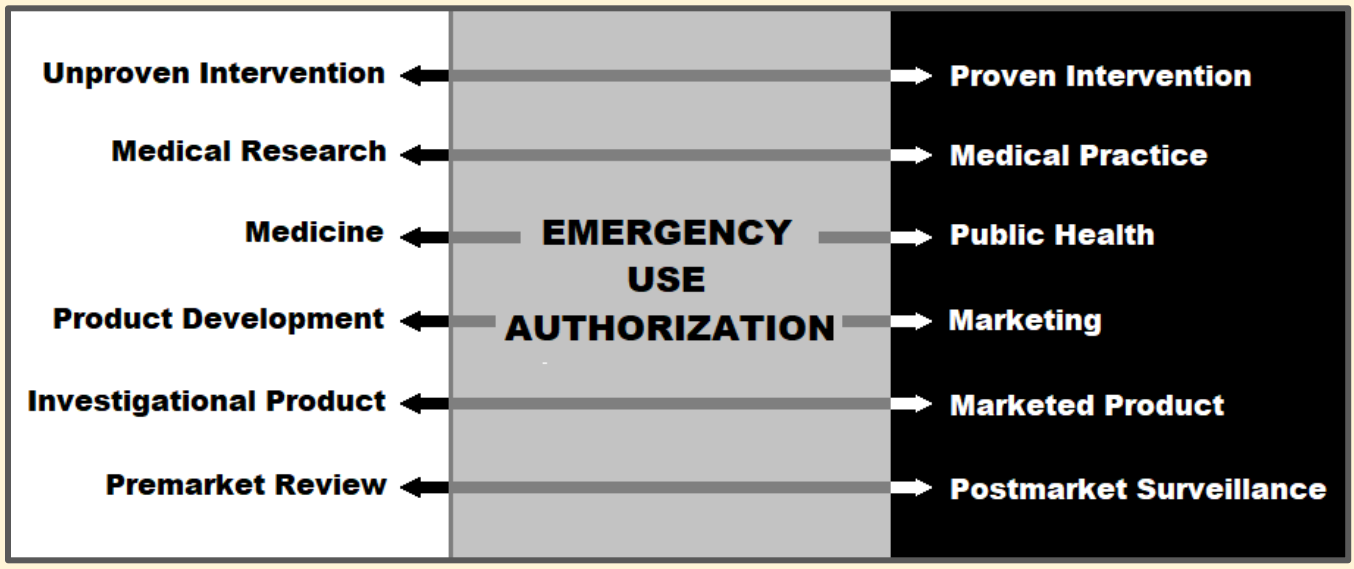
- DRAFT -

The Regulatory Watchcat

Does emergency use authorization fall into an ethical gray area?

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 usually thought of as discrete, but which can be viewed as points on a continuum, e.g., medical practice and medical research, proven and unproven medical interventions, individual health and public health, investigational and marketed products, product development and product sales, premarket review and postmarket surveillance.



An evaluation of the continuums defined by these constructs could provide a rational framework for addressing ethical concerns that have emerged with the widespread use of the EUA, such as the potential need for independent ethical review and informed consent, as well as for determining the appropriate regulatory review, and appropriate use of the clinical data generated from the use of an EUA product.

In this paper, I consider some of these continuums and the types of ethical questions they raise.

UNPROVEN ⟷ PROVEN

Informed Consent

Declaration of Helsinki

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 of "proof" compare to the regulatory standards for investigational approval or market approval? What are the implications for informed consent?

MEDICAL RESEARCH ⟷ MEDICAL PRACTICE

Ethical Review

AMA Code of Medical Ethics

From the perspective of the US medical profession, ethical review is of professional conduct, rather than of medical practice or research per se.

> ***Code of Medical Ethics Opinion 9.4.1***
> *Physicians have mutual obligations to hold one another to the ethical standards of their profession. Peer review, by the ethics committees of medical societies, hospital credentials and utilization committees, or other bodies, has long been established by organized medicine to scrutinize professional conduct.*

The Belmont Report

The Belmont report acknowledged that difference between medical practice and medical research has implications for ethical review:

> *"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.*

It defined both "practice" and "research," plus a third concept, "experimental," which could potentially be viewed as a gray area between practice and research:

> ***Practice*** *– "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success.*
>
> ***Research*** *– "an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge"*
>
> ***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.*

Declaration of Helsinki

The Delaration of Helsinki establishes independent ethical review as an requirement only for medical research:

> *23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher….*

Informed Consent

AMA Code of Medical Ethics

The American Medical Association has established informed consent as 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 to a medical intervention might be documented by the practitioner in the patient's medical records, but the patient's, parent's or guardian's signature is usually required only for high-risk medical interventions, and then for the purpose of releasing the provider from liability, rather than for the protection of the patient.

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 review and informed consent?

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"?

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 ethics committee? By individual practitioners?

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

MEDICINE ⟷ PUBLIC HEALTH

Ethical Review

US Code of Federal Regulations

HHS public welfare regulations require ethical review of research involving human subjects:

> ***TITLE 45—Public Welfare***
>
> ***§46.101 To what does this policy apply?***
>
> *"…to all research involving human subjects…*
>
> ***45 CFR §46.109 IRB review of research.***
>
> *(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy, including exempt research activities under §46.104 for which limited IRB review is a condition of exemption (under §46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7), and (8)).*
>
> *(b) An IRB shall require that information given to subjects (or legally authorized representatives, when appropriate) as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.*
>
> *(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.*

The Belmont Report

In addition to noting the importance of distinguishing between medical practice and medical research in order to know what activities ought to undergo review for the protection of human subjects of research, the Belmont Report also addresses the situation in which an actvity might serve both purpposes:

> *Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.*

In a footnote to this discussion, it also acknowledges that interventions might serve a public health purpose, and cites vaccination as an example of this type of activity:

> *[2] …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).*

It concludes that interventions to protect the public health are not research and do not need to be reviewed as research:

> *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.*

Informed Consent

US Code of Federal Regulations

HHS public welfare regulations require informed consent in research involving human subjects:

> ***TITLE 45—Public Welfare***
>
> ***§46.101 To what does this policy apply?***
>
> *"…to all research involving human subjects…*
>
> ***45 CFR §46.116 General requirements for informed consent***
>
> *Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.*
>
> ***45 CFR §46.117 Documentation of informed consent.***
>
> *(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written informed consent form approved by the IRB and signed (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form.*

Questions:

What if the benefit of a public health intervention to society is "unproven"? Is the intervention still practice, as it would be if the public health benefit were "proven"? If data will be collected from this intervention to assess its value to the public health, does this intervention become research? If it is not research, and therefore it does not need to be reviewed as research, should it be reviewed solely as practice? Or does this scenario fall into a gray area between the two?

INVESTIGATIONAL ⟷ MARKETED

The Belmont Report does not define "investigational," which regulators and industry often use informally to refer to products used in clinical trials, especially when the trial data are intended to support a regulatory decision. Under FDA's drug regulations, the alternative to "investigational" is "marketed."

> ***TITLE 21 Food and Drugs***
>
> ***PART 312—INVESTIGATIONAL NEW DRUG APPLICATION***
>
> ***§312.3(b) Definitions and interpretations***
>
> *"Investigational new drug means a new drug or biological drug that is used in a clinical investigation. Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.*

Prior to the EUA, "marketed" generally conveyed "FDA approved," and it was assumed that FDA would not approve a product until it had been "proven." Thus, the EUA seems to also have created a gray area between "investigational" and "marketed," one in which a product that is neither "investigational" nor "proven" may be marketed.

FDA does not regulate the practice of medicine, so it has no regulations addressing ethical use of the products it has approved.

Ethical Review

FDA regulations require ethical review of clinical investigations that will support applications for investigational and market approval of medical products.

> ***TITLE 21—Food and Drugs***
>
> ***§56.101 Scope. (a)***
>
> *… an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration*
>
> ***§56.103 Circumstances in which IRB review is required.***
>
> *(a) …any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.*
>
> *(b) … the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part.*

Informed Consent

FDA regulations require ethical review and informed consent in research involving human subjects:

> ***TITLE 21—Food and Drugs***
>
> ***21 CFR §50.20 General requirements for informed consent***
>
> *Except as provided in §§50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.*

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?

EUA PRODUCTS

Emergency use authorizations are issued under Section 564 of the Food, Drug & Cosmetic Act for medical products that are not approved by FDA or were previously approved for some other, non-emergency use.

Ethical Review

Food, Drug & Cosmetic Act

Section 564 of the Food, Drug & Cosmetic Act does not require any independent ethical review of the emergency use. Instead, it requires the Secretary of Health and Human Services to periodically review emergency authorizations and specifies circumstances under which authorizaiton may be revoked:

> ***§564 (g) Revocation of authorization***
>
> ***(1) Review***
>
> *The Secretary shall periodically review the circumstances and the appropriateness of an authorization under this section.*
>
> ***(2) Revocation***
>
> *The Secretary may revoke an authorization under this section if the criteria under subsection (c) of this section for issuance of such authorization are no longer met or other circumstances make such revocation appropriate to protect the public health or safety.*

Subsection (c) potentially provides protection of patient safety, but it neither requires the Secretary to review the results of the "conditions designed to ensure" that patients are informed, nor, in the event that they are not, does it require the Secretary to address the inadequacies.

> ***§564(c) Criteria for issuance of authorization***
>
> *(1) that an agent specified in a declaration under subsection (b) of this section can cause a serious or life-threatening disease or condition;*
>
> *(2) that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that—*
>
> *(A) the product may be effective in diagnosing, treating, or preventing—*
>
> *(i) such disease or condition; or*
>
> *(ii) a serious or life-threatening disease or condition caused by a product authorized under this section, approved or cleared under this chapter, or licensed under section 262 of title 42, for diagnosing, treating, or preventing such a disease or condition caused by such an agent; and*
>
> *(B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product;*
>
> *(3) that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition; and*
>
> *(4) that such other criteria as the Secretary may by regulation prescribe are satisfied.*

Informed Consent

Section 564 of the Food, Drug & Cosmetic Act requires informed consent for the use products that have been authorized for emergency use:

FD&C Act, §564

(1) Unapproved product

(A) Required conditions

With respect to the emergency use of an unapproved product, 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:

(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.

"Informed"

FDA's EUA guidance, published January 2017, confirms the informed consent requirements in the Act

b. Information for Recipients

Although informed consent as generally required under FDA regulations is not required for administration or use of an EUA product…the statute requires that FDA ensure that recipients are informed to the extent practicable given the applicable circumstances:

- That FDA has authorized emergency use of the product;
- Of the significant known and potential benefits and risks associated with the emergency use of the product, and of the extent to which such benefits and risks are unknown;
- That they have the option to accept or refuse the EUA product and of any consequences of refusing administration of the product;46 and
- Of any available alternatives to the product and of the risks and benefits of available alternatives.

FDA's guidance recommends the submission of a fact sheet that includes the information required under Section 564. It also recommends the inclusion of some additional information:

- Product name and explanation of the intended use of the product;
- A description of the disease/condition;
- A description of items to discuss with a health care provider and adverse event information, including contact information for how to get more information and for reporting adverse reactions; and
- Dosing information (if applicable), including specific instructions for home use or preparation (if applicable).

FDA has posted two-page patient fact sheets for many, but not all, of the products that it has authorized for emergency use. For COVID-19 EUA products, the fact sheets appear to have been prepared from a template, which is apparently provided to manufacturers by FDA.

QUOTE

Section 564 requires patients to be informed that "*the product has been authorized for emergency use*," echoing one of the elements of informed consent found in 21 CFR Part 50, that subjects be informed that "*the study involves research*." The problem with both statements is that patients and subjects don't know what they mean.

Clinical researchers have had 40 years to figure out how to explain "*the study involves research*" to subjects. When it comes to "*the product has been authorized for emergency use*," it's not clear that anyone has yet arrived at the point of thinking that this needs to be figured out.

Much of the language addressing "*the product has been authorized for emergency use*" has been lifted directly from Section 564, which was not written to inform patients of anything, nor is it likely that any effort was made to assure that it was written in language understandable to patients or providers.

In describing EUA, the fact sheets "inform" patients about emergency use authorization by referring to "the totality of scientific evidence available," a phrase lifted directly from the FD&C Act, and otherwise refer vaguely to "certain" criteria, probably raising more questions than they answer.

> *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*

What patients really need to understand about EUA is how it differs from approval and the implications of these differences for what can be reasonably expected in terms of safety and effectiveness.

"Consent"

So far, I haven't found any language in a fact sheet that informs the patient that they have an option to accept or refuse administration of the product. Nor is there anything in the fact sheets I have reviewed to indicate that they are intended to inform patient consent.

Some fact sheets seem clearly intended to be given to patients before use of the EUA product and some to be given to patients after use. In others, the timeframes are ambiguous.

One exception to the requirement for consent is found in a footnote in the FDA guidance:

> …the option to accept or refuse may not be practicable with regard to certain diagnostics because, for example, when a sample is taken from an individual it may be unknown, even to the health care professional, which diagnostic test will be used to test the sample. For this reason, Fact Sheets for both health care professionals and recipients may not accompany an EUA diagnostic product, but instead be publicly posted for reference when receiving test results.

So far, I have not found anything in Section 564 that supports this exception. However, consistent with this footnote, all of the fact sheets for COVID-19 in vitro diagnostic tests are clearly intended to be read by patients ***after*** they have 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].*

The fact that all of these fact sheets begin with this language suggests that "may not" means "shall not," or that someone decided that the option to accept or refuse was not practicable for all COVID-19 tests, regardless of the circumstances under which samples were taken or the test was conducted.

Other fact sheets include language that seems to indicate that the fact sheet might be 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]...

Other fact sheets seem designed to be provided to the patient in advance of intervention, but apparently without the option of consent:

…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]...

I have not yet come across a description of the conditions the Secretary thinks are “appropriately designed to ensure” that individuals administered EUA products are informed per the requirements of Section 564.