

1 Commentary: The FDA Reboot of Antibiotic Development

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11 Running Title – FDA Antibiotic Reboot

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18 *(The views expressed in this Commentary do not necessarily reflect the views of the*

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

34 The first warning of the exodus of industry from antibacterial development was
35 published as far back as 2002 [4]. The change in industry interest in this area was
36 due to a convergence of unattractive economics around antibacterial development
37 [5-7] combined with a fundamental re-think regarding statistical principles of non-
38 inferiority trial designs that began in the late 1990s [8-10]. Although this re-think
39 was not specific to antibacterial agents, it disproportionately affected antibacterial
40 development [9]. A dangerous inflection point occurred in 2006, after the public
41 spectacle surrounding telithromycin, which was discovered to cause very rare but
42 life-threatening hepatotoxicity only after the drug was approved [9-11]. Ironically,

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

46 In the aftermath of telithromycin, FDA rules governing trial conduct became
47 increasingly stringent, to the point of making antibacterial trials infeasible, non-
48 sensical, or both. For example, changes to trial design meant to increase the
49 scientific purity of the trials (such as excluding any patients who receive even 1 dose
50 of pre-study antibiotic from enrollment in a clinical trial) made it virtually
51 impossible to enroll patients into the trials in the US. Worries that antibiotics were
52 no more effective than placebo were finally put to rest by the FDA's own analysis of
53 pre-antibiotic era data showing treatment effects consistently higher than 20% and
54 frequently over 50% depending on the infection (eg, 12, 13). In spite of these large
55 treatment effects, some of which would justify non-inferiority margins greater than
56 20%, the FDA always "discounted" the treatment effect by a sufficient amount such
57 that the resulting non-inferiority margins were always 10% (lower margins = higher
58 samples sizes, more patients and greater costs) (14).

59 A new endpoint for skin infections was developed in which patients whose
60 infections have not improved at all after 3 days of therapy are declared treatment
61 successes merely because they stop getting worse [15-16]. This endpoint was
62 convenient for statisticians because they could comfortably calculate a treatment
63 effect of oral sulfonamide antibiotics versus placebo-equivalent (UV lamp therapy)
64 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).

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

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

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

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

103 analyzed data for the years 2009-2012. Because there was little variation for these
104 years among the strains and resistance monitored, we present average data here.
105 In the report from CDC in 2008, taken from ICU isolates, the resistance among *E. coli*
106 to third generation cephalosporins was 5% while in our analysis (using different
107 methods) it stands at 8-11%. *K. pneumoniae* resistance to third generation
108 cephalosporins was 15% in the CDC study. In our updated analysis it ranges from
109 20-27%. Resistance to carbapenems among these isolates is now between 7 and
110 11%. For *A. baumannii* the resistance is even more drastic. In the CDC report 11%
111 were carbapenem resistant while our data show that number to be over 50%.

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

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

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

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

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

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

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

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

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

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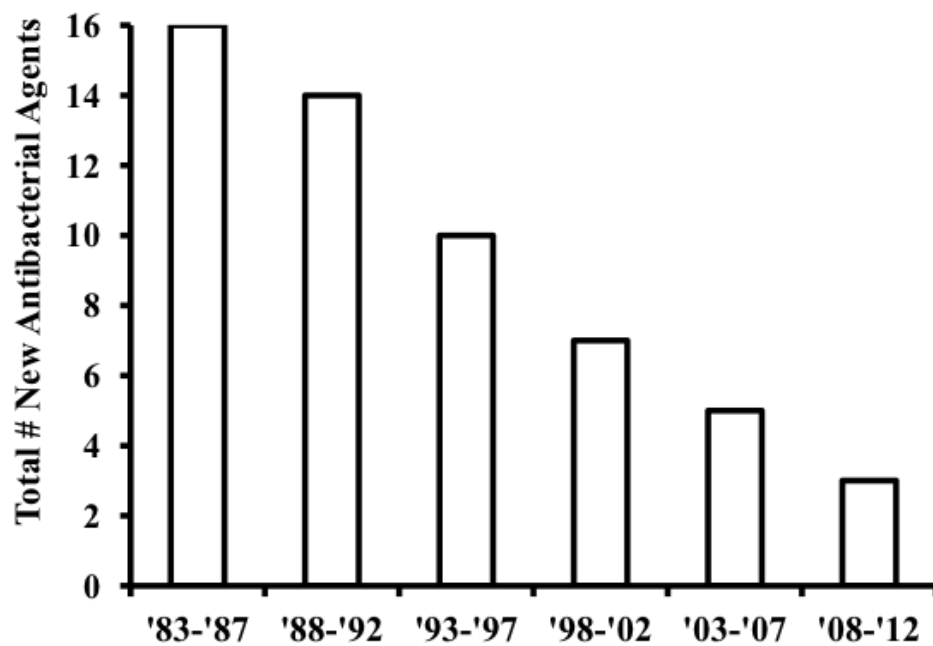
Table: Resistance among key Gram negative pathogens in US hospitals 2009-2012.

	Non Urinary Isolates							
	ICU				Non-ICU			
	Ceftazidime-resistant(N)		Imipenem-resistant (N)		Ceftazidime-resistant (N)		Imipenem-resistant (N)	
<i>E. coli</i>	11.0%	(3084)	0.3%	(3287)	6.9%	(43,445)	0.1%	(47,559)
<i>K. pneumoniae</i>	26.8%	(1780)	11.5%	(1907)	14.5%	(16,475)	5.8%	(17,228)
<i>A. baumannii</i>	60.1%	(550)	52.0%	(535)	35.4%	(5532)	28.0%	(4370)
<i>P. aeruginosa</i>	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)	
<i>E. coli</i>	8.0%	(10,258)	0.1%	(11,537)	3.7%	(744,532)	0.0%	(794,072)
<i>K. pneumoniae</i>	19.3%	(3583)	7.1%	(3834)	8.0%	(130,088)	2.4%	(131,464)
<i>A. baumannii</i>	71.7%	(247)	56.7%	(230)	37.1%	(3,436)	23.9%	(2,758)
<i>P. aeruginosa</i>	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.



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