Abuse Deterrent Assessment Template: Assessment of In Vitro Abuse Deterrent Evaluation Studies Submitted in Abbreviated New Drug Application (ANDA)

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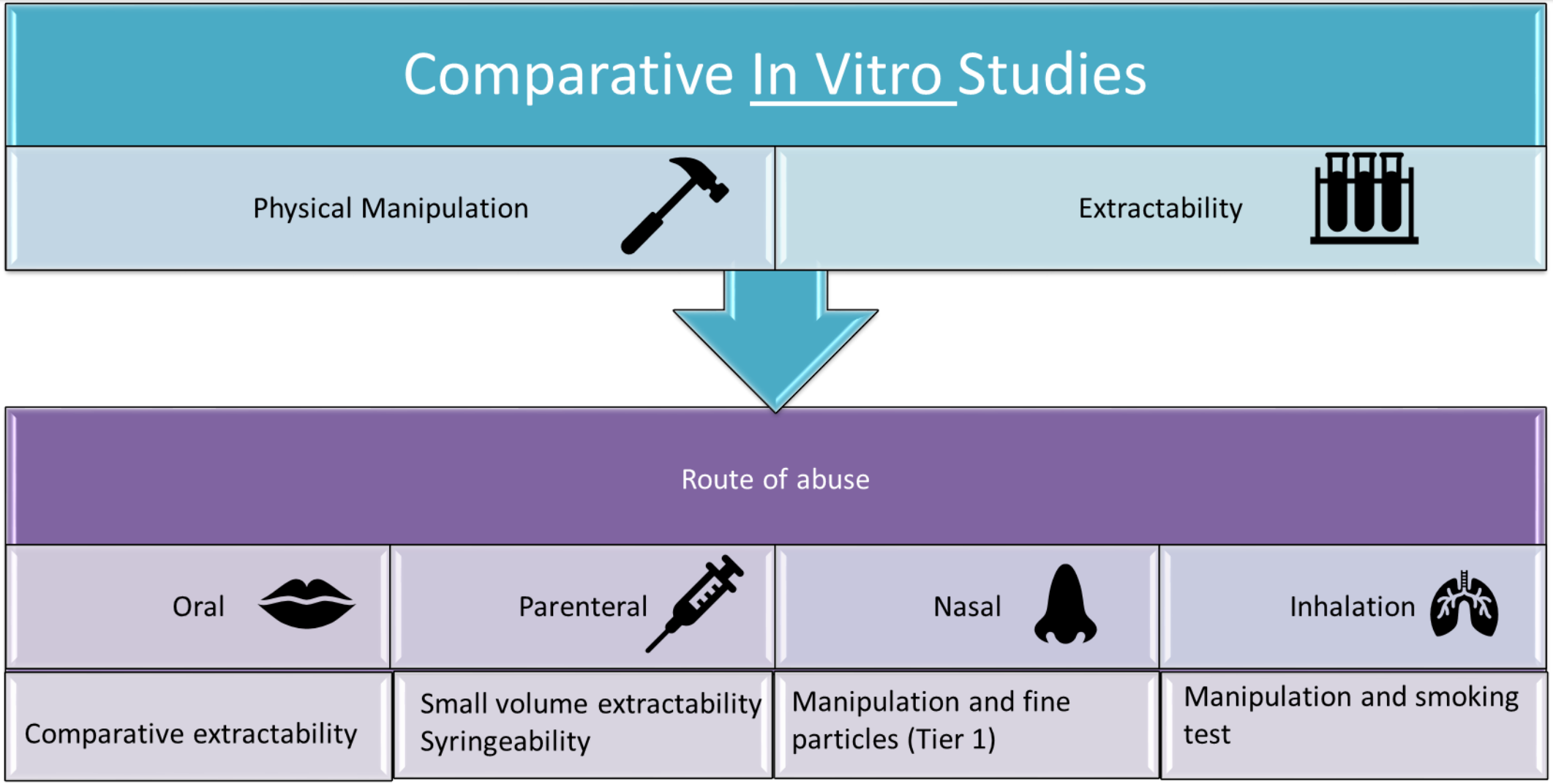
Overview

- This part of the course includes:
  - Summary of the in vitro abuse deterrent (AD) evaluation studies submitted in an ANDA
  - Location of the in vitro AD evaluation in Common Technical Document (CTD)
  - Overview of the assessment approach in each section of the review template
    - Section 1: General assessment
    - Section 2: Strengths tested
    - Section 3: Physical manipulation
    - Section 4: Statistical evaluation
    - Section 5: Tier-based evaluation

In-Vitro AD Evaluation Studies



In Vitro AD Evaluation Studies

- Located in Module 3.2.P.2 of the CTD in an ANDA submission
- Module 3 sections such as Product Composition and Manufacturing are also helpful in assessment
- Summarize representative data above the General Assessment section in the review template

Tip: If in vitro AD studies are missing, check the Product Development Report and/or Module 5

SECTION 1: GENERAL ASSESSMENT

Section 1:General Assessment

- Includes:
  - A summary of AD properties described in the labeling (Section 9.2) of the Reference Listed Drug (RLD)
  - General assessment on the routes of abuse evaluated
  - AD risk assessment based on product attributes
- Regulatory documents used in assessment :
  - Guidance for industry on General principles for evaluating the abuse deterrence of generic solid oral opioid drug products (Nov 2017)
  - Product Specific Guidance(PSGs)

Opioid Products with AD Properties

Brand	API	Dosage Form	AD Design	AD Route	Product Specific Guidance	Generic
Embeda*	Morphine/Naltrexone	ER Capsule	Agonist / Antagonist	Oral, Nasal	07/2018	--
OxyContin	Oxycodone HCl	ER Tablet	Physical	IV, Nasal	07/2018	--
Targiniq ER*	Oxycodone HCl/Naloxone	ER Tablet	Agonist / Antagonist	IV, Nasal	11/2020	--
Hysingla ER	Hydrocodone Bitartrate	ER Tablet	Physical	IV, Oral, Nasal	07/2018	Yes
MorphaBond*	Morphine Sulfate	ER Tablet	Physical	IV, Nasal	09/2018	--
Xtampza ER	Oxycodone	ER Capsule	Physical	IV, Nasal, Oral	09/2018	--
Troxyca ER*	Oxycodone HCl/Naltrexone	ER Capsule	Agonist / Antagonist	Nasal, Oral	--	--
Arymo ER*	Morphine Sulfate	ER Tablet	Physical	IV	09/2018	--
Vantrela ER*	Hydrocodone Bitartrate	ER Tablet	Physical	IV, Nasal, Oral	--	--
RoxyBond*	Oxycodone HCl	IR Tablet	Physical	IV, Nasal	09/2018	--

ER: Extended release; IR: Immediate release; IV: Intravenous
*Discontinued

As of Sep 2022

Example: PSG for Oxycodone Hydrochloride Extended-Release Tablet

Abuse Deterrence Evaluation: Since the FDA has determined that the RLD for oxycodone hydrochloride extended-release tablet (NDA 022272) has properties that are expected to deter abuse (as described in Section 9.2 of the approved Full Prescribing Information), you should refer to the guidance, "*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*," regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the RLD with respect to all potential routes of abuse. Consistent with the guidance, the potential ANDA applicants should consider, among other things, the following:

(a) Conducting all in vitro abuse deterrence studies using a bracketing design based on appropriate justification (e.g., extremes of the ratios of opioid to excipients contributing to abuse deterrence) or the highest strength based on compositional proportionality of the proposed generic formulations across all strengths.

(b) Specifying and justifying the total number of tablet units used in a manipulation run (e.g., milling).

(c) Determining the drug content in manipulated drug products (e.g. cut, grated or milled) and quantifying the drug loss in samples prior to evaluating extractability

Drug loss during physical manipulation:

Increasing the number of tablets used in manipulation reduces drug loss

To ensure low/no drug loss and to avoid underestimation of drug extraction

The Route of Abuse Evaluated

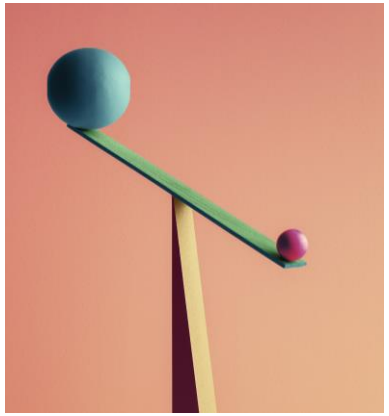
- Evaluating ALL potential routes of abuse

  To ensure the generic drug is no less abuse deterrent than the RLD with respect to all potential routes of abuse and minimize the risk of shifting abuse to other, potentially more dangerous, routes




Risk Assessment based on Product Attributes

- Product attributes that may impact AD
  - Generic drug product is not required to be Q1/Q2*
  - Evaluation is performance based
  - Risk assessment based on product quality attributes:
    - Materials
    - Manufacturing process
    - AD design



*The inactive ingredients are Q1 (qualitatively) and Q2 (Quantitatively) same as that used in the RLD

Case 1-Material Risk Assessment: Polyethylene Oxide Grade

- The RLD (OxyContin, NDA 022272) contains polyethylene oxide(PEO) polymer (POLYOX WSR 301) that is responsible for AD design
- Proposed generic uses lower grades of PEO

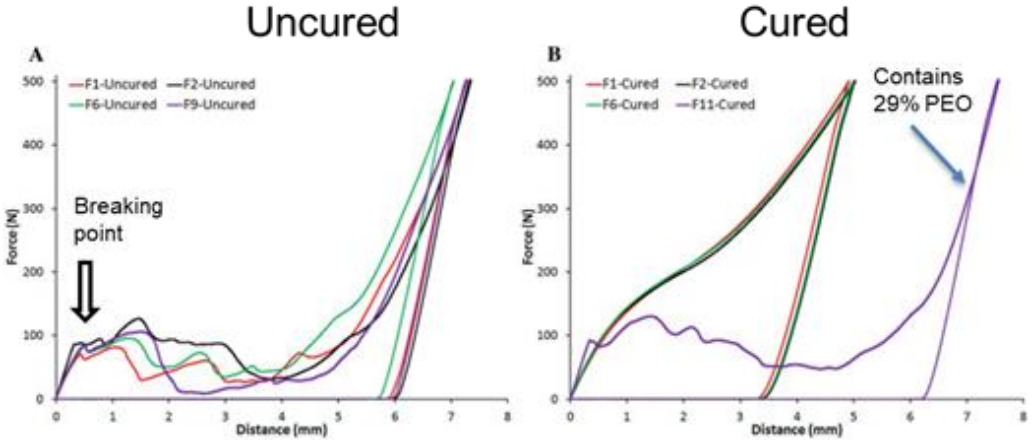
Risk assessment: The lower grades of PEO have lower viscosity upon contact with water than the one used in RLD and thus extractability and syringebility might be impacted

From ANDA 213564

Case 2-Material and Process Risk Assessment: Curing of PEO Tablet

Direct compressed tablets:

- **Material:** PEO of various grades and percent in tablet
- **Process:** Curing at various temperatures and time



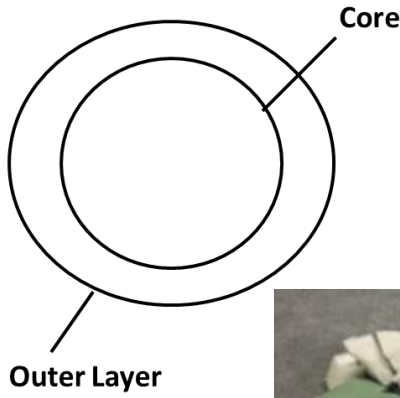
Hardness Profile

Risk assessment: The formulations with lower percent of PEO or curing temperature of 60° C have similar hardness profiles as uncured tablets thus physical manipulation might be impacted

Rahman Z, et al. Int J Pharm. 2016;502(1-2):138-50
Rahman Z, et al. Int J Pharm.(2017) 2017;517(1-2):303-11

Case 3-Design Risk Assessments: Physically Distinguishable Components

- The proposed generic
  - ➢ has tablet-in-tablet design like RLD (Hysingla , NDA 206627)
  - ➢initially added a yellow color to the core



RLD(20mg)

Proposed generic (20mg)

Risk assessment: the colored core may be identified and separated which could facilitate abuse of the generic because the core has a high percentage of drug and less PEO

- Another example of physical distinguishable component that can pose risk for ADF is with agonist/antagonist components

From ANDA 213564

SECTION 2: STRENGTHS TESTED

Section 2: Strengths tested

- Two Approaches:
  1. All strengths
  2. Bracketing: Ratio of opioid to AD excipient is different across strengths or other justification

Summary Table of the ratio of opioid to polymer in generic proposed drug product

Strength (mg)							
Ratio of opioid to Polymer							
Tested	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N

Summary Table of the ratio of opioid to polymer in RLD [not to be released by FOIA]

Strength (mg)							
Ratio of opioid to Polymer							

SECTION 3: PHYSICAL MANIPULATION

Section 3: Physical manipulation

- Evaluate:
  - The method of manipulation used by the applicant e.g. cut, grate, and mill
  - Effort:
    - Number of steps
    - Time
    - Thermal pretreatment
  - The sample size: may impact manipulation efficiency and drug loss
  - Reported results
  - The rationale behind identifying the most effective manipulation (MEM)

Section 3: Physical manipulation

- Efficiency of manipulation:

Reaching a relevant endpoint (e.g. particle size) under specified condition (e.g. less than 5 min)

- Endpoint depends on AD design
- Identifying MEM is critical because it will be used to conduct subsequent comparative studies
- Drug loss during manipulation may impact subsequent comparative studies

Tips: Milling is usually the MEM method for tablets

MEM method for capsule is opening the capsule and emptying the content

Case 4- Manipulation Efficiency

- **Background:**

The applicant uses various manipulation methods for proposed generic Test (T) and reference (R) products including cutting, grating, and milling using a coffee grinder on the proposed generic and reference products. Only one tablet was used for the various methods.

- **Results :**

Neither grating nor milling could generate more than 50% of particles having size less than 1 mm.

Cutting was identified as the most effective manipulation

Table 3: Percent of <1mm Particles for Arymo 60-mg Tablets after Grating

Sample #	Temperature (°C)	Thermal Time (min)	Weight of <1mm Particles (mg)	%w/w of <1mm
1	RT	N/A	248.79	33.6
2	RT	N/A	174.83	23.2
3	RT	N/A	182.47	24.2
4	-20	30	175.07	23.5
5	-20	60	179.36	23.9
6	70	15	N/A	N/A

Notebook reference: DD2041/77

Table 4: Percent of <1mm Particles for Teva 60-mg Tablets after Grating

Sample #	Temperature (°C)	Thermal Time (min)	Weight of <1mm Particles (mg)	%w/w of <1mm
1	RT	N/A	254.26	34.8
2	RT	N/A	239.31	33.4
3	RT	N/A	281.58	38.4
4	-20	30	227.67	31.1
5	-20	60	219.42	30.4

Table 5: Percent of <1mm Particles for Arymo 60-mg Tablets after Milling

Sample #	Temperature (°C)	Thermal Time (min)	Milling Time (min)	Weight of <1mm Particles (mg)	%w/w of <1mm
1	RT	N/A	0.5	12.52	1.7
2	RT	N/A	1	82.09	11.0
3	-20	30	1	37.02	4.9
4	70	15	0.5	59.96	7.9
5	70	15	1	47.76	6.5

Table 8: Percent of <1mm Particles for Teva 60-mg Tablets after Milling

Sample #	Temperature (°C)	Thermal Time (min)	Milling Time (min)	Weight of <1mm Particles (mg)	%w/w of <1mm
1	RT	N/A	1	18.72	2.6
2	70	15	5	143.92	20.3
3	70	30	5	164.3	22.8
4	90	15	1	81.19	11.6
5	-20	30	1	78.54	11.1

Notebook reference: DD2041/39

'igure 4: Cut Arymo Tablet, 60-mg

DD2041/96

Figure 5: Cut Teva Tablet, 60-mg

DD2041/96

From ANDA 210533

Case 4- Manipulation Efficiency

Assessment: The use of one tablet may not produce effective milling because as the number of tablets increases, milling effectiveness is expected to improve.

From ANDA 210533

Example of Deficiencies Language: Identifying MEM Method

- "…You identified the (instrument name) as the most effective tool to obtain fine particles. **To support your conclusion**, please provide data regarding the amount of fines, i.e., particles of size less than 1mm, obtained after manipulation. This may be provided via photographic images with scale, a sieve analysis, or laser diffraction data on the cut, grated and milled tablets…"
- "… **identify** the most effective manipulation conditions for R and T products and provide evidence supporting such identification…"

Examples of Deficiencies Language: Number of Units and Drug Content

- Recommendations on number of units and drug content is based on current agency knowledge of that specific product
- "…Specifying and justifying the **total number of units used** in a manipulation run …"
- "… determine the drug content in manipulated drug products and quantify the **drug loss** in samples prior to evaluating extractability."

SECTION 4: STATISTICAL EVALUATION

Section 4: Statistical evaluation

Evaluate:

- The rationale of the number of replicates
- Statistical approach for the comparison of T and R (noninferiority test)
- Applicant conclusion: T is no less abuse deterrent than R for abuse by extraction, injection, and smoking

Non-inferiority Test: Past Practice

- Division of biostatics was consulted for non-inferiority test
- Template is provided
- Summary of data was populated and attached to the consult

Summary of In Vitro Extraction Data for Abuse-deterrence Evaluation

Drug substance:
ANDA#
File loc:
Table 1. Strength=
(add more tables for different strengths)

Sample Type	Tier Level	Solvent	Temp.	Vol	%Extraction at 30 min																R/T Comparison Needed?	T≥R+10%? (NI test)
					R								T									
					1	2	3	4	5	6	Mean	SD	1	2	3	4	5	6	Mean	SD		
Intact	1	Water	RT	Large (240 mL)																	#DIV/0!	
Intact	2A	Vinegar	RT	Large (240 mL)																	#DIV/0!	
Intact	2A	0.2% Baking soda	RT	Large (240 mL)																	#DIV/0!	
Intact	2A	40% Ethanol	RT	Large (240 mL)																	#DIV/0!	
Intact	2A	Carbonated drink	RT	Large (240 mL)																	#DIV/0!	
Intact	3A	100% Ethanol	RT	Large (240 mL)																	#DIV/0!	
Intact	3A	100% IPA	RT	Large (240 mL)																	#DIV/0!	
Intact	3A	Acetone	RT	Large (240 mL)																	#DIV/0!	
Intact	3A	0.1N HCL	RT	Large (240 mL)																	#DIV/0!	
Intact	3A	0.1N NaOH	RT	Large (240 mL)																	#DIV/0!	
Intact	2B	Water	ET	Large (240 mL)																	#DIV/0!	
Intact	3B	Vinegar	ET	Large (240 mL)																	#DIV/0!	
Intact	3B	0.2% Baking soda	ET	Large (240 mL)																	#DIV/0!	
Intact	3B	40% Ethanol	ET	Large (240 mL)																	#DIV/0!	
Intact	3B	Carbonated drink	ET	Large (240 mL)																	#DIV/0!	
MEM	1	Water	RT	Large (240 mL)																	#DIV/0!	
MEM	2A	Vinegar	RT	Large (240 mL)																	#DIV/0!	
MEM	2A	0.2% Baking soda	RT	Large (240 mL)																	#DIV/0!	
MEM	2A	40% Ethanol	RT	Large (240 mL)																	#DIV/0!	
MEM	2A	Carbonated drink	RT	Large (240 mL)																	#DIV/0!	
MEM	3A	100% Ethanol	RT	Large (240 mL)																	#DIV/0!	
MEM	3A	100% IPA	RT	Large (240 mL)																	#DIV/0!	
MEM	3A	Acetone	RT	Large (240 mL)																	#DIV/0!	
MEM	3A	0.1N HCL	RT	Large (240 mL)																	#DIV/0!	
MEM	3A	0.1N NaOH	RT	Large (240 mL)																	#DIV/0!	
MEM	2B	Water	ET	Large (240 mL)																	#DIV/0!	
MEM	3B	Vinegar	ET	Large (240 mL)																	#DIV/0!	
MEM	3B	0.2% Baking soda	ET	Large (240 mL)																	#DIV/0!	
MEM	3B	40% Ethanol	ET	Large (240 mL)																	#DIV/0!	
MEM	3B	Carbonated drink	ET	Large (240 mL)																	#DIV/0!	

NITest_template.xlsx

Microsoft Word 97 - 2003 Template

Example of Deficiencies Language: Replicates and Statistical Analysis

- "For your comparative studies, … the T product should be shown to be **statistically non-inferior** (NI) to R product. To do this, perform the statistical hypothesis test …"
- "… The [x ,y and z] tests were performed on [one or two] samples. Please explain how you selected **sample size** as a statistically meaningful sample or repeat these tests…"

ANDA 210533

SECTION 5: TIER-BASED EVALUATION

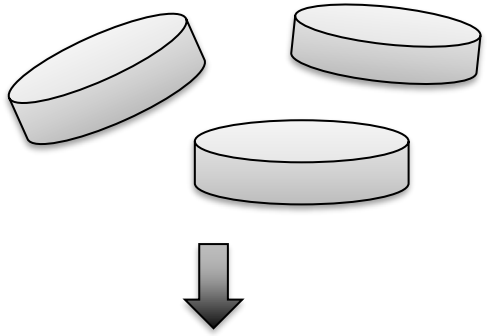
Section 5: Tier-based evaluation

Evaluate:

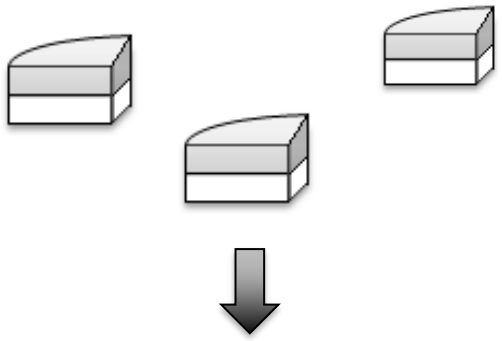
- The extraction methods:
  - volume of solvents
  - solvents used
  - time points
  - temperature
- Results and statistical analysis
  - The tier extraction comparison is performed at least for intact product and MEM of T and R.
  - For specific products, an intermediate manipulation maybe considered

Special Consideration: Intermediate Manipulation and Product Design

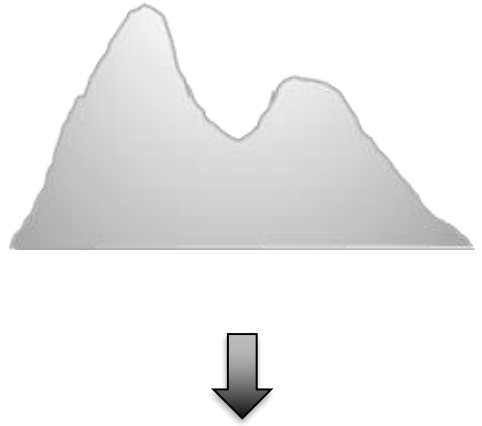
- When the AD feature is related to the **drug product design**, adding an intermediate manipulated sample that retains the design could be suitable in the comparative studies.



Intact
Extractability <10%



Intermediate
Extractability 10-50 %



Most effective
manipulation
Extractability > 50%

PSG of Hydrocodone Bitartrate ER Tablet, NDA 206627

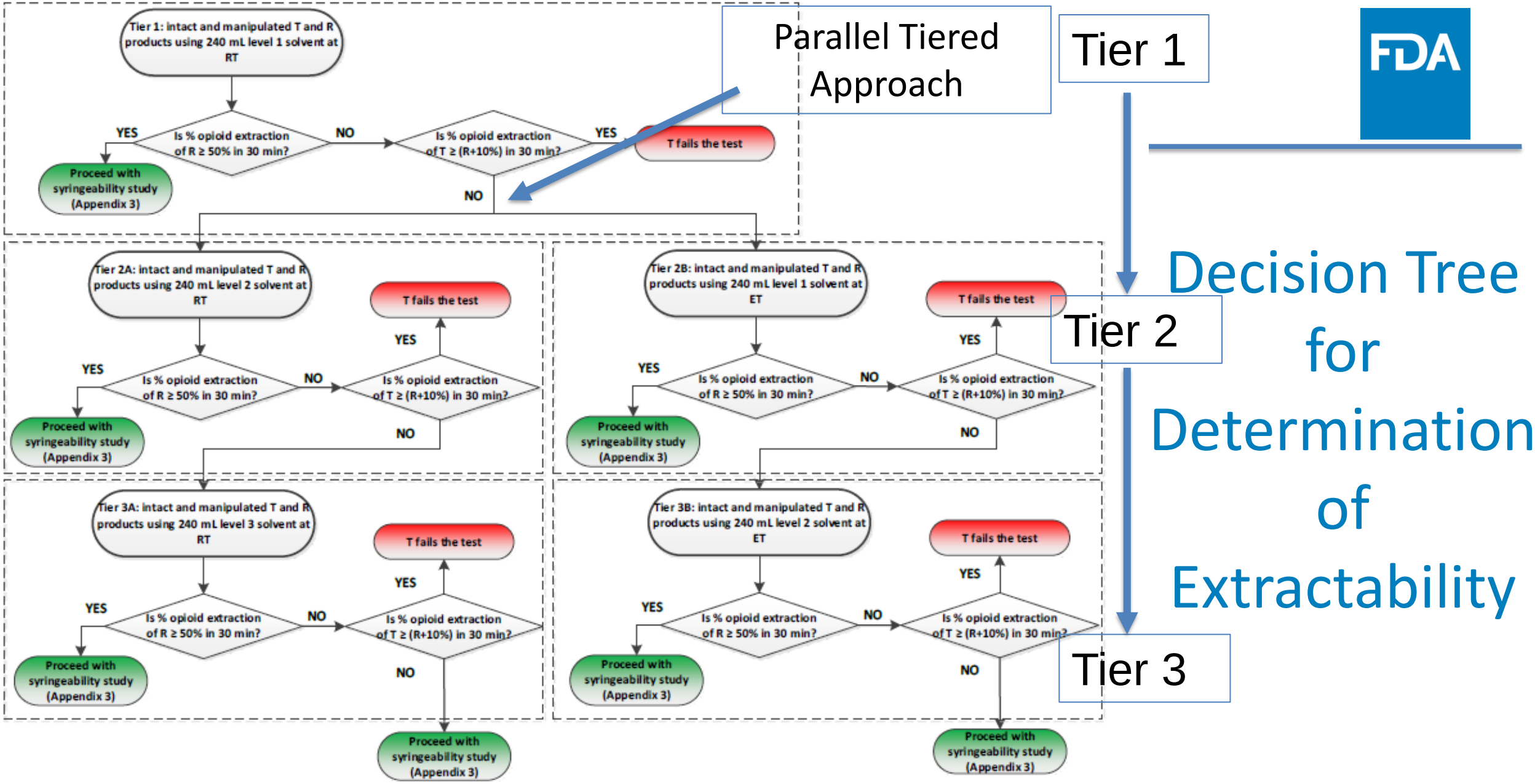
Summary of Recommended Extraction Conditions

Volume	Large volume (e.g., 240 mL)
Solvent	<table><tr><td>Level 1 solvent</td><td>deionized water</td></tr><tr><td>Level 2 solvents</td><td>commercially available food-grade vinegar, 0.2% baking soda solution, 40% ethanol, and carbonated drink</td></tr><tr><td>Level 3 solvents</td><td>100% ethanol, 100% isopropyl alcohol, acetone, 0.1 N HCl, and 0.1 N NaOH</td></tr></table>
Time points	30 min for comparison
Temperature	Room temperature (RT)* or Elevated temperature (ET)**
Stirring	With or without
Analyte	-Drug opioid substance in extraction media (expressed as percent of label) -Opioid antagonist extracted (If present, expressed as ratio of agonist to antagonist)

Guidance for Industry: General principles for evaluating the abuse deterrence of generic solid oral opioid drug products
*U.S. Pharmacopoeia (USP) controlled room temperature (20° C to 25° C)
**Boiling temperature of the solvents used

Assessment of Extraction Results

- For comparison reasons, applicants should provide opioid extraction % at 30 min
- Tier-based determination depends on two questions:
  - Is the R extraction % at one tier equals or more than 50%?
  - If yes, Is the T extraction % equal or more than the reference (+10%) [Non-inferiority test]?
- The conclusion depends on the totality of evidence
- Syringebility test condition depends on the tier-based extraction condition


Parallel Tiered Approach
Tier 1
Tier 2
Tier 3
Decision Tree for Determination of Extractability
Tier 1: intact and manipulated T and R products using 240 mL level 1 solvent at RT
Is % opioid extraction of R ≥ 50% in 30 min?
YES
NO
Is % opioid extraction of T ≥ (R+10%) in 30 min?
YES
T fails the test
NO
Proceed with syringeability study (Appendix 3)
Tier 2A: intact and manipulated T and R products using 240 mL level 2 solvent at RT
Tier 2B: intact and manipulated T and R products using 240 mL level 1 solvent at ET
Tier 3A: intact and manipulated T and R products using 240 mL level 3 solvent at RT
Tier 3B: intact and manipulated T and R products using 240 mL level 2 solvent at ET

Directions to Fill the Tier-based Analysis Table

Is the % opioid extraction of R ≥ 50% at 30 min **% extraction of RLD**	≥ 50% Yes, tier ends, syringeability study evaluated	< 50% {Pass and continue evaluation }
Is % opioid extraction of T≥ (R +10%) in 30 min **difference in Avg %T-%R**	≥ 10% Yes, check stats to see if T fails the test	< 10 % {Pass, continue evaluation in next tier }
If it passes Tier 1, 2A and 3A (Solvent challenge)	syringeability study evaluated	
If it passes Tier 1, 2B and 3B (Temperature challenge)	syringeability study evaluated	

Tier-Based Analysis Table

Tier 1: Intact and manipulated using 240 mL level 1 solvent (water) at RT.	**Intact**			**[MEM Method]**		
	Strength 1	**Strength 2**	**Strength 3**	**Strength 1**	**Strength 2**	**Strength 3**
Is the % opioid extraction of R ≥ 50% at 30 min **% extraction of RLD**						
Is % opioid extraction of T≥ (R +10%) in 30 min **difference in Avg % R-% T**						

Tier 1: Intact and manipulated using 240 mL* level 1 solvent (water) at RT.	Intact **-Stop at Tier 3A and 3B**			Cut **-Stop at Tier 3A and 2B**			Ground **-Stop at Tier 1**			Grated **-20 failed at tier 1** **-60 and 120 failed at tier 3a 100 ethanol** **-60 and 120 stop at 2B**		
	20 mg	60 mg	120 mg	20 mg	60 mg	120 mg	20 mg	60 mg	120 mg	20 mg	60 mg	120 mg
Is the % opioid extraction of R ≥ 50% at 30 min** **% extraction of RLD**	1.7	1.7	1.8	30.7	24.1	24.7	56.3	56.0	59.5	40.6	50.7 (46.2-58.8)	54.2 (45.9-59.7)
Is % opioid extraction of T≥ (R +10%) in 30 min** **difference in Avg % R-% T**	-1.2	-0.1	+0.1	+ 3.9	+2.1	+1.5	Yes, STOP, syringeability study evaluated			-15.7	+3.3	-7.0

Example (to be continued)

Tier 1

Tier 2A: Intact and manipulated using 240 mL* level 2 solvent at RT.		Intact			Cut		
Is the % opioid extraction of R ≥ 50% at 30 min* **%extraction of RLD**	Vinegar	2.6	2.2	2.0	33.7	33.4	20.4
	0.2% baking soda	Not included. Check 0.1 N NaOH					
	40% ethanol	3.1	0.9	1.2	17.4	17.5	12.2
	Coke	5.9	2.5	2.3	23.9	22.1	21.7
Is % opioid extraction of T≥ (R +10%) in 30 min** **difference in Avg %R-%T**	Vinegar	0.0	-0.4	0.0	-2.0	+5.1	-0.2
	0.2% baking soda	Not included. Check 0.1 N NaOH					
	40% ethanol	+2.1	-0.8	+0.2	+0.8	+1.3	+1.2
	Coke	+0.7	-0.2	-0.4	+0.2	+1.5	+1.5

Tier 3A: Intact and manipulated using 240 mL* level 3 solvent at RT.		INTACT			CUT		
Is the % opioid extraction of R ≥ 50% at 30 min** **%extraction of RLD**	100% ethanol	ND	0.1	0.0	14.0	11.0	11.6
	70% isopropyl alc**	1.9	0.7	0.6	8.0	6.7	8.3
	acetone	2.8	0.3	0.4	20.7	10.9	13.5
	0.1 N HCl	2.6	2.6	2.6	25.5	31.6	41.1
	0.1 N NaOH	2.6	1.2	1.2	14.7	22.0	20.6
Is % opioid extraction of T≥ (R +10%) in 30 min** **difference in Avg %R-%T**	100% ethanol	-0.4	0.0	-0.2	+1.2	-0.1	+1.4
	70% isopropyl alc**	-0.6	0.0	+0.2	-2.0	+0.2	+1.3
	acetone	+1.1	+0.1	0.0	+1.7	-2.2	+1.1
	0.1 N HCl	-0.5	-0.7	-0.2	-0.5	+3.4	+2.3
	0.1 N NaOH	-0.3	-0.5	-0.2	-0.9	+6.3	0.0
		No, syringeability study evaluated			No, syringeability study evaluated		

Example (to be continued)

Tier 2 and 3 A

Tier 2B: Intact and manipulated using 240 mL* level 1 solvent (water) at ET	INTACT			CUT		
Is the % opioid extraction of R ≥ 50% at 30 min** %extraction of RLD	15.4	36.6	29.8	85.6 STOP	89.6 STOP	102.6 STOP
				Yes , syringeability study evaluated		
Is the % opioid extraction of R ≥ 50% at 30 min** %extraction of RLD	+2.6	+25.6	+2.6			

Tier 3B: Intact and manipulated using 240 mL* level 2 solvent at RT. Is the % opioid extraction of R ≥ 50% at 30 min** %extraction of RLD	Vinegar	26.9	19.5	17.6	
	0.2% baking soda	Not done			
	40% ethanol	7.5	11.1	10.6	
	Coke	24.2	12.0	27.2	
Is % opioid extraction of T ≥ (R +10%) in 30 min ** difference in Avg %R-%T	Vinegar	+4.8	+5.9	+1.2	
	0.2% baking soda	Not Done			
	40% ethanol	+2.1	-0.8	+0.2	
	Coke	+5.7	-0.8	+4.1	
		No, syringeability study evaluated			

Example (to be continued)

Tier 2 and 3 B

Case 5 - Extractability Method

- The applicant performed solvent extraction studies on the R and T products in all three levels of solvents. The studies were conducted using 240 mL solvent, at 50 rpm, and with 30 min duration. Both intact and cut tablets were tested (note: the applicant claimed it was not possible to obtain fine particles using coffee grinder). For the 60-mg strength, a single tablet was used for extraction tests. For the 15-mg strength, four tablets were used.

Table 10: Tier 1: Percent of Morphine Sulfate Extracted in Level-1 Solvent at RT, Intact (n=6)

Solvent	Strength (mg)	Test Mean (%LC)	SD (%LC)	Reference Mean (%LC)	SD (%LC)	Mean Difference T – R (%)
Water	15	1.7	0.2	2.1	0.2	-0.4
	60	3.8	0.5	3.3	0.6	0.5

Notebook reference: DD2042/27, 120

Table 11: Tier 2B: Percent of Morphine Sulfate Extracted in Level-1 Solvent at ET, Intact (n=6)

Solvent	Strength (mg)	Test Mean (%LC)	SD (%LC)	Reference Mean (%LC)	SD (%LC)	Mean Difference T – R (%)
Water	15	12.5	0.5	19.0	1.1	-6.5
	60	16.8	1.9	20.0	1.9	-3.2

Notebook reference: DD2042/27, 120

From ANDA 210533

Case 5 - Extractability Method

Assessment: Using more than one tablet (or equivalent to one tablet) in extraction may lead to an unusually high amount of PEO in the extraction medium, which could potentially slow down drug release and result in underestimation of extractability.

From ANDA 210533

Cases 6- Extractability Method

- The applicant performed large volume extraction studies for T and R in level 1 and level 2 solvents at both room temperature and elevated temperature. In the elevated temperature extraction, the applicant did not disclose the method used for heating. From the information provided, it was not clear whether the elevated temperature conditions were maintained through the sampling time points.

Assessment: The fluctuation in temperature during the sampling duration of the extraction study may change the effectiveness of the extraction.

From ANDA 211178

Filled Examples of the Template

ANDA 208269

ANDA 210533

FDA U.S. FOOD & DRUG ADMINISTRATION

Publications

1. Xu X, Gupta A, Al-Ghabeish M, Calderon SN, Khan MA. Risk based in vitro performance assessment of extended release abuse deterrent formulations. Int J Pharm. 2016;500(1-2):255-67.
2. Rahman Z, Yang Y, Korang-Yeboah M, Siddiqui A, Xu X, Ashraf M, et al. Assessing impact of formulation and process variables on in-vitro performance of directly compressed abuse deterrent formulations. Int J Pharm. 2016;502(1-2):138-50.
3. Rahman Z, Zidan AS, Korang-Yeboah M, Yang Y, Siddiqui A, Shakleya D, et al. Effects of excipients and curing process on the abuse deterrent properties of directly compressed tablets. Int J Pharm. 2017;517(1-2):303-11.
4. Xu X, Siddiqui A, Srinivasan C, Mohammad A, Rahman Z, Korang-Yeboah M, et al. Evaluation of Abuse-Deterrent Characteristics of Tablets Prepared via Hot-Melt Extrusion. AAPS PharmSciTech. 2019;20(6):230.
5. Externbrink A, Sharan S, Sun D, Jiang W, Keire D, Xu X. An in vitro approach for evaluating the oral abuse deterrence of solid oral extended-release opioids with properties intended to deter abuse via chewing. Int J Pharm. 2019;561:305-13.
6. Feng X, Zidan A, Kamal NS, Xu X, Sun D, Walenga R, et al. Assessing Drug Release from Manipulated Abuse Deterrent Formulations. AAPS PharmSciTech. 2020;21(2):1-11.
7. Meng, Z., Boyce, H.J., Sun, D. *et al.* Preferential Oxycodone Loss of Physically Manipulated Abuse Deterrent Oxycodone HCl Extended Release Tablets Prepared for Nasal Insufflation Studies. Pharm Res.2021; 38: 1263–78.
8. Raofi S, Kinjo M, Sun D, Li Z, Boyce H, et al. Particle size affects pharmacokinetics of milled oxycodone hydrochloride tablet products following nasal insufflation in nondependent, recreational opioid users. Clinical and translational science. 2021;14(5):1977-87.

Statistical evaluation deficiency question language

You should statistically compare the T product directly to the R product to evaluate whether T product is no less abuse deterrent than R product, defined as the mean percent extraction of opioid drug substance from T product is less than that from R plus 10 percent. That is, the T product should be shown to be statistically non-inferior (NI) to R product

To do this, perform the statistical hypothesis test

H_0: T - R ≥10% versus H_A: T-R < 10%

Rejecting the null hypothesis (H_0) in favor of the alternative hypothesis (H_A) supports the claim of NI. The acceptable Type I error probability (α) is generally set at 5%.

The NI test may be performed by comparing the upper bound of the 95% confidence interval for the difference T- R in mean % extracted to 10%. If the upper bound is less than 10%, NI is demonstrated.

Deficiency language

- The reference listed drug, X, includes a description of abuse deterrent properties in the labeling. The proposed drug product should be no less abuse deterrent than the RLD with respect to all potential routes of abuse. Please provide the following information to help us to further assess the abuse potential of the drug product. It is important to note that completion of the below studies do not necessarily confirm the abuse deterrent properties of your product:

Example of Design Risk Assessments: Physically Distinguishable Components

- Physical distinguishable component can pose risk for ADF with agonist/antagonist components