectrum. However, if narrow spectrum, then concomitant antibacterial treatment will be required and this may complicate the interpretation of the results. Phase II[11]: two single-arm open-label trials one in HABP and one in VABP. Primary outcome measure is clinical response rate. Secondary outcome measure is clinical response rate at late follow-up assessment. Phase I: single arm trial or trials in HABP or VABP. Primary endpoint is these trials safety and tolerability. Secondary outcome measure is PD effect. Phase I will also include low dose PK studies in healthy volunteers.	Three trials in parallel: Trial 1. Prospective randomized open-label study of drug X plus ertapenen[12] versus best available therapy in patients with newly acquired hospital-acquired or ventilator-associated pneumonia, complicated intra-abdominal infection, or complicated urinary tract infection. Recruitment enriched for conventional-drug-resistant Pseudomonas infection based on rapid diagnostics or local bacterial flora plus clinical presentation. Concomitant anti-Pseudomonas treatment either prohibited or the same in both groups. Efficacy analysis at end of trial to focus on patients who are subsequently found to have had culture-proven P. aeruginosa infection. Trial 2. Open label non-comparative study of drug X for patients who cannot be enrolled in (1) but who have few treatment options. This might include patients with infections at other sites, or a pathogen so resistant that best available therapy cannot be easily defined. Outcomes hard to interpret – although see trial (3) – but experience adds to safety database Trial 3. Observational study (possibly retrospective) of outcomes for patients who resemble those in studies (1) and (2) and who had confirmed infections with P. aeruginosa, but who received standard care.
Number patients enrolled in trials	Total = 1300 to 1700 Phase III: 1000 to 1200 (i.e., 500to 600 per Phase III trial) [13] Phase II: 240 to 400 (i.e., 2 x 150 to 200) Phase I: 50 to 100	Total = 650 to 1150[14] ~400 to 800 for Trial 1. ~200 to 300 for Trial 2. ~0 for Trial 3 which is a retrospective study based on historical records Phase I: 50 to 100

[11] For an estimate of what is required see www.clinicaltrials.gov, and search for Phase I and Phase II trials in HABP and VABP

[12] This is a drug that is effective against most pathogens that are not Pseudomonas aeruginosa

[13] FDA suggests around 268 patients per trial arm in its 2014 guidance on HABP/VABP

[14] Rex *et al*, (2013) suggest that Trial 1 recruits 200 patients with the sensitive pathogen per treatment arm. Thus, if there was a perfect rapid diagnostic and the trial was comparing novel drug X with a single dosing regimen vs, best available standard of care, the total recruitment would be around 400 patients. However, if diagnosis was difficult and the trial recruited also pathogens not sensitive to drug X, the recruitment would be higher in order to achieve 200 patients per arm who were subsequently confirmed to carry the drug X sensitive pathogen.

3. Estimates of the Costs of Antimicrobial R&D – Implications of New Regulatory Environment

We have tried to estimate the R&D cost implications of Tier A, Tier C, and Tier D regulatory paths for antimicrobial agents. In summary, estimates of average R&D costs per approved drug following the Tier A path, including the cost of failed projects and the time cost of money[15], are in the order of $1.6bn to $2.2bn. If one accepts these cost estimates for Tier A, it is possible that costs per Tier C approval for a narrow spectrum agent would be nearly two thirds less ($752m), while a Tier D approval would cost only a tenth as much.

However, all of these analyses are **extremely** sensitive to failure rate assumptions. Failure rates are, in turn, extremely sensitive to the quality of preclinical drug candidates, to their novelty (Porges, Shi, & Pancratov, 2014), to regulation, and to the diagnostics that are available to enrich clinical trials for patients whose pathogens are likely to be sensitive to the drug in hand. So, for example, if we consider the $2.2bn Tier A estimate, the direct spending on the single drug that finally reached the market was only $232m, or just 11% of the average R&D spend per new approved drug.

Our estimates draw heavily on those published recently by Serktaya *et al* (2014). The figures were produced for report commissioned by the US Department of Health and Human Services to support policy development around what became the GAIN[16] provisions of the FDA Safety and Innovation Act of 2012. We have talked with the lead author of the report, and we understand that the cost estimates were subject to considerable scrutiny and debate, with back and forth between government agencies and industry experts[17].

The phase-specific costs estimates struck us as reasonable (see rows "OOP cost per successful candidate $m", in Table 3, below), particularly in light with some other pieces of fragmentary evidence we have seen on antibacterial phase III costs (Rex, *et al*., 2013). However, the estimates of the probability of success during preclinical development and Phase I trials initially struck us as low. This means the overall cost estimates appear high at first sight. However, there are, in retrospect, good explanations for low success rate estimates, and we return to this point later.

There are some other features of the analyses of Sertkaya *et al*. (2014) that struck us as unusual. For example, preclinical studies can be shared across a range of indications. It may even be possible to share Phase I trial costs across a range of Phase II and Phase III programmes. Therefore, even if the probability that a preclinical programme successfully leads to a HABP/VABP clinical trial programme is only 35%, there is a chance that the same preclinical programme could lead to success in CABP, or in a range of other infections. Therefore, it seems that there is an element of double counting in their preclinical and Phase I cost estimates. The revenue estimates are also unusual. On one hand, the authors make assumptions about market share gain that appear optimistic for any new antibiotics launched into a world of "stewardship" and highly effective generics. On the other hand, they consider only US sales and profits. Most drugs are sold globally, and US profits average around 50% of the total (but this varies by drug and therapy area).

However, if we accept that the R&D cost and probability estimates are reasonable, we can start to understand the R&D cost implications of the novel approval pathways.

Sertkaya, *et al*. (2014) analysed the costs and economic benefits of R&D investment in a range of therapy areas to both private sector sponsors such as drug companies, and to society as a whole.

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[15] We have assumed an 11% cost of capital for the entire R&D process, which is in line with some recent studies (Paul, *et al*., 2010) but lower than the current ~9.5% cost of equity of major drug companies (Scannell, Hinds, & Evans, submitted). Note that drug companies generally have low debt, so the cost of equity is close to their average cost of capital. Some authorities would, however, apply a much higher cost of capital to earlier stages of R&D (Cockburn & Lerner, 2006).

[16] GAIN means "Generating New Antibiotics Now". A legislative attempt called the GAIN Act was subsumed within the Food and Drug Administration Innovation and Safety Act of 2012. For an overview, see: (The Pew Charitable Trust, 2013) or (Woodcock, 2014).

From a commercial investor's perspective, the least attractive therapy area was HABP/VABP (hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia). HABP/VABPs are life threatening conditions, and are common causes of death among seriously ill hospitalized patients. The most attractive therapy area, in their analyses, was CABP (community-acquired bacterial pneumonia). Several other conditions (e.g., acute middle ear infections, complicated urinary tract infections, etc.) had intermediate levels of attractiveness for private sector investors. Table 3 (below) shows the extreme scenarios, and illustrates the expected R&D investment required per molecule approved for HABP/VABP and for CABP.

The R&D process for HABP/VABP takes ~12 years from the initiation of preclinical studies to drug launch (Table 3, top panel). The direct out of pocket (OOP) cost for a molecule that successfully negotiates the entire process is around $150m. However, if we add the cost of failures (e.g., the ~30 preclinical programmes that were required to yield the one successful molecule) and the cost of capital (e.g., the preclinical programmes which involved investment between 12 and 9.5 years before drug launch, at a cost of capital – analogous to interest rate – of 11% a year[18]), then the total capitalized cost of R&D at the time of launch is $2,190m per drug. Furthermore, the HABP/VABP market is relatively small. Thus the returns on commercial investment are poor.

Note that the "capitalized" cost estimate we present ($2,190m) is viewed from the point of launch. The out of pocket cost, not adjusting for the time cost of money, is $975m (Table 3, "OOP cost including R&D failures"). This becomes $2,190m at the point of launch because the cost of capital is 11% per year, the R&D process takes 12 years, and most of the money is spent early in the process on failed projects. To use an alternative terminology, the net present value (NPV) of the $975m when discounted to the point of launch at 11% a year is $2,190m. If we chose to discount the $975m to another point in time, the NPV would be different. The same $975m when viewed from the start of the process, 12 years before launch, would have an NPV of only $626m. Of course, an identical time-based scaling effect would apply to any profits or incentives that might induce the R&D investment. The NPV of the profits or incentives – long distant in the future – would be smaller too, when viewed from the start of the R&D process.

The R&D process for CABP is a little less expensive. It takes ~9.5 years from the initiation of preclinical studies to drug launch (Table 3, bottom panel). This is because clinical trials take less time. The direct out of pocket cost for a molecule that successfully negotiates the process is around $81m, mainly as a result of lower Phase III trial costs. If we add the cost of failures and the cost of capital, then the total capitalized cost of R&D by the time of launch is $1,560m. The CABP market is larger. Thus the returns on commercial investment are at least higher than the cost of capital.

[18] We have assumed an 11% cost of capital for the entire R&D process, which is in line with some recent studies (Paul, *et al*., 2010) but lower than the current ~9.5% cost of equity of major drug companies (Scannell, Hinds, & Evans, submitted). Note that drug companies generally have low debt, so the cost of equity is close to their average cost of capital. Some authorities would, however, apply a much higher cost of capital to earlier stages of R&D (Cockburn & Lerner, 2006).

Table 3. R&D Investment Scenarios for New Antimicrobial Drugs (Costs in 2012 Dollars)

	Preclin	PI	PII	PIII	NDA/BLA sub.	Total R&D
Tier A / Conventional Approval Scenarios (Sertkaya, et al., 2014)						
HABP / VABP with conventional regulatory route						
Phase duration (years)	5.5	0.9	1.5	3.3	0.8	**12**
Time to commercial launch (years)	12.0	6.5	5.6	4.1	0.8	
Phase midpoint vs. launch (years)	9.3	6.1	4.9	2.5	0.4	
Real cost of capital	11%	11%	11%	11%	11%	
Time cost of money vs. launch	2.6	1.9	1.7	1.3	1.0	
OOP cost per successful candidate $m	21.1	9.7	15.6	101.4	2.0	**150**
Capitalized cost per successful candidate $m	55.4	18.1	25.9	130.9	2.0	**232**
Phase success probability	35%	33%	50%	67%	85%	
Candidates required per successful launch	30.2	10.6	3.5	1.8	1.2	
OOP cost including R&D failures $m	637.4	102.7	54.9	178.0	2.3	**975**
Capitalized cost including R&D failures $m	**1673.7**	**193.1**	**91.1**	**229.9**	**2.4**	**2190**
Memo item: Total market size ($m)						*3470*
Memo item: private ENPV of project ($m)						*-4*
CABP with conventional regulatory route						
Phase duration (years)	5.5	0.9	1.3	1	0.8	**9.5**
Time to commercial launch (years)	9.5	4	3.1	1.8	0.8	
Phase midpoint vs. launch (years)	6.8	3.6	2.5	1.3	0.4	
Real cost of capital	11%	11%	11%	11%	11%	
Time cost of money vs. launch	2.0	1.4	1.3	1.1	1.0	
OOP cost per successful candidate $m	21.1	9.7	9.1	38.8	2.0	**81**
Capitalized cost per successful candidate $m	42.6	14.0	11.8	44.5	2.0	**115**
Phase success probability	35%	33%	50%	67%	85%	
Candidates required per successful launch	30.2	10.6	3.5	1.8	1.2	
OOP cost including R&D failures $m	637.4	102.7	32.1	68.2	2.3	**843**
Capitalized cost including R&D failures $m	**1289.3**	**148.8**	**41.4**	**78.1**	**2.4**	**1560**
Memo item: Total market size ($m)						*7940*
Memo item: private ENPV of project ($m)						*37*
Tier C Approval Scenario						
Narrow spectrum agent (e.g., activity limited to Psuedomonas aeruginosa)						
Phase duration (years)	5.5	0.9	3.3	3.3	0.8	**10.5**
Time to commercial launch (years)	10.5	5.0	4.1	4.1	0.8	
Phase midpoint vs. launch (years)	7.8	4.6	2.6	2.6	0.4	
Real cost of capital	11%	11%	11%	11%	11%	
Time cost of money vs. launch	2.2	1.6	1.3	1.3	1.0	
OOP cost per successful candidate $m	21.1	9.7	10.4	67.6	2.0	**111**
Capitalized cost per successful candidate $m	47.3	15.5	13.6	88.2	2.0	**167**
Phase success probability	69%	54%	50%	67%	85%	
Candidates required per successful launch	9.4	6.5	3.5	1.8	1.2	
OOP cost including R&D failures $m	198.7	62.8	36.6	118.7	2.3	**419**
Capitalized cost including R&D failures $m	**446.2**	**100.9**	**47.8**	**154.9**	**2.4**	**752**
Tier D Approval Scenario						
Drug that cannot be prospectively tested in man						
Phase duration (years)	5.5	0.9			0.8	**7.2**
Time to commercial launch (years)	6.3	1.7			0.8	
Phase midpoint vs. launch (years)	3.6	1.25			0.4	
Real cost of capital	11%	11%			11%	
Time cost of money vs. launch	1.4	1.1			1.0	
OOP cost per successful candidate $m	25.3	9.7			2.0	**37**
Capitalized cost per successful candidate $m	36.6	11.0			2.0	**50**
Phase success probability	25%	100%	100%	100%	85%	
Candidates required per successful launch	4.7	1.2	1.2	1.2	1.2	
OOP cost including R&D failures $m	119.1	11.4	0.0	0.0	2.3	**133**
Capitalized cost including R&D failures $m	**172.5**	**12.9**	**0.0**	**0.0**	**2.4**	**188**

Sources: (Sertkaya, et al., 2014), (Rex, et al., 2013), and project team analysis and estimates

3.1 R&D Costs Sensitive to Failure Rates

For readers who do not have a background in drug and biotechnology investment, it might be surprising to note that the main difference in capitalized R&D cost between the two scenarios does not come from the different unit costs for Phase III trials ($101m for HABP/VABP vs. $38.8m in CABP). Rather, it comes from the time cost of money. The CABP trials take less time than the VABP trials. Thus, out of pocket Preclinical costs of $637m (identical for both programmes) have a capitalized cost of $1,673m in the case of HABP/VABP but only $1,289m in the case of CABP.

We would also point out that most of the out of pocket (OOP) cost, in both scenarios, follows from transition probability assumptions that require 29 failed preclinical programmes for each drug that reaches the market (see the rows labelled "Candidates required per successful launch" in Table 3)

Figure 1 (below) provides a quantitative overview of these points. The graph represents the HABP/VABP scenario in Table 3 (above), but varies the joint preclinical and Phase I transition probability (i.e., the probability that a drug passes both preclinical and Phase I) and also the cost of capital (WACC is the weighted average cost of capital). The figure shows that the expected value of R&D investment required per drug approved varies by a factor of 4 as we flex the probability of success of preclinical and Phase I trials. Cost of capital assumptions, which vary the time cost of money, are also important but less so, at least within the range we have examined (9% to 13%).

Figure 1. R&D Cost Estimates Very Sensitive to Transition Probability Assumptions

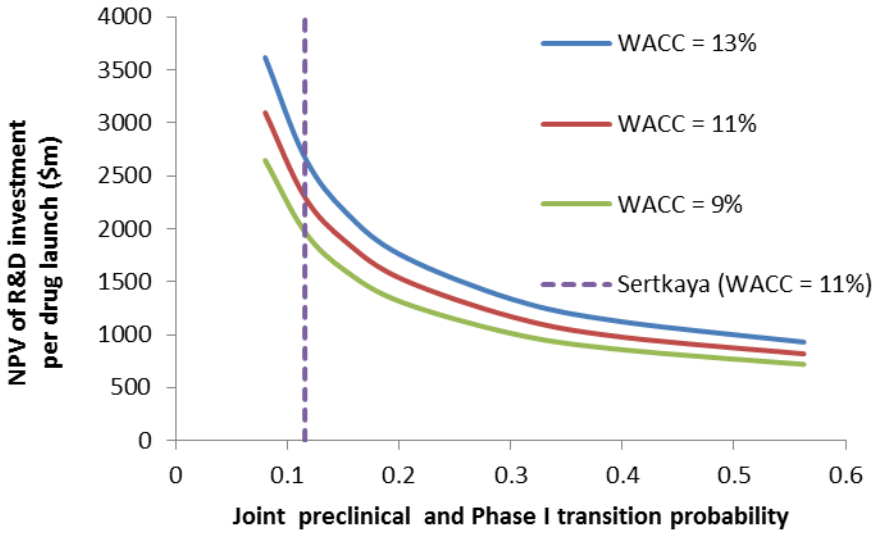

Figure 1 Legend. *Net present value (NPV) of total R&D investemnt per approved drug, when discounted to the time of approval. Dollar values are expressed in millions of real 2008 dollars. The vertical dashed line shows the joint preclinical and Phase I transition probability assumed by Sertkaya et al. (2014). We flex the joint probability of preclinical and Phase I transition (horizontal axis) while keeping other parameters the same as the HABP/VABP scenario as in Table 3. We also run the analysis at 3 different costs of capital (WACC); 9%, 11%, or 13%.*

3.2 Costs of R&D Given Recent Regulatory Changes

While we might quibble with some of the assumptions of Sertkaya, *et al.* (2014), our analyses of their figures (top 2 panels in Table 3) make it clear where the main costs of R&D often to lie. They lie in high attrition rates (i.e. the cost of failure) and in the time cost of money. They are not generally dominated by the direct expenses of Phase III trials.

Historically, it has been hard to bring narrow-spectrum agents to market for both commercial (Payne, *et al*., 2007) (Silver, 2011) and regulatory reasons (Rex, *et al*., 2013). Under the previous regulatory guidelines, the logistics of narrow-spectrum trials appeared difficult: *"*[Conventional regulatory approaches require] *availability of a sufficient number of study participants with one target disease, which creates a paradox for drugs that target rare pathogens or newly emerging, but still less common, forms of resistance. In particular for the latter, if investigators wait until resistance is sufficiently widespread to implement a tier A programme, the consequence is that the epidemic arrives before the treatment."* (Rex, *et al*., 2013). It has also been difficult to discover new broad spectrum agents. Major investment in genomic and high throughput screening-based antimicrobial drug discovery by several of companies in the 1990s and early 2000s led to no new broad-spectrum agents, and a series of narrow spectrum candidates that were abandoned for commercial and/or regulatory reasons before clinical trials started (Payne, *et al*., 2007) (Silver, 2011) (Figure 2). Some have even suggested that we have exhausted the plausible set of broad-spectrum targets (Bumann, 2008).

Figure 2. Failure of Genomics and HTS to Deliver New Antibiotics: GSK 1995-2002 (Payne *et al*., 2007)

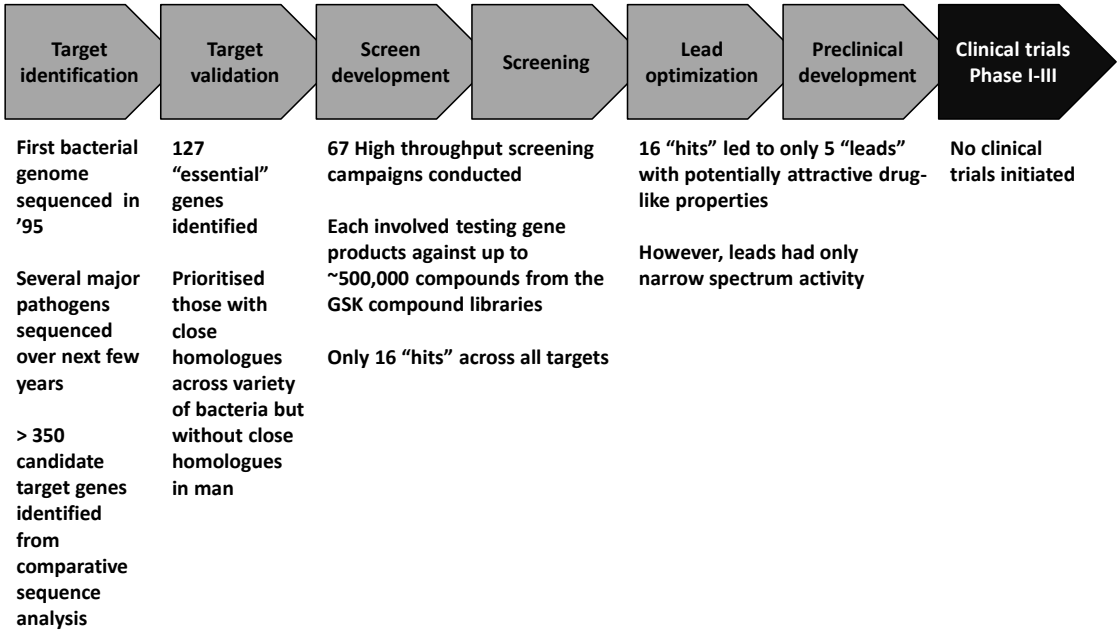

Figure 2 Legend. *According to Payne et al. (2007): "GSK was not the only company that had difficulty finding antibacterial leads from HTS. A review of the literature between 1996 and 2004 shows that >125 antibacterial screens on 60 different antibacterial targets were run by 34 different companies. That none of these screens resulted in credible development candidates is clear from the lack of novel mechanism molecules in the industrial antibacterial pipeline." See also Silver (2011).*

The combination of the difficulty of discovering new broad-spectrum classes and the historic regulatory and commercial barriers faced by narrow spectrum agents may explain the industry's poor performance in recent years. This also justifies to a large extent the low preclinical to Phase I, and Phase I to Phase II transition probabilities that were chosen by Sertkaya, *et al*. (2014). Their Phase transition probabilities look reasonable when set against the failure of the drug industry to

discover novel broad spectrum classes worth putting into clinical trials between the mid-1990s and the mid-2000s.

If we consider a Tier C regulatory process (Table 1, Table 2, Table 3), it becomes substantially cheaper to run trials for narrow spectrum agents. These are the agents that current drug discovery technologies seem to be more capable of finding. The investors' cost perspective is shown in Table 2 (see the panel labelled "Tier C Approval Scenario" in Table 3). Here we have reduced overall clinical trial costs in proportion to the lower number of patients (Sertkaya, *et al*., 2014). We have shortened the clinical trial times to reflect some trials run in parallel, rather than sequential Phase II and III trials. We have also assumed that the preclinical and Phase I attrition rates shift to current estimates of the industry average (Paul, *et al*., 2010). This can be justified for several reasons. First, in the pre-genomic 1970s and 1980s, clinical trial success rates for antimicrobial agents were relatively high (DiMasi, 1995). Second, results in animals *are* relatively predictive of activity in man in a variety of infection models, when compared with many other therapy areas. Third, the preclinical investment can be spread across all infection types in one set of Phase II and Phase III trials. In other words, the drug does not have to work in all infection types, provided that it works in enough to yield a result that is positive in aggregate. Fourth, there seem to be plausible scientific reasons to expect narrow spectrum drug candidates to be less toxic to humans than broad spectrum drugs.

Under these assumptions, the capitalized cost per molecule approved under this Tier C scenario is a little over a ***third*** of the capitalized cost per molecule using a conventional Tier A process for HABP/CABP, with a capitalized cost of $752m vs. $2,190m (Table 3).

Turning next to a Tier D approval (lower panel, Table 3), there are no clinical trial costs. However, we have assumed more stringent and expensive preclinical testing (e.g., a greater investment in PK/PD studies and in animal toxicology). We have also assumed that the preclinical failure rate is very high (75%). This reflects particularly stringent requirements for preclinical efficacy and toxicology signals in the absence of clinical efficacy trials in man (although we do assume Phase I trials for PK/PD, etc.). None the less, the capitalized cost is less than one a ***tenth*** of the cost of the conventional HABP/VABP pathway: $188m vs. $2,190m.

In summary then, our analyses support impressions in the industry that options exist to bring antimicrobial agents to market at more reasonable cost. However, neither our cost analysis nor anyone else's provides a definitive answer. Consensus among analysts, investors, and drug companies on the average success-weighted cost of an R&D project starting today is unachievable. Different players will make different assessments and they will invest, or not, accordingly.

4. The Impact of EU and US Regulatory Systems on Diagnostic Innovation

Readers may want to consult Appendix 1 for a brief guide to microbiology testing before reading this part of the report. In this section we focus on in vitro diagnostics (IVDs) that are sold by diagnostics companies to microbiology laboratories or other health care users to use in situations where wrong results might put patients at risk. This would correspond to most PCR-based diagnostics and many point of care tests. We focus less on the generally less onerous regulation of conventional microbiology supplies such as swabs, culture-media, or reagents; or the regulation of tests that are developed for use within individual microbiology laboratories but which are not sold to other laboratories as commercial test kits[19]. For a concise and digestible review of the FDA's approach readers may want to consult Mansfield *et al*. (Mansfield, *et al*., 2005). There is also accessible material on the contrast between the US and Europe from NIH & EU Directorate for Health Research (2011).

Recall that among our biopharmaceutical interviewees, there was the view that drug regulation had converged between the EMA and the FDA, that regulation had become more reasonable, and

[19] Although many of the comments we make later on the practical challenges of test validation would apply here too.

that the main barriers are now commercial. For diagnostics, the story was more complicated. The European and American regulatory environments have major differences in both philosophy and detail. Among the in vitro diagnostic (IVD) industry interviewees, the view was that the EU approach is more innovation friendly. In contrast to the branded pharmaceutical market which is global, regulatory differences are such that some IVDs are sometimes brought to market and sold successfully in the EU, without seeking or gaining FDA approval in the US[20]. Over the next 5 years, however, EU regulation is likely to take a step upward in terms of stringency. It will increase cost. This was a concern for industry interviewees. However, our rough analyses suggest that the cost increases will be small as a proportion of the industry's R&D expenses.

As with drugs, however, IVD regulation was not regarded as the ***primary*** barrier to innovation, even among relatively small companies with nascent technology. According to our interviewees:

- *"The main barriers for the diagnostics companies are not regulatory. They relate to reimbursement, access, and adoption.* [The IVD companies] *know how to get through the FDA and EU requirements. It might cost* [them] *$2m or $3m to do the studies for the* [FDA] *PMA process for a panel of PCR-based molecular diagnostics… However, they then hit the adoption barrier ….. We see lots of very good tests that never get adopted in the market."*
- *"The science is harder than the regulation. With point of care diagnostics, for example, there is a real question about what you should measure."*
- *"The main R&D barrier is getting* [hold of clinical] *samples to validate the tests."*
- *"The short answer is that EU regulatory issues are not the major problem at present when it comes to diagnostics use or diagnostics innovation. The overwhelming barrier is commercialization and adoption; in getting things bought by health systems."*

Part of the reason here is that it is easier to predict on the basis of preclinical data whether or not an IVD is likely to have adequate clinical performance. IVDs do not suffer the same proportionate cost of regulatory failure as do drugs. Furthermore, the R&D process is substantially shorter, which means lower capitalized costs when taking account of the time cost of money.

Some recent estimates of the costs of developing and commercialising molecular diagnostic tests for the US market are shown below (Table 4). The costs here are one or two orders of magnitude lower than the cost of drug R&D. Note also that clinical utility trials are only 5% to 10% of the out of pocket costs. Many of the other activities in Table 4 would be required if a company hoped to sell a test to sophisticated user, even in the absence of any formal regulation.

[20] This is very rare in the case of drugs, and when it occurs, it usually reflects some kind of failure in the clinical trial programme, and/or a difference in risk tolerance between the FDA and EMA.

Table 4. Estimates of Costs to Develop and Commercialize Molecular Diagnostics for the US Market

All figures in $m	Low range	High Range
Development and manufacturing costs		
Technology acquisition and protection	0.6	4.0
QSR and FDA compliance	1.0	3.0
GMP manufacturing	0.5	5.0
Platform development	3.0	20.0
R&D (based on 1-3 years of FTEs)	3.0	8.0
Clinical utility trials (retrospective or prospective)	1.0	10.0
Administration and financing	3.0	5.0
Subtotal costs to launch of IVD	*12.1*	*55.0*
Sales and marketing costs (assume US only)		
Direct sales team	3.0	12.0
Health technology assessment and payer negotiations	1.0	4.0
Clinical education	2.0	25.0
Marketing	2.0	10.0
Subtotal costs to drive adoptions	*8.0*	*51.0*
Total costs to commercialize	***20.1***	***106.0***

Source: Diaceutics (http://www.diaceutics.co.uk/insight/publications)

4.1 Europe vs. the US: Regulatory Divergence Today

Some of the major differences between the current EU approach and the FDA's regulation of IVDs are illustrated in the comments below. We focus here on regulatory philosophy on both sides of the Atlantic, and on its implications for the development and introduction of new IVDs.

Our interviewees highlighted the following differences between the US and Europe:

- *"The EU regulatory procedure is relatively easy and inexpensive. Much is based around self-certification. The main point is that the diagnostic test has to do what it says it does….. The novel-product FDA* [PMA] *pathway* [in the US] *is much more expensive and may require clinical trials."*
- *"There are big differences between EU and US regulation for IVDs….. The US process classes products on the basis of risk, and then assigns them to one of two routes. The lower risk products are generally approved via the 510(k) route under which they have to show substantial equivalence to an existing product[21]. Under the PMA route, they have to show both technical and clinical validity. Pretty much all companion diagnostics* [which are important in oncology but less so in microbiology] *fall within the PMA pathway…. The* [current] *EU*

[21] Class I and Class II devices have a relatively abbreviated approval path. They can be approved via the so-called "510(k)" route. Under the 510(k) route, the manufacturer submits to the FDA that the new device is as safe and effective (in technical terms, "substantially equivalent" to) a legally marketed device that is not subject to premarket approval (PMA). "Substantial equivalence" can often be shown, for example, with analytical studies using clinical samples. If the new device produces very similar results to the old device, it is "substantially equivalent". Clinical studies are only very rarely required. Certain IVDs can be approved via the 510(k) route.

situation is completely different. [There is] *just self-certification which leads to CE marking. Companies need to have evidence that the test does what it says it does in narrow technical terms. They don't need to show that it is useful in a clinical sense."*

- *"Imagine, for example, that you have a machine that runs an array of 50 PCR-based genetic tests on lung cancer samples. For, let's say, 6 of the genes you are testing, there are clear and well validated therapeutic consequences (e.g., you should get drug X, or you won't respond to drug Y), but for the other 44, there is only academic research evidence of some influence on risk or drug response. It can be hard to get the entire kit approved* [by the FDA] *(or rather, there is haggling over the marketing claims that can be made), because no one really knows what the other 44 tests actually mean. Therefore, you end up with 6* [FDA] *approved tests plus 44 that are "for research use only"…. This is a relevant topic because the firms compete have the broadest panel of tests."*
- *"The US requirements for sample collection make it very hard to validate tests for diseases that are rare in the US.* [The FDA] *generally requires that the samples come from US patients…. This means, for example, you might not get a test approved in the US for an epidemic that had not yet reached the US[22]. In Europe* [it is easier to justify enriching] *the sample set to introduce more positives. This makes validation much easier[23]."*
- *"The US is daunting for a small company, however we have a US partner that should make things easier…. The CE marking process in Europe seems pragmatic and sensible."*
- *"To get approved in the US via the 510(k) path, you need to operate to the US quality standards, with a US quality system. You apply with a dossier of information that proves that your device is substantially equivalent to an existing device that is on the US market. Sometimes companies "bootstrap" their way up the 510(k) process. They apply with a very novel device but do not seek approval for the novel features. Once the novel device is on the market, they put in additional 510(k) applications on a feature by feature basis and build up the marketing claims. One problem here, of course, is that the 510(k) route encourages comparison vs. something that is out of date."*
- *"Note that the FDA has trouble getting qualified staff. They are resource limited. This means the FDA tends to be a bottleneck, and misses its targets on regulatory review times."*
- *"In my view, there is not a big difference between the kind of evidence you have to show to get 510(k) approval from the FDA and what you would do for a good EU CE mark. However, the FDA is more picky. The FDA does not necessarily trust EU notified bodies (since the IVD firms pay them, among other things)…. The FDA can be more strict about things like inter-operator and inter-site variability* [even for 510(k) approvals]*."*

These comments reflect the practical consequences of differences in regulatory principles. Europe applies self-certification to nearly all IVDs, while the US applies FDA scrutiny. The scrutiny involves clinical trials in the case of the FDA's pre-market approval or PMA pathway for certain very novel IVDs. The scrutiny requires the demonstration of *"substantial equivalence"* to established diagnostics under the FDA's so-called 510(k) pathway. Europe focuses more on narrow validation (i.e. the test must perform as it claims to perform, but it is then up to the market to decide whether or not the test is useful in the clinic), while the US places more emphasis of clinical validation[24] (i.e.

[22]The FDA does allow approval based entirely on non-US data under certain limited circumstances. See Section III.18 of: http://www.fda.gov/downloads/MedicalDevices/.../ucm071230.pdf

[23]Under certain circumstances, the FDA does allow enrichment of samples under certain circumstances. See Section VI.5 of: http://www.fda.gov/downloads/MedicalDevices/.../ucm071230.pdf

[24]IVDs that are classified by the FDA as Class III devices and which are approved via the premarket approval or "PMA" route have to provide data that demonstrates that they are safe and effective for their intended use. The emphasis is generally on false positive and false negative test rates and their potential impact on patient health. In most cases, the demonstration involves: (1) preclinical evidence that shows that the test produces accurate and reproducible results under controlled conditions; (2) Evidence of clinical performance. For example, the manufacturer may show very high congruence between the new test and a "gold standard" existing test using real clinical samples. The clinical section of the submission (Mansfield, *et al*., 2005): "must show that the test provides the expected result, whether positive or negative, in defined patient populations that reflected the intended use of the [test]."

the test can generally only be marketed after it demonstrates validity under the real-world usage conditions it would face in the US (Mansfield, *et al*., 2005)).

Given the lower cost of satisfying the EU requirements, it is common for IVDs to launch in Europe first. A European launch may or may not be followed by an application to the FDA and commercialisation in the US:

- *"In contrast to drugs, where you generally see a global commercial approach that engages both the EMA and FDA roughly simultaneously, many devices are launched in Europe without any necessary ambitions to capture the US market. The prizes in the US are bigger, but so are the costs of getting on the market. Therefore, it often makes sense to launch in Europe under the more benign regulatory environment. Then, if things go well, you can justify the investment required to produce the data for FDA approval."*
- *"The EU is the first market. Our second market will be China….. "*
- *"Europeans have access to better diagnostic tests. Even big firms like Roche and Becton Dickinson will sometimes CE mark their tests in Europe first, and then maybe move the test to the US later."*

4.2 Some Industry Concerns over Proposed Changes in Europe

Current IVD regulation in the EU is based on a European Parliament Directive from 1998 (Directive 98/79/EC). After a long gestation period, major revisions of the regulatory framework are now imminent (European Commission, 2012) (European Commission, 2014) (EDMA, 2014) (BSI, 2014). The expectation is that the new regulations will be finalized in late 2014.

There is a sense that IVDs will suffer from the sins of some implantable medical device manufacturers, given recent scandals that followed from breast implants manufactured using industrial silicone, and failure-prone metal-on-metal artificial hips:

- *"The [European Parliament], and even more so its Environment, Public Health and Food Safety (ENVI) committee, have been advocating the strictest possible procedure for 'innovative' products via the European Medicines Agency (EMA), regardless of the fact that breast implants and metal-on-metal hip implants that caused the political concern were not particularly innovative devices at all. This has resulted in a very polarized debate about the right choices that do justice to both patient safety and innovation."* (BSI, 2014)

There seems to be a degree of consensus in the industry regarding the content of the new regulations (see, for example: (EDMA, 2014) (BSI, 2014)). The following changes to IVD regulation are likely. First, self-certification for the majority of IVDs will be replaced by third-party audit. This is something of a halfway house between the current approach in Europe and FDA scrutiny in the US. The audit of will be paid for by the diagnostic company, and conducted by "notified bodies" such as the British Standards Institute (BSI). Bodies such as the BSI are already required to oversee the quality and performance of certain critically important diagnostic tests (e.g., some tests that screen for infectious agents in blood for transfusion). Second, post-marketing surveillance requirements will be increased. Third, there will be more formal scrutiny, traceability, and quality assurance within the IVD supply chain. Fourth, the classification of IVDs will change from a now obsolete list-based system[25], originating with the 1998 Directive, to what is becoming a standardized global[26] risk-based system. So, for example, in the new system, the highest level of scrutiny will be given to IVDs that protect public health (e.g., screening for infectious agents in blood for transfusions; testing for transmissible agents such as HIV in individual patients), followed by IVDs that test individual patients for serious diseases where the risk to the individual from erroneous diagnosis is high, but the risk to public health is lower (e.g., sepsis, cancer).

[25] The 1998 Directive provided a list of specific devices, and allocated each to a particular certification process. However, the list was not kept up to date as technology changed.

[26] The framework is becoming standard outside of the US. See Global Harmonisation Task Force guidance document: GHTF/SG1/N045:2008, titled *"Principles of in vitro Diagnostic (IVD) Medical Devices Classification"*

Importantly, the new certification process must be applied to old tests over the next 3 to 5 years if they are to remain on the market.

According to our interviewees:

- "*The EU is moving towards a regulatory environment that is more like the US. Things are still in the consultation period. Like most European initiatives, it is going to take a long long time. No-one really knows yet exactly how it will turn out."*
- *"I think the current EU system is fine provided that you do post-marketing surveillance. The new EU system will add cost. You will need to get a notified body to audit your calibration work (e.g., BSI). This* [will remain] *less expensive than the FDA, but it is a step-up from what happens now. The new EU system will* [be applied to existing products]. *Companies will have to put their existing tests through the new process over the next 5 years. You will lose the CE mark unless you re-do the validation."*
- *"One potential threat to the benign regulatory environment in Europe may from planned changes in European device and diagnostic regulation. There may, under certain circumstances, be requirements to show more evidence of clinical utility* (rather than simply doing what you say you do, and leaving it up to users to decide if that is useful or not)."
- *"While the new* [EU] *diagnostics directive has not been signed into law, it seems fairly clear how things will end up. There is less clarity regarding new medical device regulations, which are currently being redesigned in parallel with IVD regulations. It looks as if the IVD regulation will come into force in 2015, with a 5 year transition period. In other words, in other words, you are allowed/encouraged to put things through the new process from 2015, but everything must have gone through it by 2020. You can still put new tests through the old system until 2020, but this may not be wise as there could be something of a bottleneck in 2020…. In short, the new approach will make it more expensive and demanding (in quality / data / evidence terms) to bring an IVD onto the market in Europe. There will be a move towards a common international template of what is required for regulatory submission. Provided the disease is the same, then the evidence that gets you on the market in Europe in future, should also get you an FDA approval via the 510(k) route."*

A European Commission impact analysis suggests that transition to the new system (including re-certifying existing devices) will cost the medical device industry as a whole around €170m (European Commission, 2012). There will also be incremental annual compliance costs of around €50m per year. To give a sense of scale here, annual sales of medical devices into Europe are worth around €100bn (MedTech Europe, 2013). In very crude terms, and making a rough allocation, these sales are associated with R&D costs of around €5bn. Thus the regulatory transition costs a little over 3% of annual European R&D expenses, but spread over 3 to 5 years. The incremental run-rate costs are around 1% of European R&D expenses. No doubt these costs will fall much more heavily on some companies than others, but their scale suggests that they may be a financial irritant rather than a major barrier.

5. Scope for Adaptation of Current Regulatory Models

We see several ways in which the regulation of drugs might be further improved to support AMR-related innovation. First, the EMA and FDA should consider a single integrated set of guidelines for the development of some or all antibacterial drugs. Second, requirements for preclinical data should be tailored more specifically to the novel technology in hand. So, for example, preclinical data requirements that might be sensible for a conventional small molecule drug or monoclonal antibody might be irrelevant for bacteriophages or transcription factor traps. Third, the regulator might take a more public role in educating the industry and investors about its evolving thinking on preclinical and early clinical trial requirements for new therapeutic technologies. Fourth, and ***importantly***, there should be coordination between any new mechanisms for incentivising antimicrobial R&D and FDA and EMA regulation. New financial incentives for will likely have regulatory implications and vice-versa.

5.1 Unified Regulatory Guidance from FDA and EMA

There was substantial agreement that there has been an improvement in the regulatory environment, but interviewees in the drug industry and in regulatory agencies accepted that the EMA and FDA have not converged entirely. There are still differences in detail in guidance on patient recruitment and on statistical analysis. The sense is that the FDA is still more stringent with respect to details such as non-inferiority margins and antibiotic pre-treatment. There were requests to see if the EMA and FDA could converge entirely with respect to their guidance in some cases. As one senior drug discovery scientist said: *"Although there has been a huge improvement in the FDA and EMA regulations, it would still be very helpful if there could be a single unified set of guidelines.* [When] *you get into the very gritty details of trial design and end-point measurement, there are still differences. These mean that you take a risk with at least one of the regulators if you optimise your trials for the other one.*"

The preference in the industry would probably be for the FDA to edge closer towards the EMA.

5.2 Special Pleading for Novel Technologies

We heard suggestions on how the regulator might improve the prospects for novel therapeutic agents such as bacteriophages or oligonucleotide-based agents. There were two suggestions here. The first related to application of standards that might not be relevant for the new technology. So, for example, from a small biotechnology firm: *"*[Our experience with the] *EMA was generally positive, but could be improved in some areas. The regulator is insufficiently sympathetic to "biologically-justified special pleading". In other words, there may be some things that are absolutely necessary for* [conventional] *small molecule drugs (e.g. detailed PK/PD)* [but which are] *not applicable – or at least differently applicable – to a new technology* [such as transcription factor traps, immunomodulation, or phage-based approaches]*. Thus you are required to go through 'standard* [regulatory] *steps' that add very little real information to the regulatory package, but which are costly from a small company's perspective."*

This links with a proposal for more public sector or charitable investment in preclinical models for novel therapeutic technologies (see later).

5.3 Regulatory Education on Novel Technologies' Prospects

We also heard the suggestion that regulatory guidance or advice on early-stage technologies, and their possible route into clinical trials, could be published in some kind of digestible form. This would provide a credible source of information to investors, so might make it easier to raise capital: *"VC firms are paid to say "no"…… Therefore, some kind of public information on possible regulatory frameworks for novel approaches would help make investors better informed and the market for capital for new ideas more liquid. In fact, anything that makes you appear more credible and less futuristic and strange helps."*

We have sympathy with this idea. However, there is a chance that it could undermine some firms' confidence that the content of their scientific advice sessions with the regulator would not somehow leak into the public domain and help their competitors. The regulatory approach for new therapeutics often evolves during the back-and-forth discussion between companies and regulators.

5.4 Linking Financial Incentives with Regulation

Several of our interviewees stressed that incentive systems designed to stimulate R&D should mesh with EMA and FDA regulation. For example:

- *"It is still not obvious how financial incentives and regulation could come together to help the world build a stockpile of antimicrobials that might be more useful in future than they are today. To provide some context, 10 years ago, everyone thought MRSA was going to be the big problem. In fact, we now have much more trouble with resistant gram negative bacteria. 10 years ago, no one was trying to develop anything for resistant gram negatives because we didn't know they would be a problem today. If regulators and payers took a view towards future public health, they would encourage the creation and approval of diverse antimicrobial*

agents even if not all of them had large, or even obvious, commercial niches today. There needs to be more thinking about how to incentivise and regulate the creation of stockpile of products (and technological experiences) that might come in handy but which are not important today. Or, to put it another way, it is hard to demonstrate a positive risk-benefit profile [as required by EMA and FDA] *for a product that will only become useful if patterns of antimicrobial resistance chance in response to current selection pressures. However, by the time the resistance patterns have changed, it is too late to come up with something new. "*

- *"…there does need to be some serious thinking about if or how incentives and regulation are used to deliver a stockpile of antimicrobial drugs, some of which may not be very useful today, but which may become useful if resistance patterns change. For example, how could a regulator adjudicate on the profile of a therapeutic that had a potential future use but not an actual use today? What about a drug that was slightly worse than today's best available care, but which had a different mechanism of action, so which would still work if today's best available drug stopped working?"* [The point here is that such a drug would fail in non-inferiority trials against the best standard of care, so would be unethical to test in clinical trials]

There are also other factors that would desirable in new antimicrobials, such as mechanistic novelty or in-vitro or animal evidence that bacterial resistance to the new agent evolves slowly or not at all. These have implications for both the design of incentives and for regulation, as one presumes that FDA and EMA would adjudicate on the mechanistic novelty and on the likely rate of evolution of bacterial resistance before incentives payments were made.

Here we are also struck that the US already has an incentive systems for new antimicrobial agents. BARDA has already commissioned antimicrobial products. The FDA Safety and Innovation Act of 2012 already provides for 5 years of "orphan-like" market exclusivity to new antimicrobial drugs (Qualified Infectious Disease Products, or QIDPs) active against a list of ~21 "Qualifying Pathogens" and perhaps against other pathogens too[27,28]. In 2 years, the FDA has awarded QIDP status to around 40 antibiotics in clinical development (Woodcock, 2014). These include, for example, dalbavancin[29] (which is effective against MRSA), relabactam[30] (which blocks a common mechanism of resistance to other antibiotics such as penicillins, cephalosporins and carbapenems), cadazolid[31] (for Clostridium difficile), and an inhaled formulation of ciprofloxacin[32] (an old antibiotic reformulated to treat chronic Pseudomonas aeruginosa infection in patients with a rare lung

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[27] https://www.federalregister.gov/articles/2014/06/05/2014-13023/establishing-a-list-of-qualifying-pathogens-under-the-food-and-drug-administration-safety-and

[28] See: http://www.raps.org/regulatory-focus/news/2014/06/19395/FDA-Final-Rule-On-Qualifying-GAIN-Act-Pathogens/ Interestingly, there may be some practical confusion with respect to the implementation here, because there is no unambiguous mapping between the list of Qualifying Pathogens and the definition of a Qualified Infectious Disease Product. The QIDP is defined without reference to the pathogen list.

[29] Dalbavancin is produced by Durata Therapeutics. It is approved by the FDA to treat acute bacterial skin and skin structure infections (ABSSSI), caused mainly by Staphylococcus or Streptococcus bacteria.

[30] Merck states that *"Relebactam is an investigational, class A and C, beta-lactamase inhibitor that is being evaluated in combination with imipenem/cilastatin in ongoing Phase 2 clinical trials for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. In preclinical studies, relebactam administered in combination with imipenem/cilastatin demonstrated antibacterial activity against a broad range of Gram-negative and beta-lactam-resistant pathogens. Merck plans to initiate Phase 3 studies with relebactam in combination with imipenem/cilastatin in 2015.".*

[31] Cadazolid is a drug from Acetelion. It is in Phase III trials. According to Actelion*:" cadazolid is a strong inhibitor of Clostridium difficile protein synthesis leading to strong suppression of toxin and spore formation. In preclinical studies cadazolid showed potent in vitro activity against Clostridium difficile clinical isolates and a low propensity for resistance development. In a human gut model of CDAD, cadazolid had a very limited impact on the normal gut microflora."*

[32] The drug is in Phase III trials. According to Aradigm, the drug sponsor: *"Ciprofloxacin, available in oral and intravenous formulations, is a widely prescribed antibiotic. It is used to treat acute lung infections and is often preferred because of its broad-spectrum antibacterial activity against various bacteria, such as Pseudomonas aeruginosa. Pulmaquin is a dual release formulation composed of a mixture of liposome encapsulated and unencapsulated ciprofloxacin. It is being evaluated in two ongoing Phase 3 studies to determine its safety and effectiveness as a once-a-day inhaled formulation for the chronic treatment of non-CF BE."*

disease, non-cystic fibrosis bronchiectasis). Furthermore, additional regulatory support, over and above QIDP, has been applied, or is likely to be applied, to many of these drugs (FDA, 2014).

Neither BARDA nor the QIDP designation has a direct parallel in Europe. Thus the US is already sending commercial signals to the industry on where to direct antimicrobial investment in a way that the EU is not. This is not necessarily a problem. It may well be a cost-effective way for Europeans to get new antimicrobials. As a drug investment analyst told us recently: *"Drug R&D is like NATO from 1949 to 1989; something from which Europeans derive huge benefit, but largely paid for by Americans."*

However, it will become a problem should Europe decide that it wants a different set of antimicrobials to those incentivised by the US, or if the US decides to restrict some of its BARDA-derived drugs to domestic use. Given the commercial importance of the US market (~50% of global drug industry profits), the small size of most other markets (the UK provides around 2% of global drug industry profits), the glacial pace of international politics, and the practical difficulties in linking incentives and regulation, one can't help wondering if unilateral action by the US will dominate the drug industry's R&D investment decisions. A similar point was made by some of the interviewees:

- "*Some of the UK activities look parochial in terms of incentives to bring drugs to market. Some of the parliamentarians don't seem to realize that the UK is irrelevant as a drug market when it comes to stimulating investment. Maybe the US and China get bored waiting for the EU to put serious money towards incentives and* [will] *go it alone?*"
- *"…will governments really coordinate to commit the money? Only the US is really big enough on its own to direct R&D."*

6. The Importance of Other Factors in Drug and Diagnostic Innovation

6.1 Antimicrobial Drugs

We suggest four non-regulatory factors that appear to be important for drug innovation. These are the attractiveness, or otherwise, of the markets for which new drugs may be discovered and developed; the interaction between rapid pathogen identification and clinical trial costs for narrow spectrum agents; the ability of better diagnostics to create new markets for narrow spectrum agents; and financial and other support for early-stage R&D efforts. We consider the first three of these in more detail.

Antimicrobial Drugs and (Non Average) Economics

The overwhelming consensus among our drug and biotechnology industry interviewees was that a lack of clear financial incentives is the main barrier to antimicrobial innovation:

- *"The MAJOR external uncertainty is how – and how much – the company will get paid* [if our] *drugs come to market. This is the question that makes the investors scratch their heads more than any other."*
- *"There is still no consensus among the* [big] *drug companies on whether they should be involved in antimicrobials or not. Some firms… seem to be positioning themselves now for the day that commercial route finally becomes clear. Other firms…* [seem to be] *either getting out of antimicrobials and/or waiting until the commercialisation route is clear."*
- *"*[The major] *problem is lack of clarity on commercialisation route and pricing. No-one has yet got an antibiotic to market with modern 'orphan' type pricing. Even* [the most] *expensive antibiotics have never cost more than around $5000 per treatment…. This is not an easy problem given payer resistance and the way different kinds of drugs are reimbursed. So, for example, most antibiotics for serious infections are prescribed within the hospital setting and are not reimbursed separately from the rest of the treatment episode* [in contrast, for example, to most cancer drugs or high priced orphan drugs]."

An important point to understand here is that the details of antibiotic reimbursement mean that antibiotics, particularly those dispensed in hospitals, will rarely achieve the high prices that have made some niche drug markets very attractive for R&D investment. Furthermore, new agents are likely to be held in reserve for the patients who really need them. It is hard to convince the private sector to invest to discover cheap drugs that hardly anyone will use.

There is a large literature on this problem with work by various academics, by the IMI, Chatham House, and OHE, and others. As one of our interviewees told us: *"the policy space is rather crowded and densely filled, and pretty much every conceivable incentive or model has been proposed and evaluated to some extent."* For a digestible review of the various models see Section 2 of Sertkaya *et al*. (Sertkaya, *et al*., 2014).

Rather than rehash familiar arguments on financial incentives, we would make the following points. First, it may be wrong to give too much weight to analyses of the attractiveness or unattractiveness of antimicrobial R&D based on historic average costs and historic average sales. Drug R&D investment is not a field in which the historic averages are of overwhelming importance. This is for several reasons. First, financial returns on R&D at the project level are rarely "average". Across all therapy areas, there is good evidence that returns are extremely variable and highly skewed (DiMasi & Grabowski, 2012) (Scannell, *et al*., 2015) with the vast majority of projects losing money, a small fraction of projects generating the vast bulk of the value, and no one really knowing beforehand which will win and which will lose (Cha, Rifai, & Sarraf, 2013). In this respect, investing in drug R&D is a bit like buying lottery tickets (Figure 3). The same kind of skewed returns and investment uncertainty also probably occur within therapy areas.

Figure 3. Top 10% of Marketed Products Generate Around Half of the Drug Industry's Profits

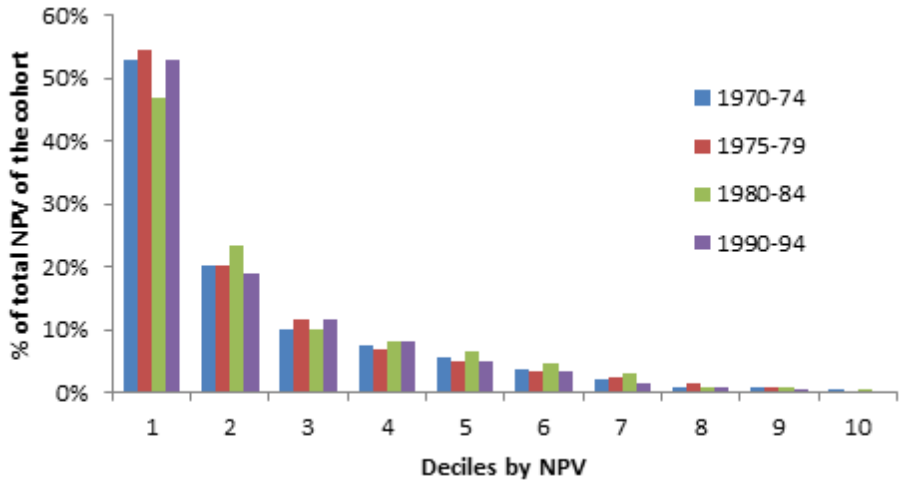

Figure 3 legend. *This graph, redrawn from (Grabowski, et al., 2002), shows the distribution of NPV (i.e., Net present value, which corresponds here to net post-tax profits adjusted for the time cost of money) for cohorts of drugs that were approved and launched over various time periods. The top decile of drugs accounts for around half of the value. While results have varied somewhat between cohorts, deciles 4 to 10 have been worth less than the average NPV of R&D per approved drug. Decile 3 has generally been marginally more valuable than the average NPV of R&D per approved drug. See also: (Grabowski & Vernon, 1990) (Grabowski & Vernon, 1994)*

Second, companies' and investors' R&D returns estimates will be very sensitive to their own estimates of their likely R&D success rates and market potential. In this respect, scientists, company managers, and investors rarely regard themselves as "historic" or "average", particularly as technologies change (e.g., with the advent of IVDs that might allow small trials that are heavily enriched with patients whose pathogens are likely to be sensitive to the drug that is being tested).

Remember (Table 3, Figure 1) that the Sertkaya, *et al.* (2014) cost estimates are dominated by the assumption that around 29 preclinical projects fail for each new drug that comes to market. The capitalized costs per drug launch were $2.2bn, but the direct capitalized spend on each successful drug was around $250m.

Third, the returns on incremental investment in R&D change through the R&D process.

For investors or companies deciding to invest in initial drug discovery projects, the expected cost of the entire R&D process, including failures in drug discovery, preclinical studies, and Phase I, is highly salient. Furthermore, profits will be long distant. Therefore, the kinds of analyses shown in Table 3 are important. However, specific decisions on incremental investment made during the R&D process should be regarded differently. Surviving drug candidates generally become more valuable later in the R&D process. By the time the decision comes to initiate Phase III trials, for example, most of the costs of R&D have already been sunk but potential profits are relatively close at hand. Thus profits that would not have justified any investment in early stage drug discovery activities can still look very attractive when compared with the often modest incremental investment required to bring late-stage candidates to market. This point is illustrated in Table 5 and Figure 4 (below). Both illustrations take the HABP/VABP, CABP, and Tier C scenarios (as per Table 3) and suppose that a $500m incentive payment is made at the point of drug approval. They then show the financial return, expressed as a measure called "Internal Rate of Return" or IRR.

The IRR of an investment can be thought of as the rate of interest at which cash outflows and cash inflows, when both time-discounted at that rate of interest, are equal to one another other. So, for example, if one invested a dollar today, and received a dollar and ten cents in exactly one year's time, the IRR would be 10%. If one invested a dollar today and received $1.21 in exactly 2 years' time, the IRR would also be 10%. IRR can cope with more complicated cash flows, of the kind that occur in drug R&D, and collapse them to a single measure of financial reward. For any given level of investment risk, investors prefer opportunities with a higher IRR.

While different companies will apply different hurdle rates, any IRR below a drug company's cost of equity (often around 9.5% for a major drug company) will almost certainly look unattractive. IRRs above 25% will probably look very attractive. Table 5 suggests that the promise of a real-terms $500m incentive payment may not stimulate investment in de-novo drug discovery (assuming, of course, that these particular cost and attrition assumptions are thought to apply). However the incentive would probably look attractive (in some cases extremely attractive) for an experimental drug that was already a plausible candidate for Phase II or Phase III trials. It might also, for example, be enough to stimulate the development of novel combinations of existing agents.

Table 5. IRR on Incremental R&D Investment Made from the Start of the Phase

	Preclin	PI	PII	PIII	NDA/BLA sub.	Incentive
Tier A / Conventional Approval Scenarios (Sertkaya, et al., 2014)						
HABP / VABP with conventional regulatory route						
Phase duration (years)	5.5	0.9	1.5	3.3	0.8	0.0
Time to commercial launch (years)	12.0	6.5	5.6	4.1	0.8	0.0
Phase midpoint vs. launch (years)	9.3	6.1	4.9	2.5	0.4	0.0
OOP cost per successful candidate $m	-21.1	-9.7	-15.6	-101.4	-2.0	0.0
Phase success probability	35%	33%	50%	67%	85%	100%
Candidates required per successful launch	30.2	10.6	3.5	1.8	1.2	1.0
OOP profit / (cost) including failure	**-637.4**	**-102.7**	**-54.9**	**-178.0**	**-2.3**	**500**
IRR on incremental investment from start of Phase	***-9.1%***	***10.1%***	***27.2%***	***52.1%***		
CABP with conventional regulatory route						
Phase duration (years)	5.5	0.9	1.3	1	0.8	0.0
Time to commercial launch (years)	9.5	4	3.1	1.8	0.8	0.0
Phase midpoint vs. launch (years)	6.8	3.6	2.5	1.3	0.4	0.0
OOP cost per successful candidate $m	-21.1	-9.7	-9.1	-38.8	-2.0	0.0
Phase success probability	35%	33%	50%	67%	85%	100%
Candidates required per successful launch	30.2	10.6	3.5	1.8	1.2	1.0
OOP cost including R&D failures $m	**-637.4**	**-102.7**	**-32.1**	**-68.2**	**-2.3**	**500**
IRR on incremental investment from start of Phase	***-9.0%***	***38.1%***	***142.5%***	***360.0%***		
Tier C Approval Scenario						
Narrow spectrum agent (e.g., activity limited to Psuedomonas aeruginosa)						
Phase duration (years)	5.5	0.9	3.3	3.3	0.8	0.0
Time to commercial launch (years)	10.5	5.0	4.1	4.1	0.8	0.0
Phase midpoint vs. launch (years)	7.8	4.6	2.6	2.6	0.4	0.0
OOP cost per successful candidate $m	-21.1	-9.7	-10.4	-67.6	-2.0	0.0
Phase success probability	69%	54%	50%	67%	85%	100%
Candidates required per successful launch	9.4	6.5	3.5	1.8	1.2	1.0
OOP cost including R&D failures $m	-198.7	-62.8	-36.6	-118.7	-2.3	**500**
IRR on incremental investment from start of Phase	***3.3%***	***29.0%***	***57.8%***	***75.4%***		

Table 5 Legend. *Expected internal rate of return (IRR) on incremental investment required to bring a single drug to approval for a one-off $500m incentive payment. Red figures are costs and green are revenues. In all scenarios, returns for the entire project lifecycle are below the cost of capital (which we assume is around 11%). However, for the Tier C and CABP scenarios, returns on incremental investment from Phase I onwards look attractive. For HABP and VABP, returns look attractive from the start of Phase II onwards. In this illustrative example, a $500m incentive would encourage R&D investment for candidates that had been abandoned during clinical development, but would probably not encourage the initiation of de-novo discovery projects. Note that all dollar values are in millions of real 2008 dollars.*

Figure 4. IRR on Incremental R&D Investment Made from the Start of the Phase

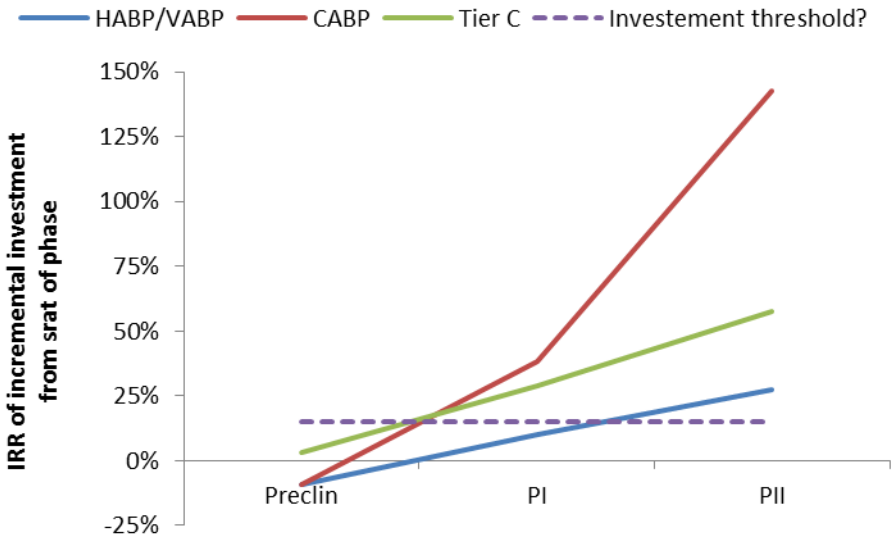

Figure 4 Legend. *Expected internal rate of return (IRR) on incremental investment required to bring a single drug to approval for a one-off $500m incentive payment. The analysis is exactly as in Table 5, but showing preclinical to Phase II decisions. We have assumed an IRR hurdle of 15% stimulates investment (dotted line). If so, the $500m incentive payment would stimulate Phase I, Phase II, and Phase III trials for Phase I-ready candidates for CABP or Tier C. It would also stimulate Phase II and Phase III investment for any Phase II-ready candidate for HABP/VABP. It would not stimulate de-novo discovery efforts. Nor would it stimulate Phase I investment for HABP/VABP.*

Fourth, and importantly, money ***is*** being invested today by a reasonable number of companies (e.g., Cubist, Durata, Bayer, Aradigm, Actelion, Merck, and others) on antimicrobial projects throughout the R&D lifecycle. The FDA has given around 40 QIDP designations to antibacterial drug candidates in clinical trials over the last ~2 years (Woodcock, 2014). These companies and their investors presumably think they can make money by investing today. They are probably more optimistic for several reasons which include:

- For early-stage R&D investment, the belief that financial incentives may have improved sufficiently by the time the drugs could reasonably come to market;
- The sense that the cost or attrition assumptions applied in various policy-related economic analyses are too high. This belief will tend to grow if there is an increasing conjunction between narrow spectrum drugs and rapid IVDs;
- The level of incremental investment to move a drug candidate to market is low. This would be the case, for example for drugs that are reformulations of existing agents, or for drugs which were previously abandoned late in the R&D process with acceptable safety and a large package of regulator-ready data[33]. For more information on how the returns on incremental investment change through the R&D process see Scannell *et al.,* (2015);
- Or because there is a commercial niche in which pricing is likely to be more attractive than at the typical hospital pharmacy. This could apply to antibiotics used for prophylaxis in the outpatient setting, for example[34].

[33] Dalbavancin is an example here. The drug was first submitted to the FDA for approval by Pfizer. However, in 2007, the FDA required more data and Pfizer withdrew its application. Pfizer sold the rights of the drug to Durata in 2009. Durata then initiated 2 new Phase III trials which led to FDA approval and QIDP status in 2014.

[34] This might apply to Aradigms' plan to reposition ciprofloxacin for use as an inhaled drug for non cystic fibrosis bronchiectasis, for example. Chronic outpatient use would likely give rise to better pricing than acute use in hospitals.

Among the R&D-active firms we interviewed for this project, the first two reasons were the dominant ones; the hope that incentives will get better and that clinical trials for narrow spectrum agents will get cheaper and less failure prone. If new incentives do not materialize and if diagnosis does not improve, then their R&D investment could stall.

However, it is clear that some firms that we did not have a chance to interview, particularly those with drug candidates currently in Phase II and Phase III trials, believe that at least one specific market is attractive given the R&D path that they expect to follow. It would be interesting and important to understand why these companies disagree with what appears to be the wider industry, academic, and health policy consensus on the unattractiveness of antibiotic R&D.

It is also important to understand the kind of agents that these firms are likely to bring to market in the next few years. Will these drugs have sufficient mechanistic novelty to change the AMR problem? Or is the field dominated by drugs that look like good business, and which will help a select group of patients, but which will not address the AMR problem to a great extent.

Rapid Diagnostics for Antimicrobial Drug Trials

The current enthusiasm shown by the drug industry and its investors for R&D in oncology stems in part from the fact that it is possible to run small and cheap clinical trials that are highly enriched for patients whose tumours are likely to respond to the experimental drug. Some recent oncology drugs have been approved on the basis of trials involving only a few hundred patients[37]. This, in large part, follows from advances in molecular diagnostics.

The statistics of clinical trials are such that diluting a group of responders with non-responders reduces a trial's signal to noise ratio, and increases overall trial size and the number of responders you have to recruit to show an effect (Figure 5, note the logarithmic vertical axis).

Suppose, for example, that we wanted to run an adequate clinical trial for a new narrow-spectrum antimicrobial drug X against the sensitive pathogen A which sometimes causes pneumonia. Our statistical power calculations might tell us that if only 12.5% of pneumonia patients were likely to be infected with pathogen A, we would have to recruit 6400 pneumonia patients in total, of whom 800 (12.5%) would have pneumonia caused by pathogen A, with the remaining 5400 cases caused by other pathogens insensitive to drug X.

We could achieve the same statistical power, however, with only 100 patients if we could somehow identify and recruit only patients whose pneumonia was caused by pathogen A. This represents as 64 fold reduction in trial size, but also an 8 fold reduction in the number of patients recruited who were infected with pathogen A (Figure 5).

[37] See, for example, recent approvals by the FDA and EMA of crizotinib, vemurafenib, and vismodegib.

Figure 5. Enriching the Clinical Trial Sample for Likely Responders Reduces Trial Size - Illustration

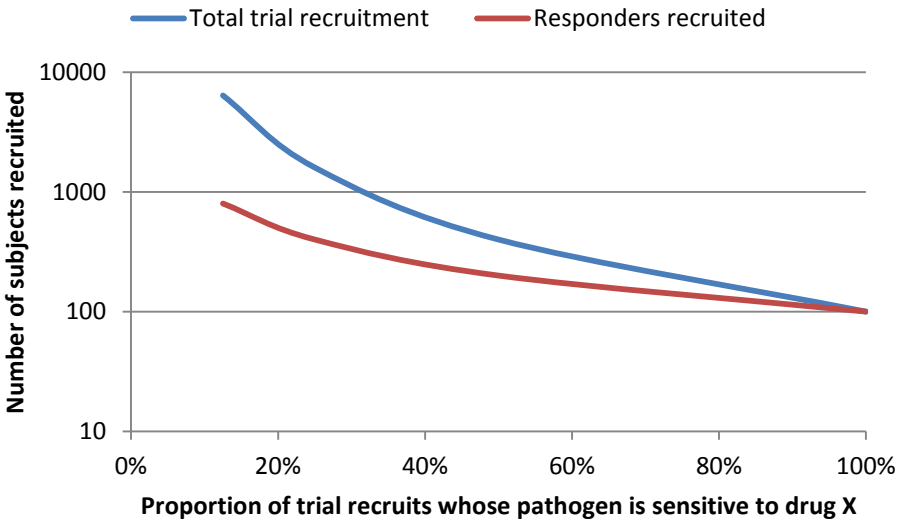

Figure 5 legend. *The relationship between the proportion of patients likely to respond to a drug and clinical trial size. Note the logarithmic vertical axis. The 'Total trial recruitment' line represents a line of constant statistical power (i.e., the likelihood that the trial will detect a true therapeutic effect). If only 12.5% of patients had a pathogen that was likely to sensitive to the drug, then in this scenario one would need to recruit 6,400 patients, of whom 800 would be infected with the sensitive pathogen. However, if one could identify patients with the sensitive pathogen and enrich the trial with these patients, the required trial size falls. If we only recruited patients with the sensitive pathogen (100% on the horizontal axis), then we could achieve the same statistical power with only 100 patients. The relationship has this form because the size of the effect that we are trying to detect is proportional to the number of responders, but the random error (noise) that masks the effect is proportional to the square root of the total number of subjects recruited.*

While this illustration is simplistic (ignoring, for example, the need for trials to provide safety data and not just efficacy data), it shows the large effect that diagnostics can have on trial size and cost. As one interviewee said:

- *"There is a huge economic complementarity between rapid diagnostics and antimicrobial drug R&D. The need to pre-treat severely ill patients with a broad spectrum agent while waiting for conventional microbial identification means that trials are bigger, noisier, more expensive. If you really could do rapid diagnosis when patients present, you could run the antibiotic trials much more like some of the recent anti-cancer drug trials; fewer patients recruited, better signal to noise ratio, hence easier and more profitable R&D."*

For some infections, those with a longer time course for example, current microbiological tools are probably adequate. However, for conditions such as sepsis, or HABP/VABP, it is still the case that it will generally be necessary to recruit patients into trials and to begin empiric treatment before the causal pathogen has been definitively identified. This will tend to increase trial size and cost and reduce the signal to noise ratio when testing a narrow spectrum agent. This will remain true, but to a lesser extent, even if the trial design and regulatory framework allow outcomes analyses to focus on patients who are subsequently found to have been infected with the target pathogen.

Routine Microbiological Diagnosis to Create Narrow Spectrum Drug Markets

A longer term hope expressed by some of our interviewees is the development of routine diagnostic tools and services that could shift narrow spectrum agents into much more widespread

use in the community. This might create more commercial opportunities without an unacceptable increase in AMR. According to one interviewee:

- *"There are huge benefits from the perspective of evolution of resistance if you use narrow spectrum agents. With broad spectrum agents, every bug in the patient is exposed to a selective* [evolutionary] *pressure* [that can ultimately lead to resistance]. *With narrow spectrum agents, most bugs in the patient are not exposed to any selective pressure. There is also much less chance then of horizontal acquisition of resistance (i.e., cross-species DNA transfer). This means, among other things, that narrow spectrum agents should have a much longer useful life."*
- *"Many broad spectrum antibiotics have "promiscuous" / messy target binding profiles; they have to because they have to bind a family of homologous but slightly different protein targets in a wide range of bugs. This also tends to increase their toxicity in man, which in turn often makes combination use difficult. With more selective narrow-spectrum agents, it should be possible to develop relatively non-toxic combination products from which it will be very unlikely that bacteria evolve resistance. The analogy here is the evolution of combination drugs for HIV and Hep-C. These are now extremely effective, relatively tolerable in man, and hard to evolve around."*

6.2 Diagnostics Innovation

Our work has identified four factors that appear to have important influences on IVD innovation. The first three have an indirect effect. They reduce adoption, which reduces the financial incentive to invest in R&D. They are the ability of diagnostic tools to fit into existing health system work flows; the ability of diagnostic tools to fit into existing health care budgets; and the scale economies of laboratory supply. The fourth factor applies directly to R&D. It is the cost of validating IVDs for rare diseases.

Factor 1. Health System Work Flows

One of our interviewees had a particularly striking observation which we present here in slightly modified form: *"The ideal* [novel IVD] *is very boring. It should provide new information but change absolutely nothing else about the way the physician* [or the health system] *works."*

Even highly innovative drugs often fit with this sense of "very boring" in a way that many diagnostic technologies cannot. It is easy for a health system to substitute a better newer antibiotic for a worse old antibiotic. It is easy for a primary care physician to prescribe a new pill that works instead of an old pill that doesn't. This is illustrated by the fact that some drugs can approach their peak sales in a particular market within several years of launch. However, diagnostic technologies are more prone to changing the way busy individuals in the health system have to work. If they change workflows, they are more likely to fall at the adoption hurdle:

- *"Drug firms love the idea of point of care tests, because they can drive use of their particular drug. However, there are lots of practical problems. First, point of care tests have to be completely "idiot proof". This means the regulatory standards tend to be higher. Second, the drug firms forget that the patient usually takes a cocktail of drugs and has a whole lot of things wrong with them, so the doctor is rarely interested in taking the time to do a test that tells* [him or her about] *just one thing. It is often easier for the doctor to get the nurse to take a blood sample and send it to lab to measure everything at the same time."*
- *"If you have to hope that you change how the physician works, you generally fail to get adoption. To give you an example, suppose you wanted a point of care blood test to help psychiatrists in the US to get their drug dosing right. Well, most community psychiatrists haven't taken blood for 30 years, and they don't have practice nurses. Therefore, this plan would be dead in the water. Also, if the test adds 5 minutes to a primary care consultation, it will struggle."*

Factor 2. Costs and Budgets

The success of IVD innovation will depend on both who pays for tests and on how much tests cost. So, for example, tools that save money at the level of the health system frequently struggle if they shift payment from one budget to another. A primary care physician may be reluctant to use a relatively cheap point of care test paid for by his or her own budget, if the same results could be provided more slowly by sending specimens to a microbiology laboratory whose costs fall within someone else's budget:

- *"The main barriers for the diagnostics companies are not regulatory. They relate to reimbursement, access, and adoption."*
- "[Health systems] *exist in silos. New things are hard to fit into existing budgets."*

Furthermore, many new tests simply increase cost, because the health system has to continue to run the old service:

- *"One practical challenge with the new* [IVD] *technologies is that they may be additive rather than "instead-off". We may still have to run all the old stuff, while adding the new stuff. This means it may make things more costly."*

National differences in price sensitivity and in the buying process for specific tests also make it hard to draw general conclusions. US physicians are often self-employed entrepreneurs, insensitive to the price of diagnostic tests which are paid for either by the hospital or by an insurance company, but sensitive to the risk of litigation if they under-test. Many European physicians, on the other hand, are employees working within systems with fixed budgets. A specific test might benefit from the pricing and reimbursement arrangements in one country, but suffer from the arrangements in another. There are major differences even within Europe:

- *"Very few UK SMEs find the UK / NHS a particularly amenable customer. Scandinavia, Germany, France, Switzerland, etc., (in fact, most places other than the UK in Western Europe) are easier markets to sell to."*
- "[The NHS is not an] *attractive as a customer. The NHS insists on proving cost effectiveness. What this means is that they expect the diagnostics firm to pay for a big study in various UK hospitals before they think about buying anything. However, it sometimes costs you more to prove to the NHS that your test is cost effective, than you would ever make from the test if the NHS became your customer."*
- *"In Germany, for example, the health system will not pay for next generation sequencing. There are machines sitting idle in pathology labs because no-one will pay for their use. Next generation sequencing seems to have more routine clinical use in the US already, but certainly not in Europe."*

Factor 3. Economics of IVD provision

The first two factors relate to the challenge of slotting a new activity or a new cost into a complex health system. We also heard that the economics of the IVD industry and of laboratory activity tend to count against certain kinds of test. We have done less work on this point, but we understand that tests that are complex and which are used rarely are hard to slot into the laboratory workflow, and tend to be unattractive for IVD manufacturers. If we consider oncology drugs and their companion diagnostics, for example, the companion diagnostics would not make sense for the IVD companies without cross subsidy. They make commercial sense only because they support the sale of an expensive cancer drug. Thus the drug companies generally pay for the development of the test and the use of the test:

- *"The laboratories are a volume business, where the diagnostics firms make money with the platform (i.e., a big machine) and/or the consumables (the tests). The consumable market depends on volume. You struggle with expensive, low-volume, non-routine tests. In oncology, the expectation is that the drug company pays for the development of the companion diagnostic* [to help sell an expensive and profitable drug], *because the diagnostics firm*

would not see a return on its investment. The more complex and esoteric your diagnostic test, the less attractive it is to a diagnostics company."

Similar cross subsidies allow the health system to administer the test:

- *"Panels of molecular tests often end up being costly* [to administer]*, particularly if you are looking for relatively rare diseases. To give an example, in lung cancer, the drug* [crizotinib] *works very well in the 5% of lung cancer patients with an ALK mutation. That means you have to test 20 patients to get a single positive. Even if each test is "only" 500 Euros* [to the health system, including collecting the tissue sample, etc.]*, this means you spend 10,000 Euros per patient detected. The expectation in oncology is that the drug company ends up paying for the companion diagnostic. The mechanics of this varies between countries, but* [in oncology] *the drug company always pays."*

The obvious concern is that IVDs for relatively rare pathogens, or rare forms of resistance may be expensive to users and similarly unappealing to IVD companies. However, in this case, there is no lucrative cancer drug that can be sold to subsidise test development and test administration.

Factor 4. The costs of validating tests for rare diseases

Not only are the economics of esoteric IVDs difficult once tests are on the market. It can be expensive to validate IVDs for rare diseases. Most specific forms on AMR are still rare.

The statistical assessment of test quality is both more complex and less familiar to most people than the statistical assessment of drug efficacy. To put it crudely, most people believe that a clinical trial has shown that a drug "works" if the difference in outcome between the patients who got the drug and those who didn't is "statistically significant" at the $p < 0.05$ level. There is no such simple single rule that can be used to decide whether a diagnostic test has been shown to work (Greiner, Pfeiffer, & Smith, 2000).

For most diagnostic tests, it is important for vendors, customers, auditors such as the BSI, and regulators to know at least four parameters. The first two are intrinsic to the test. The second two depend on the context in which the test is used. The parameters are:

- Sensitivity: the proportion of true positives that the test correctly identifies as positive;
- Specificity: the proportion of true negatives that the test correctly identifies as negative;
- Positive predictive value (PPV): the proportion of positives identified by the test that are true positives. This depends on both test sensitivity and the rarity of true positives. Clearly, if there are no true positives, then all test positives are false positives.
- Negative predictive value (NPV): the proportion of negatives identified by the test that are true negatives. This depends on test specificity and the rarity of true negatives.

The usefulness of the test will depend on the acceptable trade-offs between these parameters. In general, if sensitivity goes up, specificity goes down. If the disease is very dangerous and very expensive, while the curative drug is very safe and very cheap, then you are happy to accept false positives from the test, but are anxious to avoid false negatives.

Let's suppose that obtaining a reasonably precise estimate of sensitivity would require calibrating the test using 100 samples of pus that the "gold standard" had deemed to be positive for a pathogen (TDR Diagnostics Evaluation Expert Panel, 2010). If 50% of the samples collected are positive by the "gold standard", then the calibration can be achieved by collecting only 200 samples of pus. However, if only 1% of the samples are positive by the "gold standard", then calibration requires the collection of 10,000 pus samples. From our interviews:

- *"When you have multiplexed tests* [i.e., a panel of tests for different pathogens run simultaneously using the same test kit on the same machine]*, the cost of validation* [in R&D] *goes up. So, for example, consider a panel of tests for sepsis. Practically any bacteria can cause sepsis in certain patients. Technically, we could easily make a panel of 100 yes/no PCR tests. However, it is only the 10 most common pathogens that you encounter frequently enough to effectively validate the tests. With the very rare pathogens, you cannot estimate your false*

positive and false negative rates without testing an inordinately large number of samples, the overwhelming majority of which will be negative. Importantly, AMR is still relatively rare and specific mechanisms of resistance are often very rare. Therefore, broad panels of PCR-based tests for resistant bugs will be expensive to validate."

7. Conclusions: Policy or Regulatory Initiatives and Future Research

After what has been a relatively short piece of work in a large and complex field, it is a difficult to make proposals that are both novel *and* sensible. We have spent most of our time talking to industry and reviewing the literature on regulation. We have spent very little time surveying the plethora of AMR related initiatives that are underway. We are also sensitive to the scope of our project, and do not intend to stray too far from regulation and its impact on innovation. With these provisos, we have a number of suggestions.

The first four are for initiatives that, if implemented, would be large, complex, and expensive. In some cases, we know there is on-going work. Thus the practical next step for these would be a feasibility assessment of some kind. The final two suggestions are smaller pieces of work.

7.1 Complete Convergence in FDA and EMA Guidelines

It is now usual practice in the drug industry to run a single set of pivotal trials that aim to satisfy both the FDA and EMA. In general, the FDA matters more. In the rare cases when a drug is approved by the EMA but not the FDA (or vice versa) it is generally because something has gone wrong and the results of the trials only satisfy one regulator (more often the EMA). Therefore, the existence of subtly different guidelines from the two major regulators usually adds little to the public good in terms of the evidence that is generated[39]. To be frank, it also probably adds relatively little cost, since pivotal trials will generally be designed to satisfy the FDA, with features added if necessary for the benefit of the EMA or national health-economic agencies. However, several industry scientists argued that trial design would become a more predictable exercise, if they did not have to optimise for one regulator, and then hope that they could still convince the other. Our sense is that the factors that matter here are things like inclusion and exclusion criteria, prior or concurrent treatment with other antibiotics, acceptable clinical trial locations, and other details of trial conduct. It may be easier to accommodate slightly divergent regulatory views on the statistical analysis of the trials (e.g., the breadth of non-inferiority margins).

It seems reasonable suppose that convergence could happen indication by indication, or could start with drugs for patients with serious infections and few other treatment options. Perhaps the agencies could also move towards joint scientific advice? It also seems reasonable to wonder if the mechanisms and relationships established through the TATFAR programme could help achieve this objective[40].

7.2 Public Sector Support for Diagnostics as an Economic Complement to Private-Sector Drug R&D

Better pathogen identification could make drug development much less expensive (Figure 5, Table 3). In the long run, better diagnostics could also create new drug markets, particularly for narrow spectrum drugs. Furthermore, and importantly, diagnostic R&D appears to be between one and two orders of magnitude less expensive than drug R&D (see Table 3 vs. Table 4).

However, diagnostics are less profitable than drugs, and adoption and reimbursement are problematic. In oncology, an area where the drug industry is investing heavily, these problems are often overcome because drug companies are prepared to subsidise IVD development and IVD

[40] While it is conceivable that guidelines on clinical trial design, conduct, endpoints, etc., can be unified we would expect that legislative and regulatory barriers would prevent unified regulatory scrutiny of the final dossier and would prevent unified approval. In other words, unified trial guidance will produce trials that still feed into two separate regulatory jurisdictions; one at the FDA and one at the EMA.

provision so they can sell expensive drugs. Without expensive cancer drugs, there may not have been a flowering of molecular cancer diagnostics.

Cross subsidy is unlikely to occur with antimicrobials. Might there be a case, therefore, for substantial public sector support for the diagnostic technologies and microbiological services that are most likely to reduce the size of individual drug trials and their aggregate failure rates?

It might be possible to create a number of centres in the UK or at a European level that develop and validate diagnostic technologies and microbiology workflows, and which specialize in running clinical trials for antimicrobial drugs.

7.3 Public Sector Support for Sample Banks to Reduce the Cost of Diagnostic Test Validation

Regardless of the regulatory environment, it can be difficult to generate robust evidence on the performance of diagnostic tests (Jennings, *et al*., 2009) (TDR Diagnostics Evaluation Expert Panel, 2010) (Greiner, Pfeiffer, & Smith, 2000). The difficultly can apply to tests that are sold as kits, and to tests that are developed in-house and run in microbiology laboratories.

It would seem reasonable to ask if public sector institutions such as the NHS, the Health Protection Agency, or perhaps European agencies, might be well placed to work as sample collectors and repositories at relatively low incremental cost, and whether such bodies could be encouraged to collaborate with private sector test developers.

7.4 Pre-competitive Preclinical Models for New Therapeutic Technologies

This is a speculative suggestion and much of this may be funded already.

A great deal of generally unglamorous but important work goes on in what is called "preclinical development". This deals with regulatory requirements for toxicology and safety. It also deals with some animal models of disease, with drug absorption, metabolism, excretion, the potential drug-drug interactions, options for routes of administration and formulation, etc., etc. Preclinical development is much easier for therapies for which there is long commercial and regulatory experience. If, for example, you are bringing yet another insulin formulation to market, then the standards are set and the pitfalls are known. For familiar drug classes, much preclinical development can be somewhat mechanistic. Thus, a company with no in-house preclinical facilities can even buy the services necessary to create the package of preclinical data for the FDA. However, for new therapeutic technologies such as bacteriophages or transcription factor traps, there are few existing standards or familiar pitfalls.

One of our interviewees, at a large company with little current exposure to such technologies, suggested that public sector support for work relevant to validation and preclinical development might have wider benefits: *"People like the MRC and Wellcome Trust could think about investing more to allow academics to do critical proof-of-concept studies for technologies such as phages, oligonucleotides, immuno-modulation* [e.g., development of robust animal models of both efficacy and – as far as is possible – toxicology and safety]*. These kinds of things are a necessary pre-requisite for serious regulatory consideration."*

7.5 Analysis of Commercial Assumptions of Firms Investing in Antimicrobial Drug R&D

Our drug and biotechnology interviewees said that a lack of economic incentives is the major barrier to investment in antimicrobial R&D. However, there are at least 40 projects in clinical development with QIDP status from the FDA which show that many companies and investors see economic incentives that are at least adequate for certain kinds of R&D investment.

We have started to skim the surface on this topic. While it is clear that there are various recent reviews on the molecular, pharmacological, and potential antimicrobial properties of drugs in the R&D pipeline (See, for example, de Souza Mendes & de Souza Antunes, (2013) for a list of reviews), we have not yet come across work that sets out the likely investment or commercial case for the observed pattern of activity. We think it is important to characterise the clinical and late-preclinical pipeline of antimicrobial drugs from a commercial and investment perspective, to

understand why certain projects are attracting funds today, and to understand what this means for the design of any future incentives.

It is clear, for example, that one of the QIDP drugs is an agent that was abandoned in late-stage development, probably for commercial reasons; that has been resurrected, probably with the expectation of low incremental investment to bring it to market; and which has a degree of clinical differentiation around dosing convenience which may improve hospital economics and justify a price premium[41]. Others are reformulations of established drugs that are seeking niche markets that lie outside of hospitals, which may allow more attractive pricing[42]. Yet others seem to be combinations of existing agents. Our guess here is that the investment logic could be a combination of modest spending on new preclinical toxicology studies (to rule out synergistic toxicity in man); a high chance of efficacy in clinical trials (since the agents are already known to have antimicrobial activity); perhaps enhanced efficacy or activity against resistant strains (from the combination effect); combined with five years of QIDP-based market exclusivity (important for combinations of old drugs where patent protection may be hard to secure in the absence of demonstrably unexpected synergy).

What is not clear to us yet is the extent to which drugs that will substantially address the AMR problem are emerging from preclinical development and progressing through clinical trials.

7.6 Creating and Maintaining AMR Data Resources

A secretariat could be established that collates and publishes on a timely basis data likely to be of use to a wide range of people working on the AMR problem but which are currently scattered. As one specific example, it would be useful if those engaged in AMR policy work or in scientific work were able to obtain structured information on drug pipeline status. This should include, for example, antimicrobial agents in preclinical and clinical development, the indications in which they are being tested, their stage of development, their drug class and presumed molecular mode of action, etc. This could then be compared, over time, with changes in regulation, technology, or financial incentives. So, for example, have the GAIN provisions and QIDP status in the US been correlated with an increase in clinical trial activity? How many agents are reformulations or combinations of existing products? How many are new drug classes? What is the mix of broad spectrum vs. narrow spectrum agents? Where are venture capital firms investing? What kind of small companies are the drug majors acquiring? How does the pattern of pipeline activity and progress match the perceived medical need?

There are several companies that provide this kind of data on a commercial basis to clients in the drug industry and in the finance sector. Perhaps one or more of these firms could be persuaded to support broader efforts on the AMR problem?

No doubt there would also be other kinds of data that would be of use to a variety of people working on the AMR problem (e.g., summaries of the major strands of activity in different countries; headline epidemiological data; a curated and indexed bibliography; etc.).

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[41] Dalbavancin is the example here. The drug was first submitted to the FDA for approval by Pfizer. However, in 2007, the FDA required more data and Pfizer withdrew its application. Pfizer sold the rights of the drug to Durata in 2009. Durata then initiated 2 new Phase III trials which led to FDA approval and QIDP status in 2014.

[42] This may be the case for Aradigms' plan to reposition ciprofloxacin for use as an inhaled drug for non cystic fibrosis bronchiectasis.

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APPENDIX 1. SUMMARY OF MICROBIOLOGY WORKFLOW AND DIAGNOSTICS TECHNOLOGIES

This Appendix is based largely on Livermore & Wain (2013) and Didelot, *et al*. (2012). It is fairly basic, without novelty, and may contain some errors. However, it may help some readers digest the sections of the main report that deal with in vitro diagnostics and bacterial identification.

Classical Laboratory-Based Microbiology

The standard hospital microbiological workflow is illustrated in Figure A1 from Didelot, *et al* (2012). The general principles here have changed little for 50 years. However, many processes are substantially automated and streamlined.

Samples from patients (e.g., blood, pus) are added to nutrient-containing media. The media are chosen to match the likely pathogens and the likely clinical interest. After ~24 hours, there will be sufficient bacteria for classical identification (based on Gram staining, microscopic morphology, characteristics of bacterial colonies, etc.). This allows species identification which is a guide to antibiotic selection. However, species may contain drug resistant variants that cannot be identified on the basis of morphology, staining, etc.

Therefore, drug susceptibility testing is required. This sometimes starts to run in parallel to species identification (e.g., if bacteria are from a site that should be sterile, such as blood or CSF) but is often serial since it requires pure cultures. The pathogen is cultured in a range of media that contain a range of antibiotics at a range of concentrations. This provides a direct in-vitro measure of the ability of antimicrobial drugs to inhibit bacterial growth. Susceptibility testing is now semi-automated[43], with growth being measured automatically with optical measures (e.g. cloudiness of the media from bacterial growth) or with metabolic measures (e.g., production of carbon dioxide from bacterial respiration). It can take 4 to 10 hours with modern semi-automated systems.

Even with modern implementation of the classical methods, the combination of species identification and susceptibility often takes 30 hours or more.

Figure A1 (From Didelot *et al*. (2012))

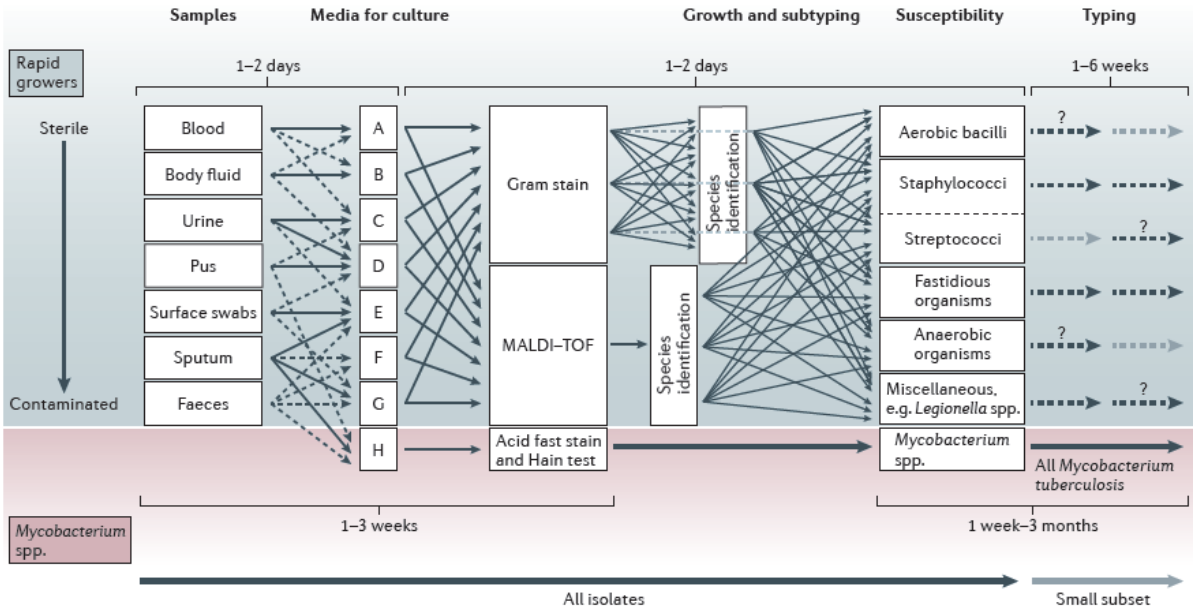

Figure A1 legend. *Workflows for samples taken for microbiology assessment. Samples (e.g., blood, pus, urine, swabs) are taken from the patient. Samples that should come from a sterile site (e.g., blood,*

[43] See, for example, Vitek (bioMeriux) and Phoenix (BD)

cerebrospinal fluid) are generally cultured on media that will support the growth of a very wide range of organisms. Samples that are from sites that typically harbour a range of bacteria (faeces, pus, surface swabs) are typically cultured in media that support the growth of likely pathogens. Once organisms are growing in culture (~1 day or more) they are identified via conventional staining and morphological criteria or with rapid automated methods such as MALDI-TOF (which is based on mass spectroscopy). Identification at the species level provides a guide to antibiotic choice, but cannot identify resistant subtypes. Thus bacteria are grown with a range of antibiotics to identify the drugs to which the bacteria are susceptible. Although this often starts at the same time as species identification, results generally take longer. The processes are substantially automated and relatively streamlined in modern labs.

Newer Pathogen Characterisation Methods

There are a range of methods that supplement the classical approach.

- MALDI-ToF: This is a rapid alternative to species identification of the kind that would occur in a conventional microbiology laboratory. It is a spectroscopic method that can rapidly identify a molecular signature that is characteristic of bacterial species. The method is applied once bacterial samples have been cultured. It makes species identification easier and more efficient. However, it needs to start with a pure culture, which often takes 24 hours to produce. As with conventional species identification, it provides a guide to drug choice but is not definitive because resistant variants can exist within species. Recent commercial MALDI-ToF systems have been approved via the less onerous 510(k) pathway in the US.
- PCR-based molecular diagnostics – stand-alone tests: These methods depend on amplifying and identifying pathogen-specific or drug resistance-specific DNA sequences. They are now widely used, having gained an initial foothold in virology. Each individual test provides a "yes/no" answer on the presence of a pathogen (or, more precisely, the presence of a DNA sequence characteristic of the pathogen). They are commonly used to help diagnose gonococci, Chlamydia, or tuberculosis. Tests can be applied more or less directly to clinical specimens, without culturing the pathogens. This means that PCR-based results are available in a few hours. PCR-based tests can be approved via the 510(k) route if there is an established marketed test against which they can be compared. Sometimes PCR-based diagnostics have been approved via the PMA route (e.g., companion diagnostics for novel cancer drugs).
- PCR-based molecular diagnostics – multiplexed systems: Several manufacturers produce multiplexed systems[44], where an array of yes/no tests is applied to a sample from a patient with a particular clinical syndrome (e.g., a diarrheal infection, a respiratory infection, a meningitis-encephalitis, a sexually transmitted infection[45]). The arrays are chosen to identify the pathogens that are likely to be important in that syndrome and the drug resistance genes that are likely to be important in that set of pathogens. Consequently, negative results definitively rule out neither infection nor resistance. Furthermore, if your array finds a gene for antimicrobial resistance and a gene for a pathogen, it does not mean that the resistance gene belongs to the pathogen. As with single tests, results can be available in a few hours.
- Next generation sequencing (NGS): While PCR-based molecular diagnostics amplify and identify a specific DNA sequence that is characteristic of a pathogen, NGS captures the pathogen's entire genome. Spectacular declines in cost are making NGS more viable as a routine diagnostic tool. The method is already being piloted in real-world use by the UK's

[44] See, for example, FilmArray (bioMerieux), GI-panel (Luninex), SeptiFast (Roche), Magiplex (Seegene)

[45] There is an interesting recent innovation here. Randox now offers a home testing kit for 10 common pathogens responsible for sexually transmitted diseases. The patient receives a kit in the post, and then mails returns a urine or swab sample to Randox, who run the test. See: http://www.bivda.co.uk/News/PressReleases/tabid/73/articleType/ArticleView/articleId/823/Default.aspx

Health Protection Agency. NGS requires sufficient pathogen-specific DNA. At present, this means that pure cultures are the best starting point. Thus NGS will start after the ~24 hour culture process. NGS presents data handling and data analysis challenges, in so far as sequence data has to be collected and stored, and then compared against up-to-date reference data to allow species identification and to provide an estimate of drug sensitivity. In principle, estimates of drug sensitivity are likely to be more current and perhaps better than those derived from PCR-based molecular diagnostics. However, they will be worse than those derived from conventional in-vitro susceptibility testing.

- Antigen detection: There are a range of commercially available immunological methods[46] which can detect pathogens or substances produced by pathogens in blood or tissue samples (Hazan, 2103).
- Nitrites test and the leukocyte esterase test: I have included this example because it is commonly used at the point of care to help diagnose urinary tract infections. The nitrite and leukocyte esterase tests are generally two of several tests (the others being non-microbiological) that are available on urine dipsticks. Some bacteria convert nitrates in the urine into nitrites. Thus the presence of nitrites in the urine is suggestive of bacterial infection. Leukocytes are white blood cells and are also associated with infection.

Biomarkers of Infection

It is sometimes easier or more effective to base diagnosis on the patient's response to infection, rather than the infectious agent itself. For example:

- Leucocyte counts and C-reactive protein levels: These measures are sensitive (i.e., if you have a bacterial infection, they go up) but they are not specific (i.e., they can also go up if you have a viral infection or for other reasons). Furthermore, they do not help differentiate between different kinds of bacterial infection.
- Procalcitonin: Levels of this hormone precursor tend to rise in bacterial infections but not viral infections. Procalcitonin testing requires a blood sample. The test can be done, just about, at the point of care (but rarely is, even when it is used). The test seems to have some clinical utility. However, procalcitonin levels can be raised by surgery, or injury. It does not seem to rise much in cases of appendicitis (a bacterial infection). It appears that procalcitonin testing has become routine in some countries (e.g., Switzerland) but not others (e.g., the UK).
- Antibody detection: If patients have been exposed to a pathogen, and mount an immune response, they will have circulating antibodies that are specific to that pathogen. Detection of antibodies is the basis of range of a number of routine tests (Hazan, 2103) (e.g., certain HIV tests, although some serological tests are declining in the face of PCR-based molecular diagnostics.

[46] See, for example, agglutination tests, ,

APPENDIX 2. INTERVIEW HIGHLIGHTS

The following pages contain material from interviews with 15 individuals with expertise relevant to the AMR problem[47]. Around half were from the drug industry or pharmaceutical trade associations. Around half were from the diagnostics industry or allied trade associations or consulting firms. We spoke with people from both large and small companies.

We also interviewed an NHS consultant microbiologist on the practicalities of diagnosis and susceptibility testing, and had various other brief discussions with individuals in the venture capital industry, and with participants at a recent conference on antimicrobial drug research and development.

The team also conducted several interviews with regulators at the EMA and MHRA. These are written up in the companion report by Dr John Purves.

Drugs

Drug Regulation

"In broad terms, the regulatory environment has improved over the last 5 years. Regulation no longer appears to be a major barrier. However, the devil is in the detail…."

"The FDA and EMA have put in a lot of work. [Regulation] *is not regarded as a major bottleneck.* [We have] *nothing yet in the clinic, but we could probably access the patients, testing, etc. to run the trials* [we need] *to today, if* [we] *had to.*

"… the regulatory environment has moved and is moving in the right direction, mainly as a result of the GAIN [provisions] *in the US. The FDA and EMA have also converged to an extent."*

"Although there has been a huge improvement in the FDA and EMA regulations, it would still be very helpful if there could be a single unified set of guidelines. [When] *you get into the very gritty details of trial design and end-point measurement, there are still differences. These mean that you take a risk with at least one of the regulators if you optimise your trials for the other one. "*

Drug Financial Attractiveness

"The MAJOR external uncertainty is how – and how much – the company will get paid [if our] *drugs come to market. This is the question that makes the investors scratch their heads more than any other."*

"There is still no consensus among the [big] *drug companies on whether they should be involved in antimicrobials or not. Some firms (e.g., Roche?) seem to be positioning themselves now for the day that commercial route finally becomes clear. Other firms (e.g., AstraZeneca? Biota?)* [seem to be] *either getting out of antimicrobials and/or waiting until the commercialisation route is clear."*

"[The major] *problem is lack of clarity on commercialisation route and pricing. No-one has yet got an antibiotic to market with modern 'orphan' type pricing. Even* [the most] *expensive antibiotics have never cost more than around $5000 per treatment…. This is not an easy problem given payer resistance and the way different kinds of drugs are reimbursed. So, for example, most antibiotics for serious infections are prescribed within the hospital setting and are not reimbursed separately from the rest of the treatment episode* [in contrast, for example, to most cancer drugs or the higher priced orphan drugs]*."*

[47] This Appendix is based on notes we made during interviews, and not on transcripts from recorded conversations. Therefore, it is possible that we have not always captured the detail or the intention of the interviewees.

"There has been a huge amount of work done on business models (i.e., incentives and support to make antibiotic R&D a worthwhile exercise for the commercial sector). There is the O'Neill review for the government. IMI is working on incentives, business models, and value propositions. There is work by Chatham House. There is work by the OHE. Therefore, the policy space is rather crowded and densely filled, and pretty much every conceivable incentive or model has been proposed and evaluated to some extent. What remains is to build some kind of international consensus and then for somebody to actually pay enough money to get things going. Some money is already being paid (e.g., the Wellcome Trust for "push" incentives; BARDA to GSK for an anti-anthrax agent)."

"Some recently approved antibiotics and some current agents [in development] *look much more like corporate social responsibility than good business. AstraZeneca, for example, has a late stage antibiotic that may be developed but is unlikely to generate* [meaningful] *sales. Johnson & Johnson's recent drug for multiple-resistant tuberculosis has a tiny market; only people who have failed numerous other lines of treatment, combined with a low price. It is a piece of philanthropy or enlightened self-interest rather than a commercial proposition. There is also the fact that good new antibiotics are also likely to experience very keen stewardship; i.e., they won't get used much."*

"[Our approach is]*'If we build it, they will come'.* [We are] *going full speed ahead* [on antimicrobial drug R&D] *with no clear view of the reimbursement or payment environment that might be in place by the time the drugs come to market.* [We are] *hoping the market will be ready by the time the drugs arrive. There is a lot of work going on in this area and the problem is soluble, although not yet solved. One can imagine a mixture of a licence payment by countries or insurers in return for the right to use the drug, voucher schemes, and longer exclusivity periods."*

"Most of the larger European [drug] *companies are probably looking for some kind of major risk sharing from government before they can commit seriously. They appear to believe that drug pricing mechanism is unlikely to be able to solve the problem. In other words, the availability of generics for most bugs, the likelihood of stewardship programmes and very restrictive usage for novel agents, will ensure very small sales."*

"From the perspectives of small start-up, the biggest problem relates to the changing demands and/or uncertainty among big drug companies and big biotechs, who are the kind of people who might do a deal [with us to fund R&D]*. It feels as if the goalposts are constantly shifting. This, in turn, may relate to their own uncertainties about the final commercial demand for antimicrobial products."*

"…will governments really coordinate to commit the money? Only the US is really big enough on its own to direct R&D."

"Some of the UK activities look parochial in terms of incentives to bring drugs to market. Some of the parliamentarians don't seem to realize that the UK is irrelevant as a drug market when it comes to stimulating investment. Maybe the US and China get bored waiting for the EU to put serious money towards incentives and go it alone?"

Drug and Diagnostic Complementarity

"There is a huge economic complementarity between rapid diagnostics and antimicrobial drug R&D. The need to pre-treat severely ill patients with a broad spectrum agent while waiting for conventional microbial identification means that trials are bigger, noisier, more expensive. If you really could do rapid diagnosis when patients present, you could run the antibiotic trials much more like some of the recent anti-cancer drug trials; fewer patients recruited, better signal to noise ratio, hence easier and more profitable R&D."

"The ability to diagnose pathogens with specific drug sensitivity or resistance would make a huge difference to the practicalities of using antimicrobial drugs. This appears to have been woefully neglected, given its importance, although there are some encouraging signs from NESTA and the Longitude Prize. Technically, this is a hard nut to crack and there are no easy or obvious mass solutions. If you don't have a quick and cheap diagnostic, new drugs become ultra-specialist life-saving treatments for hospital patients with catastrophic infections. If you have a quick and cheap diagnostic, then the new drugs might be used in the community setting."

"Phages are necessarily narrow spectrum. This means, like some of the other new agents likely to emerge, phage therapy will depend on rapid diagnostics. This is technically feasible already but physicians need to 'wise up'. Some of the best hospital labs can already identify pathogens within a couple of hours"

Support of Preclinical Models for Novel Technologies

"[Our experience with the regulator regarding scientific advice has been positive but the] *regulator is insufficiently sympathetic to "biologically-justified special pleading". In other words, there may be some things that are absolutely necessary for small molecule drugs (e.g. detailed PK/PD) where the standards are not applicable – or at least differently applicable – to a new technology"*

"There are a number of technological strands that may be getting mature enough to look interesting to the drug industry. These include bacteriophages and various immune modifying agents. [The industry] *is already talking with the* [research councils] *about setting up some kind of joint activity to try to work on these things but commercialisation and regulatory paths are largely unknown."*

"People like the MRC and Wellcome Trust could think about investing more to allow academics to do critical proof-of-concept studies for technologies such as phages, oligonucleotides, immuno-modulation (e.g., development of robust animal models of both efficacy and – as far as is possible – tox and safety). These kinds of things are a necessary pre-requisite for serious regulatory consideration. "

Link between Incentives and Regulation

Perhaps going back to the incentives question, but also related to regulation, there does need to be some serious thinking about if or how incentives and regulation are used to deliver a stockpile of antimicrobial drugs, some of which may not be very useful today, but which may become useful if resistance patterns change. For example, how could a regulator adjudicate on the profile of a therapeutic that had a potential future use, and not an actual use today? What about a drug that was slightly worse than today's best available care, but which had a different mechanism of action, so which would still work if today's best available drug stopped working?" [The point here is that such a drug would fail in non-inferiority trials against the best standard of care, so would be unethical to test in clinical trials]

"It is still not obvious how financial incentives and regulation could come together to help the world build a stockpile of antimicrobials that might be more useful in future than they are today. To provide some context, 10 years ago, everyone thought MRSA was going to be the big problem. In fact, we now have much more trouble with resistant gram negative bacteria. 10 years ago, no one was trying to develop anything for resistant gram negatives because we didn't know they would be a problem today. If regulators and payers took a view towards future public health, they would encourage the creation and approval of diverse antimicrobial agents even if not all of them had large, or even obvious, commercial niches today…. there needs to be more thinking about how to incentivise and regulate the creation of stockpile of products (and technological experiences) that might come in handy but which are not important today. Or, to put it another way, it is hard to demonstrate a positive risk-benefit profile [as required by EMA and FDA] *for a product that will only become useful if patterns of antimicrobial resistance chance in response to current selection pressures. However, by the time the resistance patterns have changed, it is too late to come up with something new. "*

Other Comments

"There are huge benefits from the perspective of evolution of resistance if you use narrow spectrum agents. With broad spectrum agents, every bug in the patient is exposed to a selective pressure. With narrow spectrum agents, most bugs in the patient are not exposed to any selective pressure. There is also much less chance then of horizontal acquisition of resistance (i.e., cross-species DNA transfer). This means, among other things, that narrow spectrum agents should have a much longer useful life."

"Expect more combination therapy. Many broad spectrum antibiotics have "promiscuous" / messy target binding profiles; they have to because they have to bind a family of homologous but slightly different protein targets in a wide range of bugs. This also tends to increase their toxicity in man, which in turn often makes combination use difficult. With more selective narrow-spectrum agents, it

should be possible to develop relatively non-toxic combination products from which it will be very unlikely that bacteria evolve resistance. The analogy here is the evolution of combination drugs for HIV and Hep-C. These are now extremely effective, relatively tolerable in man, and hard to evolve around."

"At present, industry is scratching its head thinking about how antimicrobial vaccines would [help with the AMR problem], *with all of the associated questions around regulation and commercialisation. So, for example, if you had a potential MRSA vaccine how and when would you use it? Would you use it prophylactically in people who were going to be admitted to hospital for orthopaedic surgery? What performance would the vaccine require to make this worthwhile (e.g., how long immunity takes to develop, how broad is the immunity, how good is the immunity, etc.). Who would pay for the vaccine? Might there be unintended consequences (e.g., vaccine used to cover for poor hygiene, etc.)?"*

"In general, there is likely to be a move towards narrow spectrum agents in markets with well-developed health systems. However, there will also have to be "reserves" of broad spectrum agents that are used sparingly (e.g., in dangerous sepsis, where you need to treat first and diagnose second) and probably some other broad spectrum agents that remain in widespread community use, particularly in countries that are unlikely to have good diagnostic / susceptibility testing infrastructure. How should one think about managing this portfolio of agents, to maximise the chances that people can get access to treatment, while minimising the risk of unmanageable resistance? A narrow question on the same general topic would be how to manage access as some drugs go off patent. So, for example, linezolid is soon to go off patent. Because, up to now, it has been a patented and relatively expensive drug that is used sparingly in hospitals, antimicrobial resistance to linezolid is not a major problem. Once the drug goes generic, one could imagine that it will be used much more widely. Will it go generic in the West and be sold over the counter in India? Should it? Is there a need for some kind of control mechanisms to provide limited access to generic linezolid in controlled (e.g. hospital) settings? How might such a mechanism work? Another related topic is an analysis of the changes in real-world antibiotic use through genericisation. Do we see a massive uptick in resistance in the community once drugs go generic?"

"The vast bulk of R&D activity that is going on is focused on narrow spectrum agents. These will need accompanying microbiological diagnosis or susceptibility testing. There is [lack of work on new] *broad spectrum agents, where there seems to be very little R&D activity. First, the better a broad spectrum agent there is, the more likely it will face intense "stewardship" and not get used. Second, in good microbiological diagnosis requires a good health system and can be relatively expensive. What this means is that the next generation of narrow spectrum agents may be very useful in developed countries, but are not going to be practically useful in poor countries, unless there is the development of very cheap and flexible diagnostics. This seems a real challenge."*

Diagnostics

IVD Regulation

"The EU regulatory procedure is relatively easy and inexpensive. Much is based around self-certification. The main point is that the diagnostic test has to do what it says it does….. The FDA is very different. There are two pathways. One is for minor modifications to an existing approved device [the 510(k) pathway]. *This can be relatively painless. The other is for wholly novel devices and can involve expensive clinical trials* [the PMA pathway]. *The novel-product FDA pathway is much more expensive and may require clinical trials. In contrast to drugs, where you generally see a global commercial approach that engages both the EMA and FDA roughly simultaneously, many devices are launched in Europe without any necessary ambitions to capture the US market. The prizes in the US are bigger, but so are the costs of getting on the market. Therefore, it often makes sense to launch in Europe under the more benign regulatory environment. Then, if things go well, you can justify the investment required to produce the data for FDA approval."*

"There are big differences between EU and US regulation for in-vitro diagnostics (which are classed as medical devices in both jurisdictions). The US process classes products on the basis of risk, and then

assigns them to one of two routes. The lower risk products are generally approved via the 510(k) route under which they have to show substantial equivalence to an existing product. Under the PMA route, they have to show both technical and clinical validity. Pretty much all companion diagnostics fall within the PMA pathway…. The [current] *EU situation is completely different.* [There is] *just self-certification which leads to CE marking. Companies need to have evidence that the test does what it says it does in narrow technical terms. They don't need to show that it is useful in a clinical sense. The evidence should auditable, but there is no formal regulatory review process. "*

"The CE marking process in Europe seems pragmatic and sensible. It cost us around $1m to do the testing required to validate our test to the CE mark standard and to a standard that we are comfortable with. The main cost [is] *sample acquisition* [i.e., samples of infected and uninfected material from patients]*… I think the current EU system is fine provided that you do post-marketing surveillance. The new EU system will add cost. You will need to get a notified body to audit your calibration work (e.g., BSI). This* [will remain] *less expensive than the FDA, but it is a step-up from what happens now. The new EU system will* [be applied to existing products]. *Companies will have to put their existing tests through the new process over the next 5 years. You will lose the CE mark unless you re-do the validation."*

"The US requirements for sample collection make it hard to validate tests for diseases that are rare in the US. [The FDA] *generally requires that the samples come from US patients.* [The FDA] *generally requires prospective samples (i.e., not from historic tissue banks). This means, for example, you might not get a test approved in the US for an epidemic that had not yet reached the US. In Europe* [it is easier to justify enriching] *the sample set to introduce more positives. This makes validation much easier. Europeans have access to better diagnostic tests. Even big firms like Roche and BD sometimes CE mark their tests in Europe first, and then maybe move the test to the US later. "*

"Companies rarely fail to get regulatory approval for tests, although there are some challenges with more complex multiplexed tests. Imagine, for example, that you have a machine that runs an array of 50 PCR-based genetic tests on lung cancer samples. For, let's say, 6 of the genes you are testing, there are clear and well validated therapeutic consequences (e.g., you should get drug X, or you won't respond to drug Y), but for the other 44, there is only academic research evidence of some influence on risk or drug response. It can be hard to get the entire kit approved [by the FDA] *(or rather, there is haggling over the marketing claims that can be made), because no one really knows what the other 44 tests actually mean. Therefore, you end up with 6 approved tests plus 44 that are "for research use only"…. This is a relevant topic because the firms compete have the broadest panel of tests."*

"[In the US] *IVDs have the same regulatory options as devices. Note that the FDA has trouble getting qualified staff. They are resource limited. This means the FDA tends to be a bottleneck, and misses its targets on regulatory review times."*

"To get approved in the US via the 510(k) path, you need to operate to the US quality standards, with a US quality system. You apply with a dossier of information that proves that your device is substantially equivalent to an existing device that is on the US market. Sometimes companies "bootstrap" their way up the 510(k) process. They apply with a very novel device but do not seek approval for the novel features. Once the novel device is on the market, they put in additional 510(k) applications on a feature by feature basis and build up the marketing claims. One problem here, of course, is that the 510(k) route encourages comparison vs. something that is out of date."

"In my view, there is not a big difference between the kind of evidence you have to show to get 510(k) approval from the FDA and what you would do for a good EU CE mark. However, the FDA is more picky. The FDA does not necessarily trust EU notified bodies (since the IVD firms pay them, among other things)…. The FDA can be more strict about things like inter-operator and inter-site variability [even for 510(k) approvals]*."*

"While the new [EU] *diagnostics directive has not been signed into law, it seems fairly clear how things will end up. There is less clarity regarding new medical device regulations, which are currently being redesigned in parallel with IVD regulations. It looks as if the IVD regulation will come into force in 2015, with a 5 year transition period. In other words, in other words, you are allowed/encouraged*

to put things through the new process from 2015, but everything must have gone through it by 2020. You can still put new tests through the old system until 2020, but this may not be wise as there could be something of a bottleneck in 2020…. In short, the new approach will make it more expensive and demanding (in quality / data / evidence terms) to bring an IVD onto the market in Europe. There will be a move towards a common international template of what is required for regulatory submission. Provided the disease is the same, then the evidence that gets you on the market in Europe in future, should also get you an FDA approval via the 510(k) route."

"While the science is harder than the regulation, keep the size of the diagnostics profit pool in perspective when considering regulatory barriers. Don't discount the regulatory barriers too much. Remember that diagnostics markets are smaller and less lucrative. If you say to a drug industry person that it cost $2m to bring a product through FDA approval they tend to laugh because it is such a small number. However, $2m is a lot of money for many diagnostics companies, and it is also a lot when set against the market for that specific product. "

Other Comments on IVD Innovation

"The short answer is that EU regulatory issues are not the major problem at present when it comes to diagnostics use or diagnostics innovation. The overwhelming barriers are commercialization and adoption; in getting things bought by health systems. [Health systems] *exist in silos. New things are hard to fit into existing budgets."*

"One practical challenge with the new technologies is that they tend to be additive rather than "instead-of" the old technology. Labs still have to run all the old stuff, while adding the new stuff. This means they make things more costly."

"Turning to the main problems: reimbursement, access, and adoption: We see lots of very good tests that never get adopted in the market. The laboratories are a volume business, where the diagnostics firms make money with the platform (i.e., a big machine) and/or the consumables (the tests). The consumable market depends on volume. You struggle with expensive, low-volume, non-routine tests. In oncology, the expectation is that the drug company pays for the development of the companion diagnostic [to help sell an expensive and profitable drug], *because the diagnostics firm would not see a return on its investment. The more complex and esoteric your diagnostic test, the less attractive it is to a diagnostics company."*

"Drug firms love the idea of point of care tests, because they can drive use of their particular drug. However, there are lots of practical problems. First, point of care tests have to be completely "idiot proof". This means the regulatory standards tend to be higher. Second, the drug firms forget that the patient usually takes a cocktail of drugs and has a whole lot of things wrong with them, so the doctor is rarely interested in taking the time to do a test that tells [him or her about] *just one thing. It is often easier for the doctor to get the nurse to take a blood sample and send it to lab to measure everything at the same time."*

"…the ideal test is very boring. It should provide new information but change absolutely nothing else about the way the physician works. If you have to hope that you change how the physician works, you generally fail to get adoption. To give you an example, suppose you wanted a point of care blood test to help psychiatrists in the US to get their drug dosing right. Well, most community psychiatrists haven't taken blood for 30 years, and they don't have practice nurses. Therefore, this plan would be dead in the water. Also, if the test adds 5 minutes to a primary care consultation, it will struggle. Etc., etc. The GP market is very conservative. They cannot and do not stay abreast of everything. In some ways, that is absolutely right. The specialists are different, and it is easier to slot a new test into a lab (provided it is not expensive or esoteric)."

"The main barriers for the diagnostics companies are not regulatory. They relate to reimbursement, access, and adoption. [The IVD companies] *generally know how to get through the FDA and EU requirements. It might cost them $2m or $3m to do the studies for the PMA process for a modest panel of PCR-based molecular diagnostics…... However, they then hit the adoption barrier. In Germany, for example, the health system will not pay for next generation sequencing. There are machines sitting*

idle in pathology labs because no-one will pay for their use. Next generation sequencing seems to have more routine clinical use in the US already, but certainly not in Europe."

"The science in harder than the regulation. With point of care diagnostics, for example, there is a real question about what you should actually measure. If, for example, you want to distinguish between a bacterial infection and a viral infection with a point of care device, then you are probably going to want to combine measures of things that the patient produces in response to infection. You might combine procalcitonin (which is OK but not great on its own as a marker of bacterial infection) with other markers of the patient's response such as cytokines. But which cytokines? How do you aggregate the results of several different biomarkers to optimise test performance? These are scientific questions in the first instance."

"Panels of molecular tests often end up being costly [to administer]*, particularly if you are looking for relatively rare diseases. To give an example, in lung cancer, the drug* [crizotinib] *works very well in the 5% of lung cancer patients with an ALK mutation. That means you have to test 20 patients to get a single positive. Even if each test is "only" 500 Euros* [to the health system, including collecting the tissue sample, etc.]*, this means you spend 10,000 Euros per patient detected. The expectation in oncology is that the drug company ends up paying for the companion diagnostic. The mechanics of this varies between countries, but the drug company always pays."*

"When you have multiplexed tests [i.e., a panel of tests for different pathogens run simultaneously using the same test kit on the same machine]*, the cost of validation* [in R&D] *goes up. So, for example, consider a panel of tests for sepsis. Practically any bacteria can cause sepsis in certain patients. Technically, we could easily make a panel of 100 yes/no PCR tests. However, it is only the 10 most common pathogens that you encounter frequently enough to effectively validate the tests. With the very rare pathogens, you cannot estimate your false positive and false negative rates without testing an inordinately large number of samples, the overwhelming majority of which will be negative. Importantly, AMR is still relatively rare and specific mechanisms of resistance are often very rare. Therefore, broad panels of PCR-based tests for resistant bugs will be expensive to validate."*

"…. the NHS is not interested in helping with sample collection. Nor is it attractive as a customer. The NHS insists on proving cost effectiveness. What this means is that they expect the diagnostics firm to pay for a big study in various UK hospitals before they think about buying anything. However, it sometimes costs you more to prove to the NHS that your test is cost effective, than you would ever make from the test if the NHS became your customer."

"Very few UK SMEs find the UK / NHS a particularly amenable customer. Scandinavia, Germany, France, Switzerland, etc., (in fact, most places other than the UK in Western Europe) are easier markets to sell to."