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June 21, 2006

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: PIND number 73,739 - arbidol

Dear Madam or Sir:

I am writing in response to the letter of April 21, 2006 of Debra Birnkrant, M.D., a copy of which is attached at TAB A. The responses below track the format of Dr. Birnkrant's letter.

Good Earth Medicine LLC is a company formed for the purpose of developing research, awareness, and possible marketing of the antiviral arbidol, which has been used and tested successfully for more than 20 years in Russia for the prevention and treatment of types A and B influenza.

As noted in Dr. Birnkrant's letter, Good Earth Medicine is interested in qualifying arbidol for Emergency Use Authorization for influenza in the event of the declaration of a public health emergency involving the H5N1 virus or another influenza virus by the Secretary of public health under Section 319 of the Public Health Service Act (PHS Act).[1]

1. Summary of the data available regarding the activity and toxicity of arbidol.

At TAB B to this letter, we have provided copies of four published scientific papers in Russian (with professional English translations), as well as three papers in their

[1] Good Earth Medicine is also interested in qualifying arbidol for over-the-counter (OTC) marketing, and will further address that issue following further research and analysis.

original English versions. These papers demonstrate the effectiveness of arbidol in the prevention and treatment of influenza, including that caused by the H5N1 virus.

The attached studies also show that arbidol is effective at a very low level of toxicity. We have noted Dr. Birnkrant's concern that an opinion casting doubt about such use of arbidol was received from a testing laboratory assigned under the NIAID screening program. However, we wish to emphasize that the testing utilized by the laboratory followed a protocol different from those shown in the enclosed medical literature, and we otherwise question why those recent test results were contrary to the results in the published literature, as attached.[2]

Arbidol is widely used for prophylaxsis and therapy of Influenza A and B in Russia. Based upon the long and effective use of arbidol in Russia, public health officials in that country rely on it as Russia's primary defense against the H5N1 virus. According to the Voice of America online and other publications, President Putin has confirmed that Russia will be using arbidol as its primary drug for prevention and treatment of avian influenza. A copy of the Voice of America article is attached at TAB C.

Because of a severe shortage of Tamiflu in the United States (currently the United States has stockpiled enough Tamiflu for only about two percent of the population), we believe that the people of United States would greatly benefit from availability of arbidol to help to counter the risks of an avian flu pandemic.

Additionally, the recent cluster infections of H5N1avian influenza in Indonesia has shown that Tamiflu has limited effectiveness against the strain of virus responsible for those resulting deaths. It is vitally important to have access in the United States to another antiviral such as arbidol, which a number of studies have shown to be effective against influenza viruses including H5N1.

As also requested by Dr. Birnkrant, we have enclosed at TAB D all reports regarding recent testing results received through the NIAID screening program.

2. List of additional testing and studies proposed and plans for development of arbidol.

a. Draft Protocols.

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[2] In addition to the papers showing the effectiveness of arbidol which are attached at Tab B, abstracts of a number of other scientific papers are set forth in Good Earth Medicine's informational website at arbidol.com.

We request that additional testing be done with respect to the original raw samples of arbidol which we provided for the NIAID screening program (ARB Numbers 06-000914 and 06-000966), as well as for the raw sample and the Russian consumer product which we have provided under IND number 73,739. We request that the specific protocols set forth in the following medical literature attached at TAB B be utilized:

1. I.A. Leneva, *et al.*, Therapeutic Archives No. 8 (2005).

2. D.K. Lvov, *et al.*, Emerging Infectious Diseases (Peer Review, Manuscript ID: EID-05-1609). Please note that in addition to numerous co-authors at the D.I. Ivanovsky Institute of Virology in Moscow, the non-Russian co-authors include M. Peiris of the Dept. of Microbiology of the University of Hong Kong, and D.L. Suarez of the United States Department of Agriculture, Agriculture Research Service.

3. I.T. Fedyakina, *et al.*, Vopr Virusol No. 6 (2005).

4. T.A. Semeneko, et al., Zh Mikrobiol Epidemiol Immunobiol No. 6 (2005).

The protocols used in the above studies resulted in evidence that arbidol inhibits the reproduction of influenza A viruses, at concentrations far below the level which is toxic to cells.

b. Plans to Meet Draft Guidelines for Emergency Use Authorization.

In accordance with the recommendation for data to support a request for consideration for an EUA (at page 12 of the Draft Guidance), we submit the following:

1. Description of the product and its intended use. Arbidol is described as follows, and is intended to be used for the prevention and treatment of influenza A and B, including forms of the H5N1 virus:[3]

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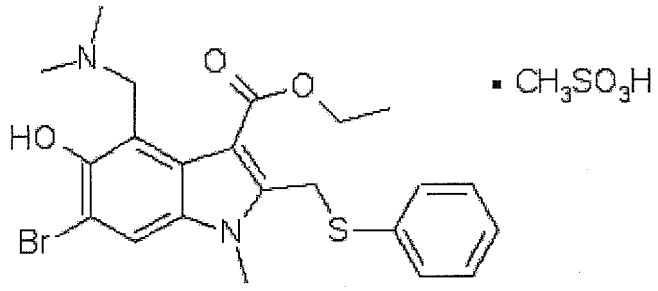
[3] Arbidol has also been shown to be an antioxidant. See O.V. Vasilyeva, *et al.*, "The antioxidant properties of arbidol and its structural analogs". An EUA is not requested based upon those antioxidant properties. However, Good Earth Medicine is separately analyzing arbidol as a dietary supplement, based solely upon its antioxidant properties.

Mesylate of 1-methyl-2-feniltiometil-3-carbethoxy-4-dimetilaminometil-5- hydroxy - 6-bromindola, which has following structural formula:




2. Explanation of unmet need. Avian influenza type H5N1 is considered by public health officials to present the imminent potential to mutate into a form capable of causing a pandemic in which millions of Americans may die. As noted above, the primary line of defense at this time, Tamiflu, is held in quantities which would leave approximately 98 percent of the population of the United States without any effective drug coverage to prevent or treat the disease once contracted. The 2 percent coverage of Tamiflu which is currently available is not enough to even provide protection to police, firemen, medical personnel, food transportation workers, and other essential service providers. Moreover, in the recent cluster outbreak in Indonesia, Tamiflu is reported to have been of limited effectiveness. The unmet need in the United States is therefore enormous, and a drug such as arbidol which has a long history of effectiveness against influenza A, should be made available to our population.

3. Description of the product's approval or clearance status. Arbidol is not currently approved or cleared under the FD&C Act or licensed under the PHS Act. An IND has been submitted for raw arbidol under ARB Numbers 06-000914 and 06-000966, with testing results of that product by one testing laboratory attached at TAB D. Another IND has been established under pre-IND Number 73,739 for a second batch of raw arbidol and for the Russian consumer product. As noted in the attached medical literature, arbidol is licensed for use in Russia, where it has been widely used for more than 20 years with success.

4. List of manufacturing sites. The manufacturing sites for arbidol which are known to us are as follows:

a. Jiangyin Eastern Medical Raw Materials Co., Ltd., No.4 North Road, Huangtu Town, Jiangyin City, Jiangsu, China 214445.

b. Shchelkovsky Vitamin Factory, #2 Fabrichnaya Street, City of Shchelkovo, Moscow Oblast, Russia 141100 (for Masterlek).

The manufacture of arbidol is within the regulatory systems of China and Russia, respectively, and the GMP status of each manufacturer is not otherwise known to us at this time.

5. Approved alternative products, their availability, and their adequacy. As noted above, there is a severe shortage of Tamiflu, which puts virtually the entire population of the United States at risk. M-2 blockers such as amantadine and rimantadine are other alternative products, but they have proven to be of limited effectiveness against certain strains of the H5N1 virus, as have neuraminidase inhibitors such as Tamiflu in the recent Indonesian clusters.

6. Available safety and effectiveness information for the product. The following medical research literature attached at TAB B demonstrates that arbidol is both safe and effective, including against the H5N1 virus:

i. The literature includes a recent manuscript under peer review for the journal Emerging Infectious Diseases[4], in which the co-authors are not only prominent Russian scientists, but also scientists from the University of Hong Kong and from the United States Department of Agriculture. That study found that arbidol (as well as rimantadine, amantadine, and ribavirin) "effectively inhibited reproduction of HPAI/H5N1 virus in *in vitro* effective doses from 1.50 up to 9.70 μg/ml, whereas all tested compounds were not toxic up to 40 μg/ml."

[4] D.K. Lvov, *et al.*, Emerging Infectious Diseases (Peer Review, Manuscript ID: EID-05-1609).

ii. A 2005 Russian study[5] similarly showed that arbidol in the concentration of 10 mcg/ml effectively inhibits influenza virus A/H5, considerably below the IC50 for arbidol of 40 mcg/ml. Table 1 of that study shows arbidol's effectiveness as compared to other classes of antivirals:

**Table 1: The influence of antiviral drugs on viral reproduction of various strains of human influenza virus A, B and C in MDCK cell culture**

| 1. Virus | % inhibition of viral reproduction | | | | | | |
|---|---|---|---|---|---|---|---|
| | arbidol | amanta-dine | riманта-dine | virazol | ribamidil | zanam-ivir | Carbox-ylate ozel-tamivir |
| Influenza Virus A: | | | | | | | |
| H1N1 | | | | | | | |
| A/PR/8/34 | 80 | 50 | 40 | 59 | 59 | 75 | 73 |
| A/WSN | 85 | -- | -- | -- | -- | -- | -- |
| H2N2 | | | | | | | |
| A/Singapore/1/57 | 80 | 79 | 81 | 60 | 60 | 81 | 79 |
| A/Japan/305/57 | 87 | 84 | 85 | -- | -- | -- | -- |
| H3N2 | | | | | | | |
| A/Taiwan/79 | 79 | 85 | 80 | -- | -- | 85 | 77 |
| A/Mississippi/85 | 83 | 82 | 87 | 66 | 66 | 84 | 80 |
| Influenza Virus B: | | | | | | | |
| B/Lee/40 | 60 | 6 | 8 | -- | -- | 65 | 68 |

[5] I.A. Leneva, *et al.*, Therapeutic Archives No. 8 (2005).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Influenza Virus C: | | | | | | | |
| C/SSSR | 20 | n/a | 10 | -- | -- | -- | -- |
| C/Leningrad | 22 | 15 | 15 | -- | -- | -- | -- |

iii. A 2005 Russian study[6] concluded that arbidol, "in doses nontoxic to cells, effectively inhibits reproduction of avian influenza viruses A/H5, isolated from wild birds on Russian territory."

iv. A further 2005 Russian study[7] showed that the production of interferon increases under the effect of arbidol, enhancing the effectiveness of influenza vaccine. "The results of the study point to an immunomodulating effect of arbidol, of the vaccine and of the combination of the two, shown by the increase in number of T-lymphocytes and killer-T lymphocytes, the stimulation of phagocytic functions, and the induction to active state of natural killers, and also by the rise in frequency of seroconversion and the growth of titer levels of specific anti-influenza antibodies."

v. A 2005 Russian-UK study[8] which was co-authored by Alan J. Hay of the National Institute for Medical Research, London, "showed that arbidol inhibited viral reproduction of all antigen subtype of human influenza A and B viruses, avian influenza viruses, possessing H5 and H9, and rimantadine-resistant strains of influenza A viruses."

vi. In an extensive American-Australian review titled "Approaches and Strategies for the Treatment of Influenza Virus Infections", J.M. Colacino, *et al.*, Antiviral Chemistry & Chemotherapy 10:155, at 174 (1999), the authors note as follows concerning arbidol:

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6 I.T. Fedyakina, et al., Vopr Virusol No. 6 (2005).

7 T.A. Semenenko, *et al.*, Zh Mikrobiol Epidemiol Immunobiol No. 6 (2005).

8 I.A. Leneva, A.M. Shuster, A.J. Hay, and R.G. Glushkov, Antiviral Research 65(3): A63-64 (March 2005).

Arbidol [6-bromo-4(dimethyl-aminomethyl)-5-hydroxy-1-methyl-2-(phenylth-iomethyl)-1H-indole-3-carboxylic acid ethyl ester hydrochloride monohydrate] has been launched by the Russian Federation as a treatment for influenza A and B virus infections. This compound is an antiviral and immunostimulatory agent that appears to inhibit the fusion of the influenza envelope with the hose cell membrane (Leneva IA, Fadeeva NI & Fedykina IT; The study of effect of a new antiviral drug arbidol on different stages of viral reproduction. *7th International Conference on Antiviral Research*, 1994, Abstract 187). Additionally, the antiviral activity of arbidol may be related, in part, to the ability of this drug to induce interferon and activate 2,5-oligoadenylate synthetase (Guskova TA, Nikolaeva IS & Zakharova NG: Experimental and clinical study of arbidol, an antiviral drug. *9th Mediterranean Congress of Chemotherapy*, 1994, Abstract 82). Arbidol has been evaluated in clinical trials involving more than 9000 patients and no adverse events were reported (Glushkov, 1992). In clinical studies involving 2000 patients, arbidol was administered orally at a dose of 200 mg daily for 5-10 days and was shown to prevent influenza and other acute respiratory diseases in 85% of the contacts of infected patients. Also, arbidol prophylaxis was shown to be 80% effective during influenza outbreaks (Guskova TA, Nikolaeva IS & Zakharova NG: Experimental and clinical study of arbidol, an antiviral drug. *9th Mediterranean Congress of Chemotherapy*, 1994, Abstract 82).

In accordance with the Draft Guidance recommendations regarding effectiveness of the product (at page 14 of the Draft Guidance), we respond with the following:

(a) Mechanism of the product's action to treat or prevent the disease. "Arbidol inhibits the reproduction of influenza viruses A/H5, and its inhibitory effect is directly proportional to its concentration." I.A. Leneva, *et al.*, *supra*. Arbidol "effectively inhibited reproduction of HPAI/H5N1 virus ." D.K. Lvov, *et al., supra.* "Arbidol interacts with influenza viruses HA to increase its stability against conformational changes induced by a lowering of pH, and as a result inhibits the fusion of the virus' lipid membrane with the endosomal membrane, which would lead to release of the virus nucleocapsid and the start of virus genome transcription." I.T. Fedyakina, *et al.*,

*supra*. "Arbidol inhibited viral reproduction of all antigen subtype of human influenza A and B viruses, avian influenza viruses, possessing H5 and H9, and rimantadine-resistant strains of influenza A viruses." I.A. Leneva, A.M. Shuster, A.J. Hay, and R.G. Glushkov, *supra*.

(b) Preclinical testing data, such as *in vitro* evidence, of the effect of the product in preventing influenza. Please see the attached studies, which included *in vitro* evidence of arbidol's ability to inhibit virus reproduction.

(c) Demonstration of effectiveness in treating or preventing influenza in at least one relevant animal species. Please see (d) below regarding studies in humans.

(d) Evidence of effect in humans. Arbidol has been in use in Russia for over 20 years. Additionally, one study using humans showed that arbidol increased interferon production, and in combination with vaccine led to an increase in immune response. T.A. Semenenko, *et al., supra*. Additionally, in testing among Russian servicemen arbidol was shown to have high effectiveness in the prophylaxsis of influenza and other acute viral respiratory infections. A.M. Shuster, *et al.*, Voen Med Zh. 2004 Sep; 325(9):44-5, 80.

(e) Data to support proposed dosage. Attached at Tab E is a copy of the Russian patent of arbidol, with English translation, setting forth dosages.

7. Discussion of the risks and benefits. As set detailed above and according to the clear weight of the published medical literature (see TAB B), arbidol is effective at a very safe dose. The risks of arbidol appear to be very low, and the potential benefit, given the virtual absence in the United States of supplies of any effective drug to combat an avian flu pandemic, is enormous. Moreover, evidence that neuraminidase inhibitors such as Tamiflu have limited effectiveness against certain strains of avian influenza points to the urgent need for alternative antivirals.

8. Description of information for health care providers, authorized dispensers, and recipients of the product. Such information is readily available because of the long use of arbidol in Russia. Attached at TAB F is

the Russian language package insert setting forth such information, together with English translation.

9. Information on chemistry, manufacturing and controls. The chemistry of arbidol is set forth above at page 4. Controls on the manufacturing process are through the relevant regulatory agencies of Russia and China.

10. Instructions for use of the EUA product. These are attached at TAB F.

11. Proposed labeling. Proposed labeling is attached at TAB G.

3. Questions to the FDA regarding our data and our development plans.

None at this time.

4. Conclusion.

On behalf of Good Earth Medicine LLC, we request that further testing be performed as described above, and that arbidol be approved for Emergency Use.

Sincerely,

Good Earth Medicine LLC

By: _____
Gary Rohrabaugh, Business Manager

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