

Exhibit  
4

## NSURE<sup>®</sup> (Natamycin Feed Additive)

### Exhibit 4: Chronology of Events

<u>Date</u>	<u>Event</u>
5/1/89	Investigational Food Additive Petition (IFAP) was filed requesting the use of antifungal substance Natamycin at the rate of 10 g per ton of poultry feed in broiler chickens.
5/8/89	The FDA received and acknowledged the IFAP submitted on May 1, 1989 and assigned it a case number 6454.
6/7/89-6/12/95	Safety evaluations, assay methods, utility studies, field trial evaluations, environmental assessments, genetic toxicology studies, manufacturing protocols, and mixing trial protocols were submitted in response to FDA communications. (Further detail can be provided if needed.)
6/30/95	Food Additive Petition (FAP) was filed for the use of Natamycin as a mold retardant of <i>Aspergillus Parasiticus</i> , <i>Penicillium rubrum</i> , and <i>Fusarium moniliform</i> .
7/17/95	Amendment to FAP submitted on 6/30/95 addressing the issue of "proposed tolerances for the food additive" was filed.
8/18/95	Amendment to FAP submitted on 6/30/95 was filed.
9/6/95	The FDA received and acknowledged that FAP, submitted on 6/30/95, is acceptable and given FAP No. 2234. FDA indicated that a detailed review of the petition will be completed within 90 days.
10/26/95	Manufacturing facility compliance documents were submitted to the FDA in response to a phone conversation held with Dr. Ron Bloom of the Environmental Staff of the Center for Veterinary Medicine.
11/13/95	The Colorado manufacturing facility confirmed that the FDA had visited the facilities on 11/1/95, 11/6/95, 11/7/95 and 11/8/95 and conducted an exit interview on 11/13/95.
12/26/95	The FDA extended the review period for FAP 2234 from 90 to 180 days as per 21 CFR § 571.100(b).

6/6/96

The FDA issues Response regarding FAP 2234 stating that the petition contained the following deficiencies and required additional information to support a claim of efficacy. The FDA requested:

1. The product packaging must be changed.
2. Proper evidence to show materials were sterilized by the autoclave. New tests should include microbiological analysis before and after autoclaving including total aerobic counts for the presence and absence of molds.
3. Additional experiments including negative controls consisting of only sterilized feed.
4. Experimentation indicating the moisture content of feed samples determined by AOAC methods.
5. Experimentation indicating the spore concentration used for inoculation as determined by the standard dilution and pour plate techniques.
6. The specific amounts of natamycin premix in the various concentrations of natamycin tested must be provided.
7. An explanation for the pre-incubation periods.
8. An explanation of how the cumulative values for the third experiment were derived.
9. Explanations of the discrepancies between the raw, hand-written data and the recorded data.
10. Re-conducting the experiments for retardation of growth of *penicillium rubrum*.
11. A further, detailed analysis for experiment number 6.
12. Re-conducting experiment number 7.
13. An explanation for the deficiencies of experiment 11 or re-conducting experiment 11.

The extensive requests by the FDA in their review of FAP 2234 resulted in a meeting with FDA scientists, in which the conclusion was to re-run the experiments similar to those conducted as part of the original FAP submissions. New tests were agreed to be limited to one organism, *Aspergillus parasiticus*.

6/6/96 - 7/31/01

Following the instructions of FDA scientists, Ducoa re-ran experiments and ran several new experiments, all documented by internal study numbers. (A more detailed list can be provided as needed.)

These studies included, but were not limited to:

1. A series of autoclave studies supporting sterilization of instruments, glassware and feed handling items. Studies also included moisture effects on feed samples during autoclave sterilization.
2. Sterilization studies of feed. Comparative analysis of effects of sterilization by way of irradiation.
3. Moisture studies analyzing moisture content of feed.

4. Mixing studies, including the purchase and validation of new blending machines.
5. Inoculum studies.
6. Air-flow studies of chambers in each of four respirometers used in the studies, including an analysis of over 400 valves within the respirometers.
7. Equipment validation studies of the 4 respirometers including extensive consulting by the manufacturer.
8. Complete re-design of existing mold measurement procedure used to obtain approval by the FDA in review of feed additives for inhibiting mold in order to meet FDA requirements.

6/99 - 4/00	Applicants did not actively pursue approval due to lack of funding during this period.
7/31/01	Ducoa submits to FDA an amendment to FAP 2234, that includes the results from the extensive re-run studies.
10/26/02	Franklin Carter submits notification to FDA of assignment from Ducoa LP to Arkion Life Sciences.
3/12/03	FDA acknowledges receipt of change of ownership.
3/13/03	FDA acknowledges receipt of July 31, 2001 amendment to FAP 2234 and has completed a review. FDA indicates that amendment to FAP 2234 filed on July 31, 2001 is satisfactory in establishing the utility of natamycin in retarding growth of <i>Aspergillus parasiticus</i> in broiler chicken feed for up to 14 days. FDA, however, requires correction of two minor deficiencies and suggests label changes to that effect.
Undated letter	Undated letter by Arkion referencing the 3/13/03 letter of the FDA and agreeing to the suggested changes.
4/14/03	FDA acknowledges receipt of undated Applicant's response to the FDA's March 13, 2003 letter and indicates that FAP 2234 is satisfactory in establishing the utility of natamycin (in the form of a premix containing calcium carbonate, natamycin, and lactose) in retarding growth of <i>Aspergillus parasiticus</i> in broiler chicken feed for up to 14 days. Again, FDA notes discrepancy in the specification on the approved product and asks Applicant to clarify. FDA also suggests additional label changes.
4/21/03	Arkion clarifies discrepancy and submits label changes as suggested by the FDA.
8/03 - 11/03	Several teleconferences were held between FDA and Arkion regarding status of approval letter. No formal communications from FDA have issued, however, since the April 14, 2003 communication referred to above.

3/25/04

Received letter from Stephen Sundlof, Director of the Center for Veterinary Medicine, FDA indicating Arkion's Food Additive petition of 31 July 2003, which is an appended petition to 6 September 1995, will be officially approved upon publication in the Federal Register.

4/13/04

Publication in the Federal Register that the Food and Drug Administration (FDA) is amending the regulations for food additives permitted in feed and drinking water of animals to provide for the safe use of natamycin in broiler chicken feeds. natamycin. This action is in response to a food additive petition filed by Arkion Life Sciences of Wilmington, DE.