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UV-VIS Spectrophotometric Analytical Method Development of Favipiravir by Implementing QbD Approach

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ABSTRACT

Regulatory agencies like USFDA have recommended implementing Quality by design (QbD) a systematic process for pharmaceutical development. Development of various pharmaceutical processes including analytical methods by applying Quality by design aids in ensuring the robustness of the method. An analytical method was developed for the estimation of favipiravir (FPV) by applying QbD approach by UV-VIS spectrophotometry. Solvent distilled water was utilised and 233.8 nm was the wavelength for measurement of absorbance. Effect of input variables on spectrum characteristics were studied for selection of critical parameters and developed method was validated as per ICH Q 2 R1 regulatory guidelines. Linearity of the drugs was ascertained over the conc range 5-40mcg/ml (microgram/ml). The accuracy was found within acceptable limit with SD 0.05079-0.78188 %; and the precision study was shown acceptable data as % RSD 0.6259-0.6559 for FPV. The stability of the method was studied by minor variation in the wavelength and minor change in the scan speed. The developed method is rigid, robust and efficient for the estimation of FPV from the dosage form. QbD was applied to build rigid robust method through risk assessment at early stage and defining the design space at the later stage. The analytical methods, developed based on the QbD concept are more robust and reduce the number of out of trend (OOT) and out of specification (OOS) results during the actual usage in quality control.

INTRODUCTION

Favipiravir (FPV) is a viral RNA polymerase inhibitor that is expected to have an effect against a range of influenza viruses[1]. It is reserved for the treatment of novel or remerging influenza. favipiravir RTP binds to and inhibits RNA dependent RNA polymerase (RdRp) which ultimately prevents viral transcription and replication[2].

Favipiravir (FPV) chemically is 6 Fluoro-3-hydroxy pyrazine-2-carboxamide[3]and pharmacologically it is effective against ebola virus and covid 19[4].

For estimation of FPV methods such as Spectrophotometric method[5-7], RP-HPLC[8-12], potentiometric method [13], Stability indicating HPLC-UV detection[14-17], UPLC-MS/MS[18], Bio analytical method [19-20] have been reported for estimation of FVT alone or in combination with other drugs.

The drug is official in recently published Indian Pharmacopoeia[3]. Chemical structure of drug is shown in (Fig No 1).

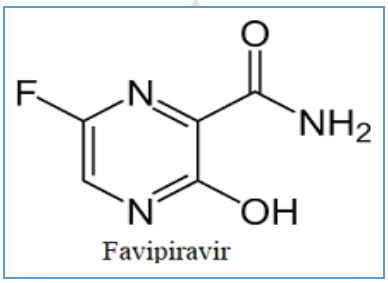

Fig. No. 1: Chemical structure of Drug molecule

Product with predefined quality will be assured by applying Quality by design concept in the development of pharmaceutical process. QBD concepts are mentioned in ICH guidelines Q8 (R1) (Pharmaceutical development), Q9 (Quality risk management), and Q10 (Pharmaceutical quality system) [21-23]. ICH guidelines Q8 (R2) defines QBD as a "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"[24]. QBD approach in analytical method summarizes a complete understanding of how the analytical technique attributes and operating conditions affect the analytical performance[25,26]. Factors to study in analytical quality by design (AQbD) approach may include the type of analytical technique chosen; reagents used and instrument parameters[27, 28].

There are similar advantages of applying QbD principles to analytical methods as to manufacturing processes and product[27]. AQbD approach can be beneficial in the development of suitable, robust, low cost and eco-friendly (eco-friendly solvent, chemicals) method which is applicable at any stage of the lifecycle of the product. Also, some regulatory guidelines have mentioned flexibility of changing analytical method without revalidation if the AQbD approach has been implemented during analytical method development. The first stage of AQbD approach is to fix an analytical target profile (ATP) for the method. ATP defines the goal of the analytical method development process and it is the sign of method performance[28,29]. For analytical method validation ICH Q2 (R1) has given various method performance characteristics. Thus, a QbD based UV spectrophotometric was developed, QbD approach was implemented with the study of the effect of method input variables on spectral shape, intensity of absorbance, and absorbance maxima λ_{max} and critical parameters were selected for the proposed method and method was validated as per ICH guidelines Q2 (R1).

MATERIALS AND METHODS

Instrumentation

Analysis was performed with a Shimadzu Double beam UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan) with spectral bandwidth of 2 nm and wavelength accuracy of ± 1 nm with 10 mm matched Quartz cells was used. Electronic balance Afcoset balance (The Bombay Burmah Trading corpo Ltd) with accuracy ±0.1 mg Model No. ER 200A was used for weighing and for degassing the solutions Digital Ultrasonic cleaner 1.8 Ltr (Labman scientific Instruments Chennai) was used.

Reagents and Chemicals

Pharmaceutically pure samples of favipiravir from Glenmark pharmaceuticals, Mumbai, Maharashtra was procured as a gift samples and the commercial formulation containing Favipiravir 400mg was procured from local market. Distilled water available in the laboratory was utilised.

AQbD approach application in method development

Many literatures have given efforts to elaborate QbD and its significance in the pharmaceutical development [30]. (Fig. No. 2) broadly explains the advantages on implementation of QbD. As a AQbD approach the influence of input variable parameters on

spectrophotometric analytical method performance was studied shown in diagram (Fig. No. 3).

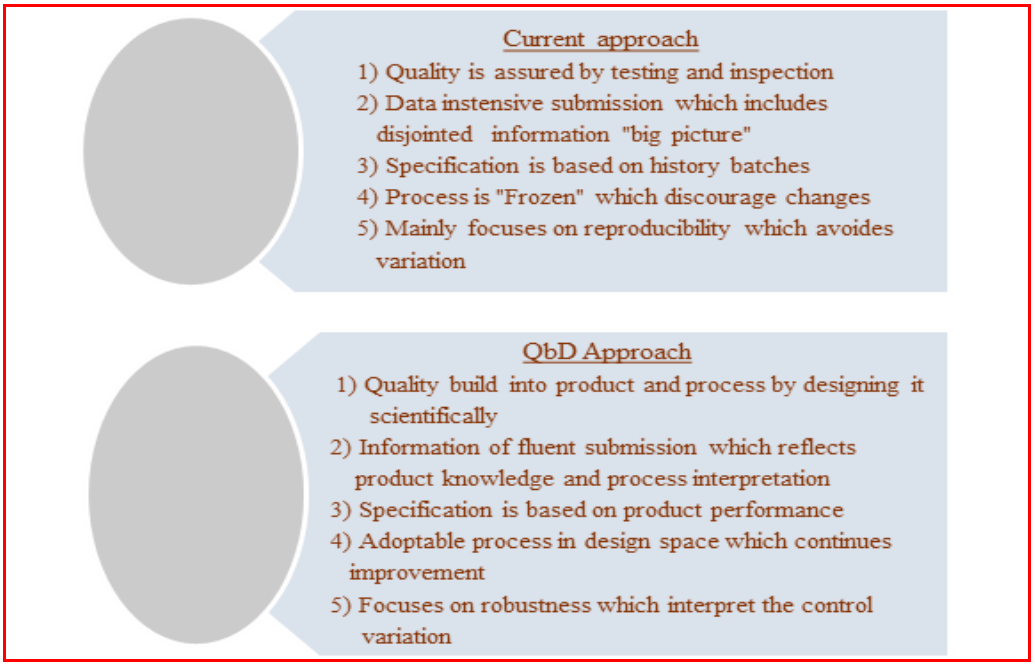

Fig. No. 2: Significance of QbD approach in pharmaceutical development

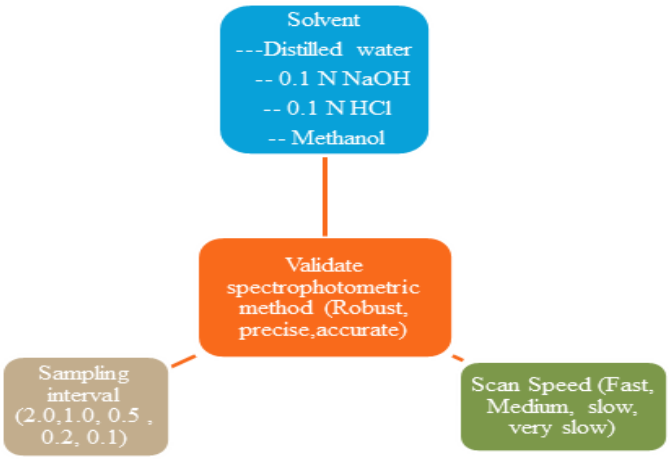

Fig. No. 3: Diagram showing the relationship between input variable parameters and the spectrophotometric method performance characteristics

Solvent selection

FPV is soluble in water, methanol and ethanol. Although the solubility of the procured drug was studied in water, methanol 0.1 N NaOH and 0.05 N HCl separately; and each solution with known conc of analyte were scanned in UV range of 210 nm to 400 nm. It was found that suitable solvent is water (Fig. No. 4) as compare to other solvent 0.1 N NaOH (Fig. No.

5) with respect to more absorbance of FPV in this solvent, low cost, robust and precise in producing result.

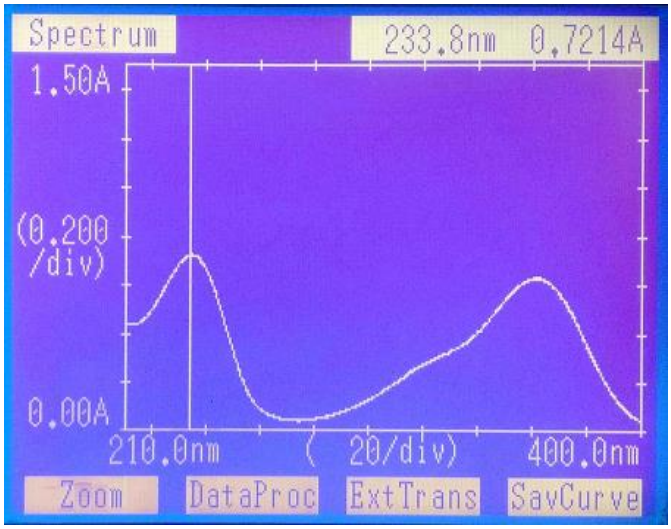

Fig. No. 4: UV spectra of FPV in water

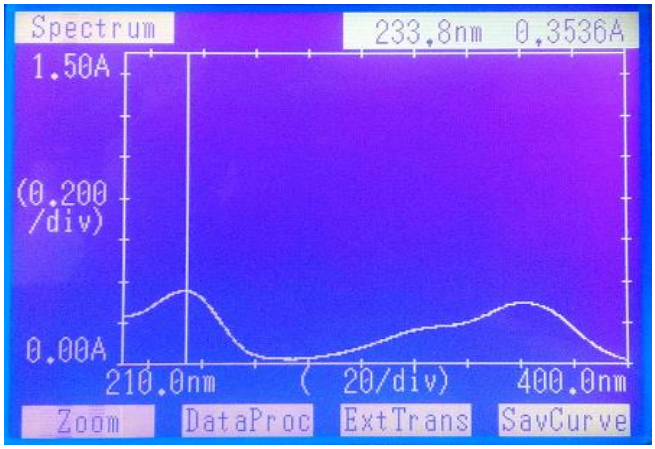

Fig. No. 5: UV spectra of FPV in 0.1 N NaOH

Preparation of stock solutions and standard solutions

100 mg of pure drug FPV was accurately weighed; and transferred into 100 ml volumetric flask. Dissolved into water and volume was made to 100 ml with solvent. Subsequent drugs standard solution of conc 100µg/ml was prepared by diluting aliquot 10 ml of stock solution to 100 ml capacity volumetric flask.

Selection of wavelength and conc range

From UV spectra it was found that FPV has measurable absorbance at 233.8 and 361.5 nm. From the nature of spectra and sharpness of the peak, wavelength 233.8 nm was selected for

this method. Pure drugs standard solutions were prepared in the conc range 5–30 µg/ml. Above discussed observations was guided to select critical parameters listed in Table No. 1 and by using these; method was validated as per ICH guidelines and by analysing marketed preparations.

Table No. 1: Selected critical parameter for UV-VIS analytical method of FPV

Parameter	**Selected variables For FPV**
Wavelength range	200-400
Wavelength	233.8 nm
Solvent	Distilled water
Scan speed	Medium
Sampling interval	0.2 nm

Experimental Method for estimation

Two simple methods calibration curve method and single point absorbance method were applied for estimation of the formulation/dosage form. Calibration curve method employed preparation of six standard solutions from stock solution in the working conc range and measurement of absorbance was recorded at selected wavelength; followed by plot of calibration curve absorbance against conc. Best linear relationship between conc and absorbance was ascertained after three replicates of calibration curve prepared from different stock solutions. The regression line equation Y = mX + c where m is the slope and c is the intercept was used for the calculation of sample concentration. Also instruments quantitation mode was utilised to know the conc of sample/formulation solution.

Single point absorption method standard solution and sample solution were prepared and conc of sample solution was calculated by applying formula:

$$\text{Csample} = \text{A sample} \times \frac{\text{C std}}{\text{A std}}$$

Where

A_{std} = Absorbance of FPV standard solution at 233.8 nm

C_{std}= Conc of FPV standard solution

A_{sample} = Absorbance of sample solution

C_{sample} = Conc of sample solution

Validation of the Method

To attain analytical target profile of the method, selected critical parameters should meet the performance characteristics of the analytical method. In order to implement AQbD approach an ICH guideline Q2 R1 was applied to study methods performance with critical parameters. The method was validated as per ICH guidelines.

System suitability

System suitability is studied to demonstrate the suitability of the developed procedure under consideration for the analytical method. Six replicates of working standard solutions with conc 15 mcg/ml of FPV were prepared separately and absorbance was recorded; SD and % RSD of the response was calculated. Stability of the solution was also studied by bench top stability at laboratory temp.

Linearity

The linearity of an analytical method is its ability to obtain response i.e. absorbance which is directly proportional to the conc of analyte. series of working standard solutions were prepared in conc. range of 5 to 30 mcg/ml (µg/ml)and scanned in 200 to 400 nm range in spectrum mode of the spectrophotometer, absorbance of the standard solutions were recorded at 233.8 nm for FPV in spectrum order. Microsoft office excel software tool was used to obtain the standard regression curve and its analysis as slope, intercept, and correlation coefficient.

Assay of formulation

Assay was carried out by proposed methods and method was validated by statistical parameters.

Method I: Estimation of formulations by calibration curve method

Tablets were weighed, powdered and tablet powder equivalent to 100 mg FPV was weighed and transferred into 100 ml volumetric flask. Dissolved into water and volume was made with solvent. Solution was filtered through whatman filter paper No 40 and aliquots of

solution were diluted to obtain tablet solution. Solution was scanned in the range of 200 to 400 nm to obtain absorbance of tablet solution at 233.8 nm in spectrum order. Obtained absorbance was utilised to estimate unknown conc of formulation; and results are statistically validated to obtain % of nominal conc, standard deviation and % of RSD.

Method II: Estimation of formulations by single point absorbance method

Standard solutions of conc 10mcg/ml and 20 mcg/ml were prepared separately scanned in 200 – 400 nm range; and absorbance at 233.8 nm was recorded. Also above prepared tablet Solution was scanned in 200 to 400 nm range and absorbance was recorded. Equation was applied to determine conc of sample solution; and obtained results are statistically validated to obtain % of nominal conc, standard deviation and % of RSD.

Accuracy and Precision

The accuracy of an analytical method expresses the closeness of an agreement between test result and true result. Accuracy study was performed by recovery study i.e. standard addition method; diluted standard solution of FPV was prepared and standard solutions added in 80, 100 and 120% proportionate to the tablet solution. Three replicates at each of these three levels were prepared and measured and % of conc, SD and RSD of replicates were calculated.

The precision study was carried out by performing assay of tablet six times; also the reproducibility in result was studied by interday and intraday precision.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ of FPV by the proposed method were determined using calibration graph method and calculated as 3.3 σ/s and 10 σ/s for LOD and LOQ respectively. σ is the standard deviation of calibration curve and s is the slope of regression line.

Robustness and Ruggedness

It is measure of capacity of analytical procedure to remain unaffected by small but deliberate variations in method parameter.

RESULTS AND DISCUSSION

Method development comprises numerous steps of which solvent selection, method for measurement selection are significant one. Uses of eco-friendly solvents have got remarkable weightage due to low cost, readily available and environmentally sound. Drugs underlying analysis must have appreciable solubility in the selected solvent. Chemical structure of the drug and physico-chemical properties available in the literature guides about use of appropriate solvent in the method. Solubility of FPV was studied in each solvent and spectra of drug shown in Fig. No. 4. In solvent distilled water drug FPV was shown maximum and consistent absorbance as compare to other solvent.

System Suitability

The absorbances of six replicates of standard solutions (15mcg/ml) are reported in Table No. 2. The SD and % RSD was found for FPV and meets the system suitability requirements indicates method was suitable for analysis.

Table No. 2: System suitability study of FPV

Sr. No.	Conc in mcg/ml	Absorbance of FPV
1	15 mcg/ml	0.7551
2	15 mcg/ml	0.7611
3	15 mcg/ml	0.7560
4	15 mcg/ml	0.7667
5	15 mcg/ml	0.7751
6	15 mcg/ml	0.7773
	SD RSD	0.00558 0.7218

Linearity

The overlay spectra obtained in linearity study was shown in Fig. No. 6 and the calibration curve of drug found to be linear in the conc range of 5-30 µg/ml as shown in Fig. No. 7. The regression equation of line and its parameters slope, r^2 value and intercept are tabulated in Table No. 3, which proved the linear relationship between conc and obtained response.

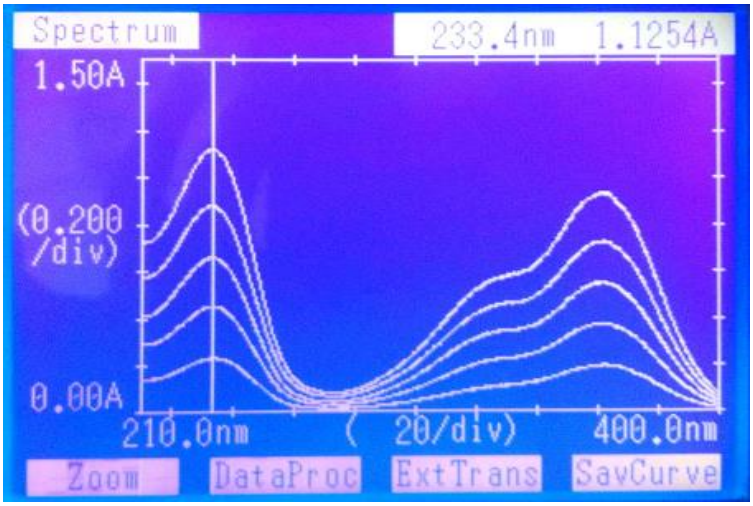

Fig. No. 6: Overlay UV spectra of FPV in linearity study

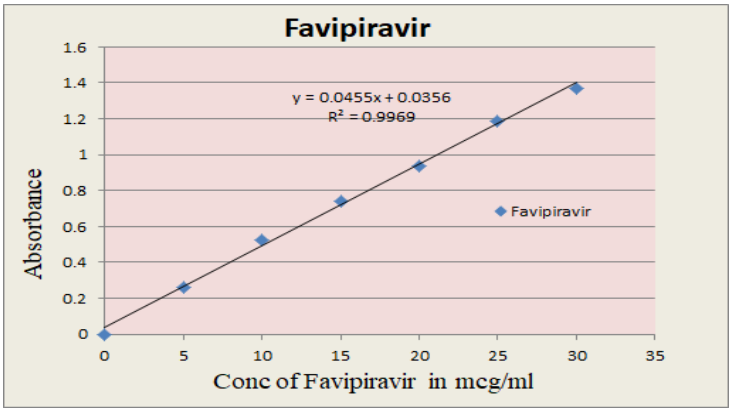

Fig. No. 7: Obtained calibration curve of FPV in water

Table No. 3: Parameters of regression equation obtained in Microsoft excel

Parameters	**FPV**
Detection wavelength	233.8
Beer's law limit (µg/ml)	5 – 30 mcg/ml
Correlation coefficient (r^2)	0.9969
Regression equation (y = mx + c)	Y = 0.0455X+0.0356

Assay

The assay was carried out by both the methods. The spectra of formulation were shown in Fig. No. 8. The assay of formulation was carried out by proposed method and calculated % of nominal conc and RSD was found within acceptable limits are summarized in Table No. 4. The results indicated applicability of the method for estimation of Formulation.

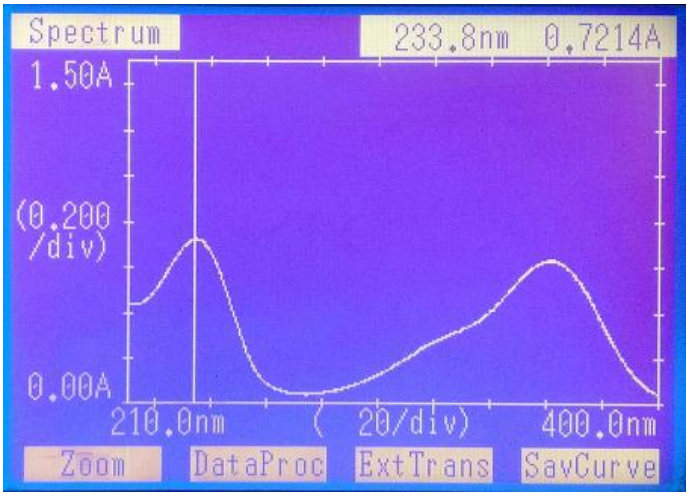

Fig. No. 8: UV-VIS spectra of FPV Tablet solution

Table No. 4: Results of assay of formulation by proposed method

Formulation	Drug	Label Claim (mg/Tablet)	Amount found/mg; n=6	Drug Content %	Std Deviation	% RSD
Feravir-400 By I method	FPV	400 mg	392.91	98.227	3.2775	3.3366
Feravir-400 By II method	FPV	400 mg	405.16	101.29	2.5817	2.5488

Accuracy and Precision

The results of accuracy are summarised in Table No. 5, the obtained results were within acceptable limit; and methods accuracy was justified by calculating % drug content. The precision study was carried out by performing assay of solutions; further the reproducibility in result was studied by interday and intraday precision. The values obtained SD and % RSD was shown methods precision and are summarised in Table No 5.

Table No. 5: Results of accuracy and precision

S. No.	Parameter	Level of study	Data Title	Obtd Data	S.D.	RSD
1	Precision study of FPV	Intraday Precision	Mean of Abs n= 6	0.7496 (Abs of 15 mcg/ml)	0.01993	-
		Interday precision		0.7678 (Abs of 15 mcg/ml)	0.01752	-
2	Accuracy study of FPV	80%	% amount found	96.717%	1.3683	1.4147
		100%		97.998%	0.6354	0.6484
		120%		97.541%	1.3153	1.3481

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ of FPV by the proposed method were shown in Table No. 6. The standard deviation of the calibration curve was obtained in Microsoft office excel word.

Robustness and Ruggedness

Robustness was studied and capacity of analytical procedure to measure analyte was remain unaffected by small but deliberate variations in method parameter like variation in the wavelength ± 1 nm, variation in the solvent strength by ± 0.01 N. The analytical method was found rugged during development; similarity the result was produced by performing the analysis by different analyst given in Table No. 6.

Table No. 6: Results of LOD and LOQ, robustness

Parameters		FPV
LOD mcg/ml		0.09 mcg/ml
LOQ mcg/ml		0.20 mcg/ml
Robustness	± 1 nm	0.6855 (conc10 mcg/ml) 0.6853(conc10 mcg/ml)
	Distilled Water	0.6909 (conc 10 mcg/ml) 0.6949 (conc 10 mcg/ml)
Ruggedness	Analyst 1	SD ± 0.007797
	Analyst 2	SD ± 0.0085264

CONCLUSION

The method was developed with eco-friendly and readily available distilled water solvent. Favipiravir was estimated from the formulation by both the method and satisfactory results were obtained. The calibration graph method was given reproducible results; however obtained results of both the methods were within acceptable limits given in the pharmacopoeia. The validated method is economical, precise, accurate, robust and reproducible hence can be routinely used for estimation of favipiravir from the dosage form.

CONFLICT OF INTEREST

All Authors declared that there is no conflict of interest.

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