CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-519

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-519

Solvay Pharmaceuticals, Inc.
Attention: Rex Horton
Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Horton:

Please refer to your new drug application (NDA) dated June 28, 2002, received on July 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox (fluvoxamine maleate) 25 mg, 50 mg, and 100 mg Tablets.

We acknowledge receipt of your submissions dated April 13, and 19, 2004, May 5, 2004, March 21, 2005, September 16, 2005, November 17, 2005, May 16, 2006, June 7, 2006, and October 25, 2006.

Your submission dated May 16, 2006, constituted a complete response to our February 9, 2004 action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following comments and requests.

Pharmacology/Toxicology Review

The specification [redacted] in the drug product is set at [redacted], which is above the threshold for qualification (i.e., above 0.2%). Based on the most recent stability data, it appears that you are unable to lower this specification. Consequently, you will need to qualify this impurity/degradant in the following studies prior to approval: b(4)

- a general toxicology study in one species, of 14-90 days duration, which should include microscopic, as well as macroscopic, evaluation of the standard battery of tissues;
- *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]); and
- an embryofetal development study in one species.

The specification for [redacted] in the drug substance is set at [redacted] which is above the threshold for qualification (i.e., above 0.15%). You have indicated that you intend to lower this specification, but have not provided us with documentation of your revised specification. Such documentation or qualification of this impurity in the studies listed above will be needed prior to approval. If qualification is required, this impurity is currently considered to be qualified for embryo- b(4)

fetal toxicity, but not for genotoxicity or general toxicity, as communicated in our previous AE letter (dated 2/9/04).

Although the [redacted] is considered to be adequately qualified for the current [redacted] specification in drug substance and product, the [redacted] level of this impurity in the Ames test will not be adequate to qualify specifications higher than [redacted] b(4)

Chemistry, Manufacturing, and Controls

The following issues need to be addressed:

1. Provide drug substance and drug product specifications that list both the common and chemical names of the impurities with the previously agreed upon limits. As noted under the Pharmacology/Toxicology comments, the footnotes regarding the [redacted] impurity in the drug product specification will also need to be revised to reflect the revised limit. In particular, we note that the the [redacted] impurity remains specified at the [redacted] limit in the drug substance specification, although you repeatedly committed to lowering this limit to 0.15%. b(4)

2. For clarification purposes, please provide a complete list of all the proposed packaging configurations. If this application provides for a [redacted] configuration for commercial distribution, provide mock-ups of these carton and [redacted] labels. b(4)

3. Provide an explanation for the fluctuating levels of the [redacted] in the stability studies for drug product lots #92994, 92995 and 92996. b(4)

4. The Agency has conveyed deficiencies to the holder of DMF [redacted] These deficiencies will need to be adequately resolved before this application can be approved. b(4)

Dissolution Method and Specification

We note your acceptance of our proposed dissolution methodology and specification (below) for all tablet strengths. Additionally, your proposal to sample at only 30 min (Q=[redacted] in 30 min) is acceptable. b(4)

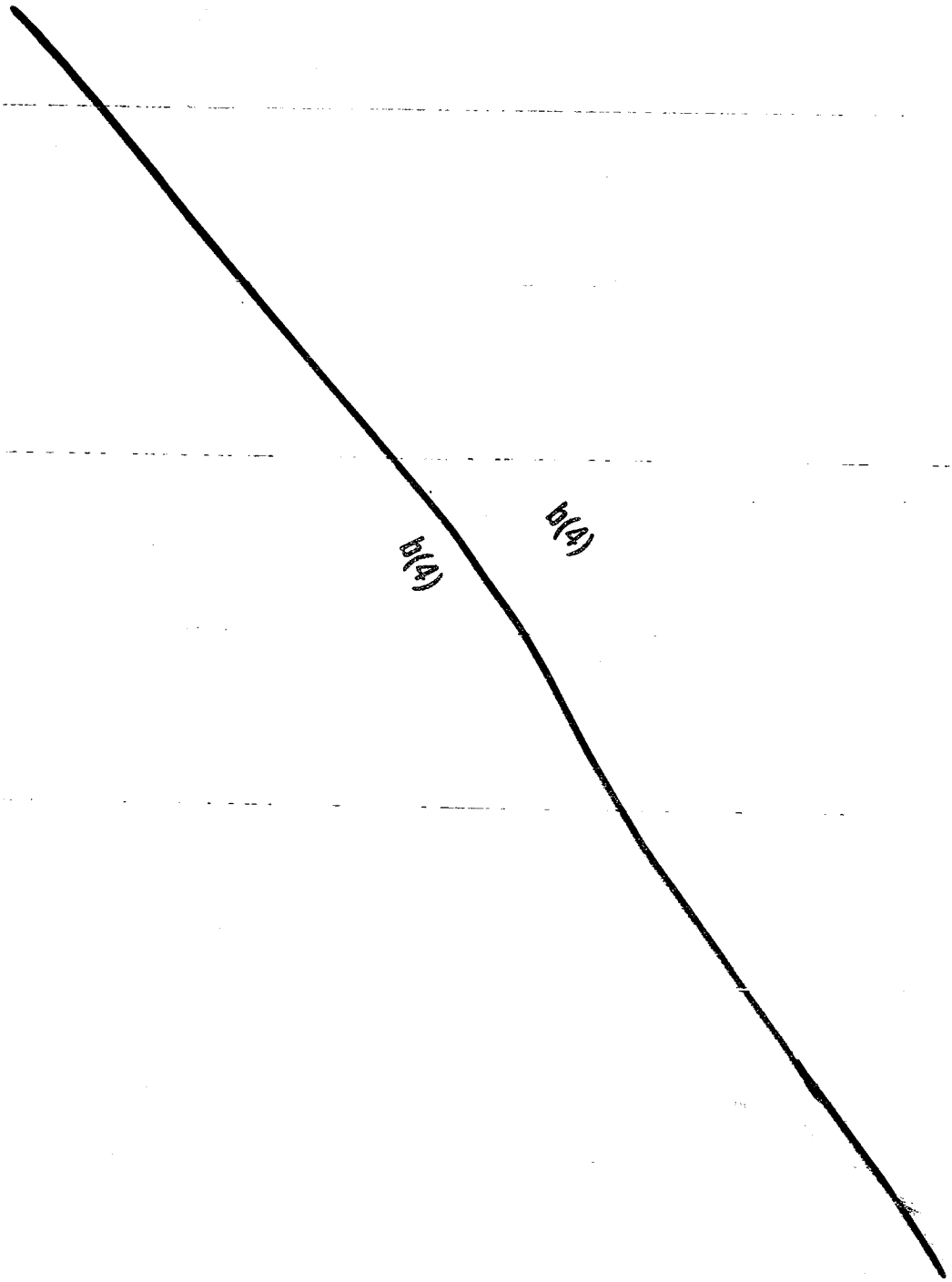
Medium: 900 ml water at 37 $_{o}$C
Apparatus II : [redacted] at 50 rpm
Sampling Times: 10, 20 and 30 min
Q = [redacted] in 30 min b(4)

Labeling

Below is the Agency's proposal for revisions to the labeling of Luvox (fluvoxamine maleate) Tablets. We have based our revisions from the labeling submitted in your May 16, 2006 submission. You must submit revised, draft labeling for Luvox (fluvoxamine maleate) Tablets as part of your response to this

letter. If you propose revisions to the labeling, we ask that you provide a highlighted or marked-up copy that shows all changes.

In addition, submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.



4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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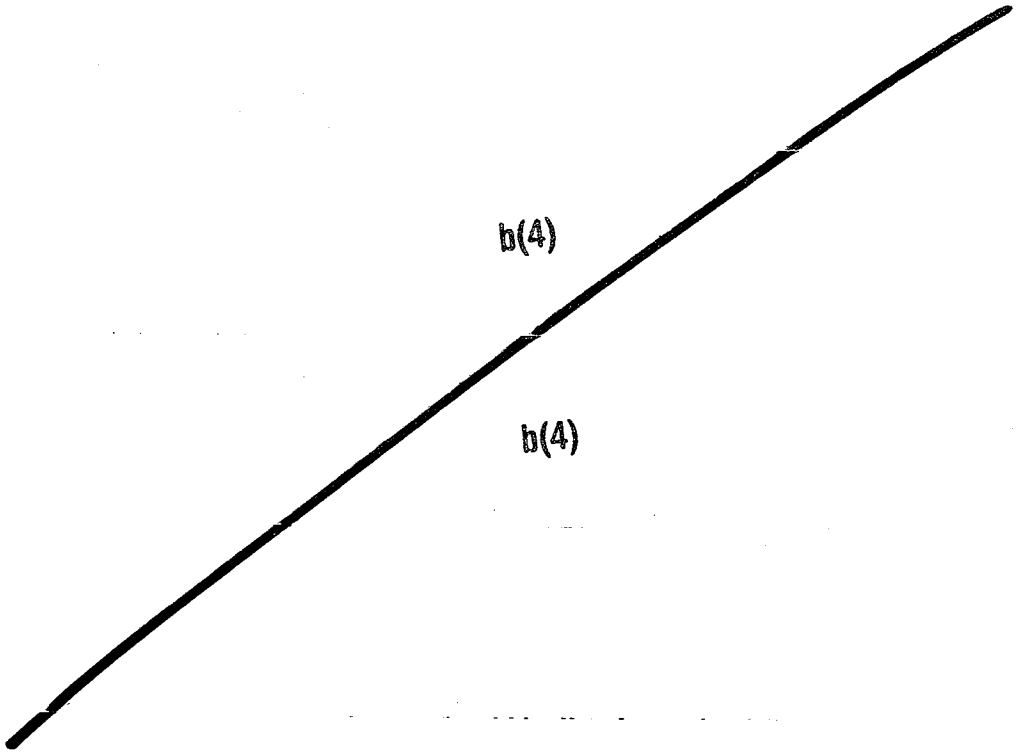

Request for Post-Marketing Study Commitment

1. We note that Luvox has not yet been evaluated in juvenile animals. Although we previously requested (in our Approvable letter dated 2/9/04) that you conduct juvenile studies in rodent and non-rodent, our thinking on juvenile studies has evolved and we will only require a juvenile study in the rat. As previously communicated (in our Approvable letter dated 2/9/04), the impurities present in drug substance and/or drug product at levels above the thresholds for qualification should be tested in this study.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Bill Bender, Regulatory Project Manager, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
11/16/2006 02:01:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-519

Solvay Pharmaceuticals, Inc.
Attention: Suzanne LoGalbo, J.D., RPh.
Vice President, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. LoGalbo:

Please refer to your new drug application (NDA) dated June 28, 2002, received July 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox (fluvoxamine maleate) Tablets 25 mg, 50 mg, and 100 mg.

We note that, at the time of NDA submission, this application was subject to the provisions of the Application Integrity Policy (AIP), and as such, our normal substantive scientific review could not be initiated. We also reference the Agency's April 9, 2003, letter, in which Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, notified you that the substantive scientific review of Solvay's applications could be resumed. Therefore, the 10-month standard review clock for this application started on April 9, 2003, resulting in a PDUFA goal date of February 9, 2004.

We acknowledge receipt of your additional submissions dated:

July 22, 2002	April 23, 2003	June 5, 2003	September 5, 2003	December 22, 2003
August 12, 2002	May 7, 2003	June 20, 2003	November 10, 2003	
April 16, 2003	May 29, 2003	August 22, 2003	November 26, 2003	

We have completed our review of this application, as amended, and have determined that it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following comments and requests.

Chemistry, Manufacturing, and Controls

1. We have sent a Deficiency letter (dated October 30, 2003) to the holder of DMF [redacted]. This Type II DMF [redacted] must be found adequate to support NDA 21-519 before we can approve your NDA. b(4)

2. Please revise the Raw Material Specification for Product Code 3363 and 3367 so the Related Compound B. [redacted] is identified by its common name [redacted] which is used by the drug substance manufacturer rather than [redacted]. b(4)

3. When determining the amount of related compounds in fluvoxamine maleate using the HPLC assay method described in NDA 21-519, please use each related compound's reference standard to

determine the amount of the related compound. Alternatively, use each related compound's HPLC Response Factor relative to fluvoxamine maleate to determine the amount of the related compound in fluvoxamine maleate drug substance.

4. A theoretical plate determination of the HPLC column is a system suitability test in the drug substance supplier's HPLC assay method [redacted] Please include a determination of the number of theoretical plates (N) of the column, [redacted] as a system suitability test of the chromatographic system used to assay fluvoxamine maleate. b(4)

5. In order to further assure the identity and quality of the fluvoxamine maleate drug substance used to manufacture LUVOX® tablets, please add an appearance acceptance test to the raw material specification for fluvoxamine maleate drug substance.

6. In order to further assure the identity and quality of the fluvoxamine maleate drug substance used to manufacture LUVOX® tablets, please add a residual solvent acceptance test to the raw material specification for fluvoxamine maleate drug substance. The residual solvent specification limits should be consistent with the current ICH guidelines (ICH Q3C).

7. Please provide the COAs for the fluvoxamine maleate drug substance lots used to manufacture the first three validation lots of LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg, as well as the batch analysis data for the fluvoxamine maleate drug substance stability lots.

8. Please identify whether the sodium stearyl fumarate NF used to manufacture LUVOX™ Tablets 25 mg, 50 mg and 100 mg is derived from an animal or plant source. If the sodium stearyl fumarate NF is from an animal source please certify that the animals used to manufacture the sodium stearyl fumarate NF are from a non BSE country.

9. We note that synthetic iron oxide is a component in the colorants [redacted] and [redacted] used to manufacture the 50 mg and 100 mg LUVOX® Tablets. Please confirm that LUVOX® Tablets conform to 21 CFR 73.1200(c) *Uses and Restrictions* for synthetic iron oxides. b(4)

10. Please state whether any reprocessing procedures are implemented during the manufacture of LUVOX® Tablets 25 mg, 50 mg and 100 mg.

11. Please correct ATM 4202, 4205, 4210 sections 4.1.1, 4.1.2 and 4.1.3 to include a description of the shape (i.e., elliptical convex) of the LUVOX® Tablets 25 mg, 50 mg and 100 mg, and a description of the fact that LUVOX® Tablets 50 mg and 100 mg are scored on one side (as described in the Master Batch Record). Please note that we recommend that you use the term scored rather than bisected since the former is a more accurate description.

12. [redacted] reports [redacted] degradation of LUVOX® Tablets solutions exposed to light for two days in a light chamber at an intensity of 765 W/m^2 (see page 1463 in NDA 21-519). However, a standard solution stressed under similar conditions showed almost no decomposition [redacted] We ask that you comment on this difference and in particular the risk to the stability of LUVOX® Tablets of light exposure in the presence of moisture. b(4)

13. Please provide a description of the LUVOX® (fluvoxamine maleate) Tablets [redacted] count bottle container closure system. Alternatively, you can remove the [redacted] count bottle of LUVOX® (fluvoxamine maleate) Tablets from the HOW SUPPLIED section of the product label. b(4)

14. Please revise the Package Material Report for the [redacted] and [redacted] to state that if the closure is accepted on Certificate of Compliance from the supplier an ID [redacted] acceptance test needs to be performed. b(4)

15. In order to assure that the [redacted] will function properly, we ask that you verify that the [redacted] used to package LUVOX® (fluvoxamine maleate) Tablets meets the manufacturer's specified [redacted] being used to package LUVOX® (fluvoxamine maleate) Tablets.

16. Please provide a description (e.g., Package Material Report) of the acceptance testing protocols for the [redacted] material and lidding used to package LUVOX® (fluvoxamine maleate) Tablets. An acceptable protocol must include ID testing of [redacted] material and lidding before they are used to package LUVOX® (fluvoxamine maleate) Tablets 25 mg, 50 mg and 100 mg. b(4)

17. In order to demonstrate that the proposed container closure systems are adequate to package LUVOX® Tablets, you need to provide the results of USP <661> (i.e., PE containers) and USP <671> (i.e., container permeation) testing. These test results need to be performed on all the [redacted] bottles and [redacted] packages you intend to use to package all strengths of LUVOX® (fluvoxamine maleate) Tablets for both commercial sale and physician samples.

18. If you plan to market a [redacted] count [redacted] bottle of LUVOX® Tablets, please include this container/closure system in the LUVOX® (fluvoxamine maleate) Tablet stability protocol, and report the stability results at the time intervals and in the format as specified in NDA 21-519. In addition, provide an updated drug product stability protocol. b(4)

19. We note that on p. 292 of NDA 21-519, you list your Marietta, GA facility as a warehouse and distribution site. As a result, this site was not submitted for inspection. If you intend to use the Marietta, GA facility as a testing laboratory (as listed on p. 1881 of NDA 21-519), please update your NDA accordingly. We will then submit an inspection request to the FDA's Office of Compliance. Ultimately, if this site is to be used as an approved testing facility for this NDA, the Office of Compliance will need to find it acceptable.

20. [redacted] b(4)

22. Please provide labeling for the proposed [redacted] count bottles of LUVOX® (fluvoxamine maleate) Tablets 50 mg and 100 mg. Alternatively, you can revise the LUVOX® Tablets product insert **HOW SUPPLIED** section by removing any reference to a [redacted] count bottle presentation. b(4)

Pharmacology/Toxicology

The specifications set for a number of impurities are above the threshold for qualification in drug substance (i.e., above 0.15%) and/or drug product (i.e., above 0.2%). We recommend that you lower the specifications for these impurities to below the qualification threshold. If this is not possible, you need to qualify these impurities in the following studies (note exceptions below):

- a general toxicology study in one species, of 14-90 days duration;
- *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]);
- an embryofetal development study in one species;
- a juvenile study in one species.

For the general toxicology, embryofetal development, and juvenile studies, justification should be provided for the species selected for each study.

Based on the information provided, we consider the [redacted] qualified for general toxicity in a 13-week study in rats and all but [redacted] qualified in the embryofetal development study in rat (Study No. TX.114.07.05P). You indicated that there has been considerable human exposure to older formulations of fluvoxamine (possibly containing higher levels of [redacted] impurities) marketed (since late 1993) in several foreign countries. To the extent that you can provide documentation (i.e., actual levels of impurities rather than specifications) that the impurities have been qualified by this clinical use, no further testing of general toxicity would be needed. b(4)

With the exceptions noted, all the impurities with specifications set above the qualification threshold need to be qualified in the studies as listed above. These studies, except for the juvenile study, will be required prior to approval if the specifications cannot be lowered to below the qualification threshold.

Dissolution Method and Specification

We propose the following dissolution conditions for this application, which are the same as those for the original Luvox application. The conditions and specifications for all tablet strengths are:

Medium:	900 ml water at 37 $_0$C
Apparatus II :	[redacted] at 50 rpm
Sampling Times:	10, 20 and 30 min
Q =	[redacted] in 30 min

b(4)

As part of your response to this letter, we ask that you confirm your acceptance of this method and specification.

Labeling

Accompanying this letter (Enclosure) is the Agency's proposal for the labeling of Luvox (fluvoxamine maleate) Tablets. We have used, as our base labeling, the labeling submitted in your April 16, 2003 submission. Brackets [] embedded within the text that follows include comments and explanations concerning our proposed labeling.

You must submit revised, draft labeling for Luvox (fluvoxamine maleate) Tablets as part of your response to this letter. If you propose revisions to the attached labeling, we ask that you provide a highlighted or marked-up copy that shows all changes and identify which version of Luvox labeling was used as the base document. This type of labeling document will facilitate review.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Request for Post-marketing Study Commitment

We note that Luvox has not yet been evaluated in juvenile animals. Therefore, you need to conduct juvenile studies in rodent and non-rodent. The impurities present in drug substance and/or drug product at levels above the thresholds for qualification should be tested in one of these studies; the selection of species should be justified.

Promotional Material

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

33 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Russell Katz
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