May 24, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2016-D-0785; General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products; Comments of the Generic Pharmaceutical Association (GPhA)

The Generic Pharmaceutical Association (GPhA) is pleased to submit comments to the Food and Drug Administration's (FDA's) draft guidance for industry on General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products. *See* 81 Fed. Reg. 16186 (March 25, 2016) (Docket No. FDA-2016-D-0785). GPhA supports FDA's efforts to combat the endemic issue of opioid abuse by encouraging the development of abuse-deterrent technology, and appreciates guidance in demonstrating that a generic solid oral opioid drug product is no less abuse-deterrent than its reference listed drug with respect to potential routes of abuse.

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Our members manufacture more than 90% of all generic pharmaceuticals dispensed in the U.S., and their products are used in more than three billion prescriptions every year. Generics represent greater than 88% of all prescriptions dispensed in the U.S., but only 28% of expenditures on prescription drugs. GPhA is the sole association representing America's generic pharmaceutical sector. While this response letter represents the views of the association, some members of GPhA may have differing positions and may provide those positions under separate submissions.

GPhA is committed to ensuring the accessibility of affordable generic versions of opioid drug products for the millions of Americans who suffer from chronic pain. Accordingly, the majority of GPhA's comments seek greater clarity on several sections of the Draft Guidance—specifically relating to technical requirements for the evaluation and analysis of data—aligned with FDA's intention to consider the totality of the evidence when evaluating abuse-deterrent generic opioids. In addition to the comments below, GPhA seeks guidance on how FDA plans to address innovator labeling changes addressing abuse-deterrence. If a reference listed drug (RLD) is permitted to make sequential labeling updates to include new routes of abuse-deterrence, generic companies will face a moving target, lengthening the review time for generic products and impeding public access to critical, affordable generic products which treat chronic pain. Thus, GPhA would appreciate direction on the communication process and timeframe FDA intends to employ in such instances.

General Comments

Although the Draft Guidance provides several ranges of potential study conditions to assist in the identification of discrimination with respect to abuse-deterrence between the C product and the R product, it is unclear how these ranges are meant to be employed. We request FDA elaboration on the rationale for providing such large study condition ranges. For example, Appendix 3 (Abuse by Ingestion) recommends extraction conditions of "100-300 mL" at a duration of "5 to 60 minutes."[1] If the purpose of this range is to allow an applicant to identify a set of conditions demonstrating discrimination, FDA should state as much. Accordingly, GPhA requests that the Draft Guidance be supplemented to clarify the Agency's reasoning behind the ranges provided.[2] While we agree and appreciate the references to agency consultation mentioned in the guidance we also express some concern with over reliance on this tactic. We believe product specific guidance would be most valuable to sponsors, and ensure consistency in methods and approach for the best interest of patients.

Included below are detailed comments on the Draft Guidance, listed by the guidance section and line number:

III. ABUSE DETERRENCE OF GENERIC SOLID ORAL OPIOID DRUG PRODUCTS		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
General	The field of abuse deterrence testing is constantly evolving. Test methods are operator-dependent and difficult to standardize and validate. Variations may arise as a result of sampling variations between finely ground R and T products.	GPhA requests that a Δ value NMT 20 (instead of 10) between T and R product should be considered acceptable, provided that the measure of the abuse deterrence (e.g., % extraction) for the R and T products is statistically less than (superior to) the measure of the abuse deterrence for the C product (Type I error = 0.05).
81-83	"FDA intends to consider the totality of the evidence when evaluating the abuse deterrence of a generic solid oral opioid drug product." Does this mean that all studies for all routes of abuse indicated in this guidance would be required to be done for all opioid products irrespective of technology of the dosage form or this would be decided case by case based on rationale and justification?	GPhA requests clarification

[1] Draft Guidance, lines 485-489.
[2] *See* Draft Guidance, lines 139-147.

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89-92	The Controlled correspondence (CC) is expected to be sent by the generic sponsor at the start of product development to ask the Agency the type(s) of testing to be done or after the sponsor has completed the "tier-based approach" to ask the Agency is additional testing is to be done	The BE Guidance/monograph should be updated for all abuse deterrent RLDs with the type of in-vitro/pK testing to be done to prove "equivalence" to the RLD. This would eliminate individual sponsor's subjectivity.
89-92	The paragraph on "public literature" is too open-ended and, depending on the reviewer's interpretation, could lead to significant additional testing and evaluation just because of a literature reference that indicates an incidence of abuse via a mechanism not discussed in the innovator label. In this regard, the generic product may in fact be held to demonstrate abuse deterrence over and above what the brand was required to show. Thus, clarification is requested as to 1) the purpose of this language, and 2) the specific literature an applicant should consider.	GPhA requests clarification
92-94	Does the provision for generics to have a CC with FDA include the option to discuss detailed design and evaluation criteria that the generic applicant feels is suitable for its drug product? Often a generic product has a different formulation than the RLD. In addition, how would the FDA be updated on the Abuse deterrence technology being used in the T-product- will it need a face to face meeting request as a part of CC?	GPhA requests clarification

IV. GENERAL PRINCIPLES FOR EVALUATING THE ABUSE DETERRENCE OF GENERIC SOLID ORAL OPIOID DRUG PRODUCTS		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
107-110	Gives the onus on the generic sponsor to determine whether the	

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	mechanical/chemical manipulation is sufficiently destructive (Details in Appendix 1) till abuse deterrence of R-product is lost or T-product is shown to be less abuse deterrent. Appendix I states that "applicant to use mechanical manipulations to be used by abusers to evaluate abuse deterrence of T-product." Since the R-product and T-product may differ in abuse deterrent technology, should the "tier based approach" target the "R product" or "T product" instead, while methods of manipulations are being decided?	
132-136	Why is a C product required when the RLD labeling is already approved based on the evaluation done by the RLD manufacturer to prove the abuse deterrence of their formulation?	Can this be limited to comparison between T & R?
130-131 136-138	"Discriminatory conditions" are to be determined by comparing R-product with C-product, wherever C-product is available. What would be the C-product (same active ingredient is what is specified in line 137-138), does this mean an immediate release product also can be used, which may contain lesser quantity of the active ingredient or it means an Extended Release version only? Will a salt change of API classify as a C-product?	GPhA requests clarification
131-138	Footnote 8 directs applicants to submit controlled correspondence to OGD seeking input on the selection of an appropriate alternative control in case of non-availability of a marketed non-abuse-deterrent product (C product). Often these products are unavailable on the market, thus in addition to seeking guidance from OGD, there should be flexibility in testing against a non-abuse-deterrent generic product.	When available, C product should be a non-abuse deterrent version of the opioid R product that contains the same active pharmaceutical ingredient (API) as the R product (fn.8). **For testing purposes, a product with the same active ingredients, dosage form and a technology neutral mode of delivery to the non-abuse-deterrent brand, formulated and manufactured by the generic**

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		sponsor, will be acceptable.

VI. COMPARATIVE IN VITRO STUDIES		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
184-191	Does this mean that studies in all solvents have to be done even if some of them are not relevant from the formulation perspective or a justification can be provided to support not using some of them? Should this be included in the Controlled Correspondence at the onset of development or can this be discussed in another forum such as a technology meeting for the T-product?	Level 3 solvents: cooking oil, isopropyl alcohol, 0.1 N HCl, and 0.1 N NaOH. **A tiered approach should be applied against the reference product if multiple Level 1 and 2 solvents are to be evaluated.**
195-196 (Figure 1)	The decision tree consistently employs the "T less than R" notation, implying T is superior to R. The notation should be T is less than or equal to R.	The flow charts should indicate % opioid extraction of **T ≤ R**. For all comparisons, it would be helpful to explicitly state the null hypothesis that is to be applied to the data.

VII. OTHER CONSIDERATIONS		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
201-207	If the drug products are similar doses, but are not dose proportional across different strengths, should a bracketing design covering the lowest and highest strength be applied to in vitro evaluation studies?	
203-205	The draft guidance states that "the potential applicant may provide supportive data to demonstrate compositional proportionality across different strengths of R and T products..." How would the generic sponsor come to know about the compositional proportionality of the R-product?	GPhA requests clarification
208-229	If an in-vitro methodology is deemed to be overly sensitive or cannot adequately assess the abuse deterrence	…the product may be evaluated further in a PK study. **The potential applicant need only conduct the PK**

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	potential of the product and a PK evaluation is performed, ANDA applicants should only have to conduct the PK study under the chemical and/or mechanical manipulation resulting in the overly sensitive and/or inadequate in-vitro assessment. Further, as the purpose of performing PK studies with manipulated dosage forms is to demonstrate non-inferiority with regards to abuse-deterrence property, reasonable bounds on the PK parameters should be set (on a product-specific basis).	**study under the manipulation resulting in the overly sensitive and/or inadequate in-vitro assessment. GPhA also requests further clarification for what overly sensitive means.**
231-242	… or differs in the amount of the aversive agent, included in R product (see discussion relating to Reduced Likeability in Appendix 4). **An aversive agent is a substance or combination of substances that produces local irritation or unpleasant systemic effects if a drug product is used inappropriately. A substance is widely accepted as an aversive agent at the levels included in a single dosage unit.**	A definition is necessary for the term "aversive" agent. This is important because of the likability study requirements for aversive agents.

VIII. DATA ANALYSIS		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
297-313	In the case of extractability studies, if the R product only passes some of the Tier 2 and/or Tier 3 evaluations—assuming the R product passes Tier 1—then only those tests which the R product successfully passed need to be evaluated against the T product.	…in order to claim it is no less abuse-deterrence than the corresponding R product. **Only those tests which the R product successfully passed would need to be evaluated against T product.**

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APPENDIX 1: MECHANICAL MANIPULATION		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
340-342	The freezing temperature specified for thermal pre-treatment is -20°C, but no precise temperature, or range, is noted for heating. Further, clarification is requested as to how applicants should proceed if the product cannot be cut using thermal manipulation.	
350-351	Similar to the comment above, no heating range is provided for grating. Clarification is requested as to how applicants should proceed if the product cannot be grated to a size less than 1mm using thermal manipulation.	
358-362	The time frame specified is very open-ended, ranging from 5 seconds to 5 minutes. If the intent is to locate the point of failure within the range provided, then the language should be adjusted. Additionally, what is the path forward if the product cannot be milled to a size less than 1mm using thermal manipulation?	If a drug product can be milled **at any point between** 5 seconds to 5 minutes…

APPENDIX 2: ABUSE BY INJECTION (PARENTERAL ROUTE)		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
389	In regard to syringeability testing, FDA should propose a range in forces required to syringe extracted material across the range in needle gauge.	
394-398	As discussed above, the intent of the ranges provided is unclear. For instance, is the purpose of providing such a wide range in the volumes to evaluate the extremes (1 and 10mLs) or each and every mL? Moreover, the duration ranges from 5mins to 60mins: does one evaluate only the	

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	extremes (5 and 60 mins), pick a single time, or evaluate every 5mins for 60mins total time? GPhA also requests clarification on how this data should be analyzed.	
397	Line 397 of the draft guidance recommends using 18-28G needles for the syringeability studies. Needles between 22G – 28gauge are most commonly used by abuser since 18 gauge needles are not practical for misuse due to their size.	Recommendation that the Agency only include 22-28 gauge needles in the guidance.
420-421	The acceptable delta for comparing T and R products should be interpreted as an upper bound criterion; otherwise a test with less opioid release than R would fail.	The acceptable Δ for comparing T and R products **should be one-sided or "non-inferior".**

APPENDIX 3: ABUSE BY INGESTION (ORAL ROUTE)		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
469	Extractability for an organic solvent (50°C) is specified; a similar specification should be provided for ET for water.	

APPENDIX 4: ABUSE BY INSUFFLATION (NASAL ROUTE)		
Line No.	**Comment and Rationale**	**Proposed Change (if applicable)**
692-695	This language is confusing: reference is made to % mass but then lists criteria as <500 µm (not a mass unit). The criteria should be listed as a percentage reduction of the unit.	
699-721	If the % mass of fine particles (<500 µm) of R <10%, then R is deemed unsuitable for insufflation. No comparative testing of T product to R product is needed.	Include steps for Evaluation of R if deemed unsuitable for insufflation. The flow diagram only list "Tier 1 – use R to Identify milling method" in the Decision Tree.
701-704	If T product has more than 10% fine particles (<500 µm), but is less than or equal to the R product, should testing proceed to Tier 2?	

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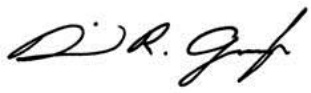
714-716	The statistical acceptance criteria are unclear for the rate and extent of absorption for the PK study.	
740-744	If the amount or concentration of aversive agent in T < R, then T product is considered to be less abuse-deterrent than R product. If this condition holds then the generic firm must do a likeability study.	If T product contains the same aversive agent as R product, the aversive agent in T product should be quantified. **In evaluating the aversive agent in T product, literature (reduced likeability study) should suffice. This evaluation should allow for differences in the amount or concentration with suitable justification (e.g. plus/minus 10%).**

GPhA appreciates the opportunity to provide feedback and trusts that these comments are useful to FDA in finalizing this guidance. GPhA looks forward to continuing to contribute to this important discussion, and commends the Agency's goal of striking a balance between patient access to medicine and efforts to minimize abuse.

Sincerely,



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