ISHA'S GMP CONSULTANCY PVT. LTD.
Ensuring Global GMP Compliance™ ®

DAPAGLIFLOZIN

API MASS BALANCE | FOUR-STAGE MANUFACTURING

Consolidated from both workbook sheets • Source-faithful technical review • Not an approved GMP record

100.00 kg	500 kg	4
FINAL API OUTPUT	SUMMARY BATCH REFERENCE	MANUFACTURING STAGES

WORKBOOK PROCESS ROUTE

STAGE 1 Reaction • Isolation — 184.60 kg intermediate

STAGE 2 Reaction • Separation — 231.36 kg intermediate

STAGE 3 Reaction • Purification — 143.16 kg intermediate

STAGE 4 Reaction • Isolation — 100.00 kg final API

STAGE 1

Reaction • Extraction • Crystallisation • Filtration • Drying

RECORDED INPUT **15,646.00 kg** RECORDED OUTPUT **15,646.03 kg**

MATERIALS IN	kg
2-Chloro-5-bromo-4′-ethoxy-diphenylmethane	174.95
2,3,4,6-tetra-O-trimethylsilyl-D-gluconolactone	250.81
Tetrahydro Furan	1,753.89
Heptane	1,271.57
s-BuLi (12 % solution in cyclohexane)	338.35
Water	2,192.36
Methyl tertiary butyl ether	511.55
Sodium chloride (30% solution in water)	511.55
Methanol	1,461.58
Methane sulphonic acid	25.14
Triethyl amine	36.39
Ethyl acetate	2,192.36
Toluene	540.78
Heptane	4,384.73

MATERIALS OUT	kg
Effluent water with inorganic salt	2,996.08
Tetrahydro Furan Recovery	1,666.20
Tetrahydro Furan Loss	87.69
Cyclohexane recovery	277.70
Cyclohexane Loss	20.02
Heptane Recovery	1,209.14
Heptane Loss	62.43
Methyl tertiary butyl ether Recovery	482.32
Methyl tertiary butyl ether Loss	29.23
Methanol Recovery	1,388.50
Methanol Loss	73.08
Ethyl acetate Recovery	2,075.44
Ethyl acetate Loss	116.93
Toluene Recovery	511.55
Toluene Loss	29.23
Heptane Recovery	4,169.46
Heptane Loss	215.27
Organic Residue Impurities	51.16
Stage - 1	184.60

STAGE 2

Reaction • Extraction • Layer separation • Distillation

RECORDED INPUT **4,989.66 kg** RECORDED OUTPUT **4,989.70 kg**

MATERIALS IN	kg
Stage-1	184.60
Tetrahydro furan	922.99
diisopropyl ethyl amine	401.19
Acetic anhydride	281.20
Methyl tertiary butyl ether	1,292.18
Water	922.99
Phophoric acid (10% solution in water)	369.19
Sodium bicarbonate (10% solution in water)	369.19
Sodium chloride (30% solution in water)	246.13

MATERIALS OUT	kg
Effluent water with inorganic salt	2,519.13
Tetrahydro furan Recovery	876.84
Tetrahydro furan loss	46.15
Methyl tertiary butyl ether Recovery	1,230.65
Methyl tertiary butyl ether Loss	61.53
organic residue impurities	24.00
Stage-2	231.36

STAGE 3

Reaction • Extraction • Carbon treatment • Isolation

RECORDED INPUT **5,478.79 kg** RECORDED OUTPUT **5,478.79 kg**

MATERIALS IN	kg
Stage-2	231.36
Acetonitrile	1,154.50
Triethylsilane	140.39
Water	6.93
Boron trifluoride etherare	108.06
Methyl tertiary butyl ether	1,431.58
Sodium bicarbonate (10% solution in water)	1,357.69
Sodium chloride (30% solution in water)	415.62
Charcoal	23.09
Ethanol	609.58

MATERIALS OUT	kg
Effluent water with inorganic salt	2,038.38
Acetonitrile Recovery	1,096.77
Acetonitrile Loss	57.72
Methyl tertiary butyl ether recovery	1,362.31
Methyl tertiary butyl ether Loss	69.27
Charcoal solid waste	23.09
Ethanol recovery	577.25
Ethanol Loss	32.33
Organic residue impurities	78.51
Stage-III	143.16

STAGE 4

Reaction • Layer separation • Distillation • Final API

RECORDED INPUT **5,365.79 kg** RECORDED OUTPUT **5,365.79 kg**

MATERIALS IN	kg
Stage-III	143.16
Tetrahydro furan	842.11
Methanol	1,263.16
Water	421.05
Lithium hydroxide	12.11
Ethyl acetate	1,578.95
Sodium chloride (30% solution in water)	1,052.63
Potassium bisulphate (5% solution in water)	52.63

MATERIALS OUT	kg
Tetrahydro furan Recovery	800.00
Tetrahydro furan Loss	42.11
Methanol recovery	1,200.00
Methanol Loss	63.16
Ethyl acetate recovery	1,500.00
Ethyl acetate Loss	78.95
Organic residue impurities	1.42
Dapagliflozin	100.00

UNRECONCILED OUTPUT STREAM: 1,580.15 kg

Listed outputs: 3,785.64 kg | Recorded output total: 5,365.79 kg

The source sheet does not identify the missing output. Verify its disposition.

TECHNICAL RECONCILIATION & DATA INTEGRITY REVIEW

REVIEW BEFORE GMP APPROVAL

01 STAGE 1 - ITEMISED
Inputs: 15,646.01 kg | Outputs: 15,646.03 kg
Reported input total: 15,646.00 kg

02 STAGE 2 - RECORDED TOTAL
Itemised output 4,989.66 kg vs reported 4,989.70 kg

03 STAGE 3 - ITEMISED
Inputs: 5,478.80 kg | Outputs: 5,478.79 kg

04 STAGE 4 - MAJOR UNRECONCILED OUTPUT
Input charges: 5,365.80 kg
Listed outputs: 3,785.64 kg | Gap: 1,580.16 kg

05 WORKBOOK CONSISTENCY
Stage 4 stated output: 5,365.79 kg
Unitemised output vs stated total: 1,580.15 kg
500 kg summary reference ≠ 100 kg final API output
Summary #REF! and ratio #DIV/0! cells need repair

Source: 10-DAPAGLIFLOZIN(1).xlsx | Sheets: Summary; DAPAGLIFLOZIN | Values reproduced as recorded; stage transfers must not be double-counted.

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