Expediting Patient Access to Products Developed for Serious or Life-Threatening Diseases: Making the Case for a Conditional Use Authorization Pathway

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1. INTRODUCTION

Stakeholders continually challenge the US Food and Drug Administration (FDA) to develop and deploy regulatory tools that hasten access to new products intended for treatment of serious or life-threatening diseases and conditions. Recently, the call for FDA to adopt a more flexible approach to the evaluation and approval of this category of products has intensified. This is particularly the case for cell and gene therapy (CGT) products which have the potential to provide curative treatments. Collaterally, Congress has been prompted to propose legislation that would codify a conditional approval pathway for products developed to treat serious or life-threatening diseases. Most recently, the FDA Commissioner has put forward a new Commissioner's National Priority Voucher pilot program for products being developed that address U.S. national priorities, which is designed to align speed of product review with gold-standard science.[1,2]

At present, the primary regulatory tools facilitating expedited patient access to products intended to treat serious or life-threatening diseases are "accelerated approval" and "priority review." Priority review provides limited time savings as it is performed at the time a marketing application is reviewed, i.e., not until the final stage of product development. Accelerated approval is a pathway intended to realize earlier approval and access to drugs and biologics that treat serious or life-threatening diseases as well as fill an

unmet medical need. Accelerated approval decisions are based on the sensitivity of a surrogate endpoint marker(s) believed to predict clinical benefit but which are not themselves an actual measure of clinical benefit. Conceptually developed during the AIDS crisis, accelerated approval has proven to be valuable in the oncology disease space. With expanded application to a broader portfolio of clinical indications, difficulties have been encountered that portend to limit the overall utility of accelerated approval, including standards of evidence necessary to support approval based on the surrogate endpoint(s), failure of sponsors to conduct required confirmatory trials post-approval that verify product efficacy, and growing concern about steep reimbursement costs for products lacking confirmed efficacy demonstration. Notably, it has been suggested by former senior FDA officials that accelerated approval may be ill-suited as an approach for getting new CGT products to patients in an expedited manner, especially in the context of rare diseases, and that development of alternative pathways underlying patient accessibility to new products is to be encouraged.

A regulatory tool that is at FDA's disposal is granting authorized use for unapproved products. During the COVID-19 pandemic, FDA effectively used its emergency use authorization authority to get unapproved products into the hands of physicians, patients, and caregivers. Product use authorization does not constitute approval and is rescinded when the conditions for granting the authorization cease to exist.

Against this backdrop, I propose that a conditional use authorization (CUA) pathway can be adopted by the agency as a mechanism for expediting patient access to promising innovative products, including CGTs, intended for treating serious and rare diseases. Eligibility for the proposed CUA pathway is to be limited to products intended to treat diseases outlined in the congressional conditional approval legislation. In its particulars, as described in this article, CUA for an investigational product is based on clinical demonstration of patient safety and evidence of substantial improvement on clinically significant endpoint(s) over what is observed for available therapies, is time-constrained in terms of its duration, and allows for cost-contained reimbursement which will enable sustained development towards product approval.

2. CURRENT EXPEDITED PATHWAY DESIGNATIONS

Regulatory authorities across the globe have engineered their drug approval frameworks to incorporate approaches for making drug products available in an expedited manner to patients suffering from serious or life-threatening diseases for which no suitable treatment option is available. Examples of expedited, non-standard approvals include Conditional Marketing Authorization (European Union, European Medicines Authority), Notice of Compliance with Conditions (Canada, Health Canada), Conditional Approval (Korea, Ministry for Food and Drug Safety; Japan, Pharmaceuticals and Medical Devices Agency), Provisional Approval Pathway (Australia, Therapeutic Goods Administration), and Accelerated Approval (United States, Food and Drug Administration).

The US Food and Drug Administration (FDA) provides guidance to sponsors engaged in development of candidate products intended to treat serious or life-threatening conditions that outlines recommendations pertaining to the expedited development and review of these potential therapies.[3,4] Investigational drug and biologic products that are being developed to treat, modify, reverse, or cure serious or life-threatening conditions may be eligible for one or more of the FDA expedited programs, including fast track designation, breakthrough therapy designation, Regenerative Medicine Advanced Therapy (RMAT)

designation (restricted to cell and gene-based products), accelerated approval, and priority review designation, presuming they meet eligibility criteria for the various programs.

Of the expedited programs referenced, accelerated approval and priority review designation are the two options likely to result in a shortened timeline for drug approval. Fast track, breakthrough, and RMAT designations are intended to provide advantages that may facilitate development during the investigational phase of clinical development and could result in an earlier time to submission of a license application for product approval. Enhancements provided by the expedited pathway designations include additional opportunities for FDA engagement and rolling review of a biologics license application that allows sponsors to submit sections of a license application to FDA as they are completed rather than compiling in a single submission.[3] These designations in and of themselves do not constitute an approval when granted and do not guarantee abbreviation of the timeline leading to eventual product approval. Under these expedited pathway designations, development timeline shortening is a hypothetical construct that may be attributed to avoidance of missteps during manufacturing optimization and clinical testing as a consequence of more frequent opportunities to engage the agency during the investigational product life-cycle.

In contrast, the priority review designation results in an actualized time savings realized during review of a biologics license application (BLA). Priority review designation is a decision reached by FDA for every product license application submitted. The designation is targeted for review of applications of drugs/biologics that if approved would lead to significant improvements in the safety or effectiveness of available treatment, diagnosis, or prevention of serious or life-threatening conditions. It is FDA's goal to act on a BLA that has received a priority review designation within 6-months as compared to 10 months for a standard review, resulting in a 4-month time savings occurring at the end of product development.

Unlike the expedited pathway designations referenced above, accelerated approval is a marketing authorization intended to expedite accessibility of products confronted by prohibitive logistical and feasibility challenges with respect to demonstrating safety and efficacy. Accelerated approval is used primarily in circumstances in which the disease course of the targeted indication is long and an extended period of time would be required to measure the intended clinical benefit of an investigational drug/biologic. Under Section 506(c) of the Food, Drug, and Cosmetic (FD&C) Act, FDA is authorized permission to grant accelerated approval for drugs and biologics, including CGTs, that are intended for serious or life-threatening diseases or conditions based on a determination that the product has an effect on an agreed-upon surrogate endpoint considered reasonably likely to predict clinical benefit taking into account the severity, rarity, or prevalence of the disease or condition and the availability, or lack thereof, of alternative treatments. FDA defines approval of a drug/biologic to mean that upon review of safety and effectiveness data collected during clinical investigation, the product's known and potential benefits outweigh known and potential risks. When FDA grants either a regular approval or an accelerated approval, this indicates the agency has determined that the evidentiary standard of safety and effectiveness have been satisfactorily met for a product's intended use. In the context of accelerated approval, FDA acknowledges there is an element of uncertainty associated with the established surrogate endpoint and whether ultimately there will be demonstrable correlation between the treatment's effect on a surrogate endpoint and ultimate clinical benefit for the targeted indication. Accordingly, accepting a greater degree of uncertainty with respect to demonstrated effectiveness represents a concession for achieving more rapid patient access to critical therapies being developed for serious or life-threatening diseases and conditions. Since July of 2020, FDA's Center for Biologics Evaluation and

Research (CBER) has granted seven accelerated approvals for CGTs (one product, ELEVIDYS, has received two accelerated approvals, each for a different patient population) as shown in Table 1 below. To date, only one of these products, ELEVIDYS (manufactured by Sarepta) for the treatment of Duchenne muscular dystrophy has transitioned from accelerated to regular approval for a defined patient population.

Table 1: Summary of Cell and Gene Therapy Accelerated Approvals

PRODUCT	MANUFACTURER	INDICATION	DATE AA[1]	OTHER EXPEDITED PATHWAY DESIGNATIONS				DATE REGULAR APPROVAL
				FT[2]	BT[3]	RMAT[4]	Priority Review	
TECARTUS	Kite Pharmaceuticals, Inc.	Treatment of adult patients with relapsed or refractory mantle cell lymphoma	07/24/2020		●		●	TBD
SKYSONA	Kite Pharmaceuticals, Inc.	Slow progression of neurologic dysfunction in boys 4-17 years of age with early active CALD	09/16/2022		●		●	TBD
ELEVIDYS	Sarepta Therapeutics, Inc.	Treatment of ambulatory patients ages 4-5 years with Duchenne's Muscular Dystrophy	06/22/2023	●			●	06/20/2024
AMTAGVI	Iovance Biotherapeutics, Inc.	Treatment of adult patients with unresectable or metastatic melanoma	02/16/2024	●		●	●	TBD
ELEVIDYS	Sarepta Therapeutics, Inc.	Treatment of non-ambulatory patients at least 4-years of age with Duchenne's Muscular Dystrophy	06/20/2024	●			●	TBD
TECELRA	Adaptimmune LLC	Treatment of adults with unresectable or metastatic synovial sarcoma and whose tumor expresses MAGE-A4 antigen (cleared companion diagnostic)	08/01/2024			●	●	TBD
KEBILIDI	PTC Therapeutics	Treatment of adult and pediatric patients with AADC deficiency	11/13/2024				●	TBD

[1]AA: Accelerated Approval
[2]FT: Fast Track
[3]BT: Breakthrough Therapy
[4]RMAT: Regenerative Medicine Advanced Therapy

Accelerated approval was adopted in 1992 as a more flexible alternative to existing review practices when deaths due to the HIV/AIDS epidemic quickly eclipsed development and approval of effective treatments. Since then, it has been used effectively to make available on an expedited basis new effective therapies for oncology indications. Successful adoption of accelerated approval in the oncology space has been tempered by its application to other indications where demonstration of likely clinical benefit has been questionable and post-approval clinical studies as required under accelerated approval have either not be conducted or have failed to confirm clinical findings premised on results for surrogate endpoints. As a consequence of these latter circumstances when the reliability of an approval decision has not been borne out, use of the accelerated approval pathway has come under increased scrutiny, with criticism levied that lower regulatory standards are tolerated than those expected for regular drug approval. It has been further intimated that required post-approval confirmatory trials are not being

pursued with due diligence and that there are undue delays in initiating withdrawal of accelerated approvals for drugs for which required post-approval studies have failed to confirm clinical benefit .[5,6]

Two examples of recent accelerated approvals deemed 'controversial' include ADUHELM, a monoclonal antibody biologic for treatment of Alzheimer's disease (accelerated approval date: June 7, 2021) and ELEVIDYS, a gene therapy for the treatment of Duchenne muscular dystrophy (accelerated approval date: June 22, 2023). In both cases, accelerated approvals were authorized by senior leadership in FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), respectively, overruling the recommendations of, and despite objections from, the respective product review teams. Discontinued development and commercialization of ADUHELM was announced by the manufacturer in January of 2024, due to an internal re-prioritization of assets to advance development of other treatment modalities. The initial accelerated approval for ELEVIDYS was converted to a regular approval in June of 2024, despite failure of the product to achieve specified primary clinical endpoints in a required follow-on confirmatory clinical trial.

3. CALL FOR CONDITIONAL USE AUTHORIZATION AS AN ALTERNATIVE PATHWAY FOR EXPEDITED PRODUCT ACCESS

Given concerns expressed regarding questionable circumstances when relying on accelerated approval, a clarion call is issuing from an expanding coalition of interested parties for establishment of a new pathway in lieu of accelerated approval to expedite patient access to new products under investigation for serious or life-threatening diseases.

In recognition that the canonical approach to product development and standard product approval is ill-suited for the rare disease space, former CBER director, Peter Marks, energetically promoted more aggressive use of accelerated approval which was rolled out as a pilot program referred to as Support for Clinical Trials Advancing Rare disease Therapeutics (START).[7] Under the START pilot, FDA reviewers are to work more closely with the companies selected to participate in the program allowing for more frequent and impromptu communication. It is projected that an increased level of collaboration could allow biotech innovators to avoid potholes encountered that have previously slowed development of cellular and gene therapy products targeted for serious and rare diseases with an unmet medical need.

This messaging has been echoed by former FDA commissioner, Robert Califf.[8] In public remarks, Dr. Califf indicated that it is unlikely that current approval pathways, including accelerated approval, can be considered optimal for rare and ultra rare diseases which are often are highly debilitating and affect small patient populations. Commissioner Califf has highlighted the need for getting creative in terms of regulatory approaches used in these contexts.

Current FDA commissioner, Dr. Martin (Marty) Makary, has taken up the cause for championing a new approval pathway to expedite patient access to new therapies.[9] Commissioner Makary has publicly stated that plans are being developed for a "new, customized conditional drug approval pathway" that could be applied to therapies for rare diseases. The approvals would be authorized "on a conditional basis" and not require execution of a randomized, controlled clinical trial but instead be based on "plausible mechanism," a criterion which has yet to be defined.

Congress has demonstrated its interest in refining FDA's approach to product approval and the Senate has introduced a bill titled *To amend the Federal Food, Drug, and Cosmetic Act to establish a time-limited conditional approval pathway, subject to specific obligations, for certain drugs and biological products, and for other purposes*, or "Promising Pathway Act 2.0" for short.[10] The Promising Pathway Act 2.0 is intended to amend the FD&C Act by introducing a conditional approval pathway for new human drugs for individuals with rare, progressive, and serious diseases. Under the proposed act, a drug or biologic (including CGTs), may be eligible for conditional approval consideration if intended to treat a disease or condition that (i) is rapidly progressive, terminal, and has substantial unmet medical need, or (ii) is a rare disease or condition that results in a substantially shortened lifespan, reduction in quality of life, or other substantial adverse health effect. With respect to requirements, a conditional approval will be granted if 1) evidence of safety has been established by completion of a phase 1 clinical study or other appropriate demonstration of safety and 2) (a) evidence of effectiveness in treating a given indication as specified in the act is established by an ongoing or completed phase 2 clinical investigation or, (b) in the case of a drug intended to treat a terminal pediatric rare disease or condition that does not primarily affect adults, the drug shows preliminary evidence of clinical effectiveness based upon studies in animal models.

Under the provisions of the Promising Pathway Act 2.0, if it is determined that a drug meets the standard for conditional approval, it is eligible for rolling submission. Conditional approval under the Promising Pathway Act 2.0 is effective for a 2-year period. A sponsor may request renewal of such conditional approval for up to 3 subsequent 2-year periods. The conditional approval status of a drug shall not exceed a total of 8 years from the initial date the drug was granted conditional approval. If a drug receiving conditional approval is granted regular approval during the period in which a conditional approval is in effect, such conditional approval shall be automatically withdrawn. Conditions for reimbursement are also provided in the Promising Pathways Act 2.0. While core elements of the Promising Pathway Act 2.0 are consistent with expedited approval pathways employed globally in other regulatory jurisdictions, an overarching concern is that adding the prefix "conditional" to approval will further erode confidence in the evidentiary standards used to justify granting an approval.

4. CONDITIONAL USE AUTHORIZATION (CUA) AS AN ALTERNATIVE PATHWAY FOR EXPEDITING PATIENT ACCESS TO INNOVATIVE THERAPIES

Current state regular and accelerated product approval pathways rely on the same evidentiary standard with respect to demonstration of safety and effectiveness. Despite this expectation, criticism has been levied against the widening use of accelerated approval, based on concern that lower regulatory standards are tolerated beyond what is expected for a regular drug approval. It isn't unreasonable to conclude that this concern regarding a perceived lowering of regulatory standards would be further exacerbated by adopting an approval pathway preceded by the prefix "conditional" because such a term could intimate a further erosion of the standard for effectiveness demonstration. Rather than additionally degrading the integrity of FDA product approval in order to expedite patient access to promising new therapies during their clinical development, consideration should be given to developing viable alternatives to product approval that achieve the objective of earlier patient access without compromising the rigor with which evidence for product safety and effectiveness is judged.

A model that can be reliably drawn upon for learnings in crafting an alternative pathway is FDA's reliance on Emergency Use Authorization (EUA) as exercised during the declared COVID-19 public health

emergency (January 27, 2020, to May 11, 2023).[11] The EUA authority allows FDA to strengthen US public health protections against chemical, biological, radiological, and nuclear (CBRN) threats including infectious diseases by facilitating availability and use of medical countermeasures as necessary during public health emergencies. When declared by the Secretary of Health and Human Services that authorized emergency use of medical products is appropriate, FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in the context of a declared emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents including infectious diseases.[12] During the COVID-19 pandemic, EUAs were granted for numerous unapproved medical products or unapproved uses of approved medical products including vaccines, convalescent plasma, drugs and non-vaccine biological products as well as medical devices (blood purification devices, continuous renal replacement therapy, hemodialysis devices, *in vitro* diagnostics, personal protective equipment, respiratory assist devices, ventilators and ventilator accessories). Of note, an emergency use authorization does not constitute approval of an unapproved product. In general, upon termination of an HHS EUA declaration, all EUAs issued under the EUA declaration cease to be in effect on the date of the termination with the exception of certain instances when, at the discretion of the HHS Secretary, there may be continued use of an EUA product even after an EUA declaration has been terminated.

Drawing on the COVID-19 pandemic EUA experience as an instructive precedent, a framework can be envisioned that is premised on the concept of a Conditional Use Authorization (CUA) intended to support development of investigational drug/biologic products, including CGTs for treatment of serious or life-threatening diseases and conditions for which no alternative effective treatments are available. In contrast to regular and accelerated approval which allows for commercial distribution of the approved product, a CUA is intended to provide patients with broader access to investigational products during their clinical development under an Investigational New Drug Application (IND).

Essential to implementation of CUA is the opportunity for reimbursement through government programs (Medicare or Medicaid) and private insurance companies in order to further clinical development of investigational products under an IND application. Costs would be contained through an enhanced cost-recovery program that incorporates an established cap. This feature will enable revenue generation necessary to support uninterrupted product development which could lead to eventual accelerated or regular approval. In public comments, former FDA Commissioner Robert Califf defines creative approaches for product approval to include regulatory pathways that permit essential sustained generation of funds necessary to permit collection of high quality clinical evidence of safety and efficacy even in the context of trials performed in small patient populations.[8] In its conception, signal features associated with introduction of a CUA pathway option will include delineating investigational product eligibility criteria, the extent of clinical evidence sufficient to support a CUA, duration of the CUA, and the opportunity for a non-commercial product level of reimbursement intended to support continued product development.

5. PROPOSED FRAMEWORK FOR CONDITIONAL USE AUTHORIZATION (CUA)

The framework for the proposed novel CUA approach is built on appreciation for the benefits afforded by existing FDA expedited programs to facilitate development of products for serious conditions and the success of Emergency Use Authorization (EUA) implemented during the COVID-19 pandemic as a tool for making unapproved products available for general distribution. As an outcome of this precedent

regulatory awareness and real-life experience, I maintain that the proposed framework for a CUA expedited pathway should include the elements summarized below in Table 2:

Table 2: Summary of CUA Key Elements

KEY ELEMENTS	DESCRIPTION
Eligibility Criteria	**Consistent with proposed Promising Pathway Act 2.0** 1. Drug/biologic product intended to treat disease/condition that is: • Rapidly progressive, terminal, substantial unmet medical need; or • Rare disease resulting in substantially shortened lifespan and quality of life 2. Sponsor confirmation of intention to pursue approval of investigational drug/biologic 3. Sponsor awarded CUA is eligible to pursue other applicable expedited pathway designations: • Fast Track, Breakthrough Therapy, RMAT, Accelerated Approval
Timing for CUA Consideration	1. Consideration for CUA should be made while performing clinical testing under an Investigational New Drug application prior to submission of a marketing authorization application 2. Adequate safety and sufficient clinical evidence to support review/decision-making has been accumulated 3. Request for CUA consideration made at Sponsor's discretion in consultation with FDA
CUA Review Standards	1. Preliminary Evidence of Safety: completion of a Phase 1 clinical investigation indicating an acceptable safety profile in the context of the disease indication 2. Preliminary Evidence of Effectiveness: data from a Phase 1 and/or Phase 2 clinical study should provide evidence of the potential for substantial clinical improvement resulting from the treatment and capacity to address unmet medical needs
Duration of CUA	1. Effective for period of 5-years following date of CUA notification, interim progress report submitted at the end of year three (3) 2. Sponsor may request one 2-year extension at the end of the 5-year effective period
Conditions for CUA Termination	1. Reach the end of a total 7-year effective period 2. Regular or accelerated approval granted at any time during 7-year effective period 3. Sponsor discontinues product development 4. CUA will be suspended if the Sponsor's IND is placed on clinical hold until resolved
Reimbursement	1. Eligible for enhanced cost-recovery reimbursed through government programs and private insurance 2. Total reimbursement capped at proposed limit of $300-$500K

- **Eligibility Criteria**

  Consistent with text contained in the proposed Promising Pathway Act 2.0,[10] a drug or biologic product, including cell and gene therapies, may be eligible for CUA if the drug/biologic is intended to treat a serious or rare disease or condition that notably shortens lifespan, significantly reduces quality of life, and is associated with substantial unmet medical need.

  It is expected that sponsors seeking CUA provide written affirmation of their intention to pursue approval of the subject investigational drug under section 505 of the Food, Drug, and Cosmetics Act of (new drug) or section 351 of the Public Health Services Act (primary pathway for regulation of biological products). Granting a CUA does not prohibit sponsors from pursuing other applicable expedited pathway designations.

- **Timing for CUA Consideration**

Given that a CUA does not constitute a new product approval pathway positioned alongside either regular or accelerated approval but is intended to facilitate overall product development during the investigational clinical stage it is expected that requests for CUA consideration will be made during product development under an Investigational New Drug application. Timing for submission of a request for CUA consideration will be determined at the discretion of the sponsor and in consultation with the FDA IND review team. The decision to grant CUA is predicated on data generated that provides preliminary evidence of safety (i.e., upon completion of a Phase 1 clinical trial) in conjunction with sufficient clinical evidence to support review and decision-making related to a CUA request submission.

- **Standard of Review for Granting a CUA**

  Analogous to evidentiary standards that apply to RMAT and Breakthrough Therapy designations,[3,4] CUA evaluation will be based on preliminary clinical evidence that is adequate to indicate that the investigational product may demonstrate substantial improvement in effectiveness or safety over available therapies. Typically, the preliminary clinical evidence will not be sufficient to establish the investigational product's safety and effectiveness for the purposes of granting an approval. The expectation is that CUA qualifying preliminary clinical evidence will derive from completed phase 1 or phase 2 trials involving a sufficient number of patients to imbue the data with credibility.

- **Duration of CUA**

  A key element of CUA is that the effective duration is time constrained. As the objective of product development is to obtain FDA approval for commercial distribution, and in acknowledgement of challenges encountered conducting clinical trials, particularly in the circumstances of rare diseases, an effective period of 5 years is proposed to complete necessary clinical testing. To substantiate that progress is being made under a CUA, the sponsor will submit an interim progress report to FDA at the end of year three (3). If at the conclusion of the 5-year effective period it becomes clear that more time will be needed to complete clinical investigations essential to supporting submission of a licensing application, sponsors may submit one renewal request for an additional 2-year period, resulting in a total CUA effective duration of seven (7) years.

- **Conditions for Termination of a CUA**

  There are conditions and circumstances which can lead to termination of a CUA. Automatic termination of a CUA may result as a consequence of
  1) expiration of the 7-year effective period,
  2) granting regular or accelerated approval of the investigational product covered by the CUA, or
  3) sponsor's discontinuation of clinical development of the investigational product.

  It is also necessary to consider circumstances in which the supporting clinical testing of the investigational product covered by a CUA is placed on clinical hold. In the event that an IND is placed on clinical hold due to patient safety concerns, the associated CUA will be suspended until such time as the clinical hold is satisfactorily resolved. No patients may be treated with the drug/biologic product under the CUA during this time.

- **Reimbursement**

  Given the considerable expense that can be associated with the manufacture and administration of biologic products such as CGTs, a critical piece of the CUA framework is reimbursement eligibility of conditional use-authorized investigational products during pre-license development. Direct and indirect costs associated with manufacturing of cell and gene therapy products coupled with patient care and monitoring post-product administration can run to the hundreds of thousands of dollars. Under the declared COVID-19 Public Health Emergency, granting an EUA allowed for reimbursement of unapproved medical products or the unapproved use of approved products through government programs (i.e., Medicare or Medicaid) and private insurance payors.

  Similar to unapproved products that are allowed to be used under an EUA, products that are granted CUA will remain unapproved investigational products being evaluated under an IND. Existing regulations allow IND sponsors to charge for investigational drugs with constraints governing what costs are recoverable when charging for an investigational drug.[13,14]

  Under CUA, an investigational drug authorized for conditional use will be eligible for 1) a more expansive spectrum of recoverable costs that in addition to direct and indirect costs associated with manufacture of the investigational product will provide coverage for costs associated with clinical care and patient monitoring that are required following product administration, and 2) reimbursement through government programs and private insurance. To provide for a measure of cost containment, under CUA reimbursement coverage I propose a cap in the range of $300-$500K.

6. IMPLEMENTING THE FRAMEWORK FOR CONDITIONAL USE AUTHORIZATION

To offer use of CUA as a means to expedite patient access while providing continued support for clinical development of products intended to treat serious or life-threatening diseases for which no suitable treatment option is available, statutory codification will be necessary. There are various avenues that can be taken to achieve this objective, each having been used successfully to enact FDA priorities. Essential will be a commitment to adopting CUA on the part of the agency, the legislative branch of government, the executive branch, or all three working in concert.

One approach to codification of the CUA pathway is via amendment of the Food, Drug & Cosmetic Act, 21 USC 356: Expedited approval of drugs for serious or life-threatening diseases or conditions. Legislatively this can be achieved by approval of an act of Congress. For example, modernization of the accelerated approval pathway was introduced in the Food and Drug Omnibus Reform Act (FDORA) of 2022 as part of the Consolidated Appropriations Act, 2023.[15]

A second viable approach is the bicameral congressional introduction of a bill such as the Promising Pathway Act 2.0[10] which proposes establishing a conditional approval pathway. A similar tack could be taken with the introduction of a new congressional bill proposing establishment of conditional use authorization for investigational new drugs/biologics intended to treat serious, life-threatening, and rare diseases.

Still further, FDA's commitment to establishing CUA could be signaled during upcoming Prescription Drug User Fee VIII reauthorization performance goal negotiations for fiscal years 2028-2032 that are slated to commence September/October 2025. Similar to the FDA Commissioner's recent announcement regarding issuance of national priority vouchers[1], a pilot program could be established to initiate use of CUA as an expedited pathway to patient access of innovative new therapies. In conjunction with the announcement of a pilot program, FDA would issue guidance describing its current thinking pertaining to implementation of CUA as part of the product clinical development program.

7. KEY TAKEAWAYS

Since its inception in 1992 for the purpose of expediting access to new medications during the AIDS public health crisis, increased use of accelerated approval as a pathway for approving new drugs and biologics for an expanding list of serious and life-threatening diseases and conditions has led to a growing disenchantment with the reliability of this approach. In particular, approvals conferred through the accelerated approval pathway are claimed to be the actionable outcome of a less rigorous application of FDA regulatory review standards with respect to evidentiary demonstration of safety and effectiveness. Former senior FDA officials have suggested that accelerated approval may not be the best-suited approach for getting new CGT products to patients, especially in the context of rare diseases, and that development of alternative pathways fostering earlier patient accessibility to new products is encouraged.

One opportunity for bringing forward patient access to promising therapies intended to treat serious diseases and conditions with unmet medical need earlier in the product development lifecycle is to capitalize on the success of Emergency Use Authorization (EUA) realized during the COVID-19 pandemic and its use as a regulatory tool for getting critical unapproved medicines, devices, and medical equipment to patients and healthcare practitioners in an expedited manner. Using EUA as a template, a time-limited Conditional Use Authorization (CUA) option could be established for drugs/biologics intended to treat serious, life-threatening, and rare diseases which demonstrate preliminary clinical evidence indicative of substantial improvement in effectiveness or safety over available therapies. Notably, CUA does not constitute an approval to be equated with demonstration of statutory safety and effectiveness requirements. Significantly, CUA will permit broader expedited access to investigational products being clinically evaluated under an investigational new drug application while encouraging and providing support for continued product development. Key features of CUA as outlined in this article include:

- Specified eligibility criteria for drug/biologic products intended for rapidly progressive, terminal diseases and conditions that include rare diseases resulting in substantially shortened lifespan and reduction in quality of life and for which there is substantial unmet medical need.

- The sponsor requesting a CUA affirms their intention to submit a marketing authorization application for the investigational product.

- The standard of review for granting a CUA is based on an adequate phase-appropriate demonstration of safety and verifiable evidence that the CUA eligible drug product has the potential for substantial clinical improvement resulting from treatment with the investigational

drug/product as well as substantiate the capacity to address unmet medical needs for serious, life-threatening and rare disease conditions.

- The duration of a CUA will be limited to a time frame of an effective period that includes submission of an interim progress report and the opportunity for a single extension upon Sponsor request.

- Under a CUA an investigational product will be eligible for expanded cost recovery reimbursement up to a capped dollar amount. This feature is critical as it will allow for generation of revenue essential to continue sustained clinical development of the investigational product with the objective being to submit a marketing application.

IN SUMMARY

As FDA strives to modernize its regulatory practices and procedures, the agency continues to be challenged by patients and medical practitioners to provide earlier access to promising innovative new products that address serious or life-threatening diseases and conditions. Initially developed for this purpose, accelerated approval has been at the forefront of FDA regulatory practice intended to expedite product accessibility. Demonstrated limitations to the utility of accelerated approval have prompted calls for refinement of this expedited development pathway. To date, modifications have proven largely cosmetic and insubstantial. This reality begs the question as to whether modifying an existing product approval pathway can achieve the goal of granting expedited product access responsibly. There is another option in FDA's regulatory toolbox which, if adopted in a unique way, could provide a flexibility not afforded by the statutory requirements for product approval: namely, providing authorization for the use of unapproved products, or products used in an unapproved way. Currently confined to public health emergency circumstances, expanding authorized use to the development of drugs/biologics for treatment of serious or life-threatening diseases offers a viable mechanism for expedited product access. Granting a Conditional Use Authorization during pre-license clinical development that is based on adequate preliminary safety and effectiveness data represents a workable alternative for addressing the conundrum of providing earlier product access. This time-constrained approach can become an integral feature of the investigational product development program allowing for expanded reimbursement that is essential to generating funds necessary to sustain clinical investigation of promising products that could eventually lead to the prospect of their approval.

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