

Draft Guidance on Copper

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Active Ingredient:	Copper
Dosage Form; Route:	Intrauterine device; intrauterine
Strength:	309 mg
Recommended Studies:	In vitro studies and in vivo study

- A. Comparative physicochemical/mechanical characterization
1. Test and Reference Listed Drug (RLD) products contain the same active and inactive ingredients.
 2. Test and Reference Standard (RS) products should have acceptable comparative physicochemical properties. Comparative characterization should be performed on at least three batches of both the Test and RS products and should include:
 - a. T-frame
 - Comparative size and appearance
 - Comparative tensile force
 - Comparative memory of T-frame
 - Comparative flexibility
 - Comparative copper collar retention force (i.e. the minimal force required to displace a collar on the arm)
 - Comparative diameter of the bulb at the tip of the vertical stem of T-frame
 - b. Copper component
 - Comparative elemental analysis
 - Comparative surface area provided by copper wire
 - Comparative surface area provided by copper collar
 - Comparative copper collar thickness, position, and length
 - Comparative copper oxide content, if any
 - Comparative copper wire diameter and length
 - Comparative closeness of both ends of copper wire to the T-frame
 - c. Removal thread
 - Comparative material and design (i.e., monofilament)
 - Comparative length and tensile strength

d. Inserter

- Comparative appearance, external characteristics, and operation
- Portions of the inserter that contact the Copper IUD while packaged must be made of the same ingredients as the corresponding portions of the RLD inserter.

B. Comparative in vitro cupric ion release testing

Acceptable comparative in vitro cupric ion release rate from the Test and RS products. The in vitro cupric ion release testing should be carried out until a steady release rate is achieved.

C. Comparative clinical endpoint bioequivalence study

Study type: In vivo study with clinical endpoint

Design: Two year, single-dose, parallel-arm, in vivo study with randomization to Test or RS, non-inferiority design

Subjects: Nonpregnant, nonlactating females who are not using a hormonal contraceptive, general population (see also additional comments below).

Analytes to measure: Not applicable

Bioequivalence based on (95% CI): Non-inferiority between Test copper IUD and the RS in pregnancy proportion.

Additional comments:

1. A non-inferiority approach can be used to demonstrate bioequivalence between the Test copper IUD and the RS, and a 5.0-6.0% non-inferiority margin is generally acceptable from clinical perspective, provided that the Test copper IUD is identical in dimensions, physicochemical and mechanical properties, and has comparable in vitro cupric ion release rate to the RS. The appropriate sample size for the comparative clinical endpoint BE study should be based on pregnancy proportion (PP) considerations and acceptable statistical analysis. In addition, the dropouts between the test and reference arms should be balanced. Sufficient number of cycles with otherwise unprotected intercourse from each arm are needed to ensure adequate data for the assessment of PP.
2. A balanced study design (1:1 ratio of Test vs RS subjects) is generally used, however, since the RS is known to have an almost perfect success rate, the sponsor may also consider an unbalanced study design, for example, a 2:1 ratio of Test vs. RS subjects, which will not reduce power in general, to meet the requirement of a sufficiently large number of subjects exposed to the Test product.
3. A statistical method that can control type 1 error within the nominal level is suggested to be pre-specified in the protocol to calculate the one-sided confidence interval for the difference in proportions. One recommended statistical method is the Z test based on un-pooled variance with continuity correction.
4. The recommended primary endpoint is the PP, which is the proportion of women who get pregnant during the 2-year period, with 95% confidence intervals.

$$PP = \# \text{ of pregnant women} / \text{total} \# \text{ of women}$$

The Per Protocol Population must be used as primary statistical analysis population to establish bioequivalence between the proposed test product and the RS.

5. The secondary/Safety endpoints include the incidence of failed IUD insertion, expulsion (partial and complete), uterine perforation (including embedment), ectopic pregnancy, pelvic infection, heavy menstrual bleeding, pelvic pain, dysmenorrhea, and dyspareunia. All serious adverse events, adverse events, and reasons for subject discontinuation of study should be reported with descriptive statistics.
6. Contraceptive efficacy should be determined based on the population of subjects <36 years of age at the time of study entry. Therefore, the study population should include sufficient subjects under 36 years of age evaluable for efficacy exposed to the test product at the end of one year (13 menstrual cycles).
7. From a safety standpoint, an additional 10-20% of the study population in women 36 years of age and older is recommended to be recruited to ensure an adequate safety profile.
8. As part of the study inclusion and exclusion criteria, OGD recommend the following:
 - a. Utilizing Medical Eligibility Criteria (MEC) categories 1 through 4
 - b. Exclusion of breastfeeding women due to possible increased incidence of uterine perforation

Other inclusion criteria include (the sponsor may add additional):

- Signed informed consent
- Regular sexual activity
- Willing to rely on the IUD used in the study as the primary method of contraception during study participation
- Regular menstrual cycles occurring every 21-35 days without use of hormones
- Typical menstrual cycle length of no more than 5 days

Select exclusion criteria include (the sponsor may add additional):

- History of infertility
- History of irregular menstrual cycles
- Known or suspected pregnancy
- Lactating
- Vaginal delivery, cesarean delivery, or abortion within six weeks
Note: postpartum insertions should be postponed until uterus is fully involuted
- History of ectopic pregnancies
- Infected abortion or postpartum endometritis within three months prior to IUD insertion
- Abnormal uterine bleeding of unknown origin
- Any genital infection (until successfully treated)
- History of, or current, pelvic inflammatory disease
- Congenital or acquired uterine anomaly
- Any distortion of the uterine cavity (e.g., by fibroids) likely to cause problems during insertion, retention or removal of the IUD
- History of, diagnosed or suspected genital malignancy, and untreated cervical dysplasia

- Concomitant use of other sex-hormone containing preparations or intrauterine devices
 - Use of any long-acting injectable sex-hormone preparations within 9 months
 - Established immunodeficiency
 - High risk for sexually transmitted disease (STD)
 - Known infection with Hepatitis B or Hepatitis C
 - History of Wilson's disease
 - Severe thrombocytopenia
 - Immunosuppressive therapy
 - History of alcohol or drug abuse
 - Use of injectable contraception within 9 months
9. In general, for IUD contraceptive studies, ultrasound, CBC, blood serology, ceruloplasmin test, and endometrial biopsy are not usual procedures and are not required for routine safety monitoring in the study.
 10. Prior to insertion of the test IUD or RS, collect demographic information, medical, gynecologic, menstrual and reproductive history (including recent methods of contraception) and record in a case report file.
 11. Prior to insertion of the test IUD or RS, ensure a baseline pelvic examination is performed to assess for presence of any uterine or cervical anomalies that would preclude IUD use should be performed
 12. At each clinic visit, assess the following:
 - a. Presence of IUD strings
 - b. Vital signs to include temperature, blood pressure and heart rate
 - c. Collection and verification of diary information
 - d. Assessment of adverse events
 - e. Use of concomitant medications
 13. All pregnancies should be followed for outcome (spontaneous or induced abortion, ectopic, stillbirth, live preterm or term delivery). Congenital malformations and anomalies should be recorded and summarized. In the event of a live birth, the baby should be followed for as long as possible to assess health outcomes.
 14. The following additional elements should be included in the protocol:
 - a. Provide a process for confirmation of IUD presence when strings are not visualized to include use of transvaginal ultrasound and abdominal X-ray
 - b. Provide a definition of on-treatment pregnancy which in IUD contraceptive studies is defined as a pregnancy conceived up to 7 days after the IUD has been removed or noted to not be in the uterine cavity
 - c. Date all pregnancies for time of conception. A process utilizing ultrasound findings, quantitative β -HCG value, last menstrual period, pelvic and/or abdominal examination, and/or timing of coitus needs to be outlined to standardize determination of the estimated date of conception.
 - d. Provide a plan for management of IUD if intrauterine pregnancy occurs.
 15. List of study termination criteria (e.g. if more than 2 episodes of uterine perforation occur, the study will be terminated early).

16. Provide a plan for study oversight including use of a Data and Safety Monitoring Board, Institutional Review Board involvement, and medical monitors.
17. In the case of using a study population that is less than 50% from North America, a justification, including justification of generalizability of the planned study population to the United States population should be provided.
18. During device insertion, capture the number of attempts and any device-related issues that occur (e.g. inserter malfunction) and reported these in the final study report using descriptive statistics.
19. Results of bleeding and pain endpoints based on subjects' entry into diaries while informative will be not labeled because the diary questionnaires need to be appropriately evaluated and tested to support claims.
20. Calculation of the pregnancy proportion at months 1, 3, and 6 are not necessary and will not be labeled.