



FDA N95 Mask Emergency Use Authorization Requirements – Questions for the FDA on the Requirements for UV Testing

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This document was written and reviewed by a diverse committee members of the International Ultraviolet Association (IUVA), an organization established to provide a forum for the discussion of all scientific and technological issues that relate to the use of ultraviolet radiation.¹ The committee (shown as co-authors) reviewed the document to ensure scientific accuracy and check that it fairly represented the general consensus of the committee members; however, this review does not necessarily infer a unanimous agreement from all IUVA members on the document or its recommendations.

Executive Summary

Overview

On May 14th, 2020, a working group consisting of IUVA members ranging from UV equipment manufacturers, scientists, engineers, academics, to consultants, and members of the medical profession, delivered a webinar (detailed below) to promote an open dialogue on the issues related to decontaminating N95 masks with UV-C disinfection technologies² specifically focused on using UV-C to help address N95 mask supply issues in combating the COVID-19 Pandemic. The webinar was intended to provide an overview of the FDA & CDC regulatory guidance, related medical & scientific basis and the issues surrounding use of UV-C in N95 decontamination. The webinar's main objective was to obtain and submit industry comments in response to the request for industry comments found in the FDA's emergency use authorization (EUA) guidance;³ this white paper is to fulfill that objective.

Results of the Webinar

The webinar, entitled “Expert Perspectives on UV as a Tool for N95 Decontamination,” included presentations by Dr. R. Martinello, a Yale infectious diseases physician and associate professor on the fundamentals of SARS-CoV-2; Dr. J. Bolton, a Yale infectious diseases physician (retired) and internationally known expert in using UV to counteract

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infectious pathogens; Mr. B. Hunt, a Canadian expert in UV technology and applications on N95 mask features and characteristics; Dr. E.R. Blatchley III, a Purdue Professor of Environmental Engineering reviewing Federal N95 disinfection guidelines; and Ms. M. Smith, a Senior ECRI staff member, reviewing current N95 mask testing protocols used by an independent medical testing agency. The presentations were followed by a five-persons panel of senior industry and medical UV experts addressing audience questions and comments on current industry, laboratory, research and healthcare practices and issues.⁴ The resulting hour-long session was watched by more than 750 audience members, who generated ~103 questions and comments, which have been compiled into 54 responses and posted on the IUVA's website.⁵

Analysis of the questions and discussion generated by the webinar revealed most questions were asked to gain a better understanding of scientific facts about UV, its applications, advantages and limitations. Several fundamental questions, though, revolved around the N95 EUA, and could only be partially addressed by the speakers and panel members. These were further analyzed and distilled down into 3 basic questions where additional FDA guidance is needed:

For the current EUA for N95 disinfection, what would be FDA's supplemental guidance on

- 1. the surrogate pathogen(s) that FDA prefers as most representative for SARS-CoV-2 efficacy testing?*
- 2. the requirement to test for both surface and internal disinfection, or to test only for surface decontamination?*
- 3. the minimum required inoculation, methods and protocols for inocula placement? and whether or not soiling is required in the inoculum? If so, what type and concentration?*

Fundamental N95 Testing Questions and Their Discussion

1. For the current EUA for N95 disinfection (N95 EUA), what would be FDA's supplemental guidance on the surrogate pathogen(s) that FDA prefers as most representative for SARS-CoV-2 efficacy testing?

1.1. re: Acceptable Surrogates --

The current understanding of the kinetics of SARS-CoV-2 inactivation by UVC radiation is incomplete, although recent evidence demonstrates that SARS-CoV-2 is highly susceptible to UV irradiation.⁶ As summarized in a companion IUVA White Paper,⁷ other available evidence further supports that UV radiation should be effective for inactivation of SARS-CoV-2 microbial pathogens. Like all common disinfectants (i.e., UV, chlorine, ozone), a need exists to quantify the kinetics of inactivation for SARS-CoV-2 for these applications.

While SARS-CoV-2's susceptibility to UVC has been demonstrated, the wide-spread and expeditious testing using SARS-CoV-2 in response to the EUA is not feasible. Based on the severity of disease caused by the SARS CoV-2 contagion, culture-based testing against SARS CoV-2 requires Bio-Safety-Level 2+ or 3 (BSL3) facilities, a very limited and expensive resource. Emphasis needs to be placed on finding the correct surrogate as a substitute in order to rapidly respond to the declared COVID-19 emergency. As the current FDA Emergency Use Authorization for N95 Tier-3 disinfection requires only a 3-log₁₀

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efficacy against a non-enveloped virus or two Gram-positive and two Gram-negative vegetative bacteria for Non-Surgical, Single User N95 masks,⁸ there appears to be some range of bacteria/fungi the FDA will accept.⁹ Surrogate candidates include human coronaviruses 229E and OC43, and coliphage MS2, a non-enveloped ssRNA virus.¹⁰ These may be acceptable and can be tested in BSL1 (for MS2) or BSL2 facilities, which are more readily available, accessible and affordable. To date FDA has not specified which surrogates may be acceptable.

One of the proposed surrogates, MS2, may be relevant for comparison because it is a single-stranded RNA (ssRNA) virus, like SARS-CoV-2. Comparing the two, it is important to consider SARS-CoV-2's classification as an enveloped ssRNA virus, whereas MS2 is a non-enveloped ssRNA virus. Therefore, it is likely that SARS-CoV-2 will be inactivated more rapidly by UV exposure than MS2, making MS2 one of several conservative surrogate options.¹¹ However, it is unknown at this time if the decontamination process should solely consider the inactivation of SARS-CoV-2 or also account for other pathogens that might be present on the masks (e.g. *S. aureus*, group A streptococcus, Influenza, etc.).

Another likely surrogate is SARS-CoV that caused a 2003 epidemic of Severe Acute Respiratory Syndrome (SARS), infecting people in 26 countries. SARS-CoV and SARS-CoV-2 are structurally-similar viruses; both are non-segmented, enveloped, single-stranded RNA (ssRNA) viruses. While a recent study reports UV dose-response behaviors of SARS-CoV and SARS-CoV-2 to be similar with SARS-CoV-2 being the more susceptible,¹² it is important to note that there is considerable variability in the reported UV dose-response behavior of SARS-CoV, which suggests additional work is needed and cautions against generalizing these findings to SARS-CoV-2 is warranted before considering SARS-CoV as a surrogate.¹³

1.2.re: Related Surrogate Issues in UV Testing--

The selection of surrogates should also consider other variables. For one, the UV dose response-curve of the surrogate should ideally be linear or exhibit a similar behavior to the targeted organisms and be at least as resistant to UV as the target pathogen (SARS-CoV-2). The presence of aggregates in the surrogate suspension may cause significant deviation from a linear response. It is also necessary to use a surrogate which can be grown at a very high concentration. Microbial losses observed during a mask contamination and their extraction from the mask after its irradiation can make it challenging to demonstrate 3-log₁₀ reduction, the FDA's EUA target for Tier 3 applications.

As noted in a companion IUVA White Paper¹⁴, there is a 20-50 times variability factor in experimentally determined pathogen-specific inactivation dosages, most likely caused by deficiencies in the experimental methods that were used in some or all of these previous studies. The resulting overestimates of required dosages is likely due to the UV absorbance of the suspensions were not reported or explicitly accounted for. Similarly, it was not clear from these earlier studies that the UV exposure conditions used would allow for accurate calculation of the UV dose applied to the viral suspension. Based on the information provided in the reported studies of SARS-CoV UV dose-response behavior, the data set that appears to represent the most accurate results, may still show falsely-high required dosages, which would force longer than required treatment times and faster than expected mask degradation.¹⁵

1.3. Conclusion

The large number of surrogate options and the significant differences in the required inactivation dosage values for pathogens comparable to the surrogates inevitably lead to high degrees of variability in test results, producing inconclusive studies that are difficult, if not impossible, to accept as conclusive and actionable, wasting resources and time. Given the nature of this pandemic emergency, it would be helpful if the FDA would, even on an interim basis, select 1-2 specific surrogate pathogens that closely mimic SARS-CoV-2 that enable accurate, reproducible and auditable results of UV efficacy against SARS-CoV-2.

1.4. Suggestion for FDA's consideration

For this pandemic declaration, IUVA proposes to standardize testing with MS2 in an standardized environment (e.g., 20°C and 50% RH) for a 3- \log_{10} or greater reduction in the test samples, comparable to FDA's Tier 3 testing requirements.¹⁶

2. For FDA's N95 EUA, what is FDA's guidance on - the requirements to test for both surface and internal disinfection, or to test only for surface decontamination?

2.1. re: Testing a Mask's Exterior and Interior Exposed Surfaces vs. the Internal Filtration Layers

In its May 2020 guidance, FDA states *“this guidance appl[ies] to systems intended to decontaminate or reduce the bioburden of surgical masks and/or respirators during the COVID-19 public health emergency.”*¹⁷ The term ‘decontamination’ is defined as the *“process of cleaning and disinfecting soiled medical devices to render them safe for handling and to the extent necessary for subsequent processing.”*¹⁸ In its most recent guidance, the CDC states *“The surfaces of a properly donned and functioning NIOSH-approved N95 respirator will become contaminated with pathogens while filtering the inhalation air of the wearer during exposures to pathogen laden aerosols. The pathogens on the filter materials of the respirator may be transferred to the wearer upon contact with the respirator during activities such as adjusting the respirator, improper doffing of the respirator, or when performing a user-seal check when redonning a previously worn respirator.”*¹⁹ Further, CDC has asserted that *“Physical contact with the filtering layer by the wearer is unlikely due to its location within the FFR. The outer surface, the surface furthest from the wearer's face, presents the highest risk for pathogen transfer to the wearer.”*²⁰ Based on these statements, it can be inferred that *“safe for handling”* means decontamination is all about cleaning and disinfecting the mask's surfaces which would be touched during routine use, not the internal filtration layers of the mask which are not intended to be handled. Accordingly, it would appear that inoculation of the mask only need be applied to the mask's exterior and interior surfaces.²¹

As stated earlier, current FDA guidance does not specify how or where testing inocula should be applied.²² If applied only to the exterior and interior surfaces, the problem is easily solved. If required to be applied internally to the filtration layers, the problem becomes infinitely more complex. What log inoculation should be used on what layers for testing and how should each sample be processed? Should the internal layer sample results be averaged in

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with the surface results, or each layer assessed separately? To ensure that the tests accurately reflect normal operating conditions, if the inoculations are to be applied to the internal filter layers, should they be applied directly, or indirectly by drawing the aerosols through the mask's exterior via induction?

Although it could be argued that ASTM standard E2720 addresses this, as it speaks to evaluating the efficacy of decontaminating air permeable materials; a close reading of that standard shows the testing is done on coupons of the materials from the devices in question, to facilitate sample inoculation and analytical processing, not intact units (i.e., masks),²³ thereby preventing the tests from addressing any issues related to improper angles of incidence or shadowing due to mask shape and geometries that could significantly degrade UV performance. Accordingly, it was concluded that no standardized approach exists that can be reproducibly applied to an entire mask, where the need is to inoculate and test for a $\geq 3\text{-log}_{10}$ concentration, to meet Tier-3 criteria.²⁴

2.2.re: Additional Complications of Considering Differing Makes & Models

The ability of UV-C of any wavelength to inactivate microorganisms on textiles such as masks depends heavily on the material, its density, its optical properties, the presence of any dyes or pigments, and its orientation/angle of incidence to the UV-C source. To assure the tests can be replicated regardless of mask make or model, the testing protocol issue arises - should inoculations be applied to standardized slides and inserted in the mask or to the materials, themselves, for each make & model tested?

In a related issue, differences in design and construction of the masks cause the thickness of the materials to vary from area to area, making it harder for the UV-C to penetrate because of 'shadows.' When UV radiation is obstructed by shadows from any parts of the mask, it limits overall disinfection efficacy in unpredictable ways. One option to partially compensate is to increase the UV-C dosage, resulting in high recommended UV exposures ($>1000 \text{ mJ/cm}^2$) that are an order of magnitude or more above requirements for conventional surface disinfection. But even this compensation for potential shadowing may not be sufficient.²⁵

The guidance provided by FDA and CDC does not explicitly recommend what level of inactivation of viruses within the internal layers of an N95 mask is required. The CDC's guidance on limited reuse of N95 masks focuses on the risk of contact transmission (i.e., due to surface contamination), while being silent on disinfection of internal filter contamination.²⁶ As mentioned above, design of the required testing protocol is problematic especially when assessing the UV-C dosage needed to penetrate the N95 outer layers. ASTM E3179 could be used as an acceptable start point for testing with N95 masks, as it tests the effectiveness of UV to kill microorganisms on fabrics containing an organic soil; however, its procedures and any associated acceptance criteria would need to be modified to account for the multiple layers of a N95 mask and variations between the various makes & models.²⁷ CDC acknowledges this need, requesting that "Decontamination methods should be evaluated for each FFR model currently being used under a facility's respiratory protection program..."²⁸

The above situation, coupled with testing issues around how best to inoculate the masks to insure there is a sufficient, uniform pathogen load to assess and measure even a 3-log_{10} kill²⁹, make development and execution of a credible and auditable testing protocol difficult if not impossible. Tests have been done using spores dried on microscopic slides inserted under the

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first layer of N95 mask, as a simple approach to understand the impact of light coming from one direction. However, this option does not account for UV coming from the opposite direction (UV light doesn't transmit through the slide), nor for the interaction of organisms with the N95 materials.³⁰ Further, microbial transfer and re-aerosolization studies have shown that $\geq 99.8\%$ of filter-captured pathogens have remained trapped on the respirator after handling or following simulated cough or sneeze, implying this additional testing for internal filter decontamination is, at best, addressing a risk of pathogen release of $\leq 0.2\%$.³¹ Finally, CDC's recently updated guidance focuses only on possible contact transmission of pathogens found in the filter materials, "during activities such as adjusting the respirator, improper doffing of the respirator, or when performing a user-seal check when redonning a previously worn respirator," with no mention of the need to address possible re-aerosolization inhalation risk.³²

2.3. Conclusions

It is clear from the above that multi-dimensional problems of testing for decontamination within the N95 filtration layers, while potentially solvable in the long term, will be difficult and costly to solve in the near term, and would result in critical time and staffing resources spent to address a problem with minimal benefit to healthcare providers (HCPs).

2.4. Suggestion for FDA's consideration

Suggest that the EUA be amended to only require testing for decontamination of the exterior and interior surfaces of the N95 masks, and forego testing of internal layer decontamination until the EUA's COVID-19 emergency declaration has expired.

3. For this N95 EUA, what is FDA's guidance on the minimum required inoculation, methods and protocols for inocula placement, and whether or not soiling is required in the inoculum? If so, what type and concentration?

3.1. re: Inoculation Methods and Protocols –

As stated earlier, per CDC, the primary pathway for pathogen transfer to healthcare providers using N95's is most likely by touching contaminated areas of a mask during routine activities (donning, doffing, adjusting, etc.).³³ Masks may become contaminated by direct contact, or through droplets, either as large respiratory droplets (i.e., $>5\text{-}10\mu\text{m}$ in diameter), or as droplet nuclei, (i.e., $<5\mu\text{m}$ in diameter), thereby enabling transfer of the pathogens that could result in infection.^{34 35}

Current FDA guidance on testing the masks provides very few recommendations for how masks should be inoculated for testing. Specifically, the guidance does not specify whether testing inocula should be applied as a surface spot (to simulate a touch contamination), random large droplets (to simulate person-to-person exposure), or applied as ambient aerosols (to simulate generic airborne exposures).³⁶ Further, no guidance is given on inocula placement for conclusive results (e.g., whole mask? on the nose bridge? the chin area? cheek area? strap-mount points?)

Additionally, it is unknown at this time, if and how UV dose requirements might differ between the different inoculation methods. The current guidance for single-user N95 masks (non-surgical Tier-3) requires evidence of a 3-log_{10} kill of a non-enveloped virus or two gram-positive and two gram-negative vegetative bacteria.³⁷ This results in testing issues

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around how best to inoculate the masks to insure a sufficient pathogen load to enable inoculant collection, assessment and credible measurement of a 3-log₁₀ kill.³⁸ It is estimated one would need to inoculate with at least 3 to 4-log virus and or spores, reasonably achievable with swabs but difficult to do reliably and accurately with droplets or aerosols.³⁹

As an example of the difficulty of contaminating masks, to simulate large droplets, one lab has been using 1-2 uL with repeat application to get a total volume of 10 uL in a 1 cm² contaminated region. With spores and phages, it is not too difficult to get the required initial load in the contaminated region. With bacteria, however, they had to centrifuge the stock suspension to increase the titer, which raises the risk of bacterial 'clumping' during inoculation (even if they vortexed them fully prior to contaminating the masks). Despite the drawbacks, it was the only way to get ~9 log/mL in the inoculum stock needed to contaminate the masks.⁴⁰ They also noted that it was more difficult to inactivate 5 droplets of 2 uL as opposed to a single drop of an equivalent volume (10 uL).

Similar issues are anticipated with applying aerosols to masks in a consistent and reproducible manner.⁴¹ These complicated protocols for accurate application of both large droplets and aerosols result in a more labor-intensive, difficult to replicate process compared to swab inoculations.

3.2. re: Inoculation Soiling --

Another consideration is 'soiling' (i.e., prepping the inoculate to more closely mimic actual field conditions). There are several choices, to include artificial human saliva, porcine saliva, bovine saliva, & sterilized fecal matter. Standardizing inoculate 'soiling' is needed for consistent, reproducible test results.⁴²

Some labs are using artificial saliva with a UVA254 of 9.4/cm (similar to human saliva), contaminating masks with droplets of 1 uL (d=1241um). The loss of UV radiation across the resulting path length through the droplet is ~97%. However, the droplets are dried prior to testing and the interference from the resulting salts and proteins (the lab used mucin) are probably not well described by the above calculation.⁴³

Regardless of inoculation method, salts in any soiling do not absorb UVC radiation at 254 nm when dissolved, but may shield radiation once crystalized.⁴⁴ If these factors are not considered and standardized, results will vary widely, making credible, auditable decisions difficult.

3.3. Conclusions

To produce timely, credible testing results requires reproducible testing using well defined protocols, to include placement, concentration and makeup of the inoculum, and method of inoculation. The current EUA guidance does not provide these key parameters, making comparative analyses between labs or between products difficult, and fact-based decision making almost impossible.

3.4. Suggestion for FDA's consideration

Assuming the Suggestion in 1.4, or something similar, is adopted, in order to acquire consistent and reproducible results, would suggest the EUA be amended to call out the inoculation specifications and concentrations, and inoculation process and locations to be used on the mask(s) to be tested.

Summation

The FDA, in issuing and continually updating its EUA guidance, has endeavored to be proactive and responsive to the rapidly evolving COVID-19 situation and ever-changing requirements for N95 masks and other personal protective equipment necessary to protect our HCP's. The comments and suggestions contained in this white paper are intended to offer constructive and simplifying options for FDA's consideration, that are intended to improve and streamline the EUA process, not only for UV-based technologies, but to efficacy testing, overall. IUVA, representing major portions of the UV Healthcare sector, remains committed to assisting the FDA in this ongoing effort to improve the EUA process, thereby increasing the number of options available to the HCP community, and enabling the rapid approval of equally efficacious and perhaps more cost-effective alternatives.

References

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²² Ibid.

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²⁶ FDA, "Recommendations for Sponsors Requesting EUAs ...",

²⁷ IUVA, "Responses to Questions Received - Response # 36

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³¹ CDC/NIOSH, "Recommended Guidance for Extended Use and Limited Reuse of N95 Filtering Facepiece Respirators in Healthcare Settings"

[<https://www.cdc.gov/niosh/topics/hcwcontrols/recommendedguidanceextuse.html>]

³² CDC, "Strategies for Optimizing the Supply of N95 Respirators," ...

³³ CDC, "Implementing Filtering Facepiece Respirator (FFR) Reuse..."

³⁴ Guidance from the World Health Organization (WHO) states,

"Respiratory infections can be transmitted through droplets of different sizes: when the droplet particles are >5-10µm in diameter they are referred to as respiratory droplets, and when they are <5µm in diameter, they are referred to as droplet nuclei.1 According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and [touch] contact routes..."

"Airborne transmission is different from droplet transmission as it refers to the presence of microbes within droplet nuclei, which are generally considered to be particles <5µm in diameter, can remain in the air for long periods of time and be transmitted to others over distances greater than 1 m."

[[https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-](https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations#:~:text=According%20to%20current%20evidence%2C,transmission%20was%20not%20reported.)

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