Document Name: Annexure 3 (Product Details)		
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Annexure-3
Product Details

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Table I: Product details

Product Name	Active Ingredient	Solubility in water	Strength	Batch Size	Lowest Recommended Daily Dose (LRDD)	Maximum Recommended Daily Dose
	Levonorgestrel	Insoluble	1.5 mg	42.00 kg	30 µg	1.5 mg
	Levonorgestrel	Insoluble	0.75 mg	28.00 kg	30 µg	1.5 mg
	Misoprostol	Soluble	200 mcg	41.00 kg	25 µg	200 µg
	Mifepristone	Insoluble	200 mg	14.35 kg	25 mg	600 mg
	Norethindrone Acetate	Insoluble	5 mg	42.00 kg	350 µg	5 mg

Risk assessment is performed to assess the effect of solubility of active ingredient (API) in water, strength, batch size, toxicity, complexity and design of equipments required for manufacturing and difficult to clean etc. on cleaning procedure and is presented in below mentioned table. The risk is classified into the three categories: high, medium and low.

Table II: Risk assessment for worst case selection:

Factors (API) ⇨ **Parameters** ⇩	**Levonorgestrel**	**Misoprostol**	**Mifepristone**	**Norethindrone Acetate**
Solubility of API in water	High (Ref-1)	Low (Ref-2)	High (Ref-3)	High (Ref-4)
Potency	High (Ref-5)	High (Ref-6)	Low (Ref-7)	Medium (Ref-8)
Batch size	High (Ref-9)	High (Ref-10)	Low (Ref-11)	High (Ref-12)
Diffcuilt to clean	High (Ref-13)	Low (Ref-14)	High (Ref-15)	Medium (Ref-16)
Toxicity	Low (Ref-17)	High (Ref-18)	Low (Ref-19)	Low (Ref-20)
Complexity and design of equipments required for manufacturing	High (Ref-21)	Low (Ref-22)	High (Ref-23)	High (Ref-24)

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Ref. No.	Item / Justification
Solubility of API in water	
1	Levonorgestrel is practically insoluble in water. As soluble products are removed easily during cleaning by solubilizing the product, so it can be rinsed away. Insoluble materials, on the other hand, will resist going into solution and must be removed by a physical means or using other methods.
2	Misoprostol is soluble in water, so it can be removed easily during cleaning.
3	Mifepristone is practically insoluble in water.
4	Norethindrone acetate is practically insoluble in water.
Potency	
5	Lowest recommended daily dose (LRDD) of Levonorgestrel is 30 µg, so it is highly potent drug.
6	Misoprostol: Lowest recommended daily dose (LRDD) is 25 µg, so it is highly potent drug.
7	Lowest recommended daily dose (LRDD) of Mifepristone is 25 mg, so it is less potent drug in the group considered for cleaning validation study.
8	Lowest recommended daily dose (LRDD) of Norethindrone Acetate is 350 µg, so it is less potent drug in the group considered for cleaning validation study.
Batch size	
9	Maximum batch size of Levonorgestrel is 42.00 kg and it is manufactured using wet granulation process. Considering the working capacity of equipments, it is concluded that, active ingredient comes in contact with maximum contact surface area of the equipments used for process.
10	Maximum batch size of Misoprostol is 41.00 kg and it is manufactured using dry mixing process. Also less equipment are used for dry mixing process than wet granulation.
11	Maximum 14.35 kg material of Mifepristone is processed by wet granulation process.
12	Maximum batch size of Norethindrone is 42.00 kg and it is manufactured using wet granulation process. Considering the working capacity of equipments, it is concluded that, active ingredient comes in contact with maximum contact surface area of the equipments used for process.

Difficult to clean	
13	PVP K-30 is used as binding agent for wet granulation process of Levonorgestrel tablets. Based on the formulation properties and interaction with operators and supervisors involved in cleaning procedure, it is concluded that product is difficult to clean from contact surfaces of the equipments used in process.
14	Misoprostol tablets are manufactured using dry mixing process. Considering the nature of excipients, experience during routine cleaning procedures and after discussion with operators and supervisors involved in cleaning procedure, it is concluded that product is easy to clean from contact surfaces of the equipments used in process.
15	Starch paste and PVP K-30 are used as binding agent for manufacturing of Mifepristone Tablet by wet granulation process. On interaction with operators and supervisors involved in cleaning procedure and considering formulation properties, it is observed that product is difficult to clean from contact surfaces of the equipments used in process.
16	PVP K-30 is used as binding agent for wet granulation process of Norethindrone tablets. Based on the interaction with operators and supervisors involved in cleaning procedure, it is observed that product is difficult to clean from contact surfaces of the equipments used in process.
Toxicity	
17	In case of Levonorgestrel value of LD50> 5000 mg / kg (Orally in rats).
18	In case of Misoprostol LD50 >81 mg/kg (Orally in rats).
19	For Mifepristone LD50> 1000 mg / kg (Orally in rats).
20	For Norethindrone acetate LD50 > 2800 mg / kg (Orally in rats).
Complexity and design of equipments required for manufacturing	
21	Wet granulation process is used for manufacturing of Levonorgestrel tablets which requires majority of equipments in production area. The complexity of the equipment is based on the number of discreet pieces, the number of transfer or process steps during manufacturing of product. For wet granulation manufacturing process, major equipments such as RMG, FBD, Cone mill, Vibrosifter, Bin Blender, Compression machine Be-coater and Packing machine are used. Also the complexity of the cleaning validation is directly proportional to the complexity of the equipment train.

22	Misoprostol tablets are manufactured using dry mixing process which requires few major equipments in the production area and it involves few proces steps such as sifting, mixing, blending, compression and packing.
23	Mifepristone tablets are manufactured by wet granulation process and major equipments in production area are used for it.
24	Norethindrone Acetate tablets are manufactured by wet granulation process, which involves process steps such as sifting, preparation of drug solution, wet granulation, drying, sizing, compression and packing.

Conclusion:_____
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Checked By: (Signature/Date)

Verified By: (Signature/Date)

Approved By: (Signature/Date)