

**Draft Guidance on Lubiprostone**

This draft guidance, once finalized, will represent the Food and Drug Administrations (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

<b>Active Ingredient:</b>	Lubiprostone
<b>Dosage Form/Route:</b>	Capsule/oral
<b>Recommended Studies</b>	Two options: for Q1 and Q2 products, and for non-Q1 and -Q2 products

**For Q1 and Q2 products**

If the test product formulations are qualitatively (Q1) (i.e., contain all of the same inactive ingredients) and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence (BE) of all capsule strengths may be established based on the following studies.

1. Comparative dissolution testing should be conducted for all strengths under the following conditions:

Apparatus:	U.S. Pharmacopoeia (USP) Apparatus 2 (paddle)
Rotation speed:	50 rpm
Medium:	0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer containing 1% polyoxyl 40 hydrogenated castor oil
Volume:	900 mL
Temperature:	37°C
Sample times:	5, 10, 20, 30, 45, and 60 minutes, or as needed for profile comparison

2. Type of study: Fed BE study with pharmacokinetic (PK) endpoints  
Design: Single-dose, two-way crossover in vivo  
Strength: 48 mcg (2 x 24 mcg)  
Subjects: Normal healthy males and females, general population  
Additional comments: Females should not be pregnant or lactating, and, if applicable, should use appropriate contraception during the study

**For non-Q1 and Q2 products**

If the test product formulations are not the same (Q1 and Q2) as the RLD with respect to inactive ingredients, BE should be established by conducting the following studies:

1. Type of study: Fed BE study with pharmacokinetic (PK) endpoints  
Design: Single-dose, two-way crossover in vivo  
Strength: 48 mcg (2 x 24 mcg)  
Subjects: Normal healthy males and females, general population  
Additional comments: Females should not be pregnant or lactating, and, if applicable, should use appropriate contraception during the study
  2. Type of study: BE study with clinical endpoint  
Design: Randomized, double-blind, parallel, placebo-controlled in vivo  
Strength: 24 mcg  
Subjects: Male and nonpregnant female subjects with chronic idiopathic constipation  
Additional comments: Specific recommendations are provided below
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**Analytes to measure (in appropriate biological fluid):** 15-OH-lubiprostone (M3, metabolite) in plasma. The applicant should use a validated analytical method such as LC-MS/MS with a lower limit of quantitation (LOQ) of < 5 pg/mL to reliably measure plasma 15-OH-lubiprostone concentrations

**Bioequivalence based on (90% CI):** 15-OH-lubiprostone (M3, metabolite) in plasma (PK study); clinical endpoint (clinical endpoint study)

**Waiver request of in vivo testing:** 8 mcg based on (i) acceptable BE studies on the 24 mcg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro quantitative capsule rupture (dissolution) testing of all strengths

**Dissolution test method and sampling times:**

A **Dissolution Methods Database** is available to the public at the Office of Generic Drugs (OGD) website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. The dissolution information for this product is available at this website. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

**Additional comments regarding the BE study with clinical endpoint:**

1. OGD recommends conducting a BE study with a clinical endpoint in the treatment of chronic idiopathic constipation. After a 2-week baseline/washout period, subjects are to be randomized to receive the generic lubiprostone 24 mcg capsule, the RLD 24 mcg capsule, or a placebo capsule twice daily at breakfast and dinner for 7 days, taken with food and at least 8 ounces of water. Use of a laxative as a rescue medication is permitted during the 2-week baseline/washout period but prohibited during the 7-day treatment period. The primary endpoint is the number of spontaneous bowel movements (SBMs) during Week 1 (study Days 1-7).

2. The FDA recommends a placebo control arm to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
3. Inclusion criteria (the sponsor may add additional criteria):
  - a. Males or nonpregnant females aged  $\geq 18$  years with a clinical diagnosis of chronic idiopathic constipation defined as, on average,  $< 3$  spontaneous bowel movements (SBMs) per week and confirmed by daily diary during the 2-week baseline/washout period. An SBM is defined as any bowel movement (BM) that did not occur within 24 hours after rescue medication use.
  - b. Having one or more of the following symptoms related to BMs for at least 6 months before the baseline visit and confirmed by daily diary during the 2-week baseline/washout period:
    - very hard (little balls) and/or hard stools for at least 25% of BMs
    - sensation of incomplete evacuation following at least 25% of BMs
    - straining at defecation at least a quarter of the time
  - c. For women of child-bearing potential: having a negative pregnancy test prior to beginning therapy, and agreeing to use effective contraceptive methods during the study
  - d. For subjects aged  $< 50$  years: documentation of the results of either a flexible sigmoidoscopy or colonoscopy performed within the 5 years prior to dosing, showing no mechanical bowel obstruction or organic disorders of the large or small bowel
  - e. For subjects aged  $\geq 50$  years, documentation of the results of either a barium enema with flexible sigmoidoscopy or colonoscopy performed within 1 year prior to dosing, showing no mechanical bowel obstruction or organic disorders of the large or small bowel
4. Exclusion criteria (the sponsor may add additional criteria):
  - a. For women: pregnancy, breast feeding, or planning a pregnancy
  - b. At any age, evidence of weight loss, anemia, or rectal bleeding AND no documentation of the results of either a flexible sigmoidoscopy or colonoscopy performed during the 6 months prior to dosing
  - c. Documented mechanical bowel obstruction (e.g., bowel obstruction due to tumor, hernia), megacolon/megarectum, or diagnosis of pseudo-obstruction
  - d. Known or suspected organic disorders of the large or small bowel (e.g., inflammatory bowel disease, ulcerative colitis, Crohn's Disease) or constipation secondary to a documented cause (e.g., surgery, bowel resection)
  - e. History of bowel resection
  - f. Hospitalization for any gastrointestinal or abdominal surgical procedure during the 3 months prior to dosing
  - g. Clinically significant cardiovascular, liver, lung, neurologic, renal or psychiatric disorder, or clinically significant laboratory abnormalities
  - h. Use within 4 weeks prior to baseline of a systemic antibiotic
5. The protocol should include a list of the prescription and over-the-counter (OTC) drug products, procedures, and activities that are prohibited during the study, such as:

- a. Prescription and OTC laxatives other than those the Investigator prescribes for use as a rescue medication during the baseline/washout period
  - b. Significant change in diet
6. The recommended primary endpoint is the number of SBMs during Week 1 (study Days 1-7). An SBM is defined as any BM that did not occur within 24 hours after rescue medication use. The use of rescue medication is permitted during the 2-week baseline/washout period but prohibited during 7-day treatment period.
7. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
8. The accepted PP population used for BE evaluation includes all randomized subjects who met all inclusion/exclusion criteria, dosed a prespecified proportion of the scheduled administrations (e.g., 75% to 125%) of the assigned product for the specified duration of the study, and completed the evaluation within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified (e.g., by the use of subject diaries).
9. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, administered at least one dose of assigned product, and returned for at least one post-baseline evaluation visit.
10. The safety population includes all randomized subjects who received study product.
11. Subjects who are discontinued early from the study due to lack of treatment effect after completing 3 days of treatment should be included in the PP population using Last Observation Carried Forward (LOCF). Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of constipation during the treatment phase of the study should be discontinued, included in the PP population analysis using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population using LOCF.
12. The start and stop dates of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.
13. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information is needed to determine whether the incidence and severity of adverse reactions is different between the test product and RLD.
14. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, the sponsor is to clearly describe the differences and provide

information to show that the differences will not affect the safety, efficacy, and/or systemic or local availability of the drug.

15. The protocol should describe the method of randomization. The FDA recommends that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
16. The protocol should provide a detailed description of the blinding procedure. The packaging of the test, reference, and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.
17. Refer to 21 CFR 320.38, 320.63 and the guidance for industry *Handling and Retention of BA and BE Testing Samples* regarding retention of study drug samples, and 21 CFR 320.36 for requirements for maintenance of records of BE testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, *Good Clinical Practice: Consolidated Guideline*, for retention of study records and data in order to conduct their studies in compliance with good laboratory practices (GLPs) and good clinical practices (GCPs). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.
18. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate BE between the products.
19. To establish BE, the 90% confidence interval (CI) of the test/reference ratio of means for the primary endpoint (mean change from baseline to Week 1 in weekly number of SBMs) must be contained within [0.80, 1.25] for continuous variables, using the PP study population.
20. As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ( $p < 0.05$ , two-sided) for the primary endpoint using the mITT study population and LOCF.
21. The FDA recommends the following statistical analysis method for equivalence testing for a continuous variable:

Equivalence Analysis

The compound hypothesis to be tested is:

$H_0: \mu_T / \mu_R \leq \theta_1$  or  $\mu_T / \mu_R \geq \theta_2$  versus  $H_A: \theta_1 < \mu_T / \mu_R < \theta_2$

Where  $\mu_T$  = mean of test treatment, and  $\mu_R$  = mean of reference treatment

Typically, we reject  $H_0$  with a type I error  $\alpha = 0.05$  (two 1-sided tests), if the 90% CI for the ratio of means between test and reference products ( $\mu_T / \mu_R$ ) is contained within the interval  $[\theta_1, \theta_2]$ , where  $\theta_1 = 0.80$  and  $\theta_2 = 1.25$ .

Rejection of the null hypothesis  $H_0$  supports the conclusion of equivalence of the two products.

22. Study data should be submitted to OGD in electronic format.
  - a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
  - b. Provide a “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS data sets (for example, Y=yes, N=no for analysis population).
  - c. All SAS transport files, covering all variables collected in the case report forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
  - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
  - e. Provide a separate data set for variables such as demographics, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance, and comments, etc.
  
23. Provide a summary data set containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
  - a. Study identifier
  - b. Subject identifier
  - c. Site identifier: study center
  - d. Age
  - e. Age units (years)
  - f. Sex
  - g. Race
  - h. Name of Actual Treatment (exposure): test product, RLD, placebo control
  - i. Duration of Treatment (total exposure in days)
  - j. Completed the study (yes/no)
  - k. Reason for premature discontinuation of subject
  - l. Subject required additional treatment for constipation due to unsatisfactory treatment response (yes/no)
  - m. Per Protocol (PP) population inclusion (yes/no)
  - n. Reason for exclusion from PP population

- o. Modified Intent to Treat (mITT) population inclusion (yes/no)
- p. Reason for exclusion from mITT population
- q. Safety population inclusion (yes/no)
- r. Reason for exclusion from Safety population
- s. Number of spontaneous bowel movements during first week of Baseline/washout
- t. Number of spontaneous bowel movements during second week of Baseline/washout
- u. Number of spontaneous bowel movements during Week 1 (study days 1-7)
- v. Treatment compliance: number of missed doses per subject
- w. Concomitant medication (yes/no)
- x. Adverse event(s) reported (yes/no)

Table 1 provides an example. Note: this sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

**Table 1: Example of a summary data set containing one line listing for each subject**

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs
101	1	01	21	YEARS	F	1	A	14	Y		N	Y		Y		Y	
101	2	01	30	YEARS	F	1	B	14	Y		N	Y		Y		Y	

bas1_sbm	bas2_sbm	tx_sbm	complan	CM	AE
1	1	3	0	Y	Y
2	2	5	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

- STUDYID: Study Identifier
- SUBJID: Subject Identifier for the Study
- SITEID: Study Site Identifier
- AGE: Age
- AGEU: Age units (years)
- SEX: Sex, e.g., M=Male, F=Female, U=Unknown
- RACE: Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
- EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo control
- EXDUR: Duration of Treatment (total exposure in days)

completd:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required additional treatment for constipation due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
bas1_sbm:	Number of spontaneous bowel movements during first week of Baseline/washout
bas2_sbm:	Number of spontaneous bowel movements during second week of Baseline/washout
tx_sbm:	Number of spontaneous bowel movements during Week 1 (study days 1-7)
complan:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

24. Provide a data set containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
- Study identifier
  - Subject identifier
  - Name of Actual Treatment (exposure): test product, RLD, placebo control
  - Visit number
  - Visit date
  - Number of days since baseline visit
  - Number of SBMs on Baseline Day 1 (study day -14),
  - Number of SBMs with very hard (little balls) and/or hard stools on Baseline Day 1
  - Number of BMs followed by sensation of incomplete evacuation on Baseline Day 1
  - Number of BMs with straining at defecation on Baseline Day 1
  - Number of SBMs on Baseline Day 2 (study day -13), etc., to Baseline Day 14 (study day 0)
  - Number of BMs with very hard (little balls) and/or hard stools on Baseline Day 2, etc., to Baseline Day 14
  - Number of BMs followed by sensation of incomplete evacuation on Baseline Day 2, etc., to Baseline Day 14
  - Number of BMs with straining at defecation on Baseline Day 2, etc., to Baseline Day 14

- o. Number of SBMs on Treatment Day 1 (study day 1)
- p. Number of SBMs on Treatment Day 2 (study day 2) , etc., to Treatment Day 7 (study day 7)
- q. Rescue medication/ laxative use reported during this visit (yes/no)
- r. If reported during this visit, provide date(s) of rescue medication use
- s. Concomitant medication reported during this visit (yes/no)
- t. Adverse event reported during this visit (yes/no)
- u. Laboratory testing during this visit (yes/no)

Table 2 provides an example. Note: this sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

**Table 2: Example of data set containing one line listing for each visit per subject**

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	b1_sbm	b1_hard	b1_incom	b1_strain	b2_sbm
101	1	A	1	2004-07-01	1	0	0	0	0	1

b2_hard	b2_incom	b2_strain	t1_sbm	t2_sbm	rescue	rescue_d	CMrpt	AErpt	LBtest
1	0	0	1	1	N		Y	Y	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

- STUDYID: Study Identifier
- SUBJID: Subject Identifier for the Study
- EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C=placebo control
- VISITNUM: Visit Sequence Number
- SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
- ELTMBS: Elapsed Time since Baseline (days)
- b1\_sbm: Number of SBMs on Baseline Day 1 (study day -14)
- b1\_hard: Number of BMs with very hard (little balls) and/or hard stools on Baseline Day 1 (study day -14)
- b1\_incom: Number of BMs followed by sensation of incomplete evacuation on Baseline Day 1 (study day -14)
- b1\_strain: Number of BMs with straining at defecation on Baseline Day 1 (study day -14)

b2_sbm:	Number of SBMs on Baseline Day 2 (study day -13), etc., to Baseline Day 14 (study day 0)
b2_hard:	Number of BMs with very hard (little balls) and/or hard stools on Baseline Day 2 (study day -13), etc., to Baseline Day 14 (study day 0)
b2_incom:	Number of BMs followed by sensation of incomplete evacuation on Baseline Day 2 (study day -13), etc., to Baseline Day 14 (study day 0)
b2_strain:	Number of BMs with straining at defecation on Baseline Day 2 (study day -13), etc., to Baseline Day 14 (study day 0)
t1_sbm:	Number of SBMs on Treatment Day 1 (study day 1)
t2_sbm:	Number of SBMs on Treatment Day 2 (study day 1), etc., to Treatment Day 7 (study day 7)
rescue:	Rescue medication/laxative use reported during this visit, e.g., Y=Yes, N=No
rescue_d:	Date(s) when rescue medication/laxative was used
CMrpt:	Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest:	Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

25. These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of lubiprostone.