

**Telavancin for the Treatment of Complicated Skin and Skin Structure Infections**

**FDA Briefing Document for  
Anti-Infective Drugs Advisory Committee Meeting  
November 19, 2008**

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## **I. BACKGROUND**

Theravance submitted New Drug Application (NDA) 22-110, telavancin for complicated skin and skin structure infection (cSSSI) indication on December 19, 2006. The Food and Drug Administration (FDA) issued an approvable letter on October 18, 2007. In the approvable letter, FDA requested that the Applicant provide information about manufacturing issues and analyses to better delineate the overall benefit: risk profile of telavancin. Theravance submitted their response to the approvable letter on January 21, 2008. In the resubmission, a safety update and additional analyses as requested by the Agency were provided.

This briefing document includes telavancin preclinical data (pharmacology/toxicology and microbiology), clinical pharmacology data, as well as a discussion of the Phase 3 cSSSI studies submitted in support of the NDA. Topics highlighted in the document to advance the advisory committee's discussion include primary efficacy and pertinent subgroup analyses and safety issues including potential nephrotoxicity and teratogenicity.

In order to obtain expert advice regarding issues pertinent to the benefit:risk assessment of telavancin, FDA had begun planning a meeting of the Anti-infective Drugs Advisory Committee (AIDAC) to be held in February 2008. However information from clinical site inspections was received just prior to the meeting that called into question the reliability of some of the data contained in the application, necessitating the meeting's cancellation. A summary of these inspectional issues are described in further detail below.

### **Summary of Data Integrity Evaluation by Division of Scientific Investigations**

The inspections performed in support of this NDA consisted of a total of 13 inspections: 11 clinical sites, a contract research organization (CRO), and the Applicant. The 13 inspections were grouped into two cycles of 6 and 7 inspections.

#### **First Cycle of Inspections**

In the first cycle, 6 inspections were conducted between March and December of 2007: 4 clinical sites, CRO, and Applicant. The inspectional findings at two of these inspections raised serious concerns about data integrity:

- **Clinical Investigator (Site 38091):** This clinical site with 51 enrolled subjects was the second largest site in study 0018 and fourth largest overall for the two pivotal studies. FDA's inspection of this clinical site revealed major deficiencies in good clinical practice (GCP) which included retrospective alteration of efficacy data and losing or discarding critical source documents. Further, the inspectional observations suggested inadequate study monitoring, which resulted in an inspection of the CRO responsible for study monitoring.
- **Contract Research Organization:** One CRO that served as the monitor for most of the clinical investigators in Studies 0017 and 0018 was inspected. FDA's inspection of the CRO's monitoring targeted the four clinical sites inspected by the FDA, including Site

38091. The inspection showed that the CRO had identified all major GCP violations that the FDA identified at this site, but study monitoring was inadequate in that the CRO failed to implement appropriate corrective actions as stipulated in the contractual agreement with the Applicant. The CRO's monitoring of the remaining 3 clinical sites was adequate.

Based on these inspectional results, the Agency determined that additional inspections were necessary to further evaluate data integrity, and as a result the FDA Advisory Committee meeting scheduled for February 2008 was cancelled.

#### Second Cycle of Inspections

Among the nearly 200 clinical sites which participated in the pivotal studies for this NDA, the additional clinical sites were selected based on: (1) large enrollment size, (2) efficacy data favoring the test article (telavancin) over the active control (vancomycin), and (3) study monitoring by the CRO noted above. The sites were selected to include at least one foreign clinical site. Seven additional clinical sites were identified.

At all 7 sites, the observed level of GCP compliance supported the integrity of the data reported from these sites. Major violations with the potential to affect data integrity consisted of electrocardiographic safety data from two sites, which were not obtained according to the time-frame specified in the study protocols. Study monitoring by the CRO routinely included the effective implementation of corrective actions when necessary. The results of FDA's inspections were also consistent with the results of the Applicant's own audit, as further described below.

#### Theravance's Targeted Audit

The Applicant conducted an internal audit of the two pivotal studies. In the Targeted Audit (4/21/08 - 6/12/08), the Applicant inspected 31 sites (24% of all sites) and audited the records for 683 subjects (36% of all subjects). The audited sites, selected by the Applicant using prior monitoring reports to identify those suggestive of significant GCP violations, included 5 of the 11 clinical sites inspected by the FDA; Site 38091 was not included in this audit. The Applicant concluded that there was no systematic pattern or incidence of GCP violations that could affect interpretation of the reported safety and efficacy data. The audit, however, identified two clinical sites (Sites 37004, 38020) (total of 22 subjects) at which study monitoring was not adequate.

#### Evaluation of Data Integrity

The results of FDA's inspections of the clinical sites, CRO, and Applicant, as well as the results of the Applicant's internal audit, support FDA's current view that the data reported in the NDA are reliable, with several exceptions as follows. Data that FDA considers unreliable in support of the NDA consists of 1) efficacy data from one inspectional site (Site 38091) and two sites where the Applicant's audit identified issues with monitoring (Sites 37004, 38020), and 2) electrocardiographic (ECG) safety data from two sites (Sites 38016 and 38163). Patient efficacy data from Sites 38091, 37004, and 38020 has been excluded from the efficacy analyses presented in this document. Electrocardiographic data for Sites 38016 and 38163 has similarly been excluded from the ECG safety analyses. This data will also be excluded from the Applicant's analyses and from the advisory committee presentations.

## II. CLINICAL DEVELOPMENT

Telavancin is a lipoglycopeptide antibiotic produced through chemical modification of vancomycin. Telavancin has activity against Gram positive bacteria.

The proposed indication in this NDA is treatment of cSSSI caused by *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis*. The recommended dosing regimen for telavancin is 10 mg/kg infused over 60 minutes every 24 hours for 7 to 14 days.

Studies submitted to support use in the cSSSI indication include two Phase 3 studies comparing telavancin 10 mg/kg to vancomycin. Two sequential Phase 2 SSSI studies comparing telavancin doses of 7.5 mg/kg q24 hr in the first study and 10 mg/kg q 24hr in the second study to vancomycin (or semi-synthetic penicillin) were used to assist in determination of the appropriate dose to advance to Phase 3 study.

Clinical development has also included a Phase 2 study of telavancin compared to vancomycin/semi-synthetic penicillin for the treatment of uncomplicated *S. aureus* bacteremia; this study has been completed, but a complete study report has not yet been submitted to the FDA. Two Phase 3 studies in hospital-acquired pneumonia (HAP) caused by Gram positive organisms have been completed by the Applicant, but only preliminary information relating to reporting of deaths, serious adverse events, and discontinuations due to adverse events has been submitted to the FDA for the purpose of a safety update.

## III. PHARMACOLOGY/TOXICOLOGY

The preclinical development program identified the kidney and the liver as potential organs of toxicity in humans. Telavancin was also noted to prolong the QT interval *in vitro*. Teratogenic effects were identified in three animal species.

### Toxicology

In the toxicological studies conducted with durations of up to 6 months in rats and 3 months in dogs, the organs of toxicity identified include the kidney and liver in both species.

Renal toxicity was evidenced by increased serum blood urea nitrogen (BUN) and creatinine (Cr) levels, urinary occult blood, granular casts, and amorphous crystals, increased kidney weight, diffusely light or mottled kidneys, proximal tubular degeneration, increased incidence/severity of tubular casts and/or dilatation, cortical tubular vacuolation, and increased interstitial inflammatory cell infiltrates. The incidence and/or severity of the lesions increased with increasing doses.

Hepatotoxicity was evidenced by marked increases in alanine transaminase (ALT) and aspartate aminotransferase (AST) levels [up to 4x AST and 28x ALT], and liver weights. Hepatocellular degeneration/necrosis (graded as slight) was also found in both species.

Multiple organ macrophage accumulation, hypertrophy, and hyperplasia were also noted.

Although some of the findings (e.g., increased BUN, Cr, AST, and ALT levels) were seen in the placebo (including hydroxypropyl- $\beta$ -cyclodextrin or HP-  $\beta$ -CD) control animals, the findings were more significant and more frequent in the drug-treated animals, leading to the conclusion that the active compound contributed significantly to the alterations. The drug was negative in an appropriate battery of genotoxicity studies.

### **Safety Pharmacology**

- Human Ether-a-go-go Related Gene (hERG) effect in human embryonic kidney (HEK) 293 cells showed inhibition of the tail current at all doses  $\geq 15$   $\mu$ g/mL, although when corrections were made for placebo effect, a half maximal inhibitory concentration (IC<sub>50</sub>) could not be calculated as it would be greater than the maximal 600  $\mu$ g/mL tested.
- Purkinje fiber (canine) effect was noted as prolongation of the action potential duration (APD) at 0.5 and 1 Hz at concentrations  $\geq 50$   $\mu$ g/mL. AMI-6424 (telavancin) demonstrated no effect in the Purkinje fiber (sheep) assay.
- An *in vivo* conscious telemeterized dog study showed no evidence of treatment-related effects on blood pressure, heart rate, or electrocardiogram (EKG) parameters. The study did demonstrate evidence of a histaminergic reaction at high doses (100 mg/kg/day as a single or repeat dose).
- See Safety Section for discussion of results of the human QT/QTc interval study.

### **Teratogenicity**

Significant concerns were raised from Segment 2 (embryo-fetal development) teratology studies conducted in rats, rabbits, and minipigs. These studies and their positive findings related to the drug are summarized below:

**1) Segment 2 study in rabbits (02-001-15\_7057-175):** Pregnant New Zealand White (NZW) rabbits (20/group) were treated intravenously (IV) with telavancin (AMI-6424) at 0 (Group 1, placebo with HP- $\beta$ -CD), 60 or 75 mg/kg/d once daily on Gestation Days (GDs) 7-20. The animals were sacrificed at cesarean-section (C-section) on GD 29. Examinations included clinical signs, body weight and food consumption, necropsy, uterine parameters (the uterus weight, number of implantation sites, early and late resorptions, and the number of corpora lutea), pregnancy parameters (pregnancy rates, early deliveries or abortions), and fetal examinations (viability, fetal weight, external, soft tissue, and skeletal examinations).

Maternal effects observed in this study were a transient body weight loss, associated with the beginning of the dosing period (GDs 7-9) and a corresponding decrease in food consumption. No significant treatment-related findings were reported in the dams at necropsy. C-section data were comparable across groups as were mean fetal weights.

In the 75 mg/kg/d group, one fetus had flexed front paws, brachymelia, and adactyly. In this fetus, there were skeletal malformations including absent ulna and adactyly. Of these findings, many were comparable to those found in Study 7057-126 (rat study), including the brachymelia, adactyly, and absent ulna. In the contract lab's study report, it was indicated that "the limb malformations noted (brachymelia, adactyly, and absent ulna) mimic or are similar to the malformations of brachymelia and syndactyly observed in rats at doses of 150 and 100 mg/kg/day, respectively, in Covance Study 7057-126. These findings further support a direct effect of AMI-6424 on the developing fetus." One animal had detectable levels of AMI-6424 in amniotic fluid. This finding increases the concern for continuous fetal exposures.

**Table 1a: Summary of fetal external/skeletal malformation (fetal incidence/litter incidence)**

Group	Placebo	60 mg/kg/day	75 mg/kg/day
Litters evaluated	18	20	19
Fetuses evaluated	138	172	156
Flexed front paws, brachymelia, adactyly, absent ulna	0	0	1/1 (0.6% for fetal incidence and 5.3% for litter incidence)

**Table 1b: Relevant Covance historical control data (%)**

Anomalies	Fetal incidence			Litter incidence		
	Mean	Min	Max	Mean	Min	Max
Flexed front paws	0.14	0	1.7	0.8	0	6.7
Adactyly	0.03	0	0.6	0.3	0	5.6
Brachymelia, micromelia or absent ulna	No incidence rates were given.					

The No-Observed Adverse Effect Level (NOAEL) for developmental toxicity in this rabbit study was 60 mg/kg/d.

**2) Segment 2 study in rats (02-001-04\_7057-126):** Pregnant CrI:CD<sup>®</sup>(SD)IGS BR rats (25/group) were treated IV with telavancin (AMI-6424) at 0 (Group 1, diluent control, 5% dextrose), 0 (Group 2, placebo with HP- $\beta$ -CD), 50, 100, and 150 mg/kg/d (Group 3, 4, and 5, respectively) once daily on GDs 6-17. The animals were sacrificed during C-section on GD 20. Examinations included clinical signs, body weight and food consumption, necropsy, uterine parameters, pregnancy parameters, and fetal examination.

Decreases in body weights and body weight gain, and food consumption were seen in Groups 4 and 5. Treatment with AMI-6424 had no effect on either embryo/fetal viability or pregnancy rates. All dams had viable fetuses. There were neither early deliveries nor abortions. Pre- and post-implantation losses were similar across treatment groups. Mean fetal weights were significantly (5.9% and 8.5%, respectively) decreased when compared to the diluent control at doses of 100 and 150 mg/kg/day of AMI-6424.

Fetal external malformations, seen in two fetuses in drug-treated groups (one in 100 mg/kg/day group and one in 150 mg/kg/day group), consisted of brachymelia and syndactyly (see table below). The contract lab's study report stated that brachymelia was considered treatment-related and syndactyly was of uncertain relationship to treatment. The fetus in the 100 mg/kg/day group had multiple findings of brachymelia (left hind

limb), syndactyly (left hind limb, middle three digits), and anophthalmia. The brachymelia observed at doses of 150 mg/kg/day was limited to one fetus in one litter and was not associated with any other external findings. No brachymelia or syndactyly was listed in historical control data of the contract lab (Covance). In the MARTA (Middle Atlantic Reproduction and Teratology Association) database, the incidence for these specific findings was 0. Brachymelia observed in this study may be attributed to treatment with AMI-6424 at doses  $\geq 100$  mg/kg/day, because this finding was not observed in historical control databases for this strain of rat. Because syndactyly had not been reported in historical control databases, and it also occurred in reproductive studies in other species with telavancin, it was considered drug-related by the reviewer.

**Table 2: Summary of fetal external malformation (fetal incidence/litter incidence)**

Group	1 (D5W)	2 (Placebo)	3 (50 mg/kg)	4 (100 mg/kg)	5 (150 mg/kg)
Litters evaluated	25	24	25	24	25
Fetuses evaluated	319	322	312	332	322
Brachymelia	0	0	0	1/1 (0.3, 4.2)	1/1 (0.3, 4.0)
Syndactyly	0	0	0	1/1 (0.3, 4.2)	0

\*(): % of fetal and litter incidence, respectively

The NOAEL is 50 mg/kg/day for developmental toxicity. The systemic exposure to telavancin at 50 mg/kg, the NOAEL, was 829  $\mu\text{g}\cdot\text{hr}/\text{mL}$ , which is similar to the human exposure at the proposed clinical dose (666-780  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ). The concerns for fetal developmental effects are high given the consistency of the effects across species and lack of safety margin.

**3) Segment 2 study in minipigs (05-013-04\_58857):** Pregnant Ellegaard Göttingen minipigs (14/group) were treated IV with telavancin (AMI-6424) at 0 (Group 1, diluent control, 5% dextrose), 0 (Group 2, placebo), 25, 50, and 75 mg/kg/d (Group 3, 4, and 5) once daily on GD 11-35. The animals were sacrificed at C-section on GDs 109-111. Examinations included clinical signs, body weight and food consumption, necropsy, uterine parameters, pregnancy parameters, and fetal examination.

There were 4 animals in the 5% dextrose group (3 miscarriages, 1 “poor health”), 4 in the placebo group (3 miscarriages, 1 “poor health”), 2 in the 25 mg/kg/d telavancin group (1 miscarriage, 1 “poor health”), 3 in the 50 mg/kg/d telavancin group (2 miscarriages, 1 “poor health”) and 4 (main group) from the 75 mg/kg/d telavancin group (3 miscarriages, 1 “poor health”) that were sacrificed in extremis (see table below). Many of these animals were treated with several other drugs in addition to the study drug. Diarrhea/loose stools (which may be related to the drug or concomitant antimicrobials) were seen across groups. Increased preimplantation and postimplantation losses were seen in all drug-treated groups.



**Table 3: Pregnancy Findings in Minipig Sows Treated with Telavancin**

Group	Confirmed mated	Early delivery (dead feti)	Killed in extremis (poor health)	Not pregnant	Early farrowing (live feti)	Pregnant on GD 109-111	Pregnancy rate*
1	14	3	1	3	0	7	50%
2	14	3	1	6	0	5	36%
3	14	1	1	3	0	9	64%
4	14	2	1	4	0	8	57%
5	14	3	1	5	1	5	36%

\*Number pregnant to term/number mated

Increased external malformations evidenced by polydactyly, syndactyly, and deformed foreleg with absent radius (described as radial agenesis) were seen in 25 mg/kg (LD) and 50 mg/kg (MD) groups (see table below). One fetus in the 50 mg/kg group with a deformed front leg with absent radius displayed malpositioned ulna, carpals malpositioned in relation to ulna, and misshapen proximal/front leg.

**Table 4a: Gottingen Minipigs: external malformations (fetal incidence/litter incidence)**

	Diluent	Placebo	25 mg/kg/day	50 mg/kg/day	75 mg/kg/day
Litters Evaluated:	7	5	9	8	5
Fetuses evaluated:	34	24	31	36	17
Syndactyly	0	0	0	1/1	0
% litter				12.5%	
Polydactyly:					
Single Limb	0	1/1	2/2	4/2	0
% litter		20%	22.2%	25%	
Polydactyly:					
Multiple limbs	0	0	2/2	1/1	0
% litter			22.2%	12.5%	
Misshapen digits & deformed limb (radial agenesis)	0	0	0	1/1	0
% litter				12.5%	
<b>Total Litter Incidence*</b>	<b>0%</b>	<b>20%</b>	<b>33.3%</b>	<b>50%</b>	<b>0%</b>

\* Historical Control Incidence for Polydactyly = 5.71%; Syndactyly = 2.86%

**Table 4b: Comparison with LAB Scantox historical control data (%)**

Anomalies	Fetal incidence			Litter incidence		
	25 mg/kg/day	50 mg/kg/day	Historical control	25 mg/kg/day	50 mg/kg/day	Historical control
Polydactyly	12.9	13.9	3.5	33.3	37.5	5.71
Syndactyly	0	2.8	0.5	0	12.5	2.86
Misshapen digits & deformed front leg	0	2.8	<0.7	0	12.5	

Additional findings not included in the table above: A fetus from sow #40 (Group 3; killed in extremis) with a deformed head and misshapen digit, a fetus from sow #47 (Group 4; killed in extremis) with “legs turned inwards”, fetus #3 from sow #51 (Group 4) that had multiple absent ossification sites, absent tarsal bones on both legs. The applicant attributed these findings to the lower birth weight of this fetus (79 g) and possible delay in development. While the absent ossification sites may be due to a delay in maturation, the absent tarsal bones on both legs cannot be due to this delay. A fetus from another sow (#43) had absent ossification sites distal to the metacarpal. This fetus did not have a reduced birth weight. Sow #60 (Group 5; killed in extremis) had a fetus with a deformed head, forelegs and snout but it was autolytic so no conclusions were made about it, and sow #61 (Group 5; killed in extremis) had a fetus with a deformed hind leg.

One mid dose fetus had exophthalmos and one had anencephaly, not seen in any other groups.

**Table 5: Other Fetal Findings in the Minipig**

Group	Litter #	Killed in extremis	Fetal findings
3 (25 mg/kg)	40	Yes	A deformed head and misshapen digit
4 (50 mg/kg)	47	Yes	Legs turned inwards
	51		Multiple absent ossification sites, absent tarsal bones on both legs
	43		Absent ossification sites distal to the metacarpi
5 (75 mg/kg)	60	Yes	A deformed head, forelegs and snout. The fetus was autolyzed.
	61	Yes	A deformed hind leg

Telavancin has been found to be a teratogen in rabbits and rats. The terata in minipigs were syndactyly and misshapen forelimbs, including radial agenesis, as well as the increased pre- and post-implantation losses. It is concerning that the lesions found in this minipig study include polydactyly (sometimes on 2 limbs), syndactyly, and a deformed foreleg with absent radius (described as radial agenesis). It can be concluded that telavancin is a teratogen in the minipig with external/skeletal (limb) malformations being the primary terata. Additional effects of telavancin dosing were found in pre- and post-implantation parameters.

**Table 6a: Toxicokinetic data**

Species		Dose (mg/kg/day)	Cmax (µg/mL)	AUC0-24 (µg-hr/mL)
Rat	Maternal plasma	50	420	829
		100	760	1236
		150	914	1726
	Amniotic fluid	50	NA	NA
		100	0.250	NA
		150	0.450	5.97
Rabbit	Maternal plasma	60	541	1027
		75	716	1387
	Amniotic fluid	Drug was only detected in one dam at 75 mg.		
Minipig	Maternal plasma	25	347	780
		50	545	1206
		75	871	1781
	Amniotic fluid	Not analyzed		

**Table 6b: Comparison of animal and human exposures**

	Segment 2 studies			Clinical studies
Species	Rabbit	Rat	Minipigs	Human
Dose (mg/kg)	75	100	25	10
AUC (µg-hr/mL)	1387	1236	780	666-780
Animal/human ratio	1.78	1.58	1	

#### Evaluation and conclusion:

The presence of limb malformations across all three species supports the conclusion that the findings are drug-related. Furthermore, although the incidence rates were low, they occurred in a dose-dependent manner and at rates significantly higher than in the historical control databases reported by the applicant or sources commonly used by the Agency. Of greatest concern is that these malformations occurred at clinically relevant maternal exposures based on area under the curve (AUC). Based on data from Segment 2 studies in rats, rabbits, and minipigs, it is concluded that telavancin is a multi-species teratogen with skeletal (limb) malformations being the primary terata.

This conclusion is supported by the consultation done by the Center for Drug Evaluation and Research (CDER) Reproductive and Developmental Toxicity, Pharmacology and Toxicology Coordinating Committee (PTCC) Subcommittee. [Appendix A].

#### IV. MICROBIOLOGY

##### Mechanism of action

Telavancin demonstrates two mechanisms of action: substrate-dependent inhibition of peptidoglycan synthesis and disruption of the cell membrane.

##### Antimicrobial Spectrum of Activity

*In vitro* study data support the activity of telavancin against *S. aureus* (including isolates resistant to other classes of antimicrobials, and isolates with specific virulence profiles), *S. pyogenes*, *S. agalactiae*, *S. anginosus* group (*S. anginosus*, *S. constellatus*, *S. intermedius*), and vancomycin-susceptible *E. faecalis* at therapeutically achievable concentrations.

##### *In vitro* activity against MRSA

Surveillance studies, as well as *in vitro* data from clinical trials conducted to support an indication for cSSSI demonstrate telavancin's activity against isolates of MRSA. In one study of clinical isolates (n = 1082) the MIC<sub>90</sub> against MRSA was 0.25 µg/mL, with a range of 0.03 – 1 µg/mL (Table 7).

**Table 7: *In vitro* activity of telavancin, vancomycin, linezolid, and daptomycin against MRSA (n = 1082)**

	MIC <sub>90</sub> (µg/mL)	MIC <sub>range</sub> (µg/mL)
Telavancin	0.25	0.03 - 1
Vancomycin	1	0.5 - 2
Linezolid	2	≤ 0.25 - > 4
Daptomycin	0.5	≤ 0.12 - > 1

*In vitro* data for MRSA isolates from clinical trials were similar to those seen in the surveillance studies described in Table 7. In one analyzed dataset, of MRSA isolates collected in the U.S. (n = 653) the telavancin MIC<sub>range</sub> was 0.06 - 1 µg/mL with a MIC<sub>90</sub> of 0.5 µg/mL. In the same dataset, the vancomycin MIC<sub>range</sub> was 0.25 - 2 µg/mL with a MIC<sub>90</sub> of 1 µg/mL. Telavancin MICs for staphylococci were unaffected by resistance to oxacillin, vancomycin, daptomycin, or linezolid. Sources of the clinical isolates included bloodstream, skin and skin structure, wound, and unknown sources, with no differences noted between specimen source and telavancin activity.

Against isolates of VISA, telavancin MICs ranged from 0.12 – 4 µg/mL. Against isolates described as hVISA (n = 44), the telavancin MIC<sub>90</sub> value was 1.0 µg/mL (MIC<sub>range</sub> = 0.12 – 2 µg/mL). In early investigations, no heteroresistance to telavancin has been observed in *S. aureus* populations. Against three isolates defined as VRSA,

telavancin demonstrated *in vitro* activity at therapeutically achievable concentrations (Table 8).

**Table 8: Activity of telavancin against vancomycin-resistant *S. aureus***

	VRSA <sub>MI</sub> MIC (MBC) µg/mL	VRSA <sub>PA</sub> MIC (MBC) µg/mL	VRSA <sub>NY</sub> MIC (MBC) µg/mL
Telavancin	4 (8)	2 (2)	2 (4)
Vancomycin	1024 (>2048)	32 (64)	64 (128)
Linezolid	1 (16)	2 (4)	0.25 (0.5)
Daptomycin	0.25 (0.25)	0.25 (0.25)	0.125 (0.125)

Source: Leuthner 2006<sup>10</sup>

*In vitro* studies indicate telavancin activity against community-associated MRSA (including isolates positive for PVL genes) (n = 60). Telavancin MIC<sub>90</sub> and MBC<sub>90</sub> values were 0.5 and 1 µg/mL respectively, which were similar to vancomycin, daptomycin, and linezolid MIC<sub>90</sub> and MBC<sub>90</sub> values.<sup>11</sup>

#### ***In vitro* activity against MSSA**

In a surveillance study of staphylococcal isolates collected in the U.S. for the period 2004-2005 (n = 1217), the telavancin MIC<sub>range</sub> for methicillin-susceptible *S. aureus* was 0.03 – 1 µg/mL, with a MIC<sub>90</sub> of 0.5 µg/mL. For the same isolates the vancomycin, linezolid, and daptomycin MIC ranges were ≤ 0.25 – 2 µg/mL, ≤ 0.25 – > 4 µg/mL and 0.12 – 1 µg/mL respectively.

#### ***In vitro* activity against Enterococcus species**

From surveillance studies, the overall telavancin MIC<sub>90</sub> for vancomycin-susceptible isolates of *E. faecalis* (n = 1230) was determined to be 1 µg/mL. The MIC<sub>90</sub> for all isolates (n = 1412) of *E. faecalis* (including vancomycin non-susceptible isolates) was 2.0 µg/mL.

In clinical studies, telavancin MIC values against vancomycin-susceptible *E. faecalis* (n = 27) ranged from 0.25 µg/mL to 1 µg/mL. In these studies, 100% eradication was demonstrated at all MIC values ≤ 0.5 µg/mL (n = 16). For isolates with MIC values of 1 µg/mL, 82% were eradicated (9/11).

#### ***In vitro* activity against Streptococcus species**

Against all streptococcal species (includes *S. pyogenes*, *S. agalactiae*, and the *S. anginosus* group), telavancin MIC<sub>90</sub> values determined from surveillance studies ranged from 0.06 - 0.12 µg/mL. MIC<sub>90</sub> values determined on isolates from cSSSI clinical trials are identical to those from surveillance data. Microbiological eradication rates for telavancin against all streptococcal species with MIC values ≤ 0.25 µg/mL, isolated in the pivotal clinical trials were ≥ 89%.

#### **Bactericidal Activity**

Data from minimum bactericidal studies and time-kill kinetic studies suggest consistent bactericidal activity of telavancin against all staphylococcal isolates (including methicillin-resistant and –susceptible isolates), and all streptococcal isolates (including β-hemolytic streptococci, *S. pneumoniae*, viridans streptococci, and the *S. anginosus*

group). Against enterococcus species, telavancin minimum bactericidal concentration:minimum inhibitory concentration (MBC:MIC) ratios exceeded 4.

### Development of resistance

*In vitro* investigations indicate a low potential for the development of resistance to telavancin in selected species of the Gram positive pathogens either in terms of spontaneous emergence or as a result of selective pressure, although in one study, a strain of Van A-type *E. faecalis* (MGH-01) appeared to demonstrate stable reduced susceptibility to telavancin, following selection on solid media. In the clinical trials, no emergence of resistance to telavancin was seen.

### Susceptibility test interpretive criteria

#### Susceptibility Breakpoints Proposed by the Agency

Pathogen	Susceptibility Interpretive Criteria					
	MIC (µg/ml)			Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤1	--	--		--	--
<i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , and <i>Streptococcus anginosus</i> group ( <i>S. anginosus</i> , <i>S. intermedius</i> , <i>S. constellatus</i> )	≤0.012	--	--		--	--
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	≤1	--	--		--	--

## V. CLINICAL PHARMACOLOGY

The pharmacokinetics of telavancin are linear following intravenous single doses from 5 to 12.5 mg/kg and multiple doses from 7.5 to 15 mg/kg administered once-daily for up to 7 days. Steady-state is achieved at approximately the third daily dose. The mean  $C_{max}$  values of telavancin after a single and multiple 60-minute intravenous infusions (10 mg/kg every 24 hours for up to 7 days) in healthy adults were 93.6 mcg/mL and 108 mcg/mL, respectively. The mean plasma clearance was 13.9 mL/hr/kg and elimination half-life was 8.0 hours following administration of a single 10 mg/kg dose to healthy adults. Inter-subject variability is approximately 15% for plasma clearance ( $CL_T$ ) and apparent volume of distribution at steady-state ( $V_{ss}$ ).

### Distribution:

Telavancin binds to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The mean binding is approximately 90%. The degree of penetration of telavancin into skin blister fluid is approximately 40% as determined by the ratio of the  $AUC_{0-24}$  in blister fluid to the  $AUC_{0-24}$  in serum.

**Metabolism:**

*In vitro* assays with human liver microsomes demonstrated that none of the following CYP450 isoforms metabolized telavancin: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP4A11. Thus, the clearance of telavancin is not anticipated to be altered by inhibitors of these enzymes *in vivo*.

A metabolite of telavancin (AMI-11352) has been identified although its formation pathway has not been identified. In a mass balance study using <sup>14</sup>C-telavancin, the amount of AMI-11352 recovered in urine based on total radioactivity was 6-11% of the administered dose.

**Excretion:**

Telavancin is eliminated primarily by the kidney. In a mass balance study, approximately 76% of the administered radioactivity was recovered from urine and less than 1% was recovered from feces (collected up to 216 hours). Of the amount of drug recovered in the urine, 82.3% was excreted as unchanged telavancin.

**Effect of Intrinsic Factors on Telavancin PK:**

Based on the results of Phase 1 clinical studies, covariates such as age and gender did not have a clinically significant effect on the pharmacokinetics of telavancin.

**Renal impairment**

The impact of renal impairment on the pharmacokinetics of telavancin was investigated in a clinical study of 28 subjects with varying degrees of renal impairment. The mean clearance was 11%, 19%, and 55% lower in subjects with mild, moderate, and severe renal impairment, respectively compared to normal renal function. A dosage adjustment is recommended for patients with moderate (7.5 mg/kg q24h) and severe renal impairment (10 mg/kg q48h). Insufficient data are available to recommend a dosage adjustment in patients with end-stage renal disease receiving hemodialysis.

**Hepatic impairment**

The impact of hepatic impairment on the pharmacokinetics of telavancin was investigated in a clinical study comparing eight adult subjects with normal hepatic function to eight adult subjects with moderate hepatic impairment (Childs-Pugh B). The mean clearance was 8% higher and AUC<sub>0-∞</sub> 7% lower in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.

**Drug Interaction Assessment:**

*In vitro* metabolism studies with human liver microsomes demonstrated that telavancin is not an inhibitor of CYP450 1A2, 2C9, 2C19, 2D6, 3A4, 3A5, and 4A11 isoforms. Thus, telavancin is not anticipated to alter the clearance of co-administered drugs metabolized by one or more of these enzymes *in vivo*.

The impact of telavancin on the pharmacokinetics of aztreonam, piperacillin-tazobactam, and midazolam as well as the impact of aztreonam, piperacillin-tazobactam, and midazolam on the pharmacokinetics of telavancin were assessed in

individual clinical studies. Telavancin did not impact the pharmacokinetics of aztreonam, piperacillin-tazobactam, and midazolam. Aztreonam, piperacillin-tazobactam, and midazolam did not impact the pharmacokinetics of telavancin.

#### **Cardiac Repolarization:**

The impact of telavancin on cardiac repolarization was assessed in a randomized, double-blind, multiple-dose, positive- and placebo-controlled, crossover study (n=160). Healthy subjects received telavancin 7.5 mg/kg, telavancin 15 mg/kg, moxifloxacin 400 mg, and placebo infused over 60 minutes once daily for three days. Based on interpolation of the data for telavancin 7.5 mg/kg and 15 mg/kg doses, the mean baseline corrected, placebo corrected QTc prolongation on day 3 was estimated to be 12-15 msec for telavancin 10 mg/kg and 24 msec for moxifloxacin.

#### **Dose Selection:**

The dosage regimen of 10 mg/kg once daily selected for evaluation in the two Phase 3 clinical trials is consistent with the findings from the PK/PD analysis using Monte Carlo simulation suggesting that doses of approximately 10 mg/kg would result in >99% probability of target attainment for organisms with MICs  $\leq 2$  mcg/mL as well as the higher microbiologic eradication rate observed in the Phase 2 clinical trials (202a and 202b) with telavancin 10 mg/kg once daily compared to 7.5 mg/kg once daily.

#### **Exposure-Response Analysis- Efficacy:**

A univariate logistic regression model was used to identify the relationship between telavancin exposure ( $AUC_{0-48}$ ) and microbiological response (i.e., eradicated vs. not eradicated/indeterminate). A trend toward a higher microbiological response rate was identified with higher telavancin exposures. Thus, telavancin 10 mg/kg q24h results in a higher microbiological eradication rate than telavancin 7.5 mg/kg q24h at the same treatment duration of 7-14 days.

#### **Exposure-Response Analysis- Safety:**

A univariate logistic regression model was used to assess the relationship between telavancin exposure ( $AUC_{0-48}$ ) and renal toxicity. Renal toxicity was defined as at least a 20% reduction in creatinine clearance (CrCL) compared to the baseline CrCL. The analysis was performed using the lowest CrCL value observed during treatment and follow-up periods as well as using the last CrCL value observed during the treatment period. A trend was observed as higher telavancin exposure ( $AUC_{0-48}$ ) yields a relatively higher incidence of renal toxicity. The results from both analyses suggest that reducing the dose from 10 mg/kg to 7.5 mg/kg may reduce the risk (4-5%) of renal toxicity ( $p \geq 0.07$ ). However, PK/PD modeling performed by the applicant from the second Phase 2 SSSI study suggested that the 10 mg/kg dose was more efficacious, as discussed further below.

## **VI. STUDY DESIGN**

The Applicant conducted two Phase 3 studies of identical design. Studies 0017 and 0018 were randomized, double-blind, active-controlled, parallel group, multicenter, multinational trials. Randomization was stratified by presence of diabetes mellitus and geographic region (three regions per study). Patients with cSSSIs (primarily due to MRSA) were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hr or vancomycin 1 gm IV q 12 hr for 7-14 days. Adjunctive aztreonam or metronidazole could be used to treat patients with infections due to suspected or culture positive Gram negative and/or anaerobic organisms.

The primary objective was to compare the efficacy and safety of telavancin to vancomycin in the treatment of adults with complicated Gram positive cSSSI with emphasis on patients with infections due to MRSA at a test-of-cure (TOC) visit 7-14 days after completion of therapy. A secondary objective was to pool the efficacy data from each of these studies to assess the superiority of telavancin to vancomycin in patients with MRSA infections.

Patients had baseline clinical and microbiological evaluation within 24 hours of study enrollment. Patients had daily assessment of the primary infection site, along with recording of concomitant medications, adjunctive surgical or significant wound procedures, and occurrence of adverse events (AEs). All pathogens isolated from deep culture specimens at the local laboratory were to be sent to the central laboratory for re-identification of organism (genus and species) and antibiotic susceptibility. After completing therapy, patients had an end-of-therapy (EOT) visit and a TOC visit 7-14 days after the EOT assessment. Efficacy assessment included clinical evaluation of the infection site and microbiological assessment only if a significant wound and/or drainage persisted at the infection site.

### **Study Treatments**

Both studies were initiated using a telavancin dose of 7.5 mg/kg IV q 24 hr. The dose of telavancin was increased to 10 mg/kg q 24 hr after the second Phase 2 SSSI study comparing telavancin 10 mg/kg dose to vancomycin was analyzed and pharmacokinetic/pharmacodynamic (PK/PD) modeling performed by the Applicant suggested that the 10 mg/kg dose was more efficacious in treatment of SSSI. Patients in the telavancin treatment arm also received a “dummy” placebo infusion at 12 hours to maintain blinding with the vancomycin treatment arm. Study medications were administered as 60 minute infusions. The dose of telavancin was to be adjusted in patients with moderate to severe renal insufficiency based on Cockcroft-Gault estimation of creatinine clearance, as shown in Table 9:



**Table 9: Dose Adjustment for Patients with Renal Impairment**

Creatinine Clearance <sup>1</sup> (mL/min)	Telavancin Dosage Original Protocol (7.5 mg/kg) <sup>1</sup>	Telavancin Dosage Protocol Amendment 1 (10 mg/kg) <sup>1</sup>
30-50	5.6 mg/kg q 24 hr	7.5 mg/kg q 24 hr
< 30	7.5 mg/kg q 48 hr	10 mg/kg q 48 hr
Hemodialysis	7.5 mg/kg q 48 hr (no supplement for dialysis)	10 mg/kg q 48 hr (no supplement for dialysis)
<sup>1</sup> Cockcroft-Gault estimation of creatinine clearance		

If renal function changed during the course of study treatment, creatinine clearance was to be re-estimated and dosage of study medication adjusted as appropriate.

Vancomycin was administered according to the manufacturer's package insert, with dose adjustments allowed according to the standard procedure of each institution by unblinded study personnel.

### **Efficacy Assessment**

#### Clinical Response

A Clinical Response assessment was to be performed by the investigator at EOT and TOC visits. The following definitions were used to assess outcome:

- **Cure:** resolution of signs and symptoms associated with the skin infection present at study admission such that no further antibiotic therapy is necessary.
- **Not Cured:** inadequate response to study therapy.
- **Indeterminate:** inability to determine outcome.
- **Missing:** no determination reported.

Patients with a Clinical Response of "Cured" or "Indeterminate" at EOT were to have efficacy (and safety) assessments performed at the TOC visit, while patients who were "Not Cured" at EOT were to have safety assessments only (and were considered to be failures). If a patient was withdrawn prematurely from study therapy, the Clinical Response at EOT could be assessed as "Indeterminate" or "Not Cured". Review of case report forms (CRFs) indicated that patients assessed as "Indeterminate" at EOT could potentially be reassessed for efficacy at TOC as "Cured" despite receipt of alternate non-study antimicrobials for their skin infection. This factor was addressed in the FDA analyses.

#### Microbiological Response

Microbiological responses were assessed by the Applicant based on either culture data (if available) at TOC or extrapolated from clinical response at TOC.

Microbiological Responses were defined as "eradicated" if the clinical response was cured or a microbiological culture of the infection site was negative at TOC. The Microbiological Response was "not eradicated" if the clinical response was failure, if the microbiological culture at TOC remained positive, or the response was missing or indeterminate.

## **Statistics**

### **Primary Analyses**

In both studies, the primary efficacy analysis was to initially test the non-inferiority of telavancin relative to vancomycin using the difference in the clinical response rate at TOC in the all-treated (AT) and clinically evaluable (CE) populations, employing a NI margin of 10%. The testing was to be performed using a 95% confidence interval (CI) for the difference in clinical response rates based on the normal approximation to the binomial distribution. If noninferiority was established, then statistical superiority would be examined in the AT population using the confidence interval approach to determine whether the lower bound of 95% CI was greater than zero.

If both studies were able to demonstrate noninferiority of telavancin to vancomycin, an additional goal was to demonstrate the superiority of telavancin over vancomycin in patients infected with MRSA at baseline in the pooled AT population stratified by study. If telavancin was shown to have superior efficacy in this subpopulation, then the efficacy and safety of telavancin in the pooled AT complement of the MRSA subpopulation was to be examined to demonstrate that the advantages in the MRSA subpopulation did not occur to the detriment of the complementary subpopulation.

## **VII. STUDY RESULTS**

### **Disposition**

A total of 862 patients at 40 sites were randomized into Study 0017 at the 10 mg/kg dose with 429 patients randomized to the telavancin treatment group and 433 patients to the vancomycin treatment group. A total of 1035 patients at 89 sites were randomized into Study 0018 at the 10 mg/kg dose with 517 patients randomized to the telavancin treatment group and 518 patients to the vancomycin treatment group.

In Study 0017, 73% of the enrolled population was from the US. In Study 0018, 65% of the enrolled population was from the US.

### **Duration of Study Therapy**

The duration of therapy was determined by the investigator based on clinical assessment of the cSSSI site. The minimum duration of therapy was to be 7 days and the maximum 14 days. Approximately 80% of patients in Study 0017 and 70% of patients in Study 0018 received greater than 7 days of study medication.

### **Analyses Populations**

In this briefing document only results of analyses based on FDA-defined populations are presented. Data from the three sites where data integrity issues were identified are excluded from all efficacy analyses presented here. Patients enrolled at site #38091 were excluded from the efficacy analyses based on DSI report and sites 37004 and 38020 were excluded from efficacy analyses based on the Applicant's internal audit. The data were however considered acceptable for safety analyses and will be included in the discussion of the safety data.

In addition to excluding data from the sites with data integrity issues, the FDA analyses took into consideration the following:

Investigator-assessed outcomes were reassessed for clinical evaluability status and outcome if patients received potentially effective non-study antibiotics for the skin infection prior to TOC and/or definitive surgical procedures (e.g. incision and drainage, amputation) performed more than 96 hours after initiation of study treatment. These patients were assessed as clinically evaluable failures in the FDA analyses.

Patients with only Gram negative bacteria isolated in baseline microbiological cultures were excluded from the microbiological all-treated (MAT) population.

Patients lacking central microbiology laboratory confirmation of pathogen identification and susceptibility were excluded from the microbiologically evaluable (ME) population.

### Baseline Characteristics

Table 10 shows the baseline demographic information for patients randomized and treated in Study 0017 and Study 0018.

**Table 10: Demographics of Study Population – All Treated Population**

	<b>Study 0017<sup>1</sup></b>		<b>Study 0018</b>	
	<b>Telavancin N=426</b>	<b>Vancomycin N=429</b>	<b>Telavancin N=458</b>	<b>Vancomycin N=481</b>
<b>Age (years)</b>				
• Mean (range)	48.9 (18-96)	47.7 (17-90)	49.2 (18-95)	49.9 (18-91)
<b>Age Distribution</b>				
• <65 years	337 (79%)	357 (83%)	377 (82%)	379 (79%)
• ≥65 years	89 (21%)	72 (17%)	81 (18%)	102 (21%)
<b>Sex</b>				
• Male	230 (54%)	248 (58%)	258 (56%)	294 (61%)
• Female	196 (46%)	181 (42%)	200 (44%)	187 (39%)
<b>Race</b>				
• Black, of African heritage	59 (14%)	52 (12%)	69 (15%)	74 (15%)
• White	349 (82%)	353 (82%)	336 (73%)	343 (71%)
• Other	18 (4%)	24 (6%)	53 (12%)	64 (13%)
<b>US vs. International</b>				
• US	306 (72%)	316 (74%)	287 (63%)	310 (64%)
• Non-US	120 (28%)	113 (26%)	171 (37%)	171 (36%)

<sup>1</sup> From CSR 0017, Table 8-3, pgs 108-109.

The treatment groups within each study and populations across studies were well balanced in regard to age, gender, sex, and race.

Table 11 shows the baseline characteristics of the populations for studies 0017 and 0018.

**Table 11: Baseline Characteristics of the All Treated Study Population**

Baseline Characteristics	Study 0017 <sup>1</sup>		Study 0018	
	Telavancin N=426	Vancomycin N=429	Telavancin N=458	Vancomycin N=481
<b>Medical/Surgical Conditions Directly Associated with cSSSI<sup>2</sup></b>				
• Recent trauma	115 (27%)	125 (29%)	59 (13%)	65 (14%)
• Diabetes mellitus	109 (26%)	109 (25%)	113 (25%)	118 (25%)
• Bite	33 (8%)	50 (12%)	34 (7%)	34 (7%)
• Recent surgical procedure	37 (9%)	42 (10%)	58 (13%)	48 (10%)
• Peripheral vascular disease	42 (10%)	28 (7%)	33 (7%)	49 (10%)
• Chronic skin disease	34 (8%)	25 (6%)	25 (5%)	44 (9%)
• Chronic edema	21 (5%)	20 (5%)	21 (5%)	32 (7%)
• Other	74 (17%)	66 (15%)	61 (13%)	73 (15%)
<b>Description of cSSSI</b>				
• Major Abscess	179 (42%)	193 (45%)	196 (43%)	204 (42%)
• Deep/Extensive Cellulitis	156 (37%)	161 (38%)	153 (33%)	176 (37%)
• Wound Infection	72 (17%)	60 (14%)	67 (15%)	61 (13%)
• Infected Ulcer	16 (4%)	12 (3%)	29 (6%)	36 (7%)
• Infected Burn	3 (<1%)	3 (<1%)	13 (3%)	6 (1%)
<sup>1</sup> From Clinical Study Report 0017, Table 8-4, pgs 110-1, Table 8-7, pg 119, Table 8-8, pg 121.				
<sup>2</sup> Counts (and percentages) represent the number (percentage) of patients with each medical condition.				

Approximately 25% of the population in each study had diabetes mellitus. Major abscesses were the most common type of infection followed by deep/extensive cellulitis. Greater than 10% of each study population had wound infections.

Table 12 shows the baseline renal function of patients enrolled and treated in each study by treatment group. Renal function was based on serum creatinine as measured by the central laboratory and estimated creatinine clearance based on the central laboratory serum creatinine.

The treatment groups in each study were well balanced in regard to baseline renal function, as were the populations across studies. Study 0017 had a slightly higher proportion of patients with moderate to severe decrease in renal function (CrCL < 50 mL/min) at baseline in the telavancin treatment group compared to the vancomycin treatment group (15% versus 11%). Study 0018 had a similar proportion of patients with moderate to severe decrease in renal function in both treatment groups (telavancin: 11%; vancomycin: 12%).

## EFFICACY RESULTS

### Primary Endpoint

The co-primary efficacy endpoints were the clinical response rates at TOC in the AT and CE populations for Studies 0017 and 0018. Table 13 shows the results of the FDA efficacy analyses for Studies 0017 and 0018.

**Table 13: Clinical Response Rates for FDA AT and CE Analysis Populations**

	<b>Telavancin Success</b>	<b>Vancomycin Success</b>	<b>Difference in Success (telavancin – vancomycin)</b>
<b>Population</b>	<b>n/N %</b>	<b>n/N %</b>	<b>% (95% CI<sup>1</sup>)</b>
<b>All Treated</b>			
Study 0017	309/426 (72.5)	307/429 (71.6)	1.0 (-5.3, 7.2)
Study 0018	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)
<b>Clinically Evaluable</b>			
Study 0017	289/343 (84.3)	288/348 (82.8)	1.5 (-4.3, 7.3)
Study 0018	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)

<sup>1</sup> 95% CI calculated using a continuity correction

In both Studies 0017 and 0018, telavancin was demonstrated to be noninferior to vancomycin for the endpoints of clinical response at TOC in both the AT and CE populations based on the treatment difference in clinical response rates using a 10% non-inferiority margin. The finding of non-inferiority was demonstrated in both FDA and Applicant analyses. Telavancin was not statistically superior to vancomycin in either of the studies.

#### **Test for Superiority of Telavancin Compared to Vancomycin for Treatment of cSSSI in Patients with Infection Caused by MRSA**

The Applicant also proposed to demonstrate the superiority of telavancin in patients with baseline MRSA infections once noninferiority of telavancin to vancomycin in the overall population had been demonstrated. The plan was to pool data across Studies 0017 and 0018 to perform this analysis. The design, populations, and results of the two studies were not found to be substantially dissimilar, so the data from the two studies were pooled for both the MRSA and the MRSA-complement analyses.

Table 14 below shows the results of the FDA analyses of clinical response rates for patients in studies 0017 and 0018 for the AT population who had MRSA isolated from baseline microbiological cultures.

**Table 14: Clinical Response Rates for the AT Population with MRSA Isolated at Baseline**

	<b>Telavancin Success</b>	<b>Vancomycin Success</b>	<b>Difference in Success Percents (telavancin – vancomycin)</b>
<b>Population</b>	<b>n/N %</b>	<b>n/N %</b>	<b>% (95% CI)</b>
Study 0017	92/135 (68.1)	110/151 (72.8)	-4.7 (-15.3, 5.9)
Study 0018	135/166 (81.3)	132/172 (76.7)	4.6 (-4.1, 13.2)
<b>Pooled<sup>1</sup> (0017 + 0018)</b>	227/301 (75.4)	242/323 (74.9)	0.9 (-5.8, 7.6) p-value 0.18
<sup>1</sup> Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights. p-value is a two-sided test based on a stratified analysis by study.			

In AT patients with MRSA isolated as a pathogen at baseline, telavancin was not superior to vancomycin in clinical response at TOC.

Table 15 shows the results of the exploratory analyses in subgroups of the FDA CE analysis populations of Study 0017 and 0018 combined.

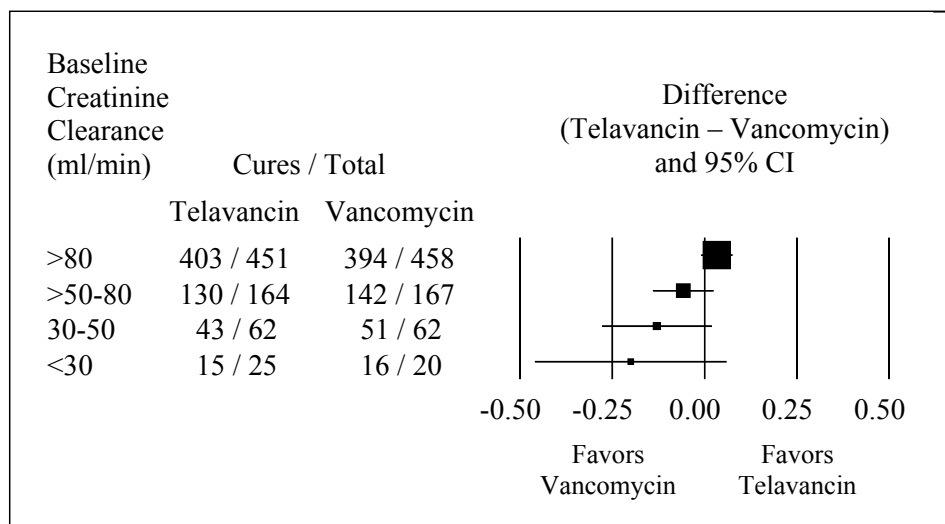
**Table 15: Clinical Response Rates in Subgroups - CE Population**

	<b>Telavancin % (n/N)</b>	<b>Vancomycin % (n/N)</b>	<b>Difference<sup>1</sup> (TLV-Comparator) (95% CI)</b>
<b>US/Non-US</b>			
• US	394/472 (83.5)	403/486 (82.9)	0.6 (-4.2, 5.3)
• Non-US	197/231 (85.3)	200/221 (90.5)	-5.3 (-11.2, 0.7)
<b>History of Diabetes</b>			
• Diabetes	128/167 (76.5)	146/183 (79.8)	-3.2 (-11.8, 5.4)
• No diabetes	462/535 (86.4)	457/524 (87.2)	-0.8 (-4.9, 3.2)
<b>Baseline Creatinine Clearance</b>			
• > 80 mL/min	403/451 (89.4)	394/458 (86.0)	3.3 (-1.0, 7.5)
• > 50-80 mL/min	130/164 (79.3)	142/167 (85.0)	-5.9 (-14.1, 2.4)
• 30-50 mL/min	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)
• < 30 mL/min	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.5, 5.2)
<b>Wound type</b>			
• Major Abscess	263/303 (86.8)	262/300 (87.3)	-0.5 (-5.9, 4.8)
• Wound Infection	87/108 (80.6)	83/96 (86.5)	-5.8 (-15.9, 4.4)
• Deep/Extensive Cellulitis	199/240 (82.9)	227/273 (83.2)	-0.2 (-6.7, 6.3)
• Infected Ulcer	30/40 (75.0)	25/31 (80.6)	-6.2 (-25.8, 13.5)
• Infected Burn	12/12 (100)	6/7 (85.7)	9.8 (-5.9, 25.6)
<sup>1</sup> Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights			

The clinical response rates were similar across geographic region (US/non-US). Response rates were lower in patients with a history of diabetes mellitus. Clinical response rates did not differ significantly across cSSSI type, although some of the groups (i.e., infected ulcer and infected burn) were small.

There was a significant difference (decrease) in clinical response rates between patients with baseline renal impairment treated with telavancin compared to those treated with vancomycin. Patients with progressive degrees of baseline renal impairment had a greater decline in clinical response rate when treated with telavancin (see Figure 1). This decline in clinical response rate seen with telavancin treatment in patients with progressive levels of baseline renal impairment is of some concern. However, conclusions regarding this finding are limited by the exploratory nature of the post hoc analyses of subgroups and small numbers. A similar pattern of decrease in clinical response rates was seen in older patients treated with telavancin while clinical response rates in patients treated with vancomycin did not decrease. The decline in response rates may be related to decreased efficacy in older patients, since aging is correlated with a decline in creatinine clearance. The decrease in apparent response rates may be related to failure to adjust (increase) the telavancin dose in response to improving renal function.

**Figure 1: Clinical Response at TOC in the FDA CE Population for Studies 0017 + 0018 -- By Baseline Renal Impairment**



### Clinical Microbiology

Table 16 shows the baseline microbiological characteristics of patients enrolled and treated in the studies.

**Table 16: Baseline Microbiological Characteristics of the MAT population**

Baseline Characteristics	Study 0017		Study 0018	
	Telavancin N=260 (%)	Vancomycin N=274 (%)	Telavancin N=291 (%)	Vancomycin N=315 (%)
Baseline Pathogen <sup>1</sup>				
• Gram positive pathogens only	224 (86)	248 (91)	254 (88)	274 (88)
• Mixed Gram positive and Gram negative	30 (12)	25 (9)	34 (12)	37 (12)
Gram positive bacteremia	16 (6)	5 (2)	6 (2)	11 (3)
Presence or Absence of PVL in <i>S. aureus</i> at Baseline				
• <i>S. aureus</i> (all)	N=230	N=240	N=256	N=282
○ PVL +	143 (62)	163 (68)	169 (66)	185 (66)
○ PVL –	87 (38)	77 (32)	87 (34)	97 (34)
• MRSA	135	151	167	172
MRSA/all SA (%)	135/230 (59)	151/240 (63)	167/256 (65)	172/282 (61)
MSSA	95/230 (41)	89/240 (37)	89/256 (35)	110/282 (39)

<sup>1</sup> Baseline pathogen based on skin isolates

The FDA Baseline MAT analysis population excluded patients with Gram negative pathogens only since telavancin and vancomycin both lack antibacterial activity against Gram negative organisms. *S. aureus* was the most common pathogen isolated. Approximately 60% of *S. aureus* isolates were MRSA and 85% of the MRSA isolates were PVL positive.

Table 17 shows the clinical response rates by pathogen for the FDA ME analysis population.

**Table 17: Clinical Response at TOC in the ME Population (Study 0017 and 0018)**

Pathogen	Study 0017		Study 0018	
	TLV	VANC	TLV	VANC
<i>Staphylococcus aureus</i> , MRSA	90/109 (82.6)	107/126 (84.9)	118/130 (90.8)	118/136 (86.8)
<i>Staphylococcus aureus</i> , MSSA	70/81 (86.4)	66/79 (83.5)	61/79 (77.2)	65/75 (86.7)
<i>Enterococcus faecalis</i>	12/12 (100)	11/14 (78.6)	10/11 (90.9)	17/21 (81.0)
<i>Streptococcus pyogenes</i>	9/10 (90)	9/10 (90)	7/9 (77.8)	10/11 (90.9)
<i>Streptococcus agalactiae</i>	8/9 (88.9)	3/3 (100)	6/10 (60)	10/12 (83.3)
<i>Streptococcus anginosus</i> group	7/8 (88)	5/5 (100)	6/8 (75.0)	4/4 (100)

The FDA assessment of the clinical response rate in the ME population for patients with MRSA infection in Study 0017 was 84.9% for the vancomycin treatment group compared to 82.6% for the telavancin treatment group; results for Study 0018 favored telavancin with a clinical response rate in the patients in the ME population for patients with MRSA infection to be 90.8% compared to 86.8% for vancomycin.

Response rates for MSSA appear similar and were slightly higher for telavancin compared to vancomycin in the FDA analysis of Study 0017; response rates for MSSA were higher for vancomycin compared to telavancin in the FDA analysis of Study 0018.

Response rates for other Gram positive organisms are difficult to interpret due to the small number of isolates.



### **Efficacy Conclusions**

- The results of two independent studies of identical design, Study 0017 and Study 0018, support the conclusion that telavancin demonstrates clinical noninferiority to vancomycin using a prespecified NI margin of 10% for the co-primary analysis populations. Superiority of telavancin to vancomycin in treatment of patients with cSSSI and in whom MRSA was isolated from baseline microbiological culture was not demonstrated in the prespecified pooled analysis of Study 0017 and 0018.
- The apparent decrease in clinical response rates for patients with baseline renal impairment treated with telavancin is not explained and may be of clinical concern.
- Investigator assessment of clinical outcome in patients who prematurely discontinued study medication could be “Indeterminate” or “Not Cured” at EOT. Patients assessed as “Indeterminate” were reassessed for both efficacy and safety at TOC, while those who were “Not Cured” were evaluated only for safety. Based on review of CRFs, some patients discontinuing study therapy prematurely and assessed as “Indeterminate” at EOT, received alternate nonstudy antimicrobial agents for their skin infections and were subsequently assessed as “Cured” at TOC. This factor was addressed in the FDA analyses.
- Blinding of the study may have been impacted by the observation of taste disturbance and foamy urine in recipients of telavancin.

### **VIII. SAFETY**

The safety database at the time of NDA submission included healthy subjects who had received telavancin in Phase 1 studies and patients with cSSSI who were treated with telavancin in phase 2 and Phase 3 studies. Additionally, there were approximately 208 patients who had received treatment with telavancin in on-going treatment-blinded HAP and uncomplicated *S. aureus* bacteremia studies. Data for an additional 180 patients were provided in the 4-month safety update (4MSU). Table 18 shows the number of patients evaluated for safety in the telavancin development program.

**Table 18: Number of Subjects Evaluated for Safety -  
All Telavancin Studies (Treatment Assignment Known)**

Study Group	Number of Subjects Exposed	
	Telavancin	Comparator
Clinical Pharmacology Studies		
Single Dose Studies <sup>1</sup> (0.25 – 15 mg/kg)	124	47
Multiple Dose Studies (7.5 – 15 mg/kg)	144	103
<b>Total Clinical Pharmacology Studies</b>	268	150
Efficacy and Safety Studies in cSSSI		
Studies 0017, 0018, and 202b, 10 mg/kg telavancin dose	1029	1033
Study 202a and Studies 0017, 0018, 202b, 7.5 mg/kg telavancin	192	189
<b>Total Efficacy and Safety Studies</b>	1221	1222
From Summary of Clinical Safety, Table 2, pg 16. <sup>1</sup> Of the telavancin-treated patients, 79 subjects received a single dose and 45 received single doses on more than one occasion separated by one week or more.		

For the purpose of the safety review, safety results for the Phase 3 cSSSI studies (Studies 0017 and 0018, telavancin 10 mg/kg) were examined separately and combined. Safety information was also examined for the entire SSSI study population (Phase 2 and Phase 3 studies). Comparison of AEs between patients enrolled in the 7.5 mg/kg and 10 mg/kg studies was examined for evidence of a dose-response relationship, however conclusions were limited by the small sample size of patients enrolled in the 7.5 mg/kg telavancin studies relative to patients treated in the 10 mg/kg studies.

### Deaths

There were 18 deaths reported for the SSSI studies for the period prior to TOC (or for 30 days after EOT in those without TOC); one death occurred in a patient treated with telavancin 7.5 mg/kg, eight deaths occurred in patients treated with telavancin 10 mg/kg, and nine deaths occurred in patients treated with the comparator. These eighteen deaths are shown in Table 19 below.

**Table 19: Deaths**

Drug/Dose Patient ID	Age/Sex	Adverse Event with Outcome of Death	Time Relative to Study Treatment	FDA Relatedness to Study Medication
<b>Telavancin 7.5 mg</b>				
0017-02008-0120	82/F	Respiratory distress Pulmonary edema Renal insufficiency Respiratory failure Sepsis	During During During During Post (1 day)	Possibly related (except for sepsis)
<b>Telavancin 10 mg</b>				
0017-022010-546	65/M	Ventricular arrhythmia	Post (1 day)	Possibly
0017-04004-0677	49/F	SIRS	Prior (8 days)	Not related
0017-27010-0474	65/F	CVA	Post (9 days)	Not related
0017-38001-0693	96/F	Ovarian cancer	Post (4 days)	Not related
0017-38002-0428	70/M	Renal insufficiency	Onset (?) Died 4 days post	Possibly DNR, no HD
0018-01002-2474	75/F	Cardiac arrest (unwitnessed)	Post (1 day)	Possibly
0018-19006-2894	84/M	Cardio-respiratory arrest	Post (2 days)	Possibly
0018-38160-2501	77/M	Acute respiratory failure MI	During	Possibly
<b>Vancomycin</b>				
0017-02001-0257	46/M	Pulmonary embolism	During	Possibly
0017-38016-0824	49/F	Cardio-respiratory arrest Pulmonary embolism	During	Not related
0017-38024-0695	53/M	Cardiac failure Respiratory failure	Post (3 days)	Not related
0017-38271-0659	47/M	Cardio-respiratory arrest Coma hepatic Respiratory failure	Post	Not related
0017-38271-1010	90/M	Respiratory distress	Post (7 days)	Possibly
0018-22000-2742	55/M	Cardiac failure	During	Possibly
0018-30907-2323	66/F	Cardiogenic shock Pulmonary edema Septic shock	During	Not related
0018-38260-2555	53/M	Cardiac arrest	Post (7 days)	Not related
202b-00903-9037	41/F	Multi-organ failure Sepsis Hepatic failure Renal failure acute Respiratory failure	During	Not related

There were 5 deaths in telavancin treated patients [2 in Study 0017, 3 in Study 0018 (including 1 in the 7.5 mg/kg group and 2 in the 10 mg/kg group)] who died outside of the study death “reporting period”. Two of the deaths in telavancin treated patients (one in Study 0017 and one in Study 0018), although outside the death reporting window, were assessed as possibly related to study medication by FDA. The patient in Study 0017 developed respiratory distress and hypotension while on telavancin, was subsequently diagnosed with acute respiratory distress syndrome (ARDS) and multi-system organ failure, and died 12 days after therapy was discontinued. The patient in Study 0018 had a history of severe heart failure and chronic renal insufficiency and developed a progressive increase in serum creatinine from baseline of 4.1 mg/dL to 10.3 mg/dL at

TOC (one week after study medication was discontinued); his death occurred 1 week after the TOC visit from acute renal failure.

The 4 Month Safety Update (4MSU) also included unblinded treatment information on patients who were enrolled in Study 203a (uncomplicated *S. aureus* bacteremia study) which compared telavancin 10 mg/kg to vancomycin (or anti-staphylococcal penicillin if MSSA isolated) for 14 days. There were five deaths in the telavancin treatment group and three in the vancomycin treatment group. The AE preferred terms with death as an outcome in telavancin-treated patients were sepsis, endocarditis bacterial, renal failure acute, dyspnea, death, renal failure chronic, pneumonia, disseminated intravascular coagulation, and empyema. None of the SAEs with death as an outcome were assessed as possibly/probably related to study medication by the investigator.

### **Serious Adverse Events (SAEs)**

In the Phase 2 and Phase 3 cSSSI studies combined, there were 122 SAEs that occurred in 91/1221 (7%) of telavancin-treated patients; 76 patients were enrolled in telavancin 10 mg/kg studies and 15 in telavancin 7.5 mg/kg studies. In the comparator treatment arm, there were 100 SAEs that occurred in 61/1222 (5%) patients; 46 patients were enrolled in telavancin 10 mg/kg studies and 15 in telavancin 7.5 mg/kg studies.

Table 20 shows the number (%) of patients in each of the Phase 3 cSSSI studies who had some of the more common SAEs reported, along with the number (%) of patients with at least one AE within a system organ class (SOC). There were 69/929 (7.4%) telavancin-treated patients who had 80 SAEs compared to 43/938 (4.6%) vancomycin-treated patients with 65 SAEs.

**Table 20: SAEs in cSSSI (Phase 3 Studies 0017 and 0018)**

	Study 0017		Study 0018		Study 0017 + Study 0018	
MedDRA SOC	TLV N=426	VANC N=429	TLV N=503	VANC N=509	TLV N=929	VANC N=938
<b>Any serious event (# patients, %)</b>	<b>31 (7)</b>	<b>27 (6)</b>	<b>38 (8)</b>	<b>15 (3)</b>	<b>69 (7)</b>	<b>42 (5)</b>
Blood and Lymphatic System	0	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
Cardiac Disorders	6 (1)	6 (1)	4 (<1)	5 (<1)	10 (1)	11 (1)
Gastrointestinal Disorders	0	3 (<1)	1 (<1)	1 (<1)	1 (<1)	4 (<1)
General Disorders and Administration Site	3 (<1)	2 (<1)	1	2 (<1)	4 (<1)	4 (<1)
Hepatobiliary Disorders <sup>1</sup>	0	0	2 (<1)	0	2 (<1)	0
Immune System Disorders	1 (<1)	2 (<1)	4 (<1)	1 (<1)	5 (<1)	3 (<1)
Infections and Infestations	1 (<1)	6 (1)	6 (1)	3 (<1)	7 (<1)	9 (<1)
Investigations	1 (<1)	2 (<1)	3 (<1)	1 (<1)	4 (<1)	3 (<1)
Metabolism and Nutrition Disorders	0	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
Renal and Urinary Disorders	5 (1)	1 (<1)	6 (1)	1 (<1)	11 (1)	2 (<1)
Reproductive System and Breast Disorders	0	1 (<1)	0	0	0	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders	7 (2)	8 (2)	4 (<1)	1 (<1)	11 (1)	9 (<1)
Skin and Subcutaneous Tissue Disorders	1 (<1)	0	2 (<1)	0	3 (<1)	0
Vascular Disorders	5 (1)	1 (<1)	4 (<1)	1 (<1)	9 (<1)	2 (<1)
<sup>1</sup> One patient in the vancomycin treatment arm in the Phase 2 202b (telavancin 10 mg) study died from liver failure which was not attributed to study medication by investigator.						

Overall, there was an imbalance in the number of SAEs in the Renal and Urinary Disorder SOC; there were 11 patients in the telavancin treatment group compared to two vancomycin treatment group patients who had SAEs in this SOC.

In the Phase 3 studies, four patients (0.5%) in the telavancin treatment group had acute renal failure reported compared to none in the vancomycin treatment group. For these studies, respiratory failure was the most frequently reported individual SAE in the comparator treatment group, occurring in three patients (0.3%) compared to one patient (0.1%) in the telavancin treatment group.

The imbalance in renal events between the telavancin and comparator treatment arms will be discussed in a later section. Although vascular events also showed an imbalance between treatment groups, there was no one specific observation (preferred term AE) which predominated; reported events included both venous and arterial events, as well as blood pressure.

#### **Discontinuations Due to AEs in SSSI Studies**

Treatment-emergent AEs (TEAEs) resulting in early discontinuation of study medication in all cSSSI studies occurred in 87/1221 (7.1%) of the telavancin-treated patients and 59/1222 (4.8%) of the vancomycin-treated patients; in the telavancin 10 mg/kg studies, 78/1029 (7.6%) of telavancin-treated and 53/1033 (5.1%) of vancomycin-treated patients

discontinued and in the telavancin 7.5 mg/kg studies, the rates of discontinuation were 5% for telavancin and 3% for vancomycin.

In the Phase 3 cSSSI studies there were a greater number of events in the following SOC: gastrointestinal (13 and 6 AEs respectively in the telavancin and vancomycin treatment groups), infections and infestations (12 events and 5 events for telavancin and vancomycin respectively), investigations (10 and 5 events for telavancin and vancomycin respectively), and renal and urinary (8 and 0 events for telavancin and vancomycin respectively). Skin disorders were balanced between treatment groups and occurred in 18 telavancin and 20 vancomycin treated patients.

Nausea (10 patients, 1%), rash (8 patients, 0.9%), blood creatinine increased (6 patients, 0.7%), vomiting (7 patients, 0.6%), renal failure acute (5 patients, 0.6%), and osteomyelitis (6 patients, 0.6%) were the most frequently reported events leading to discontinuation in patients treated with the telavancin 10 mg/kg dose. The most frequent TEAEs leading to discontinuation of study medication in the vancomycin treated group were pruritus (7 patients, 0.7%), drug hypersensitivity (5 patients, 0.5%), and rash (5 patients, 0.5%).

Renal insufficiency (2 patients, 1%) was the only TEAE resulting in discontinuation of study medication in more than 1 patient in the telavancin 7.5 mg/kg group, while the comparator group for the 7.5 mg studies had no single TEAE resulting in discontinuation in more than one patient.

### **Treatment Emergent AEs**

The overall incidence of TEAEs in the Phase 3 cSSSI studies was 79.1% (735/929 patients) in the telavancin treatment group and 72.1% (676/938) in the vancomycin treatment group.

- The most commonly reported TEAE occurred in telavancin-treated patients and was dysgeusia or altered taste which was observed in 311/929 (33.5%) of telavancin-treated patients compared to 62/938 (6.7%) of vancomycin-treated patients.
- The next most commonly reported TEAEs in the telavancin-treated patients were gastrointestinal. Nausea occurred in 249/929 (26.8%) of telavancin-treated patients compared to 142/938 (15.1%) of vancomycin-treated patients. Similarly, vomiting was twice as common in telavancin-treated patients with 127/929 (13.7%) patients experiencing an episode of vomiting compared to 69/938 (7.4%) of vancomycin-treated patients.
- Also more commonly reported in telavancin-treated patients was foamy urine (coded as urine abnormality) which was observed in 122/929 (13.1%) of telavancin-treated patients compared to 27/938 (2.9%) of vancomycin-treated patients.
- The only TEAEs which occurred with increased frequency in the vancomycin-treated group were pruritus and generalized pruritus.

### **Renal Adverse Events (all cSSSI studies)**

Preclinical studies indicated that administration of telavancin to rats and dogs at 1-2 times the human equivalent dose (HED) caused small increases in BUN and Cr along with the finding of renal tubular degeneration (see Pharmacology/Toxicology). Based on the number of renal SAEs and imbalance in renal adverse events between treatment groups, renal adverse events were examined in greater detail.

The FDA reviewer has examined narratives, CRFs, and pertinent laboratory data for patients in the telavancin clinical development program who had renal-related SAEs resulting in death or discontinuation from therapy, as well as other SAEs. The following preferred terms were included in the definition of renal impairment: renal tubular necrosis, renal failure acute, renal failure chronic, renal insufficiency, renal impairment, and increased blood creatinine.

The findings include:

- Deaths: Two patients treated with telavancin had renal insufficiency listed as an SAE with death as an outcome which were assessed by the investigator as possibly/probably related to study medication. One patient treated with vancomycin had acute renal failure listed as an SAE resulting in death, however the investigator assessed the event as not related to study medication. The FDA reviewer agrees with these assessments. Of patients in whom death occurred outside the study death-reporting period (i.e., until the TOC visit or 30 days following EOT if no TOC visit) and were reported to the Applicant, four of five patients who received telavancin had renal insufficiency or renal failure during the course of study, with one patient reported to have ongoing renal insufficiency at the time of death.
- SAEs (including deaths): Nineteen patients had renal SAEs reported during the cSSSI studies. Fifteen of the nineteen were in the telavancin treatment group and four in the comparator treatment group. Three of the telavancin patients required hemodialysis; two (one of whom had rising Cr prior to study), refused dialysis (and further care due to age/comorbidities), and died. Three patients treated with telavancin showed incomplete resolution of Cr with values still 2 times their baseline Cr.
- Discontinuation of study medication due to renal TEAEs: Fourteen patients discontinued study medication prematurely due to renal SAEs; thirteen of the patients were treated with telavancin compared to one treated with vancomycin. Nine of the thirteen telavancin-treated patients who discontinued telavancin prematurely had renal events that were considered to be SAEs. The other four telavancin-treated patients had renal AEs which resulted in early discontinuation of study medication that were possibly/probably related to study medication, but were not considered to be SAEs. There were two vancomycin-treated patients who had renal AEs assessed as possibly/probably related to study medication by investigators.

Table 23 lists those patients who had renal SAEs and provides information regarding confounding factors and course of renal impairment, along with assessment of relationship to study medication by the investigator and FDA Medical Reviewer.

**Table 23: Renal SAEs (Telavancin cSSSI Studies)**

Patient ID	Age / Gender	Comorbid Condition	Concom Meds	Renal SAE	Increase Cr on Study Med	BL Cr	High Cr	Last Cr	Investigator Relatedness	FDA Relatedness
<b>Telavancin 7.5 mg</b>										
0017-02008-0120 <sup>1</sup>	82 / F	Yes	Yes	Renal insufficiency (death)	Yes	1.0 mg/dL	3.2 mg/dL	3.2 mg/dL	Yes	Yes
0018-38160-2007	51 / M	No	Yes	ATN (resolution)	Yes	0.7 mg/dL	3.4 mg/dL	1.9 Mg/dL	No	Yes
202b-00101-7008	76 / F	Yes	Yes	Acute renal insufficiency Prerenal azotemia Elevated BUN Elevated Cr	Yes	0.9 mg/dL	3.4 mg/dL	1.2 mg/dL	Yes	Yes
<b>Telavancin 10 mg</b>										
0017-38117-0240	51 / F	Yes	Yes	Acute renal failure	Yes	1.0 mg/dL	3.1 mg/dL	1.1 mg/dL	No	Yes
0017-38271-0953	93 / M	Yes	Yes	Renal impairment (worsening of)	Yes	1.4 mg/dL	2.3 mg/dL	1.8 mg/dL	No	Yes
0017-38002-0428 <sup>1</sup>	70 / M	Yes	Yes	Renal insufficiency (death – refused dialysis)	Yes	1.0 mg/dL	2.7 mg/dL	N/A	Yes	Yes
0017-18001-0721	46 / M	Yes	Yes	Renal impairment (hemodialysis initiated)	Increasing prior to study	5.5 mg/dL	10.8 mg/dL	7.3 mg/dL	Yes	Yes
0018-06003-2353	84 / F	Yes	Yes	Acute renal failure	Yes	1.7 mg/dL	3.0 mg/dL	1.2 mg/dL	No (changed)	Yes
0018-06003-2721	56 / F	Yes	Yes	Acute renal failure	?*	0.9 mg/dL	1.7 mg/dL	0.7 mg/dL	Yes	Yes
0018-38160-3068 <sup>2</sup>	95 / M	Yes	Yes	Acute renal failure (death – refused dialysis)	Yes	4.1 mg/dL	10.3 mg/dL	N/A	Yes	Yes
0018-38148-2498	47 / F	Yes	Yes	Elevated blood creatinine Elevated blood urea	Yes	0.7 mg/dL	2.7 mg/dL	1.5 mg/dL	Yes	Yes
0018-38260-2099	50 / F	Yes	Yes	Renal insufficiency (interstitial nephritis)	Yes	0.9 mg/dL	6.0 mg/dL	2.0 mg/dL	Yes	Yes
0018-38148-2359	57 / F	Yes	Yes	Elevated creatinine	Yes	0.9 mg/dL	2.1 mg/dL	1.0 mg/dL	Yes	Yes
0018-38322-2757	66 / F	Yes	Yes	Acute renal failure	Yes	0.6 mg/dL	3.7 mg/dL	0.9 mg/dL	Yes	Yes
202b-00910-9058	28 / M	No	Yes	Acute renal failure	Yes	1.0 mg/dL	3.5 mg/dL	1.1 mg/dL	Yes	Yes



Patient ID	Age / Gender	Comorbid Condition	Concom Meds	Renal SAE	Increase Cr on Study Med	BL Cr	High Cr	Last Cr	Investigator Relatedness	FDA Relatedness
<b>Vancomycin</b>										
0017-38005-0180	77 / F	Yes	Yes	Increased Cr	Yes	1.4 mg/dL	3.4 mg/dL	1.0 mg/dL	Yes	Yes
0017-38024-0697	62 / M	Yes	Yes	Increased Cr	Yes	0.7 mg/dL	3.0 mg/dL	1.0 mg/dL	Yes	Yes
0018-38260-2555	53 / M	Yes	Yes	Renal failure chronic	Yes (?)	HD	HD	HD	No	? blinding
202b-00903-9037 <sup>1,3</sup>	41 / F	No	?	Renal failure acute	Yes	0.6 mg/dL	2.3 mg/dL (?)	(?)	No	No
<sup>1</sup> Patients died during the study <sup>2</sup> Patient died outside the study death reporting period <sup>3</sup> 202b-00903-9037 information from death narrative (CRF of limited utility – only abnormal Cr is D3 of 1.4 mg/dL or 125µmol/L)										

Fifteen patients treated with telavancin had renal SAEs reported as shown above; eleven of these events were assessed by the investigator as possibly/probably related to study medication. The FDA medical reviewer was unable to exclude study medication as possible/probable cause in any of these cases. Four patients treated with vancomycin had renal SAEs reported; two were assessed by the investigator as having renal SAEs possibly/probably related to study medication compared to three patients with events possibly/probably related as assessed by the FDA reviewer.

Clinically significant changes in renal laboratory parameters (i.e. serum Cr and BUN) were used to identify patients with potential renal impairment. These definitions were based on maximum change from baseline and included serum Cr increase to 1.25 x baseline, any post-baseline serum Cr  $\geq 133 \mu\text{mol/L}$  and increase of  $\geq 44 \mu\text{mol/L}$ , any post-baseline serum Cr  $\geq 133 \mu\text{mol/L}$  and 50% increase from baseline, and BUN post-baseline  $> 11 \text{ mmol/L}$ . Two to three times as many patients treated with telavancin in Studies 0017 and 0018 combined developed clinically significant elevations in serum Cr and BUN compared to patients treated with vancomycin, regardless of which particular functional definition of renal impairment was used.

### **Cardiac Toxicity**

#### Thorough QT Study

Based on the preclinical safety pharmacology results presented previously, the Applicant was required to perform a “thorough QT Study” which was designed with guidelines available at the time (as defined in the 2002 FDA – Health Canada Concept paper).<sup>13</sup> The study evaluated QT effects in subjects treated with either telavancin 7.5 mg/kg and 10 mg/kg IV, moxifloxacin 400 mg IV, or placebo administered for 3 days. At both doses the baseline and placebo-corrected QTcF (QT corrected using Fridericia’s formula) interval ( $\Delta\Delta\text{QTcF}$ ) was lengthened greater than 10 msec, the threshold for regulatory concern. Based on a step-wise linear mixed-effects model describing the relationship between telavancin concentrations and  $\Delta\Delta\text{QTcF}$  interval, the expected  $\Delta\Delta\text{QTcF}$  of telavancin was estimated to be 12-15 msec. The mean  $\Delta\Delta\text{QTcF}$  for moxifloxacin was 24 msec which is longer than the standard used, however moxifloxacin was administered IV and for three days, as opposed to a single oral dose.

#### Phase 2/3 SSSI ECG Monitoring

Patients in the Phase 2 and Phase 3 studies had ECGs obtained at baseline, at 3-5 days of treatment and EOT. The on-drug average and on-drug maximum change in QTcF interval compared to baseline were analyzed for both groups of study patients.

The results showed that both mean and median post-drug average change and maximum change from baseline in QTcF were greater for the telavancin treatment groups at both the 7.5 and 10 mg/kg dose than those for the vancomycin treatment groups. The average and maximum change appear to be higher where telavancin was administered at a dose of 7.5 mg/kg indicating that the higher, proposed therapeutic dose did not have any greater effect than the lower dose (i.e., threshold effect reached). However the higher values noted may

also be influenced by the more frequent ECG testing in the Phase 2 202a and 202b studies than in the Phase 3 studies with greater opportunity for measurement of outlier values.

The maximum post-drug QTcF and maximum post-drug change in QTcF were also examined to identify patients who may be more affected by drug administration than others. The maximum QTcF change from baseline was greater for patients treated with telavancin (both doses) than patients treated with vancomycin.

The Integrated Summary of Safety (ISS) dataset of AEs was searched for AEs [both investigator reported and Medical Dictionary for Regulatory Activities (MedDRA) preferred terms] that might be indicative of a problem with QT prolongation and/or ventricular arrhythmia such as Torsades de pointes. The following terms were searched: bradycardia, arrhythmia, palpitations, ventricular arrhythmias, ventricular tachycardia, ventricular extrasystoles, ventricular bigeminy, cardio-respiratory arrest, cardiac arrest, sudden death, fall, syncope, and light headedness. There were no patients treated with telavancin who had AEs that were preceded by CRF evidence of ventricular arrhythmia due to Torsades de pointes.

#### **Cardiac Adverse Event Summary**

- Deaths: Four patients treated with telavancin had cardiac events resulting in death, with two of the patient's events assessed as possibly or probably related to study medication by the investigator. The FDA reviewer could not exclude relationship to study medication in any of the four deaths, although noting multiple confounders for each patient. Six patients treated with vancomycin had cardiac events resulting in death, with none of the cardiac events assessed as related to study medication by the investigator. The FDA reviewer assessed one of the six patients treated with vancomycin as having a cardiac event leading to death possibly/probably related to study medication.
- Other SAEs: Twenty-six patients experienced at least one SAE in the Cardiac Disorders System SOC; thirteen patients were in the telavancin treatment groups (11 treated with 10 mg/kg and 2 with 7.5 mg/kg) and thirteen in the comparator treatment group.
- Discontinuations of study medication due to cardiac TEAEs were also balanced across treatment groups, with four events in the telavancin treatment group and three in the vancomycin group.

#### **Hepatic Adverse Event Summary**

Preclinical studies of 6-13 week duration were associated with elevated transaminase levels (AST, ALT) in rats and dogs. (See Pharmacology/Toxicology)

In the ISS database, there were three patients with hepatobiliary-related SAEs; two patients received telavancin and one patient comparator. One telavancin treated patient had worsening of hepatic cirrhosis following treatment with telavancin and chemoembolization of hepatic carcinoma and the other telavancin treated patient had a history of cholelithiasis and developed acute cholecystitis requiring cholecystectomy at the end of telavancin treatment. The vancomycin treated patient had elevated transaminases (ALT, AST) that were attributed to chronic alcohol use.

#### Liver Function Laboratory Studies:

Low level ( $\geq 3 \times \text{ULN}$ ) elevation in transaminases were more common in patients treated with vancomycin and seen in approximately 2% of patients. Elevation in total bilirubin and alkaline phosphatase were slightly more common in patients treated with telavancin, but were seen in approximately 1% of patients. No patients treated with telavancin or vancomycin met Hy's Rule criteria for drug-induced liver injury.<sup>14</sup>

#### **Hematologic Laboratory Adverse Events**

There were four patients treated with telavancin who had a potentially clinically significant decrease in platelet count to  $\leq 75 \times 10^9/\text{L}$  AND  $\geq 50 \times 10^9/\text{L}$  below baseline. Two patients were treated in Study 0017; one patient received 5 minutes of a telavancin infusion and had a nadir platelet count of 55,000 six days after discontinuation, most likely due to a concomitant medication and the second patient had a nadir platelet count of 38,000 on Day 8 of treatment and rebounded while on therapy to 202,000 at EOT (Day 14). Two patients in a Phase 2 study had similar decreases noted in platelet counts; one patient had necrotizing fasciitis and was noted to have a platelet count of 59,000 at the time study medication was infusing and the second patient likely had a false decrease related to clumping of platelets.

#### Safety Update

A safety update was provided with the resubmission of NDA 22-110 on January 21, 2008. This safety update contained additional unblinded safety data from a Japanese PK study (37 subjects; 24 of whom received telavancin) and unblinded summary safety data from the two recently completed hospital-acquired pneumonia (HAP) studies (full study reports not received or reviewed by FDA). There were 1503 patients treated in the two telavancin Phase 3 HAP trials; 751 patients received telavancin (10 mg/kg dose) and 752 received vancomycin. Twenty percent (149/751) of the telavancin-treated and 18% (137/752) of the vancomycin-treated patients died.

- AEs resulting in death that occurred with a 1% or greater difference between treatment groups where telavancin mortality was greater were multiorgan failure (3% telavancin vs. 1% vancomycin) and septic shock (3% telavancin vs. 2% vancomycin) and where vancomycin mortality was greater were respiratory failure (2% telavancin vs. 3% vancomycin) and pneumonia (1% telavancin vs. 2% vancomycin).
- Serious AEs occurred in 31% of telavancin-treated patients compared to 26% of vancomycin-treated patients. SAEs that occurred with an incidence of 1% or greater in either treatment group included: septic shock (4% for each treatment group), respiratory failure (3% each treatment group), multiorgan failure (3% telavancin vs. 2% vancomycin), acute renal failure (2% telavancin vs. 1% vancomycin), (pneumonia 1% telavancin vs. 2% vancomycin), sepsis (2% telavancin vs. 1% vancomycin), congestive cardiac failure (<1% telavancin vs. 1% vancomycin), and acute respiratory failure (<1% telavancin vs. 1% vancomycin).
- Discontinuations due to AEs occurred in 60/751 (8%) telavancin-treated patients and 40/752 (5%) of vancomycin-treated patients. TEAEs that resulted in discontinuation of study medication occurred more frequently in the telavancin-treated group

included acute renal failure (nine patients versus two), prolonged QTc (protocol-specified; eight versus two), and increased blood creatinine (five vs. one).

- The overall incidence of TEAEs was 82% for telavancin and 81% for vancomycin. Gastrointestinal AEs were the most commonly seen and occurred in 35% of both treatment groups.

### **Teratogenicity**

Based on the results of the Segment 2 (embryo-fetal development) teratology studies in rats, rabbits, and minipigs, the Reproductive and Developmental Toxicity PTCC Subcommittee agreed with the findings of the Pharmacology/Toxicology reviewer that the limb defects are drug-related and that telavancin is a multi-species teratogen. The Committee could not come to a consensus on whether the product should be labeled Pregnancy Category C or X and recommended that the following factors be considered in assigning a pregnancy category to this drug (Appendix A):

- Seriousness of the indication and potential for serious complications in pregnancy associated with the indication
- Availability of alternative treatments
- Teratogenic effect occurring at or near the proposed human dose
- “Potential benefit” of the treatment should exceed the risk

The Clinical review team acknowledges the results of the animal findings, but has concerns regarding the strength of findings in the minipig study given the confounding issues including: the small number of fetuses available for examination, skeletal abnormality observed in a fetus in the placebo group, no skeletal defects observed in the high dose group, and use of multiple other antibiotic agents for unspecified reasons.

In light of the teratogenicity and pregnancy labeling issues, the utility of a risk management plan to minimize fetal exposure to telavancin should be discussed. Background information on risk management can be found in the FDA guidance document titled "Development and Use of Risk Minimization Action Plans (RiskMAPs)" (Appendix B). In September 2007, Congress authorized FDA to require strategies previously referred to as "risk minimization action plans" (now called "risk evaluation and mitigation strategies (REMS)") when FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [FDAAA Section 505-1(a)]. This provision took effect on March 25, 2008. These strategies will generally replace RiskMAPs when a required risk management plan is necessary, and existing guidance will be updated to reflect the new statutory authority.

The Maternal Health Team (MHT) recommends that the drug be classified as a pregnancy category X based on lack of perceived benefit over existing therapy with an increase in risk based on teratogenicity potential. They also recommend a boxed warning, restricted distribution at the pharmacy level to include documentation of age, gender, and evidence of non-childbearing potential for females, and a risk evaluation and mitigation strategy (REMS) program that includes a pregnancy surveillance registry. If telavancin is approved as a pregnancy category C drug, then they recommend that a prospective pregnancy registry should be required in the post-marketing setting. (Appendix C).

## **IX. ISSUES FOR DISCUSSION**

1. Do the data presented demonstrate the safety and effectiveness of telavancin for the treatment of cSSSI?
  - If your answer is yes, are there specific issues that should be addressed in labeling?
  - If your answer is no, what additional data/studies are needed?
2. Are there clinical situations when the benefits of telavancin use in a pregnant woman would outweigh the risks?
  - If your answer yes, describe the situations when the benefits of telavancin use would outweigh the risks in a pregnant woman.
3. Is a risk evaluation and mitigation strategy (REMS) needed to prevent unintended use in pregnant women?
  - If your answer is yes, what elements should be included?

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**Appendix A: Consultation by CDER Reproductive and Developmental Toxicology Subcommittee, Pharmacology and Toxicology Coordinating Committee**

**Appendix B: Guidance for Industry: Development and Use of Risk Minimization Action Plans**

**Appendix C: Maternal health team (MHT) recommendations for: pregnancy category, pregnancy exposure registry, and risk evaluation and mitigation strategies (REMS) related to fetal exposure**



**Appendix A: Consultation by CDER Reproductive and Developmental Toxicology Subcommittee, Pharmacology and Toxicology Coordinating Committee**

## REPRODUCTIVE AND DEVELOPMENTAL TOXICITY PTCC SUBCOMMITTEE CONSULT

**Date:** August 1, 2007

**From:** Lynnda Reid, PhD  
RDTs Co-Chair

**To:** Zhou Chen, PhD  
Acting Pharmacology Team Leader, DAIOP

J. Christopher Davi, RPM, MS  
Regulatory Health Project Manager, DAIOP

**Date of Consultation:** July 2, 2007

**RE:** NDA 22-110: The sponsor and reviewer have different interpretations regarding the positive findings from reproductive studies in three species. Therefore, there is a difference in Pregnancy Category determination. The division would like RDTs members to have an unbiased review and evaluation for the three pivotal Segment 2 studies and make a labeling suggestion.

**Background information:** Telavancin is a glycopeptide antibiotic indicated for the treatment of complicated skin and skin-structure infections (cSSSI). Administration of telavancin is via intravenous injection at a proposed maximum recommended human dose (MRHD) of 10 mg/kg. To support potential exposures in pregnant women, three embryo/fetal developmental (Segment 2) studies were conducted in rats, rabbits and minipigs.

Following review of these studies, the primary nonclinical reviewer, Dr. Zhou Chen, concluded that telavancin is a multi-species teratogen with external/skeletal (limb) malformations. Findings across species involving limb development consisted of brachymelia, syndactyly, adactyly, and polydactyly. These effects were observed at doses comparable to human doses based on plasma AUC levels.

Comparison of Systemic Exposure to Telavancin at the Lowest Dose with Toxicity between Animals and Humans

Species	General toxicity		Segment 2 studies			Clinical studies
	Rat	Dog	Rabbit	Rat	Minipig	Human
Dose (mg/kg)	50*	25*	75	100	25	10
AUC <sub>0-24h</sub> (µg-hr/ml)	1012-1227	600-624	1387	829	780	666-780
Animal/human	1.3-1.6	0.77-0.80	1.78	1.06	1	

\* This is the dose with clear liver and renal findings. Other positive findings (e.g., macrophage hypertrophy/hyperplasia affecting the bone marrow, spleen, thymus, and duodenum) were seen at the doses as low as 6.25 mg/kg with AUC of 88-126 µg-hr/ml.

Incidence per litter of limb related external malformations (number of affected fetuses in parentheses):

#### Rats:

	<i>Diluent</i>	<i>Placebo</i>	<i>50 mg/kg/day</i>	<i>100 mg/kg/day</i>	<i>150 mg/kg/day</i>
Litters Evaluated:	25	24	25	24	25
Fetuses evaluated:	319	322	312	332	322
Brachymelia	0	0	0	1 (1) 4.2%	1 (1) 4.0%
Syndactyly	0	0	0	1 (1) 4.2%	0
<b>Total Litter Incidence*</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>4.2%</b>	<b>4.0%</b>

\* Incidence for Brachymelia, micromelia or syndactyly were not in the historical data base submitted.

#### Rabbits:

	<i>Placebo</i>	<i>60 mg/kg/day</i>	<i>75 mg/kg/day</i>
Litters Evaluated:	18	20	19
Fetuses evaluated:	138	172	156
Flexed Front Paws, brachymelia, and adactyly	0	0	1 (1) 5.3%
Absent ulna	0	0	1 (1) (5.3%)
<b>Total Litter Incidence</b>	<b>0</b>	<b>0</b>	<b>10.6%</b>

\* Historical Control Incidence for Malrotated Hindlimbs = 0.8%; Flexed front paws – 0.8%; adactyly – 0.3%; no incidence rate given for brachymelia or absent ulna.

#### Gottingen Minipigs:

	<i>Diluent</i>	<i>Placebo</i>	<i>25 mg/kg/day</i>	<i>50 mg/kg/day</i>	<i>75 mg/kg/day</i>
Litters Evaluated:	7	5	9	8	5
Fetuses evaluated:	34	24	31	36	17
Syndactyly	0	0	0	1 (1) 12.5%	0
Polydactyly: Single Limb	0	1 (1) 20%	2 (2) 22.2%	2 (4) 25%	0
Polydactyly: Multiple limbs	0	0	2 (2) 22.2%	1 (1) 12.5%	0
Misshapen digits & deformed leg	0	0	0	1 (1) 12.5%	0
<b>Total Litter Incidence*</b>	<b>0%</b>	<b>20%</b>	<b>33.3%</b>	<b>50%</b>	<b>0%</b>

\* Historical Control Incidence for Polydactyly = 5.71%; Syndactyly = 2.86%

**Discussion and Conclusions:** It was the consensus of the committee that the limb defects observed in these studies were related to the drug. While the evidence of drug-induced limb malformations in each species is weak, the weight of evidence across all three species strongly supports that the findings are drug-related. Furthermore, although the incidence rates were low, they occurred in a dose-dependent manner and at rates higher than in the historical control databases reported by the Sponsor. Of greatest concern is that these malformations occurred at clinically relevant maternal exposures based on AUC.

<i>Species</i>		<i>Dose (mg/kg/day)</i>	<i>C<sub>max</sub> (µg/ml)</i>	<i>AUC<sub>0-24</sub> (µg.h/ml)</i>
Rat	Maternal Plasma	50	420	829
		100	760	1236
		150	914	1726
	Amniotic Fluid	50	NA	NA
		100	0.250	NA
		150	0.450	5.97
Rabbit	Maternal Plasma	60	541	1027
		75	716	1387
	Amniotic Fluid	Drug was detected in the amniotic fluid from only one dam indicative of limited placental transfer in rabbits at 75 mg/kg.		
Minipig	Maternal Plasma	25	347	780
		50	545	1206
		75	871	1781
	Amniotic Fluid	Amniotic fluid from Minipigs was not analyzed.		

In the final rabbit study report from Covance, the contract laboratory responsible for conducting both the rat and rabbit studies, they concluded that “*the limb malformations noted (brachymelia, adactyly and absent ulna) mimic or are similar to the malformations of brachymelia and syndactyly observed in rats... These findings further support a direct effect of AMI-6524 [telavancin] on the developing fetus.*” The total litter incidence rates for skeletal malformations in rabbits were 5.6, 5.0, and 26% in the placebo, 60 mg/kg/day and 75 mg/kg/day groups, respectively. Five fetuses in separate high-dose litters exhibited skeletal malformations. Of note is the lack of significant maternal toxicity at the high-dose in this study.

The diluent control was 5% dextrose and the composition of the placebo and test agents were as follows:

	<b>Placebo (250 mg/vial)</b>	<b>Telavancin (250 mg/vial)</b>
AMI-6424 (telavancin)	0	250 mg
Hydroxypropyl-β-Cyclodextrin	2500 mg	2500 mg
Mannitol	312.5 mg	312.5 mg
1 N NaOH	QS to pH 4.5	
1 N HCl		

Although high concentrations of hydroxypropyl- $\beta$ -cyclodextrin were present in the test articles used in the studies, there was only one occurrence of polydactyly in a single limb in the minipig study placebo control group, and no limb malformations in placebo controlled rats or rabbits. This is also not a reported finding associated with cyclodextrin exposures. Therefore, the presence of hydroxypropyl- $\beta$ -cyclodextrin alone cannot account for the increased rates of limb malformations.

Maternal toxicity was observed in high-dose rats and rabbits as reductions in weight gain compared to controls. However, we do not think that the limb malformations were a result of maternal toxicity. Observations typically associated with maternal toxicity as evinced by decreased weight gain include increased early and/or late resorptions, decreased fetal weights and delayed ossification. None of these typical findings associated with decreased maternal weight gain were significantly increased in the high-dose litters of rats and rabbits. In minipigs, there were drug or dose-related effects on weight gain or clinical signs. Therefore, it is doubtful that the teratogenic effects observed in these studies can be attributed to maternal toxicity.

### **RDTS Conclusions and Recommendations:**

The RDTS agrees with the primary reviewer that the limb defects are drug-related. As such we recommend that the findings be detailed in labeling. As to the appropriate Pregnancy Category, we could not come to a consensus on whether telavancin should be labeled under category C or X. Either category could be appropriate based on the risk/benefit profile of the drug. The category should be based on the risk/benefit potential of the product in pregnant women. Factors which should be considered include the following:

- Seriousness of the indication and the potential for serious complications in pregnancy associated with the indication
- Availability of alternative treatments
- Teratogenic effects occurring at or near the proposed human dose

In order to label the product under Category C, the potential benefit to the mother and/or the fetus should clearly exceed any potential risk to the fetus otherwise we recommend that this product should be labeled under Category X.

## **Appendix B: Guidance for Industry: Development and Use of Risk Minimization Action Plans**

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# Guidance for Industry Development and Use of Risk Minimization Action Plans

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**March 2005  
Clinical Medical**

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# Guidance for Industry Development and Use of Risk Minimization Action Plans

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**March 2005  
Clinical Medical**



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## **Guidance for Industry<sup>1</sup>**

### **Development and Use of Risk Minimization Action Plans**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## **I. INTRODUCTION**

This document provides guidance to industry on the development, implementation, and evaluation of risk minimization action plans for prescription drug products, including biological drug products.<sup>2</sup> In particular, it gives guidance on (1) initiating and designing plans called risk minimization action plans or RiskMAPs to minimize identified product risks, (2) selecting and developing tools to minimize those risks, (3) evaluating RiskMAPs and monitoring tools, and (4) communicating with FDA about RiskMAPs, and (5) the recommended components of a RiskMAP submission to FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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<sup>1</sup> This guidance has been prepared by the PDUFA III Risk Management Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

<sup>2</sup> For ease of reference, this guidance uses the term *product* or *drug* to refer to all drug products (excluding blood and blood components) regulated by CDER or CBER. Similarly, for ease of reference, this guidance uses the term *approval* to refer to both drug approval and biologic licensure.

**Paperwork Reduction Act Public Burden Statement:** This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0001 (until March 31, 2005) and 0910-0338 (until August 31, 2005).

## **II. BACKGROUND**

### **A. PDUFA III's Risk Management Guidance Goal**

On June 12, 2002, Congress reauthorized, for the second time, the Prescription Drug User Fee Act (PDUFA III). In the context of PDUFA III, FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products. As an initial step towards satisfying that goal, FDA sought public comment on risk management. Specifically, FDA issued three concept papers. Each paper focused on one aspect of risk management, including (1) conducting premarketing risk assessment, (2) developing and implementing risk minimization tools, and (3) performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments. In addition to receiving numerous written comments regarding the three concept papers, FDA held a public workshop on April 9–11, 2003, to discuss the concept papers. FDA considered all of the comments received in developing the three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents:

1. *Premarketing Risk Assessment (Premarketing Guidance)*
2. *Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)*
3. *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)*

### **B. Overview of the Risk Management Guidance Documents**

Like the concept papers and draft guidances that preceded them, each of the three final guidance documents focuses on one aspect of risk management. The *Premarketing Guidance* and the *Pharmacovigilance Guidance* focus on premarketing and postmarketing risk assessment, respectively. The *RiskMAP Guidance* focuses on risk minimization. Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

When reviewing the recommendations provided in this guidance, sponsors and applicants should keep the following points in mind:

- Many recommendations in this guidance are ***not*** intended to be generally applicable to all products.

## ***Contains Nonbinding Recommendations***

Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (see e.g., FDA requirements for professional labeling and adverse event monitoring and reporting). As a result, many of the recommendations presented here focus on situations in which a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for all products or only this subset of products.

- It is of critical importance to protect patients and their privacy during the generation of safety data and the development of risk minimization action plans.

During all risk assessment and risk minimization activities, sponsors must comply with applicable regulatory requirements involving human subjects research and patient privacy.<sup>3</sup>

- To the extent possible, this guidance reflects FDA's commitment to harmonization of international definitions and standards.
- When planning risk assessment and risk minimization activities, sponsors should consider input from healthcare participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and third-party payers).
- There are points of overlap among the three guidances.

We have tried to note in the text of each guidance when areas of overlap occur and when referencing one of the other guidances might be useful.

### **III. THE ROLE OF RISK MINIMIZATION AND RISKMAPS IN RISK MANAGEMENT**

As described in section II.B, FDA views risk management as an iterative process encompassing the assessment of risks and benefits, the minimization of risks, and the maximization of benefits. Specifically, the premarketing guidance and the pharmacovigilance guidance discuss how sponsors should engage in evidence-based risk assessment for all products in development and on the market to define the nature and extent of a product's risks in relation to its benefits. The goal of risk minimization is to minimize a product's risks while preserving its benefits. For the majority of products, routine risk minimization measures are sufficient to minimize risks and

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<sup>3</sup> See 45 CFR part 46 and 21 CFR parts 50 and 56. See also the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law 104-191) and the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) (45 CFR part 160 and subparts A and E of part 164). The Privacy Rule specifically permits covered entities to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to manufacturers and directly to FDA (45 CFR 164.512(b)(1)(i) and (iii) and 45 CFR 164.512(a)(1)). For additional guidance on patient privacy protection, see <http://www.hhs.gov/ocr/hipaa>.

## ***Contains Nonbinding Recommendations***

preserve benefits. Only a few products are likely to merit consideration for additional risk minimization efforts (see section III.D). Efforts to maximize benefits to improve the overall balance of risks and benefits can be pursued in concert with risk minimization efforts and can be discussed with FDA.

### **A. Relationship Between a Product's Benefits and Risks**

The statutory standard for FDA approval of a product is that the product is safe and effective for its labeled indications under its labeled conditions of use (see sections 201(p)(1) and 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)(1) and 355(d)). FDA's determination that a product is safe, however, does not suggest an absence of risk. Rather, a product is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a product is considered safe if it has an appropriate benefit-risk balance for the intended population and use.

Benefit and risk information emerges continually throughout a product's lifecycle (i.e., during the investigational and marketing phases) and can reflect the results of both labeled and off-label uses. Benefits and risks can result in a range of corresponding positive and negative effects on patient outcomes that may (1) be cosmetic, symptomatic, or curative; (2) alter the course of the disease; or (3) affect mortality. Benefits and risks are difficult to quantify and compare because they may apply to different individuals and are usually measured and valued differently. Examples of factors to weigh are (1) population risks and benefits, (2) individual benefits from treatment, (3) risks of nontreatment or alternative products, and (4) modest population benefits in the context of a serious adverse effect that occurs rarely or unpredictably. Benefits as well as risks are also patient-specific and are influenced by such factors as (1) the severity of the disease being treated, (2) the outcome of the disease if untreated, (3) the probability and magnitude of any treatment effect, (4) existing therapeutic options, and (5) the individual's understanding of risks and benefits and the value they attach to each of them. Thus, assessment and comparison of a product's benefits and risks is a complicated process that is influenced by a wide range of societal, healthcare, and individualized patient factors.

### **B. Determining an Appropriate Risk Minimization Approach**

To help ensure safe and effective use of their products, sponsors have always sought to maximize benefits and minimize risks. FDA believes that, for most products, routine risk minimization measures are sufficient. Such measures involve, for example, FDA-approved professional labeling describing the conditions in which the drug can be used safely and effectively, updated from time to time to incorporate information from postmarketing surveillance or studies revealing new benefits (e.g., new indications or formulations) or risk concerns. Efforts to make FDA-approved professional labeling clearer, more concise, and better focused on information of clinical relevance reflect the Agency's belief that communication of risks and benefits through

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product labeling is the cornerstone of risk management efforts for prescription drugs.<sup>4</sup> For most products, routine risk management will be sufficient and a RiskMAP need not be considered.

There are, however, a small number of products for which a RiskMAP should be considered (see section III.D). FDA recommends that RiskMAPs be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients.

This guidance focuses on the development, implementation, and evaluation of RiskMAPs.

### **C. Definition of Risk Minimization Action Plan (RiskMAP)**

As used in this document, the term RiskMAP means a strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits. A RiskMAP targets one or more safety-related health outcomes or goals and uses one or more *tools* to achieve those goals.<sup>5</sup> A RiskMAP could also be considered as a selectively used type of Safety Action Plan as defined in the International Conference on Harmonization (ICH) guidance *E2E: Pharmacovigilance Planning* (E2E guidance).<sup>6</sup>

FDA recommends that RiskMAP goals target the achievement of particular health outcomes related to known safety risks. FDA suggests that sponsors state goals in a way that aims to achieve maximum risk reduction. The following are examples of RiskMAP goals: “patients on X drug should not also be prescribed Y drug” or “fetal exposures to Z drug should not occur.” FDA recommends that goals be stated in absolute terms. Although it might not be possible to ensure that absolutely no one on X drug receives Y drug, FDA believes that a *goal*, as the term implies, is a statement of the ideal outcome of a RiskMAP.

FDA recommends that RiskMAP goals be translated into pragmatic, specific, and measurable program *objectives* that result in processes or behaviors leading to achievement of the RiskMAP goals. Objectives can be thought of as intermediate steps to achieving the overall RiskMAP goal. A RiskMAP goal can be translated into different objectives, depending upon the frequency, type, and severity of the specific risk or risks being minimized. For example, a goal may be the elimination of dangerous concomitant prescribing. The objectives could include

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<sup>4</sup> For example, see the Proposed Rule on Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels that published in the *Federal Register* on December 22, 2000 (65 FR 81081).

<sup>5</sup> Although all products with RiskMAPs would also have FDA-approved professional labeling, the term *tool* as used in this document means a risk minimization action in addition to routine risk minimization measures. Some tools may be incorporated into a product’s FDA-approved labeling, such as Medication Guides or patient package inserts. As used in this document, the FDA-approved professional labeling refers to that portion of approved labeling that is directed to the healthcare practitioner audience. See section IV for a more detailed discussion of other non-routine risk minimization tools that focus on targeted education and outreach.

<sup>6</sup> This ICH guidance is available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November 2004.

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lowering physician co-prescribing rates and/or pharmacist co-dispensing rates. As described in greater detail in section IV, many processes or systems to minimize known safety risks are available or under development for use in RiskMAPs. These systems include:

- targeted education and outreach to communicate risks and appropriate safety behaviors to healthcare practitioners or patients
- reminder systems, processes, or forms to foster reduced-risk prescribing and use
- performance-linked access systems that guide prescribing, dispensing, and use of the product to target the population and conditions of use most likely to confer benefits and to minimize particular risks

For certain types of risks (e.g., teratogenicity of category X drug products), it may be possible to develop systems with similar processes and procedures that can be used industrywide.

The use of these systems can occur outside of a RiskMAP. For example, while most drugs do not need a RiskMAP, many would still benefit from a program of physician and patient education and outreach. At times, communication of potential product risks may be warranted before a sponsor agrees to do a RiskMAP or an agreed upon RiskMAP is completed.

### **D. Determining When a RiskMAP Should Be Considered<sup>7</sup>**

As described in the premarketing guidance and pharmacovigilance guidance, evidence-based risk identification, assessment, and characterization are processes that continue throughout a product's lifecycle. Therefore, a risk warranting the consideration of a RiskMAP could emerge during premarketing or postmarketing risk assessment.<sup>8</sup> The Agency recommends that the appropriate information for consideration in making such a determination include, as applicable, (1) data from the clinical development program, postmarketing surveillance, and phase 4 studies, and (2) the product's intended population and use.

Although it is expected and hoped that sponsors will determine when a RiskMAP would be appropriate, FDA may recommend a RiskMAP based on the Agency's own interpretation of risk information.

Decisions to develop, submit, or implement a RiskMAP are always made on a case-by-case basis, but several considerations are common to most determinations of whether development of a RiskMAP may be desirable:

- Nature and rate of known risks versus benefits: Comparing the characteristics of the product's adverse effects and benefits may help clarify whether a RiskMAP could improve the product's benefit-risk balance. The characteristics to be weighed might

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<sup>7</sup> This guidance is directed primarily toward sponsors of innovator products. However, a generic product may have the same benefit-risk balance as an innovator product and so may be considered for a similar RiskMAP.

<sup>8</sup> See section VII for a detailed discussion of RiskMAP submissions.



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include the (1) types, magnitude, and frequency of risks and benefits; (2) populations at greatest risk and/or those likely to derive the most benefit; (3) existence of treatment alternatives and their risks and benefits; and (4) reversibility of adverse events observed.

- Preventability of adverse effects: Serious adverse effects that can be minimized or avoided by preventive measures around drug prescribing are the preferred candidates for RiskMAPs.
- Probability of benefit: If factors are identified that can predict effectiveness, a RiskMAP could help encourage appropriate use to increase benefits relative to known risks.

Consider the following examples:

- Opiate drug products have important benefits in alleviating pain but are associated with significant risk of overdose, abuse, and addiction. The Agency recommends that sponsors of Schedule II controlled substances, including Schedule II extended release or high concentration opiate drug products, consider developing RiskMAPs for these products.
- Drugs that provide important benefits, but that are human teratogens would often be appropriate for a RiskMAP to minimize in utero exposure.
- Some drugs may warrant RiskMAP consideration because safe and effective use call for specialized healthcare skills, training, or facilities to manage the therapeutic or serious side effects of the drug.

Involving all stakeholders during the initial phases of considering whether a RiskMAP is appropriate allows input and buy-in by all parties who will later have roles in implementing the RiskMAP. If a RiskMAP is appropriate, stakeholders can help shape the RiskMAP to foster its success in the healthcare delivery environment. Therefore, we recommend public discussion about the appropriateness of a RiskMAP through the FDA advisory committee process. Such public advisory committee meetings can also be used to address (1) whether a RiskMAP is appropriate, (2) what the goals and objectives of the RiskMAP could be (see footnote 6), (3) the circumstances under which a RiskMAP tool might be revised or terminated, and (4) whether a RiskMAP itself is no longer appropriate. The FDA advisory committee structure and processes are well suited to foster such discussions as they arise on a case-by-case basis.

## **IV. TOOLS FOR ACHIEVING RISKMAP GOALS AND OBJECTIVES**

A risk minimization tool is a process or system intended to minimize known risks. Tools can communicate particular information regarding optimal product use and can also provide guidance on prescribing, dispensing, and/or using a product in the most appropriate situations or patient populations. A number of tools are available; FDA encourages and anticipates the development of additional tools.

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### **A. Relationship of RiskMAP Tools to Objectives and Goals**

Risk minimization tools are designed to help achieve one or more RiskMAP objectives that are directed at the overall RiskMAP goal or goals. One or more tools can be chosen to achieve a particular objective. For example, a goal might be that patients with condition A should not be exposed to product B. An objective for achieving this goal might be to communicate to patients that if they have condition A, they should not take product B. Depending on the likelihood and severity of the adverse event associated with product B in a patient with condition A, a variety of tools could be applied to achieve this objective. One possible tool would be patient labeling explaining that a patient with condition A should not take product B. On the other hand, if the potential harm to a patient with condition A is severe and/or likely to occur, a more active tool may be appropriate. For example, the sponsor could choose to develop a patient agreement where, before receiving the product, the patient formally acknowledges their understanding and/or agreement not to take product B if he or she has condition A.

### **B. Categories of RiskMAP Tools**

A variety of tools are currently used in risk minimization plans. These fall within three categories: (1) targeted education and outreach, (2) reminder systems, and (3) performance-linked access systems. A RiskMAP might include tools from one or more categories, depending on its risk minimization goals. FDA notes that the use of tools in different categories does not imply greater or lesser safety risks, but rather indicates the particular circumstances put in place to achieve the objectives and goals.

#### ***1. Targeted Education and Outreach***

FDA recommends that sponsors consider tools in the targeted education and outreach category (1) when routine risk minimization is known or likely to be insufficient to minimize product risks or (2) as a component of RiskMAPs using reminder or performance-linked access systems (see sections IV.B.2 and 3 below).

Tools in this category employ specific, targeted education and outreach efforts about risks to increase appropriate knowledge and behaviors of key people or groups (e.g., healthcare practitioners and consumers) that have the capacity to prevent or mitigate the product risks of concern.

FDA acknowledges that tools in this category are occasionally used for products where the benefit/risk balance does not necessarily warrant a RiskMAP. Educational efforts by sponsors might include one or more of the tools described below without a RiskMAP being in place. Sponsors are encouraged to continue using tools, such as education and outreach, as an extension of their routine risk minimization efforts even without a RiskMAP.

Examples of tools in this category are as follows:

- healthcare practitioner letters
- training programs for healthcare practitioners or patients

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- continuing education for healthcare practitioners such as product-focused programs developed by sponsors and/or sponsor-supported accredited CE programs
- prominent professional or public notifications
- patient labeling such as Medication Guides and patient package inserts
- promotional techniques such as direct-to-consumer advertising highlighting appropriate patient use or product risks
- patient-sponsor interaction and education systems such as disease management and patient access programs

In addition to informing healthcare practitioners and patients about conditions of use contributing to product risk, educational tools can inform them of conditions of use that are important to achieve the product's benefits. For example, a patient who takes a product according to labeled instructions is more likely to achieve maximum product effectiveness. On the other hand, deviations from the labeled dose, frequency of dosing, storage conditions, or other labeled conditions of use might compromise the benefit achieved, yet still expose the patient to product-related risks. Risks and benefits can have different dose-response relationships. Risks can persist and even exceed benefits when products are used in ways that minimize effectiveness. Therefore, educational tools can be used to explain how to use products in ways that both maximize benefits and minimize risks.

### *2. Reminder Systems*

We recommend that tools in the reminder systems category be used in addition to tools in the targeted education and outreach category when targeted education and outreach tools are known or likely to be insufficient to minimize identified risks.

Tools in this category include systems that prompt, remind, double-check or otherwise guide healthcare practitioners and/or patients in prescribing, dispensing, receiving, or using a product in ways that minimize risk. Examples of tools in this category are as follows:

- Patient education that includes acknowledgment of having read the material and an agreement to follow instructions. These agreements are sometimes called *consent* forms.
- Healthcare provider training programs that include testing or some other documentation of physicians' knowledge and understanding.
- Enrollment of physicians, pharmacies, and/or patients in special data collection systems that also reinforce appropriate product use.
- Limited number of doses in any single prescription or limitations on refills of the product.
- Specialized product packaging to enhance safe use of the product.
- Specialized systems or records that are used to attest that safety measures have been satisfied (e.g., prescription stickers, physician attestation of capabilities).

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### ***3. Performance-Linked Access Systems***

Performance-linked access systems include systems that link product access to laboratory testing results or other documentation. Tools in this category, because they are very burdensome and can disrupt usual patient care, should be considered only when (1) products have significant or otherwise unique benefits in a particular patient group or condition, but unusual risks also exist, such as irreversible disability or death, and (2) routine risk minimization measures, targeted education and outreach tools, and reminder systems are known or likely to be insufficient to minimize those risks.

Examples of tools in this category include:

- the sponsor's use of compulsory reminder systems, as described in the previous section (e.g., the product is not made available unless there is an agreement or acknowledgment, documented qualifications, enrollment, and/or appropriate testing or laboratory records)
- prescription only by specially certified healthcare practitioners
- product dispensing limited to pharmacies or practitioners that elect to be specially certified
- product dispensing only to patients with evidence or other documentation of safe-use conditions (e.g., lab test results)

Performance-linked access systems should seek to avoid unnecessary or unintended restrictions or fragmentation of healthcare services that may limit access by physicians, pharmacists, or patients, or that may lead to discontinuities in medical or pharmacy care.

#### **C. Description of RiskMAP Tools**

FDA plans to develop a RiskMAP Web site that will include (1) descriptions of tools that are currently used in RiskMAPs and (2) other information relevant to RiskMAP development (see section IV.D below). The information will be made available consistent with federal law and regulations governing disclosure of information by FDA to the public. The list of tools will be intended to assist sponsors in designing a RiskMAP but will not suggest that the listed tools are FDA-approved or -validated. On the contrary, FDA does not suggest that the tools listed on the Web site are the only tools that could be useful and encourages sponsors to develop tools that may be optimal for their particular products. See also Section V.D on making information from RiskMAP evaluations available to the public.

#### **D. Selecting and Developing the Best Tools**

Given the variety of available tools, FDA recommends that a sponsor carefully consider which tool or tools are most appropriate, given the goals and objectives of its product's RiskMAP. A tool could be developed or selected based on its individual impact and/or because of its impact when used in coordination with other tools. Generally, the best tools would be those that have a

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high likelihood of achieving their objective based on positive performance in other RiskMAPs or in similar settings and populations. Relevant non-RiskMAP evidence and experience can be found in healthcare quality initiatives, public health education and outreach, marketing, and other outcomes-based research (see section V for a more detailed discussion of evaluating tools' effectiveness).

Although FDA suggests that the best tool or tools be selected on a case-by-case basis, the following are generally applicable considerations in designing a RiskMAP. In choosing tools for a RiskMAP, FDA recommends that sponsors:

- Maintain the widest possible access to the product with the least burden to the healthcare system that is compatible with adequate risk minimization (e.g., a reminder system tool should not be used if targeted education and outreach would likely be sufficient).
- Identify the key stakeholders who have the capacity to minimize the product's risks (such as physicians, pharmacists, pharmacies, nurses, patients, and third-party payers) and define the anticipated role of each group.
- Seek input from the key stakeholders on the feasibility of implementing and accepting the tool in usual healthcare practices, disease conditions, or lifestyles, if possible. Examples of considerations could include (but would not be limited to) patient and healthcare practitioner autonomy, time effectiveness, economic issues, and technological feasibility.
- Acknowledge the importance of using tools with the least burdensome effect on healthcare practitioner-patient, pharmacist-patient, and/or other healthcare relationships.
- Design the RiskMAP to be:
  1. compatible with current technology
  2. applicable to both outpatient and inpatient use
  3. accessible to patients in diverse locales, including non-urban settings
  4. consistent with existing tools and programs, or systems that have been shown to be effective with similar products, indications, or risks
- Select tools based on available evidence of effectiveness in achieving the specified objective (e.g., tools effectively used in pregnancy prevention).
- Consider indirect evidence of tool effectiveness in a related area that supports the rationale, design, or method of use (e.g., tools applied in modifying patient or healthcare practitioner behaviors in medical care settings).
- Consider, and seek to avoid, unintended consequences of tool implementation that obstruct risk minimization and product benefit, such as obstructing patient access or

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driving patients to seek alternative product sources (e.g., Internet sales, counterfeit products) or less appropriate products.

FDA recognizes that once it approves a product for marketing, healthcare practitioners are the most important managers of product risks. FDA believes that by including information in the FDA-approved professional labeling on the conditions in which medical products can be used safely and effectively by their intended population and for their intended use or uses, the Agency and the sponsor encourage healthcare practitioners to prescribe medical products in circumstances that yield a favorable benefit-risk balance. However, as the Agency has long recognized, the FDCA and FDA regulations establish requirements governing the safety and effectiveness of medical products. FDA does not have authority under these provisions to control decisions made by qualified healthcare practitioners to prescribe products for conditions other than those described in FDA-approved professional labeling, or to otherwise regulate medical or surgical practice.

### **E. Mechanisms Available to the FDA to Minimize Risks**

This guidance focuses on the tools that industry can incorporate into RiskMAPs. As noted, FDA has a variety of risk management measures at its disposal under the FDCA and FDA regulations (see e.g., FDA requirements for professional labeling and adverse event monitoring and reporting).

FDA must occasionally invoke other mechanisms to minimize the risks from medical products that pose serious risks to the public health. These tools include:

- FDA-requested product recalls, warning and untitled letters, and import alerts
- safety alerts, guidance documents, and regulations
- judicial enforcement procedures such as seizures or injunctions

Further information on these mechanisms is available on the Internet at <http://www.fda.gov>.

## **V. RISKMAP EVALUATION: ASSESSING THE EFFECTIVENESS OF TOOLS AND THE PLAN**

As FDA and sponsors seek additional knowledge about the design, effectiveness, burdens, and potential unintended consequences of RiskMAPs, it is important to collect as much information as possible on plan performance. RiskMAPs and their component objectives and tools should be monitored and evaluated in a timely manner to identify areas for improvement.

### **A. Rationale for RiskMAP Evaluation**

At least two studies have documented poor or limited implementation and effectiveness of traditional risk minimization tools. In particular, the studies examined situations in which

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labeling changes (with or without Dear Healthcare Practitioner letters) were used to reduce safety problems.<sup>9</sup> The iterative process of risk assessment, risk minimization, and reevaluation previously described is intended to avoid repeating these experiences by identifying poorly performing or ineffective RiskMAPs or RiskMAP components as soon as possible. Ultimately, RiskMAP evaluation is intended to ensure that the energy and resources expended on risk minimization are actually achieving the desired goals of continued benefits with minimized risks. FDA considers evaluation of the effectiveness of a RiskMAP to be important and recommends that every RiskMAP contain a plan for periodically evaluating its effectiveness after implementation (see section VII for a detailed discussion of RiskMAP submissions to FDA).<sup>10</sup>

The evaluation of RiskMAPs can take several forms. Most critical is determining the performance of the overall RiskMAP in achieving its targeted health outcomes or goals. Separate but related assessments can be done for (1) individual tool performance, (2) acceptability of RiskMAP tools by consumers and healthcare practitioners, and (3) compliance with important RiskMAP processes or procedures.

Generally, FDA anticipates that RiskMAP evaluations would involve the analysis of observational or descriptive data. The specific types of data gathered in a RiskMAP evaluation will determine whether it would be appropriate to include a statistical analysis of evaluation results.

### **B. Considerations in Designing a RiskMAP Evaluation Plan**

FDA recommends that RiskMAP evaluation plans be tailored to the specific product and designed to assess whether the RiskMAP's goals have been achieved through its objectives and tools. The following are generally applicable guidelines for sponsors designing RiskMAP evaluation plans.

#### *1. Selecting Evidence-Based Performance Measures*

The Agency recommends that sponsors select well-defined, evidence-based, and objective performance measures tailored to the particular RiskMAP to determine whether the RiskMAP's goals or objectives are being achieved. An appropriate measure could be a number, percentage, or rate of an outcome, event, process, knowledge, or behavior. Ideally, the chosen measure would directly measure the RiskMAP's health outcome goal. For example, for a RiskMAP with a goal of preventing a particular complication outcome from product use, a sample performance

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<sup>9</sup> Smalley W, D Shatin, D Wysowski, J Gurwitz, S Andrade et al., 2000, *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*. JAMA 284(23):3036-3039; Weatherby LB, BL Nordstrom, D Fife, and AM Walker, 2002, *The Impact Of Wording in "Dear Doctor" Letters and In Black Box Labels*. Clin Pharmacol Ther 72:735-742.

<sup>10</sup> As noted in section III.B, sponsors should not develop a RiskMAP for a product for which routine risk minimization measures are sufficient. Similarly, formal evaluation plans and performance measures should not be developed for these products. Instead, evaluation by routine postmarketing surveillance should be sufficient, although some products may also have a Pharmacovigilance Plan as described in the *Pharmacovigilance Guidance*. If a RiskMAP is later developed for this type of product based on new risk information, then a sponsor should consider submitting a formal evaluation plan.

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measure could be the complication rate. For evaluation purposes, a target for that measure could be established to be no more than a specified number or rate of that complication. In some cases, however, a health outcome cannot be practically or accurately measured. In those cases, other measures can be used that are closely related to the health outcome, such as the following:

- Surrogates for health outcome measures (e.g., emergency room visits for an adverse consequence, pregnancy test results for determining if pregnancy occurred). The sensitivity, specificity, and predictive value of surrogate markers should be established before their use as a performance measure.
- Process measures that reflect desirable safety behaviors (e.g., performance of recommended laboratory monitoring, signatures attesting to knowledge or discussions of risk).
- Assessments of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks (e.g., provider, pharmacist, or patient surveys).

FDA recommends that the validity of a measure be judged by how closely it is related to the desired health outcome goal of the RiskMAP. Simply stated, the more closely related a measure is to the RiskMAP goal, the greater its degree of validity. For example, if the RiskMAP goal is avoidance of liver failure, then ascertainment of the rate of liver failure in the user population would be a highly valid performance measure. Hospitalization for severe liver injury would be another, but less direct, assessment of the RiskMAP goal. The frequency of liver function monitoring in users could be used to see if RiskMAP processes to prevent liver failure were being followed, but since liver function monitoring may not be tightly linked to the occurrence of liver failure, such process monitoring would have limited validity as an indicator of successful prevention of liver failure.

### *2. Compensating for an Evaluation Method's Limitations*

Most evaluation measures have limitations. FDA suggests that, in choosing among evaluation methods and measures, sponsors consider their strengths and limitations. The following are examples of some of the limitations of evaluation methods:

- Spontaneous adverse event data are a potentially biased outcome measure because reporting of adverse events varies due to many factors and represents an unknown and variable fraction of the adverse outcomes that are actually occurring. As a result, systematic data collection or active surveillance of adverse events in populations with well-defined exposure to the product would be preferred for purposes of evaluation.
- Population-based evaluation methods can use administrative or claims-based data systems that capture service or payment claims to measure rates of events, although it is usually recommended that medical records be examined to validate the actual occurrence of coded diagnoses and procedures. Administrative data may come from various insurers, purchasing groups, or networks that are tied to employment or entitlement programs, so it is important to determine if an administrative data system is



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representative of the general population being treated with the product. Also, unless enrollment in an administrative claims system is large, the number of patients exposed to any single product is likely to be limited, as will be the power to detect uncommon adverse events.<sup>11</sup> In addition, there may be data processing time lags of several months or longer before administrative data can be retrieved and analyzed.

- Active surveillance using sentinel reporting sites may be useful for evaluating adverse events, but it is costly and may not detect rare events. Surveys of healthcare practitioners or patients using various modes (in-person, mail, telephone, electronic) can be another useful form of active surveillance of knowledge, attitudes, policies, and practices of healthcare practitioners, institutions, and patients about recommended RiskMAP tools and their associated processes. However, issues relating to response rates, representativeness, and reporting biases may limit the accuracy of survey results.<sup>12</sup>

These examples illustrate how using only one evaluation method could skew assessment of the performance of a RiskMAP. Therefore, FDA recommends that, whenever feasible, sponsors design evaluation plans to include at least two different quantitative, representative, and minimally biased evaluation methods for each critical RiskMAP goal. By using two methods, one method can compensate for the limitations of the other. For example, surveys of healthcare practitioners may indicate high compliance with systems for preventing product complications. However, systematically collected or spontaneous reports might show that product complications are occurring, thus suggesting that prevention efforts in actual practice may be ineffective or incompletely applied. If it is not practical to use two complementary and representative methods, FDA suggests using other quantitative methods such as multiple site sampling or audits that aim for high coverage or response rates by the affected population. If RiskMAPs use multiple tools or interventions, it may be useful to consider using evaluation methods applicable to the program as a whole. For example, a systematic program evaluation model, such as Failure Modes and Effect Analysis (FMEA),<sup>13, 14</sup> can provide a framework for evaluating the individual RiskMAP components and the relative importance of each in achieving the overall RiskMAP goal or goals.

### *3. Evaluating the Effectiveness of Tools in Addition to RiskMAP Goals*

FDA recommends that sponsors periodically evaluate each RiskMAP tool to ensure it is materially contributing to the achievement of RiskMAP objectives or goals. Tools that do not perform well may compromise attainment of RiskMAP goals, add unnecessary costs or burdens, or limit access to product benefits without minimizing risks. Tools that are implemented

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<sup>11</sup> For further discussion of administrative claims systems, please consult the pharmacovigilance guidance.

<sup>12</sup> For a more detailed discussion of survey development and implementation, please consult the pharmacovigilance guidance.

<sup>13</sup> Stamatis DH, *Failure Mode and Effects Analysis: FMEA From Theory to Execution*, Milwaukee: American Society for Quality, Quality Press, 2003.

<sup>14</sup> Cohen Michael R ed, *Medication Errors: Causes, Prevention, and Risk Management*, Washington, DC: American Pharmaceutical Association, 1999.

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incompletely or in a substandard fashion could result in additional tools being adopted unnecessarily. For all these reasons, evaluating tools is important. Data from such evaluations may make it possible to improve a tool's effectiveness or eliminate the use of a tool that fails to contribute to achieving a RiskMAP goal. By eliminating ineffective tools, resources can be concentrated on useful tools.

Distinguishing between the evaluation of RiskMAP goals and tools is important because the achievement of goals and the performance of tools may not be linked. For example, the overall goal of a RiskMAP may be achieved despite individual tools performing poorly. The reverse situation may also occur, with component tools performing well but without appropriate progress in achieving the RiskMAP goal. This situation may occur if a surrogate objective correlates poorly to the desired health outcome. The first example (i.e., the RiskMAP goal may be achieved despite individual tools performing poorly) may afford an opportunity to discontinue a tool, whereas its converse may trigger the implementation of new or improved tools, or even a redesign of the overall RiskMAP. Two important factors that contribute to tool effectiveness are its acceptability and unintended consequences. Since tool performance will often depend upon the understanding, cooperation, efforts, and resources of healthcare providers, pharmacists, and patients, evaluation of acceptability and unintended consequences for individual tools may help to improve the use of tools and thus their performance.

### *4. Evaluating RiskMAP Tools Prior to Implementation*

FDA recommends that, to the extent possible, sponsors evaluate tools for effectiveness before implementation. As discussed in section IV.D, FDA suggests that in selecting tools to include in a RiskMAP, a sponsor consider tools that are likely to be effective. For example, the success of potential RiskMAP tools might be predicted to some extent by evidence in the scientific literature or from their use in other RiskMAPs. Application of computer modeling or simulation techniques may also assist in projecting potential outcomes of implementation of various combinations of RiskMAP tools.

Besides using literature evidence and past RiskMAP experience to identify tools with a known track record of effectiveness, sponsors can pretest or pilot test a tool before implementation. Such testing, ideally with a comparison group or time period, can help to assess comprehension, acceptance, feasibility, and other factors that influence how readily RiskMAP tools will fit into patient lifestyles and the everyday practices of healthcare practitioners. Pretesting can potentially avoid wasted time, expense, and escalation of RiskMAP tools by discriminating between high- and low-performing tools. For example, if a preventable risk is identified in Phase 2 trials, Phase 3 trials could provide an opportunity to pretest targeted education and outreach tools.

FDA recommends that pretesting methods be chosen on a case-by-case basis, depending on the product, tool, objective, and goal. For example, in certain preapproval situations, large simple safety studies may be a means of generating useful information about the effectiveness of RiskMAP tools in conditions close to actual practice.<sup>15</sup> On the other hand, for certain tools such as targeted education and outreach, published *best practices* could be used as guidelines for

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<sup>15</sup> For a detailed discussion of large simple safety studies, please consult the premarketing guidance.

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implementation. If time is particularly limited, multiple interviews or focus group testing can assist in determining acceptance or comprehension of a RiskMAP tool by major stakeholder groups. This action might be particularly useful in situations where risks and benefits are closely matched, and RiskMAP goals may include the making of informed therapeutic choices by patients and prescribers

FDA recognizes that, in some cases, tools cannot be pretested for logistical reasons. Pretesting of tools may not be practical in situations in which newly recognized adverse events dictate the importance of rapid implementation of a RiskMAP after approval and marketing. In such instances, sponsors should seek to employ tools with a proven track record of effectiveness. In general, the greater the rate or severity of risks to be minimized, the more critical it becomes to have compelling evidence of effectiveness of the tool through some form of testing or prior use.

#### **C. FDA Assessment of RiskMAP Evaluation Results**

FDA recommends that if a sponsor makes a RiskMAP submission to the Agency, the submission describe when the sponsor will send periodic evaluation results to FDA. As discussed in section VII.B, the Agency recommends that sponsors analyze evaluation results and requests that sponsors provide FDA with (1) the data, (2) all analyses, (3) conclusions regarding effectiveness, and (4) any proposed modifications to the RiskMAP. FDA, in turn, generally would perform its own assessment of RiskMAP effectiveness according to the principles of this and the other risk management guidances. At a minimum, FDA and sponsors would discuss their respective RiskMAP evaluations in a meeting or teleconference. In cases where risks are frequent and/or severe, or where results are ambiguous or uncertain, or where there is disagreement between the sponsor and FDA in the interpretation of the RiskMAP or tool effectiveness, public and expert input would be sought through the FDA Advisory Committee process. This will also allow airing and discussion of important information about effective and ineffective RiskMAPs and tools.

#### **D. Making Information From RiskMAP Evaluations Available to the Public**

As discussed in section IV.C, FDA plans to maintain a RiskMAP Web site that will describe all publicly available information about implemented RiskMAPs (and their tools). On the same Web site, FDA intends to make available, in summary format, information that has been publicly discussed or is otherwise publicly available (from sponsors or other sources) about the effectiveness of particular RiskMAP tools in achieving risk minimization objectives. The summaries may derive from materials presented and discussed at FDA Advisory Committee meetings where the effectiveness of a particular RiskMAP has been discussed and potential modifications have been entertained.

### **VI. COMMUNICATING WITH FDA REGARDING RISKMAP DEVELOPMENT AND DESIGN ISSUES**

As discussed in section III.D, because risk and benefit information emerge continually throughout a product's lifecycle, a sponsor could decide, or FDA could recommend, that a RiskMAP is appropriate at several different times. These times include:

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- before approval, when a risk is identified from clinical studies, nonclinical studies, or in similar class of products, and risk minimization is appropriate as the product is introduced into the marketplace
- after marketing, if pharmacovigilance efforts identify a new serious risk and minimization of the risk will contribute to a favorable benefit-risk balance
- when marketing a generic product that references an innovator drug with a RiskMAP

If a sponsor would like to initiate a dialogue with FDA to benefit from the Agency's experience in reviewing previously implemented plans, the Agency recommends that the sponsor contact the product's review division. The review division is the primary contact for a sponsor. The review division may choose to consult with other Offices in assisting the sponsor in developing a RiskMAP. These consulting offices could include CDER's Office of Drug Safety (ODS), CBER's Office of Biostatistics and Epidemiology (OBE), or CDER's Office of Generic Drugs (OGD), as appropriate. In any particular case, it is helpful if the sponsor and FDA:

- share information and analyses regarding the product's risks and benefits
- discuss the choice of RiskMAP goals, objectives, and tools
- discuss the evaluation plan, including (1) times for evaluation, (2) performance measures and their targets, and (3) analyses

Sponsors may wish to discuss RiskMAP issues with FDA at pre-defined meeting times (e.g., end-of-phase-2 meetings), if appropriate, or request meetings where RiskMAPs can be specifically considered. To maximize the value of their discussions with FDA, we recommend that sponsors who seek the Agency's guidance apprise reviewers of the rationale for and data underlying RiskMAPs under consideration. FDA requests that sponsors also share relevant background information and questions for discussion before their meetings with FDA.

Both CDER and CBER will develop internal Manuals of Policies and Procedures (MaPPs) (or standard operating procedures (SOPs)) regarding the review of RiskMAPS. The procedures will define milestone points at which RiskMAP discussion is logical and will promote consistency in RiskMAP review and design. All RiskMAPs involving reminder tools or performance-linked access systems will be considered at the Center level as a secondary method of ensuring consistency across product classes and across divisions.

If the sponsor decides to submit a RiskMAP before marketing approval of the product, most times the RiskMAP will be submitted to the new drug application (NDA) or biologics license application (BLA) for the product in question. However, if a risk is identified early (e.g., the product is a teratogen), and the sponsor wishes to institute formal risk management activities during Phases 1 to 3 studies, the sponsor can submit the RiskMAP to the investigational new drug application (IND). If a RiskMAP is being considered in a product's postmarket phase, FDA recommends that it be submitted as a supplement to the relevant NDA or BLA. Additional

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user fees will only be applicable to a supplement if FDA determines that new clinical data are required for its approval. This would be unlikely for a RiskMAP supplement.

FDA encourages early and open discussion of safety concerns and whether such concerns may merit a RiskMAP. Early discussion of RiskMAPs could provide the opportunity to pretest risk minimization tools.

## **VII. RECOMMENDED ELEMENTS OF A RISKMAP SUBMISSION TO FDA**

### **A. Contents of a RiskMAP Submission to FDA**

FDA suggests that a RiskMAP submission to FDA include the following sections, as well as a table of contents:

- Background
- Goals and Objectives
- Strategy and Tools
- Evaluation Plan

#### *1. Background*

FDA suggests that the Background section explain why a RiskMAP is being considered and created. We recommend that it describe the risks to be minimized and the benefits that would be preserved by implementation of a RiskMAP. Further, we suggest that this section describe, to the extent possible, the type, severity, frequency, and duration of the product's risks, with particular attention to the risk or risks addressed by the RiskMAP.

The following are sample questions regarding risk characterization that we recommend be addressed in the Background section:

- What is the rationale for the RiskMAP?
- What is the risk the RiskMAP addresses? Is there more than one risk to be minimized? If there is, how do they relate to each other with regard to the following bulleted items?
- What is the magnitude and severity of the risk?
- Who is at highest risk?
- Are particular populations at risk (e.g., children, pregnant women, the elderly)?
- Is the risk predictable?
- Is the risk preventable?
- Is the risk reversible?
- Is the risk time-limited, continuous, or cumulative?

These questions are similar in intent to what the ICH calls a Safety Specification in its E2E guidance.<sup>16</sup>

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<sup>16</sup> Available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the topic ICH Efficacy.

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FDA recommends that this section include a discussion that considers the product's risks in the context of its benefits. The following are sample questions that address benefit characterization.

- What is the overall nature or extent of benefit and what are the expected benefits over time (i.e., long-term benefits)?
- How do the populations most likely to benefit from this product compare to those that may be at highest risk?
- How would implementation of a RiskMAP affect individual and population benefits? Will it increase the likelihood that benefits will exceed risks in patients using the product? Will the RiskMAP affect access to the product by patients who benefit from it?
- Could certain individuals and/or populations likely to benefit from the product potentially have less access to the product because of the tools in the RiskMAP?

We suggest that the Background section include a discussion, if pertinent, about the successes and failures of other regulatory authorities, systems of healthcare, or sponsor actions in minimizing the risks of concern for this product. Information provided by the sponsor regarding relevant past experiences, domestically or in other countries, will assist in harmonizing plans as well as avoiding the cost of implementing RiskMAP tools already deemed unsuccessful. We encourage sponsors to provide applicable information or evaluations from past experiences with products or programs that are similar to the proposed RiskMAP.

### *2. Goals and Objectives*

FDA suggests that the Goals and Objectives section describe the goals and objectives of the RiskMAP.<sup>17</sup> In addition, we recommend that this section describe how the stated objectives will individually and collectively contribute to achieving the goal or goals.

### *3. Strategy and Tools*

FDA suggests that the Strategy and Tools section define the overall strategy and tools to be used to minimize the risk or risks targeted by the RiskMAP. We recommend that the sponsor provide a rationale for choosing the overall strategy. We suggest that the sponsor describe how each tool fits into the overall RiskMAP and its relationship to the other tools. FDA suggests that the sponsor also provide the rationale for choosing each tool (see section IV.D for a discussion of considerations in choosing tools). In particular, we recommend that the sponsor describe the available evidence regarding the tool's effectiveness and, where applicable, provide results from pretesting. In addition, we suggest that the sponsor state whether it sought input from patient or healthcare interests, and if it did, we suggest that the sponsor describe the feedback that was received regarding the feasibility of its RiskMAP. FDA plans to maintain a Web site that will

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<sup>17</sup> See section IV for a discussion of goals and objectives.

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describe publicly available summary information about effectiveness of RiskMAP tools (see section V.D).

We recommend this section also include an implementation scheme that describes how and when each RiskMAP tool would be implemented and coordinated. FDA suggests that sponsors specify overall timelines and milestones. For example, this section could address whether targeted education and outreach tools would be implemented before, or concurrently with, other tools.

### *4. Evaluation Plan*

FDA suggests that the Evaluation Plan section describe the evaluation measurements or measures that will be used to periodically assess the effectiveness of the RiskMAP's goals, objectives, and tools. For a detailed discussion of RiskMAP evaluation, see section V.

We recommend that this section include:

- The proposed evaluation methods for assessing RiskMAP effectiveness (e.g., claims-based data systems, surveys, registries) and the rationales for the sponsor's chosen measures.
- Targeted values for each measure and the time frame for achieving them. FDA recommends the sponsor include interpretations of expected results under best- and worst-case scenarios. In addition, we suggest the sponsor specify what values of measures at specific time points will trigger consideration of RiskMAP modification.
- The nature and timing of data collection, analyses, and audits or monitoring that will be used to assess the performance of each individual tool in achieving the RiskMAP's objectives and goals. Again, we suggest specifying target values for measures.
- A schedule for submitting progress reports to FDA regarding the evaluation results for the RiskMAP's individual tools, objectives, and goals (see section VII.B for a discussion of progress reports). We recommend that the timing and frequency of progress reports be based primarily on the nature of the risk, tools used, and outcomes under consideration. FDA recommends that progress reports be included in periodic safety update reports or traditional periodic reports.

Where applicable and possible, we recommend that the Evaluation Plan section discuss potential unintended and untoward consequences of the RiskMAP. Such a discussion would be particularly valuable if there are therapeutic alternatives with similar benefits and risks. We suggest that sponsors discuss how unintended consequences would be assessed after RiskMAP implementation. The goal of the assessment would be to ensure that overall population risks are minimized and specific product benefits, including access, are preserved.

## **B. Contents of a RiskMAP Progress Report**

FDA recommends that a RiskMAP progress report contain the following sections, accompanied by a table of contents:

- Summary of the RiskMAP
- Methodology
- Data
- Results
- Discussion and Conclusions

### *1. Summary*

We suggest that the Summary section briefly provide background on and an overview of the RiskMAP, and describe the overall RiskMAP goals and objectives, as well as its strategy and tools. We recommend that this section also summarize (1) the evaluation methods used and (2) the relevant measures and time frames for achieving targeted values.

### *2. Methodology*

We recommend that the Methodology section provide a brief overview of the evaluation methods used (e.g., ascertainment of outcomes, comprehension testing, patient surveys, process audits). FDA suggests that it describe the evaluation plan, sources of potential measurement error or bias for the outcome of interest, and any analytical methods used to account for them. Since RiskMAP evaluations will often rely upon observational data, we recommend that the analytical plan address issues such as measurement errors, sensitivity, and specificity of the measures, as well as power for detecting differences where appropriate.

### *3. Data*

To the extent possible, we recommend that the Data section of a RiskMAP progress report contain data that would allow FDA to analyze the information and make conclusions independently.

### *4. Results*

To the extent possible, we recommend that the Results section of a RiskMAP progress report contain the primary data from each evaluation method and analyses of the evaluation data, statistical estimation if appropriate, and the sponsor's comparison of tool, objective, and/or goal achievement relative to targeted performance measures.

### *5. Discussion and Conclusions*

FDA recommends that this section describe whether the RiskMAP has met or is making progress in meeting the stated measures for each tool, objective, and goal. We suggest that this discussion take all available data, evaluations, and analyses into consideration.



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Progress towards achieving RiskMAP goals or performance measures should be reported. Where appropriate, sponsors are encouraged to propose modifications to the RiskMAP and discuss them with FDA.

**Appendix C: Maternal health team (MHT) recommendations for: pregnancy category, pregnancy exposure registry, and risk evaluation and mitigation strategies (REMS) related to fetal exposure**

**Maternal health team (MHT) recommendations for:  
pregnancy category, pregnancy exposure registry, and risk evaluation and mitigation  
strategies (REMS) related to fetal exposure**

This background package document summarizes the Maternal Health Team's interpretation of the animal reproductive toxicology data for telavancin hydrochloride and its potential clinical relevance for pregnancy labeling. In addition, it explores the need for either pregnancy surveillance as part of a REMS program or a prospective pregnancy registry as a postmarketing requirement as defined under FDAAA.

**Animal Reproductive Toxicology Data**

Reproductive toxicology data on telavancin hydrochloride submitted to FDA and reviewed by the Division of Anti-infective and Ophthalmology Products (DAIOP) demonstrated teratogenic effects in rats, rabbits, and minipigs. On February 20, 2007, DAIOP consulted the Maternal Health Team (MHT) to obtain input on drug labeling for use in pregnant and nursing women and the need for a pregnancy registry and/or a risk minimization action plan.

Telavancin is a semi-synthetic, lipoglycopeptide antibiotic that exhibits bactericidal activity against most gram-positive bacteria. The telavancin molecule core is identical to vancomycin and its antimicrobial coverage is similar. The current NDA application is for marketing telavancin as an antimicrobial to treat complicated skin and skin structure infections (cSSSI). Based on data review by both the DAIOP microbiologist and medical officer, telavancin is equivalent to, but not superior to, vancomycin for this indication. In addition, reproductive toxicology studies show similar teratogenic effects and increased post-implantation pregnancy loss in rats, rabbits, and Göttingen minipigs at non-maternotoxic doses of drug (see Appendix A). While the presence or absence of teratogenic effects in any one animal species does not necessarily predict teratogenicity in developing humans, the occurrence of increased post-implantation loss and skeletal (limb) malformations across all three species at animal exposures 1-15 times the human therapeutic dose is highly concerning. In addition, the minipig study showed a lower fecundity ratio than that seen in either historical database, and male fertility studies in rats showed decreased sperm motility and increased abnormal sperm morphology.

There were potential confounding factors in the minipig study. Many of the minipigs were treated with other antimicrobial agents (three topical ointments and three systemic agents)<sup>1</sup>, but these animals were evenly distributed among treatment groups and these types of malformations were not seen in animal studies with these other drugs. Dr. Peters found the minipig pregnancy rates unusually low, especially in the placebo (36%) and high dose telavancin (36%) groups.<sup>2</sup> Pregnancy rates were 64% in the low-dose group and 57% in the mid-dose group. Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies. There were an

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<sup>1</sup> According to the pharmacologist, this is very unusual among toxicology studies submitted for regulatory review.

<sup>2</sup> Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies.

increased number of litters with late resorptions noted in the mid dose (mean = 0.6) and high dose (mean = 0.8) groups compared to historical controls (maximum mean = 0.4).

*Reviewer comment:*

*While these aberrations in the conduct of the minipig study should not be discounted, the study findings are still worrisome. The post-implantation loss increased by more than 100% in the high dose treatment group compared with the placebo and diluent treatment groups. Increased pregnancy loss and skeletal anomalies occurred at increased rates in all three species of animal studied. These similarities should not be attributed to coincidence and confounding alone.*

## **Pregnancy Category**

Televancin is a multi-species teratogen. Its classification with regard to use in pregnancy should be based on both its potential risk to mother and fetus as well as its potential clinical benefits above other available therapies. Currently, there are eight antimicrobial agents FDA approved for the treatment of cSSSI (see Appendix B). Vancomycin remains first-line therapy for severe infections possible caused by MRSA. Based on current labeling for these approved cSSSI antimicrobial therapies, televancin does not offer broader or better antimicrobial coverage and has a much larger, consistent, and concerning animal safety signal for teratogenic potential in humans.

For the proposed indication of cSSSI, televancin, if approved, should be assigned pregnancy category X due to:

- A consistent teratogenic signal in more than one animal species.
- A lack of evidence of clinical benefit over eight other approved therapies for this indication.

See Appendix C for the regulatory definitions for pregnancy categories of teratogenic risk. Compared to FDA-approved antimicrobial agents indicated for the treatment of cSSSI, televancin does not offer any unique antimicrobial coverage. Televancin is a drug for intravenous administration, so its once daily dosing, while convenient, would not offer substantial advantages in terms of patient compliance. It is possible that data submitted for a different clinical indication in the future could support pregnancy category C if some direct benefit to mother or fetus was demonstrated. However, for the indication of cSSSI, there is no data to support such a benefit.

## **Postmarketing Safety and Fetal Exposure: REMS or Prospective Pregnancy Registry**

The labeling for televancin use during pregnancy should help determine whether postmarketing fetal exposures should be tracked as part of a REMS program or whether a postmarketing requirement (PMR) for a prospective pregnancy registry should be considered to collect additional data on human outcomes following televancin use during pregnancy.

A highly suspected human teratogen that carries a contraindication for use during pregnancy (Category X) should have a risk evaluation and mitigation strategy (REMS) program that includes a pregnancy surveillance registry. Such a registry would track pregnancy outcomes when fetal exposure does occur despite the contraindication to use during pregnancy.

If televancin is approved for marketing and labeled with a pregnancy category C based on a theoretical potential for maternal benefit that could outweigh the teratogenic risk to the fetus, then a different approach may be appropriate. In this situation, use of televancin during pregnancy would not be contraindicated and use in pregnant women may be more likely to occur. Based on the significant safety signal from the animal reproductive toxicology data and a lack of data in human pregnancy, the MHT would recommend a postmarketing requirement for the sponsor to conduct a prospective pregnancy registry, a cohort study of pregnant women treated with televancin for therapeutic reasons. Title IX of FDAAA supports requirement of such a study in this situation.

When recommending a pregnancy category and elements of a REMS program for televancin, the following factors should also be considered:

- Televancin is administered intravenously and would potentially be used to treat acute infections (with direct or indirect physician supervision) in hospitals, chronic care facilities, physician offices, and homes with instruction or home care assistance. For these reasons, a REMS program that includes education and reminders alone may not adequately safeguard against televancin use in pregnant women.
- Use in acute care situations and settings makes it more difficult to ensure that a woman of reproductive age is not pregnant prior to drug exposure. One negative serum pregnancy test will not detect all pregnancies, especially those within five or six days of conception. Prior to initiating drug therapy, the iPLEDGE program for isotretinoin requires documented use of two forms of contraception for one month and two serum or highly sensitive urine pregnancy tests performed 19 days apart. These results must be documented and reviewed in an electronic database system before the pharmacist will dispense drug. These sorts of safeguards are not feasible when treatment with an antibiotic should be started in a timely manner. Televancin may need an informed consent procedure for women of child-bearing potential.

## **Summary**

If televancin hydrochloride is approved, the Maternal Health Team recommends the following:

1. Boxed warning informing prescribers (and patients) that televancin caused congenital anomalies and increased pregnancy loss in rats, rabbits, and minipigs and is, therefore, a suspected teratogen in humans that should not be used in women of childbearing potential.

2. Pregnancy category X (based on no increased benefit over current therapies and the potential for greater risk based on consistent teratogenic and pregnancy loss safety signals in three animal species)
  - Indicated populations should include adult men, adult women who are not of childbearing potential, and women of child-bearing potential who have an extremely low risk of recent conception. It will be important to define this group of women of child-bearing potential. This group might include women who are never sexually active by lifestyle choice (e.g. nuns), and women using highly reliable, non-user dependent contraceptive methods (e.g. tubal sterilization, IUDs, hormone implants or injections).
  - Restricted distribution at the pharmacy level that requires documentation of age and gender of the patient. If the patient is female, documentation of menopause, other evidence of non-childbearing potential, and/or highly reliable, non-user dependent contraception should be required.
  - A REMS program should include a pregnancy surveillance registry.
3. If televancin hydrochloride is approved as a pregnancy category C drug, then a prospective pregnancy registry should be required in the post-marketing setting.

Appendix A: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Televancin Hydrochloride				
Species	Study Type	Treatment Groups	Treatment Duration	Positive Findings
Rabbit	Developmental toxicity Phase I and II AMI CSN: 02-001-03	5% dextrose Placebo (diluent?) 12.5 mg/kg/d televancin 25 mg/kg/d televancin 45 mg/kg/d televancin By slow IV bolus daily  Phase I: 20 females per group Phase II: satellite groups Toxicokinetics N=4 Recovery: N=4 Amniotic fluid: N=10	Gestational days 7-20	<p>Two does in the 25 mg/kg/d group aborted and were removed from the study.</p> <p>In all televancin-dosed groups, there was a drug-related increase in post-implantation losses. This did not appear to be dose-related</p> <p>An increase in dilated lateral ventricles of the brain and missing intermediate lung lobes occurred in feti from all three televancin dose groups. This increase was statistically significant for both anomalies at the highest dose and for dilated ventricles in the low and medium dose groups.</p> <p>There was incomplete ossification of the 5<sup>th</sup> and 6<sup>th</sup> sternbrae in the high dose televancin feti but this was not a statistically significant finding.</p> <p>Maternal NOAEL = 45 mg/kg/d Fetal NOAEL = not clear</p>
Rabbit	Developmental toxicity AMI CSN: 02-001-015	Placebo (diluent?) 60 mg/kg/d televancin 75 mg/kg/d televancin By slow IV bolus daily  Main study: 20 females per group  Toxicokinetics: N=4 Amniotic fluid: N=10	Gestational days 7-20	<p>Only one animal had televancin levels detected in amniotic fluid. This suggests limited fetal exposure to drug or that the drug was rapidly metabolized.</p> <p>Overall, televancin treated animals had skeletal variations including an increased incidence of unilateral 13<sup>th</sup> ribs and presacral vertebrae.</p> <p>In the televancin 75 mg/kg/d group:</p> <ul style="list-style-type: none"> <li>▪ One fetus from each of five litters had various skeletal malformations including: absent ulna, fusion of sternbrae, adactyly, and vertebral anomalies.</li> <li>▪ Additional abnormalities noted were: one fetus with brachymelia, adactyly, and gastroschisis; one fetus with umbilical hernia; and one fetus with diaphragmatic hernia and gall bladder agenesis (the latter two conditions have been seen in historical controls)</li> </ul> <p>NOAEL for developmental toxicity – 60mg/kg/d. The Pharmtox reviewer stated that the evel of concern is quite high given “enormity of the effects.”</p>

Appendix A: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Televancin Hydrochloride				
Species	Study Type	Treatment Groups	Treatment Duration	Positive Findings
Rat	Fertility and Early embryonic development to implantation AMI CSN: 02-001-05	Diluent control Placebo 50 mg/kg/d televancin 75 mg.kg.d televancin 100 mg/kg/d televancin By slow IV bolus daily  20 males and 20 females in each group	Males dosed for at least 28 days before mating  Females dosed from at least 14 days before mating until gestation day 7.	Males: Decreased sperm motility Increased abnormal morphology  These effects were also seen in the placebo group but less often and to a smaller degree. The effects were dose dependent in the televancin treated groups.
Rat	Pre- and post-natal development, Including maternal function AMI CSN: 02-001-07	5% dextrose Placebo 50 mg/kg/d televancin 100 mg/kg/d televancin 150 mg/kg/d televancin By slow IV bolus daily  25 females per group	Gestational day 6 to Lactation day 20	Televancin treated F <sub>0</sub> dams in the two higher dose groups had decreased mean maternal body weights, mean body weight changes, and food consumption.  Total litter death in 3 F <sub>0</sub> dams: 1 placebo, 2 high dose. There was a dose-related increase in the number of stillborn pups and the number of dams with stillborn pups.  F <sub>1</sub> pups in the high dose group were cyanotic (2 litters), swollen (2 litters), and anophthalmic (3 litters), and one pup had brachymelia (limited use of a forelimb). These findings were consistent with those a previous study. Compared to controls, mean F <sub>1</sub> pup weights were decreased at 50 mg/kg/d. On necropsy, all F <sub>1</sub> pups treated with televancin had dilated renal pelvices compared with 1 control female pup.  NOAEL for F <sub>0</sub> maternal effects = 50 mg/kg/d NOAEL for F <sub>1</sub> fetal/pup effects = 100 mg/kg.d



Appendix A: Summary of Reproductive Toxicology Study Results Submitted to NDA 22-110 for Televancin Hydrochloride				
Species	Study Type	Treatment Groups	Treatment Duration	Positive Findings
Minipig	Embryo-fetal development	Diluent (5% dextrose) Placebo 25 mg/kg/d televancin 50 mg/kg/d televancin 75 mg/kg/d televancin By slow IV bolus daily  14 females per treatment group	Gestational days 11-35  Toxicokinetic satellite groups (3 animals/group) dosed gestational days 11-16 only and then euthanized	<p>Number of and reasons for dams sacrificed <i>in extremis</i> were similar by treatment group.</p> <ul style="list-style-type: none"> <li>Many of these animals were treated with other antimicrobial agents( 3 topical ointments, 3 systemic agents)<sup>3</sup></li> <li>Pregnancy rates seemed unacceptably low to the review pharmacologist, especially in the placebo (36%) and high dose televancin (36%) groups<sup>4</sup></li> <li>There were an increased number of late resorptions noted in the mid and high dose groups compared to historical controls</li> <li>There was a &gt; 100% increase in post-implantation loss in the high dose treatment group compared with placebo and diluent</li> </ul> <ul style="list-style-type: none"> <li>45% of televancin-treated litters had feti with external and soft tissue abnormalities compared to 14% of litters and 20% of litters in the diluent and placebo groups respectively.</li> <li>Among 58 feti from the placebo and diluent treated groups, the sponsor noted 1 fetus with retained testes and 1 with retained testes and polydactyly<sup>5</sup></li> <li>Among 84 feti from the televancin treated groups, the sponsor noted the following findings: 9 feti with polydactyly (3 on two limbs), 1 fetus with diaphragmatic hernia, one with discolored diaphragm, one with syndactyly, and one with retained testes</li> </ul> <p>In addition, the pharmacology reviewer noted: a low dose fetus with defomred head and a misshapen digit; a mid-dose fetus with “legs turned inward”; a mid-dose fetus with multiple absent ossification sites and bilateral absence of tarsal bones; a mid-dose fetus with absent ossification sites distal to the metacarpi; a mid-dose fetus with exophthalmos; a mid-dose fetus with anencephaly; a high-dose fetus with deformed head, forelegs, and snout (very autolytic); and a high dose fetus with a deformed hind leg.</p>

<sup>3</sup> According to the pharmacologist, this is very unusual among toxicology studies submitted for regulatory review. These animals were evenly distributed among treatment groups but call the validity of the study into question.

<sup>4</sup> Historical control pregnancy rates for Göttingen minipigs are 65-93% over three studies.

<sup>5</sup> The historical Danish database shows that the incidence of syndactyly is  $\leq 0.4\%$  and the incidence of pentadactyly was  $\leq 2.3\%$  for the past five years. However, after a change from line breeding to a population based breeding program in November 2004, these rates declined to  $<0.2\%$  and  $<0.7\%$  respectively. The historical Japanese database shows a 1.4% incidence of polydactyly among newborn piglets, a preimplantation loss rate of 11.7%, and a post-implantation loss rate of 15.6%.

**Appendix B: Comparison of Reproductive Toxicology Data and Antimicrobial Coverage for  
Telavancin and Anti-microbial Drugs Approved For the Treatment of Complicated Skin and Skin Structure Infections**

Drug	Pregnancy category	Reproductive toxicology study findings	Antimicrobial coverage for cSSSI
Telavancin	?	Reproductive studies in rats, rabbits, and minipigs showed increased post-implantation losses and increased skeletal malformations including limb abnormalities and absent or decreased ossification centers. There effects occurred at doses 1 – 15 times the human therapeutic dose. In rats, sperm motility was decreased and abnormal sperm morphology was increased.	cSSSI caused by susceptible strains of the following gram positive organisms: <i>Staphylococcus aureus</i> (including methicillin-susceptible and -resistant strains), <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , <i>Streptococcus anginosus</i> group, and <i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)
Daptomycin	B	Studies performed in rats and rabbits at doses up to 2 and 4 times the human dose showed no evidence of fetal harm.  There are no adequate and well-controlled studies in women.	cSSSI caused by susceptible isolates of the following gram positive organisms: <i>Staphylococcus aureus</i> (including methicillin resistant isolates), <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , <i>Streptococcus dysgalactiae</i> subspecies <i>equisimilis</i> , and <i>Enterococcus faecalis</i> (vancomycin susceptible isolates only)
Piperacillin/ Tazobactam	B	Piperacillin: Reproduction and teratology studies in mice and rats have not revealed impaired fertility or harm to the fetus at 0.5 to 1 times the maximum human dose.  Tazobactam: Reproduction studies in rats revealed no evidence of impaired fertility at up to 3 times the maximum human dose.  There are no adequate and well-controlled studies in women.	Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections, caused by piperacillin-resistant $\beta$ -lactamase producing strains of <i>Staphylococcus aureus</i>
Ertapenum	B	Mice and rats given three times and 1.2 times the equivalent human dose respectively showed no evidence of developmental fetal toxicity. In mice, there was a slight decrease in mean fetal weight and an associated decrease in the average number of ossified sacrocaudal vertebrae.  There are no adequate and well-controlled studies in women.	cSSSI, including diabetic foot infections without osteomyelitis, due to <i>Staphylococcus aureus</i> (methicillin susceptible isolates only), <i>Streptococcus agalactiae</i> , <i>Streptococcus pyogenes</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus mirabilis</i> , <i>Bacteroides fragilis</i> , <i>Peptostreptococcus</i> species, <i>Porphyromonas asaccharolytica</i> , or <i>Prevotella bivia</i>
Meropenem	B	Reproductive studies in the rat (1.8 times the human dose) and cynomolgus monkeys (3.7 times the human dose) revealed no evidence of impaired fertility or harm to the fetus due to meropenem. There were slight changes in fetal body weight at 0.4 times the human dose.  There are no adequate and well-controlled studies in women.	cSSSI due to <i>Staphylococcus aureus</i> (methicillin susceptible isolates only), <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , viridans group streptococci, <i>Enterococcus faecalis</i> (excluding vancomycin-resistant isolates), <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Proteus mirabilis</i> , <i>Bacteroides fragilis</i> , and <i>Peptostreptococcus</i> species
Levofloxacin	C	Not teratogenic in rats at doses up to 9.4 times the oral human dose and 1.9 times the IV dose. The higher doses caused reduced fetal weights and increased fetal mortality. No teratogenic effects were seen in rabbits at doses 0.5 to 1.1 times the human dose.  There are no adequate and well-controlled studies in women.	cSSSI due to <i>Staphylococcus aureus</i> (methicillin susceptible isolates only), <i>Enterococcus faecalis</i> , <i>Streptococcus pyogenes</i> , or <i>Proteus mirabilis</i>

Appendix B: Comparison of Reproductive Toxicology Data and Antimicrobial Coverage for Televancin and Anti-microbial Drugs Approved For the Treatment of Complicated Skin and Skin Structure Infections			
Drug	Pregnancy category	Reproductive toxicology study findings	Antimicrobial coverage for cSSSI
Linezolid	C	Not teratogenic in mice, rats, or rabbits at doses of 0.6 to 6 times the human therapeutic dose. However, embryo and fetal toxicities occurred.  There are no adequate and well-controlled studies in women.	cSSSI, including diabetic foot infections, without concomitant osteomyelitis, caused by <i>Staphylococcus aureus</i> (methicillin susceptible and -resistant strains), <i>Streptococcus pyogenes</i> , or <i>Streptococcus agalactiae</i>
Vancomycin	C	No reproductive animal studies were conducted.  There are no adequate and well-controlled studies in women. One small study of pregnant women using vancomycin in the second and third trimesters was published. This study evaluated the potential ototoxic and nephrotoxic effects of vancomycin on infants following maternal exposure. No sensorineural hearing loss or nephrotoxicity was attributed to vancomycin. The number of patients studied was limited. No other fetal/neonatal effects were reported.	cSSSI caused by susceptible strains of methicillin-resistant staphylococci
Tigecycline	D*	Not teratogenic in the rat or the rabbit. Slight reductions in fetal weight and an increased incidence of minor skeletal anomalies (delays in bone ossification) occurred at 5 times and 1 time the human daily dose. Doses equivalent to the human dose were materno-toxic in rabbits and resulted in an increased incidence of fetal loss in rats and rabbits.  There are no adequate and well-controlled studies in women.	cSSSI caused by <i>Escherichia coli</i> , <i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only), <i>Staphylococcus aureus</i> (including methicillin resistant isolates), <i>Streptococcus agalactiae</i> , <i>Streptococcus anginosus</i> group, <i>Streptococcus pyogenes</i> , and <i>Bacteroides fragilis</i>

\*To meet the regulatory requirements for pregnancy category D, a drug should have human data that demonstrates teratogenicity. There are no human pregnancy data for tigecycline that suggest a teratogenic effect. Based on current labeling, tigecycline meets the regulatory requirements for a pregnancy category C.

<b>Appendix C: Regulatory Definitions of Pregnancy Categories for Teratogenic Risk</b>	
<b>Pregnancy Category</b>	<b>Assessment of Teratogenicity</b>
A	Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal reproduction studies show an adverse fetal effect but adequate but well controlled studies in pregnant women have failed to demonstrate a risk to the fetus
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).