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Process Validation of Erythromycin Estolate Tablets IP 500 mg (Eltocin-DS)

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ABSTRACT:

The purpose of this process validation (Process performance Qualification) of the Erythromycin Estolate Tablets IP 500 mg is to establishing documented evidence to ensure that the process is feasible and to demonstrate that the product is producing a product meeting its predetermined process parameter requirements as per predefined product and quality attribute by collection and evaluation of the data from the manufacturing of tablets specification. During the work critical material attributes, critical process parameters are checked and controlled to achieve the desired critical quality attributes. The three consecutive batches are taken to validate the process. The manufacturing of the batch is done through wet Granulation technology.

1. Introduction:

Process Performance Qualification is establishing Confidence that the process is effective and reproducible. It is a documented evidence which provides a high degree of assurance that specified process will consistently producing a product which meeting its predetermined specification and quality characteristic of the product. In this all established limits of the critical process parameters are valid and satisfactory products can be are produced even under the worst condition. It is a lifecycle approach which undergo the through the various stages.

1) Process Design
2) Process Qualification
3) Continued process verification

A. Steps of process validation -

a. Process Design: The engaged manufacturing purpose is defined.
b. Process Qualification: To study the facts to determine whether the processes meet its reproducibility.
c. Process Verification: Ongoing assurances that all processes remain in a state of control.

B. Good manufacturing practices GMP requirements for Process Design

- Design of building
- Design of asset
- Design of Production
- Design of Laboratory
- Propose unit operations and operating parameters that need to be planned.
- Recognize sources of distribution of each unit operation is likely to experience.
- It will Considered possible range of variability for input in the operation.
- Determine process steps.
- Select process steps and variables for test in representative way.
- Development studies to evaluate critical operation points.
- Designed experiments
- Lab scale, pilot scale, full-scale experimental batches to gain process evaluation.
- Determine mechanisms to limit or control variation based on previous data
- Aim for a "robust process", i.e., one that can allow input variability and still produce consistent reasonable output.

C. Types of Validation

- Prospective validation
- Concurrent Validation
- Retrospective Validation
- Revalidation

Prospective validation: The objective of the prospective validation is to justifie or explain that the process will work according validation protocol prepared for the pilot production purpose. Prospective validation should complete before distribution and sale of the product. In Prospective Validation, protocol is executed before process is put into commercial use. During the product beginning phase, the production processing should be broken down into individual parts. Each process will be evaluated on the basis of experience or theoretical considerations to determine critical process parameter that may affect the quality of the finished product. A series of experiments should be designed to determine the criticalityof these factors. Each experiment should be pre-planned and fully documented in an authorized protocol.

Concurrent **validation:** It is a process where current production batches are used to monitor processing parameters. It gives present batch being studied, and provide limited assurance regarding standard of quality from batch to batch. Concurrent Validation means establishing documented evidence a process does whatit is supposed to base on data generated during actual implementation of the process. Concurrent validation is a

practical approach under certain facts. It has a great value in these cases when the systems and equipment to be used which have been validated before.

Retrospective validation: Conducted for a product which was already being marketed, and is based on previous data accumulated over several lots and over time. Retrospective Validation used for previous products which was not validated at the time that they were first marketed, and which is now to be validated for the requirements of division 2, Part C of the Regulatory Food and Drug Act.1940. Retrospective Validation can be allowed for well-established detailed processes and will be not suitable where there have recently changes in the formulation of the products, operating procedures, equipment and facility

Revalidation: Re-validation is usually performed to the confirmation of initial validation for a Periodic review. Re-validation provides the facts that change in a process that are introduced. Do not adversely affecting the process quality and product quality standard. Documentation required for the initial phase of validation of process. Re-validation becomes needed at a particular time.

Keywords: Process Validation, Process Performance Qualification, Design space, Critical material attributes, Critical Process Parameters, Critical Quality Attributes, Carbamazepine, Qualification of Equipment's and Extended Release.

A. Material and Method:

Material used: Erythromycin Estolate

A.1 Product Details:

Product Name: Eltocin-DS
Generic Name: Erythromycin Estolate Tablets IP 500 mg

B.1 Equipment Detail:

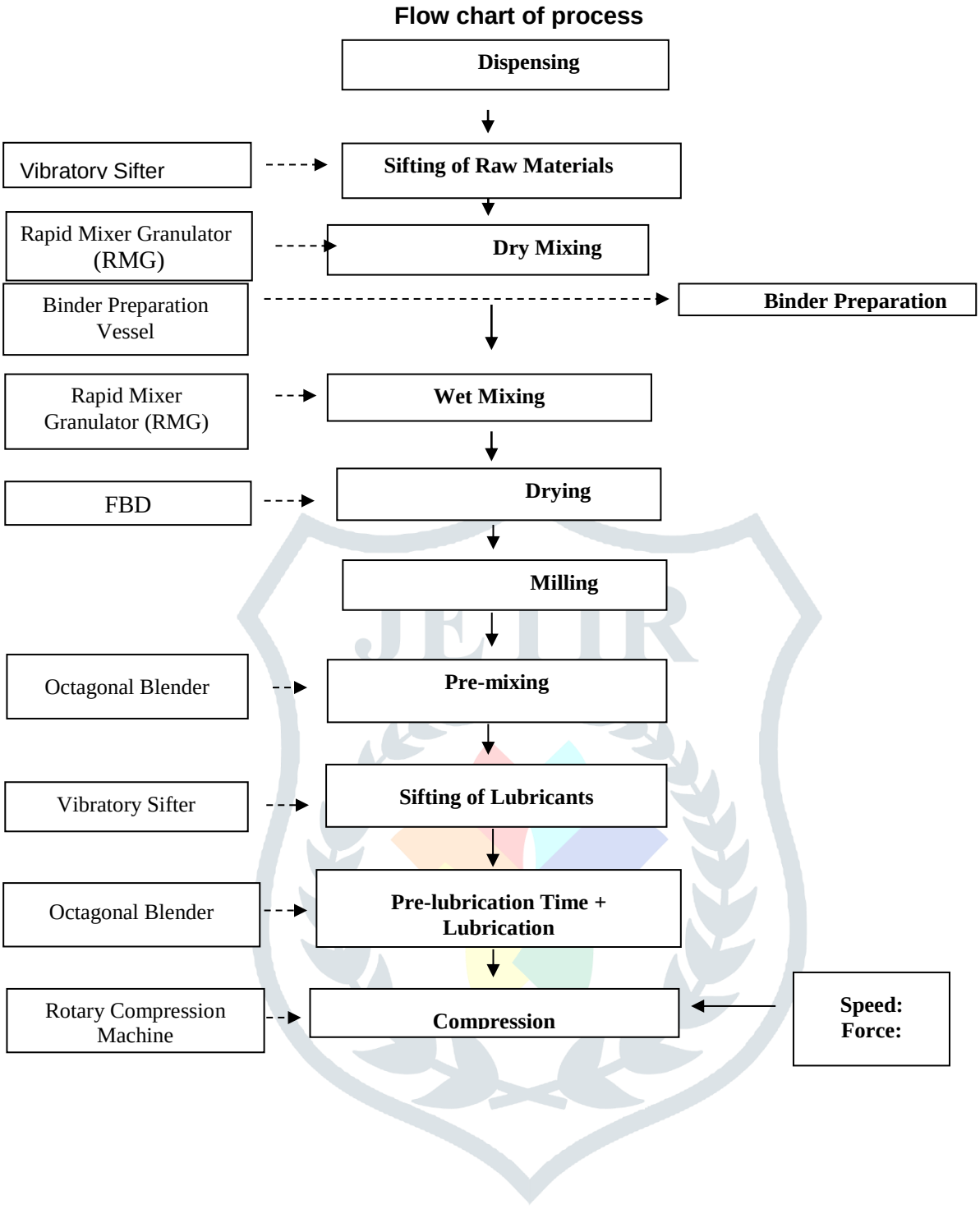
S.no.	Equipment
1	Vibro Shifter
2	Multi mill
3	Rapid Mixer Granulator RMG
4	Fluid Bed Dryer FBD
5	Octagonal blender
6	Compression machine
7	Deduster machine
8	Metal detector
9	Blister machine

0.2 Method:

Three consecutive batches for process validation of the product Erythromycin estolate tablet IP 500 mg shall be manufactured as per pre-approved master batch manufacturing data record and shall be tested as per approved standard testing procedure to prove compliance with the approved collective information.

Three validation batches were manufactured and packed and details as:

Sr. No.	Generic Name	B.No.	B. Size
1.	Erythromycin estolate tablet IP 500 mg	A22	**18.0 lac**
2.	Erythromycin estolate tablet IP 500 mg	B22	**18.0 lac**
3.	Erythromycin estolate tablet IP 500 mg	C22	**18.0 lac**



Manufacturing Process: -

Stage: Dry Mixing

A. Sifting of raw material:

1. Shift the dispensed the material Erythromycin through 12 #, Starch 100#, Tribasic Calcium phosphate through #40 & Maize starch through100# no. Sieve lot wise
2. Dry mix the materials at slow speed for 10 min in RMG.
3. Record the observation.
4. After mixing, QA withdraw the sample from 10 different locations for assay analysis, BD, TD and sieve analysis.

B. Binder Preparation:

1. Transfer 38.00 Ltr. boiled water and cool to 80-85°C in a Paste preparation vessel.
2. Add polyvinyl pyrrolidone & starch and disperse under continuous stirring.
3. Record the observations.

C. Granulation:

1. Transfer the material in granulation area.
2. Load the material into RMG.
3. Mix the material at slow speed for 10 min.
4. Add the binder paste into RMG at slow speed, Mix at slow speed.
5. Rinse the binder vessel with purified water.
6. Continue mixing at fast speed impeller, Run the chopper at high speed so as to prevent the lumps formation as and when required.
7. Record the observations.

D. Drying:

1. Load the wet mass of both lot wise in the FBD bowl and dry in FBD.
2. Dry the granules at ambient temperature for 10 min, rake the mass of bowl. Then dry at 50 – 60^0C inlet temperature intermediate raking to obtain LOD between 2.5 –3.5% w/w.
3. Note down the observation.
4. In case LOD is not within limits, continue drying or add moisture, as the case may be to bring the LOD with in Limit.

E. Sifting & Sizing of granules:

1. Sift the dried material through Sifter cum comill /multi mill.
2. Note down the observation.

F. Lubrication

Load all lubricants except Magnesium Stearate and mix for 20 min.

1. Add sifted Magnesium Stearate into the Blender mix 3 minutes.

2. QA withdraw the sample according the sampling plan.

G. Compression:

Set the Compression Machine on following parameter and compressed the tablet

S. No.	Tablet Parameter	Set value
1	**Appearance**	White, Capsule shaped biconvex uncoated tablets with monogram ELTOCIN DS, embossed on the other side
2	**Average weight**	910 mg ±5 %
4	**Uniformity of weight**	Within ± 5.0% of Average weight.

5	**Diameter**	**Length**	19.0mm ± 0.20mm
		Width	9.00 mm ± 0.20mm
6	**Thickness**		6.60-7.20 mm
7	**Hardness**		3.0 – 8.0 Kg/Cm2
8	**Friability**		NMT 1.0 % w/w
9	**Disintegration**		NMT 10 minutes

H. Blister Packing Machine setting and operation details:

1. Minimum speed, Minimum Temperature.
2. Minimum speed, Maximum Temperature.
3. Maximum speed, Minimum Temperature.
4. Maximum speed, Maximum Temperature

Assessment of Manufacturing Process

A. Dry mixing parameters

BATCH NO.	DURATION	IMPELLER SPEED	CHOPPER SPEED
A22	10 MIN.	NA	SLOW
B22	10 MIN.	NA	SLOW
C22	10 MIN.	NA	SLOW

B. Wet mixing parameters

BATCH NO.	IMPELLER DETAILS	CHOPPER DETAILS	Ampere Load
	SPEED	**SPEED**	
A22	SLOW	FAST	**8.6 Amp**
B22	SLOW	FAST	**9.5 Amp**
C22	SLOW	FAST	**8.8 Amp**

C. Dry mixing Analytical result

Sampling location	Limit:					
	BATCH NO. A22		BATCH NO. B22		BATCH NO. C22	
	Lot No.	Result	Lot No.	Result	Lot No.	Result
Top (Left)	**DMTLA22**	99.32	**DMTLB22**	102.81	**DMTLC22**	104.05
Top (Rear)	**DMTRA22**	102.39	**DMTRB22**	103.32	**DMTRC22**	101.89
Top (Front)	**DMTFA22**	101.06	**DMTFB22**	100.45	**DMTFC22**	103.05
Top (Right)	**DMTRA2**	101.44	**DMTRB22**	100.40	**DMTRC2**	100.06

	2				**2**	
Middle (Left)	**DMMLA22**	103.83	**DMMLB22**	101.15	**DMMLC22**	103.78
Middle (Right)	**DMMRA22**	103.62	**DMMRB22**	99.45	**DMMRC22**	101.12
Bottom (Left)	**DMBLA22**	101.60	**DMBLB22**	98.86	**DMBLC22**	98.62
Bottom (Rear)	**DMBRA22**	103.44	**DMBRB22**	98.55	**DMBRC22**	103.40
Bottom (Front)	**DMBFA22**	100.55	**DMBFB22**	97.62	**DMBFC22**	99.54
Bottom (Right)	**DMBRA22**	102.44	**DMBRB22**	102.67	**DMBRC22**	101.81
Average	**Not Applicable**	**101.969**	**Not Applicable**	**100.528**	**Not Applicable**	**101.732**
%RSD NMT 5.0%		**1.42%**		**1.94%**		**1.84%**

DMTL denotes dry mix samples at top left,
DMRR denotes dry mix sample at top rear

D. Drying

Drying Parameters and Test results as follows

Stage	Observation		
Drying	**B. No. A22**	**B. No. B22**	**B. No. C22**
Total Drying Time (.....mins.)	**11 min**	**11 min.**	**11 min.**
Inlet Temp of FBD.....^{0}C	54^0C	54^0C	54^0C
Outlet Temp of FBD.....^{0}C	**NA**	**NA**	**NA**

Analytical test result

	Limit 2.5-3.5%					
	BATCH NO. A22		BATCH NIO. B22		BATCH NO. C22	
	Lot No.	Result	Lot No.	Result	Lot No.	Result
Sampling Location	DGLA22	2.5%	DGLB22	3.0%	DGLC22	3.1%
	DGRA22	2.8%	DGRB22	2.5%	DGRC22	2.8%
	DGCA22	3.0%	DGCB22	2.8%	DGCC22	2.7%
	DGFA22	2.9%	DGFB22	2.8%	DGFC22	3.0%
	DGBA22	3.0%	DGBB22	3.0%	DGBC22	3.0%

Note: DGL denotes dry Granules left sample

E. Lubrication:

Lubrication Parameters and Test results as follows:

Sampling location	LUBRICATION SAMPLE					
	Batch No: A22		Batch No: B22		Batch No: C22	
	Sample No	Result	Sample No	Result	Sample No	Result
Top (Left)	LGTLA22	104.86	LGTLB22	100.42	LGTLC22	100.48
Middle (Left)	LGMLA22	101.75	LGMLB22	101.51	LGMLC22	103.63
Bottom (Left)	LGBLA22	100.22	LGBLB22	102.17	LGBLC22	101.17
Top (Rear)	LGTRA22	101.98	LGTRB22	100.97	LGTRC22	99.77
Bottom (Rear)	LGBRA22	101.76	LGBRB22	99.62	LGBRC22	98.67
Top (Front)	LGTFA22	100.24	LGTFB22	103.63	LGTFC22	102.96
Bottom (Front)	LGBFA22	102.73	LGBFB22	99.57	LGBFC22	101.85
Top (Right)	LGTRA22	104.34	LGTRB22	99.18	LGTRC22	103.51
Middle (Right)	LGMRA22	102.06	LGMRB22	102.45	LGMRC22	101.39
Bottom (Right)	LGBRA22	104.41	LGBRB22	101.98	LGBRC22	103.32
Average	NA	102.43	NA	101.15	NA	101.67
%RSD:	NA	1.61%	NA	1.43%	NA	1.67%

Observation:

F. COMPRESSION TABLET PARAMETER

TABLET PARAMETER	**SETTING REQUIRED**	**0BSERVED VALUE**		
BATCH NO.		**A22**	**B22**	**C22**
APPEARANCE	**COMPLIES**	Complies	Complies	Complies
AVERAGE WEIGHT OF TABLETS	**910 mg±5%**	908.2mg	911.2mg	909.5mg
UNIFORMITY WEIGHT	**Within ±5% of average weight**	-1.3% +1.5%	-1.2% +1.4%	-1.8% +2.0%
DIAMETER	**19.0 mm±0.20mm**	18.8mm-19.2mm	18.8mm-19.2mm	18.8mm-19.2mm
THICKNESS	**6.60-7.20mm**	6.68mm-6.74mm	6.66mm-6.71mm	6.65mm-6.75mm
HARDNESS	**3.0-8.0 kg/cm2**	4.0-5.0 kg/cm2	4.0-5.5kg/cm2	4.0-6kg/cm2
FRIABILITY	**NMT 1.0 %w/w**	0.4%	0.4%	0.4%
DISINTEGRATION	**NMT 10 minutes**	2’33’’	3.07’’	3’22’’

1. In-process test results for composite sample (Compressed Tabs) analysis:

Batch No.: A22		Specification:		
Test	Acceptance Criteria	Observation		
Appearance	**White, Capsule shaped biconvex uncoated tablets with monogram ELTOCIN DS, embossed on the other side**	Complies		
Identification	By TLC- The RF value of the principal spot obtained from the test solution corresponds to that obtained from the Standard mixture.	Complies		
Average weight	**910 mg ± 5.0%**	911.0mg		
Uniformity of weight	**Within ±5% average weight.**	-1.2% +1.6%		
Dimension	19.0 ± 0.20mm	19.0mm		
Thickness	6.60-7.20 mm	6.70mm		
Hardness	NLT 3.0 Kg/Cm2	4.0kg/cm2		
Disintegration Test	**NMT 10 Min.**	02- 03min.		
Friability	**NMT 1.0%**	0.4%		
Assay:	**NLT 90.0% & NMT 120.0% of LA**	98.2%		
Total bacterial count	**NMT 1000 CFU / g**	545CFU/g	488CFU/g	501CFU/g
Mould & Yeast	**NMT 100 CFU / g**	65cfu/g	71cfu/gm	49cfu/g
Pathogen	**Absent /g**	Absent	Absent	Absent
		Initial	**Middle**	**End**

H. In-process test results for composite sample (Compressed Tabs) analysis:

Batch No.: B22		Specification:
Test	Acceptance Criteria	Observation
Appearance	**White, Capsule shaped biconvex uncoated tablets with monogram ELTOCIN DS, embossed on the other side**	Complies
Identification	By TLC- The RF value of the principal spot obtained from the test solution corresponds to that obtained from the Standard mixture.	Complies
Average weight	**910 mg ± 5.0%**	911.8mg
Uniformity of weight	**Within ±5% average weight.**	-1.4% +2.0%

Dimension	19.0x 9.0 mm ± 0.20mm	19.1mm		
Thickness	6.60-7.20 mm	6.75mm		
Hardness	NLT 3.0 Kg/Cm2	4.0kg/cm2		
Disintegration Test	**NMT 10 Min.**	02- 03min.		
Friability	**NMT 1.0%**	0.3%		
Assay:	**NLT90.0% & NMT 120.0% of LA**	99.4%		
Total bacterial count	**NMT 1000 CFU / g**	443cfu /g	351cfu/ g	401cfu/ g
Mould & Yeast	**NMT 100 CFU / g**	25cfu/ g	33cfu/g	30cfu/g
Pathogen	**Absent /g**	Absent	Absent	Absent
		Initial	**Middle**	**End**

I. In-process test results for composite sample (Compressed Tabs) analysis:

Batch No.: C22		Specification:
Test	Acceptance Criteria	Observation
Appearance	**White, Capsule shaped biconvex uncoated tablets with monogram ELTOCIN DS, embossed on the other side**	Complies
Identification	By TLC- The RF value of the principal spot obtained from the test solution corresponds to that obtained from the Standard mixture.	Complies
Average weight	**910 mg ± 5.0%**	912.2mg
Uniformity of weight	**Within ±5% average weight.**	-1.0% +1.6%
Dimension	19.0x 9.0 mm ± 0.20mm	19.0mm
Thickness	6.60-7.20 mm	6.71mm
Hardness	NLT 3.0 Kg/Cm2	4.0kg/cm2
Disintegration Test	**NMT 10 Min.**	02- 03min.
Friability	**NMT 1.0%**	0.5%
Assay:	**NLT 90.0% & NMT 120.0% of LA**	99.8%

Total bacterial count	**NMT 1000 CFU / g**	333cfu /g	354cfu/ g	289cfu/ g
Mould & Yeast	**NMT 100 CFU / g**	22cfu/ g	20cfu/g	28cfu/g
Pathogen	**Absent /g**	Absent	Absent	Absent
		Initial	**Middle**	**End**

j. Blister packing machine

Batch No.		**Minimum Speed**	**Minimum Temperature**	**Maximum Temperature**
A	**A22**	**13 Cycle/min**	**156 °C**	**165°C**
B	**B22**	**12 Cycle/min**	**155 °C**	**163°C**
C	**C22**	**13 Cycle/min**	**155 °C**	**164°C**
		Maximum Speed	**Minimum Temperature**	**Maximum Temperature**
A	**A22**	**22 Cycle/min**	**168 °C**	**173°C**
B	**B22**	**20 Cycle/min**	**164 °C**	**171°C**
C	**C22**	**20 Cycle/min**	**165 °C**	**170°C**

K	**Environmental Control:**					
B.no	**Granulation**		**Compression**		**Packing**	
	Temp.: -	R.H.: -	Temp.: -	R.H.: -	Temp.: -	R.H.: -
A22	23.4°C	44%	20.2 °C	34%	22 °C	40%
B22	22.9°C	40%	25 °C	43%	22 °C	44%
C22	24 °C	41%	23.1°C	26%	25.4 °C	55%

L	**Batch Yield at Various Stages:**		
B.No.	**Granulation**	**Compression**	**Packing**
	Limit: -96-101%	**Limit: -96-100%**	**Limit: -93-98%**
A22	99.16%	98.39%	96.01%
B22	98.85%	98.86%	96.82%
C22	99.15%	99.22%	97.79%

M. Conclusion:

The validation batches of Eltocin DS tablet were manufactured as per approved Batch manufacturing Record. All required validation activities were completed, and results are compiled in this report. During validation study critical process parameters were monitored as All the In-process test parameters were found well within the specified limit. There is no change in method of manufacturing followed during manufacturing of all these validation batches. No anomaly was noted with respect to the testing parameters of all these batches when tested using the approved specification. This interim validationreport proves that the manufacturing process of Eltocin DS tablet and is consistent and meets the predetermined specifications and required quality attributes and based on the interim report this batch canbe release for marketing and distribution.

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