



# **FDA Regulatory Process for CAUTI Medical Devices: Expectations and Challenges**

**Shani Haugen, Ph.D.**

**Division of Reproductive, Gastro-Renal, and Urological Devices**

**Office of Device Evaluation**

**Center for Devices and Radiological Health**

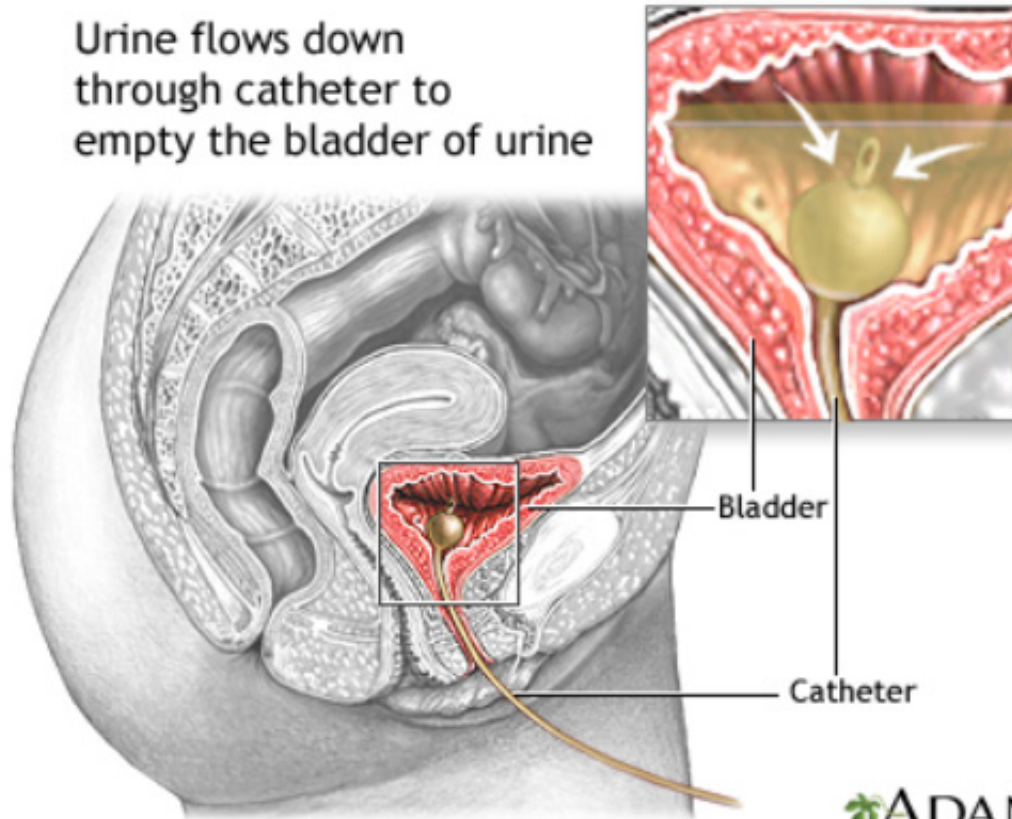
# Outline II

- Foley Catheters
- Public Health Problem and Strategies to Combat CAUTI
- FDA's Antimicrobial Foley Catheter Guidance Document
- Clinical Trial Challenges
- Conclusions and Resources

# Urological Catheter

## Foley Catheter

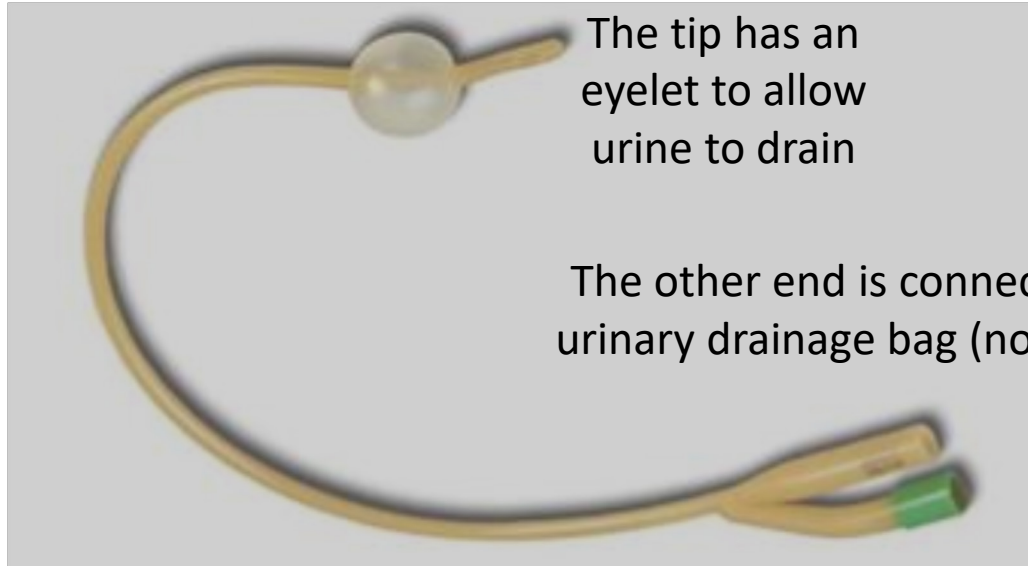
Urine flows down through catheter to empty the bladder of urine



# Urological Catheter

## Foley Catheter

Balloon filled with sterile fluid to retain the device in the bladder



The tip has an eyelet to allow urine to drain

The other end is connected to a urinary drainage bag (not shown)

The catheter has at least two lumens; one for urine drainage, and the second for instilling the balloon with fluid

# Public Health Problem



**Table 4. Estimated Numbers of Major Types of Health Care–Associated Infection in the United States in 2011.**

Type of Infection	Infections Identified in Survey	Surveyed Patients with Type of Infection	Estimated Infections in the United States*
	no.	% (95% CI)	no. (95% CI)
<b>All health care–associated infections</b>			
Pneumonia	110	24.3 (20.6–28.5)	157,500 (50,800–281,400)
Surgical-site infection	110†	24.3 (20.6–28.5)	157,500 (50,800–281,400)
Gastrointestinal infection	86	19.0 (15.6–22.8)	123,100 (38,400–225,100)
Urinary tract infection	65	14.4 (11.4–17.9)	93,300 (28,100–176,700)
Primary bloodstream infection	50	11.1 (8.4–14.2)	71,900 (20,700–140,200)
Eye, ear, nose, throat, or mouth infection	28‡	6.2 (4.2–8.7)	40,200 (10,400–85,900)
Lower respiratory tract infection	20	4.4 (2.8–6.6)	28,500 (6900–65,200)
Skin and soft-tissue infection	16	3.5 (2.1–5.6)	22,700 (5200–55,300)
Cardiovascular system infection	6	1.3 (0.5–2.7)	8,400 (1200–26,700)
Bone and joint infection	5	1.1 (0.4–2.4)	7,100 (1000–23,700)
Central nervous system infection	4	0.9 (0.3–2.1)	5,800 (700–20,700)
Reproductive tract infection	3	0.7 (0.2–1.8)	4,500 (500–17,800)
Systemic infection	1	0.2 (0.01–1.1)	1,300 (0–10,900)
<b>Total</b>			<b>721,800 (214,700–1,411,000)</b>
<b>Infections in non-neonatal intensive care units</b>			
Catheter-associated urinary tract infection	25	5.5 (3.7–7.9)	35,600 (9100–78,000)
Central-catheter–associated primary bloodstream infection	11	2.4 (1.3–4.2)	15,600 (3200–41,500)
Ventilator-associated pneumonia	35	7.7 (5.5–10.5)	49,900 (13,600–103,700)
Surgical-site infections attributed to Surgical Care Improvement Project procedures§	46	10.2 (7.6–13.2)	66,100 (18,700–130,300)
<b>Hospital-onset infections caused by specific pathogens</b>			
<i>Clostridium difficile</i> infection¶	56	12.4 (9.6–15.7)	80,400 (23,700–155,000)
MRSA bacteremia	7	1.5 (0.7–3.0)	9,700 (1700–29,600)

Excerpt from:  
 Multistate point-prevalence survey of health care-associated infections. Magill SS *et al.*, *N Engl J Med.* 2014 Mar 27;370(13):1198–208.

# Public Health Problem

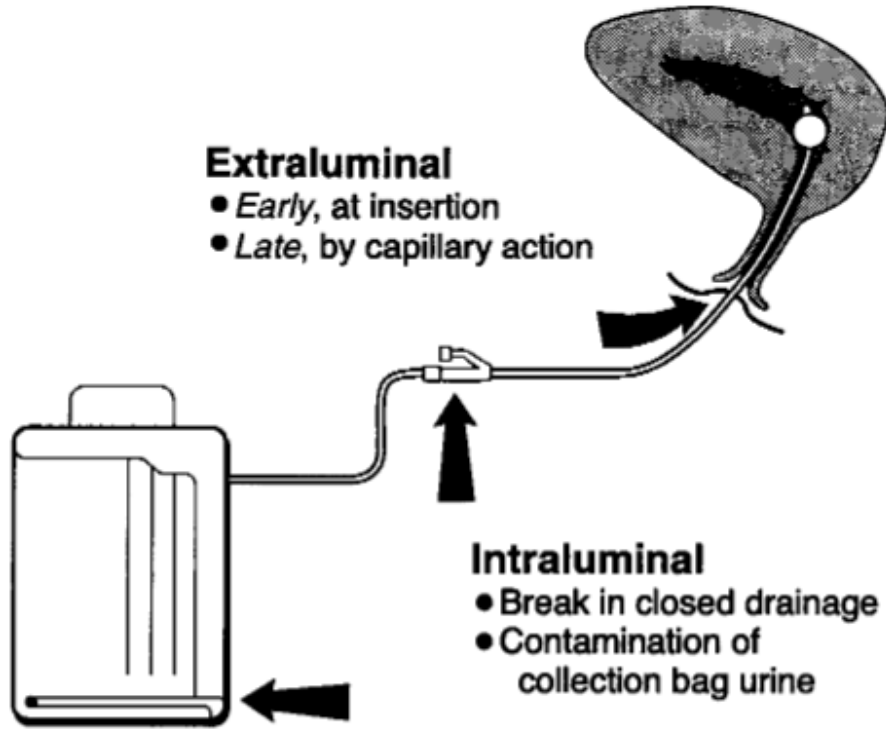


**Table 4. Estimated Numbers of Major Types of Health Care–Associated Infection in the United States in 2011.**

Type of Infection	Infections Identified in Survey	Surveyed Patients with Type of Infection	Estimated Infections in the United States*
	no.	% (95% CI)	no. (95% CI)
<b>All health care–associated infections</b>			
Pneumonia	110	24.3 (20.6–28.5)	157,500 (50,800–281,400)
Surgical-site infection	110†	24.3 (20.6–28.5)	157,500 (50,800–281,400)
Gastrointestinal infection	86	19.0 (15.6–22.8)	123,100 (38,400–225,100)
Urinary tract infection	65	14.4 (11.4–17.9)	93,300 (28,100–176,700)
Primary bloodstream infection	50	11.1 (8.4–14.2)	71,900 (20,700–140,200)
Eye, ear, nose, throat, or mouth infection	28‡	6.2 (4.2–8.7)	40,200 (10,400–85,900)
Lower respiratory tract infection	20	4.4 (2.8–6.6)	28,500 (6900–65,200)
Skin and soft-tissue infection	16	3.5 (2.1–5.6)	22,700 (5200–55,300)
Cardiovascular system infection	6	1.3 (0.5–2.7)	8,400 (1200–26,700)
Bone and joint infection	5	1.1 (0.4–2.4)	7,100 (1000–23,700)
Central nervous system infection	4	0.9 (0.3–2.1)	5,800 (700–20,700)
Reproductive tract infection	3	0.7 (0.2–1.8)	4,500 (500–17,800)
Systemic infection	1	0.2 (0.01–1.1)	1,300 (0–10,900)
<b>Total</b>			<b>721,800 (214,700–1,411,000)</b>
<b>Infections in non-neonatal intensive care units</b>			
Catheter-associated urinary tract infection	25	5.5 (3.7–7.9)	35,600 (9100–78,000)
Central-catheter–associated primary bloodstream infection	11	2.4 (1.3–4.2)	15,600 (3200–41,500)
Ventilator-associated pneumonia	35	7.7 (5.5–10.5)	49,900 (13,600–103,700)
Surgical-site infections attributed to Surgical Care Improvement Project procedures§	46	10.2 (7.6–13.2)	66,100 (18,700–130,300)
<b>Hospital-onset infections caused by specific pathogens</b>			
<i>Clostridium difficile</i> infection¶	56	12.4 (9.6–15.7)	80,400 (23,700–155,000)
MRSA bacteremia	7	1.5 (0.7–3.0)	9,700 (1700–29,600)

Excerpt from:  
 Multistate point-prevalence survey of health care-associated infections. Magill SS *et al.*, *N Engl J Med.* 2014 Mar 27;370(13):1198–208.

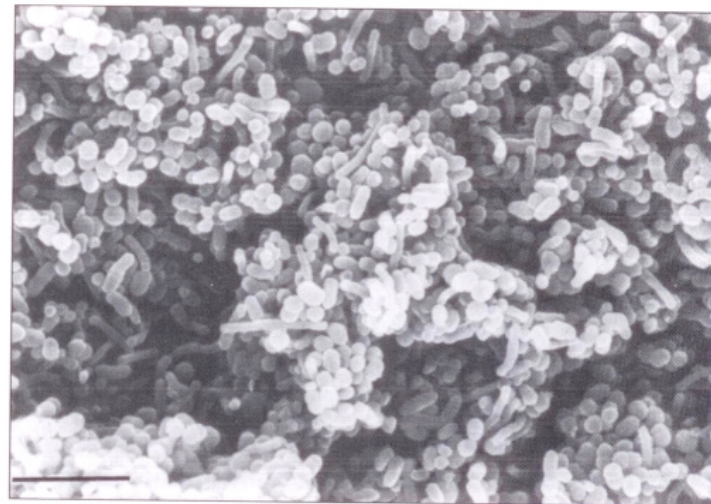
# Microbial Introduction to the Urinary System



1. Microbial migration from the exterior of the catheter (extraluminal; ~66%)
2. Microbial migration from the inner catheter surfaces (intraluminal; ~33%)

# Biofilm and CAUTI

- Biofilm: microbes that are irreversibly attached to a surface, embedded in an extracellular matrix, and have altered gene expression and growth rates.
- Urine flow pre-conditions catheter surfaces for bacterial attachment, eventually leading to biofilm formation.
- Most indwelling urological catheters will have biofilm by Day 7



Nickel JC, Costerton JW. Bacterial biofilms and catheters: A key to understanding bacterial strategies in catheter-associated urinary tract infection. *Can J Infect Dis.* 1992;3(5):261-7.

Liedl B. Catheter-associated urinary tract infections. *Current Opinion in Urology.* 2001;11(1):75-79.



# Strategies to Address Microbes on Medical Devices



1. Prevent Microbial Adherence
2. Remove/Inactivate Microbes

# Strategies to Address Microbes on Medical Devices



1. Prevent Microbial Adherence
2. Remove/Inactivate Microbes

# Strategies to Address Microbes on Medical Devices

## 510(k) Premarket Notification

[FDA Home](#)
[Medical Devices](#)
[Databases](#)

1 to 13 of 13 Results

Product Code: *MJC* Decision Date To:

02/22/2019

Results per Page  ▾

New Search [Export to Excel](#) | [Download Files](#) | [More About 510\(k\)](#)

Device Name	Applicant	510(K) Number	Decision Date
<a href="#">Bardex Lubri-Sil And Bardex Lubri-Sil I.</a>	C.r. Bard, Inc.	<a href="#">K070558</a>	12/07/2007
<a href="#">Bardex All-Silicone, Bardex Lubri-Sil, A</a>	C.r. Bard, Inc.	<a href="#">K070582</a>	12/07/2007
<a href="#">Bardex I.c. Latex Foley Catheter</a>	C.r. Bard, Inc.	<a href="#">K040658</a>	09/29/2004
<a href="#">Hydrophilic-Antibacterial Intermittent C</a>	Rochester Medical Corp.	<a href="#">K033477</a>	06/10/2004
<a href="#">Bardex Latex-Free Temperature-Sensing Fo</a>	C.r. Bard, Inc.	<a href="#">K003289</a>	01/05/2001
<a href="#">Bard All-Silicone 3-Way Foley Catheter.</a>	C.r. Bard, Inc.	<a href="#">K002868</a>	12/08/2000
<a href="#">Spectrum Silicone Foley Catheter</a>	Cook Urological, Inc.	<a href="#">K000251</a>	08/30/2000
<a href="#">Release Nf Antibacterial Foley Catheter.</a>	Rochester Medical Corp.	<a href="#">K001143</a>	07/07/2000
<a href="#">Bardex I.c. Pediatric Foley Catheter</a>	C.r. Bard, Inc.	<a href="#">K993464</a>	12/10/1999
<a href="#">Bardex Lubri-Sil I.c. Foley Catheter</a>	Bard Medical Div.	<a href="#">K984136</a>	02/16/1999
<a href="#">Bardex I.c 4-Way Foley Catheter Model 18</a>	C.r. Bard, Inc.	<a href="#">K983101</a>	11/03/1998
<a href="#">Silicone Antibacterial Foley Catheter</a>	Rochester Medical Corp.	<a href="#">K971627</a>	01/13/1998
<a href="#">Bard(R) Hydrogel/Silver-Coated Foley Cat</a>	C.r. Bard, Inc.	<a href="#">K910318</a>	08/18/1994

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>

# Urinary Catheters



## Guidance for the Content of Premarket Notifications for Conventional and Antimicrobial Foley Catheters

 SHARE	 TWEET	 LINKEDIN	 PIN IT	 EMAIL	 PRINT
--	---	--	--	---	---

# Urinary Catheters

## **Guidance for the Content of Premarket Notifications for Conventional and Antimicrobial Foley Catheters**

Recommendations on:

1. Labeling
2. Biocompatibility testing
3. Performance testing (e.g., flow rate testing, balloon inflation, etc.)
4. Sterility information
5. Performance testing for antimicrobial features (if applicable)

## **Guidance for the Content of Premarket Notifications for Conventional and Antimicrobial Foley Catheters**

“Functional and performance data for the antimicrobial component used as a coating or integrated into the device material, should demonstrate that the antimicrobial is effective in reducing the incidence of relevant nosocomial infections and that it is safe.”

## Guidance for the Content of Premarket Notifications for Conventional and Antimicrobial Foley Catheters

**in vitro test data** characterizing the spectrum and degree of activity of the antimicrobial against all clinically important microorganisms (note: microorganisms should be clinical isolates, i.e., specimens derived from actual patient cultures). These microorganisms include: *Candida* sp., *Citrobacter diversus*, *Enterobacter cloacae*, *Enterococcus*, *Escherichia coli*, *Klebsiellae pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus saprophyticus*, and *Streptococcus fecalis*. The test sample should include the finished form of the device (e.g., segments of the finished catheter). Note that if additional microorganisms are tested, justification, with supportive literature, should be provided for why they were tested;

## Guidance for the Content of Premarket Notifications for Conventional and Antimicrobial Foley Catheters

results from a **randomized, controlled clinical study** to (a) demonstrate a clinically and statistically significant decrease in the rate of infection and at least comparable safety as compared to a legally marketed conventional Foley catheter, and/or clinically and statistically similar safety and effectiveness compared to an antimicrobial coated Foley catheter; (b) quantitate the degree of change of the infection rate per duration of use of the catheter; and (c) include data to support any additional claims, including reprocessing.

Clinical information should also include: patient history of urinary tract infections (UTI) and all medications taken, urine cultures from patients and correlation of cultures taken from the urine sampled from collection bags, as well as the Foley tip for each patient in the control and experimental groups. Definitions and criteria for bacteriuria and UTI, as well as the urinary catheter care measures should be specified in the clinical protocol and be uniform across investigational sites.



# CAUTI Technology Goals

- Reduce the incidence of CAUTI or treat CAUTI
- Non-toxic/low-risk for all populations susceptible to CAUTI
- Prolonged effect for the duration of the indwelling time (without degradation from environmental conditions)
- Effective against multiple uropathogens (and not selective for other pathogens)

# Clinical Trial Challenges

Excerpt from IDSA Guidelines\*

- CAUTI Diagnosis
  1. the presence of symptoms or signs compatible with UTI (e.g., fever, pain, malaise) with no other identified source of infection AND
  2.  $\geq 10^3$  colony-forming units (cfu)/mL in urine

\* Please refer to the guidelines for a complete description of CAUTI diagnosis and catheter-associated bacteriuria

Hooton TM *et al.*, Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America, *Clinical Infectious Diseases*, Volume 50, Issue 5, 1 March 2010, Pages 625–663

<https://academic.oup.com/cid/article/50/5/625/324341>

# Clinical Trial Challenges

## Excerpt from IDSA Guidelines

- Catheter-associated asymptomatic bacteriuria (CA-ASB)
  - Presence of  $\geq 10^5$  cfu/mL in urine and no symptoms compatible with UTI
  - CA-ASB should not be screened for except in research studies evaluating interventions designed to reduce the incidence of CA-ASB or CA-UTI and in selected clinical situations, such as in pregnant women

# Clinical Trial Challenges



## Excerpt from IDSA Guidelines

- Asymptomatic Bacteriuria vs CAUTI
  - “...the vast majority of patients with CA-ASB do not progress to CA-UTI. Thus, the development of urinary symptoms must require some facilitating event(s) that is yet to be determined.”
  - “The majority of intervention trials that have been shown to reduce CA-ASB or CA-bacteriuria have not demonstrated effectiveness to reduce CA-UTI, but few trials have been designed and powered to evaluate such outcomes.”

# Clinical Trial Challenges

- Estimated tens of thousands of patients in acute care hospitals in the US with CAUTI annually
- CAUTI rate is low (up to ~ 5%) among catheterized patients
  - Large clinical trial needed to demonstrate a reduction in CAUTI

# Clinical Trial Challenges

## Development of surrogate(s) for CAUTI

- Scientifically demonstrated to correlate or predict CAUTI
- Reproducible, specific, and sensitive
- Feasible assay for a clinical study

# Conclusions

- Healthcare-associated infections are an important public health concern.
- Biofilm ≠ CAUTI
- CAUTI Technology should provide a clinically meaningful benefit for patients
- Clinical trials for CAUTI medical devices are challenged by:
  - Large sample sizes needed to demonstrate a reduction of CAUTI
  - Lack of markers or surrogates for CAUTI
- FDA is available to discuss the type of data used to demonstrate the effectiveness of antimicrobial strategies.

# FDA Resources

- FDA Guidance Document: *Guidance for the Content of Premarket Notifications for Conventional and Antimicrobial Foley Catheters*  
<https://www.fda.gov/RegulatoryInformation/Guidances/ucm080884.htm>
- FDA Guidance Document: *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*  
<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>



# Thank you!





**U.S. FOOD & DRUG**  
ADMINISTRATION