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Acceleration of new medicines–CMC lessons learned from emergency use authorizations

James Bernstein[1], Kim Huynh-Ba[2], Patrick Lynch[3], Thomas Oliver[4], Reza Oliyai[5], Scott W. Roberts[6*], Andrea Schirmer[7], David Schwinke[8], Kin Tang[9] and Jessica Ursin[9]

Abstract

The American Association of Pharmaceutical Scientists (AAPS) Chemistry, Manufacturing, and Control (CMC) Community hosted a virtual panel discussion on July 15, 2022, to provide a forum to discuss industry and regulator CMC challenges associated with emergency use authorizations.

Keywords Emergency use authorization, Accelerated regulatory pathways, Chemistry, Manufacturing, and Controls, COVID-19

Introduction

Expedited regulatory pathways are a rapidly evolving landscape leading to faster development, review, and approval of new medicines treating serious disease. Expedited regulatory pathways currently exist in the United States (US), European Union (EU), Switzerland, Canada, Australia, South Korea, United Kingdom, China, and many emerging markets. The US Food and Drug Administration (FDA) has developed multiple programs to making drugs and biologics available as rapidly as possible, including priority review, fast track, and breakthrough therapy designation process as well as the accelerated approval pathway (US Food and Drug Administration, Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review n.d.). Key elements of these approaches include shorter review times, approvals based upon the use of "surrogate or intermediate clinical endpoints," frequent FDA meetings, and senior FDA leadership support.

In addition to the expedited regulatory approaches described above, additional authority has been granted to the FDA to assure national preparedness for public health, military, and domestic emergencies involving chemical, biological, radiological, and nuclear agents as well as including emerging infectious disease threats. In 2004, the United States Congress passed the Project BioShield Act which granted FDA the power to authorize drugs, devices, diagnostics, and other medical products not previously approved, cleared or licensed to be used in well-defined, declared emergencies (US Food and Drug Administration MCM-Related Counterterrorism n.d.). In 2005, the Public Readiness and Emergency Preparedness (PREP) Act added liability protection from tort liability to incentivize sector development of medical countermeasures. In 2013, the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA)

*Correspondence:
Scott W. Roberts
OSRB@novonordisk.com
[1] Live Oak Pharmaceutical Consulting, Inc., Raleigh, NC, USA
[2] Pharmalytik Consulting, LLC, Newark, DE, USA
[3] Division of Biotechnology Review and Research II, Office of Biotechnology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA
[4] Division of New Drug Products I, Office of New Drug Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA
[5] Gilead Sciences, Inc., Foster City, CA 94404, USA
[6] Novo Nordisk A/S, Søborg, Denmark
[7] Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA
[8] AbbVie Inc., North Chicago, IL, USA
[9] Genentech, Inc., South San Francisco, CA, USA

amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to permit the Commissioner to authorize the emergency use of an unapproved medical product or an unapproved use of an approved medical product for certain emergency circumstances (US Department of Health and Human Services 2017). In 2022, the Food and Drug Omnibus Reform Act (FDORA) included provisions related to accelerated approval. Section 3210 of FDORA, "Modernizing Accelerated Approval," includes the following: (a) FDA may require sponsors to specify conditions for post-approval trials no later than the date of accelerated approval, and if the agency does not require that the sponsor of a drug or biologic approved under accelerated approval conduct a post-approval trial, FDA must publish on its website the rationale for why such trial is not appropriate or necessary, (b) no later than the date of accelerated approval, FDA must specify the conditions for a post-approval trial or trials required to be conducted with respect to such drug or biologic, which may include enrolment targets, the trial protocol and milestones, including the target date of trial completion, (c) Accelerated approval sponsors must submit progress reports every six months on required post-approval trials, (d) sponsors retain certain rights prior to any withdrawal of accelerated approval, including the opportunity to appeal, and providing an opportunity for public comment on the proposed withdrawal, (e) within one year of the bill's enactment, HHS must establish an Accelerated Approval Council, comprised of more than ten directors of various offices within FDA, to ensure consistent and appropriate use of the accelerated approval process.

While an investigational new drug (IND) is the typical regulatory pathway toward a marketing application, expanded access INDs and emergency use authorizations (EUAs) offer additional regulatory mechanisms to enable access to investigational products. The FDA may permit unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, and nuclear threat agents as well as emerging infectious disease threats, when there are no adequate, approved, and available alternatives. The criteria for authorization of a drug EUA includes the following:

1. Serious or life-threatening disease or condition
2. Evidence of effectiveness (a "may be effective" standard vs. "effectiveness standard")
3. No adequate, approved, or available alternatives
4. Risk-benefit analysis

Regarding the evidence of effectiveness, medical products considered for EUA are those that "may be effective" and thus provides for a lower level of evidence than the "effectiveness" standard that the FDA typically uses for standard approvals. However, patient safety remains a critical consideration of the risk-benefit assessment and additionally establishes the content of an EUA dossier from a CMC perspective.

Emergency use authorization of a drug product is communicated via a publicly available letter of authorization (LOA), but it is critical to note that authorization of a EUA drug does not mean that the drug is approved, and the FDA may revise or revoke an EUA if the circumstances justifying issuance no longer exist. Additional conditions of authorization include (a) information relating to an EUA product, (b) monitoring and reporting of adverse events, (c) records, and (d) waivers or limitations of compliance with other requirements (including CGMPs) (US Department of Health and Human Services 2017).

This meeting report provides a summary of discussions from the AAPS Chemistry, Manufacturing, and Controls (CMC) Regulatory Exchange Forum Virtual Panel Discussion focusing on the CMC challenges associated with products authorized by an EUA held on July 15, 2022. The session featured a speaker panel comprised of industry and FDA expert speakers who provided their insight and perspectives regarding two case studies of drugs authorized by EUAs to treat COVID-19 during the pandemic, including Regeneron/Roche's REGEN-COV®/Ronapreve® (casirivimab and imdevimab) and Gilead Sciences' Veklury® (remdesivir). Although the discussion focused on the US EUA process, insights were also provided on global considerations/pathways based on the case studies.

Virtual panel introduction and overview

An introduction was provided by Kin Tang, Thomas Oliver, Jessica Ursin, and Reza Oliyai. The team presented and discussed (a) accelerated regulatory pathways, (b) establishment and authorization criteria of the FDA's EUA, (c) global EUA considerations, and (d) the development and regulatory strategies supporting the emergency use authorization and supply for Ronapreve® and Veklury®, two medicinal products used to treat COVID-19 during the pandemic. Ronapreve® consists of the two monoclonal antibodies casirivimab and imdevimab that are mixed together and administered as an infusion or subcutaneous injection. Veklury® is a synthetic nucleotide analogue prodrug administered by injection.

The development, manufacture, and supply of treatments for emergency use (for example, during a pandemic) is a major challenge for both industry and regulators due to demands for resources, speed, and differing requirements across the global regulatory

landscape. There is currently a limited number of regulatory pathways to allow for the import and distribution of unapproved medical products by governments, including established EUA-type pathways (e.g., Canada Interim Order, Singapore Pandemic Special Access Route, and Brazil EUA for vaccines) or regulations allowing for importation during an emergency. Although EUA is the specific term used within the US, for the remainder of this publication EUA will be used as a general term to describe any pathway used to receive authorization for emergency use of an unapproved medical product prior to obtaining full approval. From a CMC perspective, some countries (e.g., US and EU) requested whatever data was available and the regulators focused their assessments on safety and efficacy, while many other countries requested full marketing authorization application (MAA) level content as the initial package. Health authority (HA) interactions included (a) increased informal HA interactions, (b) close collaboration and transparency, and (c) a unique focus on drug supply. Generally shorter review times were observed, ranging from a few days to a few months depending on the country. Review questions ranged from (a) no questions, to (b) very few questions, to (c) MAA level of questions which resulted in commitments to be resolved under the emergency use pathway or later in the MAA. Without defined EUA-type pathways, other regulatory challenges include:

- How the application is filed (submissions varied from an informal email to a formal MAA regulatory pathway)
- How to manage changes after authorization (e.g., no submission, notification, submission of additional supportive data, etc.)
- How often to update the EUA dossier as data becomes available (or wait for the MAA to provide additional data)

The case study and panel discussion of Ronapreve® focused on the global emergency use strategy, which was under Roche's responsibility, with innovator Regeneron responsible for the US EUA. The Ronapreve® global emergency use CMC package was prepared with all available information, resulting in CTD Module 3 content that could be considered between a pivotal clinical trial application (CTA) and MAA, as described below:

- MAA level content was provided when available
- More limited data was provided where activities were ongoing (e.g., method validation, process validation, comparability, etc.)
- Wider specifications were adopted (limits closer to a pivotal clinical specification than a commercial specification)
- A strong focus on safety-related aspects of the dossier was maintained
- One global product label in English only was provided with no country specific modifications unless they could be managed within the country.

The Ronapreve® global emergency use CMC package was updated as a one-time event after completion of the majority of activities and to reflect the level of content of an MAA with the exception of updating the label and specifications. Additional strategies and considerations for accelerated development in the emergency use setting include:

- Risk-benefit analysis is different in a pandemic setting and is key
- Remove barriers and accelerate development without sacrificing quality or safety
- Accelerate tech transfers to already commercially registered facilities for scale up, use existing processes where possible
- Leverage prior knowledge and protocols
- Assess limits (such as utilizing predictive stability modeling for a large molecule as supportive data for establishing shelf life, if sufficiently justified)
- Managing potential raw material shortages
- Path of communication for post-authorization changes
- Timely and transparent communication within organization and with HAs on what will be available at what time
- Leverage reliance pathways/reference countries
- Plan for transition from EUA to MAA
- Even in a pandemic, expectations for the marketing application were generally the same

In the case study of Gilead's Veklury®, the project went from Phase 1b to NDA approval in 9 months. The US Centers for Disease Control and Prevention (CDC) confirmed the first US coronavirus case in January 21, 2020. Veklury® received FDA EUA by May 1, 2020. At that point, the CMC content for the EUA was at the IND level. The New Drug Application (NDA) was submitted to the FDA on August 7, 2020, and Veklury® received FDA approval on October 22, 2020. Thus, within the span of less than 1 year, Gilead and FDA had worked closely together to complete process validation, submitted and approved multiple regulatory packages, and executed the technology transfer to 3 drug substance manufacturing sites and 8 drug product manufacturing sites. Production

was increased from an approximate initial supply of 50,000 vials to more than 10 million vials manufactured upon NDA approval. As demonstrated by the two case studies, close collaboration between sponsor companies, FDA, and other global agencies was key to success.

Virtual panel discussion

Following the introduction, FDA and industry expert panelists participated in a panel discussion. The panelists included Thomas Oliver, Patrick Lynch, Reza Oliyai, and Jessica Ursin. Kin Tang and James Bernstein moderated the panel discussion. Andrea Schirmer, David Schwinke, and Scott Roberts captured meeting minutes. Kin Tang was the AAPS lead organizer of the event and Kim Huynh-Ba provided meeting support. The key topic areas for the panel discussion included:

- Overview of the EUA and how it differs from regular drug approval pathways
- Industry and FDA CMC experiences with EUAs
- What learnings and opportunities were identified from EUAs that could be applied to accelerating medicines for patients with unmet medical needs

Knowledge sharing

What challenges did you face with respect to CMC development, manufacturing, and launch and how were these overcome?

Veklury® went from phase 1b to approval in 9 months which was a significant challenge. Additionally, the manufacturing lead time for product was shortened from 12 months to 6 months by the time of product launch based on this accelerated development program. There were many countries involved and each sought supply security which led to multiple manufacturing sites in different countries. FDA was instrumental to providing input to strategy with weekly or biweekly meetings held to share strategy for manufacturing and supply. There was no forecast other than to manufacture as much as possible.

For Ronapreve®, there were similar challenges translated into the context of large molecule drug development. Scale-up, technology transfer, and process validation were expedited. Prior knowledge and platform technology considerations were leveraged with justification. While the EUA offered flexibility, quality expectations remained at an MAA level. Flexibility was given for the assessment of shelf life based on prior knowledge, extrapolation, and predictive stability modeling, which is a newer concept for large molecules and could be an area that is explored in future submissions and/or guidance. However, in this example, global regulatory acceptance of statistical modeling to support shelf life was challenging and some countries indicated that acceptance was limited to the emergency use setting.

From a regulator's perspective, there were five main challenges regarding Veklury®: (1) the scale and introduction of new sites and manufacturing lines, (2) the accelerated pathway with simultaneous management of the EUA and NDA, (3) the identification/management of post-marketing commitments (for NDA), (4) the management of a world-wide product (labeling), and (5) human challenges due to the pandemic, including workload and new work settings and processes. For Ronapreve®, the assessment of stability data for an accelerated program was novel for a large molecule drug and there was limited experience with extrapolation. Thus, novel ways for establishing shelf life were needed and new approaches included (a) previous knowledge, (b) use of accelerated stability studies, and (c) leveraging platform technology knowledge (e.g., monoclonal antibodies and stability indicating attributes). The use of these new approaches toward modeling and platform technology was assessed and combined with risk mitigation strategies. For example, data were reviewed as soon as it became available and the real time stability data supported these novel approaches.

As a follow-up question (for industry), how did you stage interaction with agencies to incorporate multiple sites?

For Veklury®, there was a wide network of manufacturing sites. Gilead worked with FDA by reviewing quality data (e.g., container closure, process validation, sterility, etc.) to focus on sites that would be ready in time for the NDA. Manufacturing sites were evaluated and implemented based upon production capacity availability and discussions with FDA. For Ronapreve®, the number of manufacturing sites were limited for the EUA with additional sites added in the marketing application including production sites that differed from the clinical sites. Ultimately, the global marketing application included 2 drug substance and 2 drug product manufacturing sites.

As a follow-up question–regarding the monoclonal antibody platform data–did this include stability data from other mAbs?

Yes, extensive prior knowledge and experience with monoclonal antibodies helped support understanding of what to be aware of (e.g., stability indicating or shelf life limiting attributes). This insight was leveraged in the overall risk-benefit analysis.

As a follow-up question, what do wish you knew before going into this process?

From an industry-sponsor perspective, it was expected to be difficult, intense, and demanded a significant amount of resources, especially with a lack of understanding of the regulatory environment both in the US and outside of the US. The quality expectations were difficult to address given the regulatory expectations and speed of development. Both companies had previous experience with accelerated development and fast-paced submissions. Oncology products require speed, and FDA is comfortable with the activity, but the expansion of manufacturing where the patient population was the entire United States (and with knowledge that the rest of the world also needed to be supplied) was huge in scope and at an unprecedent scale.

How did you manage sponsor-health authority interactions, while also managing the demands for timely submission and review of investigational applications and EUAs?

From a regulator's perspective, traditional interactions would have been difficult. Close interactions and weekly meetings between Gilead and the FDA's Office of Pharmaceutical Quality team were critical. Concerns were discussed with the applicant followed by the issuance of information requests (IRs), or sometimes the issues were resolved during the meeting. The sponsor-agency meetings were always documented. The EUA and registration process required a close working collaboration, and critical decisions/discussions were made with confidence and transparency from each side. This collaboration continued through the registration phase. Within the FDA, there was an enhanced, multi-disciplinary approach toward internal communications with appropriate leadership involvement. However, the COVID-19 Public Health Emergency involved unique circumstances, and a significant number of resources were needed which caused a strain on other programs.

From an industry perspective, most of the global interactions were informal with a few exceptions (e.g., scientific advice with EMA). Pre-submission agreements were critical to ensure alignment of expectations between the sponsor and regulators. There were a lot of resources needed to concurrently manage and accomplish health authority interactions, the EUA filings, and MAA submissions, while still accomplishing process performance qualifications and other studies. Transparency was critical, and significant resources were needed to manage parallel activities. Sometimes knowing what not to do was just as important as knowing what to do. Finally, incorporating good science and generating high quality data was also a key factor.

Can you describe post approval management within the context of the EUA?

As a reminder, an EUA in the US is not an approval; a sponsor must still submit an NDA/BLA for approval. Thus, an EUA does not have post-marketing commitments (PMCs). PMCs were associated with assessment of the NDA or BLA, and this process was streamlined by having both the pre-and post-marketing NDA Product Quality assessment teams attending the NDA Quality meetings. As a result, the post-marketing Product Quality assessment team was aware of numerous supplements that would be forthcoming after the approval of the NDA because they were involved in the NDA review. Amendments to the EUA were managed similar to the way supplements are managed. From the global perspective, changes to emergency use applications were minimized. Changes were submitted via the available pathway (e.g., by email or through a defined pathway), often as noted in agreements with the health authorities.

To follow-up with industry, what shelf life were you able to accomplish under the EUA?

For Veklury®, a minimum shelf life of 12 months was established for the liquid product. A shelf life of 24 months was established for the lyophilized product which was extended to 36 months (post-approval). Stability packages for additional sites were often submitted post approval on a site-by-site basis. For Ronapreve®, predictive stability modeling was used to support shelf-life determination beyond the available long term stability data. The emergency use application had less than 12 months data, and a 24-month shelf life was proposed. The majority of countries accepted this approach, with all countries authorizing a minimum of 12 months as required for supply. Of note, EMA agreed to the use of stability modeling in the marketing application but noted that outside of a pandemic setting, compliance with ICH is expected. From a regulatory perspective, it would be good to see guidance generated considering the opportunities with extrapolation and modeling, especially with the upcoming revisions to the ICH stability guidelines. There were also some flexible approaches to extending the shelf life during the EUA to avoid wastage of product.

How does an application under an EUA compare and contrast to a traditional IND or NDA/BLA? Rolling review? How does an EUA in the US compare and contrast to analogous regulatory mechanisms in other countries and regions?

The management of the EUA is dependent on the level of experience with the product. There can be some manufacturing experience (e.g., for another indication), or it

could be similar to initiating an IND. For Veklury®, the EUA was commensurate with IND level document. The NDA was put together in close collaboration with FDA. Stability topics and new sites were added under post marketing commitments. Quality was never compromised, but strategies were explored to get the product to patients in the shortest timeframe possible. A rolling review was used for the NDA. The CMC sections (except stability) were submitted first, and the clinical part was submitted last. FDA IRs were issued and new information was submitted to the NDA along with the responses to IRs. For Ronapreve®, a rolling review was performed for the marketing application in the US application as well as in other countries. It was complicated for both the applicant and assessors. Outside of the US, there are very few defined emergency use pathways as previously discussed. As an example, EMA does not have a regulatory mechanism to authorize a product under emergency use for all of the EU. Under Article 5(3), EMA could review the available data and provide an opinion that the product was safe and effective which could then be referred to by EU member states. Applications for emergency use were then submitted to each individual country for authorization.

FDA preferred the rolling submission strategy, and IRs were also communicated in support of the submission. Meetings were scheduled prior to the issuance of IRs and responses were negotiated during the meetings based on available data. It facilitated the preparation of responses so that they could address the comments. For Veklury®, 64 IRs were issued during the review of the NDA.

How were mutual recognition, regulatory reliance, and regulatory collaboration leveraged to speed up the availability of emergency treatments to patients around the world? Which of these do you see promise for in the future of non-EUA expedited development settings?

From a regulator's perspective, supply and distribution issues were critical. Gilead wanted labeling that could meet global supply demands. Thus, flexibility was given to accomplish a more universal storage statement. Mutual recognition for inspection was utilized to maintain adequate coverage of manufacturing sites around the world so that resources could be focused to areas where they were needed.

From the industry sponsor perspective, there were no defined collaborative review processes; however, authorization letters and declarations were used to accelerate emergency use authorizations for several countries. For marketing registrations, mutual recognition pathways were utilized and authorization letters were leveraged to accelerate approvals. There were fewer questions from health authorities when the mutual recognition pathways were utilized. In the EU, use of the "Irish Pack" configuration (all English language labeling) was authorized for distribution for the first 12 months in order to avoid potential supply constraints due to country-specific labeling.

From the learnings from the strategies and workflow that were applied to EUA, what should be considered for non-EUA expedited development? What would not work well in non-EUA settings?

From an industry sponsor perspective, focus on high quality science and data is critical. Engagement with the health authorities with the objective of getting the medicine to patients as quickly as possible is also important. The biggest learnings are that (a) context and planning is important in the regulatory strategy, (b) aligned planning with the Agency on the content of the initial submission and where needed, later submission of data either during assessment or after initial authorization or approval, (c) understanding the risk vs. benefit of product, indication, and development strategies, (d) leveraging prior knowledge with appropriate justification to allow flexibility, and (e) transparency with HAs builds trust and partnership.

From a regulator's perspective, a lot was accomplished with high resourcing. Transparency was key as the FDA has a role to communicate clearly what the concerns are and be open to information/data which may lower these concerns. It is important to build relationships between sponsor companies and HAs.

Conclusions

As demonstrated by the open dialogue between the industry and FDA experts during the panel discussion, effective and transparent communication was critical toward building the trust needed to support the expedited CMC development and launch timelines for Ronapreve® and Veklury® during the COVID-19 pandemic. Both case studies exemplified a scientifically driven, risk-based approach toward successfully managing challenging production timelines and targets, complex contract manufacturing and testing networks, and limited stability data while maintaining product quality and speed in providing drugs to patients.

Authors' contributions

The panel discussion was designed and executed by James Bernstein, Kim Huynh-Ba, Patrick Lynch, Thomas Oliver, Reza Oliyai, Andrea Schirmer, David Schwinkle, Kin Tang, and Jessica Ursin. Meeting minutes were taken by Scott Roberts, Andrea Schrimer, and David Schwinkle. The manuscript was prepared by Scott Roberts. All authors provided final review and approval. Reza Oliyai was employed by Gilead Sciences at the time of this

panel discussion. However, his current author details include: Oliyai Consulting Corporation, Atherton, California, USA.

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