AAC Accepts, published online ahead of print on 29 July 2013
Antimicrob. Agents Chemother. doi:10.1128/AAC.01277-13

Commentary: The FDA Reboot of Antibiotic Development

David M. Shlaes MD, PhD[1], Dan Sahm PhD[2], Carol Opiela[2] and Brad Spellberg MD[3]

1. Anti-infectives Consulting, LLC, Stonington, CT, USA.
2. Eurofins Global Central Laboratory, Chantilly, Virginia, USA
3. Division of General Internal Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center; The David Geffen School of Medicine at UCLA, Los Angeles, California

Running Title – FDA Antibiotic Reboot

Correspondence to:

David Shlaes

Anti-infectives Consulting, LLC

219 Montauk Ave.

Stonington, CT 06378

Shlaes.david@earthlink.net

(*The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.*)

In May of 2012 a number of us listened spellbound as Janet Woodcock of the FDA announced at a meeting at the Brookings Institute that the agency would "reboot" their entire approach to antibiotic development (1). She recognized that there is a public health crisis of antibiotic resistance that continues to grow worse, and that development of new antibacterial agents to deal with the threat is inadequate. Finally, she acknowledged that the approach taken by the Office of Antimicrobials at FDA to change clinical trial designs for antibacterial agents over the past decade had contributed to this crisis. Dr. Woodcock went on to emphasize the need for a new pathway for development focusing on patients with unmet medical needs – that is those with infections due to pathogens that are pan-drug resistant (PDR) or that are extremely drug resistant (XDR) (2). Further discussion showed that the agency also understands that development for traditional indications such as pneumonia also needs "rebooting." Their thoughts on the reboot follow the recommendations of a working group from the pharmaceutical industry (3). How and why did we get here?

The first warning of the exodus of industry from antibacterial development was published as far back as 2002 [4]. The change in industry interest in this area was due to a convergence of unattractive economics around antibacterial development [5-7] combined with a fundamental re-think regarding statistical principles of non-inferiority trial designs that began in the late 1990s [8-10]. Although this re-think was not specific to antibacterial agents, it disproportionately affected antibacterial development [9]. A dangerous inflection point occurred in 2006, after the public spectacle surrounding telithromycin, which was discovered to cause very rare but life-threatening hepatotoxicity only after the drug was approved [9-11]. Ironically,

this statistical re-think focusing entirely on proving efficacy (and doubting that antibiotics were effective) had been triggered by a safety problem with telithromycin [10).

In the aftermath of telithromycin, FDA rules governing trial conduct became increasingly stringent, to the point of making antibacterial trials infeasible, non-sensical, or both. For example, changes to trial design meant to increase the scientific purity of the trials (such as excluding any patients who receive even 1 dose of pre-study antibiotic from enrollment in a clinical trial) made it virtually impossible to enroll patients into the trials in the US. Worries that antibiotics were no more effective than placebo were finally put to rest by the FDA's own analysis of pre-antibiotic era data showing treatment effects consistently higher than 20% and frequently over 50% depending on the infection (eg, 12, 13). In spite of these large treatment effects, some of which would justify non-inferiority margins greater than 20%, the FDA always "discounted" the treatment effect by a sufficient amount such that the resulting non-inferiority margins were always 10% (lower margins = higher samples sizes, more patients and greater costs) (14).

A new endpoint for skin infections was developed in which patients whose infections have not improved at all after 3 days of therapy are declared treatment successes merely because they stop getting worse [15-16]. This endpoint was convenient for statisticians because they could comfortably calculate a treatment effect of oral sulfonamide antibiotics versus placebo-equivalent (UV lamp therapy) based on unverifiable data from two studies published in 1937 (in which

65 background therapy for skin infections consisted of a liquid diet and a mandatory
66 hot-liquid paraffin soap-and-water enema) [17-18]. The endpoint used in these 80
67 year-old studies was cessation of spread of the skin lesion. Although this did
68 provide a feasible way forward for companies desiring to develop antibiotics for
69 skin infection, this endpoint, in our view, is invalid and has little clinical relevance
70 (19).

71 Clearly the FDA process of determining how antibacterial trials should be
72 conducted has badly lost its way. (For a general overview on this opinion, see
73 reference 19). As a result, 1) many companies do not invest in the trials; 2) those
74 that do enroll patients where it is possible to withhold therapy while the patients
75 are enrolled in trials, with resulting ethical concerns; 3) the results become less
76 meaningful and relevant to patients in the US because US patients are not enrolled.
77 Pharmaceutical companies have voted with their feet. Twenty years ago, more than
78 twenty large companies had active discovery and development programs for
79 antibacterial agents; in 2013, only four have active discovery programs (20). Our
80 approval rate for new antibiotics has fallen to dismally low levels (Figure 1).

The combination of the above has logically contributed to the hesitancy of companies to invest in the area and has led to a lack of both antibacterial drugs in the pipeline and to an absence of ongoing trials in indications where trial designs required by FDA are infeasible such as pneumonia. The FDA now recognizes that not having a robust antibiotic pipeline is a risk to patient health and safety and this recognition has, in part, led to their decision to "reboot."

At the same time, antibiotic resistance has continued its inexorable climb globally. The United States is no exception to rising resistance as recent data published by the Centers for Disease Control has dramatically shown (21,22). This clearly represents a major risk to patient health and safety and it is this medical need that drives the urgency of the FDA reboot.

We have carried out our own analysis of the situation in the US (Table). The data are derived from hospitals distributed throughout the US and, we believe, provide a fair picture of the US as a whole (supplemental table 1). In fact, this database was, in part, used by the CDC for their study (21).

As background for our view of the FDA and its implications for public health, it is worthwhile considering the rules governing new antibiotic development in terms of risk and benefit. The risk is that of a highly resistant infection. The benefit is that of having an approved, efficacious antibiotic prescribed early. Towards this end, we carried out an analysis of data from Eurofin's TSN surveillance of resistance in the US. The methods for obtaining these data are provided in supplemental Materials and Methods as are a list of geographic locations of sites providing the data. We

analyzed data for the years 2009-2012. Because there was little variation for these years among the strains and resistance monitored, we present average data here. In the report from CDC in 2008, taken from ICU isolates, the resistance among *E. coli* to third generation cephalosporins was 5% while in our analysis (using different methods) it stands at 8-11%. *K. pneumoniae* resistance to third generation cephalosporins was 15% in the CDC study. In our updated analysis it ranges from 20-27%. Resistance to carbapenems among these isolates is now between 7 and 11%. For *A. baumannii* the resistance is even more drastic. In the CDC report 11% were carbapenem resistant while our data show that number to be over 50%.

These data indicate that for *Acinetobacter baumannii* infections, the carbapenems are already obsolete. This holds true for both intensive care and non-intensive care patients and for urinary and non-urinary infections. The same can be said for our third-generation cephalosporins (here indicated by ceftazidime) in the treatment of *K. pneumoniae* infections. For these organisms, the carbapenems are also rapidly losing efficacy. Even among *E. coli* isolates, our third generation cephalosporins are no longer completely reliable although the carbapenems remain a solid backup.

Our late stage pipeline does hold out some hope for treating these infections, but none of the pipeline antibiotics by themselves can address all these resistance problems. We will therefore continue to confront serious infections caused by pathogens for which are treatment options are either limited or non-existent [23].

With this picture in mind, we need to examine the role of our regulatory system in bringing needed new antibiotics to the patients and physicians who need them. As

has been documented repeatedly by the Infectious Diseases Society of America and others, the approval rate of the FDA for new antibiotics is dismal and getting worse (Figure 1).

It has now been over a year since the FDA's announcement of the "reboot" of their approach to antibacterial drugs. Just two days after the submission of this manuscript, the FDA released their guidance on antibacterial therapies for patients with unmet medical needs (24). There are a number of very positive aspects to this guidance and much of it follows prior discussions that have occurred in the context of the Brookings Institute. To us, the two most promising aspects of the guidance are (1) the open attitude of the FDA to discussion of novel trial designs with sponsors and (2) their willingness to consider externally or historically controlled studies. The latter could include pharmacometric approaches to establishing control levels of response as has been suggested previously (2). The FDA suggests that safety databases as small as 300 patients might be acceptable in the context of unmet needs. For other details, readers are referred to the guidance document itself (24).

It is also clear from discussions with the agency that their approach to the development of antibacterials in traditional indications such as pneumonia and urinary tract infection has been mixed. In a clear sign of progress, they now allow approval for two indications (e.g. cUTI and cIAI) following a single trial in each. But the continued existence of now outdated guidance (e.g. CABP, HABP, VABP) remains confusing to industry. The FDA has not indicated whether they will rescind their

current guidance requiring what they now recognize are infeasible trial designs and, sometimes, irrelevant endpoints

We must recognize that regulatory reform may not be enough to entice large pharmaceutical companies to restart or even continue their efforts in antibacterial research and development. For example, Astra-Zeneca has announced that they will "reduce" their investment in antibacterial research in favor of other therapeutic areas. While they recognize that progress is occurring at FDA, they remain concerned about the potential return on their investment in the antibacterial space. Without the participation of industry, especially that of the large companies, our pipeline will continue to lie fallow for years to come.

Antibiotic resistance is already at crisis levels in US hospitals, especially in intensive care units. Our current late stage pipeline will address some of these resistant pathogens, but not all. That said, the complete FDA reboot cannot come too soon. It is becoming clear, though, that even this will not be enough. Industry must also clearly see that there is a path for a return on their investment in antibiotics. This will probably require, at the very least, one company to bring one of the late stage drugs with activity against resistant pathogens all the way to the marketplace such that pricing negotiations can occur. These negotiations will become as critical as the FDA reboot. We hope that value-based pricing and a rebooted FDA process will both come to pass. The alternative is too terrible to contemplate.

167 1. Facilitating Antibacterial Drug Development
168 http://www.brookings.edu/~/media/events/2012/5/09%20antibacterial%20dru
169 g%20development/may%209%20event%20summary.pdf

170

171 2. Spellberg B, Brass EP, Bradley JS, Lewis R, Shlaes D, Ambrose P, Das A, Boucher
172 HW, Doi Y, Bartlett JG, Bonomo RA, Larosa SP, Talbot GH, Benjamin D, Guidos RJ,
173 Jezek A, Gilbert DN, on behalf of the Infectious Diseases Society of America. White
174 Paper: Recommendations on the Conduct of Superiority and Organism-Specific
175 Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by
176 Drug-Resistant Bacterial Pathogens. 2012. Clin Infect Dis. 55:1031-46.

177

178 3. Rex JH, Eisenstein BI, Alder J, Goldberger M, Meyer R, Dane A, Friedland I, Knirsch C,
179 Sanhai WR, Tomayko J, Lancaster C, Jackson J. A comprehensive regulatory framework
180 to address the unmet need for new antibacterial treatments. Lancet Infect Dis. 2013
181 Mar;13(3):269-75.

182

183 4. Shlaes DM, Moellering RC Jr.. The United States Food and Drug Administration and
184 the End of Antibiotics. Letter, Clin Infect Dis 34:420-22, 2002.

185

186 5. Projan SJ, Shlaes DM. Antibacterial drug discovery: is it all downhill from here? Clin
187 Microbiol Infect. 2004 Nov;10 Suppl 4:18-22.

188

6. Sharma P and Towse A. New Drugs to Tackle Antimicrobial Resistance: Analysis of EU Policy Options. 2011. Office of Health Economics, at http://www.ohe.org/fileadmin/user_upload/Publications_PDF/NewDrugsToTackle_April2011.pdf

7. Spellberg B, Sharma P, Rex J. The Critical Impact of Time Discounting on Economic Incentives to Overcome the Antibiotic Market Failure. Nat Rev Drug Discovery. 2012. 11:168.

8. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. Ann Intern Med. 2000 Sep 19;133(6):455-63.

9. Spellberg B. "The Antibacterial Pipeline: Why Is It Drying Up and What Must Be Done About It?" In: Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies: Workshop Summary. Institute of Medicine. Rapporteurs: Choffnes ER, Relman DA, Mack A. 2010. National Academies Press, Washington D.C., pp 299-332, 2010.

10. Echols R. A long and winding road; evolution of antimicrobial drug development - crisis management. Expert Rev Anti Infect Ther 2012. 10:1311-8

11. David M. Shlaes and Robert. C. Moellering Jr. Telithromycin and the FDA: Implications for the Future. Lancet ID, 2008.

12. Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM123686.pdf

13. Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf

14. Shlaes, DM. Antibiotics – The Perfect Storm. Chapter 4, The FDA, Springer-Verlag, 2010.

15. Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf

16. Spellberg B. Acute Bacterial Skin and Skin Structure trials: The Bad is the Enemy of the Good. Clin Infect Dis. 2011. 53:1308-9.

234

235 17. Snodgrass WR, Anderson T. Prontosil in the treatment of erysipelas. A controlled
236 series of 312 cases. BMJ 1937; 2:101–4.

237

238 18. Snodgrass WR, Anderson T. Sulphanilamide in the treatment of erysipelas: a
239 controlled series of 270 cases. BMJ 1937; 2:1156–9.

240

241 19. Spellberg B.
242 http://www.brookings.edu/~/media/events/2012/5/09%20antibacterial%20drug%
243 20development/panel%201%20brad%20spellberg%20presentation

244

245 20. Cooper, M and Shlaes DM. Fix the Antibiotic Pipeline. Nature. 472: 32, 2011.

246

247 21. Vital signs: carbapenem-resistant Enterobacteriaceae. Centers for Disease Control
248 and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 2013 Mar 8;62(9):165-70.

249

250 22. Alicia I. Hidron, MD; Jonathan R. Edwards, MS; Jean Patel, PhD; Teresa C. Horan,
251 MPH; Dawn M. Sievert, PhD; Daniel A. Pollock, MD; Scott K. Fridkin, MD. Antimicrobial-
252 Resistant Pathogens Associated With Healthcare-Associated Infections: Annual
253 Summary of DataReported to the National Healthcare Safety Network at the Centers for
254 Disease Control and Prevention, 2006–2007. Infection Control and Hospital
255 Epidemiology 2008,. 29:996-1011.

256

23. Brad Spellberg, M.D., John G. Bartlett, M.D., and David N. Gilbert, M.D. The Future of Antibiotics and Resistance. N Engl J Med 2013; 368:299-302.

24. Guidance for Industry Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf

Table: Resistance among key Gram negative pathogens in US hospitals 2009-2012.

Non Urinary Isolates

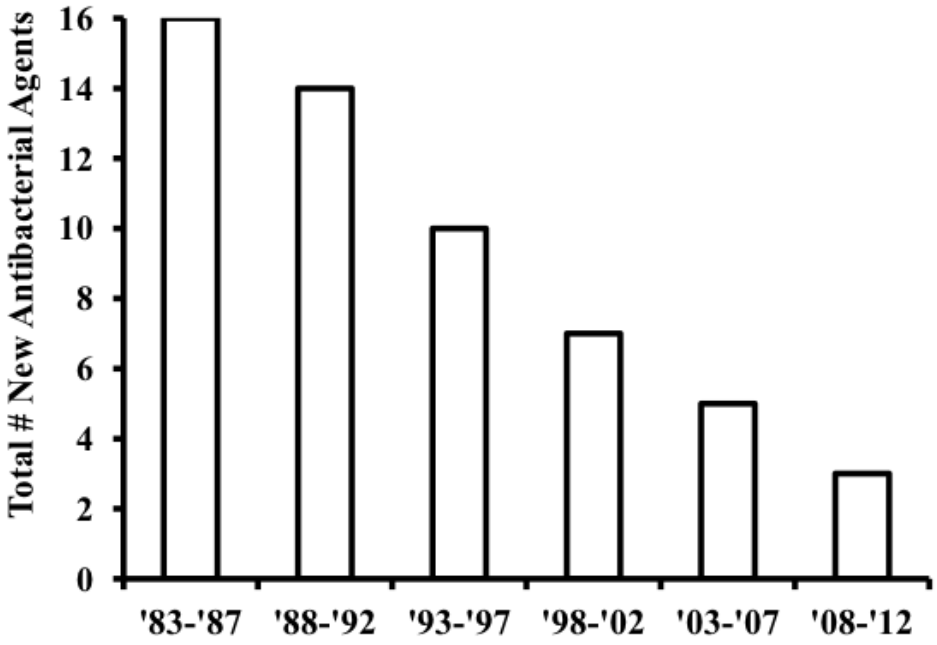
	ICU				Non-ICU			
	Ceftazidime-resistant(N)		Imipenem-resistant (N)		Ceftazidime-resistant (N)		Imipenem-resistant (N)	
E. coli	11.0%	(3084)	0.3%	(3287)	6.9%	(43,445)	0.1%	(47,559)
K. pneumoniae	26.8%	(1780)	11.5%	(1907)	14.5%	(16,475)	5.8%	(17,228)
A. baumannii	60.1%	(550)	52.0%	(535)	35.4%	(5532)	28.0%	(4370)
P. aeruginosa	18.6%	(2615)	23.2%	(2869)	7.3%	(35,210)	8.4%	(35,810)

Urinary Isolates

	ICU				Non-ICU			
	Ceftazidime-resistant (N)		Imipenem-resistant (N)		Ceftazidime-resistant (N)		Imipenem-resistant (N)	
E. coli	8.0%	(10,258)	0.1%	(11,537)	3.7%	(744,532)	0.0%	(794,072)
K. pneumoniae	19.3%	(3583)	7.1%	(3834)	8.0%	(130,088)	2.4%	(131,464)
A. baumannii	71.7%	(247)	56.7%	(230)	37.1%	(3,436)	23.9%	(2,758)
P. aeruginosa	13.8%	(3056)	17.5%	(3285)	5.8%	(53,835)	8.8%	(52,758)

N= number of isolates tested

269 Figure 1. Antimicrobial Agents Approved by FDA.



270

271

Table: Resistance among key Gram negative pathogens in US hospitals 2009-2012.

Non Urinary Isolates

	ICU				Non-ICU			
	Ceftazidime-resistant(N)		Imipenem-resistant (N)		Ceftazidime-resistant (N)		Imipenem-resistant (N)	
E. coli	11.0%	(3084)	0.3%	(3287)	6.9%	(43,445)	0.1%	(47,559)
K. pneumoniae	26.8%	(1780)	11.5%	(1907)	14.5%	(16,475)	5.8%	(17,228)
A. baumannii	60.1%	(550)	52.0%	(535)	35.4%	(5532)	28.0%	(4370)
P. aeruginosa	18.6%	(2615)	23.2%	(2869)	7.3%	(35,210)	8.4%	(35,810)

Urinary Isolates

	ICU				Non-ICU			
	Ceftazidime-resistant (N)		Imipenem-resistant (N)		Ceftazidime-resistant (N)		Imipenem-resistant (N)	
E. coli	8.0%	(10,258)	0.1%	(11,537)	3.7%	(744,532)	0.0%	(794,072)
K. pneumoniae	19.3%	(3583)	7.1%	(3834)	8.0%	(130,088)	2.4%	(131,464)
A. baumannii	71.7%	(247)	56.7%	(230)	37.1%	(3,436)	23.9%	(2,758)
P. aeruginosa	13.8%	(3056)	17.5%	(3285)	5.8%	(53,835)	8.8%	(52,758)

N= number of isolates tested

Figure 1. Antimicrobial Agents Approved by FDA.