

Date of Approval: June 14, 2018

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 098-379

CYSTORELIN®

gonadorelin

Injectable Solution

Lactating dairy cows and beef cows

Provides for the addition of a new indication 'For use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.'

Sponsored by:

Merial, Inc.

## Table of Contents

I. GENERAL INFORMATION.....	3
II. EFFECTIVENESS .....	4
A. Dosage Characterization.....	5
B. Substantial Evidence .....	8
III. TARGET ANIMAL SAFETY.....	9
IV. HUMAN FOOD SAFETY.....	9
A. Antimicrobial Resistance.....	9
B. Effects of Residues on Human Intestinal Flora .....	10
C. Toxicology .....	10
D. Residue Chemistry .....	10
E. Analytical Method for Residues.....	11
V. USER SAFETY.....	11
VI. AGENCY CONCLUSIONS.....	11
A. Marketing Status .....	12
B. Exclusivity .....	12
C. Supplemental Applications .....	12
D. Patent Information:.....	12

**I. GENERAL INFORMATION**

**A. File Number**

NADA 098-379

**B. Sponsor**

Merial, Inc.  
3239 Satellite Blvd., bldg. 500  
Duluth, GA 30096-4640

Drug Labeler Code: 050604

**C. Proprietary Name**

CYSTORELIN®

**D. Product Established Name**

gonadorelin

**E. Pharmacological Category**

Peptide hormone

**F. Dosage Form**

Injectable solution

**G. Amount of Active Ingredient**

50 mcg/mL gonadorelin diacetate tetrahydrate (equivalent to 43 mcg/mL gonadorelin)

**H. How Supplied**

10 mL and 30 mL multi-dose vials

**I. Dispensing Status**

Rx

## **J. Dosage Regimen**

The intramuscular dosage of CYSTORELIN is 100 mcg gonadorelin diacetate tetrahydrate (2 mL) per cow, used in reproductive synchrony programs similar to the following:

1. Administer the first CYSTORELIN injection (2 mL) at Time 0.
2. Administer 500 mcg cloprostenol (as cloprostenol sodium) by intramuscular injection 6 to 8 days after the first CYSTORELIN injection.
3. Administer the second CYSTORELIN injection (2 mL) 30 to 72 hours after the cloprostenol sodium injection.
4. Perform fixed time artificial insemination (FTAI) 0 to 24 hours after the second CYSTORELIN injection, or inseminate cows on detected estrus using standard herd practices.

## **K. Route of Administration**

Intramuscular

## **L. Species/Class**

Lactating dairy cows and beef cows

## **M. Indication**

For use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows

## **N. Effect of Supplement**

This supplement provides for the addition of a new indication '*For use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows.*'

# **II. EFFECTIVENESS**

Effectiveness of CYSTORELIN® for the addition of a new indication '*For use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows*' was established through a combination of sources. The original approval for CYSTORELIN®, NADA 098-379, approved March 10, 1978 (Federal Register, Volume 43 p. 9804, dated March 10, 1978), established the basis for the dose, dosage form, route of administration, formulation, and mechanism of action for the use of CYSTORELIN® for the current indication. Substantial evidence of effectiveness was established by right of reference to ANADA 200-541 for GONABreed® (gonadorelin), which is approved for use with cloprostenol injection (as cloprostenol sodium) to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows. Information from published literature was used to confirm the effectiveness for CYSTORELIN® when used to synchronize estrous cycles and to establish a range for the timing of injections and FTAI to maintain effectiveness and allow flexibility for the end user.

## A. Dosage Characterization

### 1. Dose selection

This supplemental approval does not change the previously approved dosage of CYSTORELIN® for the treatment of ovarian follicular cysts in dairy cattle. CYSTORELIN® contains 50 mcg/mL of gonadorelin diacetate tetrahydrate, which is equivalent to 43 mcg/mL of gonadorelin. The original approval of NADA 098-379, approved March 10, 1978 (Federal Register, Volume 43 p. 9804, dated March 10, 1978), contains dosage characterization information for the labeled dose of CYSTORELIN® for treatment of ovarian follicular cysts in dairy cattle, which is 2 mL per cow to deliver 100 mcg gonadorelin diacetate tetrahydrate (86 mcg gonadorelin) to the treated animal. This dose of CYSTORELIN® initiates release of endogenous luteinizing hormone (LH) to cause ovulation of ovarian follicles large enough to have acquired ovulatory capacity (Sartori et al., 2001, Souza et al. 2009).

The dose of 100 mcg gonadorelin diacetate tetrahydrate (86 mcg gonadorelin) is well-established and is the dose used in most studies in the published literature for gonadorelin-prostaglandin reproductive synchrony/FTAI regimens in cattle (Fricke et al. 1998, Gumen et al. 2003, Jordan et al. 2002, Momcilovic et al. 1998, Pursley et al. 1995, Pursley et al. 1997, Stevenson et al. 1996, Stevenson et al. 1999). Published data from these studies support the dose of 100 mcg gonadorelin diacetate tetrahydrate (86 mcg gonadorelin) as an appropriate dose for use in synchronization of estrous cycles to allow for FTAI regimens in lactating dairy cows and beef cows.

The multi-center field effectiveness studies in ANADA 200-541, as referenced by the sponsor, also provide a basis to establish the effectiveness of CYSTORELIN® for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows and beef cows.

### 2. Timing of administration

Synchronization of estrous cycles with gonadorelin and a prostaglandin (e.g., cloprostenol sodium) is commonly referred to as a "GPG protocol" because it incorporates an initial gonadorelin (G1) injection, a prostaglandin (P) injection, and a final gonadorelin (G2) injection, followed by a single artificial insemination at a predetermined time (known as fixed time artificial insemination, FTAI). The scientific literature as well as the known biology of the bovine estrous cycle was used to define the GPG treatment schedule for CYSTORELIN® and prostaglandin (e.g., cloprostenol sodium). The timing between the last gonadorelin injection and FTAI was chosen based upon information available in the scientific literature.

*Timing from G1 to P:* The purpose of administering the initial gonadorelin injection (G1) is to initiate a new wave of follicular development (Pursley et al. 1995, Pursley et al. 1997, Schmitt et al. 1996, Thatcher et al. 1989, Twagiramungu et al. 1995). The conventional interval between G1 and P is seven days. Pregnancy rate to FTAI is similar when the interval between G1 and P is six or seven days (Martinez et al. 2002). The maximum duration between G1 and P is influenced by the typical duration of an ovarian follicular

wave, which is seven to nine days (Fortune et al. 2001, Ginther et al. 2001). Extended intervals from G1 to P reduce synchrony to the GPG protocol for cows that turn over a dominant follicle, resulting in a lack of ovulatory response to G2. This supports a maximum interval of eight days between G1 and P to assure ovulation of the dominant follicle that emerged following G1. Taken together, these data support the directions for use statement "Administer 500 mcg cloprostenol (as cloprostenol sodium) by intramuscular injection 6 to 8 days after the first Cystorelin injection."

*Timing from P to G2:* The purpose of treating cows with G2 is to induce a pre-ovulatory surge in LH in a predictable manner, such that ovulation in groups of animals occurs in a sufficiently narrow time-frame to allow for FTAI. The conventional interval between P and G2 is two to three days (e.g., 48 to 72 hours). A study by Pursley et al. (1997) demonstrated that in dairy cows the pregnancy rates were similar between cows given G1 and P and bred by artificial insemination (AI) based on detected estrus compared to cows given G1, P, G2 (30 to 36 hours after P), and bred by FTAI. Intervals shorter than 30 hours do not appear to maintain the same level of effectiveness (Rantala et al. 2009, Schmitt et al. 1996, Peters and Pursley 2003). An interval between P and G2 greater than 72 hours is not supported by the scientific literature and is unlikely to provide any benefit, as the LH surge may have already occurred. These data support the directions for use statement "Administer the second Cystorelin injection (2 mL) 30 to 72 hours after the cloprostenol sodium injection."

*Timing from G2 to FTAI:* The interval between G2 and FTAI varies for different estrous synchronization regimens. Pursley et al. (1998) demonstrated that pregnancy rate per AI did not differ among cows bred to FTAI 0, 8, 16, or 24 hours after G2, but was reduced in cows bred to FTAI 32 hours after G2. The field effectiveness studies referenced below incorporated a wide range of intervals between G2 and FTAI. The referenced study conducted in beef cows performed FTAI immediately after the G2 (0 hour interval). The referenced study conducted in lactating dairy cows performed FTAI 11 to 31 hours after the G2 injection. Results from the referenced field studies combined with the data from Pursley et al. (1998) support use of FTAI 0-24 hours after G2.

Producers may opt to inseminate cows based on detected estrus after the prostaglandin (P) injection. Some cows may express estrus prior to G2 or prior to the predetermined time for FTAI. Several published studies demonstrated that the pregnancy rate in dairy cows to AI based on detected estrus after P was similar to pregnancy rates obtained after a GPG protocol with FTAI (Pursley et al. 1997, Santos et al. 2004). These results support use of AI based on detected estrus after P (with or without use of G2).

Taken together, these data support the directions for use statement "Perform FTAI 0 to 24 hours after the second Cystorelin injection, or inseminate cows on detected estrus using standard herd practices."

Based on this information from the published literature and the referenced studies, CYSTORELIN® is expected to be effective when the timing of injections and FTAI is consistent with typical GPG reproductive synchrony protocols used for lactating dairy cows and beef cows, which forms the basis for the labeled directions for use (below). End users may choose specific timing for injections and FTAI within these ranges for their specific animal and management practices.

The intramuscular dosage of CYSTORELIN is 100 mcg gonadorelin diacetate tetrahydrate (2 mL) per cow, used in reproductive synchrony programs similar to the following:

1. Administer the first CYSTORELIN injection (2 mL) at Time 0.
2. Administer 500 mcg cloprostenol (as cloprostenol sodium) by intramuscular injection 6 to 8 days after the first CYSTORELIN injection.
3. Administer the second CYSTORELIN injection (2 mL) 30 to 72 hours after the cloprostenol sodium injection.
4. Perform FTAI 0 to 24 hours after the second CYSTORELIN injection, or inseminate cows on detected estrus using standard herd practices.

### 3. Literature Cited

- Fortune, J.E., Rivera, G.M., Evans, A.C., and Turzillo, A.M. (2001). Differentiation of dominant versus subordinate follicles in cattle. *Biology of Reproduction*, 65, 648-654
- Fricke, P. M., Guenther, J.N., and Wiltbank, M.C. (1998). Efficacy of decreasing the dose of GnRH used in a protocol for synchronization of ovulation and timed AI in lactating dairy cows. *Theriogenology*, 50, 1275-1284
- Ginther, O.J., Bergfelt, D.R., Beg, M.A., and Kot, K. (2001). Follicle selection in cattle: relationships among growth rate, diameter ranking, and capacity for dominance. *Biology of Reproduction*, 65, 345-350
- Gumen, A., Guenther, J.N., and Wiltbank, M.C. (2003). Follicular size and response to Ovsynch versus detection of estrus in anovular and ovular lactating dairy cows. *Journal of Dairy Science*, 86, 3184-3194
- Jordan, E.R., Schoutent, M.J., Quast, J.W., Belschner, A.P., and Tomaszewski, M.A. (2002). Comparison of two timed artificial insemination (TAI) protocols for management of first insemination post partum. *Journal of Dairy Science*, 85, 1002-1008
- Martinez, M.F., Kastelic, J.P., Adams, G.P., Cook, B., Olson, W.O., and Mapletoft, R.J. (2002). The use of progestins in regimens for fixed-time artificial insemination in beef cattle. *Theriogenology*, 57, 1049-1059
- Momcilovic, D., Archbald, L.F., Walters, A., Tran, T., Kelbert, D., Risco, C, and Thatcher, W.W. (1998). Reproductive performance of lactating dairy cows treated with gonadotrophin-releasing hormone (GnRH) and/or prostaglandin F2a (PGF2a) for synchronization of estrus and ovulation. *Theriogenology*, 50, 1131-1139
- Peters, M.W., and Pursley, J.R. (2003). Timing of final GnRH of the Ovsynch protocol affects ovulatory follicle size, subsequent luteal function, and fertility in dairy cows. *Theriogenology*, 60, 1197-1204
- Pursley, J.R., Mee, M.O., and Wiltbank, M.C. (1995). Synchronization of ovulation in dairy cows using PGF2a and GnRH. *Theriogenology*, 44, 915-923

Pursley, J.R., Wiltbank, M.C., Stevenson, J.S., Ottobre, J.S., Garverick, H.A., and Anderson, L.L. (1997). Pregnancy rates per artificial insemination for cows and heifers inseminated at a synchronized ovulation or synchronized estrus. *Journal of Dairy Science*, 80, 295-300

Pursley, J.R., Silcox, R.W., and Wiltbank, M.C. (1998). Effect of time of artificial insemination on pregnancy rates, calving rates, pregnancy loss, and gender ratio after synchronization of ovulation in lactating dairy cows. *Journal of Dairy Science*, 81, 2139-2144

Rantala, M.H., Katila, T., and Taponen, J. (2009). Effect of time interval between prostaglandin F2a and GnRH treatments on occurrence of short estrous cycles in cyclic dairy heifers and cows. *Theriogenology*, 71, 930-938

Santos, J.E.P., Juchem, S.O., Cerri, R.L.A., Galyao, K.N., Chebel, R.C., Thatcher, W.W., Dei, C.S., and Bilby, C.R. (2004). Effect of bST and reproductive management on reproductive performance of Holstein dairy cows. *Journal of Dairy Science*, 87, 868-881

Sartori, R., Fricke, P. M., Ferreira, J. C. P., Ginther, O. J., and Wiltbank, M. C. (2001). Follicular deviation and acquisition of ovulatory capacity in bovine follicles. *Biol. Reprod.* 65:1403-1409

Schmitt, E.J., Diaz, T., Drost, M., Thatcher, W.W. (1996). Use of a gonadotropin-releasing hormone agonist or human chorionic gonadotropin for time insemination in cattle. *Journal of Animal Science*, 74, 1084-1091.

Souza, A.H., Cunha, A.P., Silva, E.P., Gumen, A., Ayres, H., Guenther, J.N., and Wiltbank, M.C. (2009). Comparison of gonadorelin products in lactating dairy cows: efficacy based on induction of ovulation of an accessory follicle and circulating luteinizing hormone profiles. *Theriogenology*, 72, 271-279

Stevenson, J.S., Kobayashi, Y., Shipka, M.P., & Rauchholz, K.C. (1996). Altering conception of dairy cattle by gonadotrophin-releasing hormone preceding luteolysis induced by prostaglandin F2a. *Journal of Dairy Science*, 79, 402-410.

Stevenson, J.S., Kobayashi, Y., & Thomjason, K.E. (1999). Reproductive performance of dairy cows in various programmed breeding systems including OvSynch and combinations of gonadotrophin-releasing hormone and prostaglandin F2 alpha. *Journal of Dairy Science*, 82, 506-515.

Thatcher, W.W., Macmillan, K.L., Hansen, P.J., and Drost, M. (1989). Concepts for regulation of corpus luteum function by the conceptus and ovarian follicles improve fertility. *Theriogenology*, 31, 149-164

Twagiramungu, H., Guilbault, L.A., and Dufour, J.J. (1995). Synchronization of ovarian follicular waves with a gonadotropin-releasing hormone agonist to increase the precision of estrus in cattle: a review. *Journal of Animal Science*, 73, 3141-3151

## **B. Substantial Evidence**

Studies to demonstrate effectiveness of gonadorelin for use with cloprostenol injection (as cloprostenol sodium) to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows were described in Parnell's approved ANADA 200-541 for GONAbreed®, to which Merial has right of reference. The approved dose of GONAbreed® is 100 mcg gonadorelin



(as the acetate salt). The studies are summarized in the Freedom of Information Summary for GONAbreed®, dated January 17, 2013.

Synchronization of estrous cycles using gonadorelin products with cloprostenol injection (as cloprostenol sodium) has been extensively researched since the mid-1990s. Information from NADA 098-379 and the scientific literature support that the dose and formulation of CYSTORELIN will have a similar effect to the referenced studies. Based on this information, a 2-mL dose of CYSTORELIN® delivering 100 mcg gonadorelin diacetate tetrahydrate (86 mcg gonadorelin) is effective for use with cloprostenol sodium to synchronize estrous cycles to allow for FTAI in lactating dairy cows and beef cows.

### **III. TARGET ANIMAL SAFETY**

No target animal safety studies were required for this supplemental approval of CYSTORELIN® (gonadorelin) with FDA-approved cloprostenol injection (as cloprostenol sodium) in lactating dairy cows and beef cows. The original approval of NADA 098-379, approved March 10, 1978 (Federal Register, Volume 43 p. 9804, dated March 10, 1978), contains a summary of target animal safety studies of CYSTORELIN®. The dose, dosage form (injectable solution), and route of administration (intramuscular) for CYSTORELIN® are the same as those for the original approval of CYSTORELIN® (NADA 098-379, March 10, 1978). The dose, dosage form (injectable solution), and route of administration (intramuscular) of FDA-approved cloprostenol injection are the same as those for FDA-approved cloprostenol injection as a standalone treatment.

Synchronization of estrous cycles using gonadorelin products with cloprostenol injection has been extensively researched since the mid-1990s. A literature-based assessment of the target animal safety of CYSTORELIN® with cloprostenol injection was evaluated in lactating dairy cows and beef cows under conditions of use similar to those on the labeling. Repeated exposure to gonadorelin and cloprostenol injection does not appear to cause any adverse effects. Gonadorelin and cloprostenol injection (as cloprostenol sodium) are rapidly and extensively metabolized in cattle, and reports in the literature indicate that levels of these products in plasma return to baseline levels within three hours of administration. The dosing intervals between the administrations of CYSTORELIN® and cloprostenol injection are substantially longer than the half-lives of the drugs. These classes of drugs have their effect through receptors with unique and specific actions; drug interactions leading to adverse effects are not anticipated.

Studies to demonstrate target animal safety of gonadorelin under intended use conditions when used with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows, were described in Parnell's approved ANADA 200-541 for GONAbreed®, to which Merial has right of reference. The studies are summarized in the Freedom of Information Summary for GONAbreed®, dated January 17, 2013.

### **IV. HUMAN FOOD SAFETY**

#### **A. Antimicrobial Resistance**

This product is not an antibacterial.

## **B. Effects of Residues on Human Intestinal Flora**

This product is not an antibacterial.

## **C. Toxicology**

CVM did not require toxicology studies for this approval. Safety of gonadorelin diacetate tetrahydrate has been established for the original approval of NADA 098-379, dated March 10, 1978. A literature-based safety evaluation supports the conclusion that the use of Cystorelin® (gonadorelin) with FDA-approved cloprostenol injection (as cloprostenol sodium) does not cause human food safety toxicology concerns due to the rapid depletion of their residues in cattle and the sufficiently long dosing intervals for the sequential use. A toxicological acceptable daily intake (ADI), a final ADI, an acute reference dose (ARfD) and safe concentrations for total residues of gonadorelin diacetate tetrahydrate and cloprostenol sodium were not needed for this approval.

## **D. Residue Chemistry**

### **1. Summary of Residue Chemistry Studies**

No residue chemistry studies were required for the approval of the sequential use of Cystorelin® (gonadorelin) with FDA-approved cloprostenol injection (as cloprostenol sodium) in lactating dairy cows and beef cows. The dose, dosage form (injectable solution), and route of administration (intramuscular) for Cystorelin® in the sequential use dosage regimen are the same as those for the original approval of Cystorelin® as a standalone treatment for cattle (NADA 098-379, March 10, 1978). The dose, dosage form (injectable solution), and route of administration (intramuscular) of FDA-approved cloprostenol injection for the sequential use are the same as those for FDA-approved cloprostenol injection as a standalone treatment. Neither a withdrawal period (*i.e.*, zero withdrawal) nor a milk discard time is assigned for Cystorelin® or FDA-approved cloprostenol injection as a standalone treatment for cattle. For the sequential use, FDA-approved cloprostenol injection is to be administered at 6 to 8 days after the administration of the first dose of Cystorelin®. A second dose of Cystorelin® is to be administered at 30 to 72 hours after the administration of FDA-approved cloprostenol injection.

An assessment of human exposure to gonadorelin and cloprostenol residues in the edible tissues and milk of cattle resulting from the sequential use, based on the information under NADA 098-379 and scientific literature, was conducted. The assessment showed that gonadorelin and cloprostenol residues deplete rapidly in cattle. The sufficiently long dosing intervals between the administrations of Cystorelin® and FDA-approved cloprostenol injection in the sequential use, and the anticipated rapid depletion of gonadorelin and cloprostenol residues in cattle after the administrations of Cystorelin® and FDA-approved cloprostenol injection in the sequential use support the conclusion that it is unlikely that the gonadorelin residues resulting from the sequential use will affect the depletion of cloprostenol residues, and *vice versa*. Therefore, the sequential use does not cause residue chemistry concerns beyond those that were addressed for the approvals of Cystorelin® and cloprostenol injection as standalone treatments. Like these individual

approvals, no withdrawal periods or milk discard times are required for the sequential use of CYSTORELIN® with FDA-approved cloprostenol injection.

**2. Target Tissue and Marker Residue**

It is not necessary to assign a target tissue or a marker residue for gonadorelin residues in cattle.

**3. Tolerances**

A tolerance for gonadorelin in cattle tissues or milk is not required.

**4. Withdrawal Period and Milk Discard Time**

The sequential use of CYSTORELIN® (gonadorelin) and FDA-approved cloprostenol injection (as cloprostenol sodium) in lactating dairy cows and beef cows does not require a withdrawal period (*i.e.*, zero withdrawal) or milk discard time (*i.e.*, zero milk discard).

**E. Analytical Method for Residues**

Because a tolerance has not been assigned for either gonadorelin or cloprostenol, a validated analytical method is not necessary for either gonadorelin or cloprostenol.

**V. USER SAFETY**

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to CYSTORELIN®:

Not for use in humans.  
Keep out of reach of children.

The product labeling for cloprostenol contains the following information regarding safety to humans handling, administering, or exposed to cloprostenol:

For animal use only.

Women of childbearing age, asthmatics, and persons with bronchial and other respiratory problems should exercise extreme caution when handling this product. In the early stages, women may be unaware of their pregnancies. Cloprostenol is readily absorbed through the skin and may cause abortion and/or bronchospasms; direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

**VI. AGENCY CONCLUSIONS**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that CYSTORELIN®, when used according to the label, is safe and effective for use with cloprostenol sodium to synchronize estrous cycles to allow for fixed time artificial insemination (FTAI) in lactating dairy cows and beef cows. Additionally, data demonstrate that residues in food products derived from species

treated with CYSTORELIN® will not represent a public health concern when the product is used according to the label.

**A. Marketing Status**

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because veterinary experience is required to properly diagnose ovarian follicular cysts and prescribe appropriate treatment, and because the use of this product for the synchronization of estrous cycles requires the use of cloprostenol injection (as cloprostenol sodium), which also has Rx marketing status.

**B. Exclusivity**

CYSTORELIN®, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the FD&C Act.

**C. Supplemental Applications**

This supplemental NADA required a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

**D. Patent Information:**

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.