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**U.S. Department of Health
And Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852**

RE: Comments related to Draft Guidance Docket # 1557

Dear Sir/Madam:

**Please find attached comments regarding the Draft Guidance for Industry and FDA Staff:
Premarket Notification [510(k)] Submissions for Medical Devices that include
Antimicrobial Agents – Docket # 1557.**

Sincerely,

**George E. Pierce
Professor
Applied & Environmental Microbiology**

2007D-0201

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Antimicrobial agents and the emergence of “resistance”.

The statement....”To say that any antimicrobial agent.... may result in the emergence of resistance”, while inherently correct is a generalization. Likewise to say that antimicrobial resistance is an increasing problem, while stating a generally recognized concern fails to address the complexity of antimicrobial resistance. Resistance has in fact not increased for all microbial infectious agents of concern. For example, the NNIS August 2003 report showed that there was actually a decline in the percentage resistant of both *Klebsiella pneumoniae* and *Enterobacter spp.* to 3rd generation cephalosporins over the period 1997-2001 versus that seen in 2002. This information when placed with other data tracking drug resistance, does not diminish concerns related to antibiotic resistance/tolerance but places that information in a proper context. (see attached Table)

Also of concern are the identification of other microorganisms. For example, similar to the trend seen with CVCs and VAPs for increased infections involving inherently resistant non-albicans or non-aeruginosa species respectively, recent reports of intrinsically resistant / multiple resistant isolates are seen in CAUTIs. In an additional example, Lombardi, *et al.*, [2002] reported, over a three year period, the isolation of carbapenem resistant *P. putida* strains, (predominantly from UTIs) Sequence analysis and mapping multidrug resistant, VIM-1 metallo- β -lactamase in *P. putida* infections over a 9 month period in a single hospital ICU and subsequent with other hospitals in Italy suggests horizontal gene transfer, in the group I pseudomonads and common ancestry to In70 in *Achromobacter xylosoxidans*.

A second example relates to the colonization by and the incidence of *Candida* infections, and candidemia in neutropenic patients, and bone marrow transplants in particular which is quite high. In an analysis of 296 Bone Marrow Transplants (BMTs), colonization by *Candida ssp.* was shown to approach 80% [Wingard, *et al.*, 1991]. As a result of the high incidence of *Candida* infections associated with bone marrow transplants, fluconazole was administered prophylactically. With prophylactic administration of fluconazole, the incidence of *C. krusei* colonization increased significantly. It was further noted by Wingard, *et al.*, [1991] that all of the *C. krusei* infections responded to amphotericin B. Based upon this new information the protocol for BMTs was amended in that Fluconazole was still administered prophylactically to address potential infections by *C. albicans* or *C. tropicalis* but if the patient became febrile, amphotericin B (or amphotericin B and flucytosine) also was administered. It was at this point, that Wingard, *et al.*, [1993] noted an increase in *C. glabrata* infections [*C. glabrata* comprised 75% of the 10% overall *Candida* infections noted in the BMTs receiving both fluconazole and amphotericin B.]

While the non-albicans species (*C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) show a decreased sensitivity to fluconazole, these same species with the exception of *C. glabrata* show sensitivity to the newer generation azole antimycotics such as ravuconazole. [Pfaller, *et al.*, 2004a]. In a study of *C. glabrata* isolates (conducted from 2001 through 2002), the resistance/sensitivity profiles to the new azole antifungals, demonstrated a significant geographic variability [Pfaller, *et al.*, 2004b]

Risk of Infection.

CAUTIs (Catheter Associated Urinary Tract Infections) are the most common nosocomial infection in the United States with over 1 million patients affected annually in ICUs and Extended Care Facilities [Orenstein and Wong, 1999; Maki and Tambyah, 2001, Wong, 2004]. It is estimated [Maki and Tambyah, 2001] that the risk of CAUTI after 7 days increases 5% per day. While *P. aeruginosa* account for 11-12% of CAUTIs for both short and long term catheterization, *Candida* infections which account for 9% of all CAUTIs for <7 days, increase to 25% of all CAUTIs for catheterization beyond 7 days.

Geographical and Source Differences in Clinical Isolates

The following examples are provided to show the source variability present in clinical isolates.

In their 3-year prospective study, Valles, *et al.*, [2004] reported *P. aeruginosa* colonization in 50% of the intubated patients. While it was shown that exogenous strains of *P. aeruginosa* accounted for 70% of the colonization isolates, 50% of the *P. aeruginosa* VAP (Ventillator Associated Pneumonia) cases were caused by endogenous strains.

Based upon chromosomal fragment pattern analysis of PFGE (pulsed field gel electrophoresis) of restricted chromosomal-DNA obtained from endotracheal tube biofilm, and from lower respiratory tract secretions in 15 patients with recurrent VAP, Cai *et al.*, [2001] showed virtually indistinguishable patterns of *P. aeruginosa* of endotracheal tube biofilm isolates versus lower respiratory secretions in 6 of the 15 recurrent cases. Based upon their findings, Cai, *et al.*, [2001] suggest that both environmental and endogenous sources of *Pseudomonas aeruginosa* need to be considered when developing and assessing strategies for reducing VAP. This suggestion received previous support in the summary recommendations from the 5th NIAID Workshop in Medical Mycology [2000].

Role of Colonization / Biofilm Development.

In the strictest sense, colonization of a medical device does not necessarily correlate with or is a predictor of device associated nosocomial infection. Fundamentally, however, microbial colonization events raise issues of concern.

In addressing the recalcitrant nature of biofilm associated infections to treatment, Trautner and Darouiche [2004] have proposed a model for the development of biofilms associated with urinary catheters that is essentially the general model proposed for biofilm development by Costerton, *et al.*, 1995; Denstedt, *et al.*, [1998]; Pratt and Kolter [1998]; Davies *et al.*, [1998], Kolter and Losick [1998]. This model recognizes four phases of biofilm development: a) deposition on the catheter, b) primary attachment, c) cell division and recruitment, and d) the mature biofilm as depicted by the "coral model with communicating channels". In their model, Trautner and Darouiche [2004] have suggested that devices impregnated with or coated with antimicrobials may be rendered ineffective during the first phase of biofilm development. With respect to some of the early devices impregnated with or coated with an antimicrobial, it has been suggested that early leaching/release of the agent from the device also can contribute to loss in effectiveness [Walder, *et al.*, 2002].

The research of Jabra-Rizk, *et al.*, [2004] with mature biofilm cells, and Mateus, *et al.*, [2004], with primary attached cells, (but each with different strains of *Candida albicans*) both showed a significant decrease in sensitivity (*i.e.*, increased tolerance) to selected azole antimicrobials by the attached cells versus respective planktonic cells. While not discounting the mechanisms suggested by Trautner and Darouiche [2004] and Walder, *et al.*, [2002] for loss of effectiveness in devices incorporating antimicrobials, the decreased sensitivity to antibiotics/antimicrobials by cells attached to device surfaces may represent an important mechanism for apparent antimicrobial resistance in device associated infections, and may contribute to the problem of drug resistance/tolerance.

Jabra-Rizk, *et al.*, [2004] implicated the *CDR* genes, *CDR1* and *CDR2*, which both encode ATP-binding cassette transporters, for decreasing the fluconazole sensitivity of *C. albicans* in mature biofilms (24-48 hours). Mateus, *et al.*, [2004] have shown that there is a third export transport protein, encoded by *CaMDR1* which also is involved in decreased fluconazole sensitivity in primary attached cells (early biofilm development) of *C. albicans*. Whereas Jabra-Rizk, *et al.*, [2004] had shown that decreased sensitivity to fluconazole required some time to develop, Mateus, *et al.*, [2004] have shown that decreased fluconazole sensitivity develops quite rapidly in *C. albicans* CaI4 cells attached to medical grade silicone. Furthermore, using null mutants it was shown that primary attached cells deficient in *CaMDR1*, *CDR1*, and *CDR2* exhibited the same level of fluconazole resistance as planktonic cells. Wild-type cells of *C. albicans* CaI4, when attached to medical grade silicone showed 2X and 5X increased levels respectively in the expression of the promoters of *CaMDR1* and *CDR1*. Primary attached, isogenic mutants deficient in *CaMDR1* were 10 fold more sensitive to fluconazole than primary attached CaI4 cells, while double mutants deficient in both *CaMDR1* and *CDR1* were 100 fold more sensitive to fluconazole than primary attached CaI4 cells.

With respect to CAUTI's, Karchmer, *et al.*, [2000] in a 12 month study of 27,878 patients showed a 32% reduction in the risk of infection when silver-coated catheters were employed. Previously, Maki, *et al.*, [1998] had shown that the same type of silver-coated catheter to be effective against *C. albicans*. In a recent review of CAUTIs, Maki and Tambyah [2002] indicated that while the role of biofilm on urinary catheters has not been fully established, the use of anti-infective impregnated and silver-hydrogel catheters significantly reduces the risk of CAUTI, and represents the first significant advance in the prevention of CAUTI since closed drainage systems were fully implemented

BENCH TESTING

It is stated that "manufacturers should assess antimicrobial effectiveness with representatives of the normal flora and relevant clinical isolates..." and that "clinical isolates used in the studies be within 1-2 passages of the original isolate".

To be effective, and reliable, it is imperative that *in vitro* tests be conducted in a manner such that results obtained can be confirmed. It also becomes important that when evaluating predicate materials, tests conducted in the past and those conducted in the future can be fairly compared and evaluated. It is recommended that these tests should be conducted using "standard", generally available, referenced strains, that are representative of the most common causes of device associated infection for a particular device, in conjunction with relevant recent clinical isolates.

Issues related to focusing on clinical isolates.

To focus on clinical isolates and to adhere to or be limited to 1-2 passages only is not only burdensome, it introduces many new questions that have not yet been addressed. It would necessitate that recently isolated clinical isolates be grown up in such a quantity so that sufficient numbers of cells are then available for: not only as a source for *in vitro* testing, but also for appropriate determinative taxonomic evaluations to properly identify the microorganism and geographically type the culture. Furthermore, identities of recent clinical isolates will need be confirmed to ensure that the microorganism has been properly identified. (For example, *C. albicans* and non-*albicans* strains will need to be identified as *C. albicans*, *C. glabrata*, *C. krusei*, *C. dubliniensis*, etc...) There is a serious adverse potential impact of employing an improperly identified strain in the *in vitro* tests. In addition, what techniques will be employed in order to provide sufficient numbers of microorganisms within 1-2 passages for the *in vitro* testing, etc (tubes, plates, vials, flasks, fermentors)? All would need to be validated and quality control procedures developed and validated.

To make a further point, there is considerable geographical diversity present (as determined by molecular methods) in many clinically relevant microorganisms. It will be necessary to confirm the geographical identity of a clinical isolate to establish its relevance as an *in vitro* model. As final example, recent clinical isolates lack the rigor and scientific confidence of the established strains. The established strains may or may not retain their infectious/pathogenic nature but they have been used in laboratories around the world for years and as such represent a control for the recent clinical isolates.

With respect to the use of "normal flora" isolates in *in vitro* testing? What is meant by this term. Does this refer to the flora of the human? Both HCWs (Health Care Workers) and the environment represent statistically relevant and important origins for device associated nosocomial infections. Are these two important sources also to be included.? Why would these not be included?

The failure to include "standard", well studied, available microorganisms representative of the major classes of pathogens isolated from device associated nosocomial infections would significantly reduce the scientific integrity and impact of *in vitro* testing. The inclusion of both "standard" and recent isolates in *in vitro* testing affords the best of both worlds.

TABLE 1. CHANGES IN ANTIBIOTIC RESISTANCE IN SELECTED PATHOGEN ISOLATES FROM ICUs: COMPARISON OF RESISTANCE PROFILES FOR THE PERIOD 1997-2001 TO JAN 1-DEC 31, 2002.

	Resistant Antibiotic	Percent Mean Rate of Resistance 1997-2001	Percent Resistance (+/- SD) 2002	Percent Change in Resistance	No. Of Isolates (2002)
Enterococci	Vancomycin	23-27	27.5	+11	2253
<i>S. aureus</i>	Methicillin	45-56	57.1	+13	4303
Coagulase (-) Staphylococci	Methicillin	86-90	89.1	+1	3675
<i>E. coli</i>	3rd gen. Cephalosporins	5-6	6.3	+14	1439
<i>K. pneumonia</i>	3rd gen. Cephalosporins	14-15	14.0	-2	990
<i>P. aeruginosa</i>	Imipenem	15-19	22.3	+32	1500
<i>P. aeruginosa</i>	Quinolone	19-28	32.8	+37	2064
<i>P. aeruginosa</i>	3rd gen. Cephalosporins	22-28	30.4	+22	2383
<i>Enterobacter spp.</i>	3rd gen. Cephalosporins	32-36	32.2	-5	1485

(Table adapted from NNIS Report August 2003)

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