Clark L. Anderson, M.D.
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The Ohio State University College of Medicine
2536 Canterbury Road
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July 19, 2021

Re: Docket No. FDA-2020-P-0763

Dear Dr. Anderson:

This letter responds to your citizen petition dated February 12, 2020 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) "revoke approval of the drug tolvaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD)" (Petition at 1). We have carefully reviewed your Petition, the letter to the editor that you submitted with the Petition, and other information available to the Agency. For the reasons set forth below, your Petition is denied.

I. BACKGROUND

A. Approval of Jynarque for Autosomal Dominant Polycystic Kidney Disease

On April 23, 2018, FDA approved Jynarque (tolvaptan) tablets, 15, 30, 45, 60, and 90 mg,[1] under new drug application (NDA) 204441. Jynarque is indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD.

ADPKD is a genetic disease characterized by the presence of numerous fluid-filled kidney cysts.[2] The development and growth of these cysts over time is thought to lead to progressive loss of renal function, including kidney failure, as well as other complications. The disease has been reported to affect 300,000 to 600,000 patients in the United States; however, the clinical course of disease is variable, and the prevalence of symptomatic disease is not well understood. "Although the disease has a variable clinical course, factors such as kidney volume (in the context of a patient's age and level of renal function), the age of onset of high blood pressure, and the causative mutation, can be used to identify patients at high risk of rapidly progressive disease."[3]

[1] For purposes of this Petition response, we use both the drug name *tolvaptan* and the brand name *Jynarque* to refer to the tolvaptan drug product approved for the treatment of ADKPD. This Petition response does not address other tolvaptan products approved for different indications.
[2] See FDA's Summary Review for Jynarque (NDA 204441) at 3, dated April 23, 2018, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000SumR.pdf.
[3] Id at 1.

Prior to 2018, no drug was approved in the United States to slow progression of kidney disease in patients with ADPKD. Thus, there was an unmet need for drugs to slow, and ideally prevent, progression to kidney failure in patients with ADPKD.

B. Jynarque REMS Program

A risk evaluation and mitigation strategy (REMS) is a required risk management plan that can include one or more elements to ensure that the benefits of a drug outweigh its risks.[4] The Agency approved Jynarque with a REMS because it determined that certain elements were necessary to ensure that the benefits of Jynarque outweigh the risks of hepatoxicity.[5] The goal of the Jynarque REMS is to mitigate the risk of serious and potentially fatal liver injury by:

1. Ensuring that healthcare providers are educated on the following:
    a. the risk of serious and potentially fatal liver injury associated with the use of Jynarque.
    b. the requirement for monitoring at baseline and periodic monitoring as described in the prescribing information.
    c. the need to counsel patients about the risk of serious and potentially fatal liver injury and the need for monitoring at baseline and periodic monitoring as described in the prescribing information.
2. Ensuring that healthcare providers adhere to:
    a. the requirement for monitoring at baseline and periodic monitoring as described in the prescribing information.
3. Ensuring that patients are informed about:
    a. the risk of serious and potentially fatal liver injury associated with the use of Jynarque.
    b. the requirement for monitoring at baseline and periodic monitoring as described in the prescribing information.
4. Enrollment of all patients in a registry to further support long term safety and safe use of Jynarque.[6]

The Jynarque REMS imposes certain requirements on prescribers, patients, pharmacies, and distributors to ensure the safe use of the product. Among other things, the REMS requires that healthcare providers who prescribe Jynarque become certified by reviewing the drug's prescribing information, completing prescriber training, and completing a knowledge assessment. Certified prescribers must also assess the patient's liver function, enroll the patient in the REMS, and counsel the patient on the risks of the product.[7] Pharmacies must become certified and obtain authorization to dispense the drug by verifying that the prescriber is certified

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[4] See section 505-1 of the FD&C Act (21 U.S.C. 355-1) and FDA's guidance for industry *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (April 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch.

[5] *See generally* the Risk Evaluation and Mitigation Strategy (REMS) Document JYNARQUE (tolvaptan) REMS Program, most recently modified on November 25, 2020, available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/204441Orig1s009ltr.pdf (for a more substantive discussion see https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204441s002lbl.pdf).

[6] *See* Id.at 1.

[7] Id. at 1- 2.

and that patients are enrolled in the Jynarque REMS.[8] It also requires that patients review a patient guide, enroll in the REMS, obtain periodic blood tests to check liver function, and receive counseling from the prescriber.[9]

II. DISCUSSION

Your Petition asks the FDA to "revoke" approval of tolvaptan for the treatment of ADPKD, arguing that the drug is of "negligible efficacy", the supporting studies were flawed, the reviewers overlooked shortcomings of the drug, and the drug is dangerous (Petition at 1-2).

A. Legal Standards for Approval and Withdrawal of an NDA

FDA's regulation of drug products is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C 301) and the Agency's implementing regulations codified in Title 21 of the Code of Federal Regulations (CFR). The FD&C Act makes it unlawful to market a new drug product without first obtaining an approved new drug application (NDA) or abbreviated new drug application (ANDA).[10] Before approving an application, FDA must determine that the drug is both safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling.[11]

The statutory standard for determining whether a new drug is effective is "substantial evidence" derived from "adequate and well-controlled investigations" conducted by qualified experts, from which those experts could "fairly and responsibly" conclude that the drug is effective under the conditions of use suggested in its labeling.[12] With respect to safety, applicants must provide evidence from "all methods reasonably applicable to show whether or not such drug is safe,"[13] including "pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs."[14]

When analyzing whether a drug meets the standard for approval, FDA conducts a benefit-risk assessment that:

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[8] Id. at 3.
[9] Id. at 2.
[10] Section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505 of the FD&C Act).
[11] Section 505(b)(1) and (d) of the FD&C Act (21 U.S.C. 355(b)(1) and (d)).
[12] Section 505(d) of the FD&C Act. The characteristics of adequate and well-controlled studies are set forth in FDA regulations at § 314.126. As stated in the regulation, these criteria were developed over a period of years and are recognized by the scientific community as the essential elements of well-controlled and credible investigations.
[13] Section 505(d)(1) of the FD&C Act (requiring FDA to deny an application lacking such information).
[14] 21 CFR 314.50(d)(5)(vi)(a); see also § 314.50(d)(5)(iv) (description and analysis of "any other data or information relevant to an evaluation of the [drug's] safety and effectiveness…from any source…including information derived from clinical investigations…commercial marketing experience, reports in the scientific literature, and unpublished scientific papers"); 21 CFR 314.50(d)(2) (requirement for submission of nonclinical pharmacology and toxicology data).

> [T]akes into account the extensive evidence of safety and effectiveness submitted by a sponsor…as well as many other factors affecting the benefit risk assessment, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks. This assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence.[15]

Only if FDA concludes that the product's benefit-risk profile is favorable will the Agency approve an NDA.[16] FDA must deny marketing approval if there is a lack of substantial evidence that the drug is effective, the results of safety testing fail to show that the drug is safe, or, on the basis of any other information before the Agency, there is insufficient evidence to determine whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling.[17]

After an approved drug enters the marketplace, FDA continues to monitor its safety through its postmarketing surveillance and may take regulatory actions when appropriate.[18] Under Section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Agency will withdraw approval of an NDA if it finds:

> (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved;
>
> (2) that new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved;[19]
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> (3) on the basis of new information before [the Agency] with respect to such drug, evaluated together with the evidence available to [the Agency] when the application was approved, . . . there is a lack of substantial evidence that the drug will have the

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[15] *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA V Implementation Plan – February 2013, Fiscal Years 2013-2017 at 1, 5-7, available at* https://www.fda.gov/media/84831/download. See also *Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA VI Implementation Plan (FY 2018-2022)* at 3-4, available at https://www.fda.gov/media/112570/download.

[16] See 21 CFR 314.105(c), which states "FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness." The information required to satisfy this requirement includes not only comprehensive safety and efficacy data, but also "an integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling." 21 CFR 314.50(d)(5)(viii).

[17] Section 505(d)(1), (d)(2), (d)(4), and (d)(5) of the FD&C Act.

[18] See FDA's webpage on Postmarketing Surveillance Programs available at: https://www.fda.gov/drugs/surveillance/postmarketing-surveillance-programs.

[19] Section 505(e)(1) and (2) of the FD&C Act (21 U.S.C. 355(e)(1) and (2)); see also 21 CFR 314.150.

> effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.[20]

For the reasons summarized below, your Petition does not present new evidence or information to support that tolvaptan should not have been approved, or to support that its approval should be withdrawn at this time.

B. Approval of Jynarque (tolvaptan) (NDA 204441) in 2018

Regarding your specific arguments, you allege the presentation of the clinical studies associated with Jynarque's review was deceptive and the studies lacked statistical significance (Petition at 1-2).

On March 1, 2013, Otsuka Pharmaceutical Development and Commercialization, Inc. (Otsuka) submitted an NDA for Jynarque (tolvaptan) to slow kidney function decline in adults at risk of rapidly progressing ADPKD.[21] This first completed study that formed the basis for the claimed indication is summarized below:[22]

> …(TEMPO) enrolled 1445 subjects with early rapidly progressing ADPKD (as determined by TKV criteria) who had relatively preserved estimated glomerular filtration rate (eGFR) by the Cockcroft Gault equation > 60 mL/min] and followed them over a 3-year period. In this trial, study subjects' doses were titrated to a maximum tolerated daily split dose of tolvaptan of up to 120 mg (90 mg in a.m. and 30 mg in the p.m.) or matching placebo. The TEMPO trial showed that reduction in eGFR in the tolvaptan treatment group was 25% less than the reduction in eGFR in the placebo group, but the absolute treatment difference was small (0.9 mL/min/ 1.73m^2 per year). This trial also showed an early effect on total kidney volume (TKV).

On August 5, 2013, the independent Cardiovascular and Renal Drugs Advisory Committee met to discuss Otsuka's application.[23,24] A majority of voting committee members determined that

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[20] Section 505(e)(3) of the FD&C Act (21 U.S.C. 355(e)(3)).
[21] See Jynarque NDA approval letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/204441Orig1s000ltr.pdf.
[22] See Jynarque Clinical Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000MedR.pdf.
[23] See the meeting announcement of the Cardiovascular and Renal Drugs Advisory Committee, available at https://wayback.archive-it.org/7993/20170404150355/https://www.fda.gov/AdvisoryCommittees/Calendar/ucm357792.htm; see also the Cardiovascular and Renal Drugs Advisory Committee Roster, available at https://wayback.archive-it.org/7993/20170404150359/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM363340.pdf.
[24] FDA's Advisory Committees provide independent advice from outside experts on issues related to human and veterinary drugs, biological products, medical devices, and food. In general, advisory committees include academician and clinician members, plus a consumer, industry, and sometimes a patient representative. Additional experts with special knowledge may be added for individual meetings as needed. Although the committees provide

there was not enough data for certain FDA-required endpoints and that follow-up was not long enough for a drug that has to be taken for a lifetime.[25] However, 6 of the 15 members voted to approve the drug at that time. As stated in the meeting minutes, the committee members that voted yes stated that they supported approval because the use of tolvaptan in patients with ADPKD met an unmet medical need.[26]

Following the Advisory Committee's determination that more information was needed, the Agency sent a Complete Response letter to the sponsor on August 28, 2013.[27] The letter stated that while the first study provided data showing some effects on kidney size, it was unclear whether these effects would translate into prolonged time until renal replacement was necessary. However, the Agency recognized that a decades-long study to confirm prolongation of renal survival would be infeasible. Instead, the Agency recommended that the sponsor conduct a second short study in patients at a later stage of the disease.[28] In recommending this later-stage study, the Agency reasoned that modest effects seen both early and late in the disease process were evidence that Jynarque would have cumulative effects throughout a patient's life and result in a clinically meaningful increase in the time to need for renal replacement therapy. In the Complete Response letter, the Agency explained, "For this application to be approved, you need to conduct an additional efficacy trial that tests the hypothesis that tolvaptan slows the loss of renal function and is successful at a p-value < 0.05."[29]

The sponsor went on to conduct the later-stage study and submitted the results to FDA in October 2017. This second pivotal trial is described in the Clinical Studies section of the Jynarque labeling:

> REPRISE-NCT02160145: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Withdrawal Trial in Later-Stage ADPKD
> REPRISE was a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18-65) with chronic kidney disease (CKD) with an eGFR between 25 and 65 mL/min/1.73m2 if younger than age 56; or eGFR between 25 and 44 mL/min/1.73m^2, plus eGFR decline >2.0 mL/min/1.73m^2/year if between age 56-65. Subjects were to be treated for 12 months; after completion of treatment, patients entered a 3-week follow-up period to assess renal function. The primary endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized by dividing by each subject's treatment duration.
> Prior to randomization, patients were required to complete sequential single-blind run-in periods during which they received placebo for 1 week, followed by tolvaptan titration for 2 weeks, and then treatment with tolvaptan at the highest tolerated dose achieved

advice to the Agency, final decisions are made by FDA. See the Agency's FDA-TRACK: Advisory Committees Dashboard web page at https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-advisory-committees-dashboard.

[25] See the Summary Minutes of the August 5, 2013, Drug Safety and Risk Management Advisory Committee meeting, available at https://wayback.archive-it.org/7993/20170404150406/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM373520.pdf.

[26] Id.

[27] See the Center for Drug Evaluation and Research's Complete Response letter, dated August 28, 2013, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000OtherActionLtrs.pdf.

[28] Id.

[29] Id.

> during titration for 3 weeks. During the titration period, tolvaptan was uptitrated every 3-4 days from a daily oral dose of 30 mg/15 mg to 45 mg/15 mg, 60 mg/30 mg and up to a maximum dose of 90 mg/30 mg. Only patients who could tolerate the two highest doses of tolvaptan (60 mg/30 mg or 90 mg/30 mg) for the subsequent 3 weeks were randomized 1:1 to treatment with tolvaptan or placebo.
> Patients were maintained on their highest tolerated dose for a period of 12 months but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to start drinking an adequate amount of water at screening and continuing through the end of the trial to avoid thirst or dehydration.
> A total of 1519 subjects were enrolled in the study. Of these, 1370 subjects successfully completed the prerandomization period and were randomized and treated during the 12-month double-blind period. Because 57 subjects did not complete the off-treatment follow-up period, 1313 subjects were included in the primary efficacy analysis.
> For subjects randomized, the baseline, average estimated glomerular filtration rate (eGFR) was 41 mL/min/1.73 m^2 (CKD-Epidemiology formula) and historical TKV, available in 318 (23%) of subjects, averaged 2026 mL. Approximately 5%, 75% and 20% had an eGFR 60 mL/min/1.73 m^2 or greater, between 30-59 mL/min/1.73 m^2, and between 25 and 29 mL/min/1.73 m2, respectively. The subjects' mean age was 47 years, 50% were female, 92% were Caucasian, 4% Black or African-American and 3% were Asian, 93% had hypertension, and 87% of subjects were taking antihypertensive agents affecting the angiotensin converting enzyme or receptor. Of the 115 (8%) of subjects who had prior genetic tests, only 54 (47%) knew their results with 48 (89%) of these having PKD1 and 6 (11%) having PKD2 mutations.
> In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow-up was -2.3 mL/min/1.73 m^2/year with tolvaptan as compared with -3.6 mL/min/1.73 m^2/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m^2/year ($p < 0.0001$). The key secondary endpoint (eGFR slope in mL/min/1.73 m^2/year assessed using a linear mixed effect model of annualized eGFR (CKD-EPI)) showed a difference between treatment groups of 1.0 mL/min/m^2/year that was also statistically significant ($p < 0.0001$).
> The efficacy profile was generally consistent across subgroups of interest for this indication; few Black or African-American patients were enrolled in the trial.

In reviewing this study, along with the previous study, the Agency concluded that tolvaptan was shown to have a persistent effect on the slowing of kidney function decline in patients with rapidly progressing ADPKD CKD stages I to early stage IV (eGFR between normal values and 25 mL/min/1.73m^2).[30] The Agency viewed the small effects seen in early and then later stages of the disease as evidence that the effect of the drug was likely to persist for many years. The Agency concluded that if taken chronically, the cumulative effects of tolvaptan should allow adults at risk of rapidly progressing ADPKD to delay or avoid dialysis or transplantation by slowing kidney disease progression. On April 23, 2018, FDA approved Otsuka's application for Jynarque as an orphan drug,[31] with a boxed warning regarding liver toxicity and a REMS.[32]

[30] See footnote 22.
[31] See Jynarque Orphan Drug Designation and Approval, available at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=347311.
[32] See footnote 21.

You also argue that the FDA reviewers "were likely deceived" and state that you can find "no evidence in the tolvaptan review . . . that the reviewers actually plumbed the investigators' data; they appeared to take the authors' conclusions of efficacy at face value." (Petition at 1.)

In reviewing an application, such as the application at issue here, the Agency is provided all data sets deriving from the studies submitted as the basis for approval. In this instance, the publicly-available clinical review identifies tables and figures that were reviewed from the sponsor's submission or derived from FDA's review of the data.[33] The Agency's independent analysis of the data is reflected in numerous tables and figures throughout the clinical review.[34]

With respect to the statistical review,[35] the main results displayed in Table 4 (p. 10) are from the sponsor's document; however, as documented in the review, FDA reviewers independently confirmed the analysis from the datasets. FDA reviewers' analyses are also shown in Tables 5 and 6 (pp. 11 and 12) and Figure 2 (p. 13). [36]

In short, the Agency carefully reviewed the data submitted and reviewed as part of the application. While additional studies of 20 to 30 years would have provided more information, the Agency determined that such studies were not necessary or feasible under the circumstances.

You also express concern with this statement in the review documents: "Ultimately it will be for patients to decide if tolvaptan is the drug for them." (Petition at 2.)[37] You write that you interpret this statement "as a blatant abdication of FDA responsibility [that] reflects . . . an underlying faint-hearted attitude of the review group." (Petition at 2.)

As discussed, FDA carefully reviewed the data associated with Jynarque prior to approving the application. Further, FDA approved Jynarque with a REMS intended to mitigate the risk of liver toxicity, which states, among other things, that healthcare providers must complete prescriber training and a knowledge assessment specific to Jynarque and counsel the patient, and that patients must receive counseling from the prescriber, including being informed of risks.[38] Through Jynarque's labeling, the Agency conveyed the risks and benefits as fully, accurately, and transparently as possible, so as to allow patients to make an informed decision with their physician. In summary, in approving Jynarque, the Agency anticipated that a patient and their provider would have an informed discussion and arrive at a decision that appropriately balanced

[33] See footnote 22.
[34] See footnote 22 at pp. 48 (Table 4); 52 (Table 5); 54 (Table 6); 57 (Table 8); 58 (Table 10); 74 (Table 14); 74 (Table 15); 75 (Figure 10); 79 (Table 17); 80 (Table 18); 82 (Table 19); 83 (Table 20); 84 (Table 21); 84 (Figure 11); 85 (Table 22); 87 (Table 23); 88 (Figure 12); 91 (Figure 13); 93 (Table 25); 94 (Figure 14); 98 (Figure 17); 99 (Table 26); 100 (Table 27); 102 (Table 28); 103 (Figure 18); 104 (Table 29); 105 (Figure 19); 106 (Table 30).
[35] See Jynarque Statistical Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000StatR.pdf.
[36] Id.
[37] See Jynarque Cross-Discipline Team Leader Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000SumR.pdf.
[38] See footnote 5.

the risks of the product with the benefit of prescribing it, given the individual circumstances of each patient.

Finally, you note the life-threatening side effects of tolvaptan (Petition at 2). The Agency shares your concern, as reflected in the decision to require a REMS in order to ensure that risks were mitigated and that the benefits of the drug outweigh the risks.

In sum, the Agency reviewed the available evidence and determined that the benefits of Jynarque outweigh the risks, as mitigated by the REMS. While we appreciate your perspective, the Agency continues to believe that the benefits of Jynarque outweigh its risks and declines to withdraw approval of the product at this time. As with all drug products, we will continue to monitor the safety of tolvaptan and take action if we determine it is appropriate to do so.

III. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

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Date: 2021.07.16 14:15:14 -04'00'

Patrizia Cavazzoni, M.D.
Acting Director
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