Document Name: Annexure-5 (Calculation of contamination limit)		
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Annexure-5
Calculation of Contamination Limit

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Product contact surface area of equipments for each product:

Equipment Name	Surface area of equipment		Misoprostol	Levonorgestrel	Mifepristone	Norethindrone
	Sq. m	Sq.cm				
RM sampling, dispensing, blending & sieving isolator	0.05	500	√	X	√	X
Fluid bed dryer	4.3680	43680	X	√	√	√
Rapid mixer granulator	2.4058	24058	X	√	√	√
Vibrosifter	2.3175	23175	√	√	√	√
Blender bin (100 L)	8.9544	89544	√	√	√	√
Tablet compression machine	0.630629	6306.29	√	√	√	√
Deduster	0.5713	5713	√	√	√	√
Metal detector	0.1428	1428	√	√	√	√
Glove box	0.3176	3176	√	√	√	√
Paste kettle	0.2953	2953	X	X	√	X
Blister machine	0.8503	8503	X	√	X	√
Tipper	0.576	5760	X	√	√	√
B-coater	4.56323	45632.3	X	√	X	X
Cone mill	0.4345	4345	X	√	√	√
Blister machine (Alu-Alu)	0.2931	2931	√	X	√	X
Scoops	0.1356	1356	√	√	√	√
Sampling rod	0.0472	472	√	√	√	√
Spatula	0.0063	63	√	√	√	√
Spatula	0.04625	462.5	X	X	X	X

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1.0 10 ppm criteria:

$$MAR \ (mg/swab) = \frac{10 \times \text{Min. batch size of next product B (in kg)} \times \text{swab surface area (in cm}^2)}{1 \times \text{Total surface area of equipment (in cm}^2)}$$

Sr. No.	Product	MAR calculation:
1	I-Pill / Unwanted -72	MAR = $\frac{10 \times 42 \times 100}{1 \times 263211.59}$ = 0.159 mg/swab = 159 µg/swab
2	Pillarnor-2	MAR = $\frac{10 \times 28 \times 100}{1 \times 263211.59}$ = 0.106 mg/swab = 106 µg/swab
3	Misoclear / Mifecon M Kit / Herwont Kit / Mariprist / Seguro Kit (Misoprostol)	MAR = $\frac{10 \times 41 \times 100}{1 \times 134664.29}$ = 0.304 mg/swab = 304 µg/swab
4	Misoclear / Mifecon M Kit / Herwont Kit / Mariprist / Seguro Kit (Mifepristone)	MAR = $\frac{10 \times 14.35 \times 100}{1 \times 215460.29}$ = 0.066 mg/swab = 66 µg/swab
5	Regestrone Tablets	MAR = $\frac{10 \times 42 \times 100}{1 \times 217579.29}$ = 0.193 mg/swab = 193 µg/swab

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2.0 Dose Criteria:

Calculation of the maximum allowable residue:

MAR (µg/swab) = $\dfrac{\text{LRDD of previous product (A) x SBS of next product (B) x SSA}}{1000 \text{ x MRDD of next product (B) x TSA}}$ x 1000 x1000x1000

LRDD: Lowest Recommended Daily Dose (in mg)
MRDD: Maximum Recommended Daily Dose (in mg)
SBS: Smallest Batch Size of next product (in kg)
SSA: Swab surface area (in cm²)
TSA: Total Surface area of equipment (product contact part) (in cm²)

Sr.No.	Maximum Allowable Residual Concentration (MAR)

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1	**Maximum Allowable Residual Concentration (MAR) of Misoprostol in a batch of Mifepristone is calculated as follows:**

Product	Misoprostol Tablets (Product A)	Mifepristone Tablets (Product B)
Strength	0.20 mg	200 mg
Batch size	41.00 kg	14.35 kg
Lowest recommended daily dose (LRDD)	0.025 mg	25 mg
Maximum recommended daily dose (MRDD)	0.20 mg	600 mg
Common total surface area of equipments	134664.29cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

MAR = $\dfrac{\text{LRDD of previous product (A) x SBS of next product (B) x SSA x 1000 x 1000 x 1000}}{1000 \text{ x MRDD of next product (B) x TSA}}$ = $\dfrac{0.025 \text{ x } 14.35 \text{ x} 100 \text{x} 1000 \text{x} 1000 \text{x} 1000}{1000 \text{ x } 600 \text{ x } 134664.29}$

= 0.444 µg/swab

2	**Maximum Allowable Residual Concentration (MAR) of Misoprostol in a batch of Levonorgestrel is calculated as follows:**

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Product	**Misoprostol Tablets (Product A)**	**Levonorgestrel Tablets (Product B)**
Strength	0.20 mg	1.5 mg
Batch size	41.00 kg	42.00 kg (Smallest batch size is 28.0 kg)
Lowest recommended daily dose (LRDD)	0.025 mg	0.03 mg
Maximum recommended daily dose (MRDD)	0.20 mg	1.5 mg
Common total surface area of equipments	131233.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

MAR = $\dfrac{\text{LRDD of previous product (A)} \times \text{SBS of next product (B)} \times \text{SSA} \times 1000 \times 1000 \times 1000}{1000 \times \text{MRDD of next product (B)} \times \text{TSA}}$ = $\dfrac{0.025 \times 28 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 1.5 \times 131233.29}$

= 355 µg/swab

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3	**Maximum Allowable Residual Concentration (MAR) of Misoprostol in a batch of Norethindrone is calculated as follows:**

Product	Misoprostol Tablets (Product A)	Norethindrone Tablets (Product B)
Strength	0.20 mg	5 mg
Batch size	41.00 kg	42.00 kg
Lowest recommended daily dose (LRDD)	0.025 mg	0.35 mg
Maximum recommended daily dose (MRDD)	0.20 mg	5 mg
Common total surface area of equipments	131233.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

$$MAR = \frac{\text{LRDD of previous product (A)} \times \text{SBS of next product (B)} \times \text{SSA} \times 1000 \times 1000 \times 1000}{1000 \times \text{MRDD of next product (B)} \times \text{TSA}} = \frac{0.025 \times 42 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 5 \times 131233.29} =$$

$$= 160 \ \mu g/swab$$

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4	**Maximum Allowable Residual Concentration (MAR) of Mifepristone Tablet in a batch of Misoprostol Tablet is calculated as follows:**

Product	Mifepristone Tablet (Product A)	Misoprostol Tablets (Product B)
Strength	200 mg	0.20 mg
Batch size	14.35 kg	41.00 kg
Lowest recommended daily dose (LRDD)	25 mg	0.025 mg
Maximum recommended daily dose (MRDD)	600 mg	0.20 mg
Common total surface area of equipments	134664.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

MAR = $\dfrac{\text{LRDD of previous product (A)} \times \text{SBS of next product (B)} \times \text{SSA} \times 1000 \times 1000 \times 1000}{1000 \times \text{MRDD of next product (B)} \times \text{TSA}}$ = $\dfrac{25 \times 41 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 0.20 \times 134664.29}$ =

= 3805760.23 µg/swab

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5	**Maximum Allowable Residual Concentration (MAR) of Mifepristone Tablet in a batch of Levonorgestrel Tablet is calculated as follows:**

Product	Mifepristone Tablet (Product A)	Levonorgestrel Tablets (Product B)
Strength	200 mg	1.5 mg
Batch size	14.35 kg	42.00 kg (Smallest batch size is 28.0 kg)
Lowest recommended daily dose (LRDD)	25 mg	0.03 mg
Maximum recommended daily dose (MRDD)	600 mg	1.5 mg
Common total surface area of equipments	209076.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

$$MAR = \frac{\text{LRDD of previous product (A) x SBS of next product (B) x SSA} \times 1000 \times 1000 \times 1000}{1000 \times \text{MRDD of next product (B) x TSA}} = \frac{25 \times 28 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 1.5 \times 209076.29} =$$

$$= 223204.01 \ \mu g/swab$$

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6	**Maximum Allowable Residual Concentration (MAR) of Mifepristone Tablet in a batch of Norethindrone Tablet is calculated as follows:**

Product	Mifepristone Tablet (Product A)	Norethindrone Tablets (Product B)
Strength	200 mg	5 mg
Batch size	14.35 kg	42.00 kg
Lowest recommended daily dose (LRDD)	25 mg	0.35 mg
Maximum recommended daily dose (MRDD)	600 mg	5 mg
Common total surface area of equipments	209076.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

$$MAR = \frac{\text{LRDD of previous product (A)} \times \text{SBS of next product (B)} \times \text{SSA} \times 1000 \times 1000 \times 1000}{1000 \times \text{MRDD of next product (B)} \times \text{TSA}} = \frac{25 \times 42 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 5 \times 209076.29}$$

$$= 100441.8 \ \mu g/swab$$

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7	**Maximum Allowable Residual Concentration (MAR) of Levonorgestrel Tablet in a batch of Misoprostol Tablet is calculated as follows:**		

Product	Levonorgestrel Tablet (Product A)	Misoprostol Tablets (Product B)
Strength	1.5 mg	0.20 mg
Batch size	42.00 kg	41.00 kg
Lowest recommended daily dose (LRDD)	0.03 mg	0.025 mg
Maximum recommended daily dose (MRDD)	1.5 mg	0.20 mg
Common total surface area of equipments	131233.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

$$MAR = \frac{LRDD \text{ of previous product (A)} \times SBS \text{ of next product (B)} \times SSA \times 1000 \times 1000 \times 1000}{1000 \times MRDD \text{ of next product (B)} \times TSA} = \frac{0.03 \times 41 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 0.20 \times 131233.29}$$

$$= 4686.31 \ \mu g/swab$$

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8	**Maximum Allowable Residual Concentration (MAR) of Levonorgestrel Tablet in a batch of Mifepristone Tablet is calculated as follows:**	

Product	Levonorgestrel Tablet (Product A)	Mifepristone Tablet (Product B)
Strength	1.5 mg	200 mg
Batch size	42.00 kg	14.35 kg
Lowest recommended daily dose (LRDD)	0.03 mg	25 mg
Maximum recommended daily dose (MRDD)	1.5 mg	600 mg
Common total surface area of equipments	209076.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

$$\text{MAR} = \frac{\text{LRDD of previous product (A)} \times \text{SBS of next product (B)} \times \text{SSA} \times 1000 \times 1000 \times 1000}{1000 \times \text{MRDD of next product (B)} \times \text{TSA}} = \frac{0.03 \times 14.35 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 600 \times 209076.29} =$$

$$= 0.343 \ \mu g/swab$$

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9	**Maximum Allowable Residual Concentration (MAR) of Levonorgestrel Tablet in a batch of Norethindrone Tablet is calculated as follows:**

Product	Levonorgestrel Tablet (Product A)	Norethindrone Tablets (Product B)
Strength	1.5 mg	5 mg
Batch size	42.00 kg	42.00 kg
Lowest recommended daily dose (LRDD)	0.03 mg	0.35 mg
Maximum recommended daily dose (MRDD)	1.5 mg	5 mg
Common total surface area of equipments	217579.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

MAR (mcg/swab) = $\dfrac{\text{LRDD of previous product (A)}}{1000 \times \text{MRDD of next product (B)} \times \text{TSA}}$ x SBS of next product (B) x SSAx1000x1000 x 1000 = $\dfrac{0.03 \times 42 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 5 \times 217579.29}$ =

= 115.81 µg/swab

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10	**Maximum Allowable Residual Concentration (MAR) of Norethindrone Tablet in a batch of Misoprostol Tablet is calculated as follows:**

Product	Norethindrone Tablets (Product A)	Misoprostol Tablets (Product B)
Strength	5 mg	0.20 mg
Batch size	42.00 kg	41.00 kg
Lowest recommended daily dose (LRDD)	0.35 mg	0.025 mg
Maximum recommended daily dose (MRDD)	5 mg	0.20 mg
Common total surface area of equipments	131233.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

$$MAR = \frac{LRDD \text{ of previous product (A)} \times SBS \text{ of next product (B)} \times SSA \times 1000 \times 1000 \times 1000}{1000 \times MRDD \text{ of next product (B)} \times TSA} = \frac{0.35 \times 41 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 0.20 \times 131233.29} =$$

$$= 54673.62 \ \mu g/swab$$

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11	**Maximum Allowable Residual Concentration (MAR) of Norethindrone Tablet in a batch of Mifepristone Tablet is calculated as follows:**

Product	Norethindrone Tablets (Product A)	Mifepristone Tablet (Product B)
Strength	5 mg	200 mg
Batch size	42.00 kg	14.35 kg
Lowest recommended daily dose (LRDD)	0.35 mg	25 mg
Maximum recommended daily dose (MRDD)	5 mg	600 mg
Common total surface area of equipments	209076.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

$$MAR = \frac{LRDD \text{ of previous product (A)} \times SBS \text{ of next product (B)} \times SSA \times 1000 \times 1000 \times 1000}{1000 \times MRDD \text{ of next product (B)} \times TSA} = \frac{0.35 \times 14.35 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 600 \times 209076.29}$$

$$= 4.003\ \mu g/swab$$

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12	**Maximum Allowable Residual Concentration (MAR) of Norethindrone Tablet in a batch of Levonorgestrel Tablet is calculated as follows:**

Product	Norethindrone Tablets (Product A)	Levonorgestrel Tablets (Product B)
Strength	5 mg	1.5 mg
Batch size	42.00 kg	42.00 kg (Smallest batch size is 28.0 kg)
Lowest recommended daily dose (LRDD)	0.35 mg	0.03 mg
Maximum recommended daily dose (MRDD)	5 mg	1.5 mg
Common total surface area of equipments	217579.29 cm²	
Swab surface area (cm²)	100 cm²	
Safety factor	1/1000	

MAR (mcg/swab) = $\dfrac{\text{LRDD of previous product (A)} \times \text{SBS of next product (B)} \times \text{SSA} \times 1000 \times 1000 \times 1000}{1000 \times \text{MRDD of next product (B)} \times \text{TSA}}$ = $\dfrac{0.35 \times 42 \times 100 \times 1000 \times 1000 \times 1000}{1000 \times 1.5 \times 217579.29}$

= 4504.10 µg/swab

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Sr. No.	Possible product changeovers	Common surface area (Sq.cm)	MAR
1	Misoprostol-Mifepristone	134664.29	0.444 µg/swab
2	Misoprostol-Levonorgestrel	131233.29	355 µg/swab
3	Misoprostol-Norethindrone	131233.29	160 µg/swab
4	Mifepristone-Misoprostol	134664.29	3805760.23 µg/swab
5	Mifepristone-Levonorgestrel	209076.29	223204.01 µg/swab
6	Mifepristone-Norethindrone	209076.29	100441.8 µg/swab
7	Levonorgestrel-Misoprostol	131233.29	4686.31 µg/swab
8	Levonorgestrel-Mifepristone	209076.29	0.343 µg/swab
9	Levonorgestrel-Norethindrone	217579.29	115.81 µg/swab
10	Norethindrone-Misoprostol	131233.29	54673.62 µg/swab
11	Norethindrone-Mifepristone	209076.29	4.003 µg/swab
12	Norethindrone-Levonorgestrel	217579.29	4504.10 µg/swab

Limit to follow:

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Calculate the final results for residual contamination using following formula:

Amount of API in ppm =

$$\frac{\text{Analyte area from swab x Weight of standard x 2 x 5 (solution taken for swab) x Potency x 1000}}{\text{Average area of standard x 100 x 100 x 1 x 100 x Recovery factor (0.89)}}$$

Conclusion:_____
_____
_____
_____
_____
_____

Checked By:
(Signature/Date)

Verified By:
(Signature/Date)

Approved By:
(Signature/Date)