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REGULATORY PATHWAYS FOR EMERGENCY USE AUTHORISATION OF VACCINES

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Abstract

Emergency use authorisation allows a vaccine to reach people during a public health emergency before the evidence normally required for full licensure is complete. This review describes the main regulatory pathways that serve that purpose, namely the United States emergency use authorisation under section 564 of the Federal Food, Drug, and Cosmetic Act, European conditional marketing authorisation with rolling review, and the World Health Organization emergency use listing. It compares the evidence standards that regulators applied to efficacy, immune correlates, manufacturing quality and safety follow-up, and it considers post-authorisation obligations. Published sources show broad agreement on principles but differences in legal basis and follow-up. The article reviews published literature and guidance and reports no new data.

1. INTRODUCTION

Ordinary vaccine development is slow by design. A candidate moves through preclinical work, three clinical phases, scale-up and a full dossier review, and the whole journey has traditionally taken ten years or more. An outbreak does not wait. When a new pathogen spreads quickly and kills many people, the question for regulators changes from whether the evidence is complete to whether the evidence is good enough to act on now, given what is known about the disease and the alternatives. Emergency pathways exist to answer that question in a disciplined way. They are not shortcuts around science, although they are

sometimes described that way, and the differences between them reflect the legal systems in which they sit [1, 2, 3]. The tension is old, and it is felt most acutely by the people who have to decide: delay costs lives in one direction, and a rushed decision can cost public trust in the other.

The pandemic of 2020 to 2022 put these pathways to their first large-scale test for vaccines. Within a year of the sequence of the virus being published, several vaccines had shown high efficacy in randomised trials and had been authorised in many countries [4, 5]. That speed rested on parallel activity rather than lowered standards: manufacturing was scaled up at financial risk while trials were running, regulators reviewed data as they arrived, and trial sponsors shared protocols early [3, 6]. Understanding which parts of the process were compressed, and which were kept intact, is the central task of any fair account of emergency authorisation and the reason for the structure of this review. Not every step was compressed equally. The long, quiet work on platform technologies in the preceding decades was probably what made such speed possible at all [7].

2. LEGAL FRAMEWORKS

The United States framework rests on section 564 of the Federal Food, Drug, and Cosmetic Act, as amended by the Project BioShield Act of 2004 and later legislation. After the Secretary of Health and Human Services declares that circumstances justify emergency use, the Food and Drug Administration may authorise an unlicensed product if the disease is serious or life-threatening, if it is reasonable to believe the product may be effective, if the known and potential benefits outweigh the known and potential risks, and if no adequate, approved and available alternative exists [2]. The wording is deliberately lower than the licensure standard of substantial evidence of effectiveness, yet the agency made clear in its guidance for vaccines that it expected randomised, placebo-controlled efficacy data, not immunogenicity alone [1, 8]. Emergency authorisation therefore sits closer to licensure than the name implies, at least for vaccines given to healthy people. The authorisation also carries conditions on fact sheets for recipients and providers [2].

European law took a different route. Rather than creating a separate temporary status, the European Union used a mechanism already on the statute book. Commission Regulation (EC) No 507/2006 allows a conditional marketing authorisation for medicines that meet an unmet need or respond to a public health threat, where the benefit of immediate availability outweighs the risk of less comprehensive data than normal [9]. The authorisation lasts one year and is renewed, and the holder must complete specified studies. The European Medicines Agency added a rolling review, in which sections of the dossier are assessed as they are completed, so that the final opinion could follow within weeks of the last data being submitted [10]. Several COVID-19 vaccines were authorised in this way [10]. Companies can also ask for accelerated assessment, which shortens the review clock, but the rolling approach proved more flexible when data arrived in instalments [10].

The World Health Organization procedure serves a different purpose again. Its emergency use listing assesses quality, safety and efficacy data to decide whether a product can be offered for procurement by United Nations agencies and recommended to countries that lack the regulatory capacity for an independent review [11, 12]. Listing relies heavily on assessments by experienced regulators and on the manufacturer's data, and it feeds into the work of the COVAX facility. The agency also published target product profiles setting out the characteristics, such as efficacy, durability and suitability for low-resource settings, that preferred vaccines should have [13]. Its role is therefore partly regulatory and partly an exercise in setting expectations for developers who need to know what will count as success. Reliance of this kind is useful for ministries of health that would otherwise wait many months for a national review, though it depends on trust in the original assessors [11, 12].

Taken side by side, the pathways show a pattern that is summarised in table 1, with the entries grouped by region and evidence type in fig. 1. All three allow the use of data that would be considered incomplete for ordinary

licensure, all three demand a favourable benefit-risk judgement, and all three carry obligations to keep collecting data. They differ on legal consequence. A United States authorisation is revocable and temporary, a European conditional authorisation is a renewable full marketing authorisation with conditions, and a listing by the World Health Organization informs but does not bind. Each system also differs in who can use the product, who bears liability and how the product is labelled, and these details shaped public understanding as much as the science did [1, 9, 11]. Liability arrangements for vaccine injury, which vary widely, are outside the scope of this review but remain a live policy question in each country.

Beyond the three main systems, national regulators used a range of temporary provisions. Some issued interim orders or temporary authorisations under their own medicines law, while many low- and middle-income countries relied on the assessment of another regulator or on the World Health Organization listing instead of repeating the full review [11, 12]. Reliance is efficient and reasonable when the original review is thorough, but it transfers responsibility for local pharmacovigilance, labelling in local languages and quality monitoring of imported lots to the national authority, which may be thinly resourced. That residual local duty is easily forgotten in discussion of global access [12, 14].

Earlier outbreaks supplied the precedents. The 2009 influenza pandemic led to the rapid licensing or authorisation of monovalent vaccines made on existing platforms, and the West African Ebola epidemic produced a ring vaccination trial in Guinea that provided efficacy evidence for a recombinant vesicular stomatitis virus vector vaccine while the outbreak was still under way [15]. That trial shows that an adaptive design can generate decision-grade evidence in the middle of an emergency. It also shows the limits of emergency work: the epidemic declined before enrolment of some planned groups was finished, and the data that regulators eventually relied on came from a design chosen precisely because a classic placebo trial was impractical [15, 16].

Table 1: Features of emergency pathways and the evidence regulators used for vaccines

Pathway or element	Main feature	Ref.
Emergency use authorisation United States, section 564	Needs an emergency declaration; product may be effective; benefits outweigh risks; no adequate alternative	[1, 2]
FDA efficacy expectation COVID-19 vaccines	Placebo-controlled efficacy with a point estimate of at least 50 per cent and a lower confidence bound above 30 per cent	[8]
FDA safety follow-up COVID-19 vaccines	Median follow-up of at least two months after the full regimen and a large safety database	[1]
Conditional marketing authorisation European Union	Less comprehensive data accepted for unmet need; annual renewal; specific obligations to complete studies	[9, 10]
Rolling review European Medicines Agency	Dossier sections assessed as they arrive, shortening the final opinion	[10]
Emergency use listing World Health Organization	Risk-benefit assessment for procurement and national reliance, not a legal authorisation	[11, 12]
Target product profiles World Health Organization	Preferred characteristics for efficacy, durability, safety and use in low-resource settings	[13]
Main efficacy trials Inactivated, vector and protein vaccines	Large randomised placebo-controlled trials gave the principal efficacy evidence	[4, 5, 17, 18, 19]
Immune correlates Neutralising antibody	Titres predicted protection and supported immunobridging for new groups and variants	[20, 21]
Rare adverse events After rollout	Thrombosis with thrombocytopenia and myocarditis were found through surveillance, not trials	[22, 23, 24]
Passive and active monitoring Post-authorisation	Spontaneous reports, smartphone-based follow-up and registries gave rapid safety signals	[25, 26]

3. EVIDENCE STANDARDS

Efficacy remained the centre of the evidence package. The large trials of authorised vaccines enrolled many thousands of adults, randomised them to vaccine or placebo, and counted symptomatic, laboratory-confirmed

infections as the primary endpoint [4, 5]. Later trials of adenoviral vector and protein vaccines followed a similar template, although they differed in geography and in the circulating variants they met [17, 18, 19]. The Food and Drug Administration's guidance indicated that a point estimate of at least 50 per cent efficacy, with the lower bound of the confidence interval above 30 per cent, would be expected as a minimum [8]. Several products exceeded that figure, which made the regulatory decision easier than it might have been for a weaker candidate [4, 5]. Secondary analyses by age, sex, ethnicity and underlying condition were reported as well, though they were not powered for firm conclusions, and small subgroups need careful reading [4, 5].

How a trial defines its endpoint matters more than headline efficacy suggests. Preventing any symptomatic infection, preventing severe disease and preventing death are different outcomes, and a vaccine may do well on one and poorly on another. Reviews of what makes a vaccine efficacious stress the importance of a clear case definition, adjudication that is blind to treatment, and enough events to estimate effects in key subgroups [27, 28]. Some commentators argued that trials should be designed to detect a worthwhile effect on severe disease, not only on mild infection, because the public health value lies mostly there [28]. Regulators partly accommodated this by asking for severe outcomes as secondary endpoints and monitoring them closely. The distinction was easier to draw in hindsight than in the autumn of 2020, when event counts were still accumulating and interim looks were being planned [27].

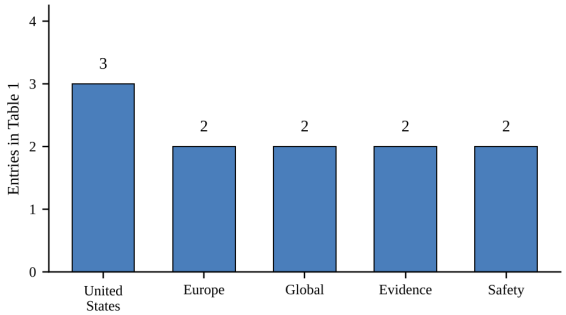


Fig. 1: Number of entries in table 1 by regulatory region or evidence type

Immune correlates of protection were the next problem. A correlate allows efficacy to be inferred from an antibody or cellular measurement, which is useful when a placebo-controlled trial is no longer ethical or practical [29, 30]. For COVID-19, neutralising antibody titres across several vaccine trials were found to be highly predictive of protection from symptomatic infection, and an analysis of one mRNA vaccine trial identified antibody markers associated with risk [20, 21]. This supported immunobridging, in which regulators accept immune response data in adolescents, children or recipients of a booster dose in place of a new efficacy trial. The approach is well established in vaccinology, yet it requires a measurement that is standardised across laboratories, and that was not always the case [29, 30]. A correlate is also not a mechanism. Even a strong statistical association between titre and protection can break down if a variant escapes the antibody being measured [21, 29].

Trial design questions multiplied once vaccines were available. A new candidate cannot ethically be tested against placebo in a population where an effective vaccine exists, so developers turned to active controls and non-inferiority designs, which require careful choice of margin and a defensible estimate of the control's effect [31]. Human challenge studies, in which volunteers are deliberately exposed to the virus, were proposed as a way of speeding evaluation and were debated at length on ethical grounds [16]. Variants complicated matters further, because efficacy against one lineage does not guarantee efficacy against another [32]. Updating vaccine composition, and judging boosters, therefore leaned on immunogenicity, preclinical data and observational effectiveness in a way that earlier trials did not [32, 33]. Regulators therefore asked sponsors to justify the margin in advance and to show that the control vaccine's effect in the new setting was reasonably well known [31, 32]. Design texts treat case ascertainment as seriously as the choice of margin [34].

Dose and schedule decisions drew considerably less public attention than efficacy but were not less important. Phase 1

and 2 studies selected doses by balancing immune response against reactogenicity, and combined phase 2 and 3 designs let sponsors proceed to efficacy testing without a long gap [3, 6]. Regulators later faced questions about intervals between doses, single-dose regimens in places with limited supply, and mixed schedules using different vaccines. These variations were generally supported by immunogenicity and observational data rather than by new randomised efficacy trials, which again places weight on the quality and interpretation of immune measurements [20, 33].

Standard texts on vaccine study design make a point that applies throughout: the same estimate of vaccine efficacy can mean different things depending on how exposure, follow-up time and case ascertainment were handled [34]. Direct protection of the vaccinated individual differs from indirect protection of the population, and waning over time can make an early estimate misleading. These issues are not specific to emergencies, but emergencies sharpen them, since the early data are the only data that regulators have when they decide. Transparent statistical analysis plans, independent data monitoring committees and pre-specified interim analyses were the main safeguards, and regulators publicly reviewed them in advisory committee meetings [8, 34].

4. SAFETY AND QUALITY EXPECTATIONS

Safety expectations were set at a level meant to detect common reactions and the first signs of anything unusual. Guidance for emergency authorisation asked for a median follow-up of at least two months after completion of the vaccination regimen and for a safety database large enough to exclude common serious adverse events [1]. The main trials reported frequent but short-lived local and systemic reactions, such as pain at the injection site, fatigue and fever, and no pattern of serious events attributable to vaccination in the participants followed up [4, 5]. That is reassuring, yet a database of tens of thousands cannot detect events occurring in one per hundred thousand recipients or fewer, and regulators said so openly. Reactogenicity was typically higher in younger adults, and some two-dose regimens produced more reactions after the second dose, a pattern that matters for how recipients are counselled [4, 5].

Rare events surfaced after rollout, as everyone in the field expected. Thrombosis with thrombocytopenia was described after adenoviral vector vaccines, with a mechanism resembling immune heparin-induced thrombocytopenia, and case series led to pauses and revised recommendations in several countries [22, 23]. Myocarditis and pericarditis were identified after mRNA vaccination, mostly in younger males after the second dose, and the absolute risk was small, and advisory groups weighed it against the benefit of vaccination [24]. These signals were found through spontaneous reporting and active surveillance rather than through trials, and they illustrate why emergency authorisation depends on a working pharmacovigilance system as much as on the original dossier [25, 26]. Public explanation was a difficulty in itself, since a rare risk announced by a regulator can be misread as a new and general danger unless the numbers are given in context [23, 24].

Interpreting signals requires background rates. During mass immunisation, many people will experience illnesses by coincidence soon after vaccination, and without knowing how often such events occur normally, causal inference is impossible [35]. The 1976 swine influenza programme in the United States is the standard cautionary tale: an excess of Guillain-Barré syndrome was detected in vaccinated people, and the programme was halted [36]. The lesson drawn by later planners was to prepare surveillance systems, case definitions and background incidence tables before the emergency arrives. Standard case definitions from the Brighton Collaboration, together with guidance on vaccine pharmacovigilance terminology, now give regulators a common language for these analyses [37, 38]. Case definitions also need to be settled before the data are collected, or reports from different countries cannot be pooled.

Quality and manufacturing evidence is often overlooked in public discussion, yet it can be the rate-limiting part of an emergency review. A new platform such as

lipid-nanoparticle-encapsulated messenger RNA raises specific questions about the identity and integrity of the nucleic acid, the characterisation of lipid components, and consistency between clinical and commercial batches, and the World Health Organization published regulatory considerations for such vaccines [39]. Regulators generally accepted less process validation data than in a standard filing, but they required evidence of comparability between lots used in trials and lots supplied commercially, adequate stability data and a plan to complete the remaining characterisation. Cold-chain requirements added a further practical burden [3, 39]. Reviewers asked for shelf-life claims to be limited to the data on hand and extended later as longer-term results came in [1, 39]. Stability data are particularly telling for a product stored at very low temperature, where a short excursion can matter.

Nonclinical data receive less attention than clinical results, but they carry weight with reviewers. Toxicology studies in animals, including repeat-dose and developmental and reproductive studies, are expected to be available before large-scale human use, and regulatory considerations for mRNA vaccines describe what should be covered for a platform product with novel lipid components [39]. Early in the pandemic, developmental toxicity results were still pending when trials began, and pregnant women were excluded from the main studies as a result. Data from animals and later from observational cohorts filled that gap over time, though not before many pregnant people had faced difficult decisions with limited guidance [12, 39].

Supply and access sit awkwardly alongside the technical assessment, yet they shape its consequences. Authorisation in a handful of rich countries does not protect people elsewhere, and analyses of global access identified production capacity, pricing, allocation and deployment as the four problems that determined who was actually vaccinated and when [14]. The World Health Organization listing was designed partly to ease that problem by providing a single assessment that national authorities could rely on, and its guidance on clinical evaluation sets regulatory expectations that developers in many countries can use [12]. Even so, the gap between authorisation and delivery remained large, and it is difficult to argue that regulation alone could have closed it [11, 14].

5. POST-AUTHORISATION OBLIGATIONS

Once a vaccine is authorised, the regulatory task changes. Sponsors are expected to continue the main trials in blinded follow-up for as long as ethically possible, to submit periodic safety updates, and to run risk management activities that match the specific concerns identified. In the United States the agency also relied on passive reporting through the Vaccine Adverse Event Reporting System and on smartphone-based active monitoring in the weeks after vaccination, which together produced a large early picture of reactogenicity [15, 25, 26]. The European system used risk management plans, periodic safety reports and a dedicated committee to evaluate emerging signals. In both settings, the data after authorisation were far larger than the trial data [10, 26]. Unblinding was a genuine dilemma: once an effective vaccine was authorised, trial participants on placebo understandably wanted it, and sponsors had to offer crossover without wasting the remaining controlled data [28, 31].

Passive reporting systems have well-known limits. They capture only a fraction of events, reporting is influenced by publicity, and the denominator of vaccinated people is not part of the system, so rates cannot be calculated directly from reports alone [26]. Their strength is early detection of unexpected patterns. Active surveillance, using linked electronic health records and vaccination registries, gives incidence figures and allows comparison of observed and expected events. Surveillance manuals produced by international bodies emphasise investigation of individual reports, classification by causality and communication of findings to the public, which is as much a part of safety work as the statistics are [37, 40]. Public trust depends on clear explanation of what is known and unknown. Linkage between vaccination registries and hospital records proved the most informative source for estimating effectiveness in routine use [40].

Differences in coding between countries limit direct comparison.

The closing of the emergency period raises a regulatory question that is easy to underestimate. Products authorised under emergency provisions need a route to full licensure if they are to stay on the market, and the sponsor must supply the data that were incomplete at authorisation, including longer follow-up, lot consistency and effectiveness estimates [1, 2]. Conditional authorisations in Europe convert to standard authorisations when conditions are met, while the listing by the World Health Organization is withdrawn or maintained according to its own review [9, 11]. Several vaccines moved to full approval after a period of use, and the evidence gathered in routine use contributed to those decisions in a way that no trial could have done. Labels may also change after authorisation, with new warnings added for rare adverse events as evidence builds and fact sheets updated accordingly [2, 22].

Authorisation and recommendation are separate decisions, and conflating them causes confusion. A regulator decides whether a product meets the legal standard for use, usually after hearing from an independent advisory committee, while a separate body, such as the Advisory Committee on Immunization Practices in the United States, advises who should receive it, in what order and at what interval [1]. This division means that a product can be authorised for a wide group and recommended for a narrower one, as happened when risks of rare events differed by age and sex. Pharmacists and clinicians who explain these decisions to patients should be clear about which of the two a particular statement concerns [2].

Updating a vaccine to match circulating variants shows how far the regulatory logic has moved. When the target changes, regulators generally do not ask for a full efficacy trial. Instead, immunogenicity against the new variant, safety data from a limited clinical study, and manufacturing comparability take centre stage, in the way that seasonal influenza vaccines are updated each year without repeating main trials [29, 32, 33]. This approach is efficient, but it depends on the credibility of the immune measurements, and it makes the correlate work discussed above increasingly important. Whether the model can be applied to a pathogen that evolves faster or more unpredictably than influenza remains unresolved, and opinions among experts differ [20, 33].

6. GAPS AND PRACTICE IMPLICATIONS

Several weaknesses remain in the way emergency pathways are described and used. The legal thresholds are broad, and the main safeguard against their misuse is the judgement of expert reviewers rather than a numerical rule, so public confidence depends on the transparency of review documents and advisory meetings [1, 2]. Harmonisation across regions is incomplete, which led to mismatches in dosing schedules, approved age groups and acceptable evidence for boosters. Evidence for pregnant women, immunocompromised people and young children usually arrived later than for healthy adults, because these groups were excluded from the main trials, and regulators therefore authorised use before the data for these groups were complete [12, 32]. Transparency has improved, with review documents and meeting recordings published, but comprehension of these materials by the public is a different matter [2, 14]. Wider sharing of raw trial data would help independent groups check the conclusions drawn.

Information given to recipients is a regulatory product in its own right. Under the United States framework, authorised vaccines must be accompanied by fact sheets for providers and recipients that state the emergency status, describe known risks and benefits, and explain that the choice to be vaccinated is voluntary [1, 2]. Those documents were revised repeatedly as new safety information emerged. Their value depends on being readable and accurate, and on reaching the person being vaccinated before the injection and not after it. Studies of public understanding were limited, so how well the materials achieved their purpose is largely unmeasured, and it would be a sensible target for evaluation during future emergencies.

For pharmacists, regulatory scientists and public health professionals, the practical points are fairly concrete. Know the legal status of each product handled, since an emergency authorisation carries conditions about labelling, fact sheets and reporting that differ from a licensed vaccine. Learn the reporting channels for adverse events and use them. Be ready to explain to patients that authorisation under emergency rules still required randomised efficacy evidence and a defined benefit-risk judgement [1, 4, 5]. Hospital and community pharmacy teams also carry responsibility for storage, handling and traceability, which the quality guidance emphasises, and these functions cannot be improvised once supply arrives [3, 39]. A written local procedure for receiving, documenting and escalating a suspected reaction is a good start.

Looking ahead, three directions seem most useful. The first is to prepare platform-based regulatory dossiers and template protocols in advance, as planners have urged since the outbreaks of the last two decades, so that the next emergency starts from a ready framework instead of a blank page [3, 7]. The second is to invest in standardised assays and shared reference materials so that correlates of protection can be used with confidence across laboratories [20, 21, 30]. The third is to link authorisation decisions to equitable access commitments from the start, because a regulatory success that does not reach people at risk is only a partial success [13, 14]. None of this is simple, but all of it is within reach. Funding agencies could support these steps cheaply compared with the cost of failure [3, 7].

7. CONCLUSION

Emergency pathways for vaccines share a core logic: a serious threat, a favourable but provisional benefit-risk judgement, and a commitment to keep collecting data. The legal routes differ, as table 1 and fig. 1 show, but the evidence expected in practice converged on randomised efficacy trials, careful quality characterisation and an active safety system [1, 8, 9, 11]. The COVID-19 experience showed that these requirements could be met quickly when development steps ran in parallel and regulators reviewed data as they arrived [3, 4, 5, 6]. Speed came from running steps in parallel and sharing information early, not from skipping them.

The weaker points are the ones this review has stressed. Immune correlates need standard assays, evidence for special populations lags behind that for healthy adults, and access depends on factors that regulators do not control [14, 20, 21]. Readers should treat emergency authorisation as a defined and accountable process, not as a lowering of standards, and should expect transparent post-authorisation reporting from all parties [2, 25, 26]. Preparation made before the next emergency will matter more than any improvisation made during it [7, 13]. The next emergency will not be identical, so flexibility inside a clear framework is worth protecting.

8. ABBREVIATIONS

EUA-Emergency use authorisation, EUL-Emergency use listing, CMA-Conditional marketing authorisation, FDA-Food and Drug Administration, EMA-European Medicines Agency, WHO-World Health Organization, mRNA-Messenger ribonucleic acid, VAERS-Vaccine Adverse Event Reporting System, TTS-Thrombosis with thrombocytopenia syndrome, COVAX-COVID-19 Vaccines Global Access facility, CI-Confidence interval

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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