Executive Summary

On May 4, 2007, the General Hospital and Personal Use Devices Advisory Panel will be asked to discuss and make recommendations on the scientific and clinical issues raised by the addition of antimicrobial agents to personal protective equipment (PPE). The PPE to be discussed are surgical masks and surgical N95 respirators, surgical and isolation gowns and medical gloves, both examination and surgeons' gloves.

Personal protective equipment devices are intended to provide a protective BARRIER function. They are Class II devices (surgical masks and surgical N95 respirators, surgical gowns) or Class I, nonexempt devices (medical gloves) which are subject to the 510(k) premarket notification requirement prior to marketing. Isolation gowns are Class I devices, normally exempt from the premarket notification requirement. However, the addition of an antimicrobial agent to an isolation gown would exceed the limitation of its exemption and require the submission of a 510(k) premarket notification. In order to be legally marketed, PPE must be found "Substantially Equivalent" to a predicate, i.e., a legally marketed device of the same type. This clearance decision is based on the review, by FDA, of the submitted data regarding the safety and effectiveness of the subject device.

While FDA has evaluated and cleared for marketing many medical devices which incorporate antimicrobial agents, FDA has not yet cleared for marketing any medical gloves (either surgeons' gloves or examination gloves), any surgical masks or any surgical N95 respirators which incorporate antimicrobial agents. We are aware of two early submissions, cleared in 1978 and 1979 respectively, for surgical gowns that were coated with an antimicrobial agent. These devices were cleared decades ago. Consequently, they do not reflect current scientific knowledge, and are unable to provide clear direction today on the requirements for PPE with antimicrobial agents.

Although FDA has not yet cleared any medical gloves, surgical masks or surgical N95 respirators with added antimicrobial agents, it believes that there is interest on the part of industry in bringing such products to the health care market in the United States. FDA also believes that there are certain scientific and clinical issues raised by the addition of antimicrobial agents to PPE. FDA is seeking the advice of this Advisory Panel in order to prepare for scientifically sound review of these devices.

FDA will present to the Advisory Panel an overview of the manner in which personal protective equipment devices are currently reviewed for "substantial equivalence" to legally marketed devices. We will summarize the performance evaluation of the barrier functions of these devices and of other pertinent aspects, such as device safety (biocompatibility testing). We will present possible new indications for use or labeling statements for PPE with added antimicrobial agents gleaned from such public sources as the internet and scientific publications. For each device - medical gloves, masks and respirators and medical gowns - we will present the possible performance issues and safety questions which might arise from the addition of antimicrobial agents to these devices. We will include in the References for the Advisory Panel the FDA guidance

documents relevant to the review of these devices as background information for this presentation.

FDA will then present to the Advisory Panel its current thinking about the evaluation of antimicrobial agents added to medical devices other than PPE as the Agency currently reviews such submissions. The Infection Control Devices Branch assists other branches and divisions by consulting on such submissions. FDA will discuss the general issues of indications sought for antimicrobial agents added to devices which are not PPE, basic information needed to evaluate antimicrobial agents added to devices and important aspects of performance testing provided to support label indications for antimicrobial agents added to devices which are not PPE.

FDA believes that there are several important differences between personal protective equipment devices and the other devices to which antimicrobial agents have been added and which FDA has cleared/approved for marketing. Theses differences are important with respect to the indications for use statements which might be made for PPE and for the review of the performance testing to be done to support the labeling of these devices. First, PPE are almost exclusively single use, disposable devices. The only exceptions to this are surgical gowns or isolation gowns which can be laundered and then reused. Second, all PPE are used for short periods of time before being discarded or removed and sent for laundering. Third, PPE themselves are not direct causes of "device-related infections" although, once contaminated during use, PPE can serve as passive vehicles for the transfer of microorganisms from one physical location to another. Standard Infection Control practice, therefore, recommends the prompt removal of contaminated gloves, followed by handwashing, and the prompt changing of contaminated gowns used in patient care.

In contrast, the medical devices already cleared/approved by FDA which incorporate antimicrobial agents, have been devices such as urinary catheters and vascular catheters which are associated with a definite risk of device-related infection. For these devices, the risk of infection is clearly related to the duration of use of the device and is usually preceded by "colonization" of the device with a microflora drawn from the organisms present at the site of insertion, augmented by organisms added during device care. "Colonization" in clinical use, is a quantitative measurement of the microorganisms on the surface of an inserted device which correlates with the risk of subsequently developing a device-related infection. Indications for use statements made for such devices may include "preventing device-related infection" or "preventing device colonization". Such indications, as well as safety studies for these devices, have often been supported by clinical trials and in-vivo as well as in-vitro data.

FDA has also cleared for marketing devices incorporating antimicrobial agents which are at risk for contamination during use over a period of days, such as wound care dressings and similar products. The indications for use for these devices are generally "prevents contamination" or similar wording. FDA has also cleared surgical drapes incorporating antimicrobial agents with an indication for use to "reduce skin flora contamination

throughout a surgical procedure", an indication supported by in-vivo as well as in-vitro performance testing.

FDA believes that the questions raised by the concept of adding antimicrobial agents to personal protective equipment include the following:

- Is it possible for the addition of antimicrobial agents to "enhance" the normal barrier function of PPE by quickly killing pathogens as they reach the surface of the device?
- Can antimicrobial agents make gloves or gowns "safer" for their wearers?
- Can they make gloves or gowns safer for patients, presumably by reducing/preventing the transfer of microorganisms from one site to another?
- Can the addition of antimicrobial agents make surgical masks or surgical N95 respirators more effective barrier devices?
- Can antimicrobial agents actually kill microorganisms on the surface of a mask before they could be inhaled by the wearer?
- Could an antimicrobial agent in/on a mask kill microorganisms as they are drawn into the mask's filter matrix?
- Will such agents be effective during the typical time period of use (e.g., hours)?

FDA is very aware of the increasing concern nationwide about the problem of hospital-acquired (nosocomial) infections, especially those to antibiotic-resistant pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE) and multidrug-resistant gram-negative bacilli. It is well established that such nosocomial infections cause significant morbidity and mortality for patients and significantly increase the cost of health care for all Americans. Multidisciplinary efforts are underway all over the country to attempt to improve these problems. Various hospitals, hospital consortiums and quality improvement organizations are studying methods to improve health care worker compliance with handwashing when needed and to maintain improved performance. Recent publications have demonstrated significant reductions in the rates of vascular catheter infections by adherence to CDC-recommended guidelines. Responsible prescribing of antibiotics in both inpatient and outpatient settings is a focus for many efforts.

Against this background, the interest in the possibility that the addition of antimicrobial agents to PPE may be another useful tool in the struggle against nosocomial infections is understandable. However, the possible drawbacks to such an approach must also be considered. One very important concern would be whether the addition of antimicrobial agents to PPE might result in health care workers assuming that the presence of the antimicrobial agent on the PPE might compensate for any errors in practice /technique by the health care worker so that proper practice might not be always and consistently needed. Another concern would be the wearer and patient safety aspects of the antimicrobial agents added to PPE. In FDA's past experience with clearing antimicrobial agents added to devices, most of the added agents have already been approved by CDER as drugs for systemic or topical use. Some "antimicrobial agents", however, have not been approved as "new drugs" but only as "agents" added to specific devices. Such a clearance of an antimicrobial agent on a device applies only to that agent/device

combination. The amount of user/patient safety data available for these antimicrobial agents has varied. Only a few antimicrobials added to devices have been approved systemic antibiotics such as minocycline/rifampin; most have been topical antimicrobials. Finally, can antimicrobial agents function effectively as desired in the environment of actual clinical use of PPE which are used in patient care for only brief periods, ranging from minutes to a few hours, prior to being discarded? We will be asking the Panel to comment on this particular issue.

FDA will present to the Advisory Panel information relevant to these issues. Industry and Public Speakers will also have an opportunity to address the Advisory Panel. FDA will then ask the Panel to discuss the following questions and provide comments and counsel to FDA.

Various indications for use statements describing the performance of antimicrobial agents might be sought for PPE incorporating antimicrobial agents. Please discuss what types of indications for use statements may be appropriate for such devices? In your discussion please describe the meaning of such indications statements and what sort of data should be presented to support such indications. In particular, what would a "reduces contamination" or a "protects from microbial contamination" indication mean for PPE? How might performance for such an indication be evaluated? What might "reduces colonization" mean for PPE, which can become contaminated during use but are promptly discarded afterwards? How should such an indication be supported?

The indication for use statement made by a device is a very important element in the review of that device. It is FDA's belief that the specific indications sought by the manufacturer should be supported by appropriate performance testing data. In the past, for devices which are not PPE, FDA has cleared such statements within the indications for use as "prevents microbial growth"(on the dressing) and "prevents microbial contamination" (of the dressing) based solely on in-vitro data. FDA currently believes that indications for "prevents infection" require clinical trials for adequate scientific support. However, indications to "reduce colonization" have been supported by in-vitro and in-vivo (animal studies) data without clinical trial data. Indications for use to "prevent microbial growth" or "prevent microbial contamination" may also be considered as surrogate indications but with no quantitative definition and no validated link to a clinical outcome, they offer less of a defined benefit to the user of the device.

The term "colonization" is a somewhat difficult one in device review. This term is quantitatively defined for vascular catheters and urinary catheters and correlates, though not absolutely, with clinical outcomes such as the risk of catheter-related infection. If a label indication for a surgical mask or a surgical N95 respirator were submitted as "prevents colonization of the device", FDA would need to ask for a definition of the term "colonization" when applied to a respiratory tract protective device during its (usually brief) use. FDA would hope that such a definition would be quantitative and clinically

relevant. FDA would appreciate the Panel's discussion of what "colonization" might mean in reference to PPE, especially since these are devices which may become "contaminated" during their short periods of use, but are immediately discarded, with appropriate precautions, after use.

Another indication which could raise questions in review is "protects the device from microbial growth". This is an example of an indication which can be called a "preservative" label indication. This sort of labeling on a non-medical product is one which the Environmental Protection Agency (EPA) would consider to be exempt from regulation by the EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). EPA would ask that the language on such a product label indicate that this use of a "preservative" provided no public health benefit. FDA also believes that an indication worded in such a manner may pose additional questions and concerns in a submission review. After all, the purpose of adding an antimicrobial agent to a device should be to provide a benefit for the device wearer or the patient who is receiving care from the wearer of the antimicrobial-treated PPE. FDA currently believes that "preservative" indications may not be appropriate for many medical devices which incorporate antimicrobial agents although they may be appropriate when the purpose of the added material is to preserve the device from contamination during repeated use over a long period of time (for instance, a multiuse container of wound treatment gel).

This would be especially true for products such as PPE. PPE are normally clean or sterile (in the case of surgeons' gloves and surgical gowns); "contamination" of these devices prior to use, when properly stored, is extraordinarily rare. FDA is uncertain that "contamination" needs to be addressed once a PPE device has been properly discarded. FDA believes it might be more useful to address the prevention of microbial growth on PPE during use. Such an indication could be specifically worded to indicate just which microbes are being killed/inhibited at what site and time and the intended purpose/effect of this antimicrobial activity. FDA would appreciate receiving the panel's opinion on these issues and what might be considered appropriate wording for antimicrobial indications for PPE which incorporate antimicrobial agents.

As part of Question 1, the Panel will be asked to comment on what type of supporting performance data should be requested based on the indication statements sought. As the panel discusses its response, please consider the points listed below:

- Would only in-vitro performance data be enough to support indications for use for antimicrobial agents on PPE?
- Could in-vivo testing be of use in evaluating either safety or performance? If so, what type of data or study might be feasible?
- Should clinical studies be requested? If so, under what circumstances and what types of studies might be appropriate?

For each of the following types of PPE with antimicrobial agents added, please discuss what time frame would be appropriate for demonstrating antimicrobial efficacy in order

to kill/inhibit microbes and to reduce the risk of transferring organisms from one site to another.

- *Medical gloves (examination gloves and surgical gloves)*
- *Surgical masks*
- *Surgical N95 respirators*
- *Medical gowns (isolation gowns and surgical gowns)*

Most assays of antimicrobial activity use an 18 to 24 hour of incubation prior to reading the results. However, PPE are worn for much shorter periods of time - less than an hour, often only a few minutes in the case of examination gloves and surgical masks used to care for patients on isolation precautions. Even surgical gloves, masks and gowns are generally worn for, at most, a few hours in the operating room. FDA believes that for PPE, it might be most useful to demonstrate antimicrobial performance under conditions similar to the conditions of actual use. Previously cleared medical devices with added antimicrobial agents (which are not PPE) are devices used for periods of days to months. Conventional antimicrobial testing incubation periods are very reasonable for such devices. However, antimicrobial agents added to PPE have much less time in which to be effective during use. This would suggest that performance ought to be demonstrated over very short periods of time - probably minutes in the case of gloves and surgical masks and respirators. This is, admittedly, a severe challenge for an antimicrobial agent and very different from conventional testing. However, FDA believes that performance testing should mimic, insofar as possible, the conditions for performance for the actual device containing the antimicrobial agent. FDA hopes that the Advisory Panel will address this concept in some detail and provide your opinion on this point during your discussion of Question # 2.

Clearly in-vitro performance data for the antimicrobial agent will be needed to support the review of a device incorporating an antimicrobial agent. In our experience with clearing devices containing antimicrobial agents which are not PPE, the test data typically encompasses a broad range of microorganisms in order to support use of the term "antimicrobial" agent for a device indication. Antimicrobial activity assays are performed that utilize clinically relevant levels of inoculum challenge and quantitative endpoints for microbial reduction. Since the usual antimicrobial activity assay starts with a clinically relevant inoculum, usually on the order of log 6 of the test agent (abscesses frequently have an inoculum of this magnitude), a significant reduction in the starting inoculum is recommended to properly evaluate efficacy. The range of error in measurement in most antimicrobial activity assays such as time kill curves (broth dilution methods) is at least log 1, often almost to log 2 of organisms. Therefore an inoculum reduction of at least log 4 would typically be an acceptable, clinically relevant endpoint which can be adequately distinguished from the range of error of the assays.

For antimicrobial agents added to surgical N95 respirators or surgical masks, please comment on whether performance testing for antimicrobial efficacy should be expected to

- *significantly reduce an aerosol of infectious inoculum (compared to an untreated device) or*
- *simply demonstrate an ability to kill pathogens on the surface of a device*

As masks and respirators conventionally have at least 3 layers, the middle layer serving as the "filter" for the device, please also discuss whether the location of the antimicrobial agent in the device should determine, in part at least, the type of performance testing needed?

Surgical masks and surgical N95 respirators are intended as protective barriers against materials which might be splashed or coughed in the face of the health care worker and also to protect against aerosols of airborne pathogens. Surgical masks historically have been designed for comfort when worn for long periods of time in the OR as well as barrier function. The tightness of fit can vary significantly with the design style of the mask and so surgical masks are less useful in protecting the wearer against airborne pathogens than against splashes and fluid challenges. Surgical N95 respirators are protective devices first designed for industrial protection against airborne particulate hazards of various types. To be effective, they must both fit very tightly to the face and filter aerosolized hazards, such as airborne microbes, effectively. NIOSH certifies their compliance with NIOSH filtration performance requirements and OSHA requires that in occupational use, such as for health care workers, that the employer provide all respirator wearers with respirator training and fit testing. Both masks and respirators conventionally have at least 3 layers. The intermediate layer usually provides the filtration function. Therefore, depending on both the indications for use desired and the type of device (mask or respirator), in Question # 3, FDA will be asking the Panel whether performance testing for the antimicrobial efficacy testing of a respiratory tract protective device should be supported by demonstrating significant reductions in aerosol challenges of microorganisms. Since performance testing is typically performed on devices that are the "final finished product" ready for marketing, an aerosol challenge might be the only way to evaluate a mask or respirator which contains its antimicrobial agent in the internal filter layer and not on an external surface of the device. This might pose a burden in terms of the number of organisms which would need aerosol challenge studies. However, testing only individual material layers may not provide an accurate evaluation of the 'In use" performance of the final finished product.

If an antimicrobial agent is present only on the outer or inner surface, should performance testing be limited to the demonstration of inhibition/killing of microbes only by the treated surface(s)? Should any testing be done to determine whether inhibition/killing of microbes on an outer surface would also result in a reduction in the inoculum passing through the mask/respirator when compared to an untreated device? Please discuss these issues and provide your comments.

For antimicrobial agents added to surgical masks and N95 respirators please discuss the safety issues or risks to which the device wearer might be exposed and how these might be evaluated including but not limited to:

- *Effects on the oral, nasal or ocular mucosa*
- *Effects on the lower respiratory tract*

FDA is concerned about the potential safety issues raised by the addition of antimicrobial agents to PPE, both for the health care worker wearing the PPE and the patient in direct contact with the PPE. There is a potential for the antimicrobial agent to dissociate from the treated device. The manner in which the antimicrobial leaches or physically detaches from the device under conditions of use may be different at different body sites. For instance, if an antimicrobial agent were to be added to the inside of a glove, there is a potential for skin toxicity for the wearer. This would be exposure under increasingly warm and moist conditions which might enhance the risks of wearer to skin irritation and/or sensitization to the antimicrobial agent and might also lead to increased agent "leach off" and possibly to transcutaneous absorption depending on the antimicrobial agent, the condition of the wearer's skin and the duration of exposure. That exposure could be hours in duration if the glove in question were a surgeon's glove worn during a long procedure.

Since FDA has not yet cleared surgical masks or N95 surgical respirators incorporating antimicrobial agents, the evaluation of potential safety for the health care wearer of such devices is a new task for the agency. The usual safety evaluation of such devices without antimicrobial agents is biocompatibility testing performed as described in the FDA guidance, Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing for devices with limited contact devices, including intact skin. The currently used materials in surgical masks and N95 respirators are well understood and well characterized. Tests for biocompatibility on only intact skin are very effective evaluating safety during wear for current devices. The potential for an antimicrobial agent to "leach off" or “gas off” or physically detach from a treated mask or respirator due to contact with saliva or exhaled warm breath or to detach due to physical trauma during use is real. If a mask or a respirator contained an antimicrobial agent which might "leach off" or even "gas off" under conditions of use, would only a simple skin evaluation be adequate? Should evaluation for toxicity of the oral, nasal or even ocular mucosa also become part of the evaluation of masks and respirators containing antimicrobial agents? FDA would appreciate receiving the panel's opinion on this point.

For antimicrobial agents added to PPE, especially medical gloves, please discuss the safety issues or risks for patients exposed to such devices and how these should be evaluated. Should the potential for an antimicrobial agent on the surface of medical gloves or other PPE to leach off into body sites or onto surfaces being touched be evaluated? In your discussion, please comment on whether your concerns about such exposure are increased in pediatric and neonatal patients.

A medical glove with an antimicrobial agent bound to its outer surface will come into contact with intact skin, non-intact skin, deep wounds both clean and dirty, all mucosal cavities, the eyes, all penetrating and external patient care devices, enteral feedings during preparation as well as during the preparation and administration of medications. If an antimicrobial agent were able to "leach off" or physically detach from the surface of the glove at one or more of these sites during the performance of patient care tasks, the patient might absorb that agent. The manner in which "leach off" or "fall off" might occur as well as its extent might vary from one site to another. The "dose" of a leaching antimicrobial agent could vary for each patient with the site and frequency of glove contact. The impact of the "dose" would vary with the size and health status of the patient. Small neonates and young children would be a particular concern for such a safety evaluation.

The potential for an added antimicrobial agent to "'leach off" or physically detach from the surface of a mask or respirator or isolation gown or surgical gown during use in patient care activities and procedures is also a concern.

In view of the lack of scientific information in the literature regarding the safety and performance of PPE with antimicrobial agents, and the complexity of the scientific and clinical issues raised by the addition of antimicrobial agents to PPE, FDA is requesting the assistance of this Advisory Panel in clarifying the extent of safety testing with respect to patients which would be useful in properly evaluating PPE and in identifying special aspects of the evaluation process appropriate to PPE.

Should "leach off" or physical detachment of an antimicrobial agent added to PPE be studied under conditions which mimic mucosal contact? Non-intact skin contact? Deep tissue contact? Contact with enteral feeds, irrigation solutions, medications? Should exposure levels be calculated (if an agent has been shown to leach off or detach from its device) for all patient populations likely to be exposed in order to evaluate product safety?

Please discuss whether there is a reasonable possibility that the presence of an "antimicrobial agent" on PPE might lead the wearer of the PPE to be less likely to follow correct infection control procedures or proper techniques. If such risk seems to be a possibility, what steps could be taken, including product labeling, to help reduce such a risk?

The modification of a medical device may, in some instances, impact on the practice of medicine. Does this potential exist for PPE with added antimicrobial agents? The

Infection Control scientific literature documents the ongoing challenges in motivating health care workers to adhere to hand washing guidelines. As early as 1991, Patterson et al documented a small outbreak of Acinetobacter colonization/infection in an ICU due, in part at least, to failure of health care personnel to change their contaminated gloves between patients and between care episodes for contaminated sites in the same patient. These authors pointed out that the increased use of gloves in patient care following the CDC recommendation for "Universal Precautions" in 1987 created new opportunities for pathogen transmission when gloves were not promptly changed and hands then washed between patients or between tasks for the same patient. Can the presence of an antimicrobial agent on PPE lead a health care worker to assume that the presence of the antimicrobial agent will inhibit/kill microbes on/in the PPE during use? As a result, might these same health care workers disregard infection control practices? Can this potential risk be addressed by carefully crafted labeling? If so, would cautionary statements be helpful? Should additional means of promoting proper use of PPE with antimicrobial agents be considered? FDA would like the Advisory Panel to discuss this issue in order to provide guidance for the Agency.

The Panel is not being asked to address the issue of antimicrobial resistance at today's meeting. This information on antimicrobial resistance is provided as background information.

While the emergence of antimicrobial resistance in response to the use of systemic antimicrobials has been well documented in the clinical and scientific literature, much less information has been published on antimicrobial resistance associated with topical agents. However, the extensive use of antimicrobial agents not only in hand and oral hygiene products but also in a very broad range of consumer products has led to some investigation of this question, especially for agents used in hand and skin care. There are reports that biocides and antibiotics share certain features for developing resistance to these agents. This antimicrobial resistance can result from de novo mutations or from transfer of plasmids carrying resistance genes. The mechanisms of action of antimicrobial resistance are similar in spite of the differences in origin. For instance, laboratory studies have shown that a multidrug efflux pump can transport out of Pseudomonas aeruginosa cells not only triclosan and pine oil but also ciprofloxacin. Multidrug resistance plasmids in Staphylococcus aureus can mediate resistance not only to gentamicin and oxacillin but also to chlorhexidine and benzalkalonium chloride, again by using multidrug efflux pumps. Outside of the laboratory setting, however, it is not clear that exposure to biocides, as opposed to exposure to antibiotics, can result in the emergence of significant antibiotic resistance in clinical practice. Antimicrobial resistance to biocides is a real phenomenon but its clinical significance appears to be modest at present and manageable by increasing the concentrations of the agent used. However, the potential for the molecular mechanisms described above to contribute in future to the emergence of antibiotic resistance is unknown. For these reasons, experts such as Rutala, Weber, Sheldon, A D Russell and McDermott suggest that the prudent use of biocides should be encouraged, along with increased surveillance to monitor potential emergence of further resistance.