Name: _____

UFID#: _____

PHA 5127

First Exam
Fall 2013

On my honor, I have neither given nor received unauthorized aid in doing this assignment.

_____

Name

Question Set/Points

I. 30 pts

II. 20 pts

III. 20 pts

IV 15 pts

V. 25 pts

VI. 20 pts

VII. 15 pts

VIII. 20 pts

IX. 35 pts

TOTAL: 200 pts

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Question Set I (True or False)

(30 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false. Assume passive diffusion as the driving force for distribution.*

1: T (F) Assume a drug that is eliminated through metabolism. The drug's plasma concentration decreases by 2 ng/ml every 2 hours. This is a first order process.

2: T (F) Assume a drug eliminated through enzymatic metabolism. The drug's plasma concentration decreases by 2 ng/ml every 2 hours. The elimination rate constant describing this metabolism will be unit-less

3: (T) F The rate with which a lipophilic drug of low molecular weight that is not an acid nor a base is taken up by tissues will significantly be related to the blood flow through those tissues.

4: T (F) The rate with which a lipophilic drug that is not an acid nor a base is taken up by brain and liver tissue is likely to be similar, as the drug will be able to cross membranes in both tissues very fast.

5: (T) F An intravenous bolus injection (iv bolus) is often given to the patient to achieve high blood concentrations immediately.

6: T (F) To prepare plasma, blood is often collected in tubes containing calcium chloride

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Question Set II (20 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false. Consider a lipophilic drug A and a protein drug (drug B, e.g. antibody). Both do not show any affinity to transporters (Ficks law applies). They both don't bind to plasma and tissue components.*

7: (T) F Drug A will enter the brain faster.

8: T (F) Drug B will be unable to enter the interstitial fluid.

9: T (F) Both drugs will have the same volume of distribution.

10: T (F) The volume of distribution of drug B will be 38L.

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Question Set III

(20 points)

11: Listed in the Table are two properties of acidic drug molecules:

- the fraction unionized at ph=7.4 and
- the partition coefficient of the unionized form.

DRUG	Fraction Unionized at pH=7.4	Partition Coefficient of Unionized form	Molecular Weight (Dalton)
1	1.0	Not determined	75,000
2	0.91	0.07	290
3	0.074	10	320
4	0.72	0.005	456

Select the correct rank order with which drugs 1-4 will enter brain tissue. Assume that the drugs are not subject to transporters at the blood-brain barrier.

A: 1 slower than 2 slower than 3 slower than 4

B: 1 slower than 3 slower than 2 slower than 4

C: 4 slower than 2 slower than 3 slower than 1

D: 4 slower than 2 slower than 1 slower than 3

(E:) None of the above

2 → 0.063

3 → 0.74

4 → 0.0036

3 > 2 > 4 > 1

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Question Set IV (True or False)

(15 points)

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false. Assume no active transport.*

Assume the same dose of penicillin G is given to patients as iv bolus injection (as solution in saline), intramuscular (i.m.) oily injection or orally.

12: T (F) Giving the drug through an i.m. injections will result in a much smaller AUC than after oral administration

13: (T) F Giving penicillin as an aqueous intravenous bolus injection will result in a higher maximum concentration

14: (T) F oily i.m. injections allow a less frequent dosing.

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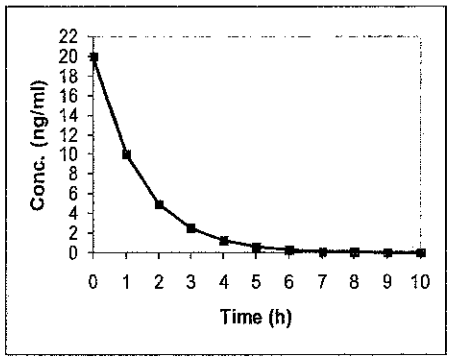
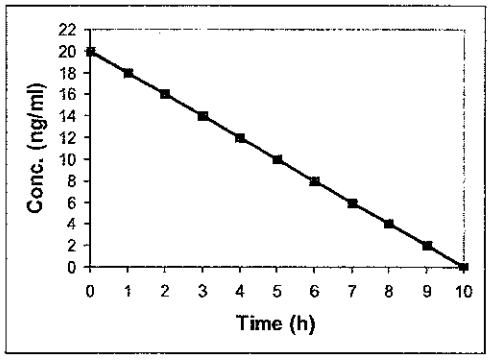
Question Set V (True or False)

(25 points)



Drug A



Drug B

True (A) or False (B). On the bubble sheet mark *A for true* or *B for false*

15: (T) F Drug A's rate of elimination is affected by the amount of drug in the body.

16: T (F) Drug B's elimination rate constant has the unit "ng/ml".

17: (T) F For Drug A, the fraction of drug eliminated per hour is constant.

18: (T) F Drug A's concentration-time profile depends on the availability of sufficient number of enzymes (no saturation of the enzymes)

19: T (F) The half-life of Drug B is 5 hours.

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Question Set VI

(20 points)

20: 200 mg of Drug A was administered to a patient through i.v bolus injection. A plasma drug concentrations of 0.78 mg/L was measured after 4 hours. A plasma drug concentration of 0.195 mg/L was measured after 8 hours. The drug's distribution is instantaneous.

Assuming a **first** order process, calculate the half-life of the drug.

A) 1 h

B) 1.5 h

C) 2 h

D) .34 h

E) None of the above

$$k_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{1.386}{4} = 0.346\ hr^{-1}$$

$$t_{1/2} = \frac{0.693}{0.346} = 1.99 \sim 2\ hr$$

21: 200 mg of Drug A was administered to a patient through i.v. bolus injection. A plasma drug concentrations of 0.78 mg/L was measured after 4 hours. A plasma drug concentration of 0.195mg/L was measured after 8 hours. The drug's distribution is instantaneous.

Assuming a **zero** order process, calculate the drug concentration after 12 hours.

A) 0 mg/L

B) 0.0975 mg/L

C) 0.0049 mg/L

D) None of the above

0.585 mg/L eliminated in 4 hr

∴ After 12 hr = 0 mg/L

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Question Set VII

(15 points)

A drug (lipophilic, unionized, low molecular weight) is showing in average a pronounced binding to plasma proteins of 99%. Between-subject variability of protein binding is pronounced. The same dose of the drug is given as an i.v. bolus injection to two patients. **Patient 1 has a much stronger plasma protein binding** for the drug (99.95%) than the second patient (99.5%) The tissue binding is identical in both the patients (90%).

Please indicate whether **patient 1** will have a larger (↑), smaller (↓) identical (↔) value than patient 2 for:

- total initial total plasma drug concentration ($\mathbf{C_0}$),
- free initial total plasma drug concentration (**free $\mathbf{C_0}$**),
- f_u
- V_d

$f_{u_T} = 0.1$

$f_{u_1} = 0.0005$

$f_{u_2} = 0.005$

22 :

A: $C_0 \uparrow$, free $C_0 \uparrow$, $f_u \downarrow$, $V_d \downarrow$

B: $C_0 \downarrow$, free $C_0 \leftrightarrow$, $f_u \downarrow$, $V_d \uparrow$

(C:) $C_0 \uparrow$, free $C_0 \downarrow$, $f_u \downarrow$, $V_d \downarrow$

D: $C_0 \uparrow$, free $C_0 \uparrow$, $f_u \uparrow$, $V_d \leftrightarrow$

E: none of above combinations.

$V_{d_1} = 3 + 38 \times \frac{0.0005}{0.1} = 3.19\,L$

$V_{d_2} = 3 + 38 \times \frac{0.005}{0.1} = 4.9\,L$

$C_{0_1} = \frac{Dose}{3.19} > C_{0_2} = \frac{Dose}{4.9}$

$f_{u_1} \cdot C_{0_1} = \frac{0.0005}{3.19} \times Dose = 0.000156 \times Dose$

$f_{u_2} \cdot C_{0_2} = \frac{0.005}{4.9} \times D = 0.00102 \times Dose$

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Question Set VIII

(20 points) Assume a drug is substrate of a specific transport protein. What of the following statements are **True (A) or False (B). On the bubble sheet mark *A for true* or *B for false***

23 T (F) Transporters do not use energy

24 T (F) Transporters only eliminate intact drugs and not metabolites from the body

25 (T) F Transporters can be the reason for drugs not able to cross the blood brain barrier.

26 (T) F The low oral bioavailability of some drugs is due to the fact that transporters prevent absorption of the drug from the GI tract.

27 T (F) Assume a membrane separating the blood stream and the GI tract. These membranes express transporters that generally prevent absorption of orally given drugs (drug that crosses membranes are pumped out again). These transporters are not relevant for the elimination of the drug when administered through intravenous bolus injection.

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Question Set IX

(35 points)

28: (T) F Free drug concentrations are assumed to be the same in plasma and tissues, when the distribution is assumed to be instantaneous.

29: (T) F Gentamycin (a small molecular weight drug) has a volume of distribution of about 18L. Assume $f_u=f_{uT}$. This drug is likely to be hydrophilic.

30: T (F) When the Vd of a drug is 700 L, This is only possible if the plasma protein binding is small.

31: T (F) A fast absorption might allow less frequent dosing.

32: (T) F A slower absorption might be advantageous for a drug with a narrow therapeutic window.

33: (T) (F) Pharmacokinetics can be used for optimizing drug therapy in a patient, as free drug concentrations in plasma and tissue are generally the same.

34: (T) F The larger the volume of distribution the smaller the starting concentration (C_o) after an i.v. bolus injection.

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Useful Pharmacokinetic Equations

Symbols

D = dose
τ = dosing interval
CL = clearance
Vd = volume of distribution
k_e = elimination rate constant
k_a = absorption rate constant
F = fraction absorbed (bioavailability)
K_0 = infusion rate
T = duration of infusion
C = plasma concentration

General

Elimination rate constant

$$k_e = \frac{CL}{Vd} = \frac{\ln\left(\frac{C_1}{C_2}\right)}{(t_2 - t_1)} = \frac{\ln C_1 - \ln C_2}{(t_2 - t_1)}$$

Half-life

$$t_{1/2} = \frac{0.693 \cdot Vd}{CL} = \frac{\ln(2)}{k_e} = \frac{0.693}{k_e}$$

Intravenous bolus

Initial concentration

$$C_0 = \frac{D}{Vd}$$

Plasma concentration (single dose)

$$C = C_0 \cdot e^{-k_e \cdot t}$$

Plasma concentration (multiple dose)

$$C = \frac{C_0 \cdot e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Peak (multiple dose)

$$C_{max} = \frac{C_0}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = \frac{C_0 \cdot e^{-k_e \cdot \tau}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Average concentration (steady state)

$$\overline{Cp}_{ss} = \frac{D}{CL \cdot \tau}$$

Oral administration

Plasma concentration (single dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(e^{-k_e \cdot t} - e^{-k_a \cdot t}\right)$$

Time of maximum concentration (single dose)

$$t_{max} = \frac{\ln\left(\frac{k_a}{k_e}\right)}{(k_a - k_e)}$$

Plasma concentration (multiple dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(\frac{e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)} - \frac{e^{-k_a \cdot t}}{\left(1 - e^{-k_a \cdot \tau}\right)}\right)$$

Time of maximum concentration (multiple dose)

$$t_{max} = \frac{\ln\left(\frac{k_a \cdot \left(1 - e^{-k_e \cdot \tau}\right)}{k_e \cdot \left(1 - e^{-k_a \cdot \tau}\right)}\right)}{(k_a - k_e)}$$

Average concentration (steady state)

$$\overline{C} = \frac{F \cdot D}{CL \cdot \tau}$$

Clearance

$$Cl = \frac{Dose \cdot F}{AUC}$$

$$Cl = k_e \cdot V_d$$

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Constant rate infusion

Plasma concentration (during infusion)

$$C = \frac{k_0}{CL} \cdot \left(1 - e^{-k_e \cdot t}\right)$$

Plasma concentration (steady state)

$$C = \frac{k_0}{CL}$$

Calculated clearance (Chiou equation)

$$CL = \frac{2 \cdot k_0}{(C_1 + C_2)} + \frac{2 \cdot Vd \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)}$$

Short-term infusion

Peak (single dose)

$$C_{max(1)} = \frac{D}{CL \cdot T} \cdot \left(1 - e^{-k_e \cdot T}\right)$$

Trough (single dose)

$$C_{min(1)} = C_{max(1)} \cdot e^{-k_e(\tau - T)}$$

Peak (multiple dose)

$$C_{max} = \frac{D}{CL \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = C_{max} \cdot e^{-k_e(\tau - T)}$$

Calculated elimination rate constant

$$k_e = \frac{\ln\left(\frac{C^*_{max}}{C^*_{min}}\right)}{\Delta t}$$

with C_{max}^* = measured peak and C_{min}^* = measured trough,
measured over the time interval Δt

Calculated peak

$$C_{max} = \frac{C^*_{max}}{e^{-k_e \cdot t^*}}$$

with C_{max}^* = measured peak, measured at time t^* after the end of the infusion

Calculated trough

$$C_{min} = C^*_{min} \cdot e^{-k_e \cdot t^*}$$

with C_{min}^* = measured trough, measured at time t^* before the start of the next infusion

Calculated volume of distribution

$$Vd = \frac{D}{k_e \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{[C_{max} - (C_{min} \cdot e^{-k_e \cdot T})]}$$

Calculated recommended dosing interval

$$\tau = \frac{\ln\left(\frac{C_{max(desired)}}{C_{min(desired)}}\right)}{k_e} + T$$

Calculated recommended dose

$$D = C_{max(desired)} \cdot k_e \cdot V \cdot T \cdot \frac{\left(1 - e^{-k_e \cdot \tau}\right)}{\left(1 - e^{-k_e \cdot T}\right)}$$

Two-Compartment-Body Model

$$C = a \bullet e^{-\alpha t} + b \bullet e^{-\beta t}$$

$$AUC_{\infty} = a / \alpha + b / \beta$$

$$Vd_{area} > Vd_{ss} > Vc$$

Creatinine Clearance

$$CL_{creat}(\text{male}) = \frac{(140 - age) \bullet weight}{72 \bullet Cp_{creat}}$$

$$CL_{creat}(\text{female}) = \frac{(140 - age) \bullet weight}{85 \bullet Cp_{creat}}$$

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL_{creat} in ml/min

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K_e for aminoglycosides

$K_e = 0.00293(CrCL) + 0.014$

Metabolic and Renal Clearance

$$E_H = \frac{Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_H = E_H \cdot Q_H = \frac{Q_H \cdot Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$F_H = \frac{Q_H}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_{ren} = RBF \cdot E = GFR \cdot \frac{C_{in} - C_{out}}{C_{in}}$$

$$Cl_{ren} = \frac{\text{rate of excretion}}{\text{plasma concentration}}$$

$$Cl_{ren} = fu \cdot GFR + \left[\frac{\text{Rate of secretion - Rate of reabsorption}}{\text{Plasma concentration}}\right]$$

$$Cl_{ren} = \frac{\text{Urine flow} \cdot \text{urine concentration}}{\text{Plasma concentration}}$$

Ideal Body Weight

Male
IBW = 50 kg + 2.3 kg for each inch over 5ft in height

Female
IBW = 45.5 kg + 2.3 kg for each inch over 5ft in height

Obese
ABW = IBW + 0.4*(TBW-IBW)

Volume of Distribution

$$V = V_P + V_T \cdot K_P$$

$$V = V_P + V_T \cdot \frac{fu}{fu_T}$$

Clearance

$$Cl = \frac{Dose}{AUC}$$

$$Cl = k_e \cdot V_d$$

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Constant rate infusion

Plasma concentration (during infusion)

$$C = \frac{k_0}{CL} \cdot \left(1 - e^{-k_e \cdot t}\right)$$

Plasma concentration (steady state)

$$C = \frac{k_0}{CL}$$

Calculated clearance (Chiou equation)

$$CL = \frac{2 \cdot k_0}{(C_1 + C_2)} + \frac{2 \cdot Vd \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)}$$

Short-term infusion

Peak (single dose)

$$C_{max(1)} = \frac{D}{CL \cdot T} \cdot \left(1 - e^{-k_e T}\right)$$

Trough (single dose)

$$C_{min(1)} = C_{max(1)} \cdot e^{-k_e (\tau - T)}$$

Peak (multiple dose)

$$C_{max} = \frac{D}{CL \cdot T} \cdot \frac{\left(1 - e^{-k_e T}\right)}{\left(1 - e^{-k_e \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = C_{max} \cdot e^{-k_e (\tau - T)}$$

Calculated elimination rate constant

$$k_e = \frac{\ln\left(\frac{C^*_{max}}{C^*_{min}}\right)}{\Delta t}$$

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measured over the time interval Δt

Calculated peak

$$C_{max} = \frac{C^*_{max}}{e^{-k_e \cdot t^*}}$$

with C_{max}^* = measured peak, measured at time t^* after the end of the infusion

Calculated trough

$$C_{min} = C^*_{min} \cdot e^{-k_e \cdot \tau^*}$$

with C_{min}^* = measured trough, measured at time t^* before the start of the next infusion

Calculated volume of distribution

$$Vd = \frac{D}{k_e \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{[C_{max} - (C_{min} \cdot e^{-k_e \cdot T})]}$$

Calculated recommended dosing interval

$$\tau = \frac{\ln\left(\frac{C_{max(desired)}}{C_{min(desired)}}\right)}{k_e} + T$$

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$$D = C_{max(desired)} \cdot k_e \cdot V \cdot T \cdot \frac{\left(1 - e^{-k_e \cdot \tau}\right)}{\left(1 - e^{-k_e T}\right)}$$

Two-Compartment-Body Model

$$C = a \bullet e^{-\alpha t} + b \bullet e^{-\beta t}$$

$$AUC_{\infty} = a / \alpha + b / \beta$$

$$Vd_{area} > Vd_{ss} > Vc$$

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$$CL_{creat}(\text{male}) = \frac{(140 - age) \bullet weight}{72 \bullet Cp_{creat}}$$

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With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL_{creat} in ml/min

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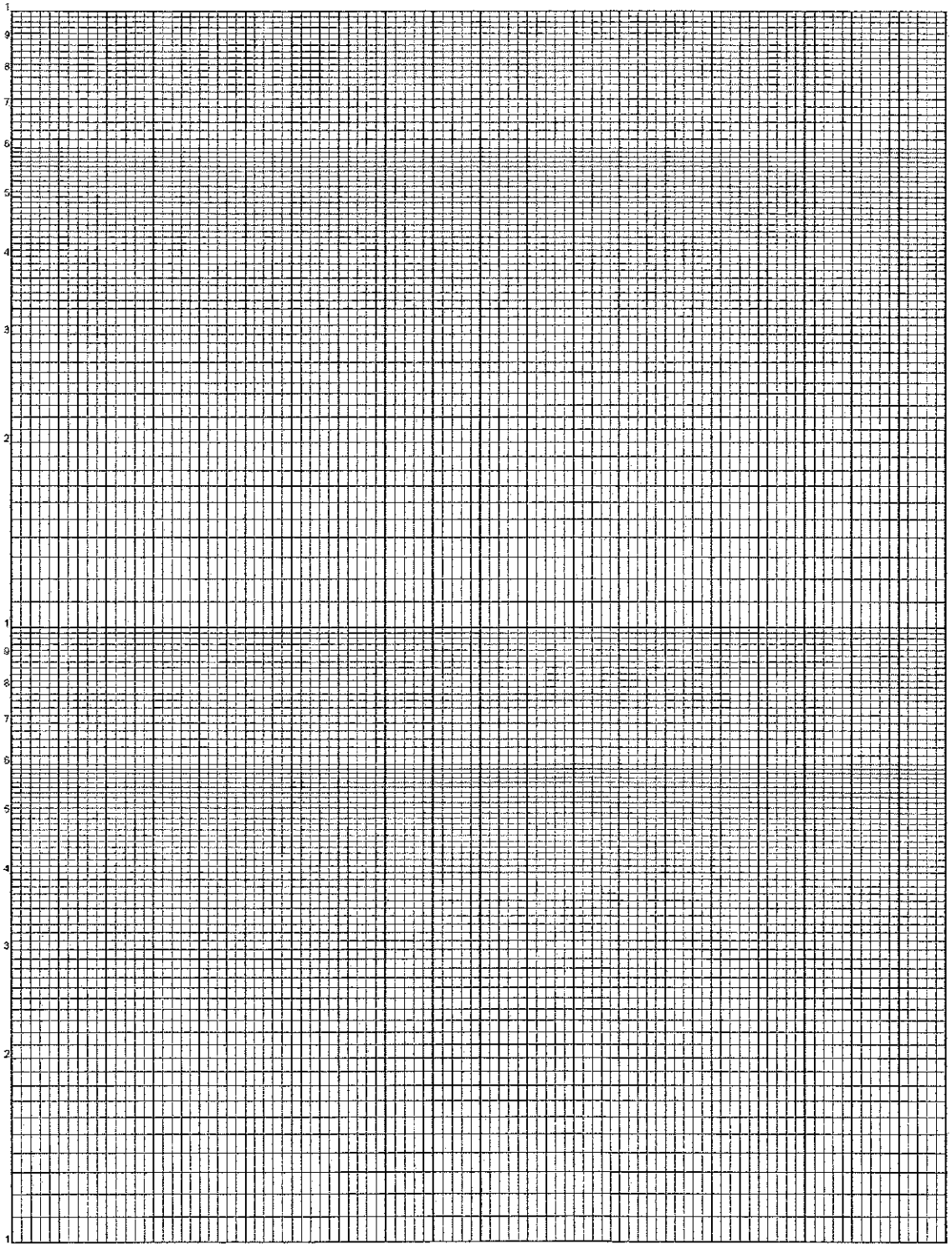

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