TITLE OF PROJECT: **Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days**

DEPARTMENT: **Obstetrics and Gynecology**

PRINCIPAL INVESTIGATOR: **Dr. Daniel R. Mishell Jr.**
COINVESTIGATORS::

TELEPHONE # **(213) 226-3416**

PURPOSE

It is possible to induce abortion in women with unwanted pregnancies by taking mifepristone in combination with a prostaglandin (misoprostol). Mifepristone is a drug which blocks the action of progesterone, a hormone needed to maintain pregnancy. One of mifepristone's actions is to interrupt pregnancy in its early stages. Prostaglandins are natural substances made by the lining of the womb during menstruation and cause contraction of the womb. During the early stages of pregnancy, mifepristone plus misoprostol cause abortion in approximately 95 per cent of women. Major advantages of this method of pregnancy termination are that no surgical instruments are pushed into the womb. Over 150,000 women in 20 countries have used mifepristone and a prostaglandin as a medical method of pregnancy interruption. Mifepristone and misoprostol have been used by over 50,000 women at the dose to be used in this study. The dosage to be studied has been approved legally for routine use in France for women who are pregnant and have experienced seven weeks or less since the last menstrual period, and in Sweden, England, and China for women who are pregnant and have experienced nine weeks or less since the last menstrual period..

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Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days

Protocol number: 166A

The aims of this study are to determine the safety, efficacy and acceptability of mifepristone plus misoprostol for pregnancy termination in women who have experienced 63 days or less from the first day of bleeding from the last menstrual period. These factors will be examined in three groups of women: 1) with pregnancies of durations of less than 50 days: 2) 50 through 56 days and 3) 57 through 63 days, all calculated from the first day of bleeding from the last menstrual period. This study is being performed in connection with the registration of mifepristone plus misoprostol with the U.S. Food and Drug Administration (FDA) so that these products can be used for early pregnancy termination in the U.S.

PROCEDURES

You understand at your initial visit (visit 1) you will receive: counseling about the method, a physical examination and a pelvic examination, a gonorrhea screening, and chlamydia screening. If you have not had a Pap smear in the last year, you will have one at this time. A medical history will be taken, and an ultrasound examination using a small instrument that is placed in your vagina. The aim is to verify the duration of your pregnancy. You will also have blood tests for Rh factor in your blood, a complete CBC to insure you are not anemic, a Beta hCG to see what your pregnancy hormone level is, and a VDRL (screen for syphilis). A total of 4 tablespoons of blood will be drawn for these tests. If you have Rh negative blood type you will be given an injection at the second visit to prevent the development of antibodies that could endanger any future pregnancies. In order to terminate your pregnancy, you will take three tablets of mifepristone (first medication) orally in the presence of study personnel. Two days later, you will return to the clinic (visit 2, day 3) and will take two misoprostol tablets (second medication) by mouth if you have not aborted and will have another tablespoon of blood drawn for a Beta hCG pregnancy hormone level. You will have 2 ultrasounds done on this visit, 1 prior to taking the misoprostol tablets to see if you have already passed the products of pregnancy. Four hours after you have taken the second medication, you will have the second ultrasound. The duration of your stay at the clinic at the second visit will be a little bit longer than four hours, during which time you will be closely

monitored by the study team. During this time there is a 60-80% chance that abortion will occur. You understand that you should arrange for someone to drive you home from the clinic after this second visit and that you should not drive yourself. You understand that if the abortion does not occur at the clinic, it is likely to occur at home and you may continue to have uterine bleeding similar to a heavy menstrual period for several days. You should use sanitary napkins until the uterine bleeding or spotting ends and not use tampons. As with surgical abortion, you cannot resume douching until the bleeding stops (about 10-12 days). You should not resume sexual intercourse for 8-10 days after taking the prostaglandin, by which time most abortions would have been completed.

A further appointment will be made for you to return to the clinic two weeks after taking the first medications (visit 3, day 15), to ensure that the treatment has been effective. If the treatment has not been effective, then a surgical procedure called vacuum aspiration or dilatation and curettage will be performed at that time to complete the abortion. This is the same surgical procedure that would have been used had you elected to undergo surgical abortion in the first instance. Because it is possible to become pregnant again after the abortion, you will be asked to select and use a contraceptive method. You understand that you should arrange for someone to drive you home from the clinic after this third visit and that you should not drive yourself.

You understand that bleeding may continue beyond your third visit. If this occurs, the clinic will contact you by telephone to determine if it has stopped or if you need additional treatment.

BENEFITS: You understand that an advantage of the mifepristone/misoprostol medical method for pregnancy termination is that it avoids a surgical procedure. Unless a surgical procedure is necessary because this medical method is not effective, there is no anesthesia-related risk or risk of uterine perforation or cervical canal injury which may rarely be observed after surgical termination of pregnancy. Another benefit is the satisfaction of participating in the study may make mifepristone/misoprostol available to women in the U.S.

DISCOMFORTS AND RISKS: You understand that experience gained so far with the combination of drugs used in this study for the termination of early pregnancy indicates that this therapy has few side effects. The frequency of short-term complications is comparable to that observed after surgical abortion performed by vacuum aspiration. The most common complaint during treatment (particularly following administration of the second medication) is lower abdominal pain or cramps which are similar to those associated with a very heavy menstrual period. You will receive appropriate medication for pain when required. You understand that you should not take aspirin, Motrin, Ibuprofen, Advil or any other drug known to block the action of prostaglandins. However, you may take Tylenol and you may receive stronger medications for pain from your doctor. You understand that cramps and abdominal pains are usual and an expected part of the abortive process. Nausea, vomiting, and diarrhea have been observed following administration of the second medication. Therefore, at the second visit it is necessary to remain at the clinic under appropriate medical supervision for approximately four hours before returning home. Uterine bleeding, similar to a heavy period and lasting at least one week, may be expected. In rare instances very heavy uterine bleeding may occur requiring surgical abortion and/or blood transfusion. You understand that drawing blood for the tests at your visits may be associated with discomfort, bruising, and rarely, infection at the site of withdrawal.

You understand that it is not advisable to allow a pregnancy to continue after taking mifepristone and/or misoprostol, since the full effects of mifepristone on the fetus are not known and misoprostol administration in early pregnancy has been associated with abnormal development of the fetus. You understand that abortion after the administration of one mifepristone/misoprostol combination is successful in termination of pregnancy in approximately 95% of treated women. When abortion is incomplete or does not occur, it is essential that vacuum aspiration or dilatation and curettage are recommended to terminate

bleeding and prevent anemia. When abortion does not occur, surgical abortion is recommended because of the possible risk to the fetus. You have previously agreed to this procedure. .

There have been no serious heart conditions in the 52,000 women using the combination of drugs in this study for pregnancy termination. However, serious cardiovascular complications, including one fatal heart attack, have occurred during medical abortion using a different drug combination. These heart conditions have occurred usually in women who are heavy smokers or have increased blood fats, diabetes, high blood pressure, or family history of heart disease. This risk also increased in women who are over 35 years of age. These complications have been seen only following an injected prostaglandin and are rare to date (1/20,000 cases); there is no indication that the oral prostaglandin (misoprostol) that you will be taking in this study and which has been used widely for prolonged periods of time in the prevention of stomach ulcers, is associated with such cardiovascular side effects.

You understand that there are no indications at present that use of an antiprogestin to end a pregnancy has prevented or harmed a woman's ability to have a baby in the future. Women who have taken mifepristone have been able to conceive and subsequently bear a healthy child. Because it is possible to become pregnant again after the abortion, you will be asked to select and use a contraceptive method.

ALTERNATIVE METHODS: You know that your pregnancy could be terminated by a surgically performed abortion procedure (dilatation and curettage or vacuum aspiration). The possible advantages and disadvantages of a surgical rather than a medical termination have been explained to you. The advantage of surgical termination of pregnancy is that it is a one day procedure. The risks associated with surgical abortion are minimal. These include the risk of an anesthetic procedure. In the U.S., less than 1% of patients who undergo a surgical

abortion experience a major complication associated with the procedure such as a serious pelvic infection, cervical tear, bleeding requiring a blood transfusion or unintended major surgery (for a uterine perforation).

CONFIDENTIALITY STATEMENT: The confidentiality of your medical records for this study will be maintained by the investigators and the _____ (IRB). Specific study-related information may be sent to the sponsor or its designated monitors, but your name will be deleted. The Food and Drug Administration (FDA) and the sponsor will be allowed access to your medical records. Unless required by law or unless you otherwise consent, the FDA and the sponsor will maintain the confidentiality of your medical records.

You understand that you may be asked to be interviewed by a representative of the sponsor. The interview will be conducted in the language that you speak and will verify that you understand the risks, benefits, procedures, and the experimental nature of the study. If you do not agree to be interviewed, this will not affect your present or future medical care from the hospital or the clinic, or your participation in the study. You understand that you can change your mind at any time. All information will be kept confidential.

OFFER TO ANSWER QUESTIONS AND FREEDOM TO WITHDRAW FROM THE STUDY: If you have any questions relating to the study please feel free to ask us at any time. You understand you may withdraw from the study at any time without jeopardy to your present or future medical care from the hospital or clinic. However, if you withdraw at anytime after taking any medication under the study for any reason you will be assessed for the completeness of the abortion, if possible. If you have received mifepristone and have at the time of early termination had an incomplete abortion, you will undergo surgical abortion. If you have any questions or problems related to this study which have not been satisfactorily answered please feel free to contact the principal investigator, Dr. Daniel Mishell (telephone 213 226-3104). You are required to read, sign, and receive a copy of the experimental subject's bill of rights (California Health and Safety Code, Section 24.782

You also understand that the Principal Investigator may require you to withdraw from the study, if in his medical judgement it is in the best interest of my health or if it becomes impossible for me to follow the experimental procedure of this study.

You understand that, if my treatment under the study does not result in an abortion, and you refuse surgical abortion and continue with your pregnancy, you risk, and the infant may risk, complications, including fetal or infant malformation.

COMPENSATION: You will receive no monetary compensation for your participation in this study.

COERCION AND WITHDRAWAL STATEMENT: Your decision whether or not to participate in this study will not interfere with your future care in this institution. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time. The study physician, Dr. Daniel Mishell and/or the sponsor may also discontinue your participation in this study with or without your consent.

INJURY STATEMENT FOR MEDICAL CENTER: If you require medical treatment as a result of injury arising from your participation in this study, the financial responsibility for such care will be yours.

WHOM TO CALL IN AN EMERGENCY: You understand that if severe uterine bleeding, or abdominal pain, or any other medical emergency arises in association with this method, you will report immediately to [redacted] Emergency Room, [redacted] Los Angeles, CA 90033, (Telephone [redacted] In addition, you will contact Dr. Daniel Mishell (Telephone # 213 226-3104) If he cannot be reached in a medical emergency related to the study, you should contact [redacted] (Telephone# 213 226-3104) When you arrive at the

Emergency Room, one of these physicians will be contacted by the Emergency Room personnel.

INFORMED CONSENT: "You are willing ( ), or you are not willing ( ) to be interviewed by a representative of the sponsor. You understand that you can change your mind at any time. If you do not agree to be interviewed, this will not affect your present or future medical care from the hospital or the clinic, or your participation in the study. The interview, conducted in the language you speak, will verify that you understand the risks, benefits, procedures, and the experimental nature of the study. All information will be kept confidential.

NEW INFORMATION: Any new information regarding these drugs which might influence your willingness to continue participation in this study will be given to you at such time as this information becomes known.

AGREEMENT: Your signature indicates that you have decided to participate having read the information provided above. The risks and benefits have been explained to you in the language you understand.

12/13/94
Date

Signature

12/13/94
Date

Signature of Witness to
Above Signature and Explanation

Revised 11/8/94

APPROVED AUG 18 1994

CONSENT VOID 1 YEAR
FROM ABOVE DATE

APPEARS THIS WAY
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TO BE SIGNED AND DATED BY STUDY SUBJECT AND PLACED IN THE HOSPITAL CHART.

HUMAN RIGHTS IN MEDICAL STUDIES

CALIFORNIA STATE LAW REQUIRES THAT YOU MUST BE INFORMED ABOUT:

1. THE NATURE AND PURPOSE OF THE STUDY.
2. THE PROCEDURES IN THE STUDY AND ANY DRUG OR DEVICE TO BE USED.
3. DISCOMFORTS AND RISKS TO BE EXPECTED FROM THE STUDY.
4. BENEFITS TO BE EXPECTED FROM THE STUDY.
5. ALTERNATIVE PROCEDURES, DRUGS OR DEVICES THAT MIGHT BE HELPFUL AND THEIR RISKS AND BENEFITS.
6. AVAILABILITY OF MEDICAL TREATMENT SHOULD COMPLICATIONS OCCUR.
7. THE OPPORTUNITY TO ASK ANY QUESTIONS ABOUT THE STUDY OR THE PROCEDURE.
8. THE OPPORTUNITY TO WITHDRAW AT ANY TIME WITHOUT AFFECTING YOUR FUTURE CARE AT THIS INSTITUTION.
9. A COPY OF THE WRITTEN CONSENT FORM FOR THE STUDY.
10. THE OPPORTUNITY TO CONSENT FREELY TO THE STUDY WITHOUT THE USE OF COERCION.
11. STATEMENT REGARDING LIABILITY FOR PHYSICAL INJURY, IF APPLICABLE.

IF YOU HAVE ANY QUESTIONS OR CONCERNS REGARDING THESE RIGHTS OR THE CHARACTER OF THE STUDY, PLEASE FEEL FREE TO DISCUSS THEM WITH THE PERSON(S) CONDUCTING THE STUDY OR YOU MAY CONTACT THE RESEARCH COMMITTEE CHAIRMAN AT THE LAC-USC MEDICAL CENTER, (213) 223-2340

• I HAVE READ AND UNDERSTOOD MY RIGHTS FOR PARTICIPATION IN THE STUDY.

_____ 12/13/94

SIGNATURE OF SUBJECT OR GUARDIAN / *FIRMA DEL SUJETO O PERSONA RESPONSABLE* — *DATE* / *FECHA*

DERECHOS HUMANOS EN ESTUDIOS MÉDICOS

LA LEY DEL ESTADO DE CALIFORNIA REQUIERE QUE UD. TIENE QUE ESTAR INFORMADO SOBRE:

1. LA NATURALEZA Y EL PROPÓSITO DEL ESTUDIO.
2. LOS PROCEDIMIENTOS DEL ESTUDIO Y CUALQUIER FÁRMACO, APARATO O DISPOSITIVO QUE SE VAYA A UTILIZAR.
3. LAS MOLESTIAS Y LOS RIESGOS QUE SE ANTICIPAN DEL ESTUDIO.
4. LOS BENEFICIOS QUE SE PUEDAN ESPERAR DEL ESTUDIO.
5. LOS PROCEDIMIENTOS ALTERNOS, FÁRMACOS O DISPOSITIVOS QUE PUEDAN SER ÚTILES Y LOS RIESGOS Y BENEFICIOS QUE ESTOS LLEVAN.
6. DISPONIBILIDAD DE TRATAMIENTO MÉDICO EN CASO QUE OCURRAN COMPLICACIONES.
7. LA OPORTUNIDAD PARA HACER CUALESQUIERA PREGUNTAS SOBRE EL ESTUDIO O EL PROCEDIMIENTO.
8. LA OPORTUNIDAD PARA RETIRARSE DEL ESTUDIO EN CUALQUIER MOMENTO SIN AFECTAR SU ATENCIÓN MEDICA FUTURA EN ESTA INSTITUCIÓN.
9. UNA COPIA DE ESTE CONSENTIMIENTO FIRMADO PARA EL ESTUDIO.
10. LA OPORTUNIDAD PARA CONSENTIR LIBREMENTE AL ESTUDIO SIN EL USO DE COERCIÓN.
11. DECLARACIÓN ACERCA DE LA RESPONSABILIDAD POR DAÑOS FÍSICOS, SI ES APLICABLE.

SI UD. TIENE CUALESQUIERA PREGUNTAS O PREOCUPACIONES ACERCA DE ESTOS DERECHOS O EL CARÁCTER DEL ESTUDIO, POR FAVOR SIÉNTASE LIBRE PARA DISCUTIRLOS CON LA(S) PERSONA(S) LLEVANDO A CABO EL ESTUDIO, O UD. PUEDE PONERSE EN CONTACTO CON EL PRESIDENTE DEL COMITÉ INVESTIGATIVO DEL CENTRO (213) 223-2340

• YO HE LEIDO ESTE DOCUMENTO Y ENTIENDO MIS DERECHOS PARA MI PARTICIPACIÓN EN EL ESTUDIO.

Daniel R. Mishell
Angeles, Calif. 90033
- 12/14/99
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COPIES FOR: ☐ PATIENT ☐ CHART ☐ INVESTIGATOR

NAME _____

P.F. # _____

WARD OR CLINIC _____

INFORMED CONSENT

ISA REV. 8 '90

MIF 005309

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Revised 11/94

INFORMED CONSENT
(Spanish)

TITLE OF PROJECT: Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days.

DEPARTMENT: Obstetrics and Gynecology

PRINCIPAL INVESTIGATOR: Dr. Daniel R. Mishell Jr.
CO-INVESTIGATORS:

TELEPHONE #: 213/226-3416

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PROPOSITO

Es posible inducir un aborto en mujeres que no desean su embarazo tomando mifepristone en combinación con protaglandin (misoprostol). Mifepristone es una droga que bloquea la acción de la progesterona, una hormona necesaria para mantener un embarazo. Una de las acciones de mifepristone es interrumpir un embarazo en etapas tempranas. Las protagladinas son sustancias naturales producidas por la cubierta del útero durante la menstruación y causa contracciones de la matriz. Durante las primeras etapas del embarazo, mifepristone más misoprostol causan aborto en aproximadametne 95 por ciento de las mujeres. La mayor ventaja de este método de terminación de embarazo son que no se introducen instrumentos quirúrgicos dentro de la matriz. Más de 150,000 mujeres en 20 paises han usado mifepristone y una prostaglandina como método médico de interrupción de embarazo. Mifepristone y misoprostol han sido usados en más de 50,000 mujeres en las dosis que usaremos en este estudio. La dosis que será estudiada ha sido aprobada legalmente para el uso de rutina en Francia para las mujeres que están embarazadas y han experimentado nueve semanas o menos desde su último periodo.

Los objetivos de este estudio son determinar la seguridad, eficacia y aceptabilidad de mifepristone más misoprostol para la terminación del embarazo en mujeres que han experimentado 63 días o menos desde el primer día de sangramiento del último periodo menstrual. Estos factores serán examinados en tres grupos de mujeres: 1) con duración de menos de 50 días; 2) 50 hasta 56 días y 3) 57 hasta 63 días desde el primer día de sangramiento desde el último periodo menstrual. Este estudio está siendo realizado como un requerimiento para la registración de mifepristone más misoprostol con la Administración de Drogas y Alimentos (FDA) para que estos productos puedan ser usados para terminar embarazos en los Estados Unidos.

PROCEDIMIENTOS:

Usted comprende que en su visita inicial (visita 1) usted recibirá consejos acerca del método, un examen físico y un examen pélvico, evaluación de gonorrea, evaluación de chlamidia y una prueba del Pap si no se ha hecho una durante el pasado año, tomaremos su historia médica y le haremos un examen de ultrasonido

usando un instrumento pequeño que es colocado en su vagina. El objetivo es verificar la duración de su embarazo. También se hará pruebas de sangre para ver el factor Rh en su sangre, un CBC completo para asegurarnos de que no tiene anemia, y un Beta hCG para ver cuales son los niveles de hormonas en su embarazo. y una prueba de VDRL (para ver si tiene sifilis). Un total de 4 cucharadas de sangre serán extraidas en estas pruebas. Si su tipo de sangre es Rh negativo le daremos una inyección en la segunda visita para prevenir el desarrollo de anticuerpos que pueden poner en peligro embarazos futuros. Para poder terminar su embarazo, usted tomará tres tabletas de mifepristone (primer medicamento) oral en presencia del personal del estudio. Dos días más tarde usted regresará a la clínica (visita 2, día 3) y tomará dos tabletas de misoprostol (segundo medicamento) por la boca si usted no ha abortado y le extraeremos otra cucharada de sangre para revisar los niveles de hormonas de embarazo de Beta hCG. Le haremos 2 ultrasonidos en esta visita, 1 antes de tomar la tableta de misoprostol para ver si ya ha eliminado los productos del embarazo. Cuatro horas después del período de observación le haremos un segundo ultrasonido. La duración de su estancia en la clínica en la segunda visita será de aproximadamente cuatro horas, durante las cuales usted será observada de cerca por el equipo del estudio. Durante este tiempo, exite un 60 a 80% de posibilidad de que ocurra un aborto. Usted comprende que usted debe hacer arreglos para que alguien la lleve a su casa y maneje por usted al salir de la clínica después de esta segunda visita y que usted no puede manejar. Usted comprende que si el aborto no ocurre en la clínica, es probable de que ocurra en su casa y usted puede continuar teniendo sangramiento uterino abundante similar a un período menstrual fuerte durante varios días. Usted debe usar una toalla sanitaria hasta que el sangramiento uterino o las manchas terminen y no puede usar tapones. Como con un aborto quirúrgico, usted no puede usar duchas vaginales hasta que el sangramiento termine (unos 10 a 12 días). Usted no debe comenzar sus relaciones sexuales hasta durante 8 a 10 días después de tomar porstaglandin, en esos momentos la mayoría de los abortos han sido completados.

Una cita adicional será hecha para que usted regrese a la clínica dos semanas despues de tomar la primera tableta (visita 3), para estar seguros de que el tratamiento ha sido efectivo. Si el tratamiento no ha sido efectivo, entonces un procedimiento quirúrgico de aspiración al vacio o dilatacion y curetage será llevado a cabo en ese momento para completar el aborto. Este es el mismo procedimiento quirúrgico que hubieramos usado si usted hubiera elegido someterse al aborto quirúrgico en primer lugar. Como que es posible que usted quede embarazada después del aborto, le pediremos que usted un método contraceptivo. Usted comprende que usted debe hacer arreglos para que alguien maneje por usted y la lleve a la casa al terminar en la clínica después de esta tercer visita y que usted no debe manejar.

Usted comprende que el sangramiento puede continuar despues de su tercera visita. Si esto ocurre, la clínica se pondrá en contacto con usted por teléfono para determinar si ha cesado o si usted necesita tratamiento adicional.

RIESGOS Y MOLESTIAS: Usted comprende que la experiencia ganada hasta ahora con esta combinación de drogas y la terminación de un embarazo en sus comienzos indica que este tratamiento ha sido efectivo. La frecuencia de complicaciones a corto plazo son comparables con las observadas despues que el aborto quirúrgico ha sido realizado con la aspiración al vacio. Las quejas mas comunes durante el

tratamiento (particularmente seguido de la administración del segundo medicamento) es dolor o calambres del bajo vientre que son similar a aquellos asociados con un periodo menstrual muy fuerte. Usted recibirá medicamentos para el dolor cuando los necesite. Usted comprende que no debe tomar aspirina, Motrin, Ibuprofen, Advil o cualquier otra droga que se sepa bloquee la acción de prostaglandinas. Sin embargo, usted puede tomar Tylenol y usted puede recibir medicamentos más fuertes para el dolor que le dará su doctor. Usted comprende que los calabres y dolores abdominales son usuales y una parte esperada del proceso del aborto. Han sido observados náusea, vómitos, y diarrea seguido de la administración del segundo medicamento. De este modo, en la segunda visita si es necesario, usted permanecerá supervisión médica durante aproximadamente cuatro horas antes de regresar a la casa. Podemos esperar sangramiento uterino similar a un período menstrual profuso y que dure una semana. En raras circumstancias puede ocurrir sangramiento uterino muy profuso que requiera un aborto quirúrgico y/o transfusión de sangre. Usted comprende que extraer sangre para las pruebas en sus visitas puede ser asociado con molestias, magulladuras y con rareza, infección en el sitio de la extracción.

Usted comprende que el aborto despues de mifepristone/misoprostol es exitoso en terminar un embarazo en aproximadamente 95% de las mujeres tratadas. Cuando el aborto es incompleto o no ocurre, es esencial que hagamos un aborto quirúrgico por medio de una aspiración al vacio o de una dilatación y curetage.

Usted comprende que no es recomendable permitir que un embarazo continue después de tomar mifepristone y/o misoprostol, ya que los efectos completos de mifepristone en el feto son desconocidos y la administración de misoprostol en etapas tempranas del embarazo ha sido asociada con el desarrollo de fetos anormales.

No han habido condiciones serias del corazón en las 52,000 mujeres que han usado la combinación de drogas en el estudio para terminar el embarazo. Sin embargo han ocurrido condiciones del corazon en mujeres que han sido fumadoras y tienen un aumento de las grasas de la sangre, diabetes, presión de sangre alta o historia familiar de enfermedad del corazón. El riesgo también ha sido aumentado en mujeres que tienen más de 35 años de edad. Estas complicaciones han sido vistas solamentes después de haberse inyectado prostaglandin (misoprostol) y son raras hasta la fecha (1/20,000 casos), no hay indicaciones de que la prostaglandina oral (misoprotol) que usted estara tomando en este estudio y que ha sido usado ampliamente durante periodos prolongados de tiempo en la prevencion en la prevención de úlceras del estómago, es asociada con este tipo de efectos secundarios cardiovasculares.

Usted comprende que no hay indicaciones en el momento actual que el uso de una antiprogestina para terminar un embarazo haya interrumpido o dañado la habilidad de la mujer para tener un bebé en el futuro. Las mujeres que han tomado mifepristone han podido concebir y subsecuetemente tener un bebe saludable. Como es posible que pueda quedar embarazada de nuevo después del aborto, le pediremos que seleccione y use un método contraceptivo.

BENEFICIOS: Usted comprende que una ventaja del metodo de mifepristone/misoprostol para la terminación del embarazo es evitar un procedimiento quirúrgico. No hay riesgos relacionados con la anestesia o riesgos

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de perforación uterina o de daños al canal cervical que son con rareza observados después de una terminación de embarazo por medio quirúrgico. Otro beneficio es la satisfacción de participar en un estudio que puede hacer mifepristone/misoprostol disponible para las mujeres en los Estados Unidos.

METODOS ALTERNATIVOS: Usted sabe que su embarazo puede ser terminado por medio de un aborto realizado con un procedimiento quirúrgico (dilatación y curetage o aspiración al vacío). Las posibles ventajas y desventajas de una terminación quirúrgica en lugar de una médica le ha sido explicada. Las ventajas de una terminación quirúrgica de un embarazo es que es un procedimiento de un solo día. Los riesgos asociados con un aborto quirúrgico son mínimos. Estos incluyen el riesgo de la anestesia. En los Estados Unidos, menos de un 1% de las pacientes que se someten a un aborto quirúrgico experimentan una compliación mayor asociada con el procedimiento, como una infeción pélvica seria, desgarro de la cervix, sangramiento que requiere transfusión de sangre o una cirugía mayor no intencional (para la perforación uterina).

CONFIDENCIALIDAD: La confidencialidad de su registro médico en este estudio será mantenida por los investigadores y el Comité de Investigaciones (IRB). Información especifica relacionada con el estudio puede ser enviada al patrocinador que es El Concilio de la Población o sus obsevadores designados, pero su nombre será omitido. A la Administración de Drogas y Alimentos (FDA) le será permitido el acceso a su registro médico. A no ser requerido por la ley, FDA mantendrá la confidencialidad de su registro.

Usted comprende que podemos pedirle que un representante del patrocinador le haga una entrevista. La entrevista será conducida en el idioma que usted habla y verificará que usted comprende los riesgos, beneficios, procedimientos y la naturaleza experimental del estudio. Si usted no está de acuerdo a que le hagan una entrevista, esto no afectará su cuidado médico presente o futuro en el hospital y la clínica, o su participación en este estudio. Usted comprende que usted puede cambiar de parecer en cualquier momento. Toda información será mantenida confidencial.

OFRECIMIENTO A CONTESTAR PREGUNTAS: Si usted tiene preguntas relacionadas con el estudio por favor, siéntase en libertad de hacerlas en cualquier momento. Usted comprende que usted puede retirarse del estudio en cualquier momento sin poner en peligro su cuidado médico o futuro en el hospital o clínica. Si usted tiene cualquiera pregunta o problemas relacionados con este esutdio que no ha sido contestada satisfactoriamente, por favor, póngase en contacto con el investigador principal, Dr. Daniel Mishell . Usted tiene que leer, firmar y recibir una copia de la Declaración de Derechos de los sujetos a experimentos (Código de Salud y Seguridad de California, Section 24.782).

COMPENSACION: Usted no recibirá compensación por su participacion en ete estudio.

INFORME SOBRE COACCION Y RETIRO: Su decisión sea participar o no participar en este estudio, no interferirá con su atención futura en esta institución. Si usted se decide a participar, usted está en libertad de retirar su consentimiento y descontinuar su participación en cualquier momento. El doctor del estudio, Dr. Daniel Mishell y/o el patrocinador pueden también descontinuar su participación

en este estudio con o sin su consentimiento.

INFORME SOBRE LESION FISICA: Si usted requiere tratamiento medico como resultado de lesión física a consecuencia de su participación en este estudio la responsabilidad financiera por esta atención sera suya.

CON QUIEN HABLAR EN CASO DE EMERGENCIA: Usted comprende que si surge sangramiento uterina, dolor abdominal, o cualquier otra emergencia medica en conección con este método, yo me reportaré inmedicatamente al

En adición usted se pondrá en contacto con el Dr. Daniel Mishell Si él no puede ser localizado en caso de emergencia relacionada con el estudio, used debe ponerse en contacto con los doctores
Cuando usted llege al uno de estos doctores sera localizado por el personal del

CONSENTIMIENTO INFORMADO: Usted desea , , usted no desea ser entrevistada por un representante del patrocinador. Usted comprende que usted puede cambiar de parecer en cualquier momento. Si usted no desea ser entrevistad, esto no afectará su cuidado médico presente o futuro en el hospital o la clínica o su participación en el estudio. La entrevista, conducida en el idioma que usted habla, verificara que usted comprende los riesgos, beneficios, procedimientos y la naturaleza del estudio experimental. Toda información sera mantenida de modo confidencial.

INFORMACION NUEVA: Cualquier información nueva acerca de este producto medicinal que pueda influir su deseo de continuar su participación en este estudio le sera proveída en el momento en que esta información sea conocida.

CONVENIO: SU FIRMA INDICA QUE USTED HA DECIDIDO PARTICIPAR HABIENDO LEIDO LA INFORMACION PROVEIDA ANTERIORMENTE.

4-19-95
Fecha

Firma

4-19-95
Fecha

Firma del Testigo a la Firma Anterior y Explicacion.

Dr. Daniel R: Mishell
Los Angeles, Calif. 90033
12/9 - 12/14/99 KST 705
Exhibit # 1 Pg. 14 of 15

APPROVED

CONSENT VOID 1 YEAR FROM ABOVE DATE

INFORMED CONSENT

TO BE SIGNED AND DATED BY STUDY SUBJECT AND PLACED IN THE HOSPITAL CHART.

HUMAN RIGHTS IN MEDICAL STUDIES

CALIFORNIA STATE LAW REQUIRES THAT YOU MUST BE INFORMED ABOUT:

1. THE NATURE AND PURPOSE OF THE STUDY.
2. THE PROCEDURES IN THE STUDY AND ANY DRUG OR DEVICE TO BE USED.
3. DISCOMFORTS AND RISKS TO BE EXPECTED FROM THE STUDY.
4. BENEFITS TO BE EXPECTED FROM THE STUDY.
5. ALTERNATIVE PROCEDURES, DRUGS OR DEVICES THAT MIGHT BE HELPFUL AND THEIR RISKS AND BENEFITS.
6. AVAILABILITY OF MEDICAL TREATMENT SHOULD COMPLICATIONS OCCUR.
7. THE OPPORTUNITY TO ASK ANY QUESTIONS ABOUT THE STUDY OR THE PROCEDURE.
8. THE OPPORTUNITY TO WITHDRAW AT ANY TIME WITHOUT AFFECTING YOUR FUTURE CARE AT THIS INSTITUTION.
9. A COPY OF THE WRITTEN CONSENT FORM FOR THE STUDY.
10. THE OPPORTUNITY TO CONSENT FREELY TO THE STUDY WITHOUT THE USE OF COERCION.
11. STATEMENT REGARDING LIABILITY FOR PHYSICAL INJURY, IF APPLICABLE.

IF YOU HAVE ANY QUESTIONS OR CONCERNS REGARDING THESE RIGHTS OR THE CHARACTER OF THE STUDY, PLEASE FEEL FREE TO DISCUSS THEM WITH THE PERSON(S) CONDUCTING THE STUDY OR YOU MAY CONTACT THE RESEARCH COMMITTEE CHAIRMAN AT THE LAC-USC MEDICAL CENTER.

I HAVE READ AND UNDERSTOOD MY RIGHTS FOR PARTICIPATION IN THE STUDY.

4-12-95

SIGNATURE OF SUBJECT OR GUARDIAN
FIRMA DEL SUJETO O PERSONA RESPONSABLE

DATE
FECHA

DERECHOS HUMANOS EN ESTUDIOS MÉDICOS

LA LEY DEL ESTADO DE CALIFORNIA REQUIERE QUE UD. TIENE QUE ESTAR INFORMADO SOBRE:

1. LA NATURALEZA Y EL PROPÓSITO DEL ESTUDIO.
2. LOS PROCEDIMIENTOS DEL ESTUDIO Y CUALQUIER FÁRMACO, APARATO O DISPOSITIVO QUE SE VAYA A UTILIZAR.
3. LAS MOLESTIAS Y LOS RIESGOS QUE SE ANTICIPAN DEL ESTUDIO.
4. LOS BENEFICIOS QUE SE PUEDAN ESPERAR DEL ESTUDIO.
5. LOS PROCEDIMIENTOS ALTERNOS, FÁRMACOS O DISPOSITIVOS QUE PUEDAN SER ÚTILES Y LOS RIESGOS Y BENEFICIOS QUE ESTOS LLEVAN.
6. DISPONIBILIDAD DE TRATAMIENTO MÉDICO EN CASO QUE OCURRAN COMPLICACIONES.
7. LA OPORTUNIDAD PARA HACER CUALESQUIERA PREGUNTAS SOBRE EL ESTUDIO O EL PROCEDIMIENTO.
8. LA OPORTUNIDAD PARA RETIRARSE DEL ESTUDIO EN CUALQUIER MOMENTO SIN AFECTAR SU ATENCIÓN MEDICA FUTURA EN ESTA INSTITUCIÓN.
9. UNA COPIA DE ESTE CONSENTIMIENTO FIRMADO PARA EL ESTUDIO.
10. LA OPORTUNIDAD PARA CONSENTIR LIBREMENTE AL ESTUDIO SIN EL USO DE COERCIÓN.
11. DECLARACIÓN ACERCA DE LA RESPONSABILIDAD POR DAÑOS FÍSICOS, SI ES APLICABLE.

SI UD. TIENE CUALESQUIERA PREGUNTAS O PREOCUPACIONES ACERCA DE ESTOS DERECHOS O EL CARÁCTER DEL ESTUDIO, POR FAVOR SIÉNTASE LIBRE PARA DISCUTIRLOS CON LA(S) PERSONA(S) LLEVANDO A CABO EL ESTUDIO, O UD. PUEDE PONERSE EN CONTACT CON EL PRESIDENTE DEL COMITÉ INVESTIGATIVO DEL CENTRO.

YO HE LEIDO ESTE DOCUMENTO Y ENTIENDO MIS DERECHOS PARA MI PARTICIPACIÓN EN EL ESTUDIO.

Dr. Daniel R. Mishell
Los Angeles, Calif. 90033
12/9 - 12/14/99 KST 705
Exhibit # 1 Pg. 15 of 15

[redacted] [redacted] T ☐ INVESTIGATOR

INFORMED CONSENT

[redacted]

WARD OR CLINIC [redacted]

MIF 005315

Proposal #948057
REVIEW CATEGORY: C

Date: 09/15/94
To: Daniel R. Mishell, Jr., M.D.
Professor and Chairman
Dept of Obstetrics and Gynecology
Women's Hospital, #L-1009
(213)226-3416

FROM:

TITLE OF PROPOSAL:
EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANCY WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

Action Date: 09/15/94 Action Taken: Approved
Committee : SECRETARY
Note:
The press release to be used for this study was reviewed and APPROVED by , Secretary on September 13, 1994. The study was assigned Review Category C. (

APPEARS THIS WAY
ON ORIGINAL

FEB 22 1979

Dr. Mishell

We appreciate the cooperation shown Mr. Lipnick during the inspection, and hope this letter is received in the constructive tone proffered.

Sincerely yours,

Division of Scientific Investigations
Bureau of Drugs

BEST POSSIBLE COPY

cc:
HFA-224

HFR-6150
HFD-130
Orig:IND [illegible]
Typed:[illegible]

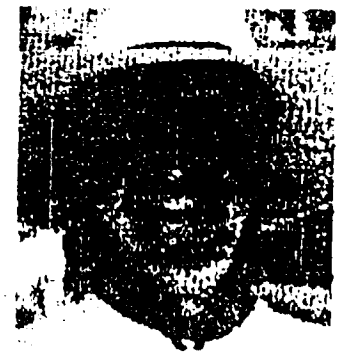
Trojan on the street

"What do you consider to be safe sex?"

Reporting and photos by Kensaka Okada

"There's no such thing. Safe sex is an illusion."

Carlos Romero
sophomore
psychology



"With a condom. It's the safest way to go."

Ian Aler
graduate student
business

"Abstinence."

Joy Ho
sophomore

APPEARS THIS WAY
ON ORIGINAL

ABORTION PILL STUDY

Women wishing early pregnancy termination are invited to participate in a Food and Drug Administration approved study of the Abortion Pill at no cost to the participant. For information please contact:

WOMEN'S HOSPITAL CONTRACEPTION CLINIC

at

213/226-3104

Daily 49er Ad - Cal State LB.

File No: 00076 Name: Daniel Mishell **GCP1**

DATE	TO:	ACTION REQUESTED
1-1-00		
[illegible]		
2-8-00		
2-9-00		
2-9-00		
2-10-		
2-10-00		
2-15-00		MAIL/COPIES/ETC
		APPEARS THIS WAY ON ORIGINAL

[redacted] Compliance Officer
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing & Product Quality, HFD-322
7520 Standish Place, Room 272
Rockville, MD 20855

August 25, 2000

Re: **C.F. No. 9615606**
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.
Product: Mifepristone
Establishment Investigation: July 24-28, 2000
Inspectional Observations (Form FDA 483): Corrective Action

Dear [redacted]

On behalf of our principals, please find herewith enclosed, a final response to the Inspectional Observations issued at the conclusion of the recent inspection of their plant. This response documents the corrective action proposed in our preliminary response dated August 10, 2000.

To facilitate your review, we have transcribed the preliminary response to each observation and have added in bold-face type our comments pertaining to the corrective action documented in this final response.

A desk copy has been sent to [redacted] for their review.

Thank you for your attention.

Sincerely,

[redacted]

President

RECEIVED
AUG 2 9 2000
By

Encl.

cc: [redacted], Investigator, U.S.F.D.A., D.E.I.O., Rockville, MD
[redacted], U.S.F.D.A., Kansas City District Office
[redacted] V.P., Manufacturing, Danco Laboratories, LLC
Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

[redacted] Investigator
Food and Drug Administration
Division of Emergency and Investigational
Operations, HFC-133
5600 Fishers Lane, Room 13-71
Rockville, MD 20857

August 25, 2000

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Thank you for your attention.

Sincerely,

[redacted]

President

[redacted]
Encl.

cc: [redacted] Compliance Officer,
U.S.F.D.A., Div. of Manufacturing & Product Quality, Foreign Inspection Team
[redacted] U.S.F.D.A., Kansas City District Office
[redacted], V.P., Manufacturing, Danco Laboratories, LLC
Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

U.S. Food and Drug Administration
Kansas City District Office
11630 W. 80th Street
Lenexa, KS 66285-5905

August 25, 2000

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Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.
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Thank you for your attention.

Sincerely,

[redacted]

President

Encl.

cc: [redacted] Compliance Officer,
U.S.F.D.A., Div. of Manufacturing & Product Quality, Foreign Inspection Team
[redacted] Investigator, U.S.F.D.A., D.E.I.O., Rockville, MD
[redacted] V.P., Manufacturing, Danco Laboratories, LLC
Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER FDA/CDER/OFFICE OF COMPLIANCE (HFD-322) 7500 Standish Place Rockville, MD 20855 Attn: [redacted]	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Li Changfa	PERIOD OF INSPECTION 7/24 - 28/2000	C F NUMBER 9615606
TITLE OF INDIVIDUAL Chairman of the Board /General Manager	TYPE OF ESTABLISHMENT INSPECTED Active Pharmaceutical Ingredients Manufacturer	
FIRM NAME Shanghai Hua Lian Pharmaceutical Co., Ltd. Xin Lian Pharmaceutical Factory	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 217 Ming Le Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE Shanghai 201419, China	CITY AND STATE Same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Mifepristone Finished Product Analytical Methods

1. The following analytical methods are incompletely validated. The raw data containing the weights, dilutions and standards used during validation was not retained.

a. [redacted] (Related Substances)

b. — analysis for [redacted] (Residual Solvents)

} Corrections promised by August 31, 2000

Mifepristone Reference Standard

2. There is no stability data for the Mifepristone working standard supporting the — month expiration date. There is only data for 12 months even though the current standard is 17 months old. — Correction promised by August 31, 2000

Crude Mifepristone Analytical Methods

3. The [redacted] method originally used to determine the Impurities was not validated. — Observation acknowledged

4. The [redacted] method for Residual Solvents has not been validated for [redacted] — Correction promised by August 31, 2000

[redacted] **in the Mifepristone Purification Suite**

5a. The efficiency of the HEPA filters were not determined during validation and there were no written procedures to monitor the efficiency on a periodic basis during production. Correction promised

5b. There was no information on the particulate counts under working conditions during validation and there were no written procedures to monitor the particulate counts on a periodic basis during production. — Correction promised

5c. The pressure differentials between the room and inside hall are not recorded. There is no monitoring device for pressure differentials in the micronizing room. → correction will start on the next batch → correction verified

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/ /S/	EMPLOYEE(S) NAME AND TITLE *(Print or Type)* [redacted] Investigator [redacted]	DATE ISSUED 7/28 /2000

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED **INSPECTIONAL OBSERVATIONS** PAGE 1 OF 1 PAGES

Shanghai HuaLian Pharmaceutical Co., Ltd. (**C.F. No. 9615606**)
Inspectional Observations - Corrective Action

Inspectional Observations: [redacted] to Li, Changfa (July 28, 2000)

OBSERVATION: **"Mifepristone Finished Product Analytical Methods**

1. The following analytical methods are incompletely validated. The raw data containing the weights, dilutions and standards used during validation was not retained.

   a. [redacted] (Related Substances)

   b. [redacted] analysis for [redacted] (Residual Solvents)"

CORRECTIVE ACTION: *"These two [redacted] methods have been revalidated following protocols that included system suitability criteria developed since the original validation of these methods.*

In the case of the [redacted] the use of the standards not available at the time of the method's original validation, was also included. Furthermore, this method was separately validated as an [redacted] ethod.

Finally, and since this method is equally followed in the analysis of [redacted] n crude Mifepristone using a [redacted] of the same type obtained from a different supplier, a separate [redacted] suitability comparison was performed following the conditions described in a previous protocol.

These protocols and the pertaining validation reports are currently being translated and will be included with our complete response to the Inspectional Observations before the end of this month."

Please refer to the attached protocols and validation reports for the methods addressed in the above referenced observation. These methods were successfully revalidated and all the raw data has been retained in the format reviewed by the Agency's Chemist for current analytical records.

August 2000

Shanghai HuaLian Pharmaceutical Co., Ltd. **(C.F. No. 9615606)**
Inspectional Observations - Corrective Action

Inspectional Observations: ——————— to Li, Changfa (July 28, 2000)

OBSERVATION: **"Mifepristone Reference Standard**

2. There is no stability data for the Mifepristone working standard supporting the — month expiration date. There is only data for 12 months even though the current standard is 17 months old."

CORRECTIVE ACTION: *"Three Mifepristone Working Standard lots were prepared in January 1999 in order to establish their quality specifications and long term stability.*

In order to address the Observation transcribed above, these three lots were re-analyzed during the firm's inspection and the results obtained showed that they remain in compliance with the established specifications. The data obtained, reflecting 17 months of storage, was reviewed in detail by the Agency's Chemist. The attached translations of the pertaining Certificates of Analysis were provided to the Agency's Chemist at the conclusion of the inspection.

Furthermore, SOP ——— reflecting the ——————— was revised in order to extend their testing to — months. This revision was also reviewed by the Agency's Chemist. A summary of the revisions to this SOP is herewith attached for your reference.

Finally, all these three lots of the Mifepristone Working Standard will be analyzed at the end of August (— months) to complete their short term stability study and a new standard will be prepared and qualified to be used in the testing of Mifepristone from September 1, 2000."

Please refer to the attached Certificates of Analysis for the three lots reflecting the test data obtained in August 2000. The data obtained supports an — month expiration date. Also enclosed is a translation of the current version of SOP ———

Shanghai HuaLian Pharmaceutical Co., Ltd. **(C.F. No. 9615606)**
Inspectional Observations - Corrective Action

Inspectional Observations: [redacted] to Li, Changfa (July 28, 2000)

OBSERVATION: **"Crude Mifepristone Analytical Methods**

3. The [redacted] method originally used to determine the Impurities was not validated."

CORRECTIVE ACTION: *"The [redacted] method originally followed in the analysis of Related Substances in Crude Mifepristone has been replaced by the [redacted] followed in the analysis of the drug substance.*

This method has been reflected in the current CMC Section for the drug substance (NDA 20-687) along with revised specifications for this [redacted], from:

[redacted]

We would like to note that, data obtained for lots of the crude product following the original [redacted] method was confirmed by the results obtained by the [redacted] followed in the analysis of the respective lots of the final product.

Taking into consideration this change in the method used in the analysis of Crude Mifepristone and that the [redacted] has been re-validated as reflected in our response to COMMENT 1, the firm does not propose to validate the discontinued [redacted] method. The firm's position was explained to the Agency's Investigators."

Final response.

August 2000

Inspectional Observations: [redacted] to Li, Changfa (July 28, 2000)

OBSERVATION: **"Crude Mifepristone Analytical Methods**

4. The [redacted] method for Residual Solvents has not been validated for [redacted]

CORRECTIVE ACTION: *"The validation of the [redacted] method followed for the analysis of Residual Solvents in Crude Mifepristone, i.e., [redacted] only included an evaluation of the method's resolution for [redacted] olvents and the internal standard and validation data for [redacted]*

The method's validation protocol has been amended in order to include its validation for [redacted]

The validation of this method is now underway and its report will be included with our complete response to the Inspectional Observations before the end of this month.

The [redacted] method for Residual Solvents has been successfully validated for [redacted] in accordance with the attached protocol. A copy of the pertaining validation report is enclosed herewith for your review.

APPEARS THIS WAY
ON ORIGINAL

Inspectional Observations: [redacted] to Li, Changfa (July 28, 2000)

OBSERVATION: [redacted] **System in the Mifepristone Purification Suite**

5a. The efficiency of the HEPA filters were not determined during validation and there were no written procedures to monitor the efficiency on a periodic basis during production."

CORRECTIVE ACTION: *"The firm engaged an outside company to determine the efficiency of the HEPA filters in the Mifepristone purification suite.*

In order to establish an adequate monitoring schedule for these filters, the firm prepared a protocol that requires the efficiency of the filters to be checked every [redacted] *for a period of one (1) year. This protocol was presented to the Agency's investigator.*

The initial testing was completed this week and the filters' certification will be included with our complete response to the Inspectional Observations before the end of this month.

At the end of the one year program a procedure will be written to define the frequency of the monitoring of the HEPA filters based on the results obtained in their quarterly evaluation. This SOP will also specify the documentation that will be required to document the testing to be performed."

The initial testing referred to in the preliminary response was successfully completed and a copy of the filter's Certification Report is enclosed herewith for your review.

Inspectional Observations: [redacted] to Li, Changfa (July 28, 2000)

OBSERVATION: [redacted]**System in the Mifepristone Purification Suite**

5b. There was no information on the particulate counts under working conditions during validation and there were no written procedures to monitor the particulate counts on a periodic basis during production."

CORRECTIVE ACTION: *"The Mifepristone purification suite is a Class [redacted] "clean area" in which the API is [redacted] micronized and packaged. The "clean area" also includes a sampling room and an employee gowning room. The air that is supplied to each of the rooms in the "clean area" is filtered through HEPA filters without recirculation.*

The Observation transcribed above pertains to those rooms in the "clean area" where there is a possibility for higher levels of dust being generated during production. Specifically, this Observation refers to the micronizing and to the packaging rooms.

During the qualification of the air handling system, the data for these areas was obtained under static conditions. The particulate count results met the requirements for a Class [redacted] area.

In order to address the Observation transcribed above, a protocol was prepared to have all of the rooms in the "clean area" monitored for particulate counts in static and dynamic conditions. The results obtained from the testing carried out under this protocol will be used to establish the frequency for this monitoring program.

The results obtained at the time of the production of the next batch of Mifepristone will be included with our complete response to the Inspectional Observations before the end of this month."

Inspectional Observations: [redacted] to Li, Changfa (July 28, 2000)

The firm executed protocol YZ-1083-00 and conducted particulate monitoring of all areas of the class [redacted] "clean area" under static, *i.e.*, at rest conditions. In addition, the micronization and packaging rooms were monitored under dynamic, *i.e.*, working conditions. The results from both the static and dynamic particulate monitoring showed that all rooms in the "clean area", met the particulate count requirements for a class [redacted] area. The reports for these studies are enclosed herewith for your review.

Based upon the successful results obtained from both the static and dynamic particulate count tests, we propose to monitor the "clean area" under static conditions in conjunction with the quarterly HEPA filter efficiency tests, as discussed in our preliminary response to Observation 5a.

It should be noted that particulate monitoring data under "working" conditions does not provide a meaningful indication of the efficiency of the HEPA filtration system, but rather only reflects the particulate matter generated in the product handling operations. For this reason, we do not propose any further or periodic monitoring of particulate counts under dynamic conditions. However, all data obtained from the dynamic particulate count testing will be retained on file for future reference.

APPEARS THIS WAY
ON ORIGINAL

Inspectional Observations: [redacted] L. to Li, Changfa (July 28, 2000)

OBSERVATION: [redacted] **System in the Mifepristone Purification Suite**

5c. The pressure differentials between the room and inside hall are not recorded. There is no monitoring device for pressure differentials in the micronizing room."

CORRECTIVE ACTION: *"A* [redacted] *was installed in the micronizing room to monitor the differential pressure between this room and the "clean area" inner hallway. This was verified by the Agency's investigator.*

A "Pressure Test Record" was designed and included in the Production Batch Records. Beginning with the next batch, this form will be used to record the pressure differentials between the micronizing room and the inner and outer hallways. The same information will be recorded for the packaging room for wich a [redacted] *was already installed."*

Please refer to the attached "Pressure Test Records" prepared during the production of Mifepristone Lots 000711, 000801 & 000802.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date September 26, 2000

From CDER Foreign Inspection Team

Subject Shanghai Hua Lian Pharmaceutical Co.
Shanghai, China
CFN: 9615606

To Memo to File

The initial inspection of Shanghai Hua Lian October 25-28, 1999 was scheduled as a pre-approval inspection of the bulk mifepristone manufacturing process re. NDA 20-687. The purpose of pre-approval inspections is to determine if the firm's process, controls, and testing of the NDA product are in accordance with those submitted in the application, to verify the data submitted, and to evaluate the firm's ability to manufacture commercial batches in compliance with good manufacturing practices if/when the application is approved.

The initial inspection revealed several of the problems, [redacted] that FDA look at. The inspection preceded the [redacted] but FDA inspections are designed to evaluate these problems. The inspection reported the firm's laboratory procedures were different than those described in the NDA, that certain analytical tests had not been validated, and other GMP deficiencies re. Recycled drums, equipment calibration, and analytical procedures. The Investigator also reported that an English translation of the analytical methods was not initially available, and when provided later, proved to be inaccurate. [redacted] is identified as the firm's consultant and was present during the inspection. He does not read or speak Chinese. Translation during the inspection was handled be the [redacted] Danco Group, in New York is identified as the firm's U.S. Agent and Importer. The report does not mention any connection between [redacted] and the firm, [redacted] or Danco Group.

The Investigator recommended withholding approval of the NDA and reinspection to evaluate corrections promised by the firm. A written response was received from [redacted] 12/2/99. CDER reviewed the EIR and written response and concurred with the recommendation to withhold approval. A letter to that effect was issued to Shanghai Hua Lian 12/14/99. A second response was received 1/4/00. Although the corrections described in the responses appeared satisfactory, a re-inspection was scheduled to verify actual implementation of the promised corrections prior to approval of the NDA.

The reinspection was conducted July 24-28, 2000 [redacted] and an FDA [redacted] Their inspection also covered the issues/suggestions in the informant's e-mail. Translations were not a problem because the [redacted]

was selected for the inspection. Integrity and accuracy of GMP records was verified. A U.S. Agent, whether [redacted] however, often provides GMP consulting services. Part of that job includes helping a manufacture understand and follow GMP and preparing documents, and should not be considered inappropriate. Scale-up was not an issue since this firm has made production batches for the Chinese market for many years. Analytical procedures and methods validation were evaluated and several deficiencies found. [redacted]

The reinspection verified that the promised corrections from the earlier inspection had been implemented, however additional deficiencies in the new methods validation studies, and in air handling equipment, were noted. Immediate corrective action was initiated and the Investigator /Chemist team recommended approval of the NDA.

CDER reviewed the EIR and two written responses from [redacted] An initial response dated 8/10/00 and a final response which included translated copies of documentation, dated 8/25/00 were evaluated and CDER reclassified the facility as acceptable as the API supplier for the NDA.

/S/

Foreign Inspection Team

APPEARS THIS WAY
ON ORIGINAL

HFD 322
Firm
File

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: [redacted]
FAX: [redacted]

August 21, 2000

Li Changfa
Chairman & General Manager
Shanghai Hua Lian Pharmaceutical Co., Inc.
370 Jiang Wan Road (West)
Shangai 200083
China

Dear Mr. Li:

We have completed review of the Inspection Report on the July 24-28, 2000 inspection of your active pharmaceutical ingredient manufacturing facility in Shanghai, China, by FDA Investigator [redacted] The inspection revealed several CGMP deficiencies, which were listed on an FDA-483, Inspectional Observations Form, issued to you at the conclusion of the inspection.

We have also reviewed the August 10, 2000, written response to the FDA-483 observations submitted by [redacted] This response indicates that your facility has corrected these deficiencies and that translated copies of the documentation for the corrections will be submitted to FDA by August 31, 2000. Based on this commitment, we have classified this facility as acceptable. The corrections will be further evaluated during the next inspection of your facility. It remains your responsibility to comply with current good manufacturing practices.

Additionally, we enclose a copy of the establishment inspection report (EIR) for the inspection. This report is being provided to you for information purposes. The Agency is working to make its regulatory process more transparent to the regulated industry. The copy being provided to you comprises the narrative portion of the report; it may reflect redactions made by the Agency in accordance with the FOIA and C.F.R. Part 20. This, however, does not preclude you from requesting and, possibly, obtaining any additional information under FOIA.

You may contact me at the address or telephone number given above if you have any questions regarding this letter.

Sincerely,

/S/

Compliance Officer
Foreign Inspection Team

Enclosure:

cc:

HFC-133 —
HFR-SW360 —
HFC-133 —————— Drugs & Biologics

HFD-322 —
HFD-322 —

HFD-580 — re. NDA 20-687

Control# 322-00-08-0181
WP: shanghai.hau

APPEARS THIS WAY
ON ORIGINAL

Shanghai Hua Lian Pharmaceutical Co., Ltd.
Xin Lian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419

7/24-28/2000

CFN: 9615606
FEI: 3002914652

SUMMARY OF FINDINGS

This was a pre-approval inspection of a manufacturer of active pharmaceutical ingredients (API) covering Mifepristone, in connection with FDA's review of NDA [redacted], Mifepristone 200 mg. Tablets. The assignment was issued by HFD-322 and the inspection was conducted according to CP 7356.002F.

The last inspection in October 1999 revealed several deficiencies which were reported on a FDA 483: Lack of procedures for handling and marking recycled solvent drums, and omissions and discrepancies of analytical methods in the firm's Standard Operating Procedures (SOP) compared to the Chemistry and Manufacturing Control (CMC) section in the submission. All the deficiencies have been either corrected or resolved.

The current inspection revealed five deficiencies which were reported on a FDA 483: 1 —— —— and related impurities and — analysis for ——— for the Mifepristone finished product were incompletely validated, 2. No stability data supporting the —months expiration date for the Mifepristone working standard, 3. The —— method originally used to determine the impurities for the crude Mifepristone was not validated, 4. The — method for residue solvents has not been validated for ——— and 5. Lack of information on the efficiency of the HEPA filters, particulate counts under the working conditions, and records of pressure differentials of the ——— system in the purification suite.

In addition to the FDA 483 observations, the following items were discussed with management: Two ——— were either reprocessed or not used, the ——— SOP had not been updated to reflect current practices, the ——— method validation has not been completed, the verification for the crude Mifepristone ——— method was incomplete, significant figures in the method acceptance criteria were not listed, and the operator used a plastic brush with wooden handle to remove —— crude Mifepristone from the ———

HISTORY OF BUSINESS

Shanghai Hua Lian Pharmaceutical Co., Ltd. was established in 1939. Over the last 60 years, it has developed into one of the top 50 pharmaceutical companies in China with — employees and total sales of ——— in 1999. The company consists of — pharmaceutical manufacturing factories, — research and development units, and — sales companies. It produces more than —products, both dosage forms and active pharmaceuticals ingredients and the products are distributed to more than 70 countries in the world. A location map and a list of products are shown in Exh. 1 and 2, respectively.

The Xin Lian Pharmaceutical Factory, one of the —manufacturing factories, was originally located in Shanghai. The Factory was moved to a new development zone in : ——— construction of the new facilities was completed in 1995, and production of Mifepristone was

started in 1996. [redacted] Production lots of Mifepristone were shipped to the US in 1999 for tests and use in exhibit batches of the dosage form.

Correspondence to the firm should be addressed to:

Mr. Li Changfa
370 Jiang Wan Road West
Shanghai 200083, China
Tel: 86 21 6540 1680 Fax: 86 21 6540 0098

The U.S. agent and importer are Danco Group, [redacted]

The consultant for the firm is [redacted]

PERSONS INTERVIEWED / INDIVIDUAL RESPONSIBILITIES

The most responsible person at the corporate level is Mr. Li Changfa, Chairman of the Board and General Manager. Mr. Li was present at the beginning and closing of the inspection and provided the information on the history of the company. The FDA 483 was issued to Mr. Li. Hua Lian's Quality Management and Quality Flow Chart are shown in Exh. 3a and 3b, respectively. The most responsible person at the factory is Mr. Ou Sidan, Factory Director. Xin Lian's Manufacturing Management and Quality Management are shown in Exh. 4a and 4b, respectively.

During the inspection, the following individuals have provided some information in their area of responsibilities:

[redacted]

The firm's consultant [redacted], both from [redacted], were present throughout the inspection. [redacted] Deputy Director, [redacted] and [redacted] Technical Translator from [redacted] served as interpreters for the inspection.

SCOPE OF INSPECTION

The inspection covered the manufacturing and quality control of Mifepristone, the API of Mifepristone 200 mg. Tablets for NDA[redacted]. Mifepristone has been produced at this site since

1996 using the in-house processes. However, in May 1998 the firm adopted the Roussel Uclaf processes obtained from the Danco Group of the United States. One of the major changes is to replace [redacted] as the [redacted] Over the last two years, modifications have been made at various stages of manufacturing to enhance the yield and to make them closer to the Roussel Uclaf processes.

Xin Lian Pharmaceutical Factory has a total of [redacted] employees, about [redacted] of them work in the Mifepristone workshop. The workshop operates [redacted] with three different shift schedules: [redacted] hours. Employees ride the company bus to work. Because the factory is about an hour drive from Shanghai where most of the employees live, most of them prefer the longer shift. Those on [redacted] shift will be working [redacted] days.

The plant was shut down in the middle of July due to the extreme hot and humid weather. However, to provide an opportunity for the FDA inspection team to observe manufacturing operations, Lot 000712 was scheduled for production on July 24, 2000.

BUILDINGS AND FACILITIES

The Xin Lian Pharmaceutical Factory layout is shown in Exh. 5. All buildings are made of concrete with a total area of [redacted], about one fifth of the area are for production which is housed in a two-story building. Two products are manufactured in this building – [redacted], on the ground floor and Mifepristone, on the upper floor.

The synthesis of Mifepristone consists of [redacted] stages and each of the stages is manufactured in a separate room. For the first [redacted] stages of manufacturing, the rooms are maintained under ambient conditions. The [redacted] stage, [redacted] is housed in a room where the air is controlled but not classed. Only the [redacted] stage, the final purification is housed in a suite with [redacted] System and the air is controlled under Class [redacted] Because the two products are manufactured on separate floors and each manufacturing stage is in a separate room using dedicated equipment, the processes are designed to minimize cross contamination.

Distilled water and steam used in the Mifepristone workshop are generated from a still located above the workshop areas. [redacted] used to [redacted] the reaction throughout the process is generated from a [redacted] tank outside the building and is pumped into the reactors in the Mifepristone workshop by dedicated pipes. All solvents are used only once; they are not recovered nor recycled.

EQUIPMENT

Equipment used in the manufacturing of Mifepristone is dedicated. Each major equipment has its identification code. There are validated cleaning procedures for each equipment used for the manufacturing. The solvent used in the reaction is the solvent used for cleaning. Documentation of cleaning and use of each piece of equipment is included in the batch records. At the end of a reaction, operators will clean the equipment and record it on the batch record. Before the

beginning of the next reaction, operators will recheck the cleanliness of the equipment to make sure that it meets the specification.

All reactor vessels are fitted with pressure gauges and with either glass thermometer or thermal couples. Most equipment is manually controlled and readings are taken and recorded on the batch sheet by operators. Pressure gauges, thermometers, thermal couples, and all other measuring instruments are calibrated according to written procedures.

PERSONNEL TRAINING

The training of employees is centrally managed at the corporate level in Shanghai. New employees will attend orientation classes to learn about the company history and to receive training in drug Good Manufacturing Practices (GMPs). Before starting on the production floor, employees will receive on-the-job training at a particular workstation. Training is provided to employees on a continuing basis and a training record is maintained for each employee.

In two consecutive production lots, 000203 and 00204, the concentration of the residual solvent was higher than the specifications. Because of the failure, all employees involved in the workstation received a special training on how to control and maintain temperature.

RAW MATERIALS/INTERMEDIATES

Raw materials grouped by their chemical characteristics and usage are stored in different rooms in the warehouse buildings located on the south side of the plant. Raw materials are quarantined, sampled, tested, and released according to written procedures. Fresh solvents are stored in color-coded dedicated drums according to the SOP ———. Drums will be refilled with fresh solvents —— times; after that they will be used for storing waste solvents and mother liquors with the color band on the drum blocked off with paint. Raw materials are sampled by QC personnel and are tested at the designated Laboratory.

Intermediates are stored in a separate warehouse and are tested at the designated Laboratory. The starting material for the synthesis of Mifepristone is ——— which is also synthesized by the Xin Lian Factory. For this reason, ——— is considered to be an intermediate and are tested by the designated intermediate laboratory, not by the raw material laboratory.

Currently the only approved source of ——— is produced in-house. According to the management, there is no other approved source for this chemical at this time. Management promised to submit a supplement when a new source is approved.

MANUFACTURING AND PROCESS CONTROLS

The synthesis and equipment used in the manufacturing of Mifepristone are as described in the CMC Section of the Supplement 048, NDA [redacted] compiled in June 2000. Ten validation lots 990803 - 09, 990901 - 03 were produced. The batch records of two of the ten validation lots

990803 and 990901, and the last completed lot 000702 were reviewed in detail. There were no in-process deviations and the finished products met the specifications.

Since last December the firm has produced over —— lots. In two of the lots, 000203 and 000204, the concentration of the residual solvent ———— was over the specifications. Theses two lots were —— according to written reprocessing procedures and subsequently the concentration of ———— in both lots met the specifications.

PACKAGING AND LABELING OPERATIONS

The packaging operation is done in two separate packaging rooms next to each other as shown in Exh. 6. There were no operations in the packaging area during the inspection. Each production lot yields about —— of Mifepristone which is packaged in ———— aluminum canister with double ethylene bags as inner packaging. A photo of aluminum canisters with Mifepristone in double poly bag is shown in Exh. 7.

Lot numbers consist of six numerals - ———————— of lot produced in a given month. For example, the lot number 990903 means the ————————

The Appendix B Information sheet of CP7356.002F was given to the firm. They will fill out the form and send it directly to the ————————

STABILITY PROGRAMS

The stability programs consist of long term studies at 25° C ± 2° C and the relative humidity of 60% ± 5%; and accelerated studies at 40° C ± 2° C, and relative humidity of 75 % ± 5%. The tests for the long-term study are at initial, 1, 2, 3, 6, 9, 12, 18, 24, and 36 months. For the accelerated study, the tests are done at initial, 1, 2, 3, and 6 months. Forced degradation studies were carried out to demonstrate the adequacy of the procedures as stability indicating method.

Based on the results from samples taken from the three validation lots, 990101 - 03, Mifepristone is stable under the accelerated and long-term conditions. Because the samples used during the stability studies were from the three earlier validation lots, at that time the manufacturing processes were somewhat different from the current processes, the firm has started accelerated studies on lots 000501, 000502, 000503, and 000305 upon the request by FDA's Review Division. So far, the product is stable from the results tested at the end of the second month.

LABORATORY OPERATIONS

This section was written by FDA ————————

The laboratory is divided into sections: Raw Materials, In-Process and Finished Product. The Finished Product group is further divided into a chemistry group and an instrumental analysis

group. The Instrumental analysis group performs only the — and — analysis for the finished product. Critical equipment is dedicated to each section. For example, the Finished Product Instrumental Analysis group, the In-Process group, and the Raw Materials group each have their own ——— The groups share the balances in the weighing room. There are — chemists in the laboratory working in 2 shifts. One shift is daily from ——— and the second shift is every other day from ———

Three lots of Mifepristone were chosen for review of analytical results. Two lots (990803 and 990901) were from process validation and the other lot (000702) is a recently produced lot. The analytical results for all of these were reviewed including the finished product, crude Mifepristone, in process, and raw material testing. All testing specifications were met for these lots of Mifepristone.

Analytical results for two additional lots (000203 and 000204) of Crude Mifepristone were reviewed since these lots originally failed for residual solvents. The original test results were approximately 10 times greater than the limit. The firm re-tested as described in their ——— SOP and the original results were confirmed. According to ——— the lot was ——— and testing conducted again. Complete testing was performed and both lots met all specifications and were released for further processing.

Method validation protocols and validation reports for the following analytical methods were reviewed. Any objectionable conditions relating to these methods are cited under the Objectionable Practices and Discussion with Management section of this report.

Finished Product

——

— analysis for ——— / Residual Solvent

Crude Mifepristone

— analysis for Impurities
— analysis for Residual Solvents

———

— analysis for Related Impurities
— analysis for Residual Solvents

———

— Assay
— analysis for Related Impurities
— analysis for Residual Solvents

In-Process Intermediates

— analysis for Completion for Reactions
——— Content
——— Content
——— Content
— analysis for Completion of ——— Reaction in — Process

The Forced Degradation study was conducted prior to May 1999. The data on pages 35 - 47 in the June 2000 submission is accurate and reliable. In January 2000, the DA review chemist requested additional oxidation degradation testing using [redacted] and a [redacted]. The plant site does not have a [redacted], so the sample was sent to another location for analysis. That laboratory performed the analysis and submitted a copy of the results to the FDA. The original results were sent to the plant site for retention. These records were reviewed during the inspection. [redacted] does degrade the Mifepristone to a level where both the parent compound and the impurities can be seen and quantified.

Maintenance and calibration records for analytical instrumentation were reviewed. With the exception of balances, all analytical equipment is certified once per year by the Shanghai Institute of Measurements and Testing Technology according to Chinese law. The Institute issues certificates that are retained by the factory calibration group. For select instruments, additional testing is performed by the analysts on a more frequent basis. For example, a [redacted] standard is analyzed once per month to determine if the instrument is operating correctly. The [redacted] analyzer is checked daily as per the instrument operations manual. The balances in the laboratory are calibrated once per year. The calibration is performed over the range of use using replicates weighings.

OBJECTIONABLE CONDITIONS AND DISCUSSION WITH MANAGEMENT

This section is written with the FDA 483 observation in bold followed by the description of the observation and any discussion with management that occurred at the time of the closeout meeting. No exhibits were collected for the laboratory observations as the original documents were in Chinese. Any document referenced was verbally translated at the time of the inspection.

Mifepristone Finished Product Analytical Methods

1. **The following analytical methods are incompletely validated. The raw data containing the weights, dilutions and standards used during validation was not retained.**

   a. **[redacted] (Related Substances)**

The [redacted] took place in November 1998. At this time, the firm did not record the actual weights and dilutions used during the validation. They stated they followed the protocol that requires a specific weight and dilutions. They were unaware they needed to record and retain the actual raw data. However, they did retain the [redacted] were briefly reviewed and appear to support the validation claims that the method is adequate to determine the Related Substances and Assay.

At the time of the initial validation, there was no ——— standard, the major impurity found. The firm has since received a standard for this impurity but additional validation work has not been performed.

During the FDA-483 closeout meeting, ———responded for the firm regarding the laboratory issues. He stated the validation was currently in-progress and was expected to be completed by July 31, 2000. This validation will include the ——— standard. During the inspection, the firm presented me with raw data for the specificity and linearity portions of this validation. Due to time constraints, I was not able to review the data to confirm the in-progress correction.

b. — analysis for ——— (Residual Solvents)

The — validation also took place in November 1998. As stated above, the firm did not record the actual weights and dilutions used during validation. They retained the ——— The ——— appear to support the validation claims that the method is adequate to determine the Residual Solvents.

——— stated the validation was currently in-progress and was expected to be completed by July 31, 2000. During the inspection, the firm presented me with raw data for the specificity and limit of detection portions of this validation. Due to time constraints, I was not able to review the data to confirm the in-progress correction.

Mifepristone Reference Standard

2. There is no stability data for the Mifepristone working standard supporting the — month expiration date. There is only data for 12 months even though the current standard is 17 months old.

During the review of SOP ——— I noted the stability test points were at 0, 1, 2, 3, 6, and 12 months while the expiration date for the Mifepristone standard was at — months. The firm did not have any stability results beyond the 12-month time point.

The firm immediately promised corrections and began to perform stability testing on the three lots of reference standard. On 7-28-00, I reviewed stability data for the standards. This data supports the reference standard is stable through 17 months. The firm promised to test the standards again in August to fulfill the —month commitment. SOP ——— was revised to reflect testing at — months. The revised SOP was presented to me on 7-27-00.

Crude Mifepristone Analytical Methods

3. The — method originally used to determine the Impurities was not validated.

Prior to June 2000, the firm used a method, supplied by Roussel Uclaf, to determine the impurities in the Crude Mifepristone. On a typical two impurity were seen. One was assumed to be the and the other was assumed to be the intermediate. When they received this method, there were no standards available. This method is similar to the other methods currently used. A sample solution of known concentration of Mifepristone is Serial dilutions of this sample solution are which correspond to a solution. Each extraneous in the original sample is compared to the of the Mifepristone. The amount of impurities is calculated based on this

On March 3, 2000, the firm completed a validation report justifying the switch from the method to an method to determine the impurities and related substances in the Crude Mifepristone. The method is the same method as the assay and related substances for the finished product. As part of the justification for the switch, the firm performed a side by side comparison of the method to the method. By this time, impurity standards for the and the intermediate were available. The sensitivity of the method was confirmed. Also, the study revealed that one of the impurity typically seen was the . But the second was NOT the intermediate as suspected but instead a true impurity. The method does not have the ability to separate the intermediate from the Mifepristone. However, the method readily separates out the intermediate.

The specifications for Crude Mifepristone were revised following the implementation of the method. The previous specifications were Not More Than and Total Other Impurities. The new specifications are more stringent at Not More Than compound and Total Other Impurities.

During the closeout meeting, reiterated the currer method used for related substances / impurities are the same method as the finished product. This method has been shown to detect the intermediates.

4. The method for Residual Solvents has not been validated for

The method for residual solvents was validated for the more toxic of the two residues tested. The validation for the included specificity, accuracy, precision, linearity, limit of detection, and ruggedness. Although the method was validated for this solvent is rarely found. However, is typically found in the crude Mifepristone and was used during the specificity portion of the validation. The firm promised to amend the validation to include This validation should begin the week of July 31, 2000.

The method for residual solvents was originally validated in 1998. Since then, the operating conditions of the were modified to reduce the run time and improve the appearance. These modifications to the method did not change the elution order or other significant parameters of the During the inspection, the firm provided me with data

comparing the two — systems. The same solution was ——— on both systems, and the results were reviewed. The modifications to the method do decrease the run time and the —— are definitely sharper.

At this point in the closeout meeting, ——— stated the laboratory corrections should be completed and translated by mid-August and a response with the corresponding data should be filed with the FDA by August 31, 2000.

——. System in the Mifepristone Purification Suite

5a. The efficiency of HEPA filters was not determined during validation and there were no written procedures to monitor the efficiency on a periodic basis during production.

The Qualification of the —— system in the Mifepristone purification suite was done according to Protocol YZ-1001-00. There were no procedures to determine the efficiency of the 99.98 % HEPA filters after they were installed and there were no procedures to monitor the efficiency on a periodic basis during routine production.

A new SOP ——— for the efficiency and leakage test of high efficiency filters has been prepared. Efficiency qualifications will be performed every three months for a period of one year for this study and filter efficiency will be tested annually under normal conditions. A copy of the English version is shown in Exh. 8a.

5b. There was no information on the particulate counts under working conditions during validation and there were no written procedures to monitor the particulate counts on a periodic basis during production.

The —— system is designed to control the particulate counts in the purification suite under Class ——— The locations where the particulate counts were taken during the qualification are shown in Exh. 7. The particulate counts during the qualification were all taken under the stationary conditions and there was no information on the particulate counts under dynamic or working conditions. Also, there were no written procedures to monitor the particulate counts on a periodic basis during routine production.

A new SOP ——— on —— Cleanliness has been prepared. Particulate counts under dynamic conditions will be determined for three months to get baseline information before the routine testing frequency is established. A copy of the English version is shown in Exh. 8b.

5c. The pressure differentials between the room and inside hall are not recorded. There is no monitoring device for pressure differentials in the micronizing room.

The —— system is designed such that within the purification suite each room maintains a positive pressure relative to the inside corridor. During qualification, the pressure differentials were measured for each of the rooms in the suite. However, there is only one ——— meter mounted on the wall between the inner packaging room and the inside corridor. The pressure

differentials in this room are not recorded in a log or in batch records during routine production. There is no monitoring device for monitoring the pressure differentials between the room and inside corridor in the micronizing room.

A pressure test record sheet has been designed to record pressure differentials during packaging operations, which will be included as a part of batch record. Pressure differential readings will be taken and recorded starting from the next production batch. A copy of the English version is shown in Exh. 8c. A ———meter was installed on the wall of the inner corridor in the micronizing room on 7-27-00.

Following the formal FDA 483 Observations, a series of verbal observations were discussed with the firm.

There were two isolated instances where a ——— was either reprocessed or not used. In both cases, there was no written justification. One ——— was reprocessed due to poor integration. The baseline was incorrectly drawn. The analyst reprocessed this ——— with a better baseline. This ——— was not crossed out with an explanation relating to the reprocessing. In the other isolated instance, a ——— was not used. When the analyst was asked about the unused ——— she replied the result was not typical. Therefore, she made another ——— of the sample. This ——— sample was used in the calculations. However, the original ——— was within specifications and should have been used. The difference between these two ———did not vary by more than 1.5%. The firm promised to cross out and explain any unused data.

There was one instance when a SOP had not been updated to reflect current practices. The intermediate —— assay SOP states system suitability will be performed at least once per week. This was an observation mentioned during the previous FDA inspection. The firm has since corrected that observation and performs system suitability at the beginning of each analytical run. However, the SOP has not been updated.

The ———————————————method validation has not been completed. The validation was initiated in 1999, but no report has been written signifying the validation is completed.

The verification for the Crude Mifepristone impurities ———ıethod is incomplete. This method is the same as the finished product assay and related substance method. The intermediate laboratory group uses a different analytical ——— During the verification, they did not record the raw weights or dilutions for the samples prepared. The firm promised correction of this during the revalidation of the finished product ——— nethod.

There were numerous instances when the significant figures in the method acceptance criteria when not listed. For example, during system suitability the resolution criteria was listed as greater than 2. However, this value should have been 2.0.

The operator used a brush with wooden handle to remove dried crude Mifepristone from the [redacted] It is difficult to maintain the cleanliness of a plastic brush with wooden handle. Management promised to replace it with one made from different material.

At the conclusion of the inspection, we reminded them this was not an all-inclusive inspection. Any observations made should be evaluated and applied to other manufacturing and laboratory operations.

LOGISTICS

Lodging was at the Shanghai Jing-An Hilton Hotel. It takes about an hour to drive from the new Pudong International Airport to the hotel and about the same time from the hotel to the factory in Pudong. The firm provided transportation to the factory each day. The accommodations were very good and the cost was within per diem. There are five restaurants in the hotel.

ATTACHMENTS

1. Assignment memo.
2. FDA 483.

EXHIBITS

1. Location map.
2. Products list.

3a. Hua Lian Quality Management
b. Hua Lian Quality Flow Chart

4a. Xin Lian Manufacturing Management
b. Xin Lian Quality Management.

5. Factory Layout.
6. Mifepristone Purification Suite Layout and Particulate Counts Sampling Points.
7. Photo of [redacted]. Aluminum Canisters.

8a. SOP [redacted]
b. SOP [redacted]
c. Pressure Test Sheet.

/S/

[redacted]

Investigator
Division of Emergency and
Investigational Operations

/S/

[redacted]

KAN-DO Laboratory

Food and Drug Administration Establishment Inspection Report

Date Assigned: 07/31/2000 **Inspection Start Date:** 07/24/2000 **Inspection End Date:** 07/28/2000

Firm Name & Address: Shanghai Hua Lian Pharmaceutical Co., Ltd. , 217 Ming Le Road , Pudong Shanghai, CN

FEI: 3002914652 **JD/TA:** **County:** **Est Size:** ———

Phone: **District:** IOG **Profiled:** No

Conveyance Type: **% Interstate:** **Inspectional Responsibility:** 96156006

Endorsement

This was a pre-approval inspection of a manufacturer of active pharmaceutical ingredients (API) covering Mifepristone, in connection with FDA's review of NDA 20-687, Mifepristone 200 mg. Tablets. The assignment was issued by HFD-322 and the inspection was conducted according to CP 7356.002F.

The last inspection in October 1999 revealed several deficiencies which were reported on a FDA 483: Lack of procedures for handling and marking recycled solvent drums, and omissions and discrepancies of analytical methods in the firm's Standard Operating Procedures (SOP) compared to the Chemistry and Manufacturing Control (CMC) section in the submission. All the deficiencies have been either corrected or resolved.

The current inspection revealed five deficiencies which were reported on a FDA 483: 1 — assay and related impurities and — analysis for ——— for the Mifepristone finished product were incompletely validated, 2. No stability data supporting the — months expiration date for the Mifepristone working standard, 3. The — method originally used to determine the impurities for the crude Mifepristone was not validated, 4. The — method for residue solvents has not been validated for ——— and 5. Lack of information on the efficiency of the HEPA filters, particulate counts under the working conditions, and records of pressure differentials of the —— system in the purification suite.

In addition to the FDA 483 observations, several minor deficiencies were discussed with management.

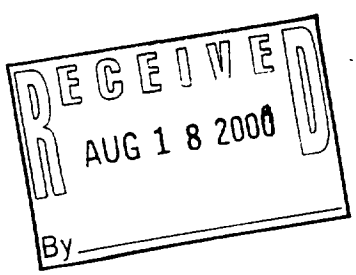
Management promised to make corrections and to prepare written responses to the FDA 483. The written responses were received by HFD-322 on 08/11/2000. The corrections appear to be adequate.

Recommendation: The firm is an acceptable supplier of API Mifepristone.

Distribution: O +Exhs: HFD-322
EIR: HFC-130, HFA-224, KAN-LAB —— DEIO —— FMD-145

Endorsement Location: HFC-130

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
———	08/15/2000 09:31 AM ET	———	08/15/2000 09:25 AM ET
———	08/15/2000 08:50 AM ET	———	08/15/2000 09:25 AM ET



3

Food and Drug Administration Establishment Inspection Report

FEI: 3002914652 **Inspection Start Date:** 07/24/2000 **Inspection End Date:** 07/28/2000

Firm Name & Address: Shanghai Hua Lian Pharmaceutical Co., Ltd. , 217 Ming Le Road , Pudong Shanghai, CN

Related Firm FEI: **Name & Addrress of Related Firm:**

Registration Type **Registration Dates**

There are no Registration Types

Establishment Type		Industry Code	
M	Manufacturer	60	Human Drugs
M	Manufacturer	64	Human Drugs
M	Manufacturer	66	Human Drugs

District Use Code:

APPEARS THIS WAY
ON ORIGINAL

FEI: 3002914652 **Inspection Start Date:** 07/24/2000 **Inspection End Date:** 07/28/2000

Firm Name & Address: Shanghai Hua Lian Pharmaceutical Co., Ltd. , 217 Ming Le Road , Pudong Shanghai, CN

Inspection Basis: Surveillance

Inspected Processes & District Decisions

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56002F	Manufacturer	64 R C S				Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	08/15/2000	Voluntary Action Indicated (VAI)		IOG

Remarks:

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
46832	Manufacturer	64 R C S				Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	08/15/2000	Voluntary Action Indicated (VAI)		IOG

Remarks:

APPEARS THIS WAY
ON ORIGINAL

FEI: 3002914652 **Inspection Start Date:** 07/24/2000 **Inspection End Date:** 07/28/2000

Firm Name & Address: Shanghai Hua Lian Pharmaceutical Co., Ltd. , 217 Ming Le Road , Pudong Shanghai, CN

Products Covered

Product Code	Est Type	Description	Additional Product Description
64 R C S 99	Manufacturer	Hormone N.E.C.; Single Ingred.Rx; Bulk Pharmaceutical	API Mifepristone

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
[redacted]	[redacted]	KAN-DO	56002F	Manufacturer	64 R C S	33
[redacted]	[redacted]	ORAHQ	56002F	Manufacturer	64 R C S	40
[redacted]	[redacted]	KAN-DO	46832	Manufacturer	64 R C S	100
[redacted]	[redacted]	ORAHQ	46832	Manufacturer	64 R C S	40
					Total Hours:	213

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration Establishment Inspection Report

FEI: 3002914652 **Inspection Start Date:** 07/24/2000 **Inspection End Date:**07/28/2000

Firm Name & Address: Shanghai Hua Lian Pharmaceutical Co., Ltd. , 217 Ming Le Road , Pudong Shanghai, CN

Inspection Result

EIR Location
HFD-322

Trips Num
2000-074D

Inspection Summary
This was a pre-approval inspection of a manufacturer of active pharmaceutical ingredients (API) covering Mifepristone, in connection with FDA's review of NDA 20-687, Mifepristone 200 mg. Tablets. The assignment was issued by HFD-322 and the inspection was conducted according to CP 7356.002F.

The last inspection in October 1999 revealed several deficiencies which were reported on a FDA 483: Lack of procedures for handling and marking recycled solvent drums, and omissions and discrepancies of analytical methods in the firm's Standard Operating Procedures (SOP) compared to the Chemistry and Manufacturing Control (CMC) section in the submission. All the deficiencies have been either corrected or resolved.

The current inspection revealed five deficiencies which were reported on a FDA 483: 1. — assay and related impurities and — analysis for — for the Mifepristone finished product were incompletely validated, 2. No stability data supporting the — nonths expiration date for the Mifepristone working standard, 3. The — method originally used to determine the impurities for the crude Mifepristone was not validated, 4. The — method for residue solvents has not been validated for — and 5. Lack of information on the efficiency of the HEPA filters, particulate counts under the working conditions, and records of pressure differentials of the — system in the purification suite.

In addition to the FDA 483 observations, several minor deficiencies were discussed with management.

IB Suggested Actions

Action	Remarks

Referrals

Org Name	Mail Code	Remarks

Refusals

Inspection Refusals: No refusal

Samples Collected

Sample Number

Recall Numbers

Recall Number

Related Complaints

Consumer Complaint Number

FDA 483 Responses

483 Issued?: Y **483 Location:** HFD-322

Response Type	Response Mode	Response Date	Response Summary

FDA

FACSIMILE

DEIO

INTERNATIONAL OPERATIONS / DRUG GROUP (HFC - 130)
5600 FISHERS LANE, ROOM 13 - 71 , ROCKVILLE, MD 20857 U. S. A.
fax _____ _____ e-mail _____

DATE: 7/31/00

TO: _____

FAX: _____

FROM: _____ TOTAL PAGES SENT: 2

The FDA 483 for Shanghai Hua Lian Pharm. Co., Ltd Xin Lian Pharm. Factory is attached.

APPEARS THIS WAY
ON ORIGINAL

[redacted] Compliance Officer
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing & Product Quality, HFD-322
7520 Standish Place, Room 272
Rockville, MD 20855

August 10, 2000

Re: **C.F. No. 9615606**
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.
Product: Mifepristone
Establishment Investigation: July 24-28, 2000
Inspectional Observations (Form FDA 483): Corrective Action

Dear [redacted]

On behalf of our principals, we are herewith enclosing a preliminary response to the Inspectional Observations issued at the conclusion of the recent inspection of their plant.

A desk copy has been sent to [redacted] for their review.

A complete response, including evidence of the completed corrective action or of corrective action underway, will be submitted before the end of this month.

Thank you for your attention.

Sincerely,

[redacted]

[redacted]

President

[redacted]

RECEIVED
AUG 14 2000
By

Encl.

cc: [redacted], Investigator, U.S.F.D.A., D.E.I.O., Rockville, MD
[redacted] U.S.F.D.A., Kansas City District Office
[redacted] V.P., Manufacturing, Danco Investors Group, L.P.
Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

[redacted] Investigator
Food and Drug Administration
Division of Emergency and Investigational
Operations, HFC-133
5600 Fishers Lane, Room 13-71
Rockville, MD 20857

August 10, 2000

Re: **C.F. No. 9615606**
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.
Product: Mifepristone
Establishment Investigation: July 24-28, 2000
Inspectional Observations (Form FDA 483): Corrective Action

Dear [redacted]

On behalf of our principals, please find herewith enclosed, a preliminary response to the Inspectional Observations issued at the conclusion of your recent inspection of their plant.

A complete response, including evidence of the completed corrective action or of corrective action underway, will be submitted before the end of this month.

Thank you for your attention.

Sincerely,

[redacted]

[redacted]

President

[redacted]
Encl.

cc: [redacted] Compliance Officer,
U.S.F.D.A., Div. of Manufacturing & Product Quality, Foreign Inspection Team
[redacted] U.S.F.D.A., Kansas City District Office
[redacted] V.P., Manufacturing, Danco Investors Group, L.P.
Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

U.S. Food and Drug Administration
Kansas City District Office
11630 W. 80th Street
Lenexa, KS 66285-5905

August 10, 2000

Re: **C.F. No. 9615606**
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.
Product: Mifepristone
Establishment Investigation: July 24-28, 2000
Inspectional Observations (Form FDA 483): Corrective Action

Dear [redacted]

On behalf of our principals, please find herewith enclosed, a preliminary response to the Inspectional Observations issued at the conclusion of your recent inspection of their plant.

A complete response, including evidence of the completed corrective action or of corrective action underway, will be submitted before the end of this month.

Thank you for your attention.

Sincerely,

[redacted]

President

Encl.

cc: [redacted] Compliance Officer,
U.S.F.D.A., Div. of Manufacturing & Product Quality, Foreign Inspection Team
[redacted], Investigator, U.S.F.D.A., D.E.I.O., Rockville, MD
[redacted] V.P., Manufacturing, Danco Investors Group, L.P.
Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

HFD-322
FF

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: [redacted]
FAX: [redacted]

December 14, 1999

Li Changfa
Chairman & General Manager
Shanghai Hua Lian Pharmaceutical Co., Inc.
XinLian Pharmaceutical Factory
370 Jiang Wan Road (West)
Shangai 200083
China

Dear Mr. Li:

We have completed review of the Inspection Report on the October 25-28, 1999 inspection of your active pharmaceutical ingredient manufacturing facility in Shanghai, China, by FDA Investigator [redacted] The inspection revealed several CGMP deficiencies and NDA discrepancies, which were listed on an FDA-483, Inspectional Observations Form, issued to you at the conclusion of the inspection.

We have also reviewed the December 2 , 1999, written response to the FDA-483 observations submitted by [redacted] The responses to FDA-483 items 1-3 appear adequate, however we are recommending withholding approval of the subject New Drug Application because the inspection revealed that the analytical methods being used were not the same as described in the NDA and therefore could not be fully evaluated. Also, the critical in-process tests for monitoring synthesis of the starting material had not been validated.

Your response indicates that an amendment to the NDA has been submitted to the FDA Review Division. We are also forwarding a copy of the inspection report and your response to the review division for review and evaluation of amendment.

Additionally, we enclose a copy of the establishment inspection report (EIR) for the inspection. This report is being provided to you for information purposes. The Agency is working to make its regulatory process and activities more transparent to the regulated industry. Releasing this EIR to you is part of this effort. The copy being provided to you comprises the narrative portion of the report; it may reflect redactions

made by the Agency in accordance with the FOIA and C.F.R. Part 20. This, however, does not preclude you from requesting and, possibly, obtaining any additional information under FOIA.

You may contact me at the address or telephone number given above if you have any questions regarding this letter.

Sincerely,

/S/

Compliance Officer
Foreign Inspection Team

Enclosure:

cc:

[ ]

APPEARS THIS WAY ON ORIGINAL

cc:

HFR-MA140
HFC-133

HFD-322
HFD-322

HFD-820 re. NDA 20-687

Control# 322-99-12-04

APPEARS THIS WAY
ON ORIGINAL

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99 —

SUMMARY OF FINDINGS

This was a pre-approval inspection of a manufacturer of active pharmaceutical ingredients (APIs) covering [redacted] for [redacted] tablets. [redacted]

This was the first FDA inspection at this site. Manufacturing facilities appeared adequate except for the lack of a clearly defined policy for handling and marking of recycled solvent drums to preclude mix-up with waste solvents which was reported on a FDA 483. Laboratory operations relating to the Mifepristone NDA, however, could not be adequately audited because of numerous errors and omissions in the methods section of the CMC.

Some of the deficiencies identified include the failure to include in the CMC the method used for assay and impurity testing of purified [redacted] failure to include in the CMC the assay method for ———— a critical starting material manufactured at the site. Since these methods had not been included in the application, no English translations were available when the laboratory inspection was initiated. A translation that was subsequently provided proved to be inaccurate and a second translation was prepared.

In addition to these omissions, significant discrepancies were identified between methods reported in the CMC and data that were presented. For example, the — related substances method for ———— and the methods for ———— used in the final purification that are described in the CMC differed significantly from methods actually performed. Because of these conflicts between the CMC and the data that were presented, it was not possible to evaluate methods actually performed since concurrent line by line translation was so time consuming.

In addition to these deficiencies, the critical in-process tests for monitoring synthesis of the ———— starting material reported in the CMC have not been fully developed. The status of these methods is not indicated in the CMC.

The inspection determined that the approved laboratory methods used in the XinLian laboratory were not used as the source documents when translating information for the NDA. The firm has committed to revise the CMC to accurately reflect current methods and specifications. They will re-submit this information to the U.S. Agent who is handling submissions to FDA for [redacted]

The firm has also committed to establish formal procedures for use and handling of recycled drums to avoid potential mix up between virgin and waste solvents.

Management indicated they would respond in writing to the FDA 483 observations through the U.S. Agent.

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99

HISTORY OF BUSINESS

According to information provided during the inspection, the Shanghai Hua Lian Pharmaceutical Company, [redacted] was established in 1939 and has manufactured steroid hormones since 1959. Shanghai Hua Lian is a partially privatized limited corporation since 1995. Private shareholders represent roughly — with the remainder held by the state. The Parent Corporation oversees — manufacturing factories, — R&D facilities and — sales companies as shown in Exhibit 1. One of the manufacturing factories, known as the ——— ——— manufactures a key starting material for [redacted] referred to as ' ——— Among the sales companies is the Material Supplying Company that purchases and distributes some raw materials, including some drummed solvents, to the manufacturing factories.

The XinLian factory has been located in the Xinghuo Development Zone of New Pudong since 1993. Two APIs are produced at this site — [redacted] and [redacted].

The most responsible individual at the corporate level for operations at the XinLian Factory is Mr. Li Changfa, Chairman of the Board and General Manager. Mr. Li maintains his office at corporate headquarters located at 370 Jiang Wan Road (West), Shanghai 200083, China. His phone ——— FDA correspondence to the firm should be addressed to Mr. Li.

The most responsible person at the factory site is ——— Plant Manager. His phone number: ———

The U.S. Agent and Importer for the firm is The Danco Group, ——— ——— The principal U.S. contact for arranging FDA inspections is ———

——— , provides consulting services to the firm relating to Pharmaceutical Quality Assurance. Contact information is as follows:

[ ]

PERSONS INTERVIEWED/RESPONSIBILITY

The most responsible individual at the corporate level for operations at the XinLian Factory is Mr. Li Changfa, Chairman of the Board and General Manager. Mr. Li was present at the initiation and closing of the inspection. The FDA 483 was issued to Mr. Li on 10/28/99.

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99

The most responsible person at the factory site is [redacted] of XinLian Factory. [redacted] was present during this inspection.

[redacted] served as interpreter during this inspection. [redacted] also accompanied me.

Some of the key individuals who provided information via [redacted] include:

[redacted] Process
[redacted] Supervisor
[redacted] Supervisor
[redacted]

PRODUCTS AND QUANTITIES SHIPPED TO THE U.S.

According to [redacted] three [redacted] batches of [redacted] have been shipped to the U.S. for use in exhibit batches of the dosage forms. Exhibit 2 shows the current packaging/labeling configuration – double poly bags inside a silver metal canister.

SCOPE OF INSPECTION

The focus of the inspection was a preapproval audit of bulk [redacted], profile class CSN, the active ingredient for [redacted] Tablets, [redacted]. The inspection included a general evaluation of facility operations, with particular emphasis on avenues that could lead to cross-contamination or extraneous contamination. Also, both the chemical process and laboratory analyses were audited for conformance to commitments described in the CMC section of the NDA. Various stages of [redacted] synthesis were in active operation during this inspection, however, [redacted], and micronizing were not observed.

[redacted] has been produced at this site since October 1995. However, in May 1998 Shanghai Hua Lian agreed to adopt the Roussel Uclaf process obtained from Danco of the U.S. This resulted in modification to the synthesis and to some equipment. The new process, the one described in NDA [redacted] has been in place since December 1998. The process validation study in the NDA is based on the first three production lots [90101, 990102, 990103]. Additional validation information was gathered on the next 7 lots. Due to time constraints, this was not covered. One lot out of [redacted] produced thus far with this process was rejected and later [redacted] because of an off-color.

The analytical review included procedures for qualifying the [redacted] reference standard, general analyst documentation and handling of OOS results, limited review of stability data, and conformance to procedures/specifications submitted in the CMC section of the [redacted] NDA. Because of the numerous discrepancies between method descriptions in the CMC and those observed during this inspection, a full laboratory inspection and data audit could not be accomplished in the time allotted.

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99 —

General Facilities

Two products, both of which are steroids, are synthesized at this plant – [redacted] and [redacted]. These products are produced in the same building but in different equipment and workshops. The building itself is divided into numerous individual workshops, separated by concrete walls that isolate key phases of synthesis. [redacted] synthesis occupies the workshops on the ground level while [redacted] synthesis occurs in the workshops on the level above this. These workshops are maintained under ambient conditions without any [redacted] systems for air conditioning, although there are solvent exhaust systems in place for containment of volatile organic fumes.

[redacted] generated from a [redacted] tank outside the building, is used extensively in the [redacted] process. The feed lines from the tank to the manufacturing workshops were dedicated to the [redacted] workshops without interconnecting to the [redacted] synthesis areas. Distilled water used in the [redacted] workshop appears to likewise feed only the [redacted] process from a distillation still located above the workshop areas. According to information provided, no solvents or mother liquors are recovered or recycled.

While the synthesis workshops for these two steroids are located on two separate levels, the final [redacted] suites are located next to one another on the upper floor with a [redacted] workshop between the two. These suites have formal [redacted] air handlers that provide for controlled temperature and humidity. The air handlers are located above the suites and are completely separate for the two steroid products. Intake air and exhaust for [redacted] are located on the North side of the building; for [redacted] air intake/exhaust are handled from the South side. In addition to these independent [redacted] systems, there are dust collection systems that exhaust air to a collection bag on the roof and, in the [redacted] suite, there are HEPA filters located in air supply ports in each room for particle control of the recirculating air.

On a half level between floors there is a vaulted storage and dispensing suite for intermediates. While there is a common entryway to the storage vault of both [redacted] and [redacted], the storage and dispensing areas themselves are separate with entry into the areas located at opposite ends. These rooms have provision for simple air circulation but not for air conditioning. The air circulation appears to be local within each suite without interconnecting between the two storage areas. Dispensing for [redacted] occurs in closed cabinets located within the [redacted] storage room.

Dispensing of raw materials for [redacted] occurs in a dedicated workshop, located near the raw material warehouses.

Equipment

For [redacted] workshops are dedicated to synthesis of the key raw material, [redacted] and [redacted] additional workshops are used for synthesis of the key intermediates. Most

reaction vessels were fitted with pressure gauges and glass thermometers, although [redacted] sensors with digital readouts were observed in several workshops. All equipment is manually monitored and data is hand recorded without use of recorder charts. Control of valves is also manual.

Water Supply

Water for the site is city water. There is a water treatment facility on the premises with sand/charcoal pretreatment followed by electrophoresis to reduce cations/anions in the source water. This is followed by deionization. DI water is stored in a tank at the water treatment workshop and is fed to the production area via pipe, covering a distance of roughly 250 meters.

For [redacted] uses [redacted] For water used immediately before this, the DI water is further treated by distillation with equipment located near to the [redacted] workshop. There is no circulation of either DI or distilled water. However, the distilled water is generated only when needed and the holding tank is drained when not in use.

[redacted] ***Synthesis***

The synthesis and equipment described in the NDA were compared in detail to actual operations. Only a few minor errors or omissions were noted.

The key raw material, [redacted] CMC page 135, is also synthesized at this factory and was audited during this inspection. According to information provided during the inspection, the starting material for this key compound, [redacted] is produced at a sister factory known as the [redacted] There are no other suppliers of the [redacted] according to management.

[redacted] ***Reference Standard***

The firm uses its own [redacted] as a working standard but has qualified this material against [redacted] prepared by Roussel Uclaf. The Roussel batch number observed during this inspection was #4V1014BJ. According to the [redacted] (Exhibit 3), this lot was manufactured 10/94 with an expiration of 11/99.

To obtain a purity value for this aged reference material, XinLian laboratory initially performed a series of 10 analyses for assay and for impurities using their own [redacted] method, rather than the Roussel [redacted] assay. Subsequently, they performed an additional 8 assays and used the 18 analytical results to derive a purity value (Exhibit 4).

For a working standard the XinLian laboratory [redacted] [redacted] Lot 990101, produced at this factory, and used the Roussel material to qualify the in-house standard.

Presently, the in-house standard is used for release testing. They have prepared a protocol for this in-

house standard that requires retesting at 6, 12, 18 and 24 months in order to establish a re-qualification date.

FDA 483 WITH ANNOTATIONS

OBSERVATION 1:
Recycled metal drums of the same type and color are used for both virgin solvents and for storing waste solvents. There is no clear policy of marking drums to assure that mix up would not occur. For example, a drum bearing complete labeling for [redacted] *was filling with waste solvent during this inspection. Other solvents such as* [redacted] *and* [redacted] *are received from the central office in drums of the same color that bear minimal identification. Some of these drums are returned to the central office for refilling and others are used for collection of waste with only a minimum of identification.*

ANNOTATIONS TO OBSERVATION 1:

According to information provided by [redacted] that supplies many solvents to the [redacted] Hua Lian factory sites, there is a central system for assuring quality of raw materials they supply. He indicated that they use their own trucks and drums when purchasing large volumes of solvents. Information obtained via the Interpreter indicates that the Material Supply Company paints metal drums for uniformity and marks the contents with paint on the drum top. They deliver solvents to the factories that use them and pick up the empty drums on subsequent delivery trips for reuse.

All of the drums I observed at XinLian that had been delivered from the Central Supply Company were painted dark green, except for [redacted] in dark blue drums. There was a paint mark on the lid to indicate content and a small, thin, hand-written paper label roughly 3" X 4" on the side or top when in the warehouse to indicate lot number. Except for the marking on the lid, which was peeling in some cases, all of the drums are identical.

Some drums are later used by the XinLian factory to collect waste solvents that are stored at the factory until they are removed for disposal. To identify drums filled with waste solvents, the painted identification on the lid is overwritten at some point. When this occurs was not clear. As noted in this observation, I observed a drum being used to collect waste solvents that still retained the full [redacted] labeling from the original supplier.

It was also not clear how they assured that drums returned to Central Supply for refilling have not been used for other purposes in the interim. For example, in synthesis o[redacted] is added into virgin drums of [redacted] however, the labeling of the drums would not reflect this. I later observed empty metal drums that had been painted dark green on the top and sides but, from the powder blue bottom, appeared to be [redacted] drums.

Although both the Central Supply Company and the XinLian factory have some fundamental procedures for handling recycled drums, the procedures for marking and handling drums all painted identically do not appear detailed enough to preclude mix-up or cross-contamination.

Corporate management committed to work with the XinLian factory to tighten up procedures. stated he would evaluate these procedures before they are finalized to assure they address the concerns that were raised.

OBSERVATION 2:
For and analyses performed prior to September 1999, no formal system suitability was performed aside from the initial of reference standard.

ANNOTATIONS TO OBSERVATION 2:

During my review of laboratory data, I requested system suitability for the and data I was reviewing. explained that system suitability was begun around September 1, 1999. This omission had been identified by in August, and at his request, they reanalyzed retain samples of for assay/impurities. The summary submitted as Exhibit 5 shows the results of this retesting of retain samples.

Although procedures for assuring system suitability have now been formalized for finished product testing, system suitability for in-process analysis, such as for the in-process analysis of the derivative, was not handled the same. For in-process analyses, system suitability checks are conducted only once per week as noted in FDA 483 Observation #4.

OBSERVATION 3:
No acceptance criteria have been established for calibration of the analyzer although Q.C. approves the monthly calibration runs.

ANNOTATIONS TO OBSERVATION 3:

Purified is micronized at the final processing step. Particle Size analysis is performed with a analyzer. I selected this instrument for a random check of calibration procedures. Documentation confirmed that calibration runs are performed once a month with a standard of . The analytical results over the last year ranged from I asked for an explanation of how the analytical results relate to particle size and what range of numbers assures that the instrument is performing properly. Supervisor, stated that verbally told her that are good numbers. There was no documentation to verify this; nor was this range mentioned in either the method or the calibration SOP.

The firm has committed to respond to 483 observations in writing via their U.S. Agent. [redacted] has agreed to assist the firm in making needed improvements.

OBSERVATION 4:
There are numerous errors and/or omissions in the CMC methods filed for NDA [redacted] for [redacted] including, but not limited to, the following:

Finished product testing:

a) *The [redacted] method used for release testing of the purified [redacted] is not described in the CMC.*
b) *The specification for residual [redacted] in finished product on CMC page 168 is incorrectly reported as [redacted] The actual specification is [redacted]*
c) *The [redacted] analysis for [redacted] on pages188-189 is incorrect.*

In- process/intermediate test methods:

a) *For [redacted] analyses of the [redacted] intermediate run prior to September 1999, reference standards were only run once per 5 samples. The data from this standard run was used in calculations for all subsequent samples run on different days.*
b) *There is limited resolution of the two major impurities from the main reactant in the [redacted] method for in-processing monitoring of the [redacted] reaction in synthesis of the key intermediate, [redacted]*
c) *[redacted] reaction, CMC 143, section 2.1.3 states that the method is [redacted] although a [redacted] analysis is run, the former [redacted] method is being used for evaluation since the [redacted] method is still under development.*
d) *The assay method for [redacted] CMC pages 135, 172-174, 144-145, is not included in the CMC. The CMC states only that the method is by [redacted] Also, the [redacted] method, section 1.3 page 172-173, is significantly mistranslated. The sample and reference dilutions are not distinguished. Sample solution "a" should be 20 mg/ml, not [redacted] mg/ml. The cited dilutions are not the ones used. The [redacted] for final reading under [redacted] is not mentioned.*

Raw Material Testing:

a) *References to USP do not reflect actual test methods in many cases. As an example, CMC section 2.12, page 180, for [redacted] states that all test methods are the same as USP 23, page 848. However, the assay method is an in-house [redacted] method, not the USP method, and [redacted] is not performed although the CMC reports that it this test is conducted.*

ANNOTATIONS TO OBSERVATION 4:

The deficiencies noted above do not represent a complete list of inaccuracies in the [redacted] CMC but reflect only those analyses that I specifically audited. I had intended to focus the data audit

on several pivotal quality control points that spanned the [redacted] synthesis. The areas I selected were the qualification of the [redacted] used in the final [redacted] steps, monitoring of the critical intermediate, [redacted], that is also synthesized at this site, and finished product tests for assay, impurities and residual solvents.

In each case the data that was provided either did not correlate with information submitted in the CMC or the CMC lacked information needed to evaluate the data. As reported in this observation, the in-house [redacted] method for assay and impurities for final product release testing of [redacted] was not included in the NDA; nor was the assay method for [redacted] included in the NDA. Consequently, there were no English translations available when the laboratory inspection was initiated. A translation that was subsequently provided proved to be inaccurate when I compared the method as described in the translation with analytical data. A second translation was then prepared. The latest translation of the [redacted] assay method is submitted as Exhibit 6 and the [redacted] assay method is submitted as Exhibit 7.

While the assay method for [redacted] had been omitted when the CMC was prepared, the [redacted] related substances method described in the CMC for this key material was significantly mistranslated as described above in observation *(d)* under *In-process/intermediate test methods.*

When I then checked the raw material analyses for the [redacted] used in the final [redacted] of [redacted] I likewise found that the CMC reference was not consistent with analyses performed. These discrepancies are described on the FDA 483 under *Raw Material Testing.*

Because of these conflicts between the English translation and the data that were presented, it was not possible to evaluate methods actually performed since concurrent line by line translation was so time consuming. Although I repeatedly asked which source documents were used for the information submitted in the NDA, and while much discussion in Chinese ensued, no specifics were provided, except that [redacted], the Interpreter, stated that it appears some information *may* have been copied from the Roussel NDA. I could not, however, confirm this. While I could not verify the ultimate source of this misinformation, the inspection determined that the laboratory methods used in the XinLian laboratory were not used as source documents when translating information for the NDA.

The firm has committed to revise the CMC to accurately reflect current methods and specifications. They will re-submit this information to their U.S. Agent who is handling submissions to FDA for [redacted].

Aside from the errors and omissions in the CMC, problems were noted with the analyses used to monitor the synthesis of [redacted] While the CMC describes this compound as a starting material, it is synthesized in the same building as the final [redacted] The chemical pathway is described in the CMC on page 135.

The initial reactant is [redacted]" obtained from a sister factory known as [redacted] There are two major stages in preparation of the [redacted] - the first phase is called the [redacted] reaction and the second is the [redacted] reaction, which are pivotal in assuring the correct molecular form for [redacted]

For the [redacted] reaction the firm uses an [redacted] in-process assay to monitor the reaction progress. They have identified [redacted] of significance in this evaluation: [redacted] is reportedly the [redacted] reactant; [redacted] = an unknown, unwanted reactant; [redacted] unreacted [redacted] For most of the analyses I reviewed, these peaks overlapped one another. Exhibit 8 is the assay method identifying the three pivotal reactants on page 4. Exhibit 9, pages 1 & 2, are examples of [redacted] showing the lack of resolution of these reactants.

For the [redacted] reaction, the CMC states on page 143 that a[redacted] method is used for monitoring the reaction end point. One of the critical concerns at this point, according to information provided during this inspection, is confirming that only one [redacted] group is formed, not two [redacted] reactant). The [redacted] method currently used, however, is still under development. They have not yet verified that the peak they are evaluating is actually the [redacted] formation. In the mean time they are using a [redacted] method for screening that provides only a rough quantitative estimate. Exhibit 10 is a representative chromatogram for [redacted] monitoring where the identity of the eluting peaks have not been confirmed..

The firm has committed to continue development and validation of these critical in-process control methods.

LOGISTICS

Lodging was at Shanghai JC Mandarin Hotel located in the city of Shanghai. It is located about 25 minutes from the Hong Qiao International Airport and about 1 ¼ hour by car from the plant site in Pudong. The firm provided transportation to the firm each day. The accommodations were very good and the cost was within per diem. There are two restaurants within the hotel and a variety of restaurants within walking distance.

SAMPLES

No samples were collected.

ATTACHMENTS

APPEARS THIS WAY ON ORIGINAL

Assignment memo
FDA 483

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99

EXHIBITS

1. Organization of parent corporation, Shanghai Hua Lian Pharmaceutical Co., Ltd.
2. Photos of packaging/labeling configuration for [redacted]
3. COA for Roussel Uclaf [redacted] Batch 4V1014 BJ
4. Summary of analyses of Roussel API as reference standard
5. Summary chart of analyses with and without supporting system suitability
6. Method for Assay of [redacted]
7. Method for Assay of [redacted]
8. method for in-process monitoring of [redacted] reaction
9. Representative chromatograms for [redacted] monitoring
10. Representative chromatograms for in-process monitoring of [redacted] reaction

/S/

Compliance Officer
Philadelphia District

APPEARS THIS WAY
ON ORIGINAL

[redacted] Compliance Officer
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing & Product Quality
Foreign Inspection Team, HFD-322
7520 Standish Place, Room
Rockville, MD 20855

File
S 1/24/2000

January 4, 2000

Re: **C.F. Number 9615606**
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd. ✓
Product: Mifepristone
Date of Inspection: October 25-28, 1999

Dear [redacted]

On behalf of our clients, the Shanghai HuaLian Pharmaceutical Company and in connection with your letter of December 14, 1999, we would like to advise you of the following:

1. A detailed review of the CMC Section submitted to the Agency on June 3, 1999 has been carried out in order to identify any errors and/or omissions in this document. Corrective action was implemented as Amendment 037 to NDA 20-687, submitted to the Division of Reproductive and Urologic Drugs Products on November 29, 1999.

2. The Division has identified topics that require further supportive data or has requested clarifications to data presented to the Agency in the original submission and in its subsequent Amendments in a Information Request Letter dated December 14, 1999. A response to this correspondence is being compiled and will be submitted to the FDA shortly.

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number

[redacted] Compliance Officer
Division of Manufacturing & Product Quality
Foreign Inspection Team, HFD-322
January 4, 2000

Finally, the Shanghai HuaLian Pharmaceutical Company wishes to stress their commitment to follow all procedures and methods described in the current CMC Section. This commitment will be ensured by responsible Quality Assurance oversight of their procedures.

Furthermore, these Quality Assurance activities will be supported and reviewed through [redacted] frequent correspondence and periodic visits to the site in order to ensure adherence to acceptable levels of Good Manufacturing and Laboratory Practices.

Should you have any further comments, please do not hesitate to contact the undersigned.

Sincerely,

[redacted]

[redacted]

President

[redacted]

cc: Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.
[redacted] V.P., Manufacturing, Danco Investors Group, L.P.
[redacted] F.D.A., Division of Reproductive and Urologic Drugs Products

APPEARS THIS WAY
ON ORIGINAL

[redacted]

facsimile
MESSAGE

Date: December 28, 1999

Company: Food and Drug Administration
Foreign Inspection Team, HFD-322

Attention: [redacted], Compliance Officer

Fax No.: [redacted]

Pages (including cover sheet): 2

Dear [redacted]

In connection with our telephone conversation of yesterday, please find herewith attached our clients letter authorizing your office to release a copy of their Establishment Investigation Report issued in connection with their October inspection.

Thank you for your assistance in this matter.

Best regards

[redacted]

[redacted]
President

[redacted]

Encl.

**APPEARS THIS WAY
ON ORIGINAL**

[redacted]

上海华联制药有限公司
Shanghai HuaLian Pharmaceutical Co., Ltd.

370 Jiangwan Road(West)
Shanghai, 200083
China
Tel: 86-21-65401680
Fax: 86-21-65400098

[redacted] Compliance Offier
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing & Product Quality
Foreign Inspection Team, HFD-322
7520 Standish Place, Room [redacted]
Rockville, MD 20855

December 28th,1999

Re: Establishment Investigation Report Request
C.F. Number 9615606
Date of Inspection: October 25-28,1999
Investigator: [redacted]

Dear sirs:

Pursuant to the Freedom of Information Act as amended, I herewith request the release of a true and unexpurgated copy of the Establishment Investigation Report prepared in connection with the referenced inspection, to our Consultants.

[redacted]
Attn: [redacted]

Telephone: [redacted]
Telefax: [redacted]

Thank you for you attention

Sincerely,
Shanghai HuaLian Pharmaceutical Co., Ltd

Li Changfa
Chairmen & General manager
Shanghai Pharmaceutical Co., Inc

cc: [redacted] President
[redacted]

HFD-322
FF

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date December 15, 1999

From Foreign Inspection Team
CDER/OC/DMPQ/HFD-322

Subject Withhold Recommendation
NDA 20-687 Mifepristone

firm: Shanghai Hua Lian
Pharmaceutical Co., Ltd.
Shanghai, China
CFN: 9615606

To [redacted] DNDCII

A PAI inspection of the referenced firm was conducted October 25-28, 1999 re. NDA 20-687 Mifepristone This firm manufactures the bulk drug substance. The inspection found several CGMP deficiencies which are adequately addressed in the firm's written response. The district has recommended withholding approval because of NDA discrepancies and because in-process test methods have not been validated. DMPQ concurs with the withhold recommendation.

The inspection revealed that the raw material, in-process, and finished product analytical procedures actually being used are different from those described in the NDA, and that the in-process tests had not been validated. The written response indicates that an amendment to the NDA has been submitted to correct these discrepancies. Since the ammendment was submitted after the inspection and the analytical methods were not available in Engish during the inspection, the procedures and validation submitted in the amendment could not be fully evaluated.

A copy of the EIR and the firm's response is also attached for your review and evaluation of the ammendment. Other CGMP issues are considered resolved. Please contact me at [redacted] if additional information is needed.

/S/

[redacted]
Compliance Officer
Foreign Inspection Team

Attachments

cc:

HFD-322
HFD-327

APPEARS THIS WAY
ON ORIGINAL

DATE ASSIGNED: 10 1999	CS#:	PRIORITY:	DATE INSPECTED: 10/25-28/1999	GRP: [redacted]
CENTRAL FILE NO: 9615606	JD/TA:	COUNTY:	PHONE: [redacted]	
NAME: Shanghai Hua Lian Pharmaceutical Co., Ltd - XinLian Pharmaceutical Factory		STREET: 217 Ming Le Road		
CITY: Pudong, Shanghai	STATE: China	ZIP: 201419	DISTRICT: %	

ENDORSEMENT

This was a pre-approval inspection of bulk Mifepristone, for NDA 20-687, Mifepristone tablets. The applicant of this NDA is the Population Council of New York.

This was the first FDA inspection at this site. Manufacturing facilities appeared adequate except for the lack of a clearly defined policy for handling and marking of recycled solvent drums to preclude mix-up with waste solvents which was reported on a FDA 483. Laboratory operations relating to the Mifepristone NDA, however, could not be adequately audited because of numerous errors and omissions in the methods section of the CMC.

Some of the deficiencies identified include the failure to include in the CMC the [redacted] nethod used for assay and impurity testing of purified Mifepristone: failure to include in the CMC the assay method for [redacted] a critical starting material manufactured at the site. Since these methods had not been included in the application, no English translations were available when the laboratory inspection was initiated. A translation that was subsequently provided proved to be inaccurate.

In addition to these omissions, significant discrepancies were identified between methods reported in the CMC and data that were presented. For example, the [redacted] related substances method for [redacted] and the methods for [redacted] used in the final purification that are described in the CMC differed significantly from methods actually performed. Because of these conflicts between the CMC and the data that were presented, it was not possible to evaluate methods actually performed since concurrent line by line translation was so time consuming.

In addition to these deficiencies, the critical in-process tests for monitoring synthesis of the [redacted] starting material reported in the CMC have not been fully developed. The status of these methods is not indicated in the CMC.

The inspection determined that the approved laboratory methods used in the XinLian laboratory were not used as the source documents when translating information for the NDA. The firm has committed to revise the CMC to accurately reflect current methods and specifications. They will re-submit this information to the U.S. Agent who is handling submissions to FDA for Mifepristone.

The firm has also committed to establish formal procedures for use and handling of recycled drums to avoid potential mix up between virgin and waste solvents.

Management indicated they would respond in writing to the FDA 483 observations through the U.S. Agent.

Follow-up: PHI-DO recommends withhold of the referenced NDA. Any future approvals/submissions regarding the inspected firm should be audited through an onsite inspection /S/ for — 12/6/99

COMPLIANCE ACHIEVEMENT DATA

PAC Code	Problem Type	Corrective Action	Date Action Verified (MM/DD/YY)	Correcting Unit[1]	Reporting District[2]	Reason for Correction
				/	/	
				/	/	
				/	/	

SIGNATURE /S/ DATE 12/3/99

FORM FDA 481(E)-CG

DISTRIBUTION

HFD-320 w/exhibits: HFC-133 — HFR-CE140 —

RECEIVED DEC 14 1999 By

DATE ASSIGNED: 10/1999	CS#:	PRIORITY:	DATE INSPD: 10/25-28/1999	GRF: —
CENTRAL FILE NO: 9615606	JD/TA:	COUNTY:	PHONE: 86 021 65401 680	
NAME: Shanghai Hua Lian Pharmaceutical Co., Ltd - XinLian Pharmaceutical Factory		STREET: 217 Ming Le Road		
CITY: Pudong, Shanghai	STATE: China	ZIP: 201419	DISTRICT: %	
RELATED FIRMS	STATE ASSIGNED:	ITS:		

REGISTRATION:

REG TYP	MM/YY	MM/YY	MM/YY	REG TYPE	MM/YY	MM/YY	MM/YY	REG TYPE	MM/YY	MMYY	MM/YY
F				D				V			
M				R				B			

ESTABLISHMENT TYPES/ INDUSTRY CODES ON OEI	1. M	2.	3.
	60		

TOTAL ESTAB SIZE	INTERSTATE BUSINESS RECEIVED	INTERSTATE BUSINESS SOLD	DISTRICT USE #1	#2	#3	RECALL NUMBER	REFUSAL CODE	PROFILE	PASS/FAIL
							0		

ESTABLISHMENT CHANGES: ☒ New Firm ☐ None ☐ Name ☐ Address ☐ Ownership ☐ Size ☐ Prod Code ☐ Other ☐ Est Type
☐ O/B ☐ Inactive ☐ Not OEI ☐ Aux Firm ☐ Registration

PAC	Process (Product) Code	Est Typ	Insp Basis	Empl1 PC: — No: — HC: —	Empl2 PC: No: HD:	Empl3 PC: No: HD:	Product	Priority	Resched Date	Insp Conc	Dist DSCN
46832		M	2	—			Mifepristone Bulk	1	5/2000	A	A

SAMPLES COLLECTED:
NO

SAMPLE #:	PRODUCT:
HEADQUARTERS UNTI REFERRED: HFD-320	FDA 483 ISSUED: ☒ YES ☐ NO
REASON REFERRED: CP 7356.002F	OTHER FED GOVT INSP OR GRADING:
INSPECTOR'S NAME AND SIGNATURE: /S/	SUPERVISOR'S NAME AND SIGNATURE: /S/ Philadelphia District (HFR-CE140)

FORM FDA 481(A)-CG

MIF 005380

DATE ASSIGNED: 10/1999	CS#:	PRIORITY:	DATE INSPECTED: 10/25-28/1999	GRP: 2
CENTRAL FILE NO: 9615606	JD/TA:		COUNTY:	PHONE: 86 021 65401 680
NAME: Shanghai Hua Lian Pharmaceutical Co., Ltd - XinLian Pharmaceutical Factory			STREET: 217 Ming Le Road	
CITY: Pudong, Shanghai	STATE: China		ZIP: 201419	DISTRICT: %
PROFILE DATA SHEET NO:			EMPLOYEE NUMBER:	

PROFILE DATA SHEET

PRO CLS	NEW STATUS		CURRENT STATUS		GMP DATE	REMARKS
	M	R	M	R		
CSN	N				10/28/1999	

APPEARS THIS WAY
ON ORIGINAL

SIGN OFF SIGNATURE	DATE OF SIGNATURE

FORM FDA 481-CG

DISTRIBUTION:

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

OBSERVATION:

"4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

In-process/intermediate test methods:

c) [redacted]reaction, CMC 143, section 2.1.3 states that the method is [redacted] Although a [redacted] nalysis is run, the former [redacted] method is being used for evaluation since the [redacted] ethod is still under development."

CORRECTIVE ACTION:

Until the development of an acceptable [redacted] .s completed and the method is validated, the [redacted] method will continue to be used in monitoring the reaction completion as reflected in the attached Pages 143 & 143-1 of the CMC Section Amendment recently submitted to the Agency.

APPEARS THIS WAY
ON ORIGINAL

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

OBSERVATION:

"4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

In-process/intermediate test methods:

d) The assay method for [redacted] CMC pages 135, 172-174, 144-145, is not included in the CMC. The CMC states only that the method is by [redacted] Also, the [redacted] method, section 1.3 page 172-173, is significantly mistranslated. The sample and reference dilutions are not distinguished. Sample solution "a" should be 20 mg/ml, not [redacted]mg/ml. The cited dilutions are not the ones used. The [redacted] for final reading under normal [redacted] is not mentioned."

CORRECTIVE ACTION:

The [redacted] Assay method is now described in detail in the attached Pages 174-1 & 174-2 of the CMC Section Amendment recently submitted to the Agency.

Also, please refer to Pages 172-174 of the same Amendment, where the description of the [redacted] method adopted for Related Substances has been revised in order to address errors in its original translation.

APPEARS THIS WAY
ON ORIGINAL

Inspectional Observations: ——————— to Changfa, Li (October 28, 1999)

OBSERVATION:

"4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

Raw Material Testing:

a) References to USP do not reflect actual test methods in many cases. As an example, CMC section 2.12, page 180, for ——————— states that all test methods are the same as USP 23, page 848. However, the assay method is an in-house —— method, not the USP method, and ——————— is not performed although the CMC reports that it this test is conducted."

CORRECTIVE ACTION: In the November 1999 Amendment to the CMC Section originally submitted to the Agency on June 3, 1999, some references to USP methods have been replaced with translations of the methods actually followed.

With regard the specific case transcribed above, please refer to Page 180-1 of this Amendment where all methods pertaining to the testing of ——————— have been described. With regard to the Assay method, the in-house procedure has been revised to reflect the conditions prescribed in the current USP monograph.

December 1999

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER U.S. Food & Drug Administration, CDER, HFD-322 Div. of Manufacturing & Product Quality, FIT 7520 Standish Place Rockville, MD 20855, U.S.A. Phone: 001 [redacted] – FAX 001 [redacted]	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Li Changfa	PERIOD OF INSPECTION 10/25-28/99	C. F. NUMBER 96-15606
TITLE OF INDIVIDUAL Chairman	TYPE ESTABLISHMENT INSPECTED API Manufacturer	
FIRM NAME Shanghai Hua Lian Pharmaceutical Co., Ltd. -- XinLian Pharmceutical Factory	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 217 Ming Le Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE *(Zip Code)* Shanghai 201419, China	CITY AND STATE *(Zip Code)* Same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Recycled metal drums of the same type and color are used for both virgin solvents and for storing waste solvents. There is no clear policy of marking drums to assure that mix up would not occur. For example, a drum bearing complete labeling for [redacted] was filling with waste solvent during this inspection. Other solvents such as [redacted] and [redacted] are received from the central office in drums of the same color that bear minimal identification. Some of these drums are returned to the central office for refilling and others are used for collection of waste with only a minimum of identification.

2. For [redacted] and [redacted] analyses performed prior to September 1999, no formal system suitability was performed aside from the initial [redacted] of reference standard.

3. No acceptance criteria have been established for calibration of the [redacted] analyzer although Q C approves the monthly calibration runs.

4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

Finished product testing:

a) The [redacted] method used for release testing of the purified Mifepristone is not described in the CMC.

b) The specification for residual [redacted] in finished product on CMC page 168 is incorrectly reported as [redacted] The actual specification is [redacted]

c) The [redacted] analysis for [redacted] on pages188-189 is incorrect. Flow rates and temperatures are incorrectly reported.

In- process/intermediate test methods:

a) For [redacted] analyses of the [redacted] intermediate run prior to September 1999, reference standards were only run once per 5 samples. The data from this standard run was used in calculations for all subsequent samples run on different days.

b) There is limited resolution of the two major impurities from the main reactant in the [redacted] method for in-processing monitoring of the [redacted] reaction in synthesis of the key intermediate, [redacted]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/	EMPLOYEE(S) NAME AND TITLE *(Print or Type)* [redacted] Compliance Officer	DATE ISSUED 10/28/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER U.S. Food & Drug Administration, CDER, HFD-322 Div. of Manufacturing & Product Quality, FIT 7520 Standish Place Rockville, MD 20855, U.S.A. Phone: 001 [redacted] — FAX 001 [redacted]	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Li Changfa	PERIOD OF INSPECTION 10/25-28/99	C. F. NUMBER 96-15606
TITLE OF INDIVIDUAL Chairman	TYPE ESTABLISHMENT INSPECTED API Manufacturer	
FIRM NAME Shanghai Hua Lian Pharmaceutical Co., Ltd. -- XinLian Pharmceutical Factory	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 217 Ming Le Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE *(Zip Code)* Shanghai 201419, China	CITY AND STATE *(Zip Code)* Same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

c) [redacted] reaction, CMC 143, section 2.1.3 states that the method [redacted] Although a analysis is run, the former [redacted] method is being used for evaluation since the method is still under development.

d) The assay method for [redacted] CMC pages 135, 172-174, 144-145, is not included in the CMC. The CMC states only that the method is by [redacted] Also, the [redacted] Related Substances method, section 1.3 page 172-173, is significantly mistranslated. The sample and reference dilutions are not distinguished. Sample solution "a" should be 20 mg/ml, not [redacted] ng/ml. The cited dilutions are not the ones used. The [redacted] for final reading under [redacted] is not mentioned.

Raw Material Testing:

a) References to USP do not reflect actual test methods in many cases. As an example, CMC section 2.12, page 180, for [redacted] states that all test methods are the same as USP 23, page 848. However, the assay method is an in-house [redacted] method, not the USP method, and refractive index is not performed although the CMC reports that it this test is conducted.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/	EMPLOYEE(S) NAME AND TITLE *(Print or Type)* [redacted] Compliance Officer	DATE ISSUED 10/28/99

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99

SUMMARY OF FINDINGS

This was a pre-approval inspection of a manufacturer of active pharmaceutical ingredients (APIs) covering Mifepristone, for NDA 20-687, Mifepristone tablets. The applicant of this NDA is the Population Council of New York.

This was the first FDA inspection at this site. Manufacturing facilities appeared adequate except for the lack of a clearly defined policy for handling and marking of recycled solvent drums to preclude mix-up with waste solvents which was reported on a FDA 483. Laboratory operations relating to the Mifepristone NDA, however, could not be adequately audited because of numerous errors and omissions in the methods section of the CMC.

Some of the deficiencies identified include the failure to include in the CMC the method used for assay and impurity testing of purified Mifepristone; failure to include in the CMC the assay method for a critical starting material manufactured at the site. Since these methods had not been included in the application, no English translations were available when the laboratory inspection was initiated. A translation that was subsequently provided proved to be inaccurate and a second translation was prepared.

In addition to these omissions, significant discrepancies were identified between methods reported in the CMC and data that were presented. For example, the related substances method for and the methods for used in the final purification that are described in the CMC differed significantly from methods actually performed. Because of these conflicts between the CMC and the data that were presented, it was not possible to evaluate methods actually performed since concurrent line by line translation was so time consuming.

In addition to these deficiencies, the critical in-process tests for monitoring synthesis of the starting material reported in the CMC have not been fully developed. The status of these methods is not indicated in the CMC.

The inspection determined that the approved laboratory methods used in the XinLian laboratory were not used as the source documents when translating information for the NDA. The firm has committed to revise the CMC to accurately reflect current methods and specifications. They will re-submit this information to the U.S. Agent who is handling submissions to FDA for Mifepristone.

The firm has also committed to establish formal procedures for use and handling of recycled drums to avoid potential mix up between virgin and waste solvents.

Management indicated they would respond in writing to the FDA 483 observations through the U.S. Agent.

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99

HISTORY OF BUSINESS

According to information provided during the inspection, the Shanghai Hua Lian Pharmaceutical Company, parent to the XinLian Pharmaceutical Factory, was established in 1939 and has manufactured steroid hormones since 1959. Shanghai Hua Lian is a partially privatized limited corporation since 1995. Private shareholders represent roughly — with the remainder held by the state. The Parent Corporation oversees – manufacturing factories, – R&D facilities and —sales companies as shown in Exhibit 1. One of the manufacturing factories, known as the Plant, manufactures a key starting material for Mifepristone referred to as ——— Among the sales companies is the Material Supplying Company that purchases and distributes some raw materials, including some drummed solvents, to the manufacturing factories.

The XinLian factory has been located in the ——— since 1993. Two APIs are produced at this site – Mifepristone and ———

The most responsible individual at the corporate level for operations at the XinLian Factory is Mr. Li Changfa, Chairman of the Board and General Manager. Mr. Li maintains his office at corporate headquarters located at 370 Jiang Wan Road (West), Shanghai 200083, China. His phone number: ——— FDA correspondence to the firm should be addressed to Mr. Li.

The most responsible person at the factory site is ——— Plant Manager. His phone number: ———

The U.S. Agent and Importer for the firm is The Danco Group, ——— The principal U.S. contact for arranging FDA inspections is ——— V.P. Manufacturing.

——— provides consulting services to the firm relating to Pharmaceutical Quality Assurance. Contact information is as follows:

[ ]

PERSONS INTERVIEWED/RESPONSIBILITY

The most responsible individual at the corporate level for operations at the XinLian Factory is Mr. Li Changfa, Chairman of the Board and General Manager. Mr. Li was present at the initiation and closing of the inspection. The FDA 483 was issued to Mr. Li on 10/28/99.

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99

The most responsible person at the factory site is [redacted] XinLian Factory. Mr. Ou was present during this inspection.

[redacted] served as interpreter during this inspection. Jose [redacted], also accompanied me.

Some of the key individuals who provided information via [redacted] include:

[redacted] Corporate Level
[redacted]
[redacted] Supervisor
[redacted] upervisor
[redacted]

PRODUCTS AND QUANTITIES SHIPPED TO THE U.S.

According to [redacted], three [redacted] batches of Mifepristone have been shipped to the U.S. for use in exhibit batches of the dosage forms. Exhibit 2 shows the current packaging/labeling configuration – double poly bags inside a silver metal canister.

SCOPE OF INSPECTION

The focus of the inspection was a preapproval audit of bulk Mifepristone, profile class CSN, the active ingredient for Mifepristone Tablets, NDA 20-687. The inspection included a general evaluation of facility operations, with particular emphasis on avenues that could lead to cross-contamination or extraneous contamination. Also, both the chemical process and laboratory analyses were audited for conformance to commitments described in the CMC section of the NDA. Various stages of Mifepristone synthesis were in active operation during this inspection, however, [redacted], and micronizing were not observed.

Mifepristone has been produced at this site since October 1995. However, in May 1998 Shanghai Hua Lian agreed to adopt the Roussel Uclaf process obtained from Danco of the U.S. This resulted in modification to the synthesis and to some equipment. The new process, the one described in NDA 20-687, has been in place since December 1998. The process validation study in the NDA is based on the first three production lots [90101, 990102, 990103]. Additional validation information was gathered on the next 7 lots. Due to time constraints, this was not covered. One lot out of [redacted] produced thus far with this process was rejected and later [redacted] because of an off-color.

The analytical review included procedures for qualifying the Mifepristone reference standard, general analyst documentation and handling of OOS results, limited review of stability data, and conformance to procedures/specifications submitted in the CMC section of the Mifepristone NDA. Because of the numerous discrepancies between method descriptions in the CMC and those observed during this inspection, a full laboratory inspection and data audit could not be accomplished in the time allotted.

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99

General Facilities

Two products, both of which are steroids, are synthesized at this plant – [redacted] and Mifepristone. These products are produced in the same building but in different equipment and workshops. The building itself is divided into numerous individual workshops, separated by concrete walls that isolate key phases of synthesis. [redacted] synthesis occupies the workshops on the ground level while Mifepristone synthesis occurs in the workshops on the level above this. These workshops are maintained under ambient conditions without any [redacted] systems for air conditioning, although there are solvent exhaust systems in place for containment of volatile organic fumes.

[redacted] generated from a [redacted] tank outside the building, is used extensively in the Mifepristone process. The feed lines from the tank to the manufacturing workshops were dedicated to the Mifepristone workshops without interconnecting to the [redacted] synthesis areas. Distilled water used in the Mifepristone workshop appears to likewise feed only the Mifepristone process from a distillation still located above the workshop areas. According to information provided, no solvents or mother liquors are recovered or recycled.

While the synthesis workshops for these two steroids are located on two separate levels, the final [redacted] suites are located next to one another on the upper floor with a [redacted] workshop (Room [redacted] between the two. These suites have formal HVAC air handlers that provide for controlled temperature and humidity. The air handlers are located above the suites and are completely separate for the two steroid products. Intake air and exhaust for [redacted] are located on the North side of the building; for Mifepristone air intake/exhaust are handled from the South side. In addition to these independent [redacted] systems, there are dust collection systems that exhaust air to a collection bag on the roof and, in the Mifepristone suite, there are HEPA filters located in air supply ports in each room for particle control of the recirculating air.

On a half level between floors there is a vaulted storage and dispensing suite for intermediates. While there is a common entryway to the storage vault of both Mifepristone and [redacted] the storage and dispensing areas themselves are separate with entry into the areas located at opposite ends. These rooms have provision for simple air circulation but not for air conditioning. The air circulation appears to be local within each suite without interconnecting between the two storage areas. Dispensing for Mifepristone occurs in closed cabinets located within the Mifepristone storage room.

Dispensing of raw materials for Mifepristone occurs in a dedicated workshop, located near the raw material warehouses.

Equipment

For Mifepristone, [redacted] workshops are dedicated to synthesis of the key raw material, [redacted] and [redacted] additional workshops are used for synthesis of the key intermediates. Most

reaction vessels were fitted with pressure gauges and glass thermometers, although [redacted] sensors with digital readouts were observed in several workshops. All equipment is manually monitored and data is hand recorded without use of recorder charts. Control of valves is also manual.

Water Supply

Water for the site is city water. There is a water treatment facility on the premises with sand/charcoal pretreatment followed by electrophoresis to reduce cations/anions in the source water. This is followed by deionization. DI water is stored in a tank at the water treatment workshop and is fed to the production area via pipe, covering a distance of roughly 250 meters.

For Mifepristone, [redacted] uses [redacted] For water used immediately before this, the DI water is further treated by distillation with equipment located near to the Mifepristone workshop. There is no circulation of either DI or distilled water. However, the distilled water is generated only when needed and the holding tank is drained when not in use.

Mifepristone Synthesis

The synthesis and equipment described in the NDA were compared in detail to actual operations. Only a few minor errors or omissions were noted.

The key raw material, [redacted] CMC page 135, is also synthesized at this factory and was audited during this inspection. According to information provided during the inspection, the starting material for this key compound, [redacted], is produced at a sister factory known as the [redacted]. There are no other suppliers of the [redacted], according to management.

Mifepristone Reference Standard

The firm uses its own Mifepristone as a working standard but has qualified this material against Mifepristone prepared by Roussel Uclaf. The Roussel batch number observed during this inspection was #4V1014BJ. According to the [redacted] (Exhibit 3), this lot was manufactured 10/94 with an expiration of 11/99.

To obtain a purity value for this aged reference material, XinLian laboratory initially performed a series of 10 analyses for assay and for impurities using their own [redacted] method, rather than the [redacted] assay. Subsequently, they performed an additional 8 assays and used the 18 analytical results to derive a purity value (Exhibit 4).

For a working standard the XinLian laboratory [redacted] Mifepristone Lot 990101, produced at this factory, and used the Roussel material to qualify the in-house standard.

Presently, the in-house standard is used for release testing. They have prepared a protocol for this in-

house standard that requires retesting at 6, 12, 18 and 24 months in order to establish a re-qualification date.

FDA 483 WITH ANNOTATIONS

OBSERVATION 1:
Recycled metal drums of the same type and color are used for both virgin solvents and for storing waste solvents. There is no clear policy of marking drums to assure that mix up would not occur. For example, a drum bearing complete labeling for ——— *was filling with waste solvent during this inspection. Other solvents such as* ——— *and* ——— *are received from the central office in drums of the same color that bear minimal identification. Some of these drums are returned to the central office for refilling and others are used for collection of waste with only a minimum of identification.*

ANNOTATIONS TO OBSERVATION 1:

According to information provided by ——— that supplies many solvents to the Hua Lian factory sites, there is a central system for assuring quality of raw materials they supply. He indicated that they use their own trucks and drums when purchasing large volumes of solvents. Information obtained via the Interpreter indicates that the Material Supply Company paints metal drums for uniformity and marks the contents with paint on the drum top. They deliver solvents to the factories that use them and pick up the empty drums on subsequent delivery trips for reuse.

All of the drums I observed at XinLian that had been delivered from the Central Supply Company were painted dark green, except for ——— in dark blue drums. There was a paint mark on the lid to indicate content and a small, thin, hand-written paper label roughly 3" X 4" on the side or top when in the warehouse to indicate lot number. Except for the marking on the lid, which was peeling in some cases, all of the drums are identical.

Some drums are later used by the XinLian factory to collect waste solvents that are stored at the factory until they are removed for disposal. To identify drums filled with waste solvents, the painted identification on the lid is overwritten at some point. When this occurs was not clear. As noted in this observation, I observed a drum being used to collect waste solvents that still retained the full ——— labeling from the original supplier.

It was also not clear how they assured that drums returned to Central Supply for refilling have not been used for other purposes in the interim. For example, in synthesis of Mifepristone, ——— is added into virgin drums of ——— however, the labeling of the drums would not reflect this. I later observed empty metal drums that had been painted dark green on the top and sides but, from the powder blue bottom, appeared to be] ——— drums.

Although both the Central Supply Company and the XinLian factory have some fundamental procedures for handling recycled drums, the procedures for marking and handling drums all painted identically do not appear detailed enough to preclude mix-up or cross-contamination.

Corporate management committed to work with the XinLian factory to tighten up procedures. stated he would evaluate these procedures before they are finalized to assure they address the concerns that were raised.

OBSERVATION 2:
For and analyses performed prior to September 1999, no formal system suitability was performed aside from the initial of reference standard.

ANNOTATIONS TO OBSERVATION 2:

During my review of laboratory data, I requested system suitability for the and data I was reviewing. explained that system suitability was begun around September 1, 1999. This omission had been identified by in August, and at his request, they reanalyzed retain samples of Mifepristone for assay/impurities. The summary submitted as Exhibit 5 shows the results of this retesting of retain samples.

Although procedures for assuring system suitability have now been formalized for finished product testing, system suitability for in-process analysis, such as for the in-process analysis of the derivative, was not handled the same. For in-process analyses, system suitability checks are conducted only once per week as noted in FDA 483 Observation #4.

OBSERVATION 3:
No acceptance criteria have been established for calibration of the analyzer although Q.C. approves the monthly calibration runs.

ANNOTATIONS TO OBSERVATION 3:

Purified Mifepristone is micronized at the final processing step. Particle Size analysis is performed with a analyzer. I selected this instrument for a random check of calibration procedures. Documentation confirmed that calibration runs are performed once a month with a standard of . The analytical results over the last year ranged from I asked for an explanation of how the analytical results relate to particle size and what range of numbers assures that the instrument is performing properly. . Supervisor, stated that verbally told her that are good numbers. There was no documentation to verify this; nor was this range mentioned in either the method or the calibration SOP.

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XinLian Pharmaceutical Factory
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10/25-28/99

The firm has committed to respond to 483 observations in writing via their U.S. Agent. has agreed to assist the firm in making needed improvements.

OBSERVATION 4:
There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

Finished product testing:

a) *The nethod used for release testing of the purified Mifepristone is not described in the CMC.*
b) *The specification for residual in finished product on CMC page 168 is incorrectly reported as . The actual specification is*
c) *The analysis for on pages188-189 is incorrect. Flow rates and temperatures are incorrectly reported.*

In- process/intermediate test methods:

a) *For analyses of the intermediate run prior to September 1999, reference standards were only run once per 5 samples. The data from this standard run was used in calculations for all subsequent samples run on different days.*
b) *There is limited resolution of the two major impurities from the main reactant in the thod for in-processing monitoring of the reaction in synthesis of the key intermediate,*
c) *reaction, CMC 143, section 2.1.3 states that the method is lthough a nalysis is run, the former method is being used for evaluation since the nethod is still under development.*
d) *The assay method for CMC pages 135, 172-174, 144-145, is not included in the CMC. The CMC states only that the method is by Also, the method, section 1.3 page 172-173, is significantly mistranslated. The sample and reference dilutions are not distinguished. Sample solution "a" should be 20 mg/ml, not ng/ml. The cited dilutions are not the ones used. The for final reading under normal s not mentioned.*

Raw Material Testing:

a) *References to USP do not reflect actual test methods in many cases. As an example, CMC section 2.12, page 180, for states that all test methods are the same as USP 23, page 848. However, the assay method is an in-house nethod, not the USP method, and is not performed although the CMC reports that it this test is conducted.*

ANNOTATIONS TO OBSERVATION 4:

The deficiencies noted above do not represent a complete list of inaccuracies in the Mifepristone CMC but reflect only those analyses that I specifically audited. I had intended to focus the data audit

on several pivotal quality control points that spanned the Mifepristone synthesis. The areas I selected were the qualification of the [redacted] used in the final [redacted] steps, monitoring of the critical intermediate, [redacted] that is also synthesized at this site, and finished product tests for assay, impurities and residual solvents.

In each case the data that was provided either did not correlate with information submitted in the CMC or the CMC lacked information needed to evaluate the data. As reported in this observation, the in-house [redacted] method for assay and impurities for final product release testing of Mifepristone was not included in the NDA; nor was the assay method for [redacted] included in the NDA. Consequently, there were no English translations available when the laboratory inspection was initiated. A translation that was subsequently provided proved to be inaccurate when I compared the method as described in the translation with analytical data. A second translation was then prepared. The latest translation of the Mifepristone [redacted] ssay method is submitted as Exhibit 6 and the [redacted] assay method is submitted as Exhibit 7.

While the assay method for [redacted] had been omitted when the CMC was prepared, the [redacted] related substances method described in the CMC for this key material was significantly mistranslated as described above in observation *(d)* under *In-process/intermediate test methods.*

When I then checked the raw material analyses for the [redacted] used in the final [redacted] of Mifepristone, I likewise found that the CMC reference was not consistent with analyses performed. These discrepancies are described on the FDA 483 under *Raw Material Testing.*

Because of these conflicts between the English translation and the data that were presented, it was not possible to evaluate methods actually performed since concurrent line by line translation was so time consuming. Although I repeatedly asked which source documents were used for the information submitted in the NDA, and while much discussion in Chinese ensued, no specifics were provided, except that [redacted] the Interpreter, stated that it appears some information *may* have been copied from the Roussel NDA. I could not, however, confirm this. While I could not verify the ultimate source of this misinformation, the inspection determined that the laboratory methods used in the XinLian laboratory were not used as source documents when translating information for the NDA.

The firm has committed to revise the CMC to accurately reflect current methods and specifications. They will re-submit this information to their U.S. Agent who is handling submissions to FDA for Mifepristone.

Aside from the errors and omissions in the CMC, problems were noted with the analyses used to monitor the synthesis of [redacted] While the CMC describes this compound as a starting material, it is synthesized in the same building as the final Mifepristone. The chemical pathway is described in the CMC on page 135.

The initial reactant is ' ' obtained from a sister factory known as Plant. There are in preparation of the - the s called the reaction and the e reaction, which are pivotal in assuring the correct molecular form for Mifepristone.

For the reaction the firm uses an in-process assay to monitor the reaction progress. They have identified of significance in this evaluation: is reportedly the reactant; ' = an unknown, unwanted reactant; = unreacted For most of the analyses I reviewed, these peaks overlapped one another. Exhibit 8 is the assay method identifying the three pivotal reactants on page 4. Exhibit 9, pages 1 & 2, are examples of showing the lack of resolution of these reactants.

For the reaction, the CMC states on page 143 that an ethod is used for monitoring the reaction end point. One of the critical concerns at this point, according to information provided during this inspection, is confirming that only one group is formed, not two reactant). The method currently used, however, is still under development. They have not yet verified that the peak they are evaluating is actually the ' formation. In the mean time they are using a method for screening that provides only a rough quantitative estimate. Exhibit 10 is a representative chromatogram for monitoring where the identity of the eluting peaks have not been confirmed..

The firm has committed to continue development and validation of these critical in-process control methods.

LOGISTICS

Lodging was at Shanghai JC Mandarin Hotel located in the city of Shanghai. It is located about 25 minutes from the Hong Qiao International Airport and about 1 ¼ hour by car from the plant site in Pudong. The firm provided transportation to the firm each day. The accommodations were very good and the cost was within per diem. There are two restaurants within the hotel and a variety of restaurants within walking distance.

SAMPLES

No samples were collected.

ATTACHMENTS

Assignment memo
FDA 483

Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Pudong, Shanghai, China 201419
10/25-28/99

EXHIBITS

1. Organization of parent corporation, Shanghai Hua Lian Pharmaceutical Co., Ltd.
2. Photos of packaging/labeling configuration for Mifepristone
3. COA for Roussel Uclaf Mifepristone Batch 4V1014 BJ
4. Summary of analyses of Roussel API as reference standard
5. Summary chart of analyses with and without supporting system suitability
6. [redacted] Method for Assay of Mifepristone
7. [redacted] Method for Assay of [redacted]
8. [redacted] method for in-process monitoring of [redacted] reaction
9. Representative chromatograms for [redacted] monitoring
10. Representative chromatograms for in-process monitoring of [redacted] reaction

/S/

Compliance Officer
Philadelphia District

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 19-Nov-1999 08:23am EST
From:
Dept: HFD-580 PKLN
Tel No:

TO:

Subject: RE: NDA 20-897

Sorry — I typed in the wrong NDA number. It should be 20-687. The firms are Shanghai HuaLian (drug substance),

Thanks,

>I need more information on this one. Supplement number, firm names??
>There's a bunch of supplements for this one, and I can't find a WH
>anywhere.
>

UF 10/19/99.
- 12/19/99.

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ON ORIGINAL

Post-it® Fax Note 7671	To	# of pages ▶
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TO:
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HFC-133
International Operations Group, DEIO
Rockville, Maryland, U.S.A.
Telephone: 001

FROM:

October 29, 1999
Total number of pages with cover: 4

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Copy of FDA 483: [X] Attached [ ] None issued

Firm Inspected:
Shanghai Hua Lian Pharmaceutical Co., Ltd.
XinLian Pharmaceutical Factory
217 Ming Le Road
Shanghai, China

CFN 96-15606

Telephone
FAX

Product(s) Inspected:
Mifepristone

Application Number(s):
NDA 20-687

Profile Classes Covered:
CSN (Non-sterile API by chemical synthesis)

GMP Compliance:
[ ] Acceptable [X] Not acceptable [ ] Will send

SUMMARY OF FINDINGS

Please let —— know I received her FAX about the cancellation of the inspection in Japan. She asked me to let her know I received it. I will be flying home tomorrow as originally planned.

Concerning the inspection at XinLian, the chemical process filed in the CMC appears to be consistent with the actual operation at this factory with only a few minor errors and the facilities appear adequate. The method and specification sections of the CMC are a different story altogether. The information in the CMC that I reviewed didn't correspond to methods and specifications used by the firm.

What the Interpreter told me happened is that they copied information from the Roussel NDA in a number of sections rather than translate their own methods from Chinese to English. —— Also, their consultant told them that FDA wants all raw materials to meet USP specifications so they inserted numerous references to general USP chapters in the CMC which have nothing to do with the testing they perform. As a result, I had nothing in English to use as a basis for the laboratory audit. They tried to prepare English translations concurrent with this inspection but it took 2 days to have two methods "correctly" translated. —— Anyway, I simply gave up after four days. They have committed to redo the CMC to reflect their own laboratory procedures. Their U.S. Agent (Danco of New York) will contact the review division about this.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER U.S. Food & Drug Administration, CDER, HFD-322 Div. of Manufacturing & Product Quality, FIT 7520 Standish Place Rockville, MD 20855, U.S.A. Phone: 001 [redacted] FAX 001 [redacted]

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED	PERIOD OF INSPECTION	C. F. NUMBER
TO: Mr. Li Changfa	10/25-28/99	96-15606
TITLE OF INDIVIDUAL Chairman	TYPE ESTABLISHMENT INSPECTED API Manufacturer	
FIRM NAME Shanghai Hua Lian Pharmaceutical Co., Ltd. -- XinLian Pharmaceutical Factory	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 217 Ming Le Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Shanghai 201419, China	CITY AND STATE (Zip Code) Same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Recycled metal drums of the same type and color are used for both virgin solvents and for storing waste solvents. There is no clear policy of marking drums to assure that mix up would not occur. For example, a drum bearing complete labeling for [redacted] was filling with waste solvent during this inspection. Other solvents such as [redacted] and [redacted] are received from the central office in drums of the same color that bear minimal identification. Some of these drums are returned to the central office for refilling and others are used for collection of waste with only a minimum of identification.

2. For [redacted] and [redacted] analyses performed prior to September 1999, no formal system suitability was performed aside from the initial [redacted] of reference standard.

3. No acceptance criteria have been established for calibration of the [redacted] analyzer although Q.C. approves the monthly calibration runs.

4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

Finished product testing:

a) The [redacted] method used for release testing of the purified Mifepristone is not described in the CMC.

b) The specification for residual [redacted] in finished product on CMC page 168 is incorrectly reported as [redacted] The actual specification is [redacted]

c) The [redacted] analysis for [redacted] on pages 188-189 is incorrect. Flow rates and temperatures are incorrectly reported.

In-process/intermediate test methods:

a) For [redacted] analyses of the [redacted] intermediate run prior to September 1999, reference standards were only run once per 5 samples. The data from this standard run was used in calculations for all subsequent samples run on different days.

b) There is limited resolution of the two major impurities from the main reactant in the [redacted] method for in-processing monitoring of the [redacted] reaction in synthesis of the key intermediate. [redacted]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	/S/	[redacted] Compliance Officer	10/28/99

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