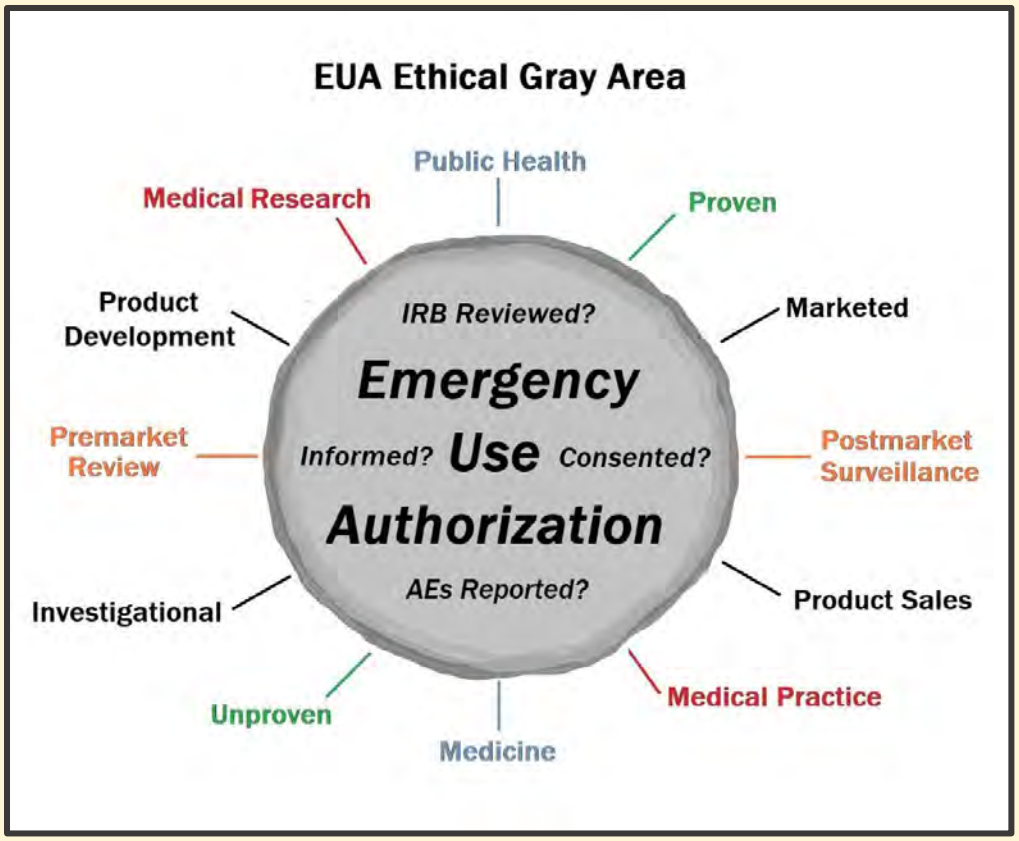
Does emergency use authorization fall into an ethical gray area?

The Regulatory Watchcat

The extensive use of emergency use authorization (EUA) during the COVID-19 pandemic has led to considerable confusion among manufacturers, providers, and patients regarding the regulatory status of authorized products and what can be reasonably expected of them in terms of safety and effectiveness.

The EUA also appears to have opened up an ethical "gray area," one that lies between constructs generally thought of as discrete, but which are instead points on a continuum: medical practice and medical research, proven and unproven medical interventions, investigational and marketed products, individual health and public health, product development and product sales, premarket review and postmarket surveillance.



If individuals with the appropriate expertise were to evaluate medical practice vs medical research, investigational vs marketed, public health vs individual health, etc, specifically as they apply to the EUA, and not as discrete alternatives, but as points along a continuum, this might lead to a rational framework for addressing ethical concerns that have emerged with the widespread use of the EUA, such as a potential need for independent ethical oversight and informed consent, as well as for determining the appropriate regulatory oversight, and appropriate use of the clinical data generated from the use of an EUA product.

In these comments, I lightly (and hurriedly) consider a few of these continuums and the types of ethical questions they might raise for future (hopefully more deeply and less hurriedly) consideration.

Proven <--> Unproven

The Declaration of Helsinki establishes informed consent as an ethical requirement for the use of "unproven" medical interventions in clinical practice:

> 37. *In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective,* the physician, *after seeking expert advice,* ***with informed consent*** *from the patient or a legally authorised representative* ***may use an unproven intervention*** *if, in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering.*

Questions: Are EUA products "proven" or "unproven"? If they are proven, what have they been proven to do, and by what standard of "proof"? How does this standard compare to the regulatory standards for IND approval or market approval? What are the implications for informed consent?

Medical Practice <--> Medical Research

The American Medical Association has established informed consent is an ethical requirement for both research and medical practice:

> ***AMA Code of Medical Ethics Opinion 2.1.1***
> *Informed consent to* ***medical treatment*** *is fundamental in both ethics and law.*
>
> ***AMA Code of Medical Ethics Opinion 7.1.2***
> *Informed consent is an essential safeguard in* ***research****.*

The information provided to subjects in clinical trials is provided in writing and is usually far more detailed than information provided to patients in medical practice. In routine medical practice, the information provided to patients may range from a package insert, a brochure, or a fact sheet, to a casual conversation. More detailed information is provided to patients considering high-risk medical interventions.

Consent provided by subjects in clinical trials is documented with their signature or that of a parent or guardian. In routine medical practice, consent may be documented in patient medical records, but signed consent is usually required only for high-risk medical interventions.

Questions: What amount of information is adequate to support informed consent for the use of EUA products? Less than for "research"? More than for "practice"? How should the adequacy of the information be determined? By FDA? By an IRB?

Questions: Should a patient considering use of an EUA product be asked to provide their signed consent? Why or why not?

The Belmont report acknowledged the ethical implications associated with the difference between medical practice and medical research:

> *"It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other,* ***in order to know what activities ought to undergo review for the protection of human subjects of research****.*

The report also defined a gray area between practice and research:

> ***Experimental*** *– When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research.*

Questions: Does a medical product that has been authorized only for emergency use fall into the gray area of "experimental"? If so, what are the implications for ethical oversight and informed consent?

HHS regulations require informed consent in research involving human subjects, including clinical investigations of products regulated by FDA:

> ***TITLE 45—Public Welfare***
>
> *PART 46—PROTECTION OF HUMAN SUBJECTS*
> *§46.101 To what does this policy apply? …to **all research involving human subjects**…*
>
> ***TITLE 21—Food and Drugs***
>
> *PART 50—PROTECTION OF HUMAN SUBJECTS*
> *§50.1 Scope. "…applies to all **clinical investigations** regulated by the Food and Drug Administration …as well as **clinical investigations** that support applications for research or marketing permits…*

Questions: Will any of the clinical data generated by the use of an EUA product be used to further assess the product's safety or effectiveness? If so, would this constitute "research"?

More Questions: Does the use of an EUA product present more or less risk than the use of a product that meets FDA's standards for approval? Does it carry more or less risk than an investigational product? What does this relative level of risk imply when it comes to an appropriate standard of informed consent for an EUA product?

Medicine <-->Public Health

In an effort to distinguish practice from research, "in order to know what activities ought to undergo review for the protection of human subjects of research," the Belmont Report defines medical practice as "interventions that are designed **solely** to enhance the well-being of an individual patient or client and that have a reasonable expectation of success." Its point is that, when medical interventions also serve the purpose of research, they should be treated as research and undergo review for the protection of human research subjects.

In a footnote to this discussion, the Report also acknowledges that protection of the public health is yet another *separate purpose* that may be pursued *in addition to* the purpose of enhancing the well-being of an individual patient:

> [2] Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or **an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others *(e.g., vaccination, which protects both the person who is vaccinated and society generally)***. The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, ***should not confuse the general distinction between research and practice***. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, ***it is practice and need not be reviewed as research***.

Questions: What if the ability of the vaccine to protect the person who is vaccinated and/or society is "unproven"? Is this intervention still practice, as it would be if the vaccine were "proven" (FDA approved)?

More **Questions:** If data will be collected from this intervention to assess its efficacy and/or safety, does this intervention not then become research? If it is not research, and therefore does it not need to be reviewed as research, does that mean it should be reviewed solely as practice? Or does this scenario fall into a gray area between the two?

Informed Consent for the Use of EUA Products

The FD&C Act requires informed consent for the use of otherwise unapproved products that have been authorized for emergency use:

> ***FD&C Act, §564***
> ***(1) Unapproved product***
> ***(A) Required conditions***
> *…the Secretary, to the extent practicable given the circumstances of the emergency, shall, for a person who carries out any activity for which the authorization is issued, establish such conditions on an authorization under this section as the Secretary finds necessary or appropriate to protect the public health, including the following:*
> *(e)(1) Conditions of authorization, unapproved product*
> *(A)(ii) Appropriate conditions designed* ***to ensure that individuals to whom the product is administered are informed****—*
> *(I) that the Secretary has authorized the emergency use of the product;*
> *(II) of the significant known and potential benefits and risks of such use, and of the extent to which such benefits and risks are unknown; and*
> *(III)* ***of the option to accept or refuse administration of the product****, of the consequences, if any, of refusing administration of the product, and of the alternatives to the product that are available and of their benefits and risks.*

For EUA products that are already approved for indications other than the emergency use, the Act requires that patients be informed, but makes consent optional:

> ***FD&C Act, §564***
> *(e)(2) Conditions of authorization, unapproved use*
> *(A) …establish conditions described in clauses (i) and (ii) of paragraph (1)(A),* ***and may establish conditions described in clauses (iii)*** *and (iv) of such paragraph.*

So far, I have not been able to find any information regarding FDA's determination of whether an EUA product is unapproved (and therefore requires consent) or approved for other indications (and therefore consent is optional).

FDA's general EUA guidance, published January 2017, confirms the informed consent requirements in the Act and also indicates the requirements of 21 CFR Part 50 are not applicable to consent to use EUA products: The guidance also recommends the submission of a fact sheet that includes the information required under Section 564.

For COVID-19 EUA products, it appears that most, if not all, of the fact sheets given to patient are based on a template provided by FDA.

"Informed"

The fact sheets typically "inform" patients about emergency use authorization and the products that have received emergency use authorization using this type of language:

> *The [EUA product] made available under this EUA has not undergone the same type of review as an FDA-approved or cleared device.*
>
> *FDA may issue an EUA when certain criteria are met…*
>
> *…based on the totality of scientific evidence available, it is reasonable to believe that [EUA product] may be effective for use*

If some of this language sounds familiar, it is because it has been lifted straight out of Section 564 of the FD&C Act. I would like to think I don't need to point out that Section 564 was not written to inform patients of anything, but at this point, I'm not taking any chances. I will also point out that it is highly unlikely that any effort was made to assure that Section 564 was written "in language understandable" to patients. Nor, I daresay, in language understandable to healthcare providers, either.

"Consent"

It seems clear that the fact sheets for COVID-19 in vitro diagnostic tests were designed to be given to patients ***after*** they had already been tested, as they all begin with this sentence:

> *You are being given this Fact Sheet because your sample(s) was tested for the Coronavirus Disease 2019 (COVID-19) using [Name of Test].*

While consent to be tested might have been given prior to testing, it was clearly not FDA's intent for patients to be informed in advance of testing. Other fact sheets also include language that indicates the fact sheet is given to patients after the fact:

> *You are being given a medicine called…*
>
> *Your child is being given a medicine called…*
>
> *This fact sheet contains information to help you understand the risks and benefits of [EUA product] you have received or may receive.*

Some fact sheets are more ambiguous with respect to timeframes:

…because your healthcare provider believes it is necessary to provide you treatment using [EUA product]...
…because your healthcare provider needs to use [EUA product]...
…because your healthcare provider believes that you may benefit from [EUA product]...
…because your healthcare provider has determined it is appropriate to use [EUA product]...
…because your healthcare provider recommends using [EUA product]...

Other fact sheets seem designed to be provided to the patient in advance of intervention:

…because you will be [treated with an EUA product]...
…because [an EUA product] will be used on you...
…because your doctor plans to use [EUA product]...

The timeframes for the Advisory Committee meeting and submission of comments have been prohibitive with respect to a thorough review of all documents that might be relevant to ethical issues potentially raised by authorization for emergency use. So far, I have been unable to find:

- Language in any fact sheet informing the patient of an option to accept or refuse administration of the product. (As noted previously, neither have I been able to find information regarding which EUA products FDA considers unapproved or approved for another indication.)
- A description of what conditions FDA thinks are appropriately designed to "ensure" that individuals administered EUA products are informed per the requirements of Section 564. I can only hope the Fact Sheets I reviewed are not considered to be these conditions, based on their mere existence and/or on the information they contain.

Nonetheless, it seems clear to me that the EUA raises ethical questions that, as best I have been able to determine, have been given little, if any, consideration, at least not in conjunction with its extensive use during the COVID-19 pandemic. I would strongly prefer to see these issues given deep and thoughful consideration before a vaccine is authorized for emergency use. Until such consideration can be given, I support making any COVID-19 vaccine available through expanded access, rather than EUA.

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