Name: _____

UFID#: _____

PHA 5127

First Exam
Fall 2008

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. 15 pts

IV 15 pts

V. 15 pts

VI. 25 pts

VII. 10 pts

VIII. 10 pts

IX. 10 pts

TOTAL: 150 pts

Name: _____

UFID#: _____

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 form for distribution.*

1: T F The value of V_t is the same for all drugs (38 L)

2: T F The value of V_p is the same for all drugs (3L)

3: T F For a drug that binds to a high affinity-low capacity binding protein in plasma, the f_u and the volume of distribution might depend on the dose of the drug.

4: T F Assume two drugs (identical molecular weight, same dose given): one neutral drug (Drug A) and one acidic drug (pka=7.4, Drug B). Drug A and the unionized form of drug B have the same partition coefficient. The fraction unbound in plasma and tissue is 0.5 for both drugs. Drug B will enter tissues somewhat slower than drug A

5: T F A weak acid, whose unionized form shows a high partition coefficient is likely to cross most membrane barriers.

6: T F A volume of distribution of 41 L for a lipophilic drug, suggest that the drug will not bind to tissue and plasma proteins.

Name: _____

UFID#: _____

Question Set II (20 points) True (A) or False (B). On the bubble sheet mark *A for true* or *B for false.*

What could be possible reasons for babies having often a smaller volume of distribution (expressed in L) for lipohilic drugs than adults. Assume for this question that plasma protein binding is the same in babies and adults. What statements might explain this finding

7: T F The term V_t is smaller in babies than in adult

8: T F The term V_p is smaller in babies than in adult

9: T F Transporters pumping the drug into the tissues are more active in babies

10: T F Assuming that adults have more fat tissue, this fact could explain it.

Name: _____

UFID#: _____

Question Set III

(15 points)

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

- the fraction ionized and
- the partition coefficient of the unionized form.

	Fraction unionized at pH 7.4	Partition coefficient
Drug A	0.5	2
Drug B	0.2	0.001
Drug C	1	0.0001
Drug D	1	3

Select the drug(s) (A, B, C, or D) that fits best (selection of 1-4 drugs is possible)

11: Drug ……... will cross well built membranes the fastest.

12: Drug ……. …….will cross well built membranes the slowest

13: In areas of the body were membranes are extremely thin and larger aqueous pores exist, drug(s) …….. will be taken up with about the same rate.

Name: _____

UFID#: _____

Question Set V (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.*

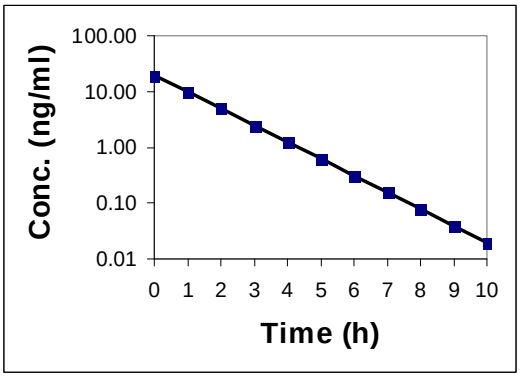
14:	T	F	Compared to skin, liver would have a higher rate of uptake for small lipophilic drugs due to its higher blood flow rate.
15:	T	F	The rate with which hydrophilic compounds will move across well-built membranes will depend on the plasma protein binding of this drug.
16:	T	F	Perfusion limited distribution is a type of drug distribution into tissue that occurs for drugs and tissues with high permeability.

Name: _____

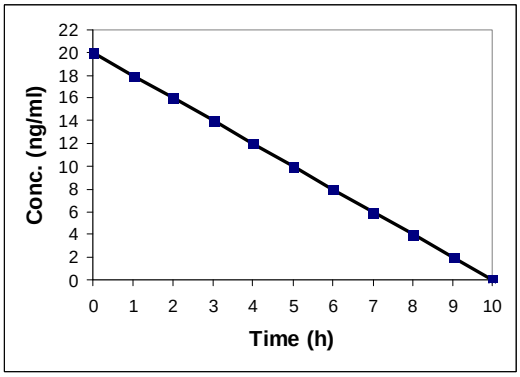
UFID#: _____

Question Set VI (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*

17:	T	F	Drug A's rate of elimination depends on the amount of drug in the body
18:	T	F	Drug B's rate of elimination is constant
19:	T	F	In Figure B, the fraction of drug eliminated per hour is constant.
20:	T	F	Drug B's behavior might be explained with saturated metabolic enzymes.
21:	T	F	For both drugs, the model assumes that drug distribution does not take any time.

Name: _____

UFID#: _____

Question Set VII

(10 points)

22: A 25 yr old, 70 kg male patient with gram-negative pneumonia, was being treated with gentamicin. Gentamicin had been given as an iv bolus (2 mg/kg). Two samples were taken after dosing, and data is shown as following:

Time (h)	Concentration (mg/L)
4	5.0
10	1.0

Calculate the $AUC_{0-\infty}$. (Assume first-order elimination for gentamicin)

A: 31mg/L*hr

B: 61 mg/L*hr

C: 20 mg/L*hr

D: 9.0 mg/L*hr

E: none of the above

23: Calculate the half-life of this drug

A: 2.6 hr

B: 3.0 hr

C: 2.1 hr

D: 9.0 hr

E: none of the above

Name: _____

UFID#: _____

Question Set VIII

(5 points)

24: **A 100 mg dose** of a drug was administered to **patient 1** by IV bolus injection. **A 200 mg dose** of the same drug was administered to **patient 2** by IV bolus injection. For patients A and B, the initial concentrations were 1.25mg/L and 2.5mg/L, respectively. This drug follows a one-compartment body model, crosses membranes easily, distributes well into all tissues, and is around 50% bound to plasma proteins. Why is the initial plasma concentration different for these two patients?

A Patient B has more fat tissue than Patient A.

B: Plasma unbound fraction in Patient B is higher than that in Patient A.

C: Tissue unbound fraction in Patient B is higher than that in Patient A.

D: Patient B has larger volume of distribution than Patient A.

E: None of Above

Name: _____

UFID#: _____

Question Set IX

(10 points)

If we know that the plasma drug concentration just after a gentamycin dose was given is 12.8 mg/L and the half live is 3.46 hours, what is the concentration after 9 hours**. Assume that the result will be between 1.0 and 9.9.mg/L.**

25: Mark A, B, C, or D, if the number **before** the decimal point is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case*

26 Mark A, B, C, or D,, if the number **before** the decimal point is 6 (A), 7(B), 8(C), 9(D), *Leave blank if this is not the case*

27 Mark A, B, C, or D, if the number **after** the decimal point is 1 (A), 2(B), 3(C), 4(D), 5(E). *Leave blank if this is not the case*

28 Mark A, B, C, or D, if the number **after** the decimal point is 6 (A), 7(B), 8(C), 9(D), **0 (E**) *Leave blank if this is not the case*

Name: _____

UFID#: _____

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

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

$$Cl = k_e \cdot V_d$$

Name: _____

UFID#: _____

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)

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

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)

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

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

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

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

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

Name: _____

UFID#: _____

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

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

$$Cl = k_e \cdot V_d$$

Name: _____

UFID#: _____

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)

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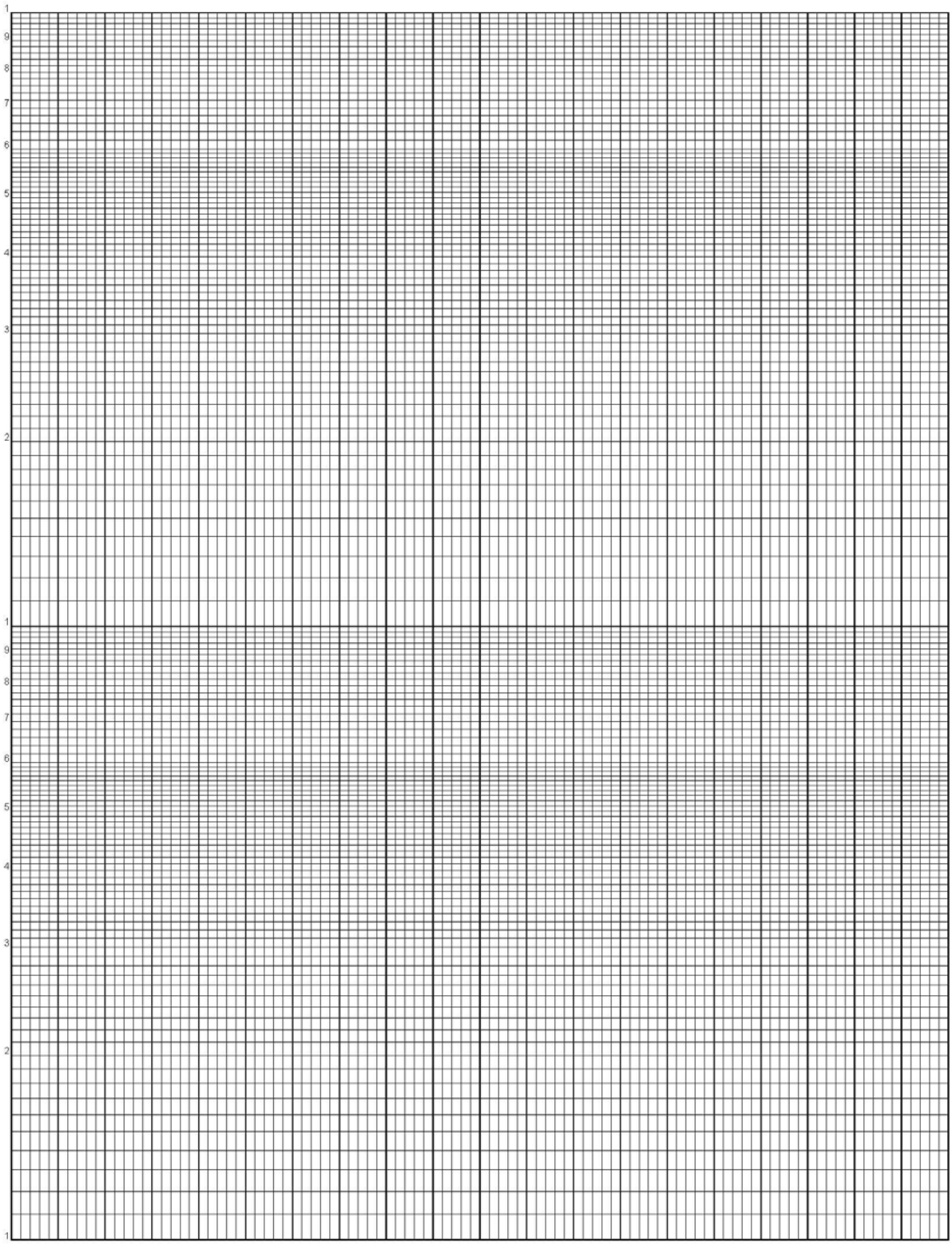
Name: _____

UFID#: _____



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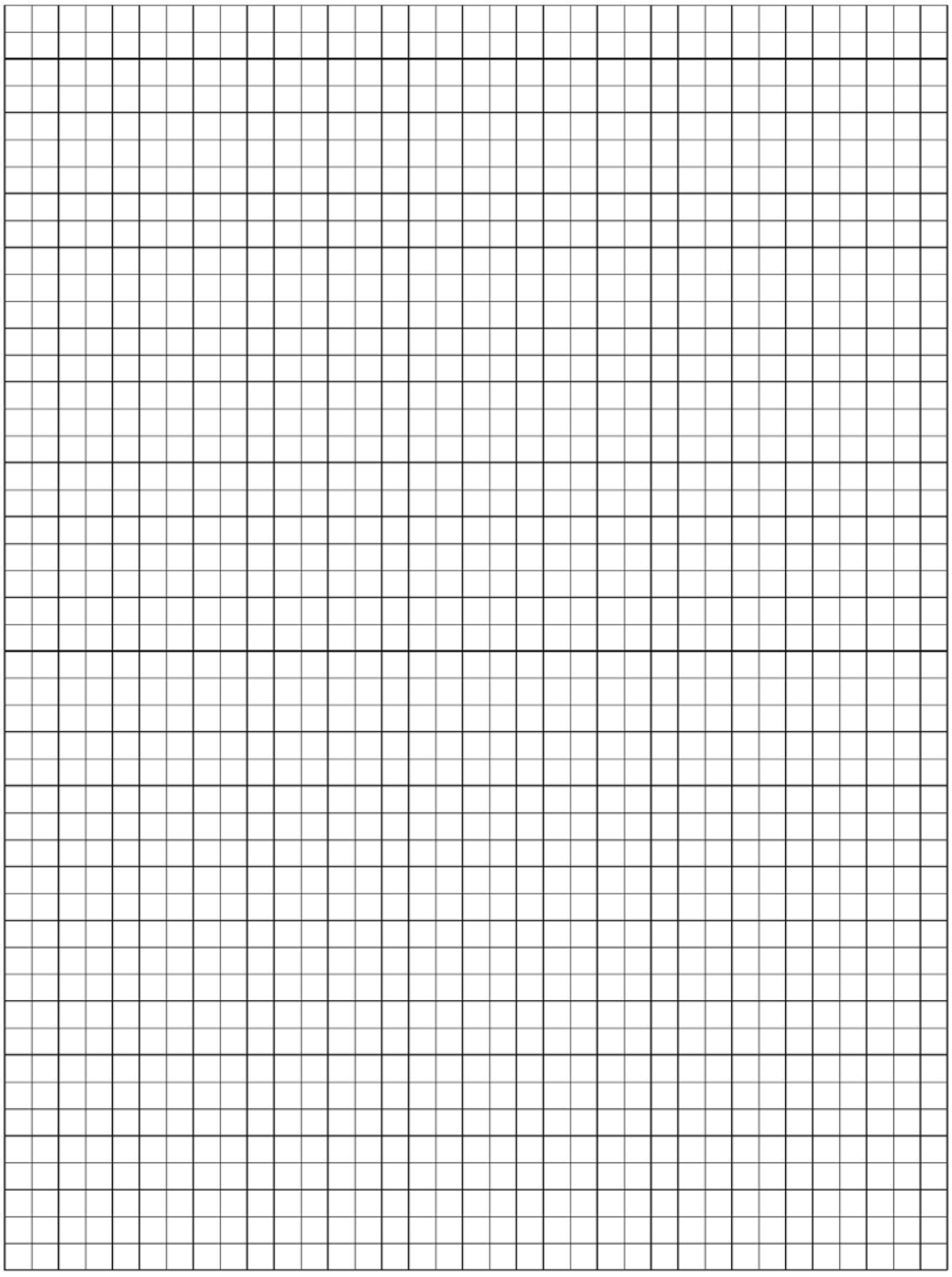

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