Protocol

Protocol Number: MT-7117-G01

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents With Erythropoietic Protoporphyria or X-Linked Protoporphyria

Version Number: 4.1
Date: 9 August 2021
NCT number: NCT04402489

Protocol Number: MT-7117-G01

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents with Erythropoietic Protoporphyria or X-Linked Protoporphyria

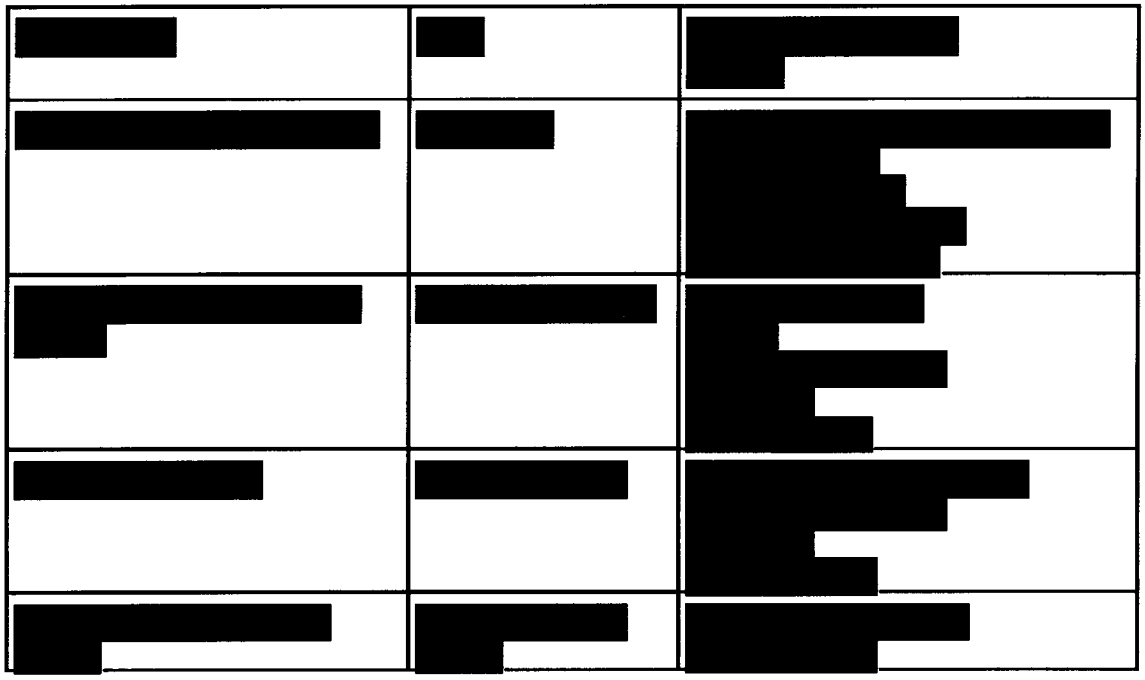
Pre-IND Number:	137573
EudraCT number:	2019-004226-16
Investigational Medicinal Product:	MT-7117
Indication:	Increased pain-free light exposure in adults and adolescents with a history of phototoxic reactions from erythropoietic protoporphyria (EPP) or X-linked protoporphyria (XLP)
Development Phase:	Phase 3
Sponsor:	Mitsubishi Tanabe Pharma Development America (MTDA), Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310, USA
Sponsor's EU Representative:	EU Legal Representative for Clinical Trials MITSUBISHI TANABE PHARMA GmbH Willstätterstraße 30, 40549 Düsseldorf, Germany
Sponsor's UK Representative:	Mitsubishi Tanabe Pharma Europe Ltd Dashwood House 69 Old Broad Street London, EC2M 1QS, UK
Sponsor's Japan Representative:	Mitsubishi Tanabe Pharma Corporation 3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan
Protocol Version and Date:	Version 4.1 9 August 2021

Protocol/ Amendment History of MT-7117-G01 study:

	Name	Version	Date	Comment
	MT-7117-G01 protocol	1.0	16-Dec-19	Original protocol
Amendment 1	MT-7117-G01 protocol	2.0	10-Mar-20	Global Master Protocol
	Country-Specific Protocol Amendment for Japan	2.1	15-Jun-20	Japan country specific
	Country-Specific Protocol Amendment for Norway	2.2	27-Aug-20	Norway country specific
	Country-Specific Protocol Amendment for Norway	2.3	11-Dec-20	Norway country specific
	Country-Specific Protocol Amendment for Germany	2.4	18-Dec-20	Germany country specific
Amendment 2	MT-7117-G01 protocol	3.0	23-Dec-20	Global Master Protocol
	Country-Specific Protocol Amendment for Japan	3.1	15-Jan-21	Japan country specific
	Country-Specific Protocol Amendment for Norway	3.2	09-Apr-2021	Norway country specific
	Country-Specific Protocol Amendment for Germany	3.3	18-Jun-2021	Germany country specific
	Country-Specific Protocol Amendment for Canada	3.4	09-Jul-2021	Canada country specific
Amendment 3	MT-7117-G01 protocol	4.0	29-Jul-2021	Global Master Protocol
Amendment 3.1	MT-7117-G01 protocol	4.1	9-Aug-2021	Global Master Protocol with non-substantial modification

[redacted]

[redacted]

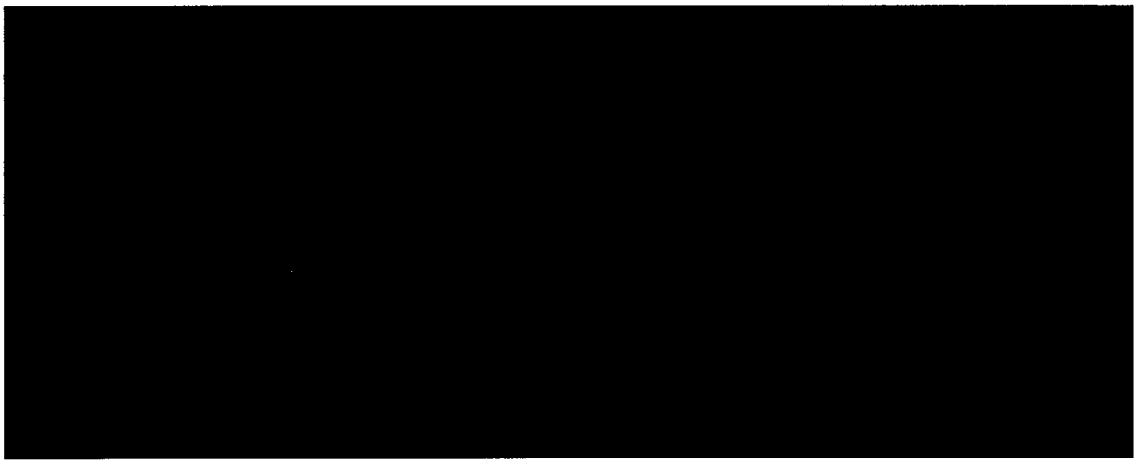


SIGNATURE PAGE (SPONSOR'S RESPONSIBLE SIGNATORY)

Protocol Number: MT-7117-G01

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents with Erythropoietic Protoporphyria or X-Linked Protoporphyria

The Protocol has been designed according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Code of Federal Regulations. It has undergone both medical and scientific review by competent Sponsor personnel. The study will be initiated at the site(s) only after Institutional Review Board/Independent Ethics Committee, regulatory, and local approvals of the necessary essential documents and study procedures will not be initiated until the subject signed the approved Subject Information and Informed Consent/Assent Form(s).



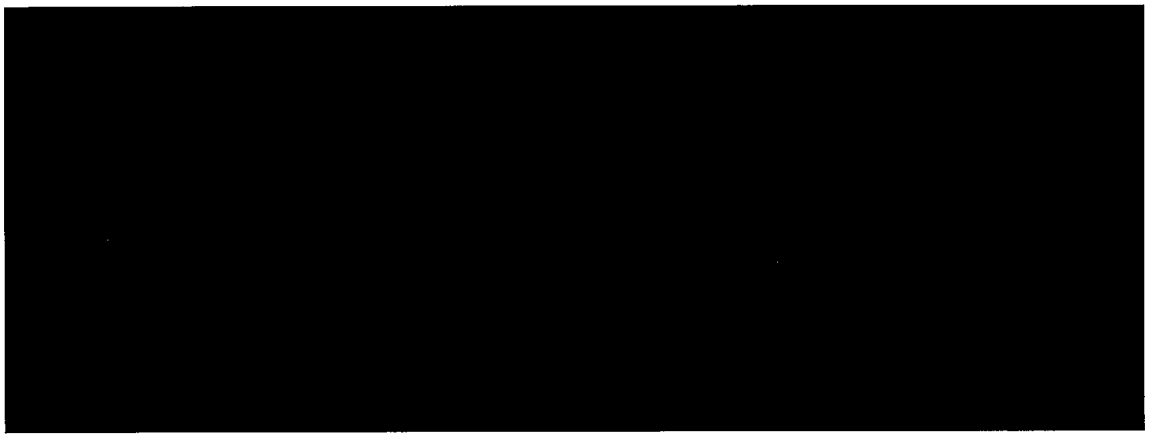
SIGNATURE PAGE (STATISTICIAN)

Protocol Number: MT-7117-G01

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents with Erythropoietic Protoporphyria or X-Linked Protoporphyria

The Protocol has been designed according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice and has undergone statistical review.

Statistician:



SIGNATURE PAGE COORDINATING (PRINCIPAL) INVESTIGATOR

Protocol Number: MT-7117-G01

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents with Erythropoietic Protoporphyria or X-Linked Protoporphyria

I confirm that I have read this Protocol and understand its contents. I agree to fully comply with its requirements. I understand it and will conduct the study in accordance with the procedures described in this protocol and:

_____ (initial here) The principles of GCP as described in 21 CFR, Parts, 50, 56, and 312, as well as any applicable local requirements

or

_____ (initial here) The principles of GCP as described in ICH E6 as well as any applicable local requirements.

I agree to make no changes to the conduct of the study as defined by the Protocol without the prior authorization of Mitsubishi Tanabe Pharma Development America, Inc. in the form of a Protocol Modification and without the appropriate Regulatory Authorities and Institutional Review Board/Independent Ethics Committee.

Address of Institution: _____

_____

_____

_____

Signed: _____

Print Name: _____

Title: _____

Date: _____

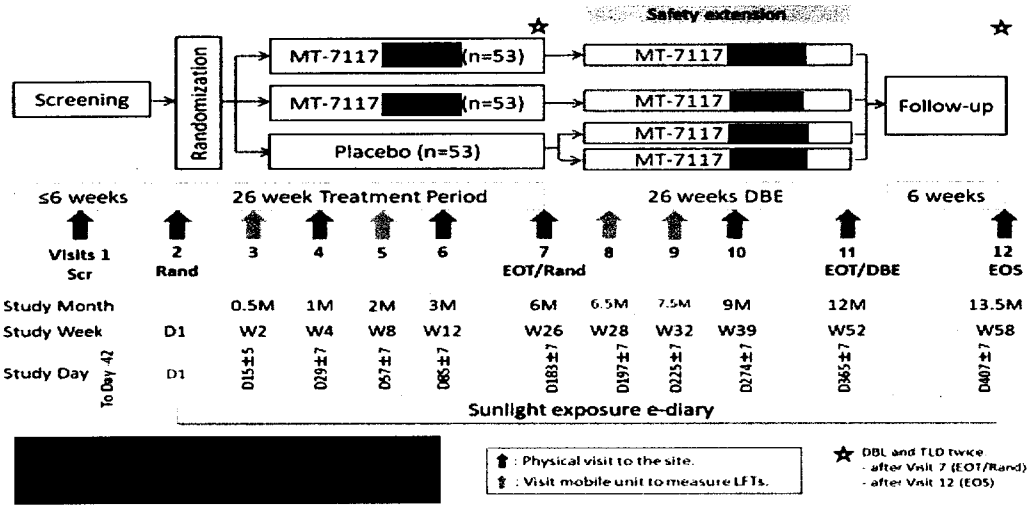
2 SYNOPSIS

Name of Sponsor/Company: Mitsubishi Tanabe Pharma Development America, Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310, USA
Protocol Number: MT-7117-G01
Title of Study: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents with Erythropoietic Protoporphyria or X-Linked Protoporphyria
Indication: Increased pain-free light exposure in adults and adolescents with a history of phototoxic reactions from erythropoietic protoporphyria (EPP) or X-linked protoporphyria (XLP)
Investigational Medicinal Product: MT-7117 [redacted] Placebo to match MT-7117 [redacted]
Treatment Regimen: **Dose**: MT-7117 [redacted], [redacted], or placebo **Route:** Oral **Frequency**: once daily in the morning with or without food
Treatment Duration: 26 weeks plus optional 26 weeks extension
Phase of Development: 3
Objectives: **Primary:** - To investigate the efficacy of MT-7117 on time to onset and severity of first prodromal symptoms (burning, tingling, itching, or stinging) associated with sunlight exposure in adults and adolescents with EPP or XLP. **Secondary:** - To investigate the effect on patient-reported quality of life (QOL) in adults and adolescents with EPP or XLP. - To investigate the effect on the percentage of responders based on the within-subject meaningful threshold for time to first prodromal symptom in adults and adolescents with EPP or XLP. - To investigate the effect on number and severity of sunlight-induced pain events (prodrome and phototoxic reactions) in adults and adolescents with EPP or XLP. **Exploratory:** - To investigate the effect on sunlight exposure duration in adults and adolescents with EPP or XLP.

- To investigate the effect on melanin density in adults and adolescents with EPP or XLP.
- To investigate the pharmacokinetic (PK)/pharmacodynamic (PD) relationship in adults and adolescents with EPP or XLP.
- [redacted]

Safety:
- To assess the long-term safety and tolerability of MT-7117.

Methodology:
This is a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy, tolerability, and safety of MT-7117 in adults and adolescents with EPP or XLP. The study consists of a 6-week screening period, a 26-week double-blind treatment period, an optional 26-week double-blinded extension (DBE) period, and a 6-week follow-up period at Week 58 (or 32 if DBE is not elected). The total participation period is approximately 64 weeks.



Subjects will attend the screening visit (Visit 1) up to 6 weeks before Randomization (Visit 2), in order to confirm eligibility and obtain pre-study safety assessments including nevi evaluation. Subjects will also be instructed how to use an electronic sunlight exposure diary (SED).

At Visit 2, subjects meeting eligibility criteria with body weight ≥ 45 kg will be randomized in a 1:1:1 ratio to receive MT-7117 [redacted], or placebo in a double-blind manner. [redacted]

The first dose will be administered at Visit 2 following baseline assessments including an in-clinic

sunlight exposure test at any time before randomization (Visit 1 or 2), and melanin density determination before randomization (Visit 2). Active or placebo [redacted] will be administered once daily in the morning with or without food.

Subjects will subsequently attend in-clinic visits at Weeks 4 and 12 (Visits 4 and 6, respectively) during which assessments will be performed. In addition, subjects may undergo mobile laboratory or in-clinic visits for sample collection at Weeks 2 and 8 (Visits 3 and 5, respectively) to measure liver function markers (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transpeptidase [GGT], alkaline phosphatase [ALP], direct and total bilirubin).

Subjects will attend the end of treatment visit at Week 26 or early termination (Visit 7 or Visit 11).

PK will be collected at scheduled visits for ≥18 to ≤75-year-olds. For ≥12 to ≤17-year-old subjects, a total of 9 PK samples at 3 time points will be collected: Day 1 (Visit 2) at 2, 4, 6, and 8 hours post-dose, Week 12 (Visit 6) at pre-dose and 3 hours post-dose, and Week 26 (Visit 7) at pre-dose and 2 and 4 hours post-dose.

Subjects will be offered participation in a 6-month extension where all participants are on active drug but are double-blinded to dose starting immediately after the end of the 26-week double-blind treatment period. If study subjects elect to participate in the 26-week DBE after end of Visit 7 (end of treatment [EOT]/Rand), subjects will remain blinded and subjects will be re-randomized. Subjects that received MT-7117 during the blinded period will continue the DBE in the same treatment arm and remain blinded. Subjects that received placebo will be randomized to receive MT-7117 [redacted] in 1:1 ratio for the 26-week DBE period. For subjects with [redacted] the [redacted] dose will be administered without re-randomization.

During the DBE, subjects will attend an in-clinic visit at Week 39 (Visit 10) where measurements will be performed. In addition, subjects may undergo mobile laboratory or in-clinic visits for sample collection at Weeks 28 and 32 (Visits 8 and 9, respectively) to measure liver function markers (AST, ALT, GGT, ALP, direct and total bilirubin).

Subjects will attend the end of treatment visit at Week 52 or early termination visit (Visit 11). Following the last treatment visit, subjects will attend a follow-up visit at Week 58 (Week 32 if DBE is not elected) or 6 weeks after early termination visit.

Subjects who are permanently withdrawn from study drug early should be encouraged to continue in the study and complete all other study assessments without receiving study drug. If a patient decides to completely withdraw consent/assent from the study, every attempt should be made to have the patient complete an early termination visit (Visit 7 or Visit 11).

Number of Subjects:
Originally a total of approximately 159 subjects are planned to be randomized in this study (approximately 53 subjects in each treatment group).

Due to the rapid enrollment rate in the last few months of the enrollment period after COVID-19 restrictions were lifted in many countries, a total of 184 subjects were randomized in this study (approximately 61 subjects in each treatment group).

Subject Population:
Subjects with EPP or XLP, aged ≥12 to ≤75 years.

Main Inclusion Criteria:

1. Subjects provided written informed consent to participate. For minor subjects, both minor assent and parental consent will be provided.
2. Male and female subjects with a confirmed diagnosis of EPP or XLP based on medical history, aged 12 years to 75 years, inclusive, at Screening.
3. Subjects have a body weight of ≥30 kg.
4. Subjects are willing and able to travel to the study sites for all scheduled visits.
5. In the Investigator's opinion, subject is able to understand the nature of the study and any risks involved in participation, and willing to cooperate and comply with the protocol restrictions and requirements (including travel).
6. Female subjects who are non-lactating and have a negative urine pregnancy test at baseline visit prior to receiving the first dose of study drug.
7. Female subjects of childbearing potential and male subjects with partner of child-bearing potential currently using/willing to use 2 effective methods of contraception including barrier method as described in Section 8.7.1.

Main Exclusion Criteria:

1. History or presence of photodermatoses other than EPP or XLP.
2. Subjects who are unwilling or unable to go outside during daylight hours most days (e.g., between 1 hour post-sunrise and 1 hour pre-sunset) during the study.
3. Presence of clinically significant hepatobiliary disease based on Liver function test (LFT) values at Screening.
4. Subjects with AST, ALT, ALP ≥3.0 × upper limit of normal (ULN) or total bilirubin >1.5 × ULN at Screening.
5. Subjects with or having a history (in the last 2 years) of excessive alcohol intake in the opinion of the Investigator.
6. History of melanoma.
7. Presence of melanoma and/or lesions suspicious for melanoma at Screening.
8. History of familial melanoma (defined as having 2 or more first-degree relatives, such as parents, sibling and/or child).
9. Presence of squamous cell carcinoma, basal cell carcinoma, or other malignant skin lesions. Any suspicious lesions or nevi will be evaluated. If the suspicious lesion or nevi cannot be resolved through biopsy or excision, the subject will be excluded from the study.
10. History or presence of psychiatric disease judged to be clinically significant by the Investigator and which may interfere with the study evaluation and/or safety of the subjects.
11. Presence of clinically significant acute or chronic renal disease based upon the subject's medical records including hemodialysis; an estimated glomerular filtration rate (eGFR) <60 mL/min as calculated by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (2009) for adults and by the Schwartz creatinine equation for adolescents (2009) (Appendix 2, Section 18.2). Modification of Diet in Renal Disease (MDRD) can be used for adults per local recommendations.
12. Presence of any clinically significant disease or laboratory abnormality which, in the opinion of the Investigator, can interfere with the study objectives and/or safety of the subjects.
13. Female subjects who are pregnant, lactating, or intending to become pregnant during the study.
14. Treatment with phototherapy within 3 months before Randomization (Visit 2).
15. Treatment with afamelanotide within 3 months before Randomization (Visit 2).

16. Treatment with cimetidine within 4 weeks before Randomization (Visit 2).
17. Treatment with antioxidant agents within 4 weeks before Randomization (Visit 2), at doses which, in the opinion of the Investigator, may affect study endpoints (including but not limited to beta-carotene, cysteine, pyridoxine).
18. Chronic treatment with any scheduled analgesic agents including, but not limited to, opioids and opioid derivatives such as morphine, hydrocodone, oxycodone, fentanyl, or their combination with other unscheduled analgesics or non-steroidal anti-inflammatory drug (Percocet and Vicodin-like prescription drugs) within 4 weeks before Randomization (Visit 2). Acute use of scheduled narcotics greater than 3 months prior to randomization, Over the counter (OTC)s, such as Non-steroidal anti-inflammatory drug (NSAID)s or aspirin for analgesia, or prior temporary use of scheduled agents within 3 months of screening are not excluded.
19. Treatment with any drugs or supplements which, in the opinion of the Investigator, can interfere with the objectives of the study or safety of the subjects.
20. Previous exposure to MT-7117 (this does not include placebo treated subjects).
21. Previous treatment with any investigational agent within 12 weeks before Screening OR 5 half-lives of the investigational product (whichever is longer).

[redacted]

Study Restrictions:

All study subjects must agree to Life Style Change and Restricted Medication:

1. Follow study attendance guidelines.
2. Follow study physical activity and daily sun exposure guidelines.
3. Follow restrictions regarding concomitant medications that are described in Appendix 1 (Section 18.1).
4. Subjects must not take any prescribed or non-prescribed systemic or topical treatment (such as zinc oxide-containing sunscreen, herbal remedies, supplements, or the use of phototherapy including tanning beds) at doses with known potential to have an effect on phototoxicity, photosensitivity in EPP or XLP, and/or increased pigmentation during the study. Such treatments include, but are not limited to afamelanotide, cimetidine, beta-carotene, cysteine, pyridoxine, and cholestyramine. Sunscreens without zinc oxide are permitted to be used.

Efficacy:

Primary Efficacy Endpoint:

1. Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 (Visit 7).

To calculate the average daily duration, a 14-day window on or before a time point (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26) will be used. For baseline, a 14-day window before Day 1

will be used. A 14-day window will be applied to similar situations for other efficacy endpoints related to sunlight exposure diary.

Secondary Efficacy Endpoints:

1. Patient Global Impression of Change (PGIC) at Week 26.
2. Total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during the 26-week double-blind treatment period.
3. Change from baseline for total score in the domain of pain intensity in the Patient-Reported Outcomes Measurement Information System (PROMIS)-57 at Week 26.
4. The percentage of subjects who are responders based on average daily sunlight exposure time to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset defined by within-subject meaningful change of 66 minutes increase from baseline to Week 26.
5. Change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

Exploratory Efficacy Endpoints:

1. Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms or end of test, whichever comes first.
2. Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptoms.
3. Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free time hours).
4. Change from baseline in the average daily mean intensity on an 11-point Likert scale of the subject's prodromal symptoms over time during the 26-week double-blind treatment period.
5. Change from baseline in average daily duration (minutes) of prodromal symptoms during the 26-week double-blind treatment period.
6. Total number of sunlight-induced pain events defined as phototoxic events during the 26-week double-blind treatment period.
7. Total number of sunlight-induced non-prodrome, phototoxic reactions during the 26-week double-blind treatment period.
8. Change from baseline in the average daily mean intensity of the subject's phototoxic reactions (associated with sun exposure) during the 26-week double-blind treatment period on an 11-point Likert scale.
9. Change from baseline in average daily duration (minutes) of phototoxic reactions (associated with sun exposure) during the 26-week double-blind treatment period.
10. Change from baseline and % change from baseline in melanin density at each visit by skin segments. Average of 6 skin segments for the change from baseline and % change from baseline in melanin density at each visit.
11. Total number of days subject is exposed to sunlight for any duration between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptoms during the 26-week double-blind treatment period.
12. Total number of days subject is exposed to sunlight for any duration between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free days) during the 26-week double-blind treatment period.

13. Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 26.
14. Change from baseline for all total score and total score in each domain of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference (including pain intensity) in the PROMIS-57.
15. Change from baseline in Patient Global Impression of Severity (PGIS) at each visit.
16. The percentage of subjects who are responders at Week 26 based on PGIC (Very Much Improved or Much Improved).
17. Qualitative exit interview questionnaire about QoL at Week 26.

Safety Endpoints:

1. Treatment-emergent adverse events (AEs) (including serious adverse events [SAEs] and adverse events of special interest [AESIs]).
2. Physical examination.
3. Vital signs (blood pressure, respiratory rate, pulse rate, and body temperature).
4. Clinical laboratory examinations (hematology, coagulation, biochemistry, and urinalysis), including liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin).
5. 12-lead electrocardiogram (ECG) at Baseline and EOT.
6. Nevi appearance (assessed by a dermatologist or other qualified site staff). Any nevi undergoing change of clinical concern during active treatment will be biopsied for follow up and evaluated by the central pathology lab.

Pharmacokinetic Endpoints:

Assessment of plasma PK: Plasma concentrations of MT-7117 will be measured at protocol scheduled visits.

Study Estimands:

Primary Estimand

The primary estimand construction elements for this study are:

- Population: All randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.
- Variable: Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 (Visit 7).
- Inter-current event of treatment discontinuation using treatment policy: Regardless of early discontinuation of study drug due to any reason until the end of the double-blind treatment period.
- Population-level summary: Absolute mean difference in change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom between MT-7117 and placebo groups.

The primary estimand will be based on effectiveness assumption (de-facto) using treatment policy: The treatment effect will be attributable to the subject's initially randomized treatment regardless of treatment discontinuation.

Secondary Estimand

The secondary estimand construction elements to be tested as supportive analysis for this study are:

- Population: All randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.
- Variable: Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 (Visit 7).
- Inter-current event of treatment discontinuation using hypothetical strategy: If subjects could have treatment completion until the end of the double-blind treatment period.
- Population-level summary: Absolute mean difference in change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom between MT-7117 and placebo groups.

The secondary estimand will be based on efficacy assumption (de-jure) using a hypothetical strategy: The treatment effect will be attributable to the subject's initially randomized treatment if subjects could have stayed on study until the end of the double-blind treatment period.

Sample Size Estimation:
For the primary estimand, the sample size of 159 is expected to provide adequate power for the comparisons between MT-7117 and placebo for change from baseline in the average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 based on the MT-7117-A01 study. The calculation of sample size assumes a 2-sided alpha level of 0.05 and a 20% dropout rate up to Week 26. The sample size of 42 completers per treatment group will provide 91% and 79% power to detect an effect size of 0.72 and 0.66 in the average daily time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 (ie, an absolute treatment difference of 57 mins between MT-7117 [redacted] vs placebo, 52 mins between MT-7117 [redacted] vs placebo, and a standard deviation [SD] of 79.3 mins). The sample size of 42 completers was calculated by SAS simulation using the fixed-sequence testing procedure in order to confirm the power affected by multiplicity adjustment in treatment comparison for primary endpoint. Taking into account for a 20% dropout rate up to Week 26, total sample size of 159 was calculated.

Due to the rapid enrollment rate in the last few months of the enrollment period after COVID-19 restrictions were lifted in many countries, a total of 184 subjects were enrolled.

Analysis Populations:

- Safety population: includes all randomized subjects who received at least 1 dose of study medication.
- Intent-to-treat (ITT) population: includes all randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.
- PK population: includes all randomized subjects who received at least 1 dose of study medication and who have at least 1 post-dose value of plasma concentration time point to be included in the PK analysis without important protocol deviations which may affect the PK of study medication.

Statistical Analysis Methods:
A Statistical Analysis Plan (SAP) containing details of all the analyses and outputs will be prepared and approved before the study database lock. The ITT population will be used for all efficacy analyses. All safety analysis will be performed on the Safety population.

Unless otherwise specified, the baseline values will be the last non-missing value before receiving the first dose of study medication.

Baseline for an efficacy endpoint based on sunlight exposure time will be the mean of the daily value of the endpoint in a 14-day window before Day 1. Similarly, for this endpoint, their values at each post-baseline time point (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 52, and 58) are the mean of the daily value of the endpoint in a 14-day window on or before the visit. To calculate the average daily duration, a 14-day window on or before time point (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26) will be used.

Continuous endpoints will be summarized with the descriptive statistics (the number of observations, mean, standard deviation (SD), median, minimum, and maximum). Categorical endpoints will be summarized using frequency counts and percentages.

All statistical tests will be 2-sided with 5% significance level. Point estimates of treatment differences will be provided with 2-sided 95% confidence intervals (CIs) where applicable.

Primary Analysis

For ITT population, the primary estimand will be tested including retrieved dropout data (after treatment discontinuation), using treatment comparisons of interest in change from baseline in average daily time to first prodromal symptoms associated with exposure to sunlight between 1 hour post-sunrise and 1 hour pre-sunset for the two MT-7117 doses ([redacted] and [redacted]) compared with placebo at Week 26 (Visit 7).

To assess the treatment effect at Week 26, change from baseline in average daily time (minutes) to first prodromal symptom associated with exposure to sunlight between 1 hour post-sunrise and 1 hour pre-sunset at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26 will be analyzed using mixed-effect model for repeated measures (MMRM). The model will include fixed categorical terms for treatment, [redacted], visit, and treatment by visit interaction together with continuous covariate terms for baseline average daily duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset to first prodromal symptom and baseline average daily duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset to first prodromal symptom by visit interaction. An unstructured correlation structure will be used to model the within-subject variance covariance errors. Should convergence of the model fail (due to the small numbers of subjects in this study), other variance covariance matrices such as autoregressive [AR(1)] correlation matrix will be used if appropriate. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. From the model described above, adjusted (least squares [LS]) means and standard errors will be produced by treatment and visit. Difference in adjusted means at each visit (each MT-7117 dose vs. placebo) with standard errors, 95% CIs and associated p values will also be produced. All available data from all subjects will be used in the primary analysis without any imputation.

Sensitivity Analysis

Multiple imputation using the Pattern Mixture model method on ITT population under Missing Not at Random assumption. In this analysis, control-group–based assumption will be used (i.e., the trajectories of the patients in all treatment groups are assumed to follow the control group after the treatment discontinuation).

Supportive Analysis

The secondary estimand will use similar estimator as for the primary analysis. The ITT population with the primary efficacy data without retrieved dropout data (after treatment discontinuation) will be used for this analysis. Likelihood based model method under Missing at Random assumption will be performed using the same MMRM as specified for the primary analysis.

Multiplicity adjustment for treatment comparison on primary and secondary endpoints

The overall study-wise type I error will be 5%. Type I error will be globally strongly controlled by employing the fixed sequence approach (i.e., each endpoint will be formally analyzed only in case the preceding endpoint will have a p value less than or equal to 0.05).

- To protect the study from type I error inflation, the lower ordered comparison will be interpreted inferentially only if a statistically significant treatment effect is detected in the higher ordered comparison (H1=>H2,..., H11=>H12). The following null hypothesis will be sequentially tested via the following order;
  - H1: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline in average daily time (minutes) to first prodromal symptom associated with exposure to sunlight between 1 hour post-sunrise and 1 hour pre-sunset at Week 26.
  - H2: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline in average daily time (minutes) to first prodromal symptom associated with exposure to sunlight between 1 hour post-sunrise and 1 hour pre-sunset at Week 26.
  - H3: There is no treatment difference between MT-7117 [redacted] and placebo in PGIC at Week 26.
  - H4: There is no treatment difference between MT-7117 [redacted] and placebo in PGIC at Week 26.
  - H5: There is no treatment difference between MT-7117 [redacted] and placebo in total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during 26-week double-blind treatment period.
  - H6: There is no treatment difference between MT-7117 [redacted] and placebo in total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during 26-week double-blind treatment period.
  - H7: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26.
  - H8: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26.
  - H9: There is no treatment difference between MT-7117 [redacted] and placebo in the percentage of subjects who are responders at Week 26 based on average daily sunlight exposure time to first prodromal symptoms using the within-subject meaningful change of 66 minutes increase.
  - H10: There is no treatment difference between MT-7117 [redacted] and placebo in the percentage of subjects who are responders at Week 26 based on average daily sunlight exposure time to first prodromal symptoms using the within-subject meaningful change of 66 minutes increase.
  - H11: There is no treatment difference between MT-7117 [redacted] and placebo in change

from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

- H12: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

Secondary Analyses

PGIC at Week 26 and change from baseline for total score in each domain of physical function and pain intensity in the PROMIS-57 at Week 26 in the secondary efficacy endpoints will be analyzed in a manner similar to the primary analysis using an MMRM approach for the continuous endpoints. The percentage of subjects who are responders based on average daily sunlight exposure time to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset defined by within-subject meaningful change of 66 minutes increase from baseline to Week 26 will be analyzed using logistic regression analysis. The model will include the treatment group, randomization strata as fixed factors together with continuous covariate terms for the corresponding baseline values. The treatment odds ratio at Week 26 will be estimated using a contrast. Total number of sunlight-induced pain events defined as phototoxic events and total number of sunlight-induced pain events defined as prodromal symptoms during 26-week double-blind treatment period will be analyzed using a negative binomial regression model with log link.

Analyses for other endpoints/details including other efficacy endpoints, safety endpoints, pharmacokinetic endpoints, and exploratory endpoints will be included into the protocol body text and SAP. The endpoints and analysis methods for the safety extension data will be specified in the final analysis SAP.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

List of Abbreviations

Abbreviation or Specialist Term	Explanation
α-MSH	α-melanocyte-stimulating hormone
AE	Adverse event
AESI	AE of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Autoregressive
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
[redacted]	[redacted]
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
C_{max}	Maximum observed plasma concentration
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical Study Report
[redacted]	[redacted]
DBE	Double-blinded extension
DNA	Deoxyribonucleic acid
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
EPP	Erythropoietic protoporphyria
FSH	Follicle-stimulating hormone

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
[redacted]	[redacted]
hMC1R	Human melanocortin-1 receptor
hMC4R	Human melanocortin-4 receptor
IC_{50}	Concentration associated with 50% inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSET	In-Clinic Sunlight Exposure Test
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web-based Response System
LFT	Liver function test
LS	Least squares
MC1R	Melanocortin-1 receptor
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
mRNA	Messenger ribonucleic acid
MTDA	Mitsubishi Tanabe Pharma Development America
MTPC	Mitsubishi Tanabe Pharma Corporation
MV	Minute volume
NCS	Not clinically significant
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
[redacted]	[redacted]
OTC	Over the counter
PD	Pharmacodynamic

Abbreviation or Specialist Term	Explanation
[redacted]	[redacted]
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
QP	Qualified Person
qRT-PCR	Quantitative reverse-transcription polymerase chain reaction
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Frederica's formula
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SED	Sunlight exposure diary
SNP	Single-nucleotide polymorphism
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
USA	United States of America
WHO	World Health Organization
WMA	World Medical Association
XLP	X-linked protoporphyria

5 INTRODUCTION

MT-7117 (dersimelagon) is a novel orally-administered, small molecule, which acts as an agonist of melanocortin-1 receptor (MC1R) and is being developed by Mitsubishi Tanabe Pharma Corporation (MTPC) to increase duration of pain-free light exposure in adults and adolescents with a history of phototoxic reactions from erythropoietic protoporphyria (EPP) or X-linked protoporphyria (XLP).

MC1R is a member of the G-protein-coupled receptors superfamily. It is the predominant melanocortin receptor expressed in cutaneous and hair follicle melanocytes. MC1R is activated by α-melanocyte-stimulating hormone (α-MSH), which can be locally synthesized in response to sunlight exposure. Activation of MC1R is positively coupled to the cyclic adenosine monophosphate signalling pathway and leads to a stimulation of melanogenesis and a switch from the synthesis of pheomelanins to the production of eumelanic pigments. MC1R regulates the amount and type of pigment production and is a major determinant of skin phototype and sensitivity to ultraviolet light induced damage.[1] In addition, activation of MC1R enhances Deoxyribonucleic acid (DNA) repair, upregulates antioxidant enzymes, reduces production of pro-inflammatory cytokines, and minimizes the protoporphyrin-mediated damage and resulting pain in EPP and XLP patients.[2] The results of pharmacological and pharmacokinetic (PK) studies in vitro and in vivo suggest that MT-7117 has melanogenic, antioxidant and anti-inflammatory properties that are hypothesized to decrease the frequency, duration, and severity of the occurrence of photosensitivity symptoms.

EPP and XLP are rare inherited disorders of the heme biosynthetic pathway that have been reported worldwide with the prevalence between 1:75,000 and 1:200,000 and results in accumulation of protoporphyrin IX (PPIX) in the bone marrow, peripheral blood erythrocytes, and plasma. Increased PPIX can result either from mutations of the ferrochelatase gene (EPP), less commonly the aminolevulinic acid synthase-2 gene (XLP), or as most recently shown of the ATP-dependent Clp protease ATP-binding subunit (CLPX).[3,4,5] Protoporphyrin IX absorbs light radiation in a range of wavelengths from 320 to 595 nm with a peak around 400 nm. The absorption of these wavelengths increases the energy content of PPIX and enables the excess energy to be transferred to oxygen, resulting in a reactive oxygen species. The oxygen species can injure tissues by complement activation and mast cell degranulation phenomena that explain the vasodilatation and edema components of the skin phototoxicity reactions in EPP and XLP patients.

Until recently, there was no recognized standard of care for EPP in the United States of America (USA). Afamelanotide was approved by the Food and Drug Administration (FDA) on October 8, 2019 as a treatment to increase pain-free light exposure in adult patients with EPP. There are currently no approved treatments for pediatric patients with EPP despite an unmet medical need. EPP and XLP are primarily managed by a preventative approach, which consists of avoidance of sun exposure (long-wave radiation and visible light). The use of adequate clothing (hats, glasses, gloves, scarfs, masks) and sunscreens with zinc oxide is also advisable. Oral antioxidants such as beta-carotene and cysteine are also used, however their efficacy remains questionable. EPP or XLP patients with severe liver complications may require liver transplantation.[6]

Both EPP and XLP are characterized by accumulation of PPIX in blood, erythrocytes and tissues, resulting in severe cutaneous phototoxicity reactions. EPP and XLP usually present early in childhood with extremely painful photosensitivity reactions which are preceded by a "prodrome" of tingling, stinging, and/or burning of sun-exposed skin. The time to onset of prodromal symptoms after direct sun exposure varies but may occur in less than 10 minutes. Importantly, continued exposure to sunlight following the onset of prodromal symptoms will lead to a phototoxicity-induced skin reaction which is intensely painful and prolonged, lasting up to several days. Photosensitivity is the main symptom of EPP/XLP and it is manifested, upon exposure of uncovered skin areas to sunlight. A cross-sectional study of 223 patients described the clinical features, treatments, and quality of life (QOL) of EPP patients ranging in age from 5 to 87 years and found the manifestations of the disease to be essentially the same across this age range.[7]

EPP is the most common porphyria of childhood and occurs worldwide. The incidence in males and females is approximately the same, as XLP occurs in only 2-10% of affected patients. Long delays in reaching a correct diagnosis are common. In the United Kingdom (UK), the reported median age of onset was 1 year, but the median age of correct diagnosis was 12 years.[8]

The prevailing and chronic need of EPP and XLP patients to avoid both long-wave radiation and visible light, responsible for triggering phototoxicity reactions, has a significant impact on their daily function and QOL resulting in profound adverse impact on daily personal and professional activity.[9] Approximately 3% of patients with EPP develop liver manifestations.[6] EPP and XLP are lifelong disorders whose prognosis depends on the evolution of the hepatic disease.[10]

There remains a high medical need for new effective and safe, orally administered treatments for EPP and XLP, especially for pediatric patients that have had no options to date.

Mitsubishi Tanabe Pharma Development America (MTDA) is developing MT-7117 for the treatment of EPP and XLP. Since MT-7117 is an investigational medication, and its safety profile in humans has not yet been fully investigated, all subjects receiving MT-7117 will be closely monitored. Further information can be found in the MT-7117 Investigator's Brochure.[11]

5.1 Nonclinical Studies

[redacted]

5.2 Clinical Studies

Results of the three completed Phase 1 studies (MT-7117-E01. MT-7117-E02, and MT-7117-E03) conducted with MT-7117 can be found in the Investigator's Brochure.[11]

Study MT-7117-A01

A Phase 2, randomized, double-blind, placebo-controlled study to assess the efficacy, tolerability, and safety of MT-7117 in subjects with EPP or XLP has been completed. Top-line

data was received on October 25, 2019 from a total of 102 randomized subjects (2 active groups at [redacted] or [redacted] doses and 1 placebo group with 33, 34, and 35 subjects in each treatment group, respectively). The efficacy results at Week 16 showed an improvement in average daily time (minutes) to first prodromal symptom, which was greater than the placebo for the [redacted] ($p<0.008$) and [redacted] ($p<0.003$) arms, respectively. In the [redacted]- and [redacted] arms, the primary endpoint of time-to-prodrome for MT-7117 versus placebo was > 50 minutes, irrespective of the season of the year. The improvement of time-to-prodrome (primary endpoint) and the duration of sunlight exposure (secondary endpoint) were observed as early as Week 6. Dose-related increase in pigmentation was observed. Treatment-emergent adverse event (TEAE)s leading to discontinuation in the [redacted] arm were higher than the placebo (14.3% vs. 0%). TEAEs were observed in System Organ Class (SOC) of nervous system disorders, gastrointestinal disorders, skin and subcutaneous disorders, and general disorders. There was no trend in hepatic adverse event (AE)s, and no trend of clinically significant changes in Liver Function Test (LFT)s were observed. A treatment-emergent serious adverse event (SAE) occurred in one subject (anaphylactic reaction) in the MT-7117 [redacted] arm and was unrelated to treatment.

Study MT-7117-A02

A Phase 1 open-label, single-center, parallel-group study to assess the pharmacokinetics, safety, and tolerability of a single dose of MT-7117 in healthy volunteers with normal hepatic function, moderately impaired hepatic function, and mildly impaired hepatic function, is ongoing. Up to 24 subjects are planned to be in this study (8 subjects in each treatment group).

Part 1 of the study has been completed. There were 8 subjects with moderate hepatic impairment enrolled and 8 normal healthy matches. All 16 subjects completed the study and will be included in the final analysis. The database has been locked. Preliminary analysis has indicated that there were no SAEs reported during this Phase 1 study. There were no clinically significant changes in laboratory, vital sign, electrocardiogram (ECG), or other safety parameters.

The results of the PK analysis demonstrated an approximate 1.7 fold increase in the mean exposure to MT-7117 in subjects with moderate hepatic impairment (Child-Pugh B) when compared with normal controls. Based upon these data, patients with mild and moderate hepatic impairment can be administered MT-7117; however, severe hepatic impairment is likely to greatly increase plasma concentrations of MT-7117. There are no studies of MT-7117 in subjects with severe hepatic impairment.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

- To investigate the efficacy of MT-7117 on time to onset and severity of first prodromal symptoms (burning, tingling, itching, or stinging) associated with sunlight exposure in adults and adolescents with EPP or XLP.

6.1.2 Secondary Objectives

- To investigate the effect on patient-reported QOL in adults and adolescents with EPP or XLP.
- To investigate the effect on the percentage of responders based on the within-subject meaningful threshold for time to first prodromal symptom in adults and adolescents with EPP or XLP.
- [redacted]

6.1.3 Exploratory Objectives

- To investigate the effect on sunlight exposure duration in adults and adolescents with EPP or XLP.
- To investigate the effect on melanin density in adults and adolescents with EPP or XLP.
- To investigate the PK/pharmacodynamic (PD) relationship in adults and adolescents with EPP or XLP.
- To investigate the effect of mutations in MC1R gene on sunlight exposure duration and melanin density in adults and adolescents with EPP or XLP.

6.1.4 Safety Objective

- To assess the long-term safety and tolerability of MT-7117.

6.2 Study Endpoints

6.2.1 Primary Efficacy Endpoint

- Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 (Visit 7).

To calculate the average daily duration, a 14-day window on or before a time point (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26) will be used. For baseline, a 14-day window before Day 1 will be used. A 14-day window will be applied to similar situations for other efficacy endpoints related to sunlight exposure diary.

6.2.2 Secondary Efficacy Endpoints

- Patient Global Impression of Change (PGIC) at Week 26.
- Total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during the 26-week double-blind treatment period.
- Change from baseline for total score in the domain of pain intensity in the Patient-reported Outcomes Measurement Information System (PROMIS)-57 at Week 26.
- The percentage of subjects who are responders based on average daily sunlight exposure time to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset defined by within-subject meaningful change of 66 minutes increase from baseline to Week 26.
- Change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

6.2.3 Exploratory Efficacy Endpoints

- Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms or end of test, whichever comes first.
- Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptoms.
- Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free time hours).
- Change from baseline in the average daily mean intensity on an 11-point Likert scale of the subject's prodromal symptoms over time during the 26-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of prodromal symptoms during the 26-week double-blind treatment period.
- Total number of sunlight-induced pain events defined as phototoxic events during the 26-week double-blind treatment period.
- Total number of sunlight-induced non-prodrome, phototoxic reactions during the 26-week double-blind treatment period.
- Change from baseline in the average daily mean intensity of the subject's phototoxic reactions (associated with sun exposure) during the 26-week double-blind treatment period on an 11-point Likert scale.
- Change from baseline in average daily duration (minutes) of phototoxic reactions (associated with sun exposure) during the 26-week double-blind treatment period.
- Change from baseline and % change from baseline in melanin density at each visit by skin segments. Average of 6 skin segments for the change from baseline and % change from baseline in melanin density at each visit.
- Total number of days subject is exposed to sunlight for any duration between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptoms during the 26-week double-blind treatment period.

- Total number of days subject is exposed to sunlight for any duration between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free days) during the 26-week double-blind treatment period.
- Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 26.
- Change from baseline for all total score and total score in each domain of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference (including pain intensity) in the PROMIS-57.
- Change from baseline in Patient Global Impression of Severity (PGIS) at each visit.
- The percentage of subjects who are responders at Week 26 based on PGIC (Very Much Improved or Much Improved).
- Qualitative exit interview questionnaire about QoL at Week 26.

6.2.4 Safety Endpoints

- TEAEs (including SAEs and adverse events of special interest [AESIs]).
- Physical examination.
- Vital signs (blood pressure, respiratory rate, pulse rate, and body temperature).
- Clinical laboratory examinations (hematology, coagulation, biochemistry, and urinalysis), including liver function markers (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transpeptidase [GGT], alkaline phosphatase [ALP], direct and total bilirubin).
- 12-lead ECG at Baseline and end of treatment (EOT).
- Nevi appearance (assessed by a dermatologist or other qualified site staff). Any nevi undergoing change of clinical concern during active treatment will be biopsied for follow up and evaluated by the central pathology lab.

6.2.5 Pharmacokinetic Endpoints

- Assessment of plasma PK: Plasma concentrations of MT-7117 will be measured at protocol scheduled visits.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy, tolerability, and safety of MT-7117 in adults and adolescents with EPP or XLP. The study consists of a 6-week screening period, a 26-week double-blind treatment period, an optional 26-week double-blinded extension (DBE) period, and a 6-week follow-up period at Week 58 (or Week 32 if DBE is not elected). The total participation period is approximately 64 weeks.

The study design is illustrated in Figure 7-1.

Subjects will attend the screening visit (Visit 1) up to 6 weeks before Randomization (Visit 2), in order to confirm eligibility and obtain pre-study safety assessments including nevi evaluation. Subjects will also be instructed how to use an electronic sunlight exposure diary (SED).

At Visit 2, subjects meeting eligibility criteria with body weight ≥ 45 kg will be randomized in a 1:1:1 ratio to receive MT-7117 [redacted], or placebo in a double-blind manner. [redacted]

The first dose will be administered at Visit 2 following baseline assessments including an in-clinic sunlight exposure test at any time before randomization (Visit 1 or 2), and melanin density determination before randomization (Visit 2). Active or placebo [redacted] will be administered once daily in the morning with or without food.

Subjects will subsequently attend in-clinic visits at Weeks 4 and 12 (Visits 4 and 6, respectively) during which assessments will be performed. In addition, subjects may undergo mobile laboratory or in-clinic visits for sample collection at Weeks 2 and 8 (Visits 3 and 5, respectively) to measure liver function markers (AST, ALT, GGT, ALP, direct and total bilirubin).

Subjects will attend the end of treatment visit at Week 26 or early termination visit (Visit 7 or Visit 11).

PK will be collected at scheduled visits for ≥18 to ≤75-year-olds. For ≥12 to ≤17-year-old subjects, a total of 9 PK samples at 3 time points will be collected: Day 1 (Visit 2) at 2, 4, 6, and 8 hours post-dose, Week 12 (Visit 6) at pre-dose and 3 hours post-dose, and Week 26 (Visit 7) at pre-dose and 2, and 4 hours post-dose.

Subjects will be offered participation in a 6-month extension where all participants are on active drug but are double-blinded to dose starting immediately after the end of the 26-week double-blind treatment period. If study subjects elect to participate in the 26-week DBE after end of

Visit 7 (EOT/Rand), subjects will remain blinded and subjects will be re-randomized. Subjects that received MT-7117 during the blinded period will continue the DBE in the same treatment arm and remain blinded. Subjects that received placebo will be randomized to receive MT-7117 [redacted] in 1:1 ratio for the 26 weeks DBE period. For subjects with [redacted] the [redacted] dose will be administered without re-randomization.

During the DBE, subjects will attend an in-clinic visit at Week 39 (Visit 10) where measurements will be performed. In addition, subjects may undergo mobile laboratory or in-clinic visits for sample collection at Weeks 28 and 32 (Visits 8 and 9, respectively) to measure liver function markers (AST, ALT, GGT, ALP, direct and total bilirubin).

Subjects will attend the end of treatment visit at Week 52 or early termination visit (Visit 11). Following the last treatment visit, subjects will attend a follow-up visit at Week 58 (Week 32 if DBE is not elected) or 6 weeks after early termination visit.

Subjects who are permanently withdrawn from study drug early should be encouraged to continue in the study and complete all other study assessments without receiving study drug. If a patient decides to completely withdraw consent/assent from the study, every attempt should be made to have the patient complete an early termination visit (Visit 7 or Visit 11).

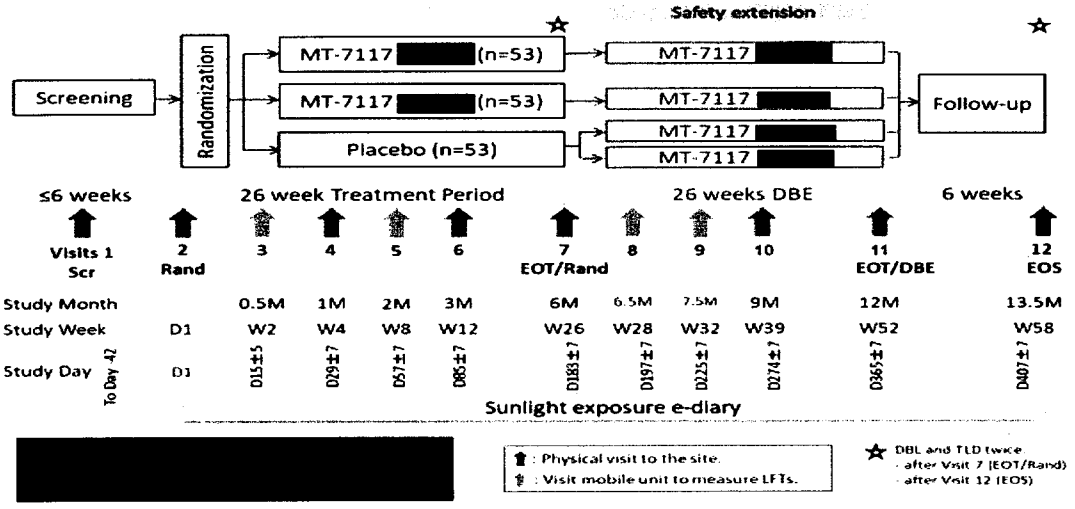


Figure 7-1 Study Design Schematic

7.2 Rationale for Study Design and Treatment Regimens

The objectives of this study are to obtain efficacy, tolerability, and safety data for the selected two doses ([redacted] and [redacted]/day) of MT-7117 and placebo when administered to adults and

adolescents with EPP or XLP over a 26-week treatment period. A standard randomized, placebo controlled, double-blind treatment allocation is considered appropriate in order to obtain unbiased results in this study. Safety, PK, PD, and efficacy effects will be evaluated based upon the comparable data from the Phase 1 (MT-7117-E01, MT-7117-E02, MT-7117-E03, and MT-7117-A02) and Phase 2 (MT-7117-A01) studies.

Abnormal changes in biochemical markers related to the hepatic function were observed in rats and monkeys. In MT-7117-E01 human study, in subjects receiving 14 days of study drug, treatment-emergent transaminase elevations were reported in 6/36 (17%) subjects receiving MT-7117 and 2/12 (17%) subject receiving placebo. Of the six subjects receiving MT-7117 for 14 days reporting treatment-emergent transaminase elevations, 4 had elevated baseline transaminase values. Therefore, frequent assessments of liver function markers are performed in this study. However, in Study MT-7117-A01 hepatic AEs and increase in hepatic laboratory parameters were comparable between MT-7117 and placebo subjects.

The 26-week treatment period is considered a sufficient duration for evaluation of the efficacy and tolerability of MT-7117 for this study. Subjects will be offered to enroll in the 26-week double-blinded extension period starting immediately at the last visit in the double-blind treatment period. Subjects will attend a follow-up visit 6 weeks after the end of treatment (or early termination visit) which is considered a sufficient duration to evaluate pigmentation recovery and safety of subjects. For the primary and secondary endpoints, the effect of MT-7117 on the time to first prodrome associated with sunlight exposure will be measured using an electronic sunlight exposure diary. Melanin density assessments are safe and routinely used in clinical studies of skin disorders. Melanin density assessments were used in the MT-7117-A01 study and will be used in this study to assess the effect of MT-7117 on pigmentation. The effect of MT-7117 on QOL will be assessed using validated questionnaires.

7.3 Risk:Benefit Statement

EPP and XLP are rare inherited disorders of the heme biosynthetic pathway that results in accumulation of protoporphyrin IX (PPIX) in the bone marrow, peripheral blood erythrocytes, and plasma. The accumulated protoporphyrin is activated by sunlight exposure, generating singlet oxygen radical reactions leading to tissue damage and excruciating pain that impair quality of life.[5]

Until recently, treatment has been limited to sun protection and there was no recognized standard of care for EPP in the USA. Scenesse (afamelanotide) was approved in Europe, US, and Australia in 2014, 2019, and 2020, respectively for the prevention of phototoxicity in adults with EPP and is a slow release implant that patients would need to get implanted every other month ongoing (six per year) to be protected continuously. There still remains a high unmet medical need for an oral treatment as an alternative treatment option for EPP patients.

Furthermore, there are no approved treatments currently for pediatric patients with EPP or XLP as well as adult patients with XLP despite an unmet medical need.

MT-7117 is an investigational drug, and its safety profile in humans has not yet been fully

investigated. Therefore, all subjects will be closely monitored based on the completed clinical study safety observations/data.

In Study MT-7117-A01, there was a significant improvement in average daily time (minutes) to first prodromal symptom in MT-7117 subjects compared to placebo subjects for the [redacted] ($p<0.008$) and [redacted] ($p<0.003$) cohorts at Week 16. The increased time to prodromal symptoms in MT-7117 subjects compared to placebo subjects was greater than 50 minutes. Seasonality did not impact the results of the primary endpoint. The improvement of time-to-first-prodrome (primary endpoint) was observed as early as Week 6 vs placebo ($p<0.027$ for [redacted] $p<0.029$ for [redacted]) and continued through Week 16.

In embryo-fetal development study in mice, the total incidence of fetuses with skeletal anomalies was increased at [redacted], the lethal dose for adult female mice, with increased incidence of fused rib and fused sternebrae. In the rat pre- and postnatal development study (ongoing study), 2 dams died on lactation day (LD) 11 and LD 18 at [redacted]. The causal relationship of these deaths to MT-7117-treatment has not been established. In the F1 offspring, MT-7117 related toxicities were observed in the [redacted] group: a total litter loss of 2 dams, a significant increase or tendency towards an increase in deaths and cannibalism, and lower body weights.

Female subjects of child-bearing potential and male subjects with partners of child-bearing potential participating in the study will be required to use adequate contraception as defined in Section 8.7.1, and female subjects who are pregnant, lactating, or intending to become pregnant during the study are excluded from the study.

The Sponsor will undertake all reasonable measures, including thorough screening and safety monitoring procedures, to minimize the risk to subjects. Due to the potential of MT-7117 to increase liver function markers, liver function markers will be monitored at all planned study visits and assessment of AEs related to elevation of liver function markers and liver injury will be conducted. Additionally, subjects will be instructed to immediately stop study treatment if they meet any of the withdrawal criteria listed in Section 8.5.

Risk related to COVID-19 has been assessed. MT-7117 is not known to compromise the human immune system. In non-clinical repeated dose toxicity studies, there were no changes suggestive of immunosuppression. Completed Phase 1 and Phase 2 studies did not show increased risk of infection. Based on the evidence available so far, it is unlikely that MT-7117 exposure will increase the risk of COVID-19 infection; however, it is unknown if MT-7117 exposure will increase the risk of COVID-19 infection. There may be additional risk to participants due to exposure to COVID-19 during study related visits (depending on the country/region conditions).

At present, pharmacological treatment for EPP and XLP is not widely available in the world. Avoidance of sunlight or strong indoor light altogether is essential to manage the disease. Data from the Phase 2 study, MT-7117-A01, suggests there will be a direct benefit for EPP/XLP patients to participate in this Phase 3 study. Spring/Summer is where the unmet need for EPP/XLP patients wanting to be outside is strongest, and even during the present pandemic, patients and patient advocate groups are urging the Sponsor to start this study.

The study design is such that it allows for 4 mobile visits, which reduces commuting exposure of the subject to the clinical site. Mobile nurses will be provided with personal protection equipment when visiting the subject's location for both the subject's and the nurse's safety. Additionally, a travel concierge service is available to subjects for their personal transportation in a private car to clinical sites for in-clinic visits (depending on mileage and area). The travel concierge service, their private cars, and chauffeuring staff will follow all the COVID-19 protection protocols to assure the safety of the subjects.

Subjects will be encouraged to observe social distancing, wear face masks/coverings, and avoid social gatherings during the conduct of the clinical trial and during on-site visits, as long as COVID-19 is prevalent. Additionally, the Sponsor will monitor country conditions and prepare contingency plans with the advice of the Principal Investigators for COVID-19 related restrictions that may prevent site visits. Based on the combination of the assessed risk and benefit assessment, the expected study timelines, and the mitigations currently in place, it has been determined by MTDA that the subjects' benefits will exceed the risk of being in contact with COVID-19.

Overall, there is a favorable benefit-risk profile to support the continued development into Phase 3 of MT-7117 in the treatment of patients for adults and adolescents with EPP or XLP for both the [redacted] and [redacted] dose.

7.4 Rationale for Dose Selection

The current Phase 3 study will investigate the efficacy and safety of MT-7117 in subjects with EPP or XLP. In the MT-7117-E01 human healthy volunteer study, single doses up to [redacted] in healthy female subjects have been shown to be safe. Some reversible increases in skin pigmentation, consistent with the expected pharmacology, were noted following repeat dosing and appeared to show a dose-related trend. No SAEs occurred during Study MT-7117-E01. In the MT-7117-A01 Phase 2 study of MT-7117 in 102 subjects with EPP or XLP, both [redacted] and [redacted] MT-7117 were associated with greater improvement compared to placebo in average daily time to prodromal symptoms at Week 16. During the 16 weeks dosing and 6 weeks follow up, there were no major safety concerns with the doses of [redacted] and [redacted] MT-7117. One SAE of anaphylaxis was observed during the study. The event causality was considered not reasonably possible in relation to the investigational drug due an identified food reaction. It was noted MT-7117 [redacted] group had a higher incidence of TEAEs, severe TEAEs, TEAEs causing discontinuations compared to MT-7117 [redacted], which were primarily driven due to hyperpigmentation events, headache, nausea, vomiting, and diarrhea. Additional details can be found in the Investigator's Brochure.[11]

A population PK model was developed from the adult data in Studies MT-7117-E01 and MT-7117-A01. Steady-state Maximum observed plasma concentration (C_{max}) and Area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24}), which were calculated from individual post-hoc parameters of 124 subjects using population PK model, were used to develop a target range for exposures in the pediatric population. The adult population PK model was then used to simulate the expected exposures in pediatric patients from ≥12 to ≤17 years

of age. [redacted] In summary, based on available clinical MT-7117 data, it is considered most likely that either [redacted] or [redacted] will demonstrate a suitable efficacy/safety profile.

8 SELECTION AND WITHDRAWAL OF SUBJECTS

The Sponsor does not operate a protocol waiver system for eligibility criteria.

8.1 Number of Subjects

Originally a total of approximately 159 subjects are planned to be randomized in this study (approximately 53 subjects in each treatment group).

Due to the rapid enrollment rate in the last few months of the enrollment period after COVID-19 restrictions were lifted in many countries, a total of 184 subjects were randomized in this study (approximately 61 subjects in each treatment group).

8.2 Recruitment Methods

A sufficient number of subjects will be screened to ensure the planned sample size will be achieved. Each subject will be screened according to the criteria described in Sections 8.3 and 8.4. Only subjects who are eligible for the study will be randomized.

8.3 Inclusion Criteria

A subject will be eligible for enrollment in the study if ALL of the following criteria apply:

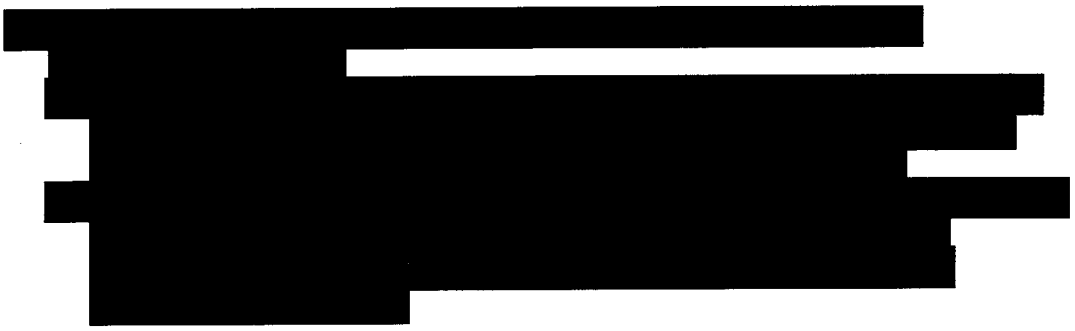
1. Subjects provided written informed consent to participate. For minor subjects, both minor assent and parental consent will be provided.
2. Male and female subjects with a confirmed diagnosis of EPP or XLP based on medical history, aged 12 years to 75 years, inclusive, at Screening.
3. Subjects have a body weight of ≥30 kg.
4. Subjects are willing and able to travel to the study sites for all scheduled visits.
5. In the Investigator's opinion, subject is able to understand the nature of the study and any risks involved in participation, and willing to cooperate and comply with the protocol restrictions and requirements (including travel).
6. Female subjects who are non-lactating and have a negative urine pregnancy test at baseline visit prior to receiving the first dose of study drug.
7. Female subjects of childbearing potential and male subjects with partner of child-bearing potential currently using/willing to use 2 effective methods of contraception including barrier method as described in Section 8.7.1.

8.4 Exclusion Criteria

A subject will NOT be eligible for this study if ANY of the following criteria apply:

1. History or presence of photodermatoses other than EPP or XLP.
2. Subjects who are unwilling or unable to go outside during daylight hours most days (e.g., between 1 hour post-sunrise and 1 hour pre-sunset) during the study.
3. Presence of clinically significant hepatobiliary disease based on Liver function test (LFT) values at Screening.

4. Subjects with AST, ALT, ALP ≥3.0 × upper limit of normal (ULN) or total bilirubin >1.5 × ULN at Screening.
5. Subjects with or having a history (in the last 2 years) of excessive alcohol intake in the opinion of the Investigator.
6. History of melanoma.
7. Presence of melanoma and/or lesions suspicious for melanoma at Screening.
8. History of familial melanoma (defined as having 2 or more first-degree relatives, such as parents, sibling and/or child).
9. Presence of squamous cell carcinoma, basal cell carcinoma, or other malignant skin lesions. Any suspicious lesions or nevi will be evaluated. If the suspicious lesion or nevi cannot be resolved through biopsy or excision, the subject will be excluded from the study.
10. History or presence of psychiatric disease judged to be clinically significant by the Investigator and which may interfere with the study evaluation and/or safety of the subjects.
11. Presence of clinically significant acute or chronic renal disease based upon the subject's medical records including hemodialysis; an estimated glomerular filtration rate (eGFR) <60 mL/min as calculated by the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (2009) for adults and by the Schwartz creatinine equation for adolescents (2009) (Appendix 2, Section 18.2). Modification of Diet in Renal Disease (MDRD) can be used for adults per local recommendations.
12. Presence of any clinically significant disease or laboratory abnormality which, in the opinion of the Investigator, can interfere with the study objectives and/or safety of the subjects.
13. Female subjects who are pregnant, lactating, or intending to become pregnant during the study.
14. Treatment with phototherapy within 3 months before Randomization (Visit 2).
15. Treatment with afamelanotide within 3 months before Randomization (Visit 2).
16. Treatment with cimetidine within 4 weeks before Randomization (Visit 2).
17. Treatment with antioxidant agents within 4 weeks before Randomization (Visit 2), at doses which, in the opinion of the Investigator, may affect study endpoints (including but not limited to beta-carotene, cysteine, pyridoxine).
18. Chronic treatment with any scheduled analgesic agents including, but not limited to, opioids and opioid derivatives such as morphine, hydrocodone, oxycodone, fentanyl, or their combination with other unscheduled analgesics or non-steroidal anti-inflammatory drug (Percocet and Vicodin-like prescription drugs) within 4 weeks before Randomization (Visit 2). Acute use of scheduled narcotics greater than 3 months prior to randomization, Over the counter (OTC)s, such as Non-steroidal anti-inflammatory drug (NSAID)s or aspirin for analgesia, or prior temporary use of scheduled agents within 3 months of screening are not excluded.
19. Treatment with any drugs or supplements which, in the opinion of the Investigator, can interfere with the objectives of the study or safety of the subjects.
20. Previous exposure to MT-7117 (this does not include placebo treated subjects).
21. Previous treatment with any investigational agent within 12 weeks before Screening OR 5 half-lives of the investigational product (whichever is longer).



8.5 Withdrawal of Individual Subjects

A subject will be withdrawn from study if ANY of the following criteria are met:

1. The subject requests to voluntarily withdraw from further participation in study.
2. The subject is significantly noncompliant with the protocol.
3. Continuing in the study would be detrimental to the subject's safety in the opinion of the Investigator, e.g.,
   a. The subject experiences intolerable AEs, SAEs, or AESIs.
   b. The subject has clinically significant changes in safety parameters at any of the post-dose time points, as confirmed with a repeat assessment performed as soon as possible after the initial out-of-range result.
   c. The subject experiences any clinically significant adverse findings from postbaseline nevi evaluation and adverse change is demonstrated histologically and confirmed by central pathologist. Visual evaluation of change will not be acceptable criteria for permanent discharge from treatment (Section 10.9.4).
   d. Development of any clinically significant liver dysfunction, as follows:
      i. ALT or AST >8 × ULN.
      ii. ALT or AST >5 × ULN for more than 2 weeks.
      iii. Elevated total bilirubin >2 × ULN and ALT or AST >3 × ULN or
      iv. Symptoms consistent with liver dysfunction (e.g., fatigue, nausea, vomiting, abdominal pain or tenderness, fever, rash, eosinophilia >5%) with concomitant ALT or AST values >3 × ULN.

Subjects meeting the laboratory criteria of ALT/AST and total bilirubin defined above (with or without alternative etiology), regardless of whether clinically significant or not, should be reported as a hepatic AE of special interest (AESI) (see Section 12.3). The Investigator should discuss with the Sponsor Medical Monitor about the determination of etiology and the potential of withdrawal. The abnormal laboratory values should be confirmed by repeated measurements at local or central laboratory as soon as possible (i.e., within 7 days after the first observation).

Any other laboratory or clinical abnormality that the Sponsor Medical Monitor and/or Investigator considered as clinically significant should be considered as potential reason for withdrawal.

These subjects will be discontinued from treatment but may be followed per protocol (see

Section 12.6). In addition, a subject may be withdrawn from treatment at any time for reason(s) other than those listed here. Subjects who have withdrawn from study drug cannot resume study drug.

Subjects who are permanently withdrawn from study drug early should be encouraged to continue in the study and complete all other study assessments without receiving study drug. In case a subject withdraws from treatment and elects not to continue in the study, every attempt should be made to have the patient complete an early termination visit (Visit 7 or Visit 11) within 14 days of withdrawal, and follow-up visit assessments (Visit 12) at 6 weeks after early termination visit. However, PK blood samplings are not required for these subjects if their last dose of study medication is 7 days or more before the time point of PK blood samplings.

If a subject is discontinued prematurely from the treatment or the study, the date the subject is withdrawn from the treatment and the study and the reason for withdrawal from the treatment and the study will be recorded on the site source documents and in the electronic Case Report Form (eCRF).

In case of permanent discontinuation from study, the end-of-treatment and follow-up visit assessments should be performed, as completely as possible (Table 9-1). Unresolved AEs and SAEs will be followed up on according to Section 12.10. For discontinued subjects who will not revisit the clinic, the site will perform scheduled phone calls for the collection and source documentation for safety information (AEs, concomitant medication, and date of last dose of medication). Return of unused medication and any other materials (e.g., diary) will be performed by courier where allowed.

In the event that a subject elects not to return to the study site for the end of treatment or follow-up visit, the Investigator must make every effort to contact the subject to review/capture all AEs, assess dosing compliance, review concomitant medication, and make every effort to complete all end of study assessments.

Subjects withdrawn from the study following randomization onto double-blind treatment may not re-enter the study. Subjects withdrawn from treatment may remain on study and continue with study procedures off treatment based on the clinical discretion of the Investigator.

8.6 Study-Stopping Criteria

The study may be terminated by the Sponsor at any time upon becoming aware of data that could compromise the safety and/or well-being of subjects, or for any other reason it deems appropriate. Subjects may be withdrawn from treatment and remain on study.

8.7 Lifestyle Restrictions

Subjects must adhere to the following restrictions:

1. Follow study attendance guidelines.
2. Follow study physical activity and daily sun exposure guidelines.

3. Follow restrictions regarding concomitant medications that are described in Appendix 1 (Section 18.1).
4. Subjects must not take any prescribed or non-prescribed systemic or topical treatment (such as zinc oxide-containing sunscreen, herbal remedies, supplements, or the use of phototherapy, including tanning beds) at doses with known potential to have an effect on phototoxicity, photosensitivity in EPP or XLP, and/or increased pigmentation during the study. Such treatments include, but are not limited to afamelanotide, cimetidine, beta-carotene, cysteine, pyridoxine, and cholestyramine. Sunscreens without zinc oxide are permitted to be used.

These restrictions are described in more detail in the following sections, and in Section 18.1, a complete list of prohibited concomitant medications is provided.

8.7.1 Subject Contraception

Female subjects of child-bearing potential* must be willing and able to practice birth control for the duration of the study, from screening until 3 months after the last dose of study drug. Male subjects must be willing and able to practice birth control for the duration of the study, from the time of the first dose of study drug until 3 months after the last dose of study drug.

- **Female subjects** must be willing to use a highly effective method of birth control (ie, contraceptive measure with a failure rate of < 1% per year), in conjunction with male barrier contraception (ie, lubricated male condom with or without spermicide). Highly effective methods of contraception include:
    - Placement of an intrauterine device or intrauterine system.
    - Established use of oral, injected or implanted hormonal methods of contraception associated with inhibition of ovulation.
    - Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.)
    - Bilateral tubal ligation.
    - True abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Female subjects must not donate ova for the duration of the study, from the time of the first dose of study drug until 3 months after the last dose of study drug.

- **Male subjects** with partners of child-bearing potential must use a barrier method of contraception (ie, lubricated male condom with or without spermicide) in addition to a second method of acceptable contraception used by their female partners. In addition to the list of highly effective contraception methods above, other acceptable methods of contraception include:
    - Progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action.
    - Cap, diaphragm or sponge with spermicide (where available).

Male subjects must not donate sperm for the duration of the study, from the time of the first dose of study drug until 3 months after the last dose of study drug.

*Note: Women are considered to be of child-bearing potential unless they meet 1 of the following criteria as documented by the Investigator:

- Post-menopausal for at least 1 year, confirmed by follicle-stimulating hormone (FSH) assessment (> 40 mIU/mL).
- Hysterectomy, bilateral oophorectomy or salpingectomy.
- Congenital sterility.

Subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study.

8.7.2 Physical Activity and Subject Sun Exposure

Subjects are requested to go outside at least once-daily during daylight hours (e.g., between 1 hour post-sunrise and 1 hour pre-sunset) during the treatment period by the Investigators or designated study site staff. Time outside should be correlated with or limited by the onset of prodromal symptoms. Subjects will be asked to make note of time period spent outside or until the onset of prodromal symptoms in the sunlight exposure diary. Outside exposure is considered locations outside of a building such as the time riding in a car or train. Time next to a window indoors is not considered outside exposure.

Patients will be informed by the Investigator regarding the objectives of the study and the importance of the patient seeking some level of direct sun exposure on a daily basis. This discussion will include clarification that the goal is not to intentionally induce phototoxic reactions, but for the subject to spend enough time to generate some level of prodromal symptoms (negligible or mild pain). The goal of the study is to determine whether the study drug has an effect on increasing the symptom-free time in the sun and/or reducing the duration or intensity of symptoms associated with sun exposure. Once randomized, no subject will be coerced into direct sun exposure that would induce phototoxicity or discontinued for noncompliance if the subject expresses a concern for their own safety and well-being.

9 STUDY PLAN

9.1 Study Time and Events Schedule

Study assessments and corresponding event schedules are summarized in the schedule of assessments (Table 9-1).

9.1.1 Screening Phase

Screening assessments will be performed up to 42 days prior to Day 1 of the double-blind treatment period. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

9.1.2 Rescreening

If a subject has not met all eligibility criteria at the end of the Screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1-time following consultation with the Sponsor and Medical Monitor.

Rescreened subjects must first be registered as screen failures and subsequently registered as rescreens. Once the subject is registered as rescreened, a new screening window will begin. The rescreened subject will be reassigned a new unique Subject Identifier and the previous Subject Identifier will be noted. If the rescreening period begins more than 30 days after the original signing of the Informed Consent Form (ICF), all screening procedures, including ICF, must be repeated.

If the subject does not meet eligibility criteria for laboratory tests, the subject may undergo repeat laboratory tests up to 2 additional times during the 6-week Screening period. Repeat of laboratory tests is not considered rescreening.

Table 9-1 Schedule of Assessments

Study Period	**Screening**	**Double-blind Treatment**						**Double-blind Extension**				**Follow-up**
Visit Number	**Visit 1**	**Visit 2 (Randomization)**	**Visit 3[g]**	**Visit 4**	**Visit 5[g]**	**Visit 6**	**Visit 7[p] (EOT/ Rand)**	**Visit 8[g]**	**Visit 9[g]**	**Visit 10**	**Visit 11[q] (EOT/ DBE)**	**Visit 12[r] (EOS)**
Study Week	**Week -6 to Week 0**		**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 26**	**Week 28**	**Week 32**	**Week 39**	**Week 52**	**Week 32 or 58**
Study Day ± Window	**Day -42 to Study Day[a]**	**Day 1**	**Day 15±5**	**Day 29±7**	**Day 57±7**	**Day 85±7**	**Day 183±7**	**Day 197±7**	**Day 225±7**	**Day 274±7**	**Day 365±7**	**Day 225 or 407±7**
Informed consent/assent[b]	X											
Inclusion/exclusion criteria evaluation	X	X										
Demographics	X											
Medical history	X	X										
Randomization		X					Xf					
Body weight	X	X		X		X	X			X	X	X
Height	X											
Physical examination[c]	X	X		X		X	X			X	X	X
Vital signs[d]	X	X		X		X	X			X	X	X
12-lead ECG[e]	X						X				X	
Hematology/ coagulation, biochemistry & urinalysis[g]	X	X	X[g]	X	X[g]	X	X	X[g]	X[g]	X	X	X
Blood collection for porphyrin and protoporphyrin levels[h]	X			X		X	X			X	X	

Study Period	**Screening**	**Double-blind Treatment**						**Double-blind Extension**				**Follow-up**
Visit Number	**Visit 1**	**Visit 2 (Randomization)**	**Visit 3[g]**	**Visit 4**	**Visit 5[g]**	**Visit 6**	**Visit 7[p] (EOT/ Rand)**	**Visit 8[g]**	**Visit 9[g]**	**Visit 10**	**Visit 11[q] (EOT/ DBE)**	**Visit 12[r] (EOS)**
Study Week	**Week -6 to Week 0**		**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 26**	**Week 28**	**Week 32**	**Week 39**	**Week 52**	**Week 32 or 58**
Study Day ± Window	**Day -42 to Study Day[a]**	**Day 1**	**Day 15±5**	**Day 29±7**	**Day 57±7**	**Day 85±7**	**Day 183±7**	**Day 197±7**	**Day 225±7**	**Day 274±7**	**Day 365±7**	**Day 225 or 407±7**
Fitzpatrick skin type assessment[s]	X			X		X	X			X	X	
Pregnancy test[i]	X	X		X		X	X			X	X	X
PK sampling (blood)[j]		X		X		X	X			X	X	
Blood sampling for PGx[b]		X										
Dispensing of study medication		X		X		X	X			X		
Medication accountability				X		X	X			X	X	
Subject Question for study medication[k]							X					
PROMIS-57		X				X	X			X	X	X
PGIC				X			X				X	
PGIS		X		X		X	X			X	X	X
EOT/Exit interview questionnaire[l]							X					
Sunlight exposure diaries[m]	←											→
In-clinic sunlight exposure test[n]	X						X				X	

Study Period	Screening	Double-blind Treatment						Double-blind Extension				Follow-up
Visit Number	Visit 1	Visit 2 (Randomization)	Visit 3[g]	Visit 4	Visit 5[g]	Visit 6	Visit 7[p] (EOT/ Rand)	Visit 8[g]	Visit 9[g]	Visit 10	Visit 11[q] (EOT/ DBE)	Visit 12[r] (EOS)
Study Week	Week -6 to Week 0		Week 2	Week 4	Week 8	Week 12	Week 26	Week 28	Week 32	Week 39	Week 52	Week 32 or 58
Study Day ± Window	Day -42 to Study Day[a]	Day 1	Day 15±5	Day 29±7	Day 57±7	Day 85±7	Day 183±7	Day 197±7	Day 225±7	Day 274±7	Day 365±7	Day 225 or 407±7
Melanin density evaluation		X		X		X	X				X	X
Nevi evaluation[o]	X			X		X	X			X	X	X
Concomitant medication	←											→
Adverse events	←											→

Abbreviations: DBE= double-blinded extension; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PGx = pharmacogenomic(s); PK = pharmacokinetic; PROMIS = Patient-Reported Outcomes Measurement Information System.

[a] A minimum of 7 days of outside exposure data is required in the 14 days prior to randomization.

[b] Blood samples will be collected for PGx analysis for those subjects who have specifically given informed consent/assent for optional PGx analysis at Visit 2.

[c] Complete physical examination will be performed at Visit 1 and an abbreviated physical examination will be performed at all other specified time points.

[d] Vital signs include measurement of sitting blood pressure, respiratory rate, pulse rate, and body temperature.

[e] ECG will be assessed at Visit 7 for subjects who do not elect DBE. For subjects who elect DBE, ECG will be assessed at Visit 11.

[f] All study subjects who elect to participate in the 26-weeks DBE will be re-randomized. Subjects that received MT-7117 during the blinded period will continue the DBE in the same treatment arm and remain blinded. Subjects that received placebo will be randomized to receive MT-7117 [redacted] or [redacted] in 1:1 ratio for the 26 weeks DBE period. For subjects with [redacted] the [redacted] dose will be administered without re-randomization.

[g] At Visits 3, 5, 8, and 9, subjects may have mobile units or in-clinic visits to measure liver function markers (ALT, AST, GGT, ALP, direct and total bilirubin). Blood samples for liver function markers will be shipped to the central laboratory.

[h] Plasma total porphyrins and erythrocyte protoporphyrin will be assessed at Visits 1, 4, 6, 7, 10, and 11.

[i] For female subjects of child-bearing potential, a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test will be performed at Visits 2, 4, 6, 7, 10, 11, and 12.

[j] For subjects who are ≥18 to ≤75: PK blood samples for MT-7117 will be collected and processed at Visit 2 (pre-dose), Visits 4, 6, 10, and 11 (any time), and Visit 7 (at the visit and 3 to 4 hours after the first PK sample collection [both post-dose]). Date and time of most recent dose, and date and time of PK sample collection will be recorded. Subjects who are ≥12 to ≤17 years old will have 9 PK samples at 3 time points collected: Visit 2 at 2, 4, 6, and 8 hours post-dose, Visit 6 at pre-dose and 3 hours post-dose, and Visit 7 at pre-dose and 2, and 4 hours post-dose.

[k] Subjects will be asked whether they believe they received active or placebo treatment.

[l] EOT/Exit interview will only be performed in selected countries.

[m] Sunlight exposure data, presence of prodromal symptoms and sunlight-induced phototoxic reactions, their severity, and their onset/duration will be collected from Visits 1 through 12. Diary training will be performed at the first in-clinic visit during the screening period.

[n] In-clinic sunlight exposure test should be done once before randomization (Visit 1 or 2) and once at Visit 7. For subjects who elect DBE, the test is also performed at Visit 11.

[o] Nevi evaluation will be performed locally by a dermatologist or qualified site staff. Baseline nevi evaluation will be performed at any time during the Screening period before Randomization (Visit 1 or 2). The Nevi evaluation at Visit 12 is to assess for the reversibility if any suspicious nevi changes were observed during treatment as per the Investigator's (and/or dermatologist's or other qualified site staff) judgment. Any follow-up will be recorded in the eCRF. Nevi assessment will be described in a separate document.

[p] These assessments will be performed at Week 26 or early termination visit from the double-blind treatment period. If the visit is due to early termination, no double-blinded extension study medication is to be dispensed.

[q] These assessments will be performed at Week 52 or early termination visit from the double-blinded extension period.

[r] All subjects will return to the study site for a 6-week follow-up visit at Week 58 (Week 32 if DBE is not elected) or 6 weeks after early termination visit. For discontinued subjects who will not revisit the clinic, the site will perform scheduled phone calls for the collection and source documentation for safety information (AEs, concomitant medication, and date of last dose of medication).

[s] Fitzpatrick skin type assessment should be done once before randomization.

9.2 Subject Informed Consent

Before performing any study procedures, the Investigator (or designated personnel) will ensure that the subject is given full and adequate oral and written information about the study and the subject must sign the Informed Consent Form (ICF), as described in Sections 10.1 and 15.2.1.

9.3 Post-Study Access to Treatment

MT-7117 will not be available to subjects following completion or termination of the study, in accordance with the study information given to the subjects.

9.4 Unscheduled Visits

An unscheduled visit is defined as follows:

- Any visit to the Investigator site outside of the protocol specified time points due to safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, measuring device failure, confirmation of out-of-range results), where the subject is seen by study personnel.
- Any visit by the mobile units or in-clinic visits outside of the protocol specified time points when a repeated measurement of liver function markers is required (e.g., safety reasons, obvious measurement errors, measuring device failure, confirmation of out-of-range results).

Additional unscheduled samples for safety assessments may be performed at the discretion of the Investigator, if deemed necessary. All unscheduled visits and assessments performed during the visits will be recorded in the eCRF.

10 STUDY PROCEDURES

Procedures will be performed according to the schedule of assessments (Table 9-1).

10.1 Informed Consent Form

The Investigator or designee will fully explain the nature of the study to subjects using the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved ICF. When the subject agrees to participate in the study, the subject must voluntarily sign an ICF before the initiation of any study procedures. A copy of the signed and dated informed consent (or assent for adolescent subjects) document will be given to the subject. The signed and dated original ICF will be retained by the Investigator. Informed consent will be obtained from all subjects. An assent will be obtained from all adolescent subjects. A subject cannot enter the study until he or she has signed and dated the ICF.

For adolescent subjects, according to local regulations, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the applicable informed consent form approved for the study prior to clinical study participation. In such cases, records on the relationship between the subject and the parent(s)/legal representative consenter should be maintained in source documents. The explicit wish of an adolescent who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigation.

The Investigator or designee is responsible for ensuring that the subject understands the risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing any new information in a timely manner that may be relevant to the subject's willingness to continue his/her participation in the study.

Any information conveyed to the subject in advance of screening visit 1 used to recruit subject or enable travel arrangements require IRB/IEC submission and approval per local requirement.

Certain procedures outlined in this protocol are optional and are not required if subject opts out. These procedures include sample collection for Pharmacogenomics (PGx) testing obtained for the noted exploratory endpoints. Biopsy may be requested for safety if they arise via the post-baseline nevi assessments per the investigator judgement. For PGx testing, DNA and messenger ribonucleic acid (mRNA) will be measured. These procedures will be performed only on subjects who specifically provided consent/assent to undergo these optional procedures. Separate informed consent/assent for PGx testing will be required.

10.2 Demographics

The following subject characteristics will be recorded at Screening: year of birth, sex, weight, height, ethnicity, race, and a unique subject identifier in MT-7117-A01 study only if the subject took placebo in the MT-7117-A01 study.

10.3 Medical History

Medical, medication, smoking, alcohol, psychiatric disease, and surgical history will be recorded. Medical/surgical history includes any medical condition or surgical history before Screening. In addition, the detailed history of hepatic injury (e.g., viral hepatitis, autoimmune hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, biliary tract disease) will be recorded.

10.4 Prior and Concomitant Medication

Prior medications are defined as any medication taken before Screening.

Any prior medication, including prescription and over-the-counter medications, taken within 1 month before Screening will be recorded on the eCRF. Information recorded will include: name of medication, dose, duration of and reason for use. It should be noted if subjects have ever used afamelanotide.

Concomitant medication is defined as any medication, other than study medication, which is taken during the study, including prescription, over-the-counter medications, herbals, dietary supplements, and recreational drugs. All concomitant medications taken while the subject is participating in the study will be recorded.

Concomitant medication will be given only if deemed necessary by the Investigator or the subject's personal physician.

10.5 Fitzpatrick Skin Type Assessment

A Fitzpatrick scale test[10] will be completed at the times shown in the schedule of assessments (Table 9-1). The results will be recorded in the source documents and the eCRF. The score for defining skin type will be recorded in the source documents. An example of the Fitzpatrick scale test is presented in Section 18.3 (Appendix 3).

10.6 Subject Questionnaire for Study Medication

At Week 26 or early termination visit (Visit 7), subjects will be asked whether they believe they received active or placebo treatment. The results will be recorded in the source documents and the eCRF.

10.7 Efficacy Assessments

10.7.1 Primary Efficacy Endpoint

10.7.1.1 Sunlight Exposure Diary – Outdoor Exposure and Prodromal Symptoms

Subjects will complete the sunlight exposure diary on a daily basis from Screening to the follow-up visit. The sunlight exposure diary is a smartphone device and examples of the questions (extract) are presented in Section 18.4 (Appendix 4).

Subjects will record their sunlight exposure time in the sunlight exposure diary. For each sunlight exposure, they will record the presence, duration (onset time of the first symptom and recovery time), and severity of the prodromal symptoms (see below). The severity of prodromal symptoms will be measured using an 11-point Likert scale ranging from 0 to 10, with 0 indicating no pain or discomfort and 10 indicating greatest severity of pain.

Prodromal symptom is the terminology used for the warning signals that have been described by EPP and XLP patients through patient roundtable discussions and literature as their signal to get out of the sun. Subjects will be instructed to recognize the following photo-induced symptoms as prodromal:

- Burning/hotness/heating up
- Tingling
- Itching/scratchy
- Stinging
- Others

Subject responses in the sunlight exposure diary will be used to investigate the primary efficacy endpoint. The data from the diary will also be used for the secondary and other efficacy assessments.

Further details will be provided in a separate study reference manual, and statistical assessment methods for this study endpoint are described in Section 14.3.2.1.

10.7.2 Secondary and Other Endpoints

10.7.2.1 Sunlight Exposure Diary – Phototoxic Reactions

A phototoxic reaction is characterized based on patient input as a painful skin reaction that occur subsequent to a prodromal symptom. Depending on duration protracted sun exposure beyond occurrence of a prodrome, the intensity of the skin reaction can be moderate to severe and lasting up to several days.

Sunlight-induced phototoxic reactions, its severity, and duration (onset time and recovery time) will also be recorded separately in the dedicated part of the sunlight exposure diary.

The severity of sunlight-induced phototoxic reactions will be measured using an 11-point Likert scale ranging from 0 to 10, with 0 indicating no pain and 10 indicating greatest severity of pain.

10.7.2.2 In-Clinic Sunlight Exposure Test

In-clinic sunlight exposure test will be performed at the times shown in the schedule of assessments (Table 9-1).

Site staff will lead subjects into a setting with sun-light exposure and subjects will be provided with a timer (e.g. preferably outdoors) to collect the period of time it takes for the subject to experience the onset of the first prodromal symptom. Upon entry of the subject into the sunlight

exposed setting, the timer will be started (as well as the time of day). Site staff will direct the subject to stop the timer upon the onset of the first sensation of prodromal symptoms. The time in minutes obtained from the time of sun-light exposure to onset of prodromal symptoms, as well as the time of day the assessment was performed, will be collected. This assessment should be performed in a manner that lends consistency to the amount of daylight exposure and/or intensity where feasible. Where weather conditions restrict the ability to capture this assessment, it will be so noted on the source and eCRF. Further instructions will be outlined in the protocol procedures manual.

10.7.2.3 Melanin Density Evaluation

Sites will assign unblinded personnel who will receive melanin density measurement training. Melanin density will be assessed at the times shown in the schedule of assessments (Table 9-1) using a hand-held spectrophotometer. The effect on pigmentation will be assessed in all subjects by measuring melanin density on 6 skin segments (forehead, left cheek, right inside upper arm, left medial forearm, right-hand side of abdomen, and left-hand side of buttock) as measured by spectrophotometer. The site will be required to successfully collect the data with specialized software and transfer to the designated data management entity.

Further details about the evaluations and unblinding protection will be provided in a separate study reference manual.

10.7.2.4 Patient-Reported Outcomes Measurement Information System Questionnaire

The PROMIS-57 questionnaire will be completed at the times shown in the schedule of assessments (Table 9-1).

The PROMIS-57 assesses each of 7 domains with 8 questions per domain; physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference (including pain intensity). The effect of treatment with MT-7117 on QOL in subjects with EPP or XLP will be assessed by measuring the change in PROMIS-57 score (total and each domain).

An example of the PROMIS-57 questionnaire is presented in Section 18.5 (Appendix 5).

10.7.2.5 Patient Global Impression of Change

The PGIC is used to assess the subject's rating of overall improvement. Subjects rate their perceived change on a 7-point scale from 'very much improved to 'very much worse'. The PGIC will be used to evaluate the subjects' perspective on the meaningfulness and impact of an increased time to prodromal symptoms and their quality of life.

The PGIC will be completed at the times shown in the schedule of assessments (Table 9-1). An example of the PGIC is presented in Section 18.6 (Appendix 6).

10.7.2.6 Patient Global Impression of Severity

The PGIS is used to assess the subject's rating of severity of overall status. Subjects rate their perceived change on a 5-point scale from 'none' to "very severe'.

The PGIS will be completed at the times shown in the schedule of assessments (Table 9-1). An example of the PGIS is presented in Section 18.7 (Appendix 7).

10.7.2.7 Qualitative End of Treatment/Exit Interview Questionnaire

The objective of the qualitative interviews is to elicit the key symptoms and impact associated with EPP or XLP as well as the effect of MT-7117 in relation to symptoms and impact experienced during the clinical study as described by patients in their own words.

A qualitative interview will be conducted by phone and within 14 days after completion of the end of treatment/early termination visit (see Table 9-1). A single individual telephone interview will be conducted with English-speaking subjects who provide informed consent/assent to participate in the interview. These interviews will be performed at selected sites/countries.

10.8 Pharmacokinetic Assessments

Blood samples will be collected by direct venipuncture in a suitable forearm vein. The actual date and time of each blood sample and the most recent dose date and time will be recorded in the source document and eCRF.

For each PK assessment in ≥18 to ≤75 years old, 1 blood sample of approximately 4 mL will be collected to ensure there is sufficient plasma for primary and contingency samples.

For each PK assessment in ≥12 to ≤17 years old, 1 blood sample of approximately 2 mL will be collected.

Subjects enrolled in Japan will have PK samples collected as described in a separate document.

Sample handling details will be described fully in a separate document.

10.9 Safety Assessments

Please refer to Section 12 for details of AE management.

10.9.1 Physical Examination

The complete physical examination will consist of a routine assessment of major body systems: abdominal, respiratory, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, and 'other'.

The abbreviated physical examination will consist of a routine assessment of the following body systems: abdominal, respiratory, cardiovascular, general appearance, and 'other'.

10.9.2 Vital Signs

The subject will undergo an assessment of blood pressure using a blood pressure recording device with an appropriate cuff size and with the subject in a sitting position. It is recommended that the subject rests for at least 5 minutes prior to this measurement. The same arm will be used for all measurements. Pulse rate, respiratory rate, and body temperature will also be measured.

The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'.

Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

10.9.3 Electrocardiogram

A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in the supine position. The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal CS', or 'abnormal NCS'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

10.9.4 Nevi Evaluation

Nevi will be assessed at the specified timepoints shown in the schedule of assessments (Table 9-1). Baseline nevi evaluation will be conducted at any time (Visit 1 or 2) before randomization.

Nevi will be assessed locally by a visual full body examination performed by a dermatologist or other qualified site staff. Any subject with suspicious nevi of clinical concern will have treatment temporarily discontinued and be referred for further nevi evaluation (e.g., biopsy), as deemed necessary by the dermatologist or other qualified site staff.

Any biopsy samples collected during the study will be sent for evaluation to the central pathology lab. If there are any clinically significant adverse findings from the biopsy, subjects will not be allowed to resume study drug and will be discontinued from study treatment. Adverse change must be demonstrated histologically and confirmed by central pathologist. Visual evaluation of change will not be acceptable criteria for complete discharge from treatment. If central assessment determines that lesion or nevi is benign, and the findings are not clinically significant, subject will be allowed to resume study treatment at the same dose when study drug was interrupted. Clinical sites will have access to a centralized dermatology specialist with experience on nevi. The centralized dermatology specialist will be available to communicate with the Investigator, dermatologist and/or qualified staff on the changes of any expected potential changes in nevi and advice on the process management prior and after biopsy.

The results will be recorded in the source documents and the eCRF as well as shared and discussed with the subject. Nevi of clinical concern must be recorded as AE.

Nevi assessment details will be fully described in a separate document.

10.9.4.1 Central Pathology Laboratory

Central pathology laboratory details will be fully described in a separate document.

10.9.5 Routine Laboratory Evaluations

Blood and urine samples will be collected for routine clinical laboratory safety evaluations according to the schedule of assessments (Table 9-1).

The specific laboratory parameters evaluated during the study are presented in Table 10-1.

10.9.5.1 Hepatic Markers

At Visits 3, 5, 8, and 9, subjects may undergo mobile laboratory or in-clinic visits for sample collection to measure biochemistry (liver function) markers (ALT, AST, GGT, ALP, direct and total bilirubin). Blood samples for liver function markers will be shipped to the central laboratory and the central laboratory will measure the liver markers.

10.9.5.2 Additional Laboratory Assessments

Additional laboratory safety evaluations will be performed at other times, if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of laboratory safety evaluations is required. Any changes to the scheduled times of laboratory safety tests will be agreed with the Sponsor and documented in the Trial Master File.

The Investigator will perform a clinical assessment of all laboratory safety data. The Investigator will record the assessment as 'normal', 'abnormal CS', or 'abnormal NCS'. Lab test abnormalities of clinical significance will be reported as AEs. Repeat lab tests or measurements will be performed if needed.

If subjects will meet treatment withdrawal criteria for elevated liver function tests, the subjects should be treated using standard of care as directed by the Investigator and followed until resolution (Section 8.5).

Table 10-1 Routine Laboratory Evaluations

Hematology:	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
Platelet count	Mean corpuscular volume
Red blood cell count	White blood cell count and differential
Biochemistry:	
Alkaline phosphatase	Cholesterol
Aspartate aminotransferase	Triglycerides
Alanine aminotransferase	High-density lipoprotein cholesterol
Gamma-glutamyl transpeptidase	Low-density lipoprotein cholesterol
Potassium	Protein (total)
Sodium	Albumin
Chloride	Creatine kinase
Inorganic phosphate	Creatinine
Glucose	Ferritin
Bilirubin (direct and total)	Vitamin D
Blood urea nitrogen	
Coagulation:	
Prothrombin time	Activated partial thromboplastin time
International normalized ratio	
Urinalysis:	
Specific gravity, pH, protein, glucose, ketones, urobilinogen, blood	
Microscopic examination[a]	

[a] Performed only if required, based on urinalysis results

Blood and urine samples will be analyzed by the central laboratory and/or specialized laboratory where applicable using standard methods. Procedures for the handling of samples will be described in full in a separate document.

10.9.6 Pharmacogenomics

Blood samples will be collected for PGx analysis for those subjects who have given their consent/assent for optional PGx analysis at Visit 2.

[redacted] Samples may be retained for future research use in genetic analysis for EPP or XLP and/or any efficacy/safety concern occur.

Sample handling processing of PGx samples will be described fully in a separate laboratory manual.

10.9.7 Porphyrin and Protoporphyrin Levels

Plasma total porphyrins and erythrocyte protoporphyrin will be assessed at Visits 1, 4, 6, 7, 10, and 11.

11 STUDY TREATMENT

11.1 Investigational Medicinal Product

11.1.1 Drug Product

MT-7117 and matching placebo [redacted] are light-orange, [redacted] with no identifying marks. MT-7117 [redacted] contain [redacted] of active drug product (its free-base form). The matching placebo [redacted] will be manufactured to be physically identical to the MT-7117 [redacted]. All MT-7117 [redacted] and the matching placebo [redacted] will be manufactured, tested, and released according to Good Manufacturing Practice (GMP).

A bulk supply of MT-7117 [redacted] and matching placebo [redacted] will be packed into [redacted], placed into [redacted] and shipped to [redacted] for packaging into finished Investigational medicinal product (IMP).

Individual subject doses will be packed in [redacted] using [redacted], then labeled and released from [redacted] according to GMP. [redacted] will perform Qualified Person (QP) certification of the finished IMP for use in the UK. [redacted] will perform Qualified Person (QP) certification of the finished IMP for use in the EU. All labeling will comply with applicable regulatory requirements.

11.1.2 Study Drug Supply

The Sponsor will provide MT-7117 and placebo [redacted] in [redacted] to each site, for each subject, for the duration of their participation in the study. The Interactive Web-based Response System (IWRS) will allocate sufficient uniquely-numbered, blinded [redacted], to be dispensed by the Investigator, study nurse or hospital pharmacist, according to the subject's randomized treatment group (MT-7117 [redacted], [redacted], or placebo) and study visits. Each subject will take 2 [redacted] per day with or without food.

Subjects will be instructed to bring their study medication with them to each visit. Subjects will return all study medication that may remain in their possession to the study staff at the end of treatment visit. In cases where subjects forget to return to the clinic with their [redacted], sites will be instructed to inquire as to the subjects daily dosing compliance, capturing total number of days missed. Subjects will be instructed to return medication packaging and empty [redacted] at the follow up visit.

11.1.3 Formulation, Packaging, Site Storage, and Labeling (MT-7117)

Study medication [redacted] will be provided in 2 strengths: 0 mg (placebo) and [redacted] (MT-7117) [redacted]. Study medication will be provided to the study sites in labeled [redacted]. All study medication should be stored according to the IMP clinical label.

Required study site documentation for MT-7117 [redacted] will include, but may not be limited to, the following information:

- Receipt date.
- Description of medication package, and medication product.
- Lot number or code/Batch number or code.
- Expiration and manufacturing dates.
- Dispensing information.
- Investigational New Drug Application (IND) number.
- Certificate of compliance.

11.1.4 Shipping, Receipt, Handling and Storage

On receiving a shipment of finished study medication at the Investigator site, the Investigator or designee will conduct an inventory check and complete a supplies-receipt document, the original of which will be retained at the Investigator site. In addition, a copy must be returned to the Sponsor or designee. The Investigator or designee will maintain a record of all study medication received and returned.

Study medication at the Investigator site will be stored according to the conditions stated on the IMP clinical label in a locked, restricted-access area. A temperature log recording the daily continuous temperature of the storage area will be maintained (including weekends). Any study medication storage temperature deviations will be reported to the Sponsor as soon as possible.

11.1.5 Dispensing

At each visit, the Investigator or designee will provide the subject with the allocated dose. A record of the study medication dispensed to each subject will be maintained by the Investigator or designee in an Investigational Product Accountability Log. Dispensed study drug will not be re-allocated to a subject.

In the cases where subject encounters a missed visit that renders a subject without sufficient medication to maintain daily dosing (e.g., a subject resides out of state relative to the Investigator's location and experiences a travel conflict), the site may ship an additional [redacted] to the subject upon written Sponsor approval. In these instances, the Sponsor [and/or the Contract Research Organization (CRO) designee] will assist the site to ensure the process is documented appropriately. Shipments made in these rare instances will require that IMP be maintained within the required temperature range along with confirmation of receipt by the study subject. This process will not be allowed where site policies prohibit it. Subjects should return to the clinical site to complete the scheduled visit, required assessments, and to have study medication dispensed.

11.1.6 Study Medication Accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study medication in an Investigational Product Accountability Log. Medication accountability will be noted by the field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused study medication and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

11.1.7 Disposal and Destruction

At study close-out, and as appropriate during the course of the study and only once full accountability has taken place, the Investigator will return all used and unused study medication, packaging, medication labels, and a copy of the completed Investigational Product Accountability Log to the Sponsor's designated monitor or to the address provided in the Investigator Binder at each site.

The study medication supply may be destroyed at the designated Sponsor facility or third party, only once authorization to destroy has been given by the Sponsor. Sites with documented drug destruction procedures and facilities may destroy drug on site only once authorization to destroy has been given by the Sponsor.

11.2 Dosing

Subjects are to self-administer study medication - 2 [redacted] once daily in the morning with or without food given as PI advice.

MT-7117 and/or placebo [redacted] should be swallowed whole with approximately 240 mL of water (subjects may drink an additional 240 mL of water if they have difficulty swallowing the [redacted]). The [redacted] are not to be chewed, crushed, dissolved, or divided.

11.3 Compliance

The prescribed dosage, timing, and mode of administration of study medication will not be changed. Subjects will be asked questions regarding the compliance, any departures from the intended regimen will be recorded in the eCRF.

Study medication accountability and subject compliance will be documented throughout the double-blind treatment period using study-specific study medication dispensing and return record forms. For subjects who do not return their [redacted], the site will question each to determine compliance (e.g. number of doses missed since the last visit).

Subjects will be asked to return all unused medication including empty and partially used [redacted]. Study medication dispensed at the previous visit will be retrieved by the Investigator or designee and compliance assessed by returned medication count.

Non-compliance will be defined as taking ≤80% or ≥120% of study medication during any evaluation period (from any visit to the following visit).

11.4 Subject Identification

Each subject will be assigned a unique subject number at the screening visit. At Randomization, each subject will receive a unique randomization number. Both the subject number and the randomization number will be documented in the subject's source documents. The subject number will be used to identify subjects in the study.

A list identifying the subjects by their subject number will be kept at the Investigator site. The randomization numbers will be stored in IWRS database until the database lock.

11.5 Procedures for Assigning Subjects to Treatment Groups

Randomization will take place after confirmation of inclusion/exclusion criteria before the first administration of study medication on Day 1. Subjects will be randomly allocated on a 1:1:1 basis to 1 of 3 treatments (Section 7.1). For subjects with [redacted] subjects will be randomized to placebo or [redacted] in a 1:2 ratio. [redacted] eDiary data will be used to generate the stratum. A minimum of 7 days of outside exposure data is required within the 14 days prior to randomization.

If study subjects elect to participate in the 26-weeks DBE after end of Visit 7 (EOT/Rand), subjects will remain blinded and subjects will be re-randomized. Subjects that received MT-7117 during the blinded period will continue the DBE in the same treatment arm and remain blinded. Subjects that received placebo will be randomized to receive MT-7117 [redacted] or [redacted] in 1:1 ratio for the 26 weeks DBE period. For subjects with [redacted] the [redacted] dose will be administered without re-randomization and will not be blinded during the extension period.

11.6 Maintenance of the Study Blind and Unblinding

All study treatments will be double-blinded during the 52-week study; neither the subject nor the study site personnel will know which treatment is being taken. Each subject's treatment will be given a unique code number, traceable to the identity, dose, and batch number of the study medication. The IWRS will be used to hold treatment codes for each subject. The codes will only be accessible to authorized unblinded IWRS users.

The IWRS should not normally be accessed with a request to break the treatment code for reasons other than safety or in an emergency. Should the Investigator wish to break the code for such reasons, he/she are advised to consult the Sponsor (or designee) in advance where feasible. If this is not possible, the Investigator may access the IWRS to obtain the treatment code and provide the system with the reason for breaking the blind. The Sponsor should be notified as soon as possible thereafter. If the blind is broken for any individual subject, the subject must be withdrawn from the study, and any procedures accompanying withdrawal will be performed (Section 8.5).

The Sponsor and study team will remain blinded throughout the duration of the double-blind treatment of the study.

Because PK analysis will only be performed on samples from subjects receiving active medication, unblinded randomization codes will be given to PK lab.

An electronic list of randomization codes will be retrieved from IWRS and transferred to the Sponsor at the end of the study.

Since melanin density values could potentially be unblinding, adequate measures will be taken to protect the spectrophotometry data from disclosure to the sponsor and the study team until the end of the study. Melanin density component data will be measured by the dedicated unblinded site staff, securely uploaded to and processed by the dedicated unblinded data management team. The data handling procedure for melanin density will be described in the data management plan.

The handling of data that could potentially unblind the study will be defined in relevant study procedures documents (e.g., Unblinded Data Management plan or equivalent).

If study subjects elect to participate in the 26-weeks DBE after end of Visit 7 (EOT/Rand), subjects will remain blinded and subjects will be re-randomized. Subjects that received MT-7117 during the blinded period will continue the DBE in the same treatment arm and remain blinded. Subjects that received placebo will be randomized to receive MT-7117 [redacted] or [redacted] in 1:1 ratio for the 26 weeks DBE period. For subjects with [redacted], the [redacted] dose will be administered without re-randomization and will not be blinded during the extension period.

MT-7117 and placebo [redacted] will be physically identical in appearance and will be packaged identically and suitably labeled to maintain the blind for both the 26-week double-blind treatment period and the 26-week DBE treatment period.

12 ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs that occur from the time written informed consent/assent is obtained until the end of the follow-up period (6 weeks after the last treatment visit, for safety monitoring) will be recorded in the eCRF.

Even if the AE is assessed by the Investigator as not related to study medication, its occurrence must be recorded in the source documents and eCRF. AEs will be classified as occurring at 'baseline' if they occur before the administration of study medication. AEs will be classified as 'treatment-emergent' if they arise following the first administration of study medication in the double-blind treatment period (after randomization) or if a pre-dose AE increases in severity following dosing in the double-blind treatment period (after randomization).

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator or designee should inquire about the occurrence of AEs. The questioning should be open-ended and non-leading to avoid notifying either the subject or study site personnel of the actual treatment being administered.

12.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drugs, whether or not considered related to the study drugs

12.2 Definition of a Serious Adverse Event

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

Medical and scientific judgment should be exercised in deciding whether an AE is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of medication dependency or medication abuse. These should also usually be considered serious.

The term 'life threatening' refers to an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

Admission to a hospital as a new subject is deemed as meeting this criterion, even when the length of hospital stay was less than 24 hours. Transfer to other departments of the same hospital due to a newly emerged event during the hospitalization (e.g., transfer from the psychiatry ward to the internal medicine ward, from the internal medicine ward to the coronary intensive care unit, or from the neurology ward to the tuberculosis ward) is also counted as hospitalization.

SAEs will be recorded and reported as described in Section 12.8.

12.3 Adverse Events of Special Interest

One AESI that will be considered during this study includes hepatic AESIs, defined as

- Develop liver dysfunction defined as any one of the following:
  - ALT or AST >8 × ULN.
  - ALT or AST >5 × ULN for more than 2 weeks.
  - Elevated total bilirubin >2 × ULN and ALT or AST >3 × ULN or
  - Symptoms consistent with liver dysfunction (e.g., fatigue, nausea, vomiting, abdominal pain or tenderness, fever, rash, eosinophilia >5%) with concomitant ALT or AST values >3 × ULN.
- Hepatic AEs or hepatic laboratory abnormalities that lead to study medication interruption or discontinuation (see Section 8.5).
- Any other laboratory or clinical abnormality that Sponsor Medical Monitor and/or Investigator considered as significant.

12.3.1 Management and Evaluation of Hepatic Adverse Events of Special Interest

Hepatic AESIs should be treated per the Investigator's approved standard of care and assessed for possible alternative etiology(ies). Hepatic AESIs will be followed clinically until resolution.

Subjects meeting the laboratory criteria of ALT/AST and total bilirubin defined in Section 12.3 (with or without alternative etiology), regardless of whether clinically significant or not, should be reported as a hepatic AE of special interest (AESI). The abnormal laboratory values should be confirmed by repeated measurements as soon as possible (i.e., within 7 days after the first observation) at local or central laboratory. Regarding any subject who meets the AESI criteria, the Investigator should discuss with the Sponsor Medical Monitor about the determination of etiology and the possibility for suspension of dosing. Resumption of dosing will be considered based on the discussion with the Sponsor Medical Monitor and Investigator.

All hepatic AESIs (including event management and evaluation) will be recorded and reported similar to SAEs as described in Section 12.8.

12.4 Severity of Adverse Events

The severity of AEs will be classified according to the following criteria:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes discomfort and interferes with the subject's general condition.

Severe: The event causes considerable interference with the subject's general condition and may be incapacitating.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This will not be the same as 'serious', which will be based on subject/event outcome or action criteria usually associated with events that would pose a threat to a subject's life or functioning. Seriousness (not severity) will serve as a guide for defining regulatory reporting obligations.

12.5 Relationship of Adverse Events to Investigational Medicinal Product

The causal relationship of the AE to study medication will be determined as either 'a reasonable possibility' or 'no reasonable possibility,' and will be defined as having either one of the following:

- **A Reasonable Possibility** – The relationship of the clinical event to the study medication makes a causal relationship possible, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
- **No Reasonable Possibility** – The relationship of the clinical event to the study medication makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

12.6 Clinical Laboratory Abnormalities, and Other Abnormal Assessments

The Investigator will exercise medical judgment in deciding whether abnormal laboratory test results are clinically significant. Laboratory abnormalities which are clinically significant will be recorded as AEs or SAEs.

If an abnormal laboratory value or assessment is clearly related to a medically-defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values.

All 'abnormal, clinically significant' laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the

Investigator to be no longer clinically significant. Repeat laboratory tests or measurements will be performed if needed.

The criteria for determining whether an abnormal objective test result should be reported as an AE include:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. Test result leads to discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
4. Test result is considered to be an AE by the Investigator or Sponsor.

12.7 Recording and Reporting of Adverse Events

All AEs, regardless of the relationship to study medication, occurring from the time written informed consent/assent is obtained from a subject until the end of the safety follow-up period or the withdrawal of the subject from the study, and any AEs or SAEs reported spontaneously through the end of the safety follow-up period, should be reported to the Sponsor or designee.

NOTE: elective hospitalization or procedure/surgery planned before subject enrollment for a preexisting medical condition does not constitute an AE unless the underlying disease or condition worsens after signing informed consent/assent.

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The questioning will be open-ended and non-leading.

All AEs will be recorded in the source documents and AE eCRF. The AE eCRF will contain a description of the event, date of onset, date of resolution, severity, treatment required, relationship to study medication, action taken with the study medication, outcome, and whether the event is classified as serious.

The Investigator will evaluate the severity of the AEs (as defined in Section 12.4) and will assess the causality between the AEs and the study medication (as defined in Section 12.5).

Pre-existing illnesses, which started before entry and is still ongoing at the start of the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as medical history.

If the Investigator becomes aware of any new safety information, or any safety information which appears to be either study or study medication related after the final follow-up period, then they must notify the Sponsor or the designee immediately.

12.8 Recording and Reporting of Serious Adverse Events or Hepatic Adverse Events of Special Interest

All SAEs and Hepatic AESI occurring from the time written informed consent/assent is

obtained from a subject until the end of the safety follow-up period or the withdrawal of the subject from the study must be reported to the Sponsor or the designee using the ***Serious Adverse Event/Adverse Event of Special Interest (SAE/AESI) in a Clinical Study Form*** within 24 hours of the Investigator becoming aware of the SAE/AESI. All SAE/AESIs must also be entered in the AE section of the eCRF as soon as possible.

The SAE/AESI report should be completed as thoroughly as possible, including an assessment of causality. All such reports will identify subjects by unique code numbers assigned to the study participants, rather than by the subjects' names, personal identification numbers, or addresses.

The reporting contact for SAE/AESIs by email is as follows:

Email: [redacted]

In case of any email problems, the SAE/AESI form will be sent to [redacted] via fax to:

Fax: [redacted]

Reports of pregnancy, although not classified as an SAE, will be handled and reported as in Section 12.9.

The Sponsor will comply with the applicable regulatory requirements related to the reporting of suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities and central IRB/IEC(s). The Investigator will be responsible for informing the local IRB/IEC(s) of SUSARs, as per local laws and requirements.

12.9 Pregnancy

If a female subject who has been exposed to the study medication becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. Where possible, if a female partner of a male subject who has been exposed to the study medication becomes pregnant and the subject provides this information, then the pregnancy will be documented based on information provided by the subject.

A pregnancy that occurs in a subject who has been exposed to the study medication must be reported using the same timelines and contact details as an SAE (Section 12.8) by a paper ***Pregnancy in a Clinical Study Notification Form***, although pregnancy alone will not be classified as an SAE. If the outcome of the pregnancy or an event occurs during the course of pregnancy that involves an SAE (e.g., a congenital anomaly), then the ***Serious Adverse Event (SAE) in a Clinical Study Form*** will also be completed.

Subjects who become pregnant while on study must be withdrawn from treatment, as described in Section 8.5.

12.10 Follow-up of Adverse Events

The Investigator should follow up with subjects who experience AEs/SAEs, until the event has resolved or stabilized, and any abnormal laboratory values have returned to baseline; or until there is a satisfactory explanation for the changes observed. In the case of death, if possible, a pathologist's full report should be supplied.

The reference safety information for this clinical study is the Investigator's Brochure.[11]

12.11 Overdose

There is no known antidote for MT-7117. Any signs or symptoms of a possible overdose will be treated supportively. In the case of an emergency, standard emergency procedures and supportive medical care will be given.

If the subject takes a dose which is greater or more frequent than that specified in the protocol (with or without associated symptoms), this overdose is an AE and must be reported to the Sponsor or the designee on the AE eCRF.

If the overdose results in AEs that meet serious criteria, the SAE must be reported to Sponsor or the designee immediately or within 24 hours of awareness using the ***Serious Adverse Event (SAE) Form in Clinical Study*** according to SAE reporting procedures (see Section 12.8).

If the subject experiences any other associated symptoms as a result of the overdose, the Investigator will record this as a separate AE/SAE.

13 DATA COLLECTION AND PROCESSING

13.1 Data Collection

Subject data will be collected on individual eCRFs and will be substantiated by source documents (such as laboratory reports, medical records, or ECGs) at the Investigator site. All relevant data will be transcribed into the eCRF from source documents, entered into the study database directly from source documents, or transferred electronically to the study database. Where no printed or electronic source documents exist, data will be entered directly into the eCRF and the eCRF will be considered the source document.

Subjects will record sunlight exposure time, prodromal symptoms and sunlight-induced phototoxic reactions, their severity and their duration on an ongoing basis using a sunlight exposure diary, which includes an electronic patient-reported outcome (PRO) instrument. The instrument will transmit data to a technology service provider database, where it will be stored as electronic source data for efficacy endpoints.

Before the start of the study, the Investigator will complete a Delegation of Responsibility List. The Sponsor or designee will provide training for completion of the eCRF. The eCRF will be completed according to guidelines provided by the Sponsor or its designee in writing, electronically, and/or verbally.

Completed eCRFs will be reviewed by the Study Monitor for the study to ensure data accuracy, completeness, and consistency in accordance with the study monitoring plan and other relevant procedural documents. Any relevant discrepancies found during the eCRF review or during data validation and/or quality assurance reviews of the data by data management or other functions are to be clarified by the Investigator (or his/her designated personnel).

The Investigator or designee must record all required subject data using the previously specified data collection method defined by the Sponsor. An explanation must be documented for any missing data where required. The Investigator must sign and date a declaration on the eCRF attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study. The data collected in the eCRF will be returned to the Sponsor, and an electronic copy will be retained by the Investigator.

13.2 Case Report Form Completion

The eCRF will be presented in an electronic casebook comprising a series of electronic forms. The Subject Number should always be indicated and date (and time, if applicable) of each assessment should be entered in the eCRF.

The eCRFs must be completed in timely manner so that this does not delay the ongoing data validation, review, and quality control. The final, completed eCRF for each subject must be signed and dated by the Investigator on the appropriate eCRF form to signify that he/she has reviewed the casebook and certifies it to be complete and accurate.

The eCRF will feature a special means for correcting errors in the previously entered data. A complete audit trail of the original entries, changes and deletions, session dates and times, and the credentials of the eCRF user who performed the operation will be maintained by the system.

13.3 Data Processing

The data collected on the eCRFs will be captured in a specially constructed and validated database. The data will be validated using both manual and electronic means. Clarification of data will be requested from the Investigator site as required. An audit trail of the original database entries, changes and deletions, session dates and times, and the credentials of the database user who performed the operation will be maintained by the system. The completed database will be quality assured and locked to prevent further changes. A full database extract, including sunlight exposure diary data, will be made available for statistical analysis according to the methods outlined in Section 14 and the Statistical Analysis Plan (SAP).

AEs and medical history entries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Medication Dictionary. Versions of the dictionaries used will be documented in the Data Management Plan and SAP.

13.4 The Impact of COVID-19

Since study subjects may not be able to come to the clinical site for protocol-specified visits, specific information on COVID-19 will be captured via eCRFs to explain the missed protocol-specified information due to COVID-19.

If any study procedures are deemed unsafe or in need of special precautions to safeguard the subject or others from the transmission of COVID-19, these will be documented in the TMF, and, if altered in any way relevant to data collection or interpretation, or statistical analysis, will be addressed in the final SAP.

13.5 The Independent Data Monitoring Committee

An external independent Data Monitoring Committee (iDMC) will be established to perform regular review of the safety data to ensure the ongoing safety of participating subjects until the last subject completes the double-blinded extension period. The frequency of data review will be described in the iDMC Charter. Analyses required for the iDMC's review will be performed by a Contract Research Organization as described in the iDMC SAP. The committee's composition and a description of its responsibilities will be provided in the iDMC Charter.

14 STATISTICAL METHODS AND PLANNED ANALYSES

This section provides the basis for the SAP for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect planned analyses.

The following analyses related to the objectives including will be done twice:

Primary Week 26 Analysis: takes place when the last subject completes the last visit and includes all subject data collected up to the Week 26 visit. The primary efficacy analysis will be conducted at this time. No alpha adjustment for final analysis is needed, as this Week 26 efficacy analysis will be the final primary efficacy analysis. The results will not be disclosed to any site-facing personnel or to any personnel directly involved with the conduct of the study.

Final Analysis: takes place when the patient data collected up to the time the last subject completes the last visit of Week 52 visit or the safety follow up period.

The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect.

The database locks will be done for each of the above time points respectively. Each database lock will be associated with a designated SAP that will describe primary Week 26 and Final analyses, respectively. Each SAP will be approved and signed prior to the corresponding database lock. All data until Week 26 will be locked for 26-week analysis as double-blinded. The endpoints and analysis methods for the safety extension data will be specified in the final analysis SAP.

14.1 Study Estimands

Primary Estimand

The primary estimand construction elements for this study are:

- Population: All randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.
- Variable: Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 (Visit 7).
- Inter-current event of treatment discontinuation using treatment policy: Regardless of early discontinuation of study drug due to any reason until the end of the double-blind treatment period.
- Population-level summary: Absolute mean difference in change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom between MT-7117 and placebo groups.

The primary estimand will be based on effectiveness assumption (de-facto) using treatment policy: The treatment effect will be attributable to the subject's initially randomized treatment regardless of treatment discontinuation.

Secondary Estimand

The secondary estimand construction elements to be tested as supportive analysis for this study are:

- Population: All randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.
- Variable: Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 (Visit 7).
- Inter-current event of treatment discontinuation using hypothetical strategy: If subjects could have treatment completion until the end of the double-blind treatment period.
- Population-level summary: Absolute mean difference in change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom between MT-7117 and placebo groups.

The secondary estimand will be based on efficacy assumption (de-jure) using a hypothetical strategy: The treatment effect will be attributable to the subject's initially randomized treatment if subjects could have stayed on study until the end of the double-blind treatment period.

14.2 Sample Size Estimation

For the primary estimand, the sample size of 159 is expected to provide adequate power for the comparisons between MT-7117 and placebo for change from baseline in the average daily sunlight exposure time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 based on the MT-7117-A01 study. The calculation of sample size assumes a 2-sided alpha level of 0.05 and a 20% dropout rate up to Week 26. The sample size of 42 completers per treatment group will provide 91% and 79% power to detect an effect size of 0.72 and 0.66 in the average daily time (minutes) to first prodromal symptom associated with sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset at Week 26 (ie, an absolute treatment difference of 57 mins between MT-7117 [redacted] vs placebo, 52 mins between MT-7117 [redacted] vs placebo, and a standard deviation [SD] of 79.3 mins). The sample size of 42 completers was calculated by SAS simulation using the fixed sequence testing procedure in order to confirm the power affected by multiplicity adjustment in treatment comparison for primary endpoint. Taking into account for a 20% dropout rate up to Week 26, total sample size of 159 was calculated.

Due to the rapid enrollment rate in the last few months of the enrollment period after COVID-19 restrictions were lifted in many countries, a total of 184 subjects were enrolled.

14.2.1 Analysis Populations

- Safety population: includes all randomized subjects who received at least 1 dose of study medication.
- Intent-to-treat (ITT) population: includes all randomized subjects who received at least 1 dose of study medication with baseline and post-randomization sunlight exposure diary assessment.
- PK population: includes all randomized subjects who received at least 1 dose of study medication and who have at least 1 post-dose value of plasma concentration time point to be included in the PK analysis without important protocol deviations which may affect the PK of study medication.

14.3 Statistical Analysis Methods

A SAP containing details of all the analyses and outputs will be prepared and approved before the study database lock. The ITT population will be used for all efficacy analyses. All safety analysis will be performed on the Safety population.

Unless otherwise specified, the baseline values will be the last non-missing value before receiving the first dose of study medication.

Baseline for an efficacy endpoint based on sunlight exposure time will be the mean of the daily value of the endpoint in a 14-day window before Day 1. Similarly, for this endpoint, their values at each post-baseline time point (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 52, and 58) are the mean of the daily value of the endpoint in a 14-day window on or before the visit.

To calculate the average daily duration, a 14-day window on or before time point (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26) will be used.

Continuous endpoints will be summarized with the descriptive statistics (the number of observations, mean, standard deviation (SD), median, minimum, and maximum). Categorical endpoints will be summarized using frequency counts and percentages.

All statistical tests will be 2-sided with 5% significance level. Point estimates of treatment differences will be provided with 2-sided 95% confidence intervals (CIs) where applicable.

14.3.1 Demographics and Other Baseline Characteristics

Baseline demographic such as age, sex, body weight, body mass index, ethnicity and race, and other baseline characteristics such as will be summarized by treatment group using descriptive statistics on the ITT population.

14.3.2 Efficacy Assessments

14.3.2.1 Analysis of Primary Efficacy Endpoints

Primary Analysis

For the ITT population, the primary estimand will be tested including retrieved dropout data (after treatment discontinuation), using treatment comparisons of interest in change from baseline in average daily time to first prodromal symptoms associated with exposure to sunlight between 1 hour post-sunrise and 1 hour pre-sunset for the two MT-7117 doses ([redacted], and [redacted]) compared with placebo at Week 26 (Visit 7).

To assess the treatment effect at Week 26, change from baseline in average daily time (minutes) to first prodromal symptom associated with exposure to sunlight between 1 hour post-sunrise and 1 hour pre-sunset at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26 will be analyzed using mixed-effect model for repeated measures (MMRM). The model will include fixed

categorical terms for treatment, [redacted], visit, and treatment by visit interaction together with continuous covariate terms for baseline average daily duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset to first prodromal symptom and baseline average daily duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset to first prodromal symptom by visit interaction. An unstructured correlation structure will be used to model the within-subject variance covariance errors. Should convergence of the model fail (due to the small numbers of subjects in this study), other variance covariance matrices such as autoregressive [AR(1)] correlation matrix will be used if appropriate. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. From the model described above, adjusted (least squares [LS]) means and standard errors will be produced by treatment and visit. Difference in adjusted means at each visit (each MT-7117 dose vs. placebo) with standard errors, 95% CIs and associated p-values will also be produced. All available data from all subjects will be used in the primary analysis without any imputation.

Sensitivity Analysis

Multiple imputation using the Pattern Mixture model method on ITT population under Missing Not at Random assumption. In this analysis, control-group–based assumption will be used (i.e., the trajectories of the patients in all treatment groups are assumed to follow the control group after the treatment discontinuation).

Supportive Analysis

The secondary estimand will use similar estimator as for the primary analysis. The ITT population with the primary efficacy data without retrieved dropout data (after treatment discontinuation) will be used for this analysis. Likelihood based model method under Missing at Random assumption will be performed using the same MMRM as specified for the primary analysis.

Multiplicity adjustment for treatment comparison on primary and secondary endpoints

The overall study-wise type I error will be 5%. Type I error will be globally strongly controlled by employing the fixed sequence approach (i.e., each endpoint will be formally analyzed only in case the preceding endpoint will have a p value less than or equal to 0.05).

To protect the study from type I error inflation, the lower ordered comparison will be interpreted inferentially only if a statistically significant treatment effect is detected in the higher ordered comparison (H1=>H2,..., H11=>H12). The following null hypothesis will be sequentially tested via the following order;

H1: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline in average daily time (minutes) to first prodromal symptom associated with exposure to sunlight between 1 hour post-sunrise and 1 hour pre-sunset at Week 26.

H2: There is no treatment difference between MT-7117 [redacted] and placebo in change from

baseline in average daily time (minutes) to first prodromal symptom associated with exposure to sunlight between 1 hour post-sunrise and 1 hour pre-sunset at Week 26.

H3: There is no treatment difference between MT-7117 [redacted] and placebo in PGIC at Week 26.

H4: There is no treatment difference between MT-7117 [redacted] and placebo in PGIC at Week 26.

H5: There is no treatment difference between MT-7117 [redacted] and placebo in total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during 26-week double-blind treatment period.

H6: There is no treatment difference between MT-7117 [redacted] and placebo in total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) with pain rating of 1-10 on the Likert scale during 26-week double-blind treatment period.

H7: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26.

H8: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of pain intensity in the PROMIS-57 at Week 26.

H9: There is no treatment difference between MT-7117 [redacted] and placebo in the percentage of subjects who are responders at Week 26 based on average daily sunlight exposure time to first prodromal symptoms using the within-subject meaningful change of 66 minutes increase.

H10: There is no treatment difference between MT-7117 [redacted] and placebo in the percentage of subjects who are responders at Week 26 based on average daily sunlight exposure time to first prodromal symptoms using the within-subject meaningful change of 66 minutes increase.

H11: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

H12: There is no treatment difference between MT-7117 [redacted] and placebo in change from baseline for total score in the domain of physical function in the PROMIS-57 at Week 26.

Subgroup Analysis

The consistency of treatment effect on the primary endpoint across different subgroups will be explored based on the ITT population and the primary estimand for age category, [redacted] Country and Race (as entered in the eCRF) etc. This subgroup analysis method will be prospectively defined in Primary Week 26 SAP. This analysis is exploratory and the results from this analysis will not affect the choice of terms used in the model for the primary analysis.

14.3.2.2 Analysis of Secondary and Other Efficacy Endpoints

The following secondary and other efficacy endpoints will be analyzed using the MMRM similar to the analyses for the primary endpoint.

- Secondary Efficacy Endpoint) PGIC at Week 26.
- Change from baseline in the average daily mean intensity on an 11-point Likert scale of the subject's prodromal symptoms over time during 26-week double-blind treatment period.
- Change from baseline in average daily duration (minutes) of prodromal symptoms during 26-week double-blind treatment period.
- Change from baseline in the average daily mean intensity of the subject's phototoxic reactions (associated with sun exposure) during 26-week double-blind treatment period on an 11-point Likert scale.
- Change from baseline in average daily duration (minutes) of phototoxic reactions (associated with sun exposure) during 26-week double-blind treatment period.
- Secondary Efficacy Endpoint*) Change from baseline for all total score and total score in each domain of physical function*, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference (including pain intensity*) in PROMIS-57.
- Change from baseline in PGIS at each visit.

The following secondary efficacy endpoints and exploratory efficacy endpoint will be analyzed; a negative binomial regression model with log link will be fitted. The model will include treatment as fixed effect, and baseline total number of sunlight exposure episodes with prodromal symptoms as the covariate. The estimated incidence rate (IR) and its 95% confidence interval for each treatment group, incidence rate ratio (IRR) of each active MT-7117 treatment group versus placebo, 95% confidence interval of the IRR together with relevant p-values will be reported.

- Secondary Efficacy Endpoint) Total number of sunlight-induced pain events defined as prodromal symptoms (burning, tingling, itching, or stinging) during 26-week double-blind treatment period.
- Total number of sunlight-induced pain events defined as phototoxic events during 26-week double-blind treatment.
- Total number of sunlight-induced non-prodrome, phototoxic reactions during 26-week double-blind treatment.

The following efficacy endpoints will be analyzed; a logistic regression model will be fitted. The model will include the treatment group, randomization strata as fixed factors together with continuous covariate term for the corresponding baseline value. The treatment odds ratio at Week 26 and its 95% confidence interval with p-value for each treatment group will be estimated using a contrast.

- Secondary Efficacy Endpoint) The percentage of subjects who are responders based on average daily sunlight exposure time to first prodromal symptom associated with sunlight

exposure between 1 hour post-sunrise and 1 hour pre-sunset defined by within-subject meaningful change of 66 minutes increase from baseline to Week 26.
- The percentage of subjects who are responders at Week 26 based on PGIC (Very Much Improved or Much Improved).

The following other efficacy endpoint will be listed and summarized by treatment and planned time point using descriptive statistics. The value of melanin density, change from baseline, and % change from baseline in melanin density at each visit by skin segments and average of 6 skin segments will be plotted by treatment. For average of 6 skin segments for the value of melanin density, change from baseline in melanin density at each visit, will be analyzed using MMRM similar to the analyses for the primary endpoint.

- Change from baseline and % change from baseline in melanin density at each visit by skin segments. Average of 6 skin segments for the change from baseline and % change from baseline in melanin density at each visit.

The following endpoint will be analyzed using ANCOVA or ANOVA model:

- Change from baseline for in-clinic sunlight exposure time (minutes) to the first prodromal symptoms or end of test, whichever comes first.
- Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptoms.
- Total time (hours) during the 26-week double-blind treatment period in duration of sunlight exposure between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free time hours).
- Change from baseline in average daily duration of sunlight exposure regardless of time of day without prodromal symptoms assessed at Week 26.

The following endpoint will be summarized using descriptive statistics and Wilcoxon's rank sum test.

- Total number of days subject is exposed to sunlight for any duration between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptoms during 26-week double-blind treatment period.

- Total number of days subject is exposed to sunlight for any duration between 1 hour post-sunrise and 1 hour pre-sunset without prodromal symptom with the severity of greater than 0 on 11-point Likert scale and without phototoxic reactions (pain-free days) during the 26-week double-blind treatment period.

For qualitative exit interview questionnaire about QoL, the data will be presented in a separate report generated outside of the CSR.

14.3.3 Safety Assessments

Adverse Events

The TEAEs are summarized for subjects with at least one TEAE, at least one treatment-emergent adverse reaction, at least one serious TEAE, at least one serious treatment-emergent adverse reaction, at least one TEAE leading to drug withdrawn, at least one treatment-emergent adverse reaction leading to drug withdrawn, at least one hepatic AE and at least one adverse event of special interest (AESI).

The frequency and incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment and overall. For this table, SOC is sorted by International order; then within SOC, PT is sorted by descending counts under MT-7117 Total group, then descending counts under Placebo group, then alphabetic order for PTs with the same count.

The AE summaries will be presented for the following:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- TEAEs by SOC, PT, and relationship
- Treatment-emergent adverse reactions by SOC and PT
- Treatment-emergent adverse reactions by SOC, PT, and severity
- Serious TEAEs by SOC and PT
- Serious treatment-emergent adverse reactions by SOC and PT
- TEAEs leading to drug withdrawn by SOC and PT
- Treatment-emergent Hepatic AEs by SOC and PT

For each of the summaries will be done at the subject level - multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum intensity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility, no reasonable possibility). If intensity or relationship is found to be missing the most severe occurrence will be imputed for that particular summary.

All AEs for each subject, including multiple occurrences of the same event, will be listed.

Deaths that occur during the study will be listed in a data listing. The data listings for serious TEAE and TEAE leading to drug withdrawn will be generated as well.

Safety laboratory tests

Lab test values and changes from baseline will be summarized descriptively by treatment and visit.

The lab tables will be generated for each lab categories (Hematology, Coagulation, Biochemistry and Urinalysis).

All laboratory data will be listed with clinically relevant values flagged (L=Lower than lower limit of normal range, H=Higher than upper limit of normal range or A=Abnormal).

The number of subjects with post-baseline assessments $\geq 2 \times$ ULN and $\geq 3 \times$ ULN and so on will be calculated for ALT, AST, GGT, ALP, direct and total bilirubin and summarized by treatment group for each post-baseline visit.

The figure of mean (or median) and standard error value of ALT, AST, total bilirubin and alkaline phosphatase by visit will be plotted.

Vital signs and electrocardiogram data

Vital signs and 12-lead ECG variables and changes from baseline will be descriptively summarized at each visit by treatment group.

The baseline for the vital sign parameters and 12-lead ECG measurements will be the last valid assessment obtained on Day 1 prior to the administration of double-blind treatment period.

For ECGs, number and percentage of subjects meeting the criteria listed below will be presented in tables:

- Baseline Corrected QT interval (QTc) <450 msec and >500 msec at EOT
- Baseline QTc <450 msec and 500 msec ≥ QTc > 480 msec at EOT
- Baseline QTc <450 msec and 480 msec ≥ QTc > 450 msec at EOT
- Increase from baseline at EOT in QTc > 30 msec
- Increase from baseline at EOT in QTc > 60 msec

These criteria will be applied to both Corrected QT interval using Bazett's formula (QTcB) and Corrected QT interval using Fridericia's formula (QTcF).

Physical examination and Nevi evaluation

Physical examination data will be summarized descriptively (number and percentage of the subjects) in tables by treatment and time point.

Nevi appearance will be summarized descriptively (number and percentage of the subjects) in tables by treatment and analysis visit for subjects' suspicious nevi found.

14.3.4 Pharmacokinetic Endpoints

Plasma MT-7117 concentrations will be listed for each subject and scheduled visit and treatment

period with the same precision as provided by the bioanalytical laboratory. PK sample collection times, most recent dosing times, as well as derived actual sampling time relative to the most recent dose will be provided in a listing. The actual sampling time relative to the most recent dose will be calculated in hours and rounded to 2 decimal points. Plots of individual concentration vs actual sampling time will be presented overlaid with treatment in different symbols for each treatment by visit or overlaid with visits.

Population PK analysis will be performed using the plasma concentration of MT-7117 obtained in this study in combination with data obtained from other clinical studies. Population PK analysis results will be reported separately from the Clinical Study Report (CSR).

14.3.5 Exploratory Endpoints

[redacted]. The details of the statistical analysis method will be fully described in Primary Week 26 Analysis SAP.

Porphyrin and protoporphyrin levels will be listed and summarized by treatment using descriptive statistics.

15 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

15.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in compliance with the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki. This study will also be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines. This study will also be carried out in accordance with regional and local legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements will be met.

15.2 Investigator Responsibilities

15.2.1 Informed Consent

Before undergoing any study-specific procedure, all legally competent subjects must consent in writing to participate. An IRB/IEC approved ICF will be given to each subject.

The process of obtaining the informed consent will be in compliance with all regulatory regulations, ICH requirements, and local laws.

15.2.2 Ethical and Regulatory Approval

The study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP as described in:

- Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
- ICHE6_R2.
- Code of Federal Regulations (21 CFR).

The Investigator and Sponsor will sign this protocol to confirm agreement to abide by it.

Before any study-related procedure is performed on a subject, all IRB/IEC, regulatory authorities, and local approvals of this protocol will be obtained. While the study is ongoing and at study completion/discontinuation, the Sponsor or Investigator will submit information to the IRB/IEC(s) in accordance with institutional/local regulations, for example:

- Information on SUSARs.
- Periodic reports on the progress of the study.
- Notification of the end of study or early termination.
- Final study summary upon completion or closure.

The Sponsor will ensure that any SUSARs from this study and other studies with this study medication are reported promptly to the regulatory authorities.

If it is necessary to amend the protocol during the study, proper notification will be made to the regulatory authorities and IRB/IECs in the form of a Protocol Modification. Protocol Modification requiring IRB/IEC approval may be implemented only after a copy of the IRB/IEC's approval/favorable opinion letter has been transmitted to the Sponsor and regulatory authority approval has been obtained (if required). Protocol Modifications that are intended to eliminate an apparent immediate hazard to subjects may be implemented before receiving Sponsor, regulatory, and/or IRB/IEC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Any protocol or other deviations that occur during the study will be documented and reported to the Sponsor. Depending on the nature of the deviation, this may be reported to the regulatory authority and the IRB/IEC.

15.2.3 Source Document Requirements and Document Access During the Study

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation (including, but not limited to: essential documents, copies of protocols, eCRFs, source data such as original reports of test results, study medication dispensing logs, correspondence, records of informed consent/assent, and other documents pertaining to the conduct of the study) that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator/institution will permit study-related monitoring, audits, IRB/IEC reviews, and regulatory inspections providing direct access to source data/documents.

15.2.4 Study Records Retention

Study-related documentation must be kept for at least 25 years or until notified by the Sponsor. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

15.2.5 Protocol Deviations

The Sponsor does not allow prospective deviations from the protocol. Any significant deviations affecting subject eligibility and/or safety must be reviewed or approved by the

IRB/IEC and regulatory authority, as per applicable requirements. The Investigator is responsible for complying with all protocol requirements, and applicable to laws pertaining to protocol deviations. If a protocol deviation occurs (or is retrospectively identified) after a subject has been enrolled, the Investigator is responsible for notifying their IRB/IEC, regulatory authorities (as applicable), and assigned Clinical Monitor or Sponsor.

Protocol deviations considered to be clinically significant will be escalated to the Sponsor and may include corrective measures.

15.3 Study Monitoring

In accordance with applicable regulations, GCP, and the procedures of the Sponsor or its designees, the Study Monitor will periodically contact the Investigator site, and conduct on-site visits. The extent, nature, and frequency of on-site visits will be based on study complexity, enrollment rate, and data quality at the Investigator site. Through these visits and frequent communications (e.g., letter, email, and telephone), the Study Monitor will verify that the investigation is conducted according to protocol, regulatory, and Sponsor requirements.

The Investigator will allow the Study Monitor direct access to all relevant documents and allocate his/her time and the time of his/her personnel to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the Investigator site personnel before the start of the study to discuss the protocol and data collection procedures.

At study closure, the Study Monitor will conduct all activities as indicated in Section 15.5.

15.4 Quality Assurance and Auditing

Authorized representatives of the Sponsor, IRB/IEC, and/or regulatory authorities may conduct an audit or inspection of this study either during or after completion. In such cases, the Investigator will give the auditor/inspector direct access to all relevant documents and source data and will allocate his/her time and the time of his/her personnel as may be required to discuss findings and any relevant issues.

15.5 End of Study and Site Closure

The end of the study is defined as the last visit for the last subject. Upon completion of the study, or if the study or an Investigator site is prematurely discontinued, the following activities, where applicable, must be conducted by the Study Monitor in conjunction with the Investigator:

- Return of all study data to the Sponsor.
- Completion of data clarifications and/or resolutions.
- Accounting, reconciliation, and final disposition of used and unused study medication.
- Review of Investigator site study records for completeness.

Any unresolved AEs of SAEs will be followed according to Section 12.10.

15.6 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the study because of safety concerns, ethical issues, or serious and/or persistent non-compliance with the protocol.

If the study is suspended or terminated, the Sponsor will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator or Sponsor is responsible for promptly informing the IRB/IEC, in accordance with institutional/local regulations, and providing the reason(s) for the suspension or termination of the study.

For all subjects, the end-of-treatment and follow-up visit assessments should be performed, as far as possible (Table 9-1).

Any unresolved AE or SAE will be followed up according to Section 12.10.

In the event that a subject elects not to return to the study site for the Follow-up visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The Investigator site personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required end of study assessments.

In addition, all general Investigator site activities required for the scheduled end of study and site closure should be completed, as described in Section 15.5.

15.7 Premature Discontinuation of Individual Investigator Sites

The Sponsor may at any time, at its sole discretion, discontinue the Investigator site for various reasons, including, without limitation, the following:

- Failure of the Investigator to enroll subjects into the study at a reasonable rate.
- Failure of the Investigator to comply with applicable laws and/or pertinent regulations.
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or regulatory authorities.
- Insufficient adherence to Protocol requirements.

The Sponsor will issue a written notice to the Investigator, which will contain the reasons for taking such action. If the Investigator site is terminated for noncompliance, appropriate regulatory authorities will also be notified by the Sponsor.

For all subjects, the end-of-treatment and follow-up visit assessments should be performed, as far as possible (Table 9-1).

Any unresolved AE or SAE will be followed up according to Section 12.10.

In the event that a subject elects not to return to the study site for the end of study visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The Investigator site personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required end of study assessments.

In addition, all general Investigator site activities required for the scheduled end of study and site closure should be completed, as described in Section 15.5.

15.8 Liability and Insurance

Please refer to the written study information given to the subject.

16 DISCLOSURE OF DATA

16.1 Confidentiality

All information concerning MT-7117 is the sole property of the Sponsor. For the avoidance of doubt, the Sponsor has full ownership of the eCRFs completed as part of the study. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

Subjects will be informed that all personal information made available for inspection will be handled in confidence and in accordance with applicable laws and regulations. All personnel involved in the study will observe and work within the confines of applicable data protection regulations.

16.2 Publication

By signing the study Protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the Sponsor's approval requirements.

The Sponsor or designee will prepare a final report on the study. This Clinical Study Report will be signed by the designated coordinating (principal) investigator. The Investigator's right to publish or present any information on the study, and publication procedures to be followed, will be defined in the Investigator site agreement.

17 LIST OF REFERENCES

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18 APPENDICES

18.1 APPENDIX 1: [redacted]

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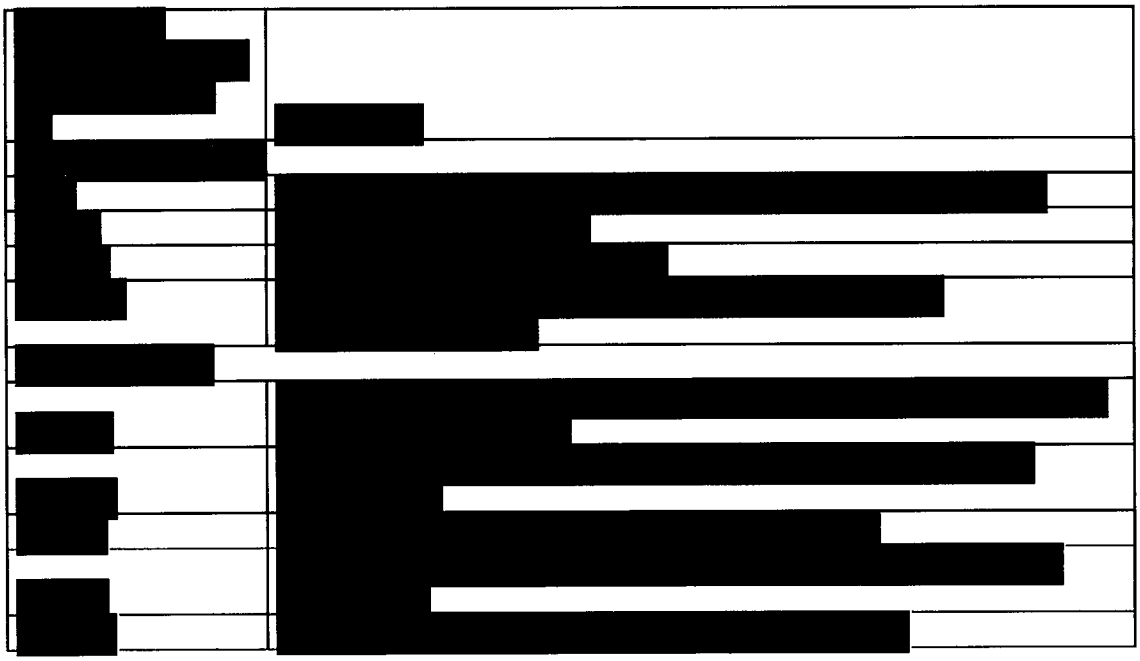

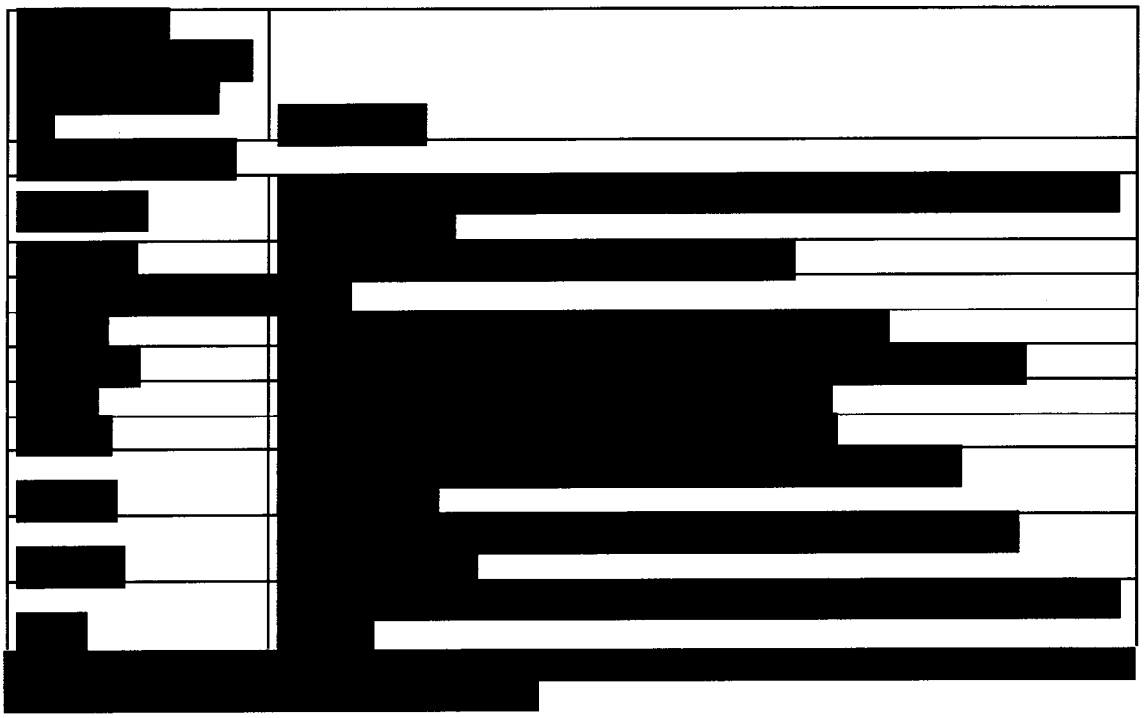

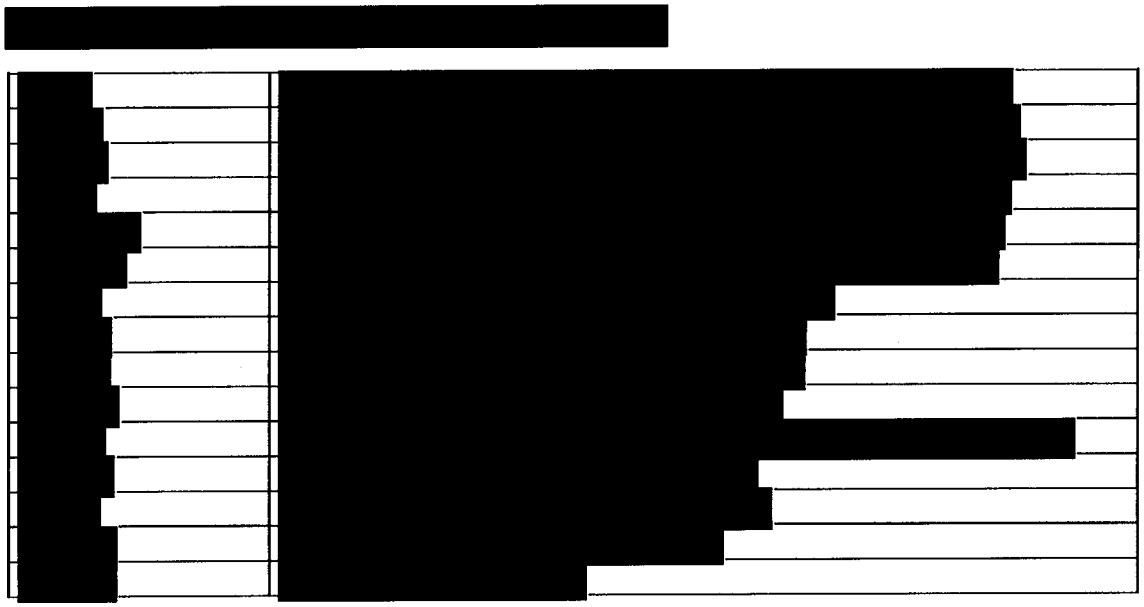

18.2 APPENDIX 2: CKD-EPI equation (2009) and Schwartz equation (2009) for GFR

CKD-EPI equation for adults:

Expressed as a single equation:

eGFR =
141 x $\min(S_{Cr}/\kappa, 1)^{\alpha}$ x
$\max(S_{Cr}/\kappa, 1)^{-1.209}$ x
0.993^{Age} x
1.018 [if female] x
1.159 [if Black]

Abbreviations / Units
eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2
S_{Cr} (standardized serum creatinine) = mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of S_{Cr}/κ or 1
max = indicates the maximum of S_{Cr}/κ or 1
age = years
https://www.kidney.org/content/ckd-epi-creatinine-equation-2009

Schwartz equation for adolescents:

eGFR =
0.413 x (height/Scr) if height is expressed in centimeters
OR
41.3 x (height/Scr) if height is expressed in meters

Abbreviations / Units
eGFR (estimated glomerular filtration rate) = mL/min/1.73 m2
Scr (standardized serum creatinine) = mg/dL

https://www.kidney.org/content/creatinine-based-%E2%80%9Cbedside-schwartz%E2%80%9D-equation-2009

18.3 APPENDIX 3: [redacted]

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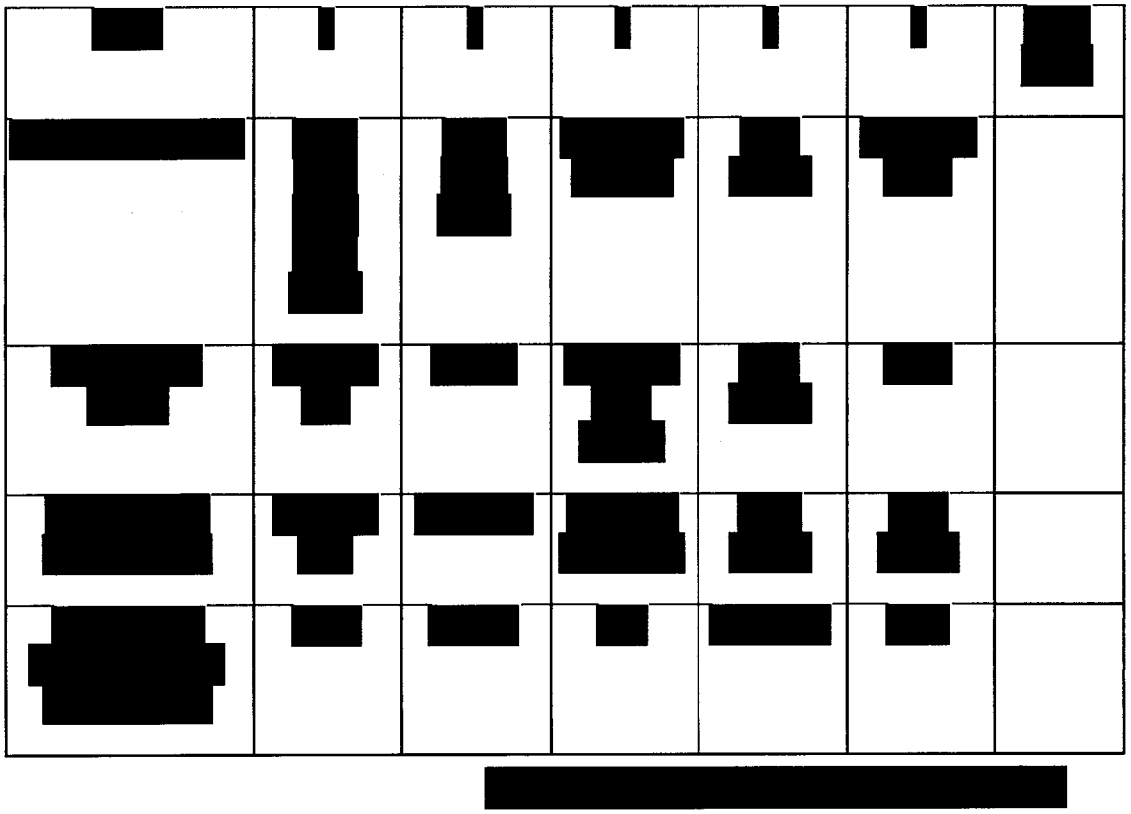

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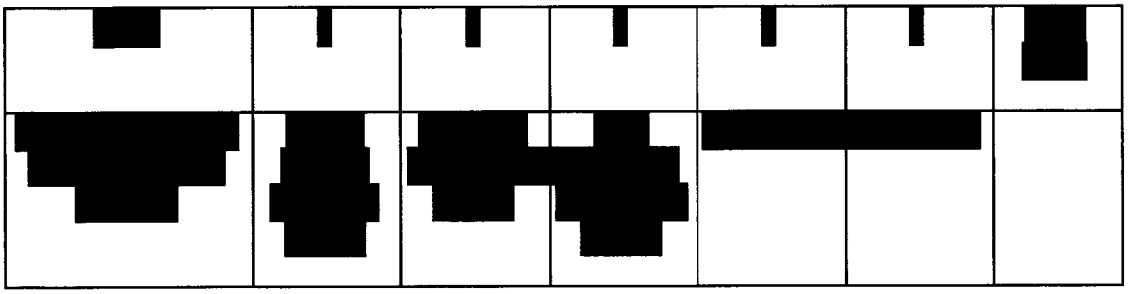

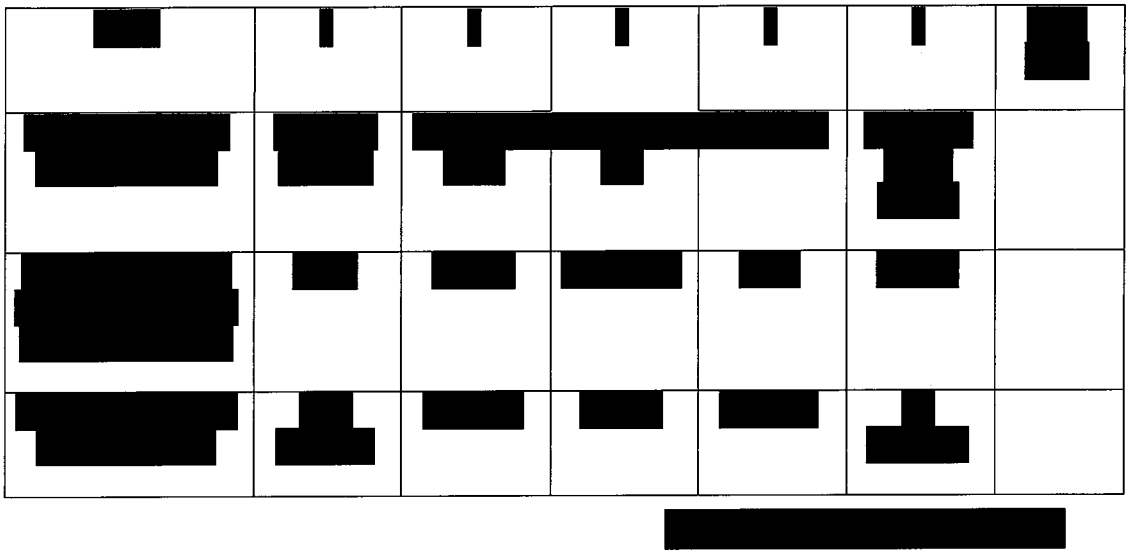

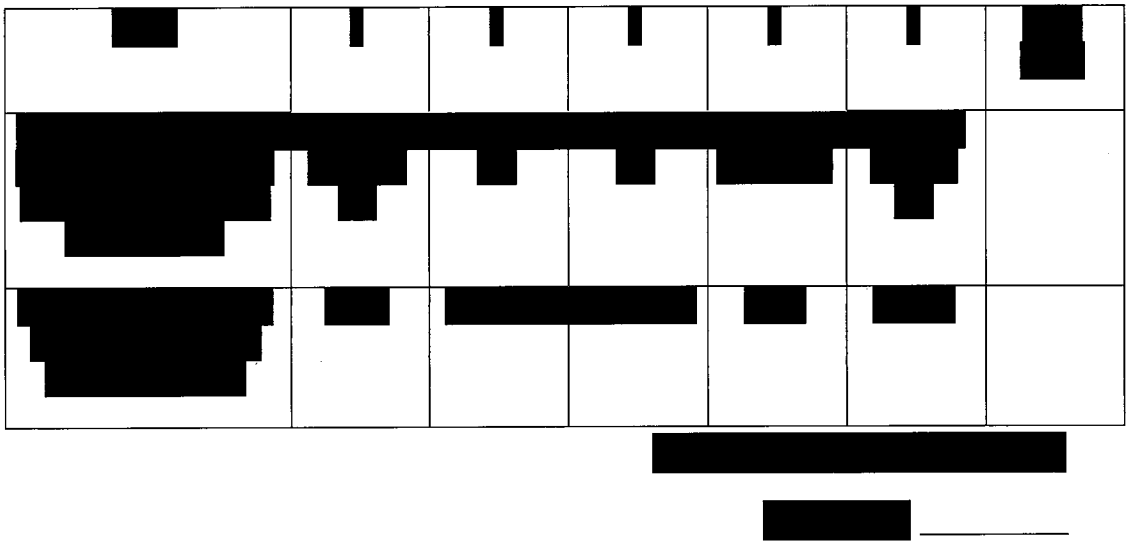

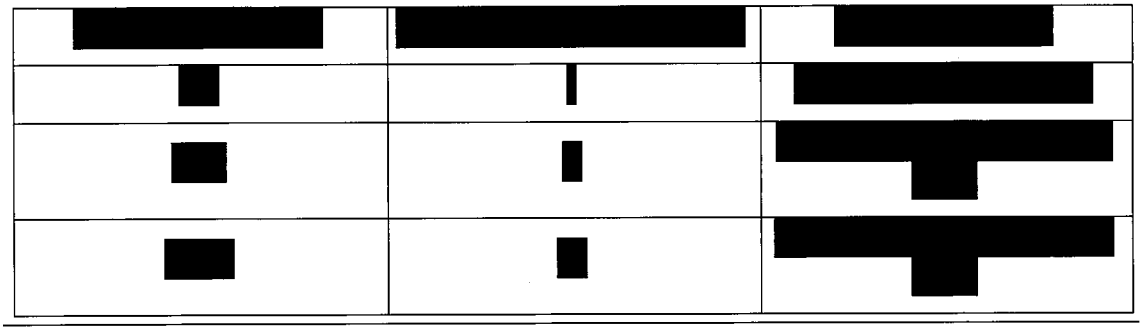

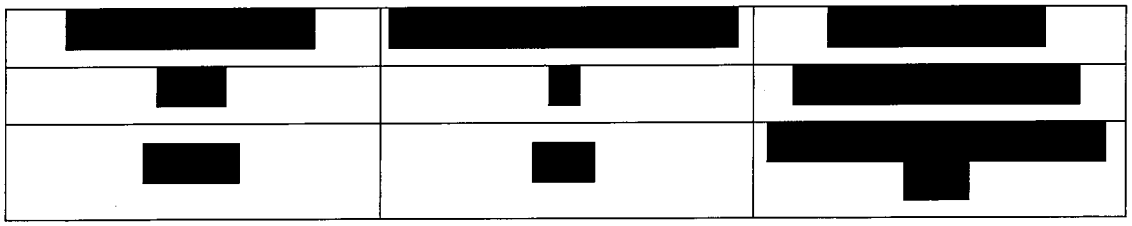

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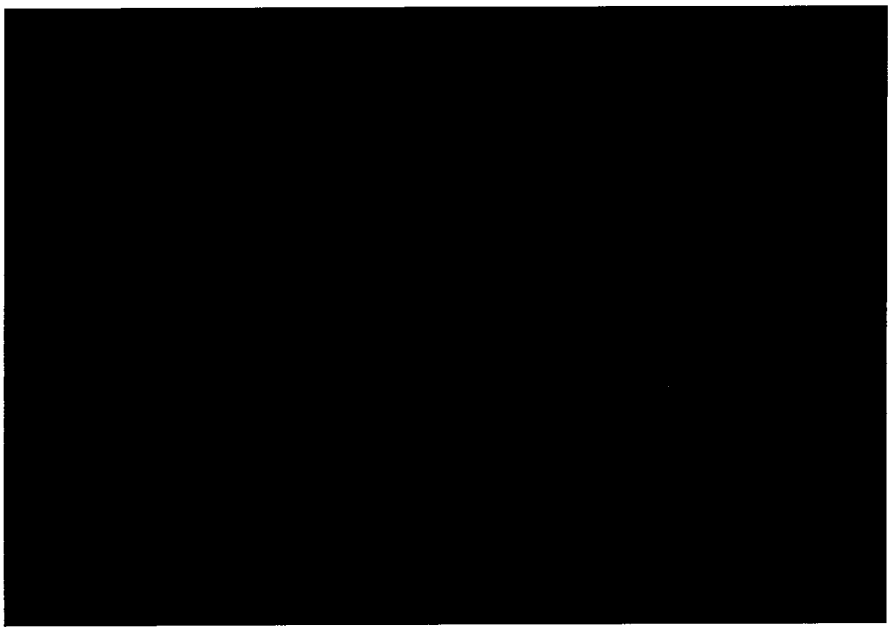

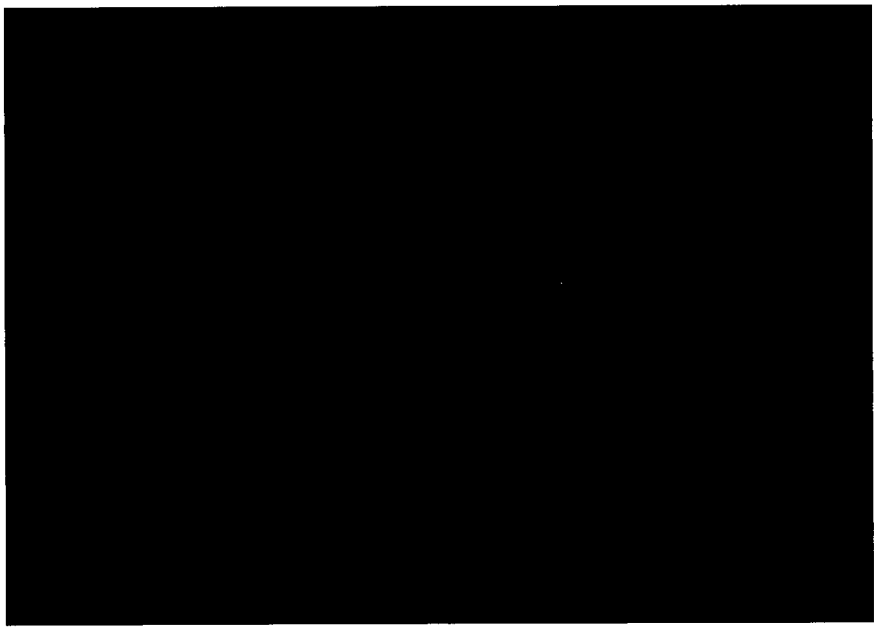

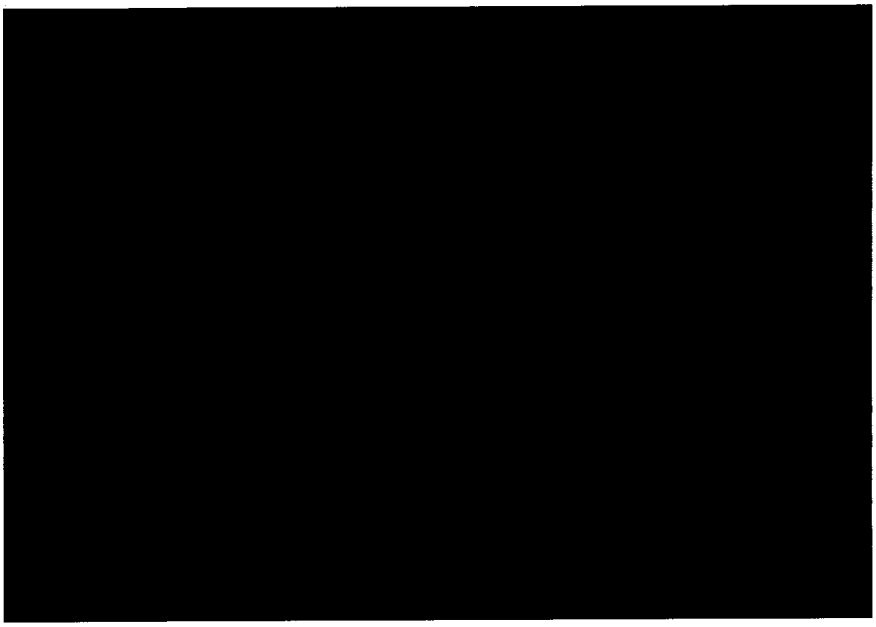

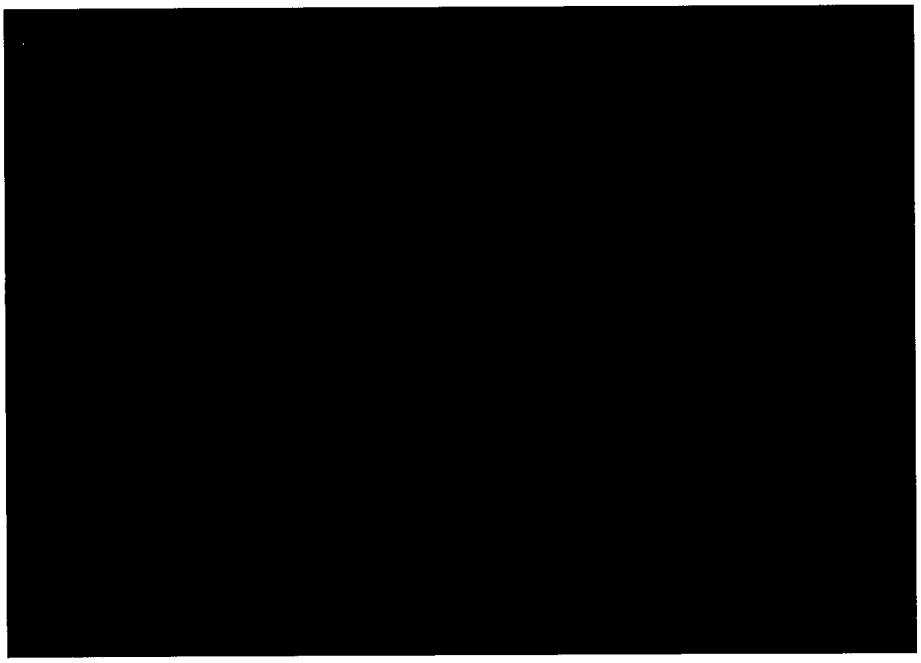

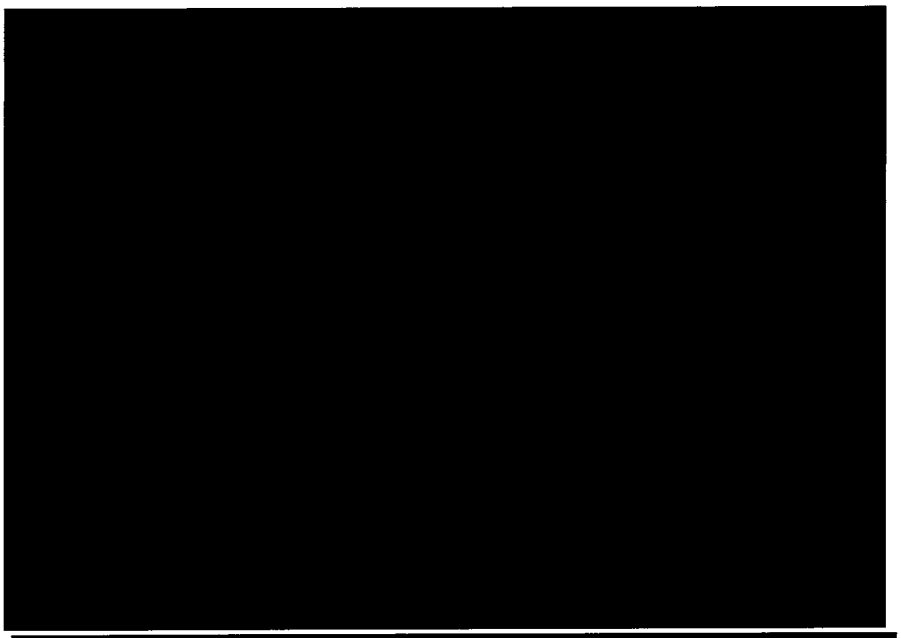

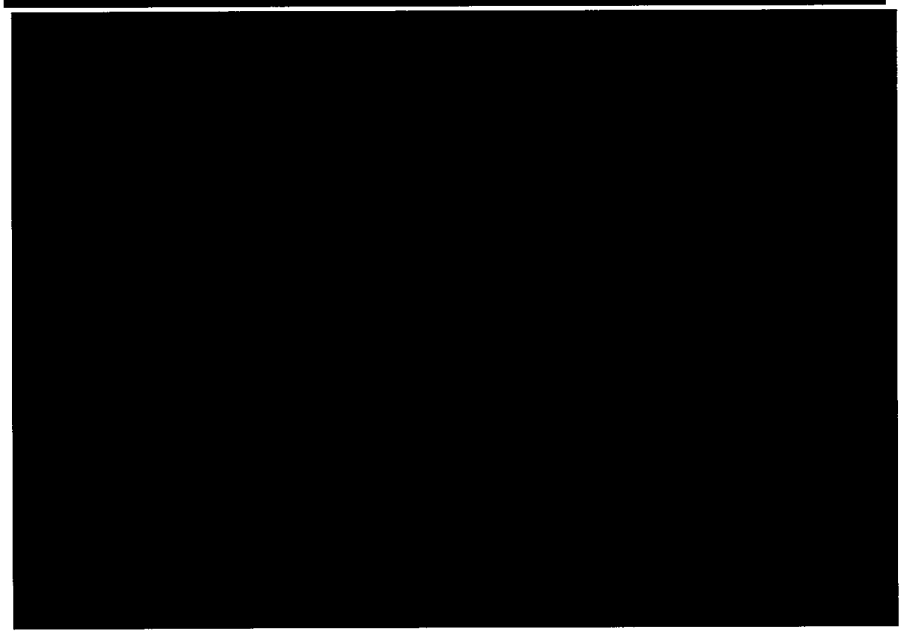

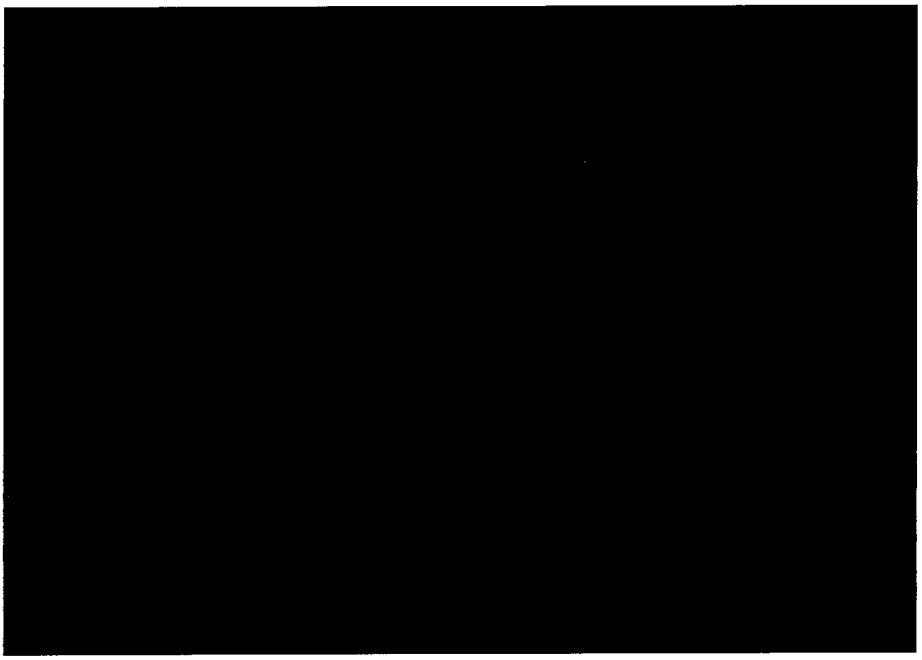

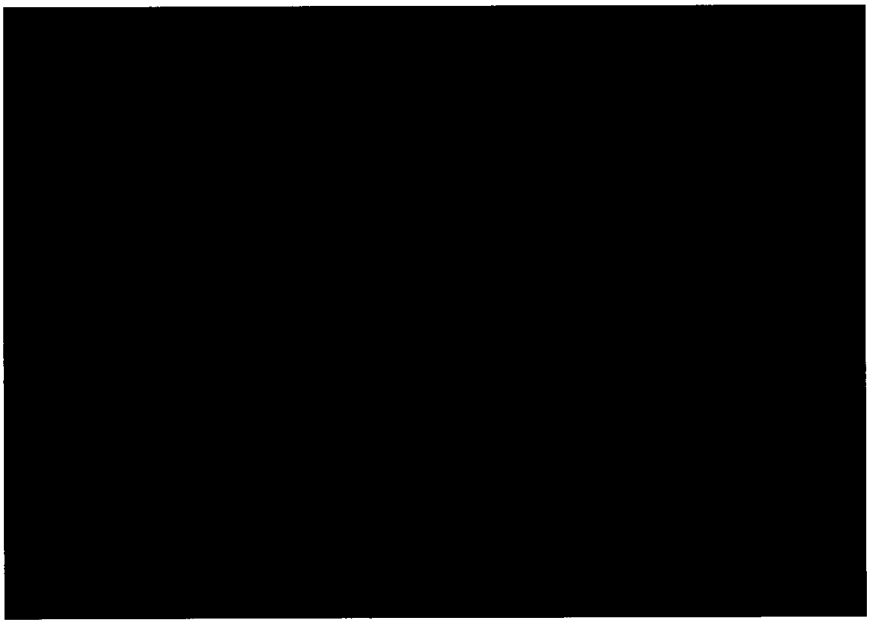

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18.6 APPENDIX 6: [redacted]

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18.7 APPENDIX 7: [redacted]

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18.8 APPENDIX 8: [redacted]

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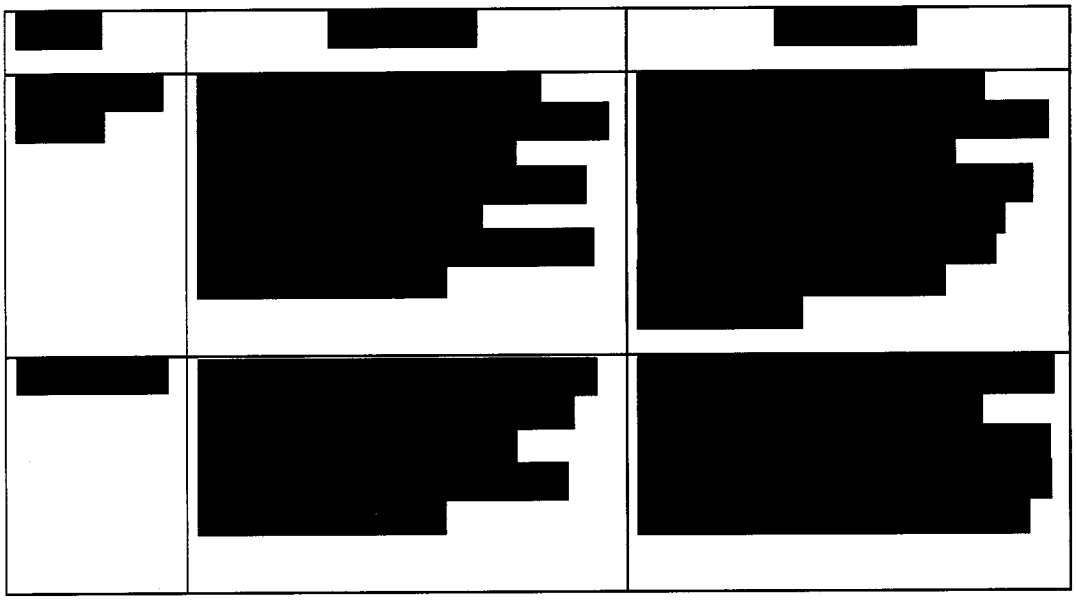

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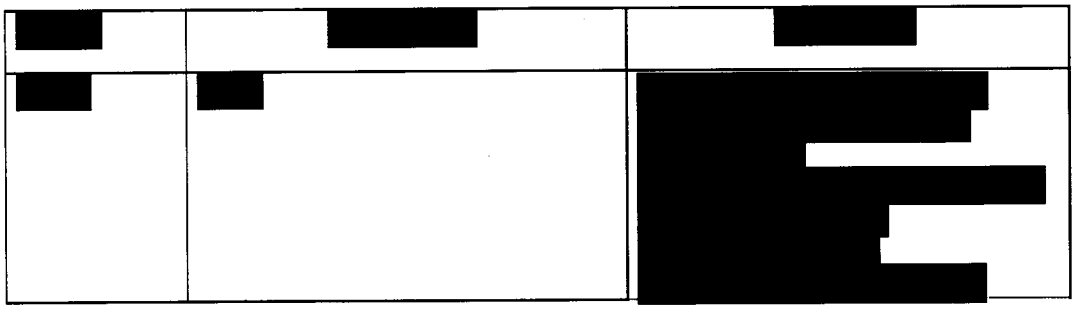

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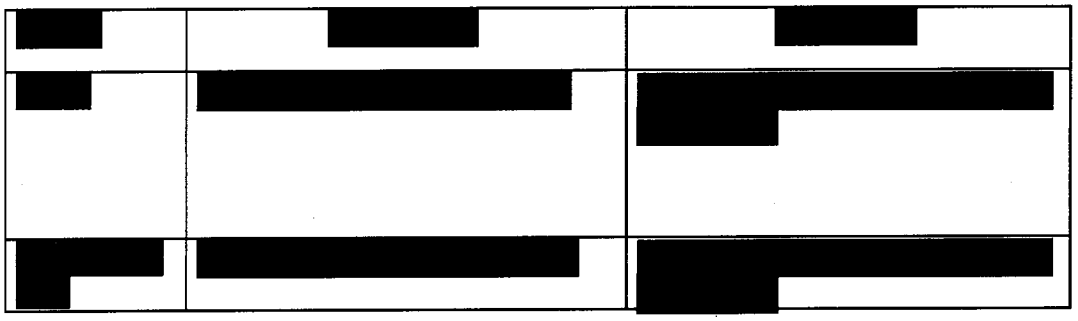

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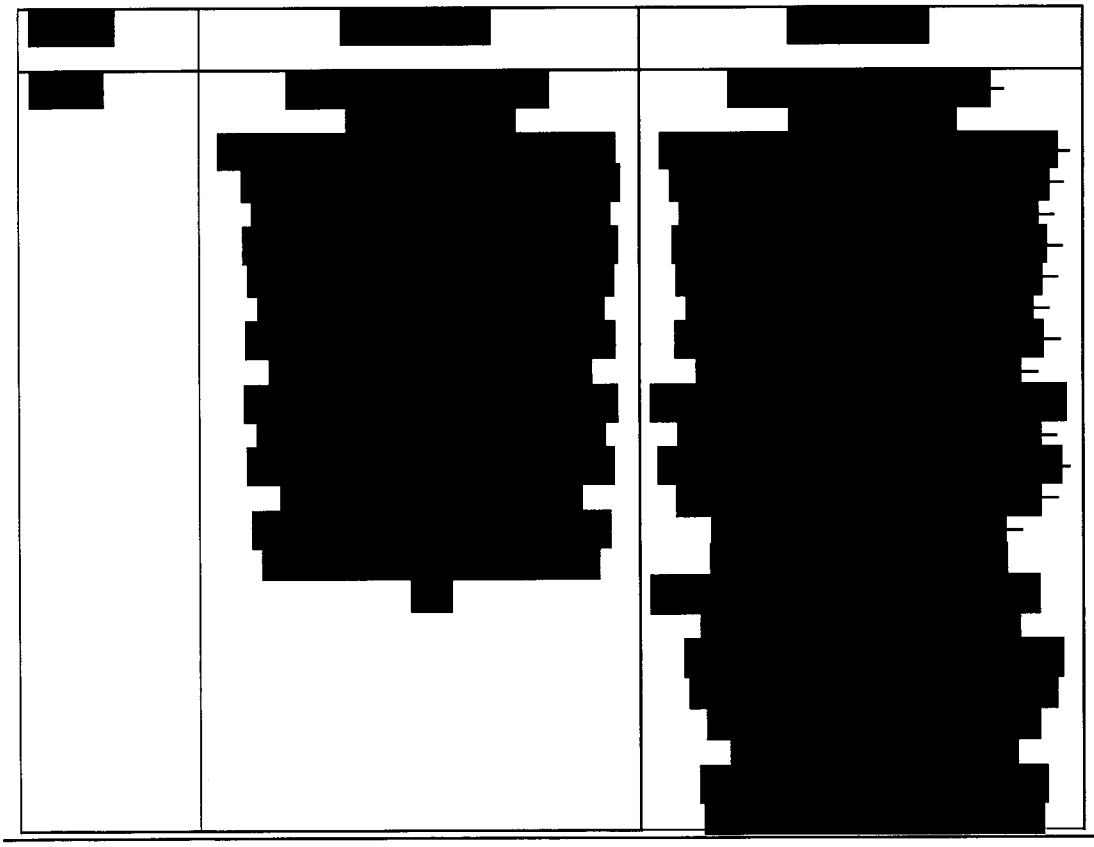

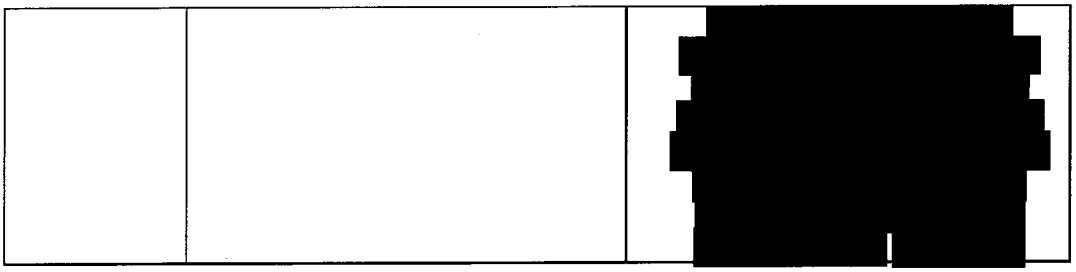

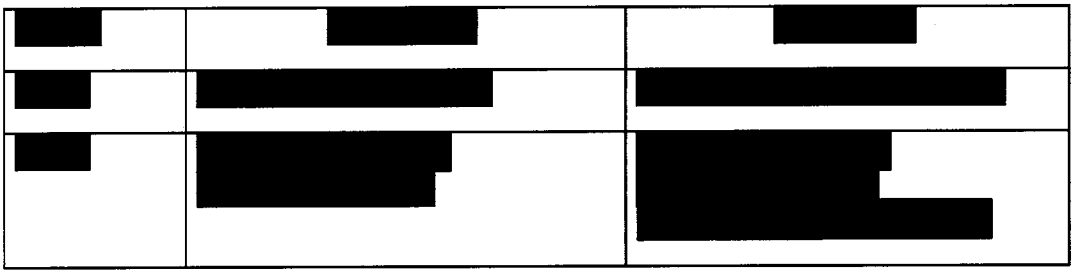

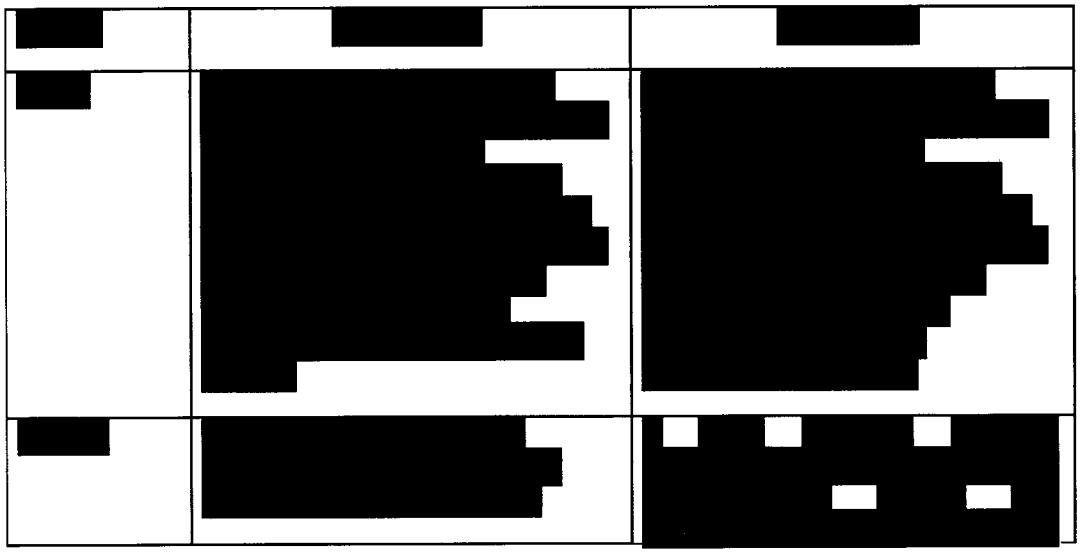

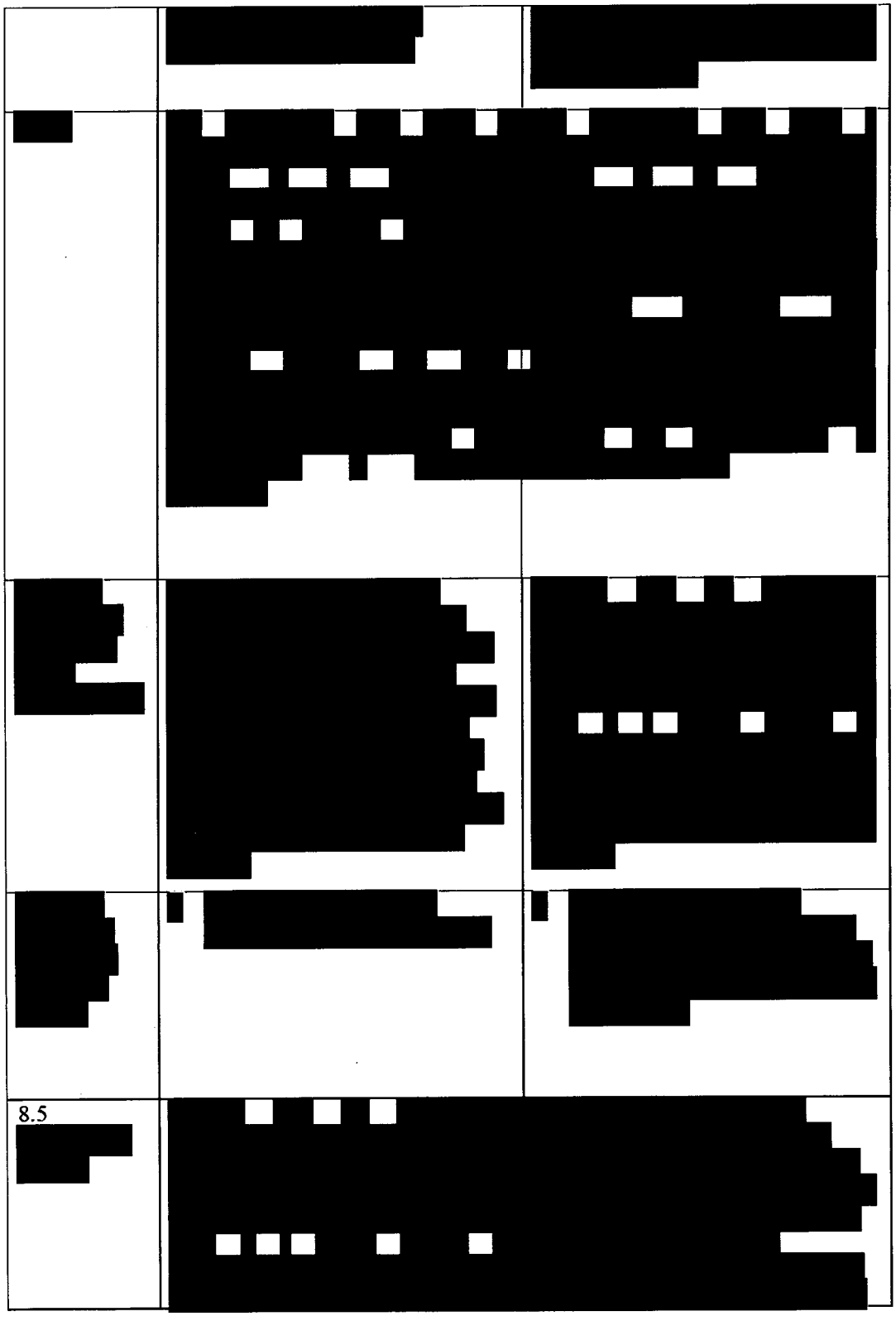
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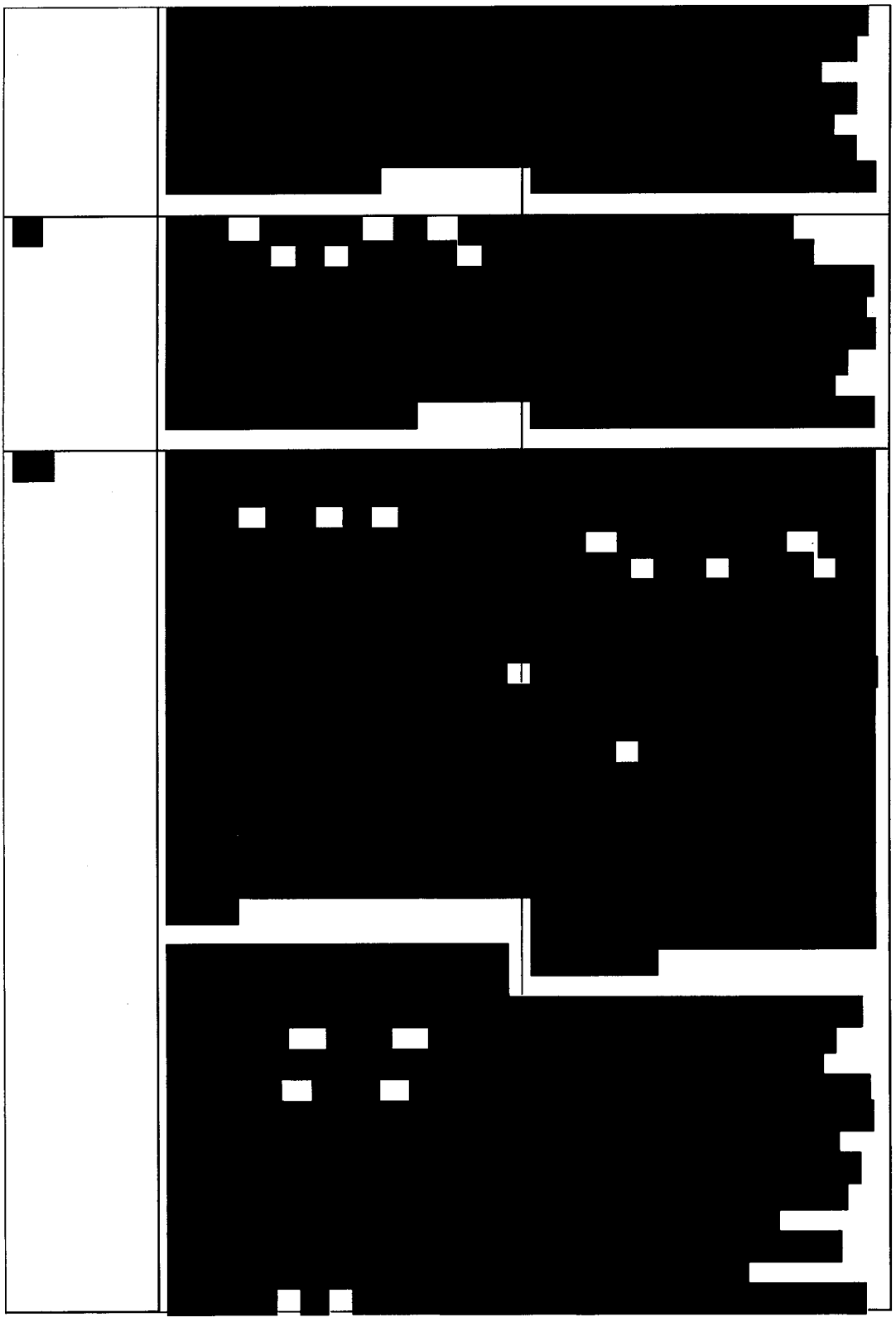

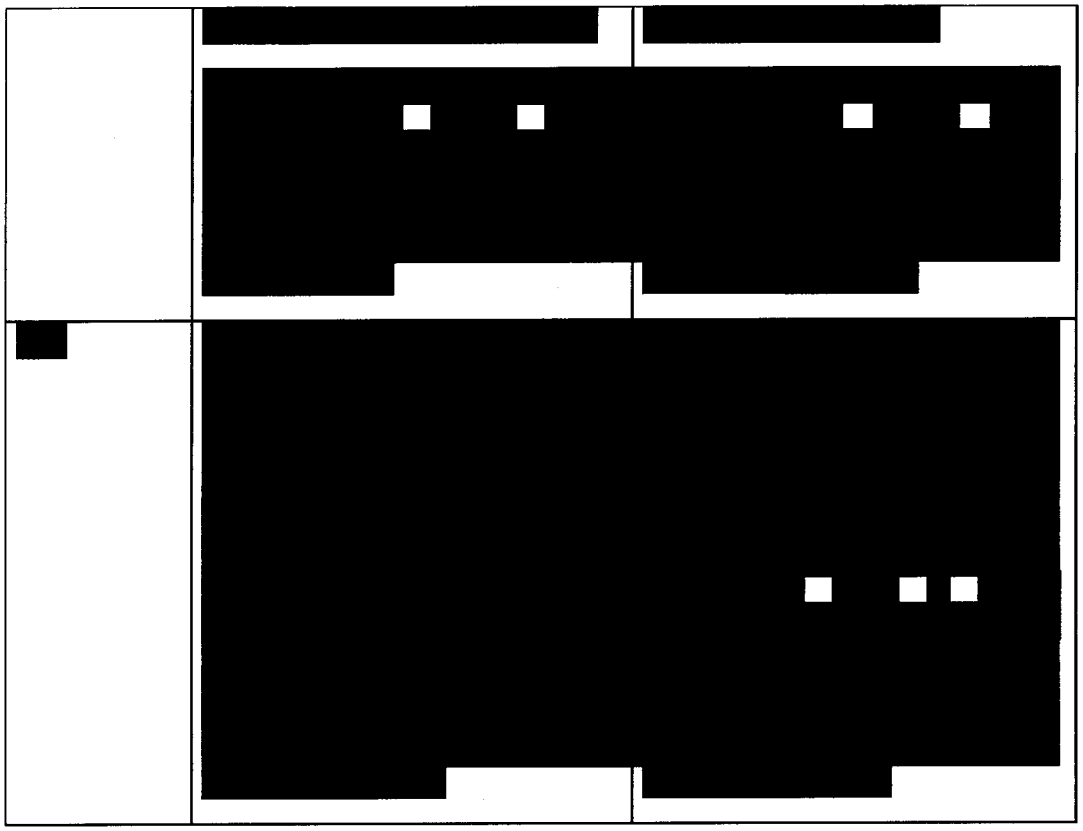

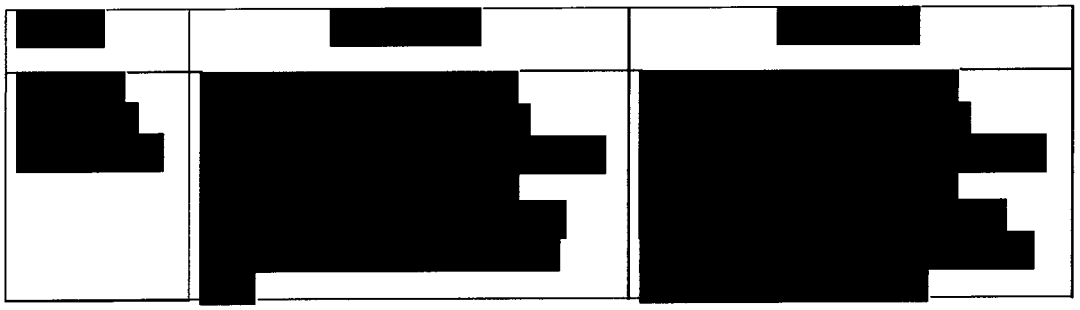

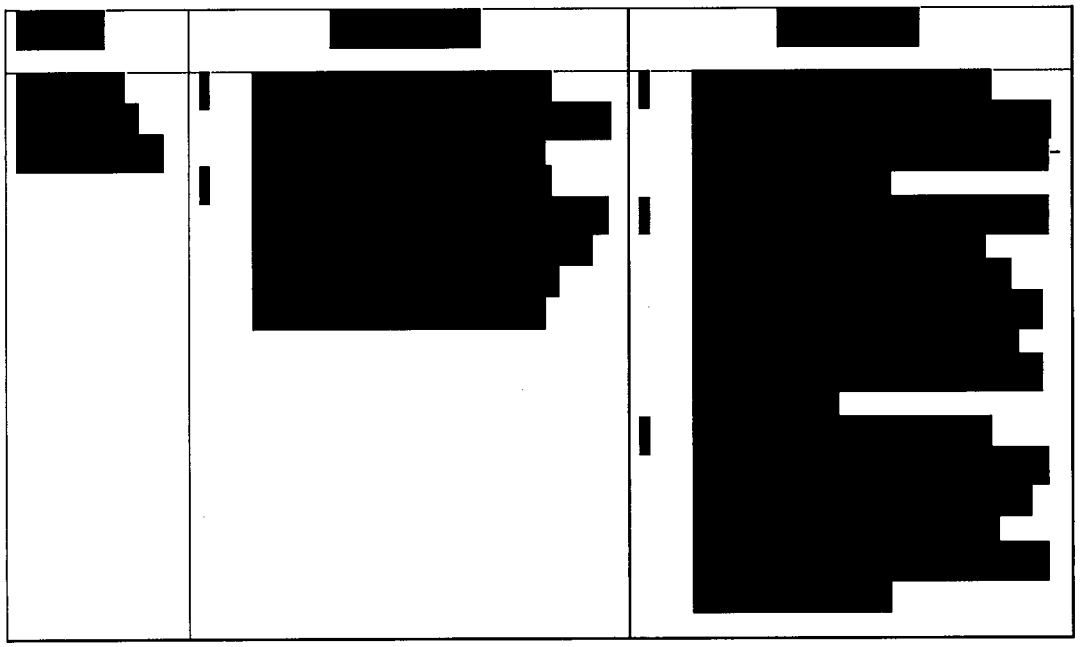

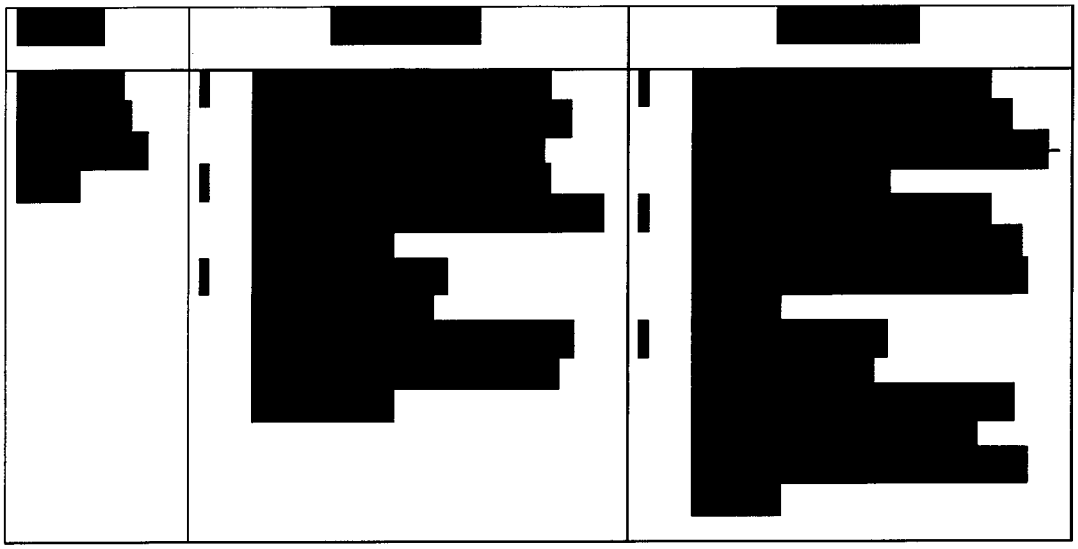

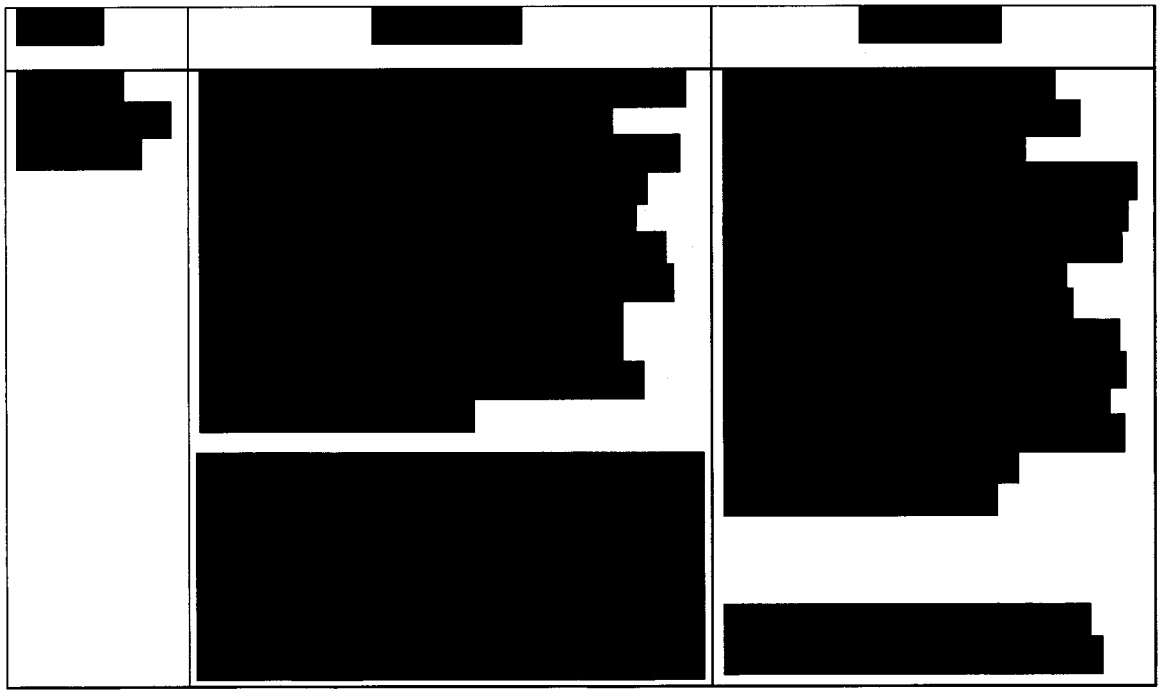

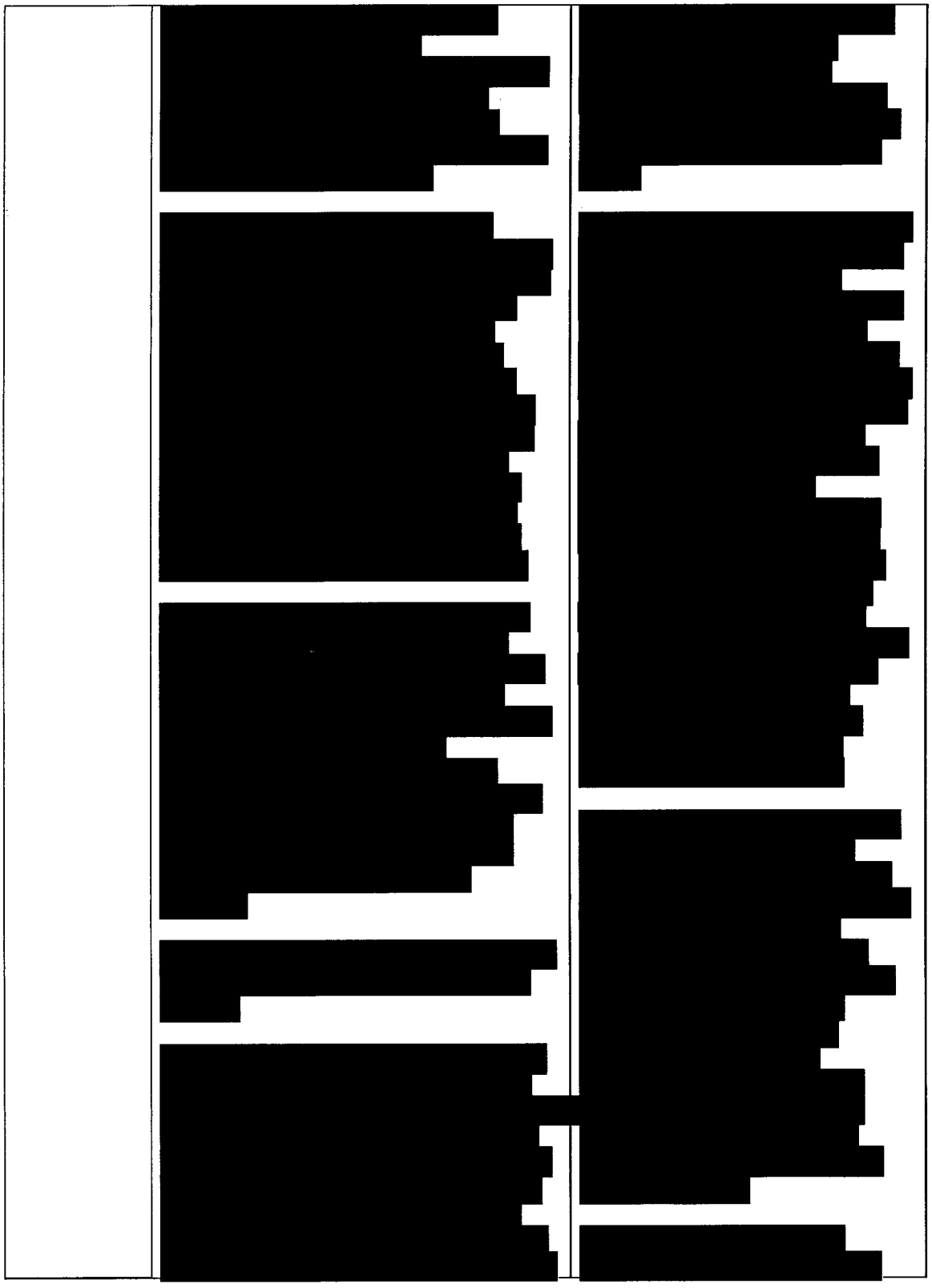

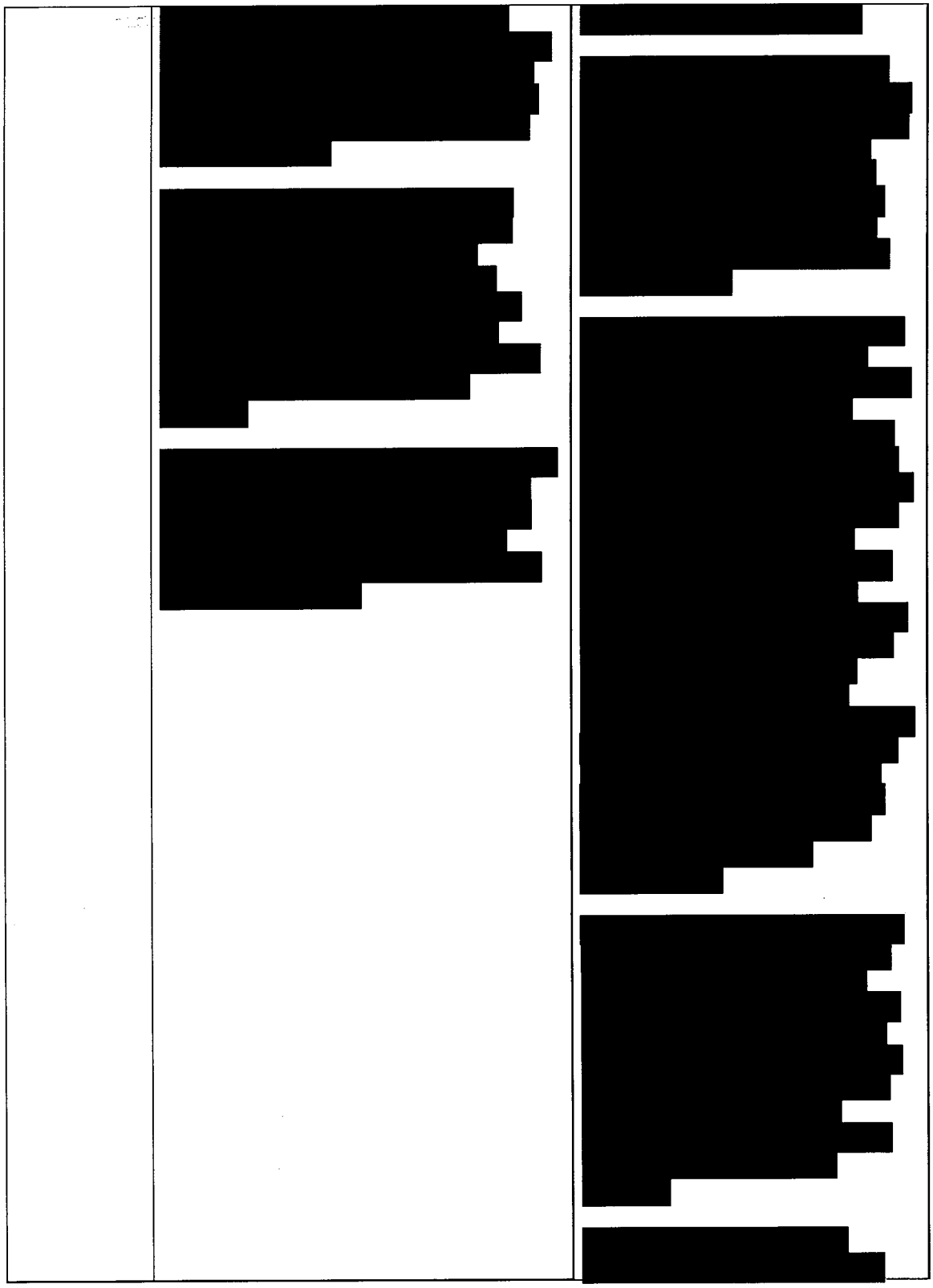

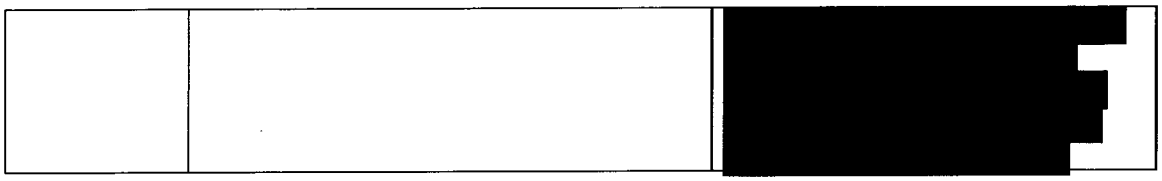

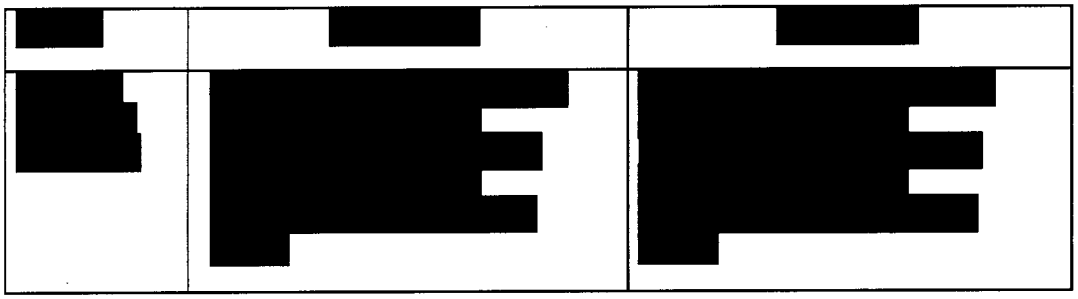

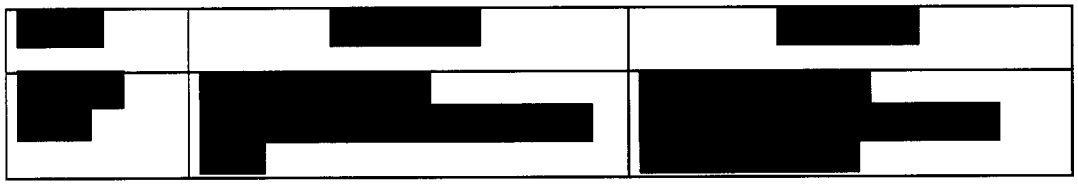

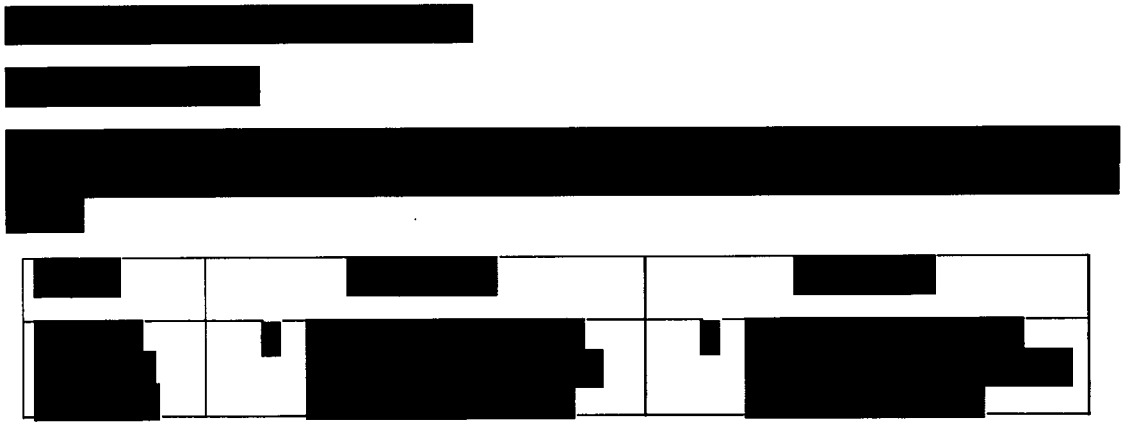

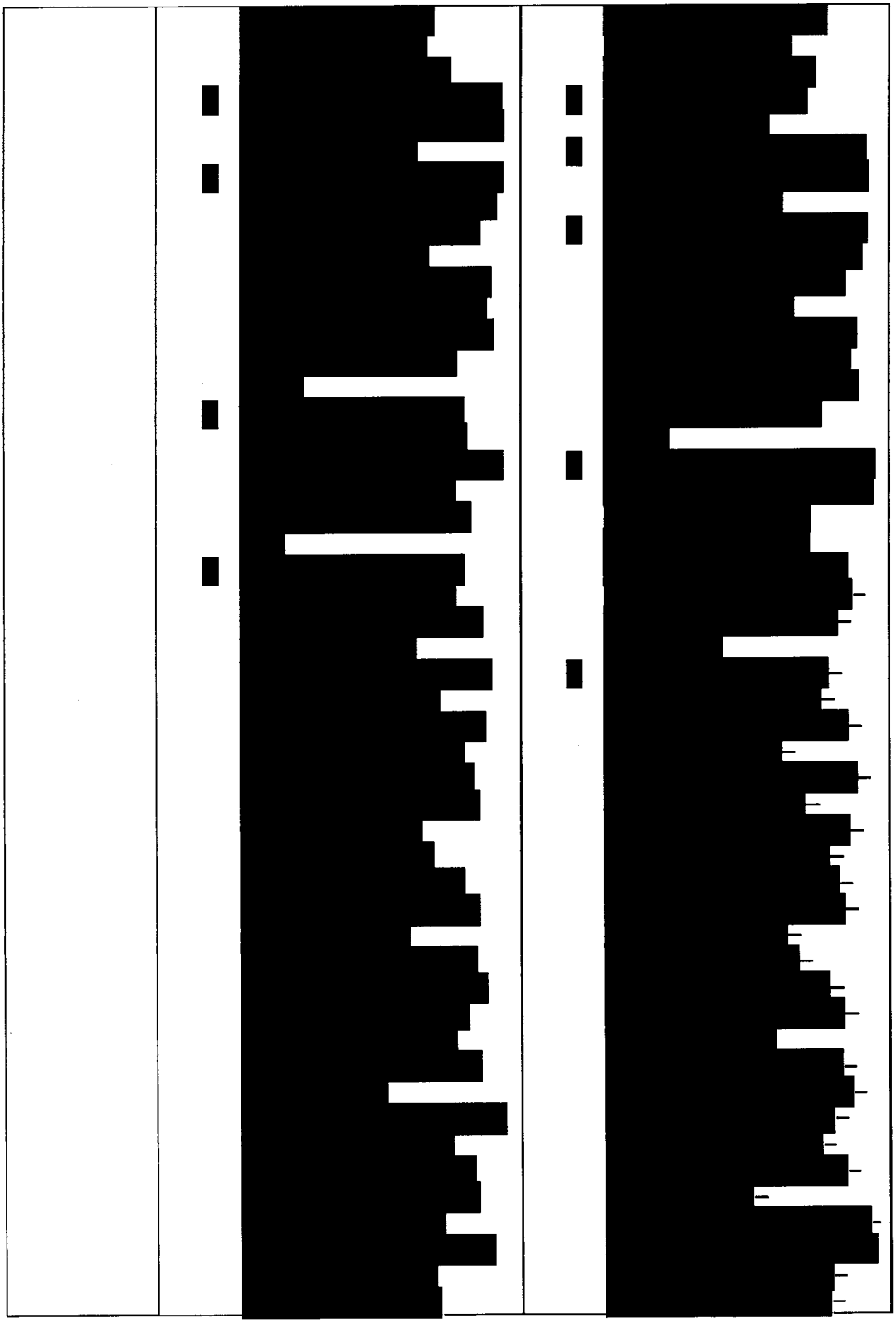

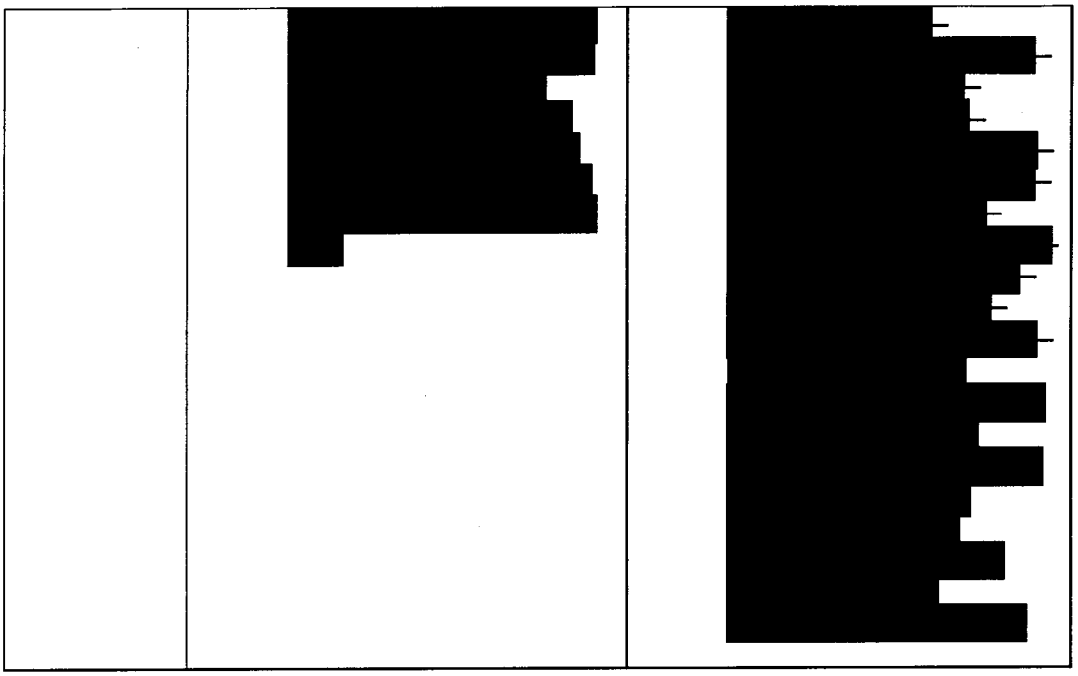

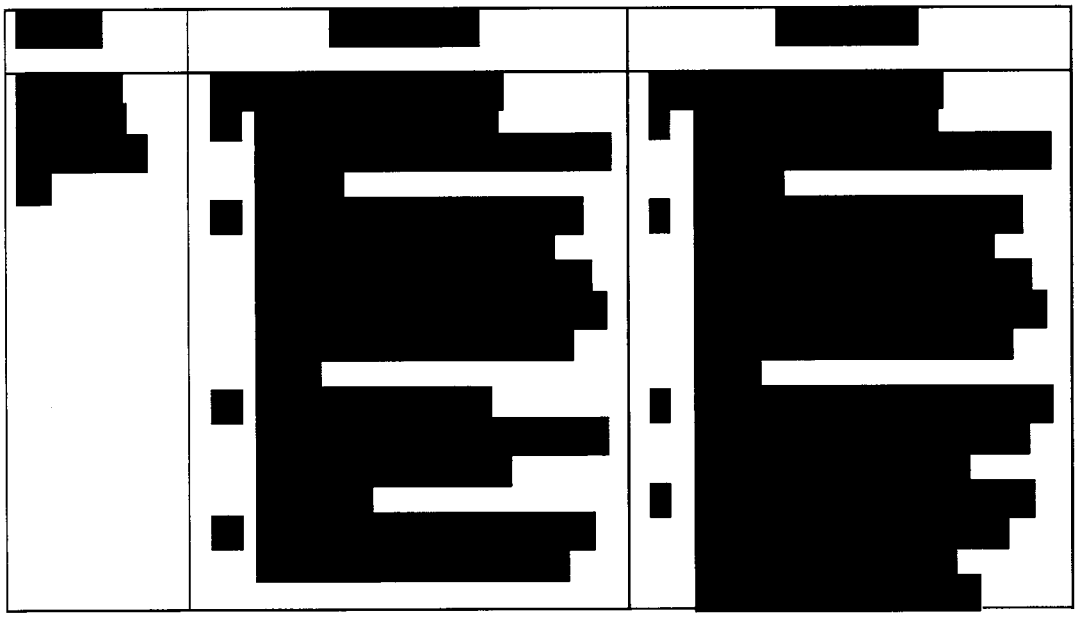

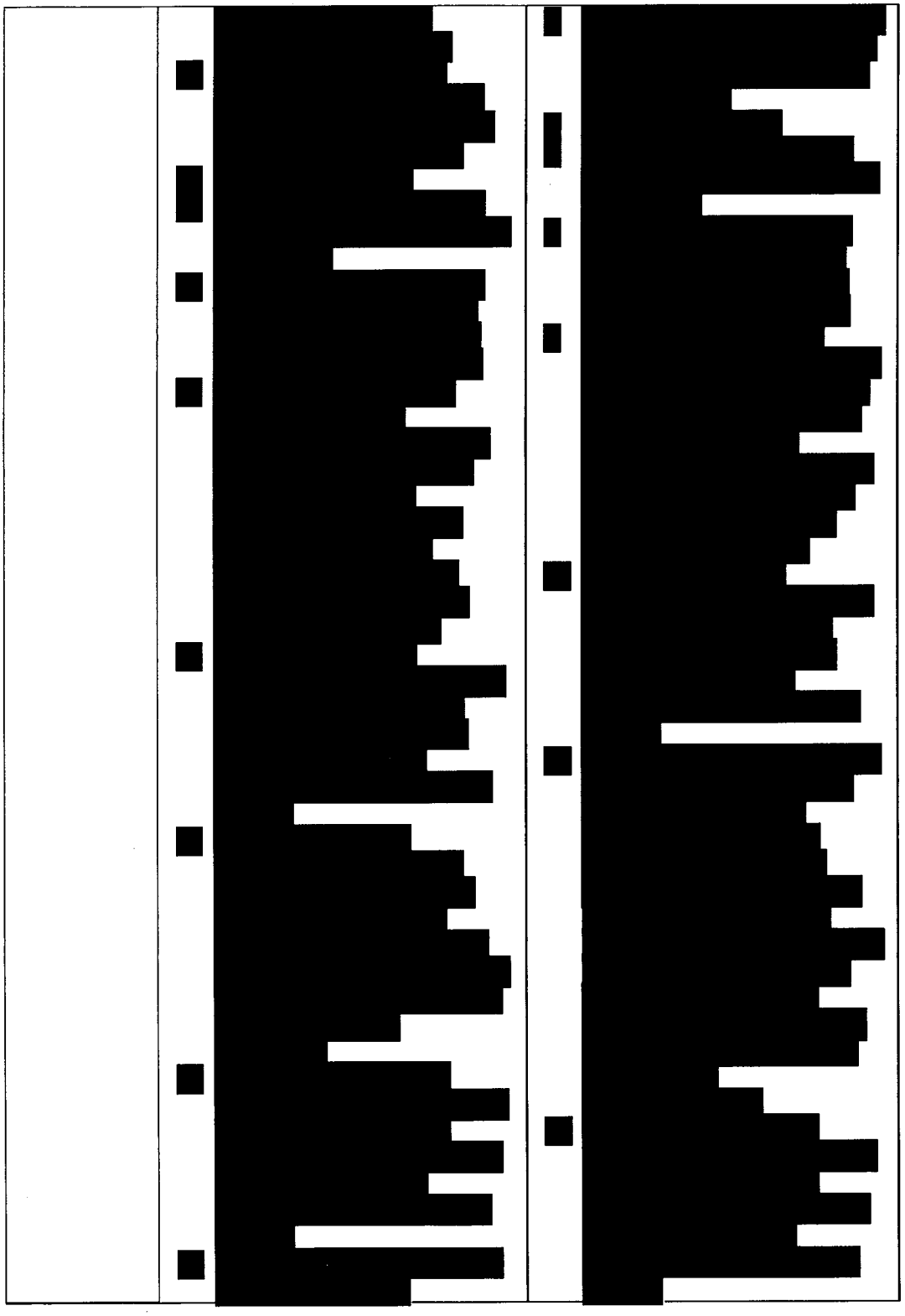

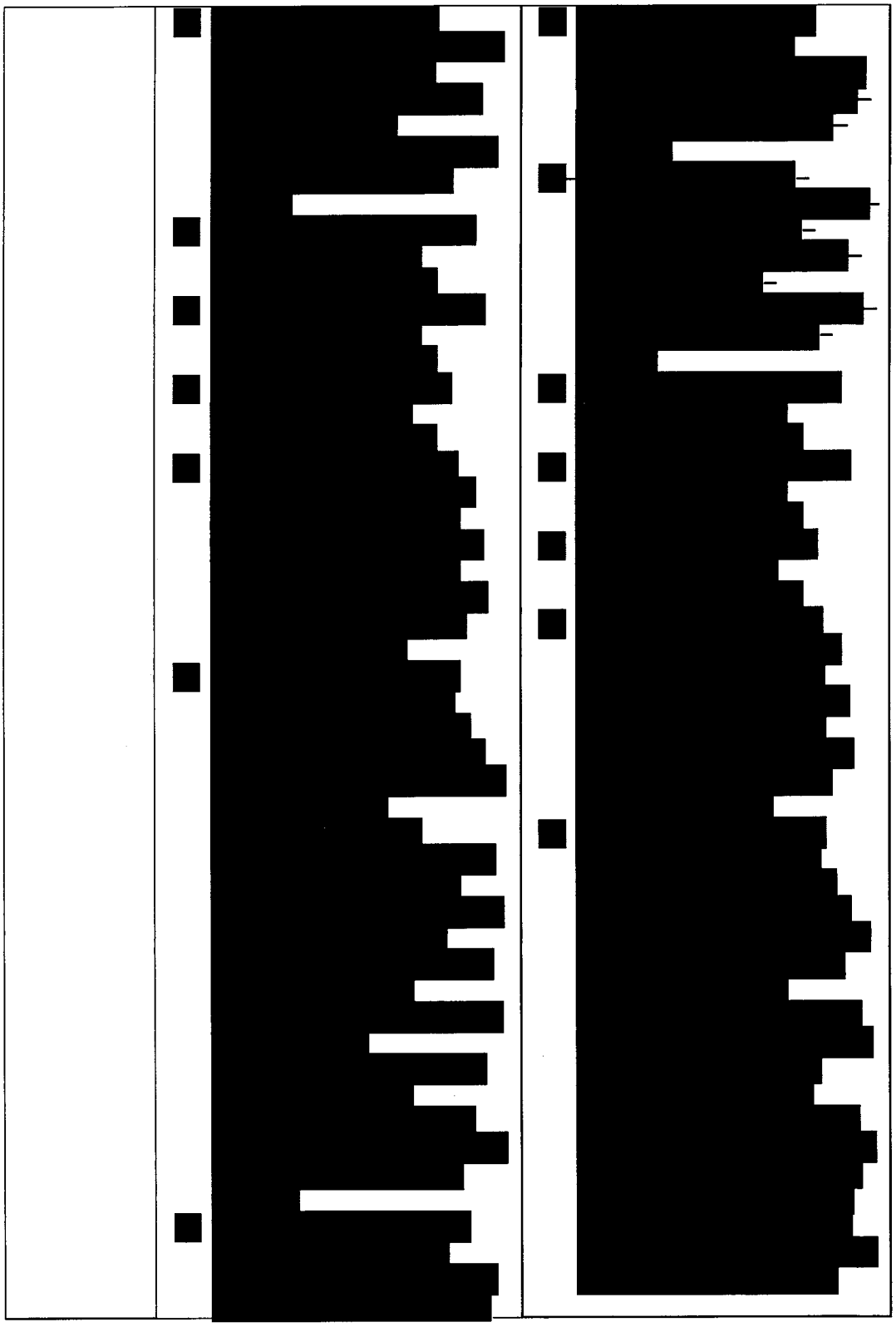

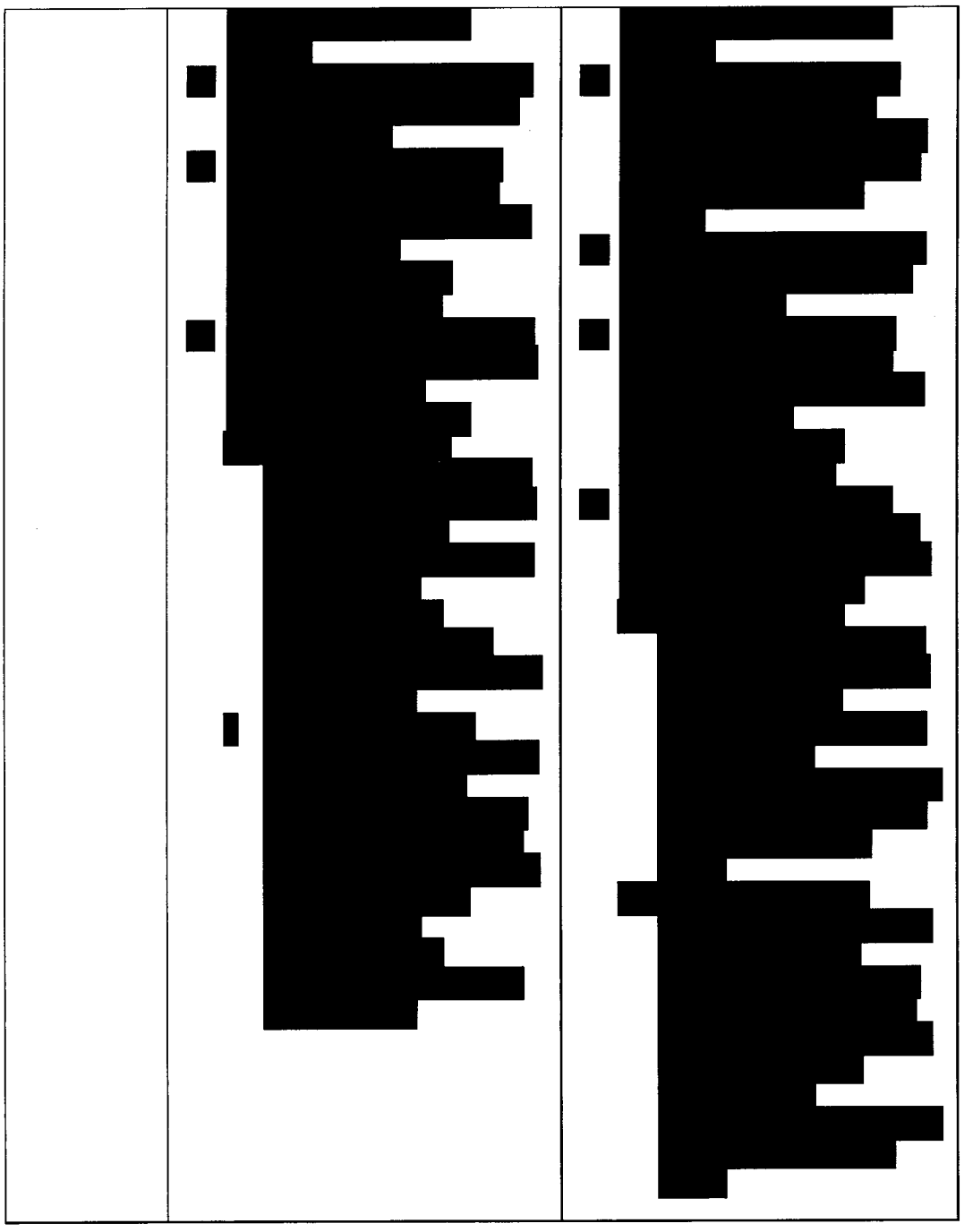

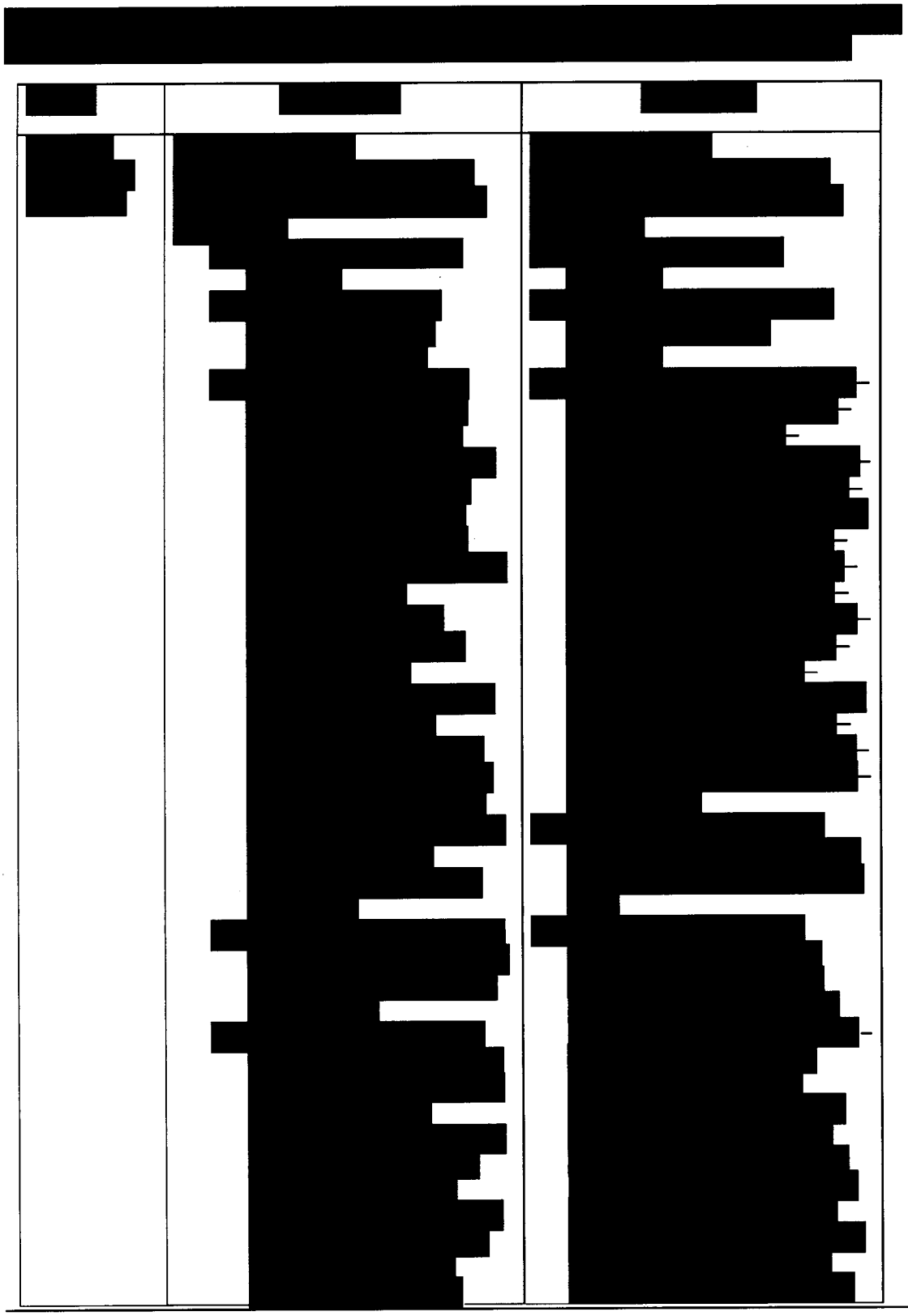

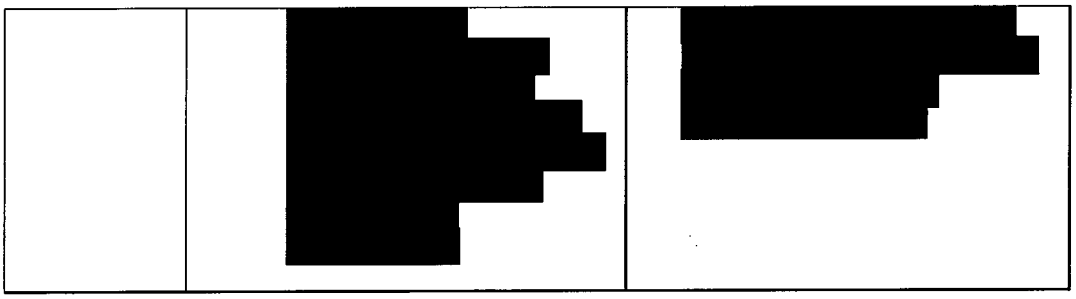

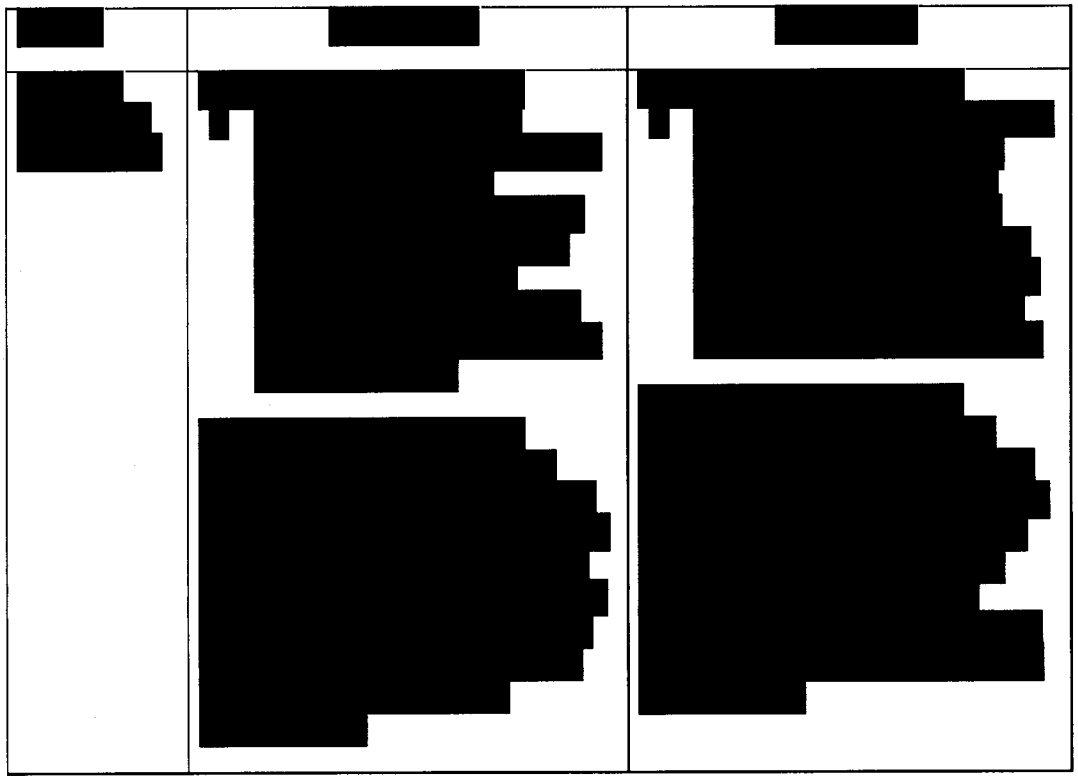

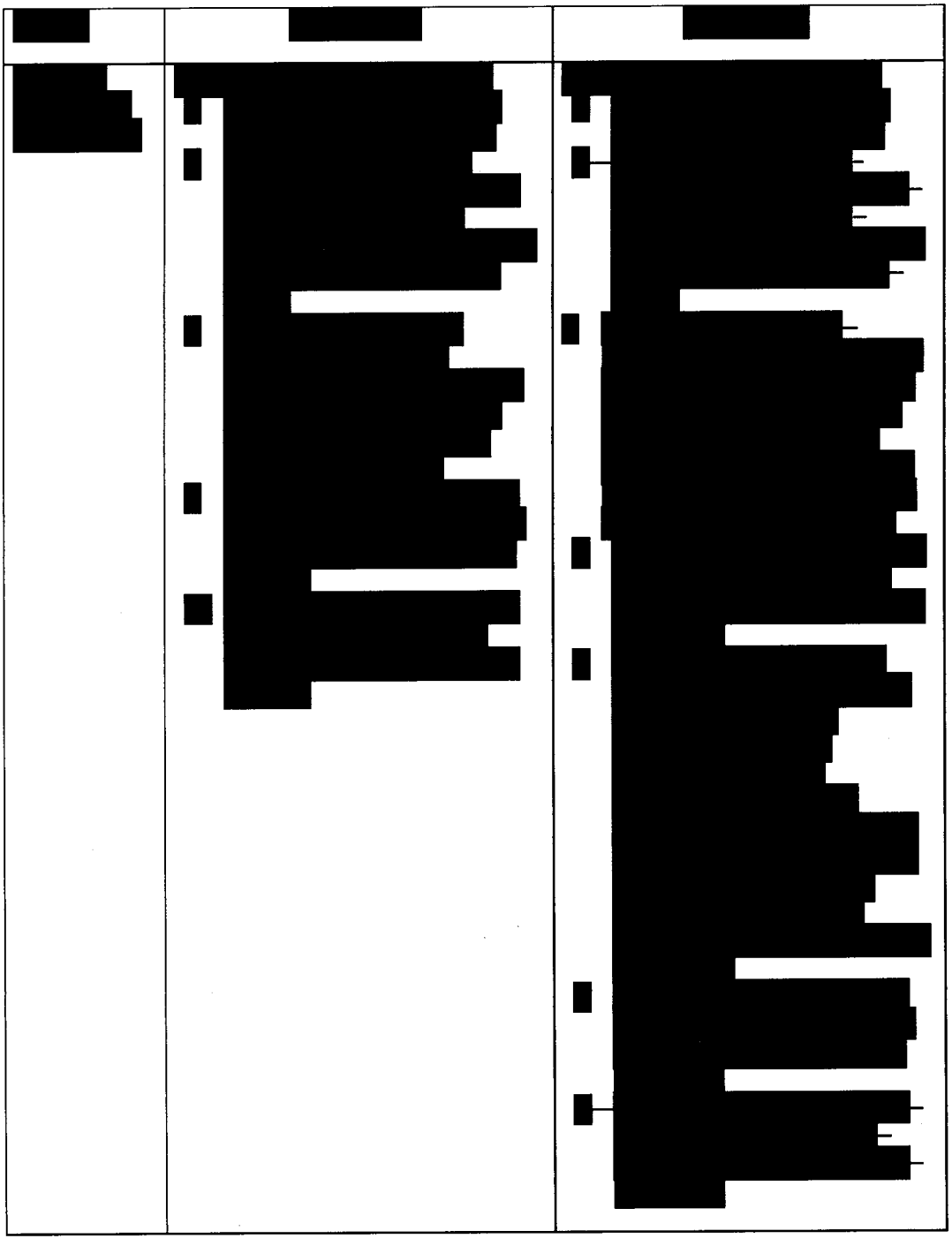

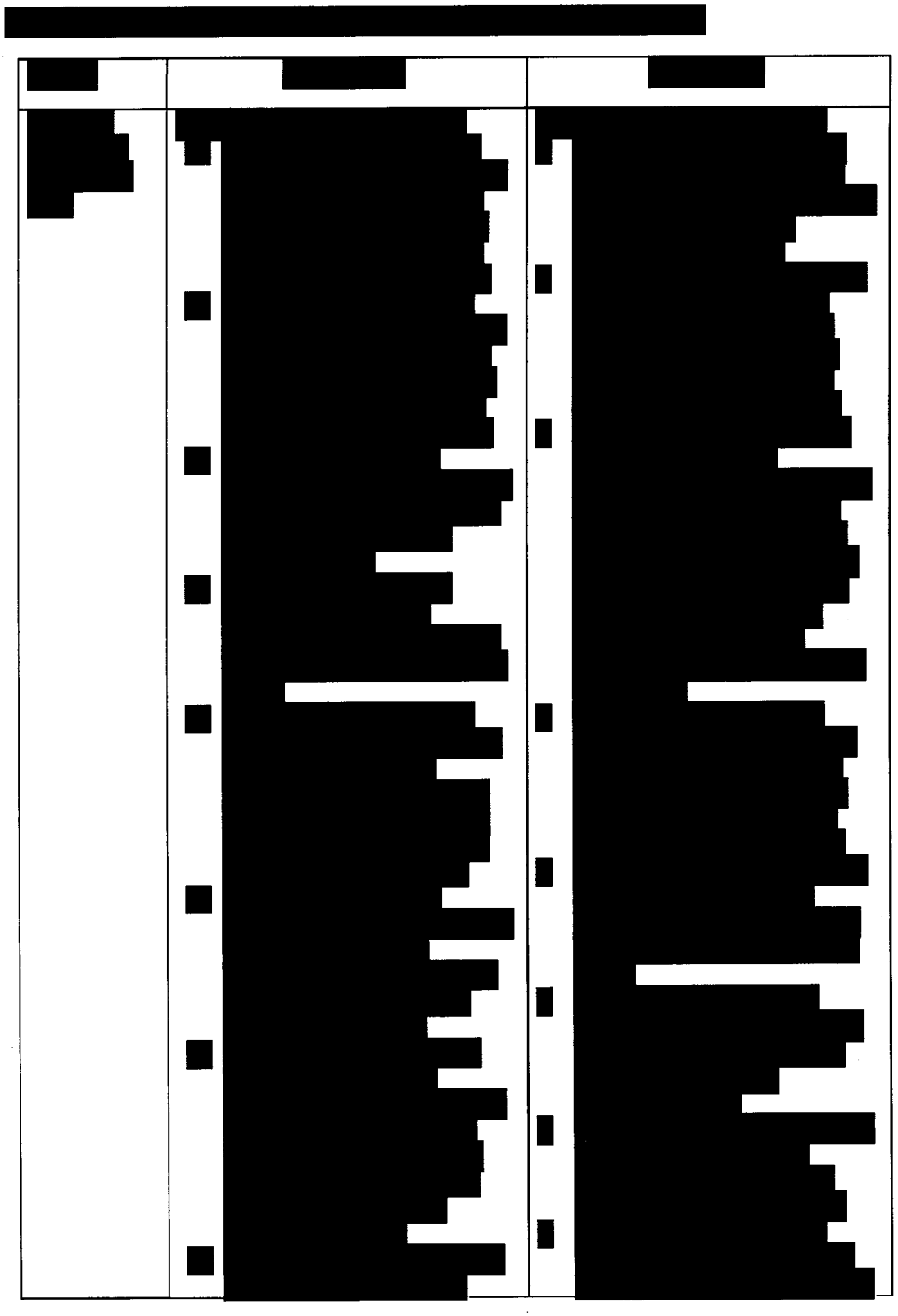

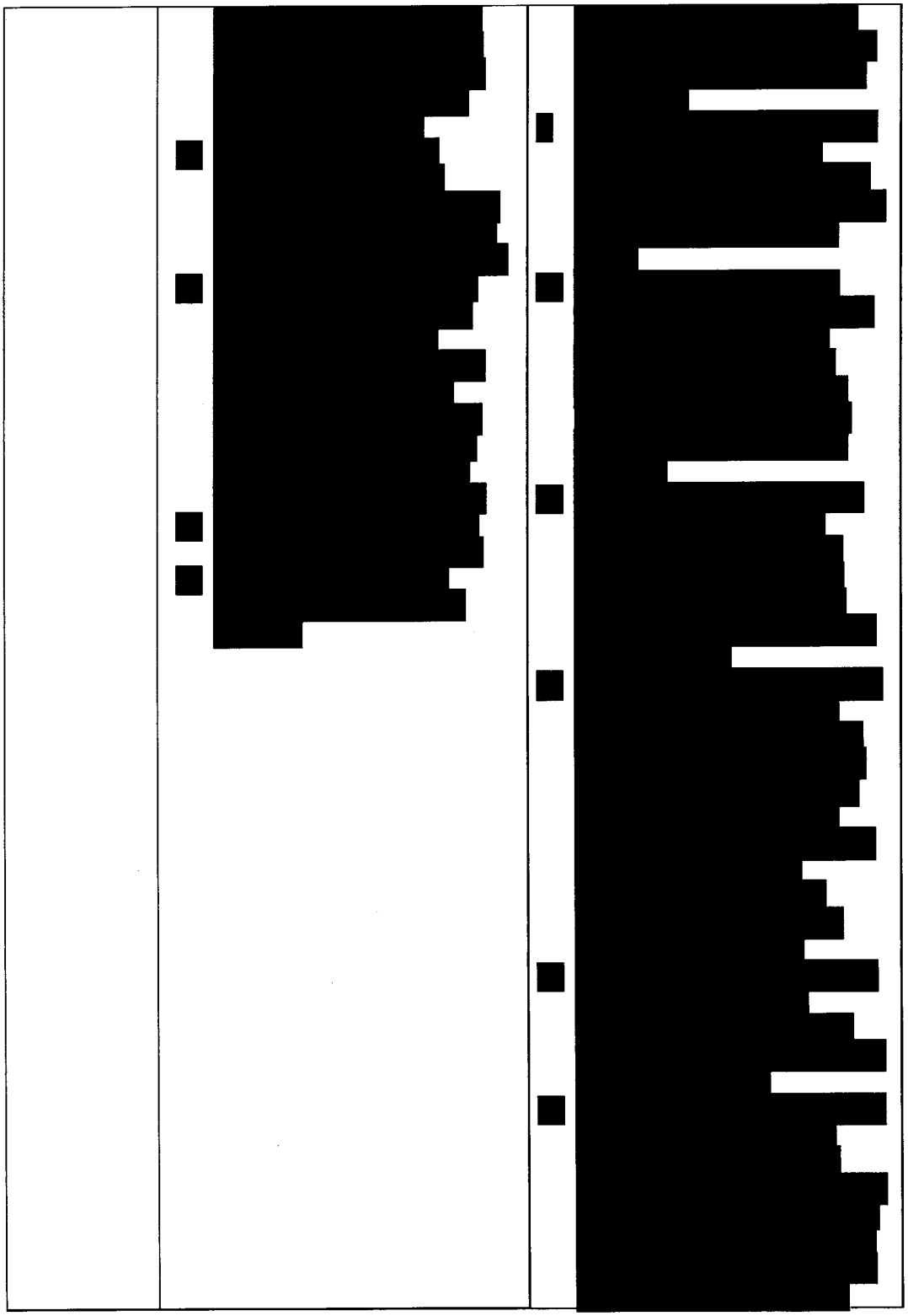

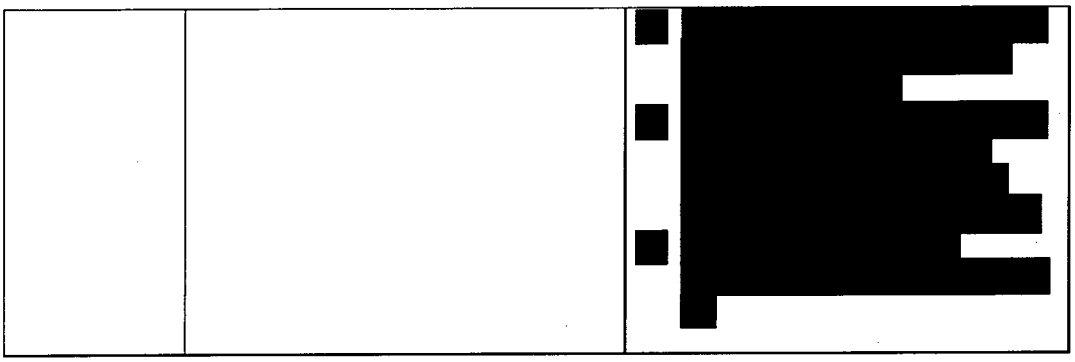

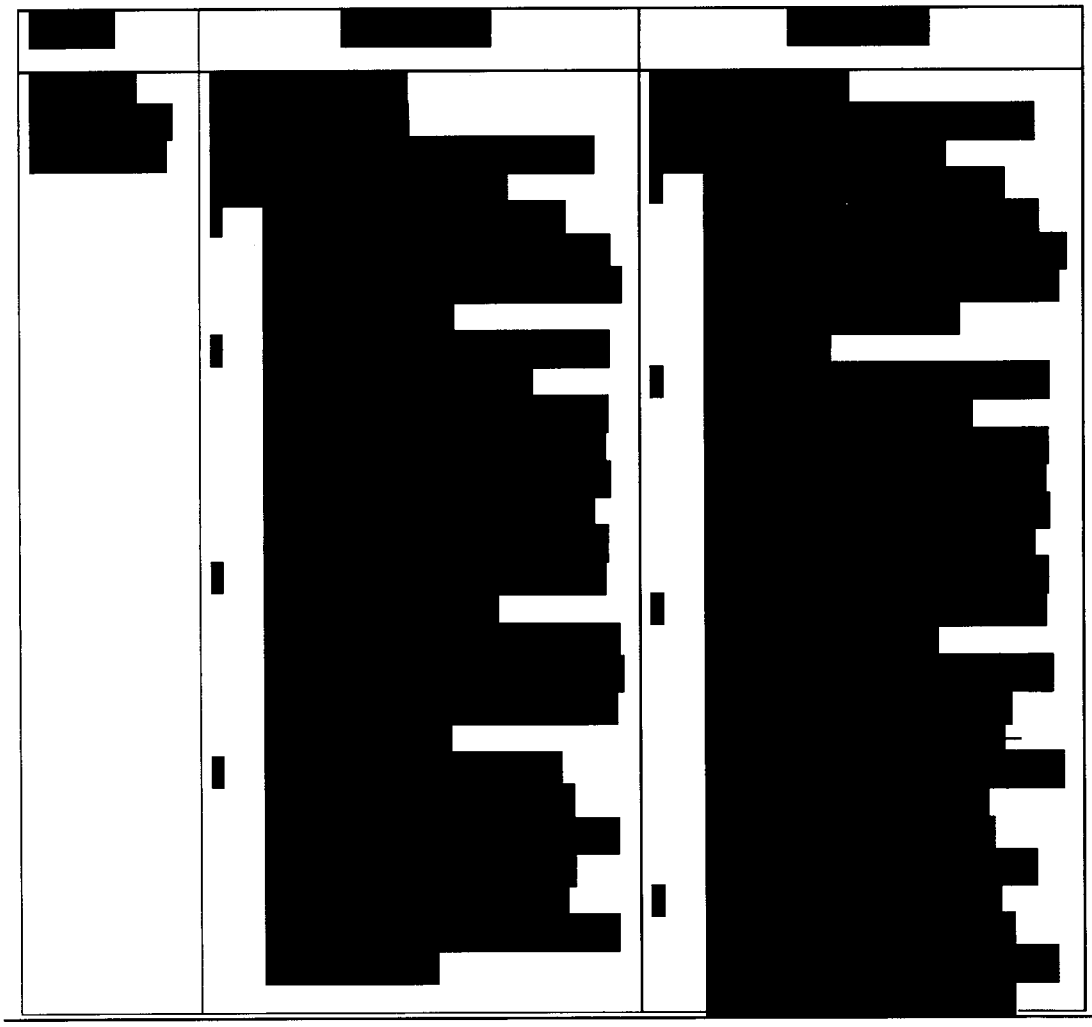

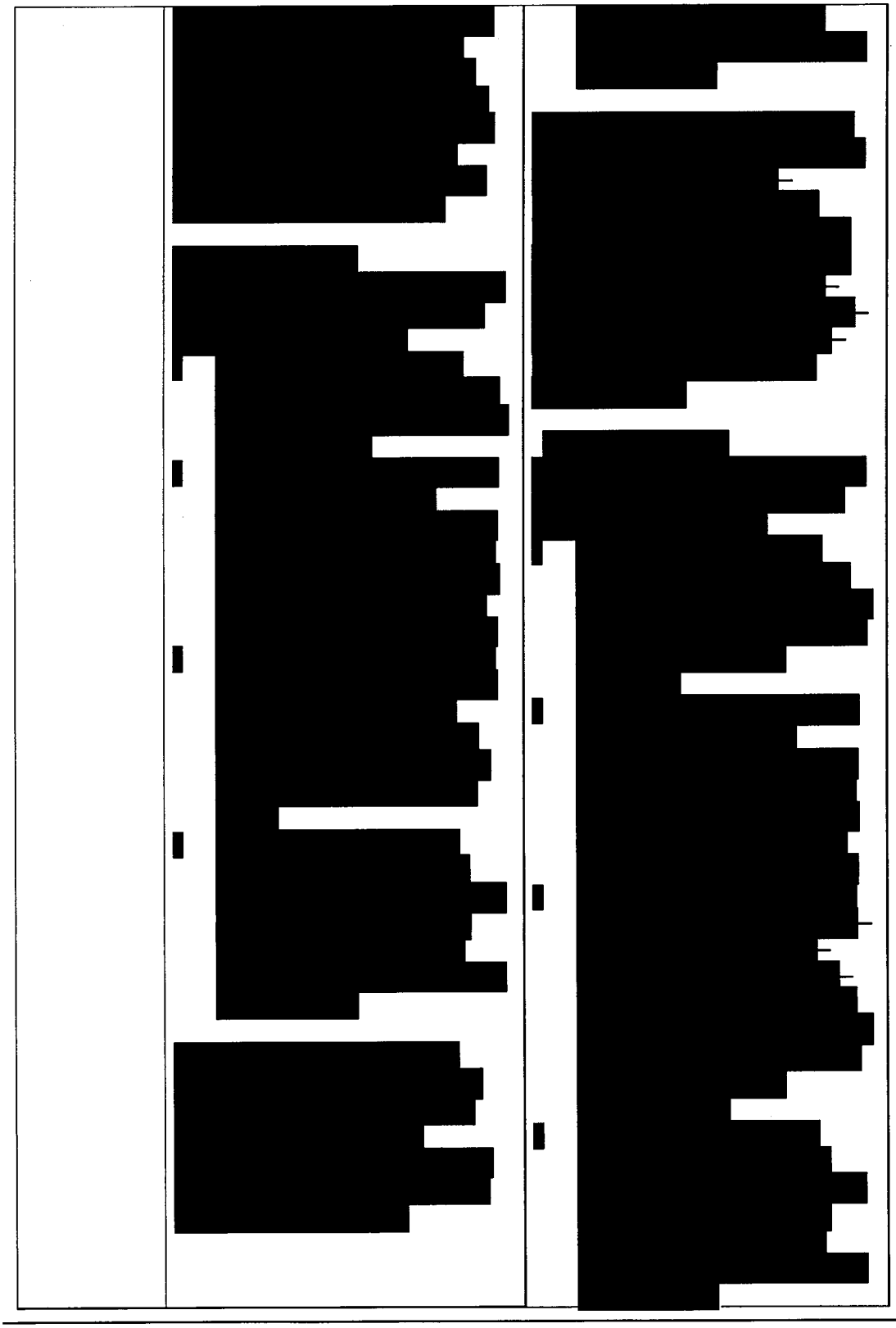

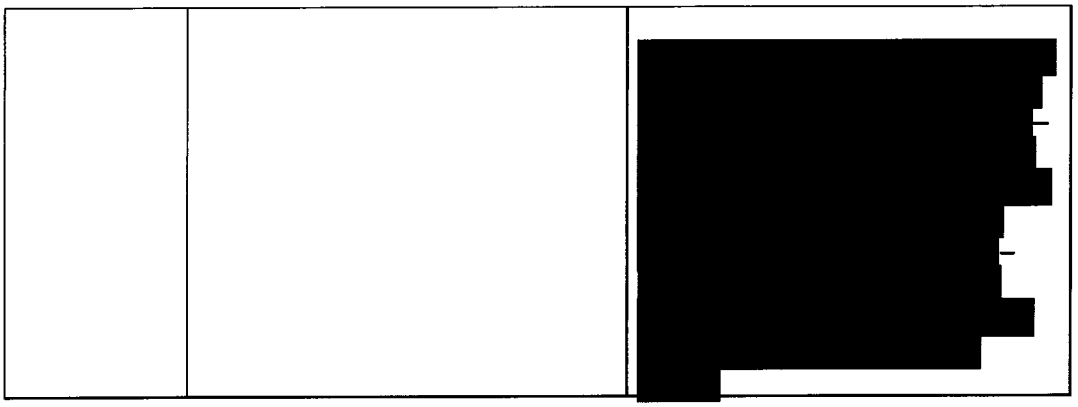

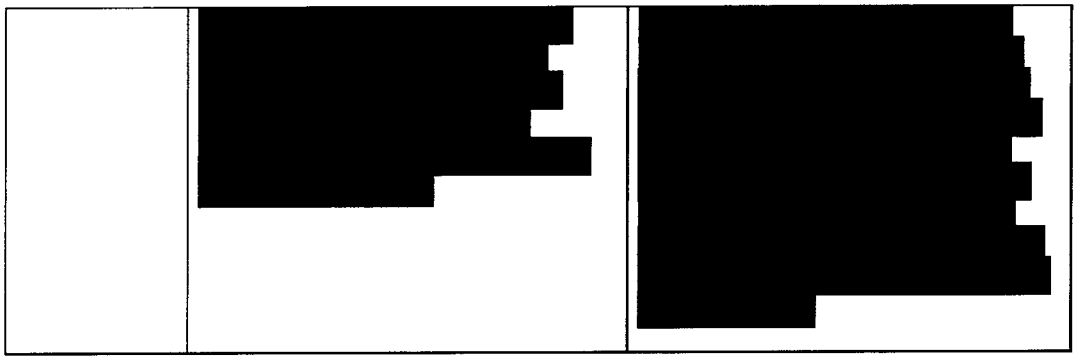

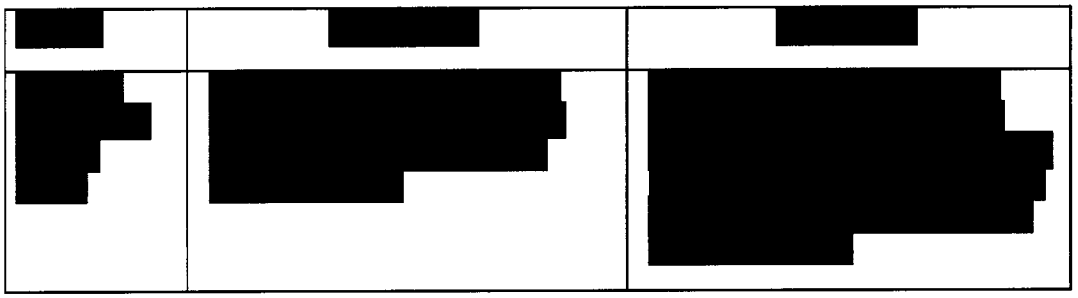

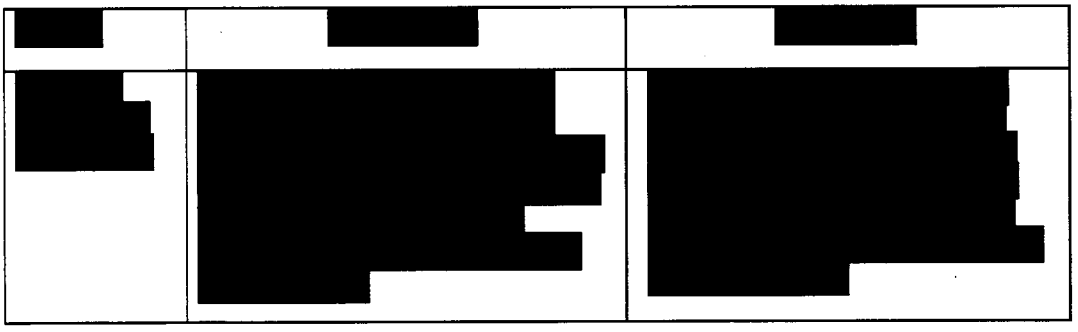

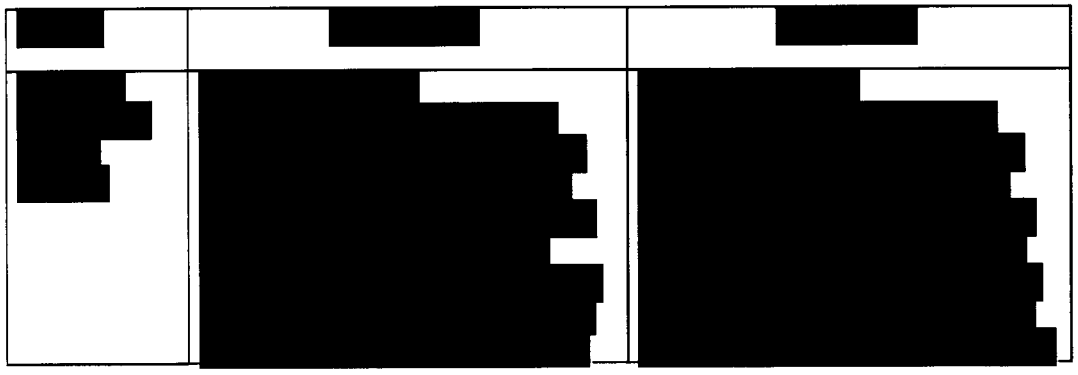

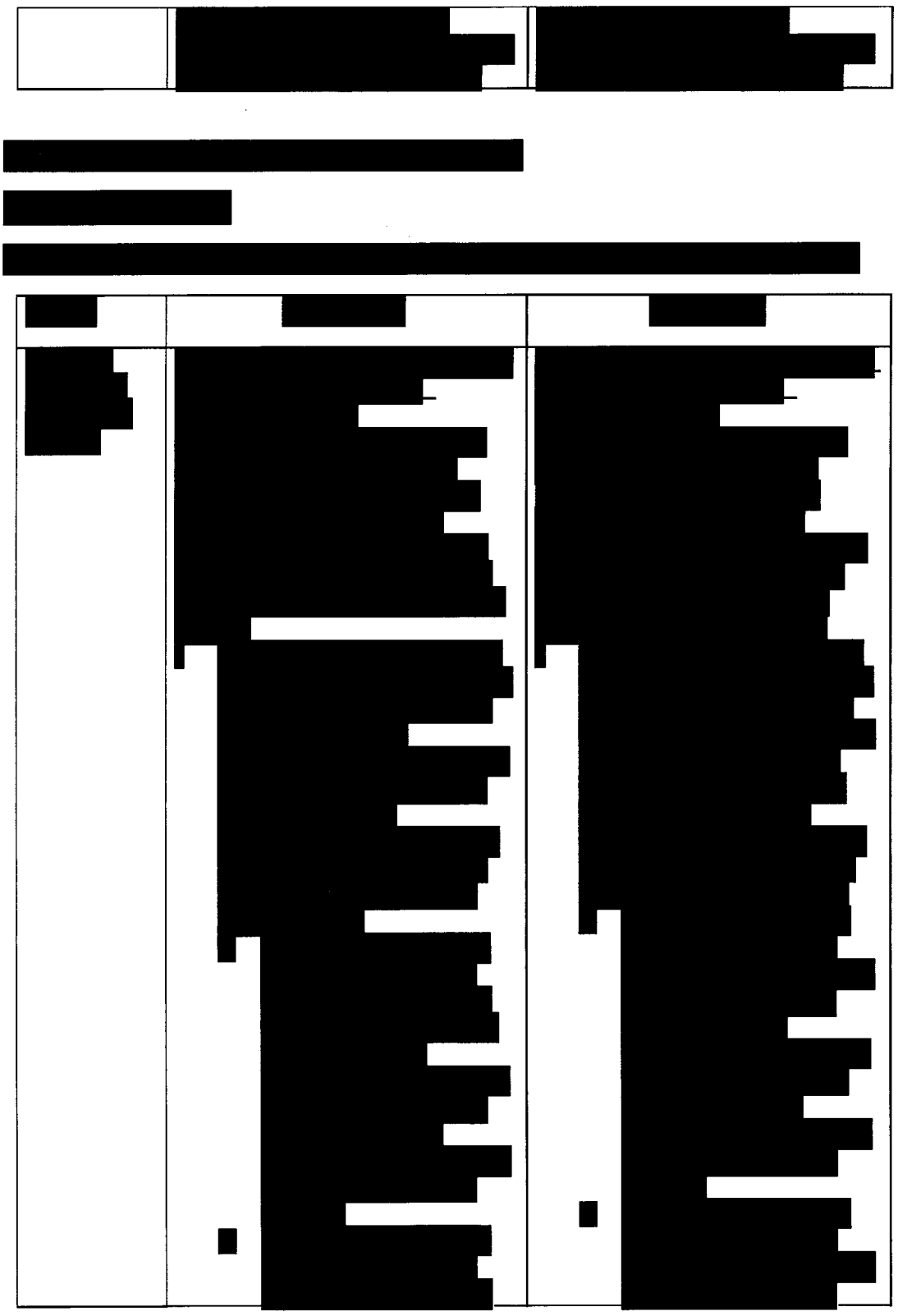

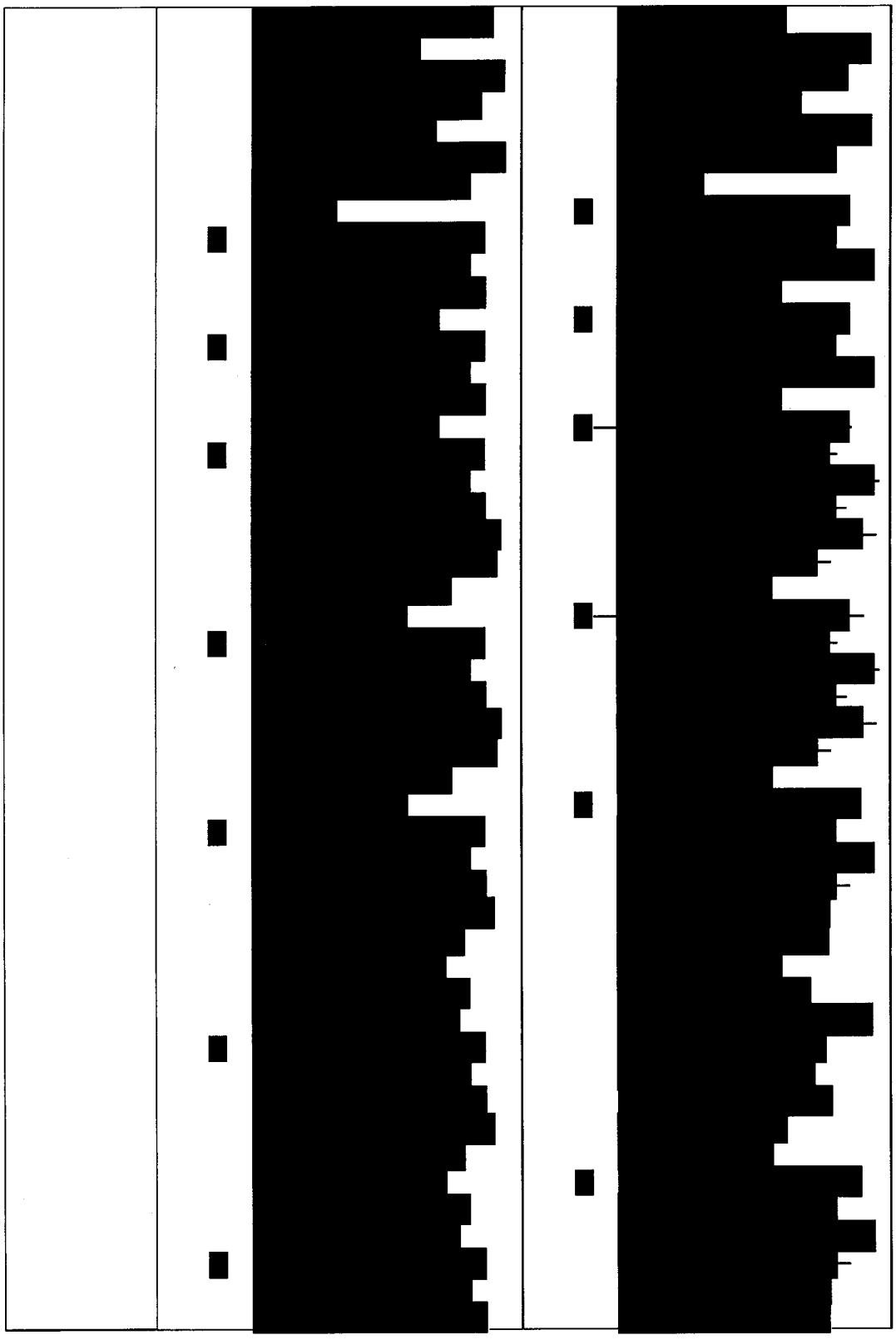

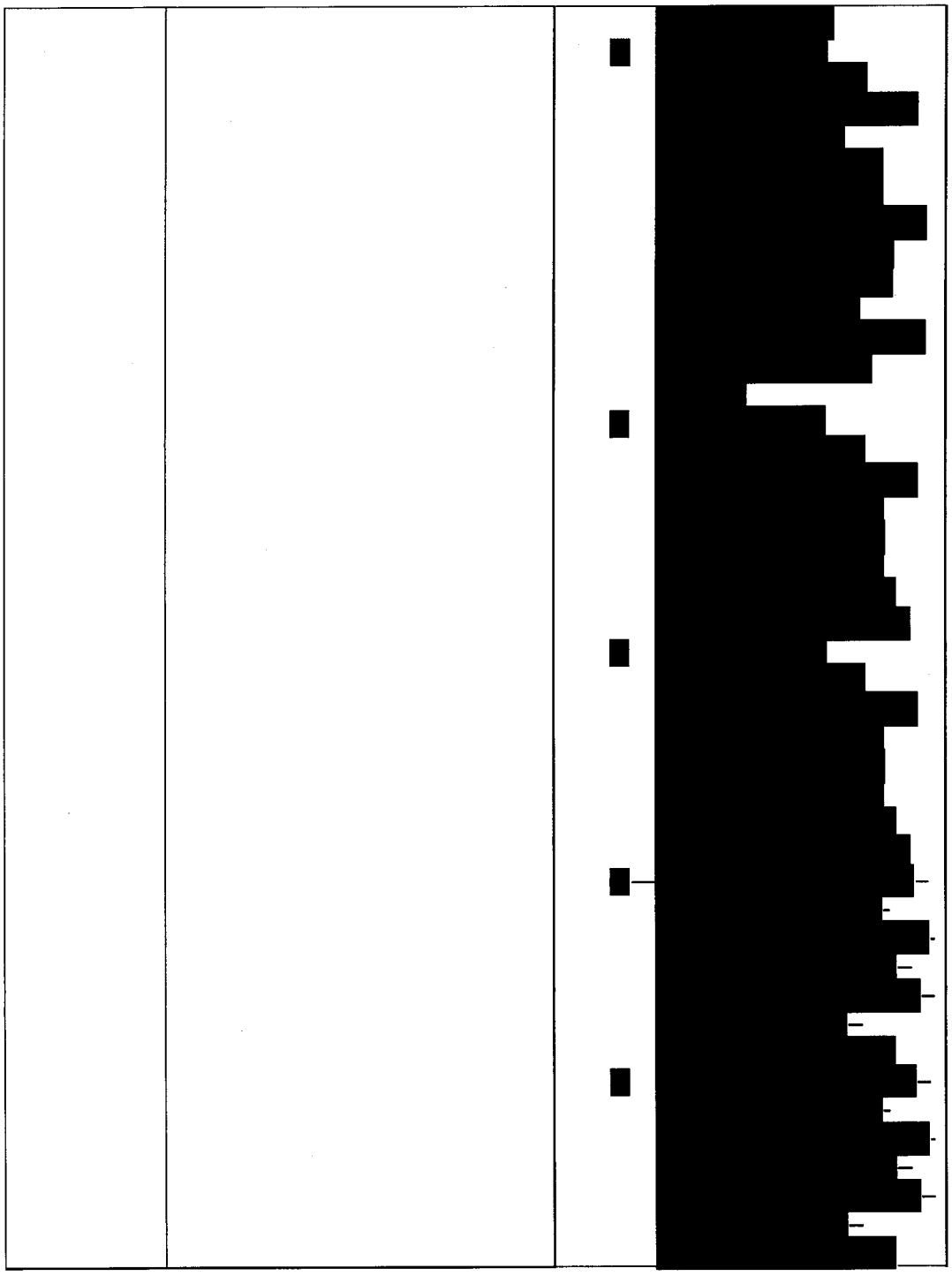

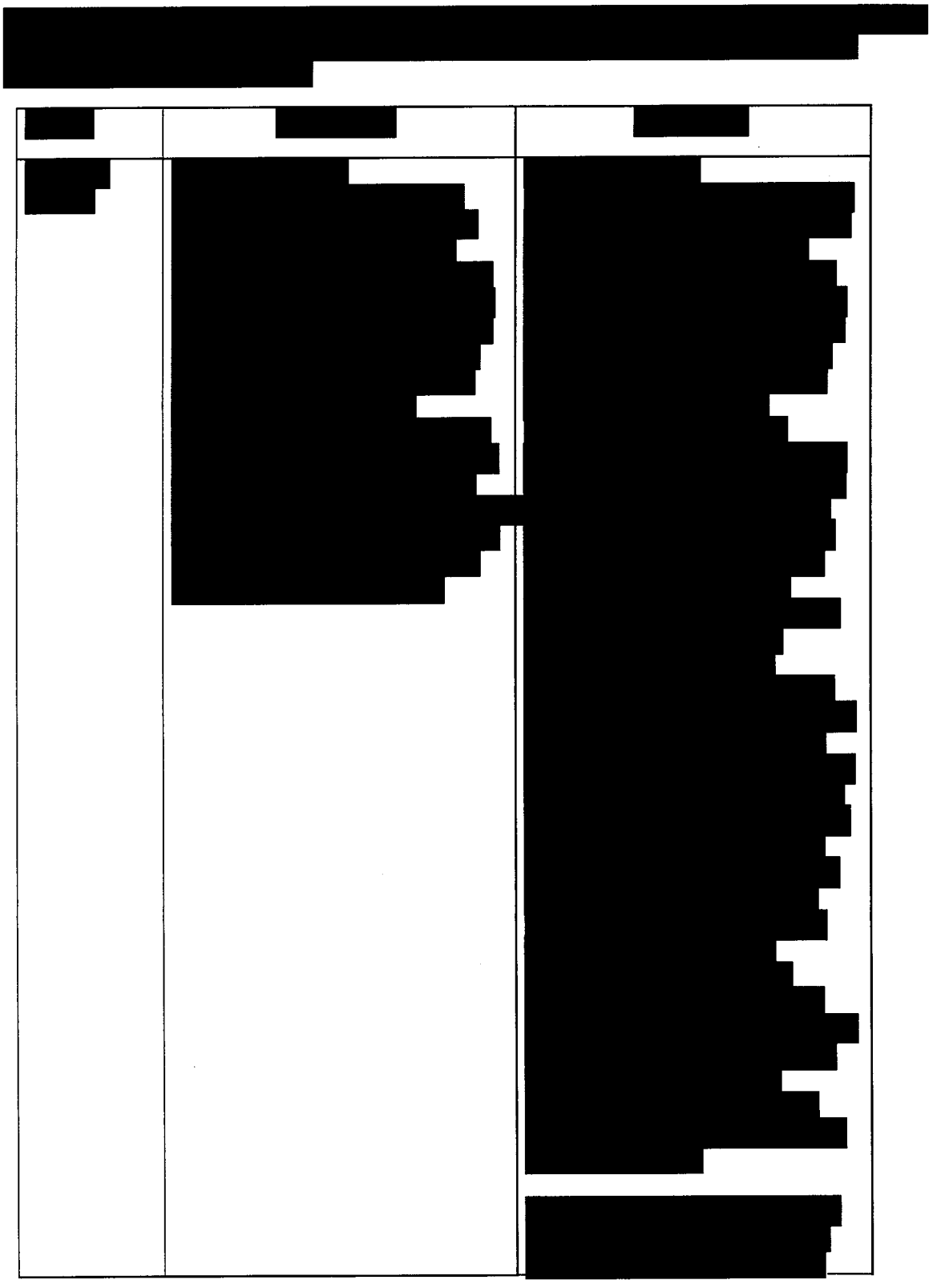

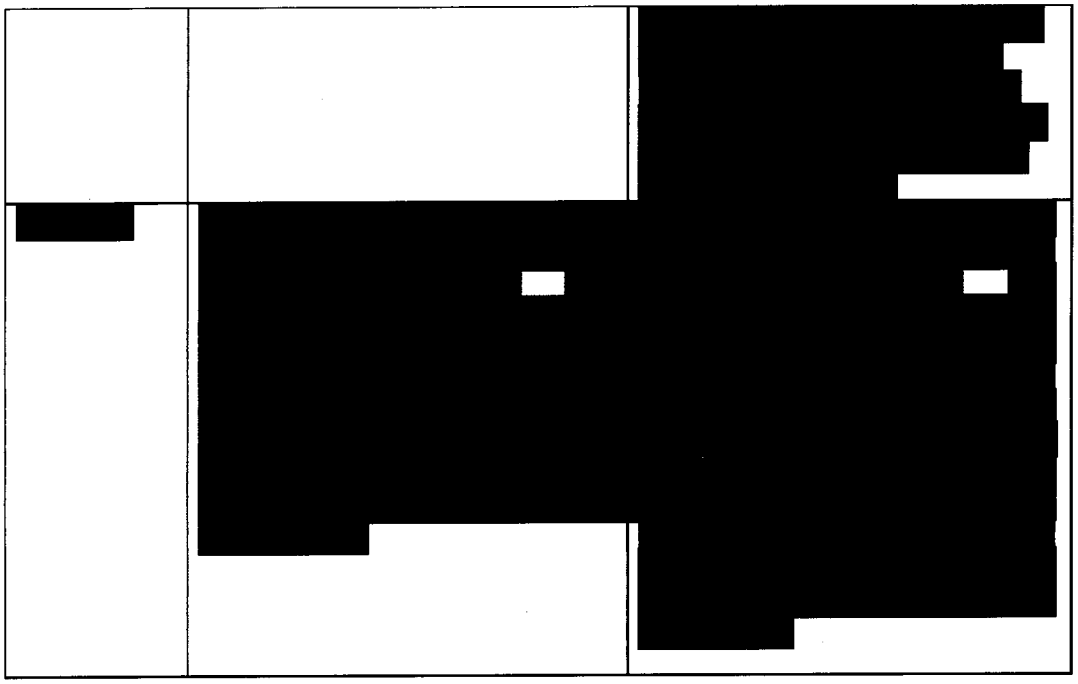

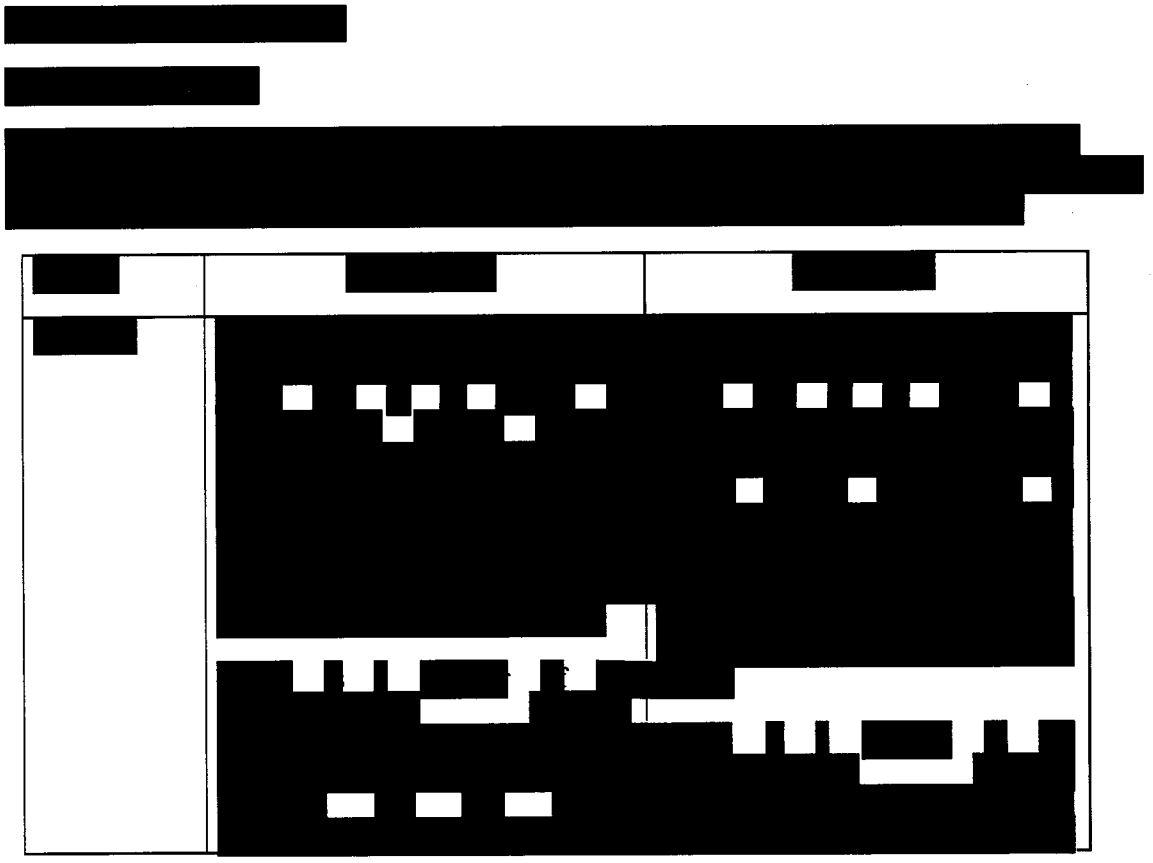

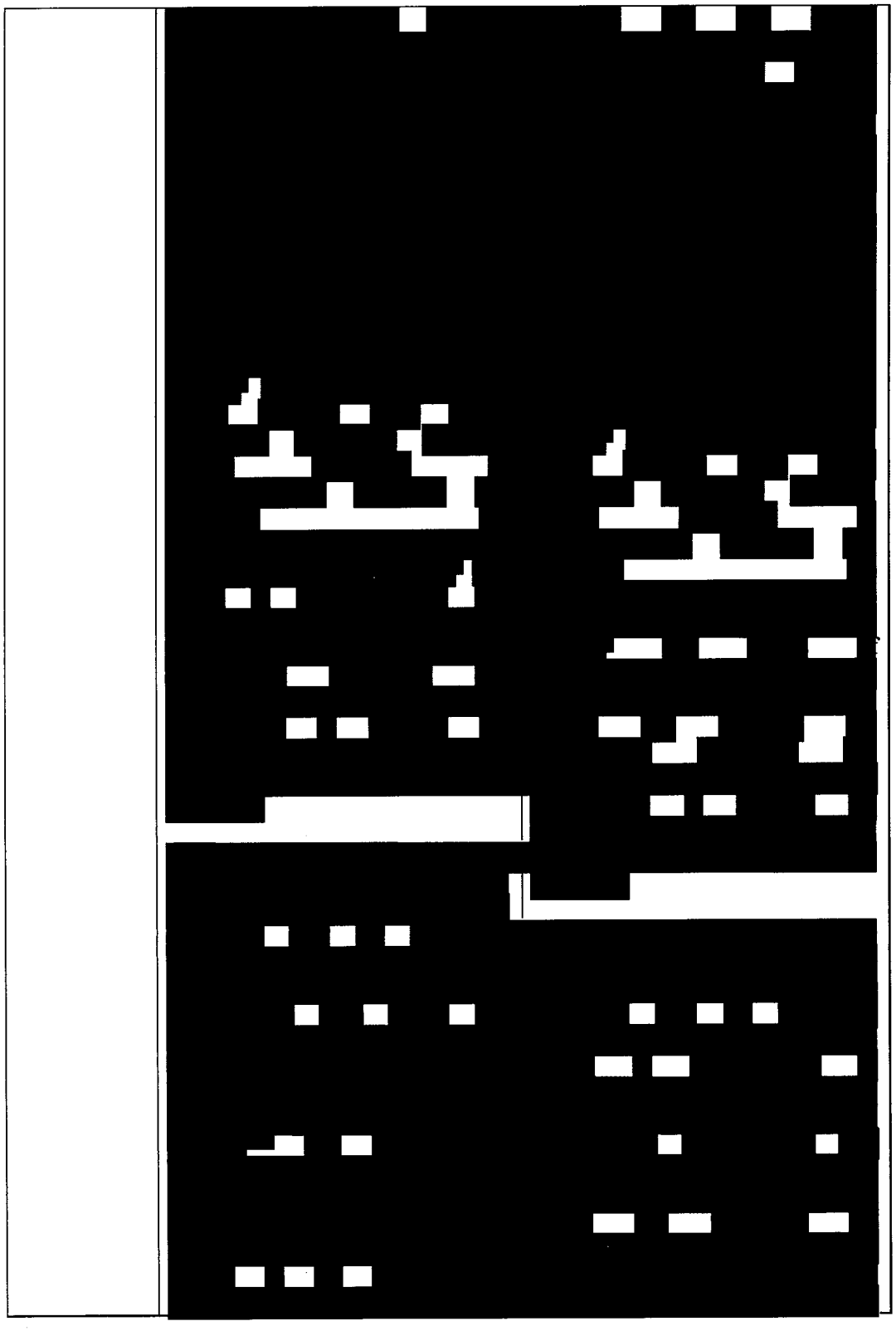

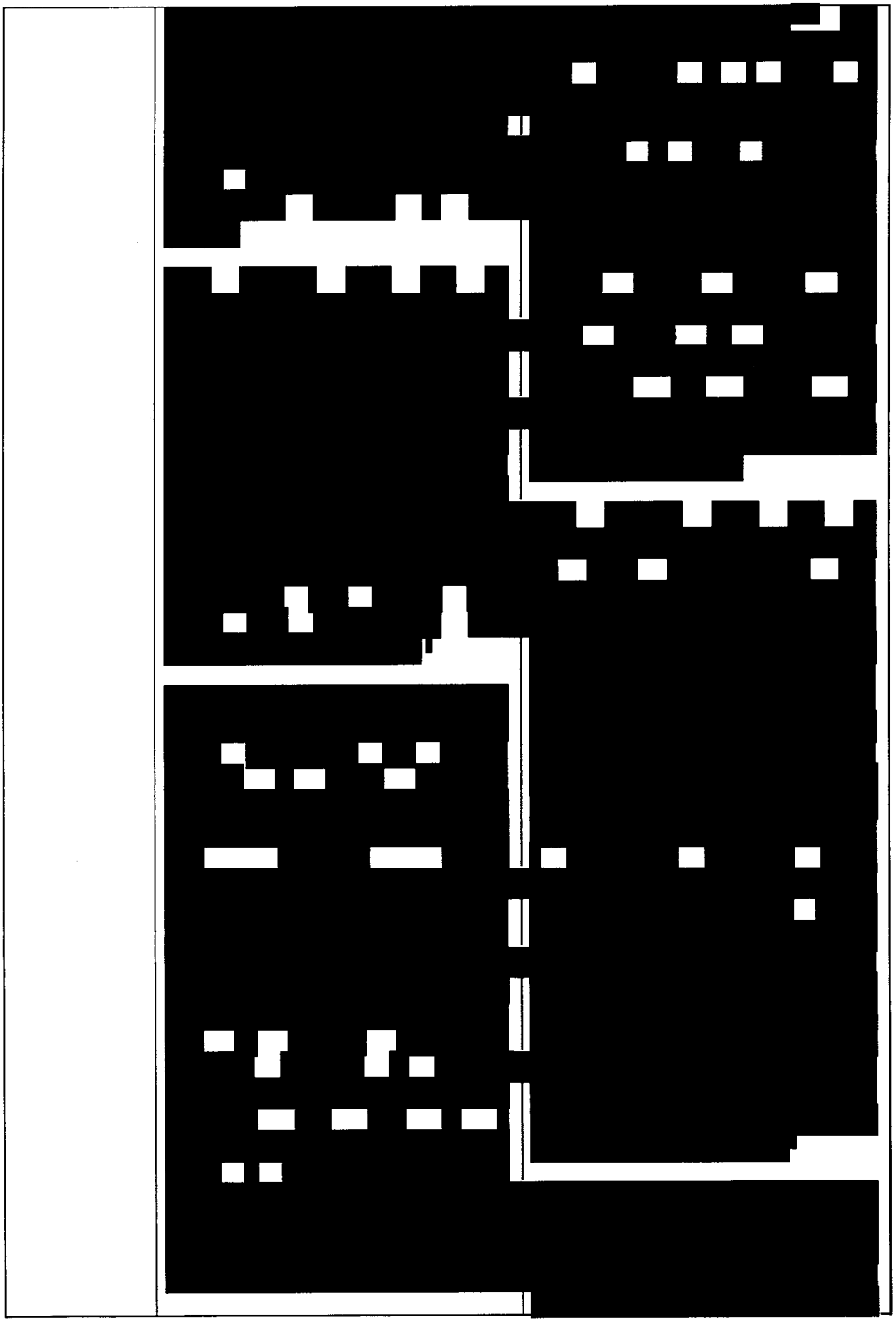

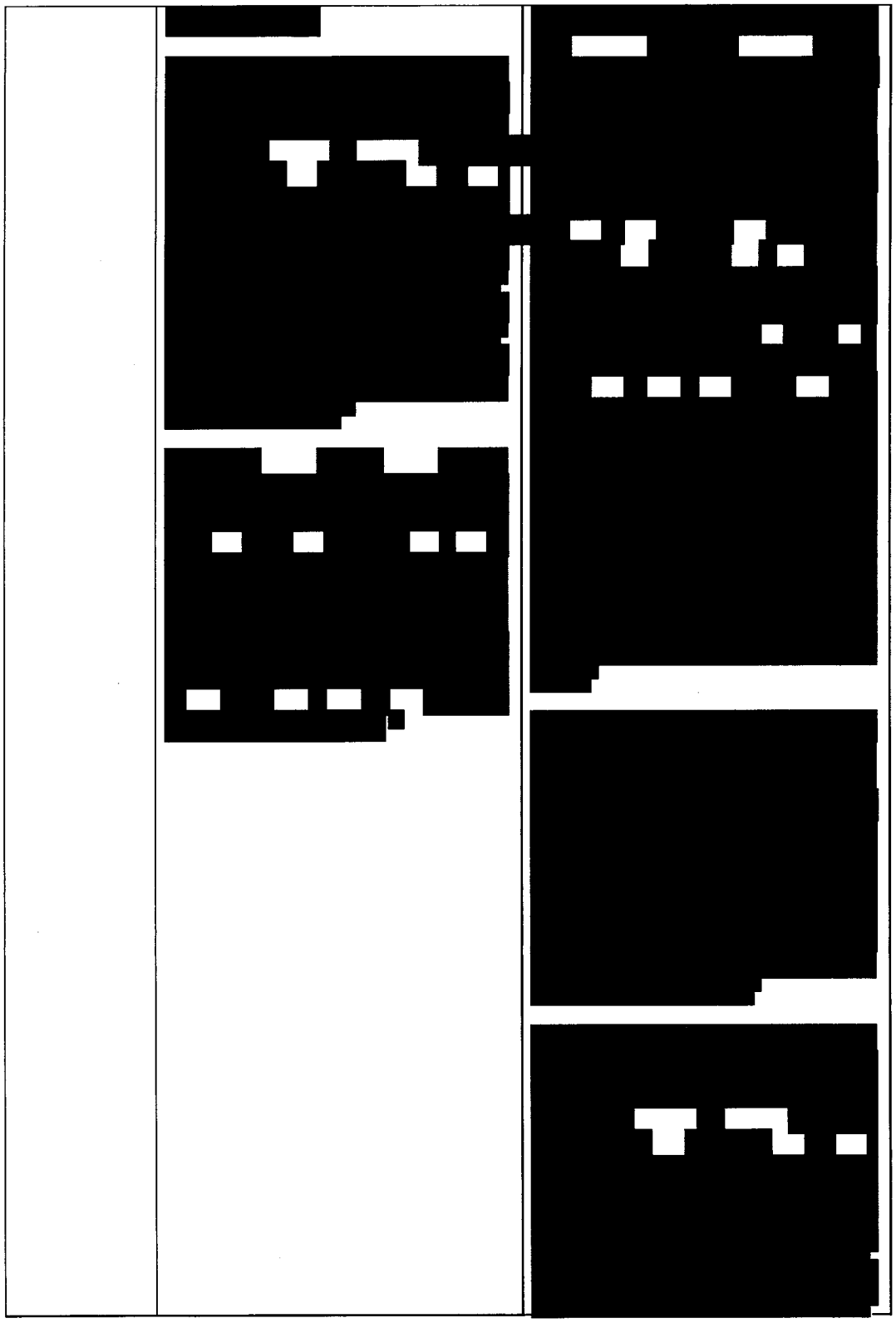

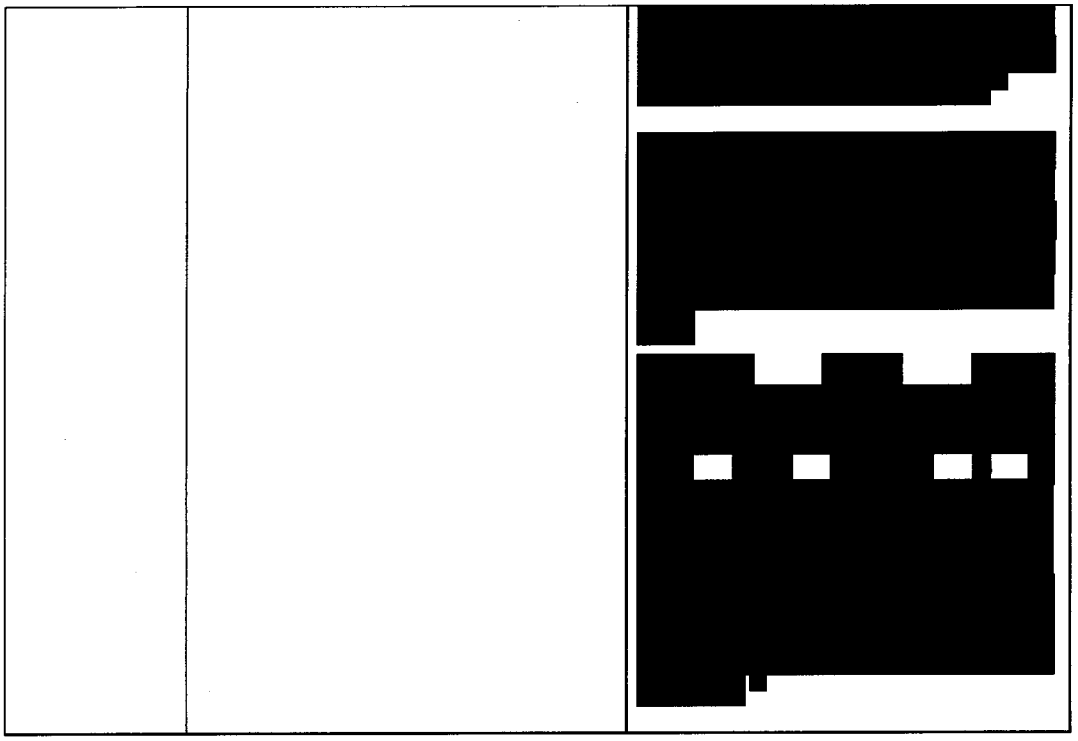

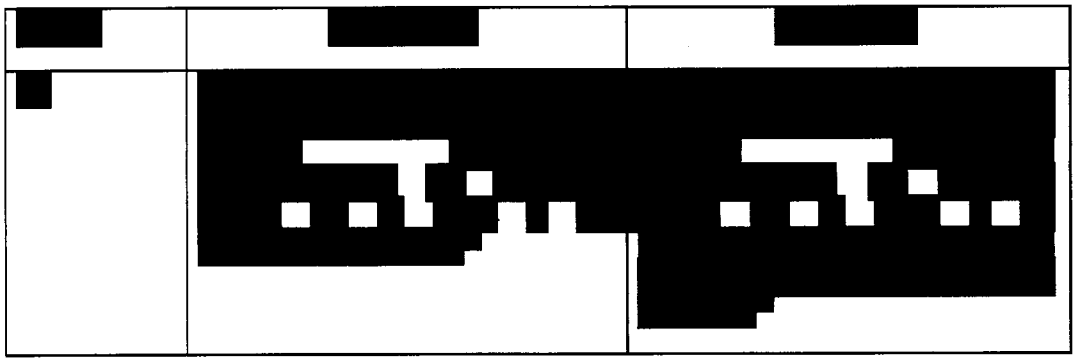

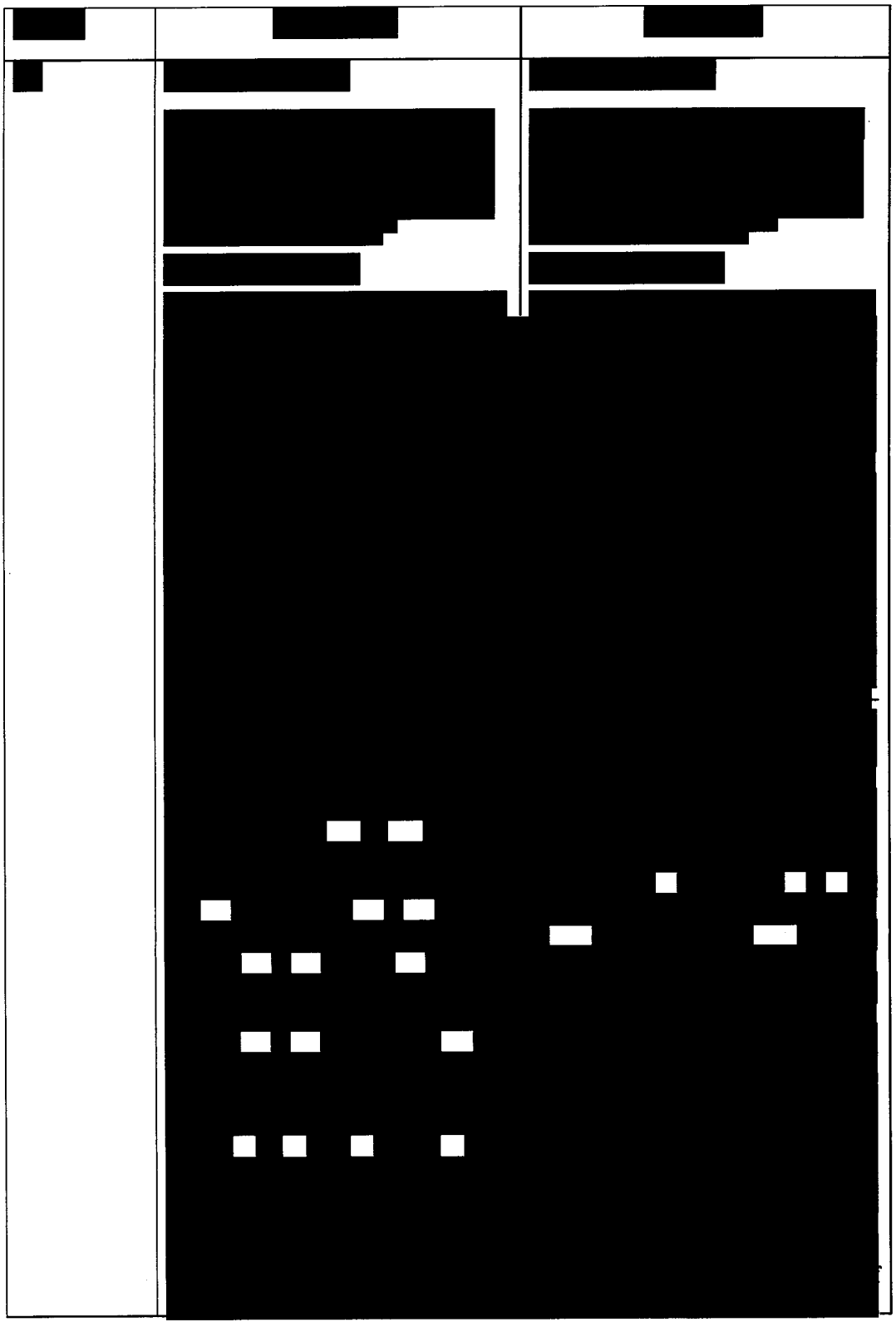

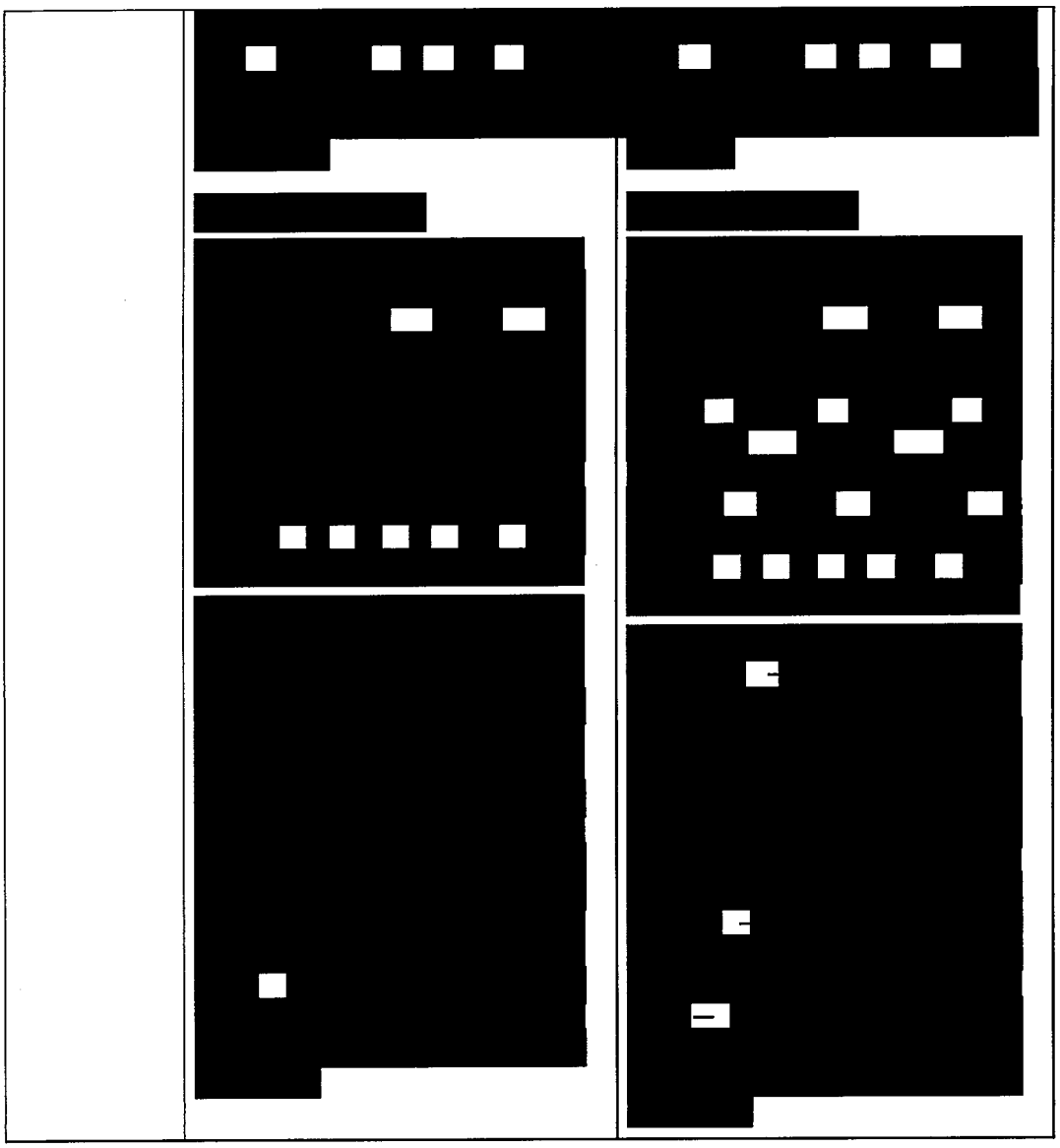

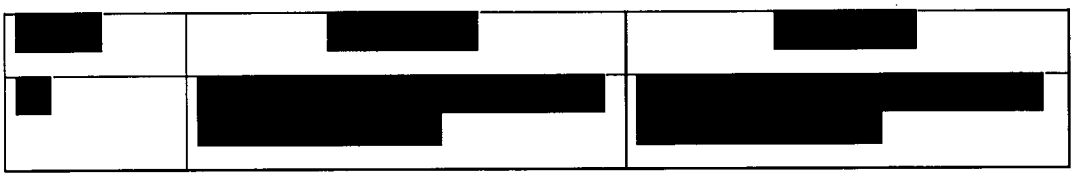

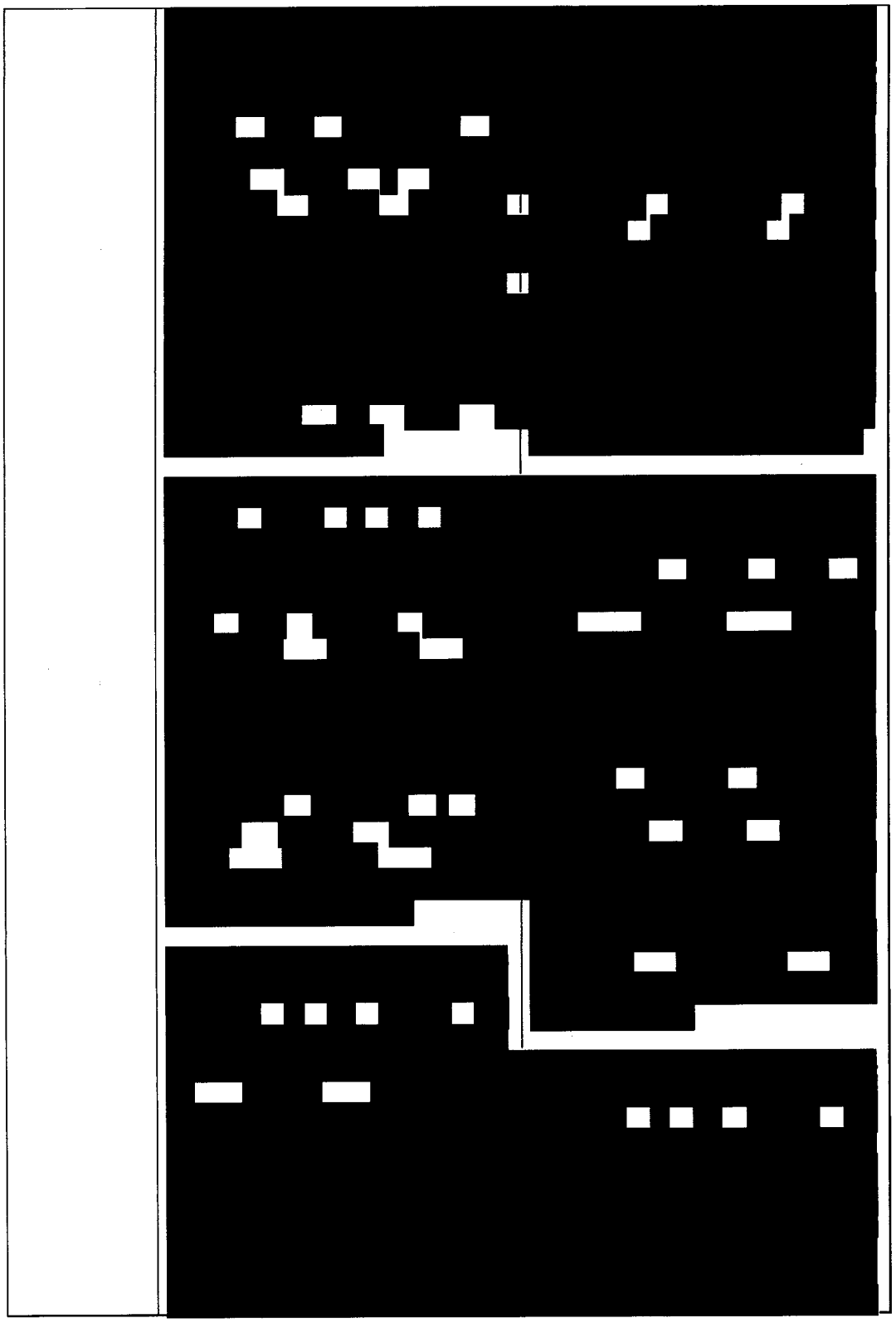

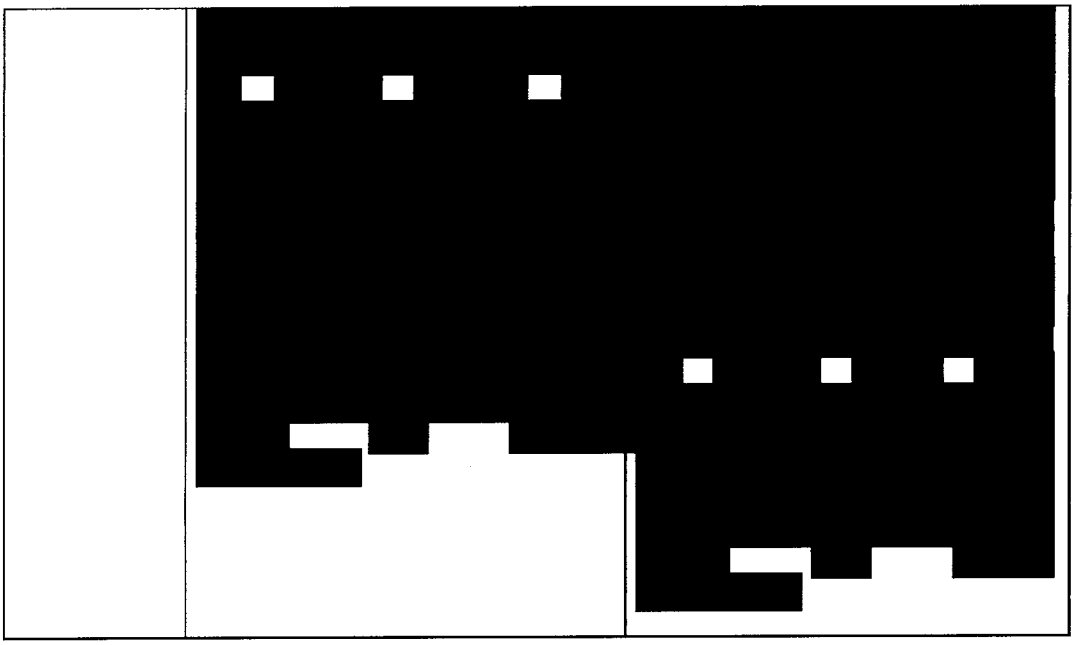

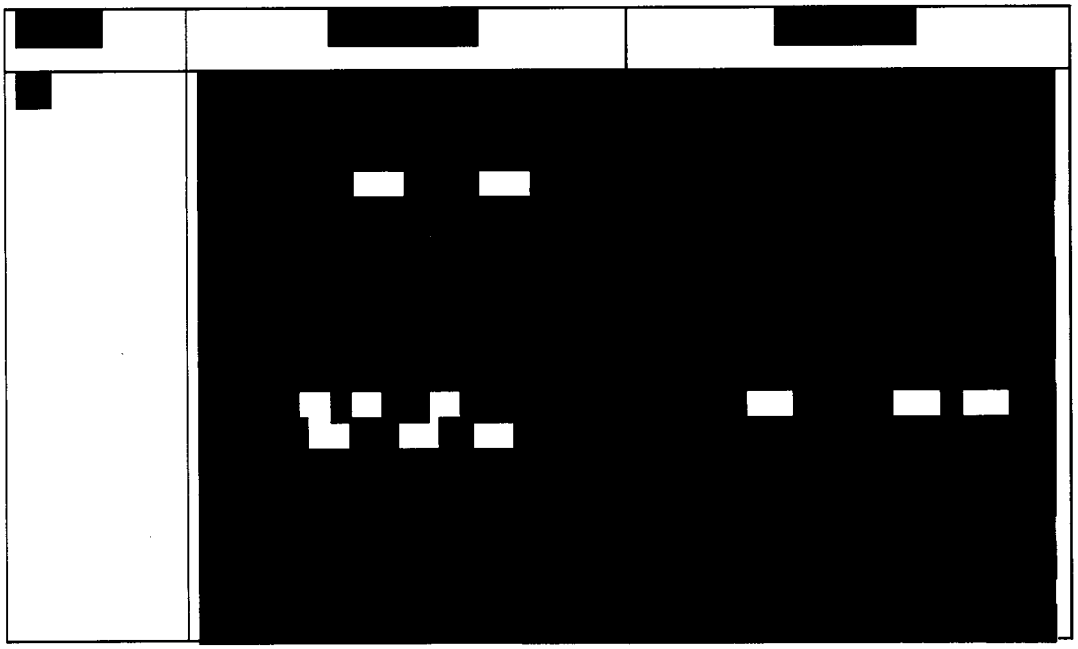

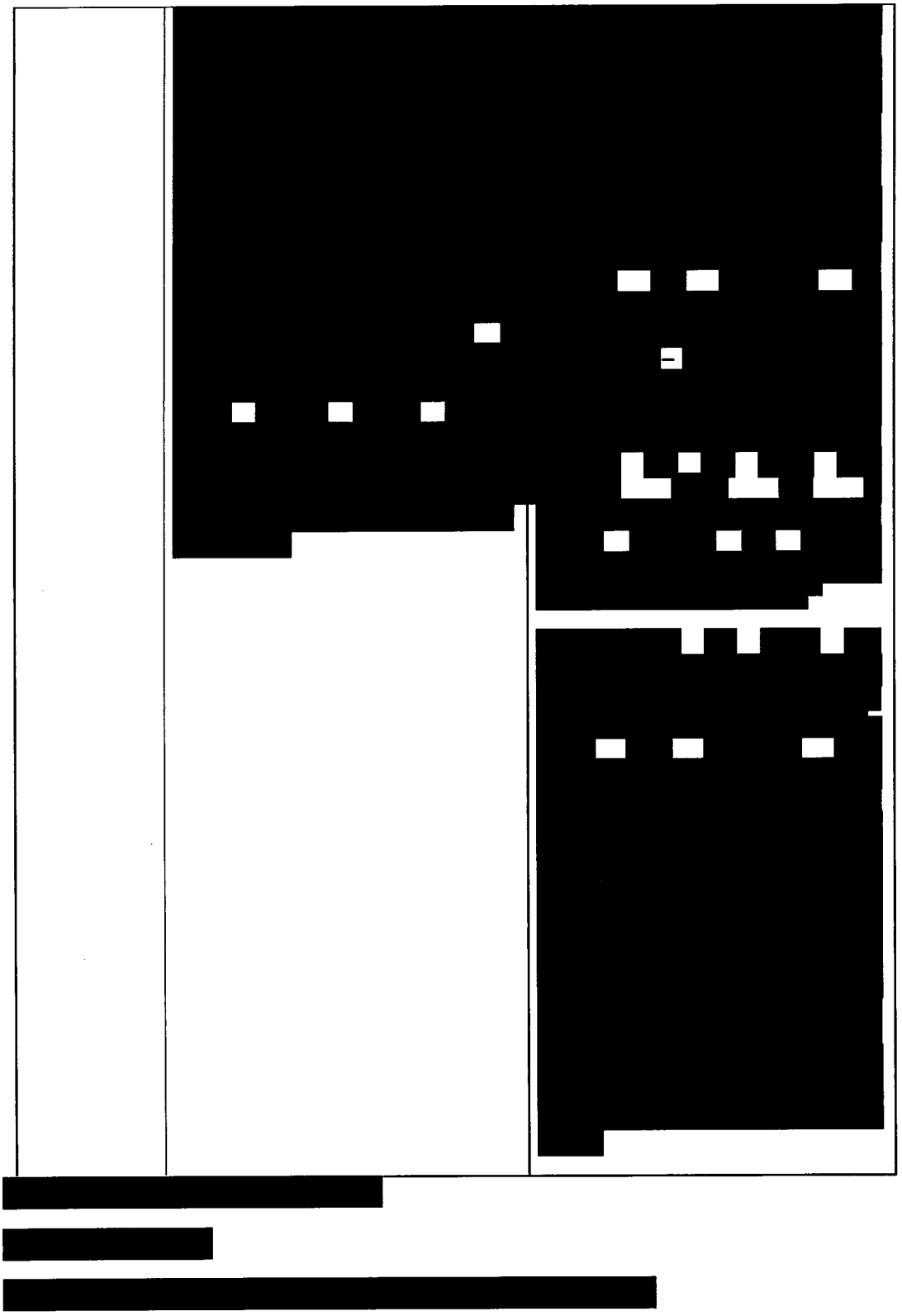

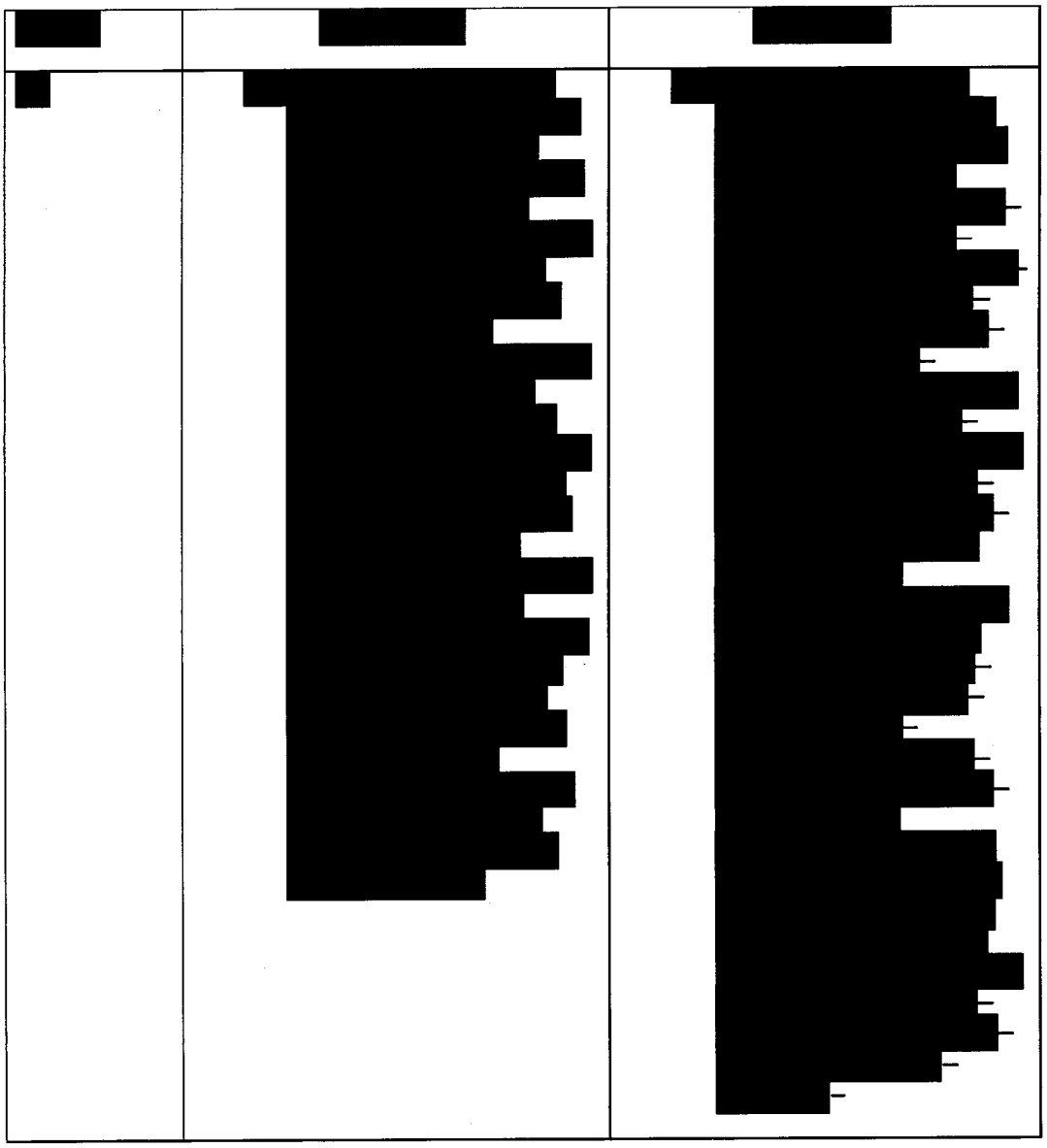

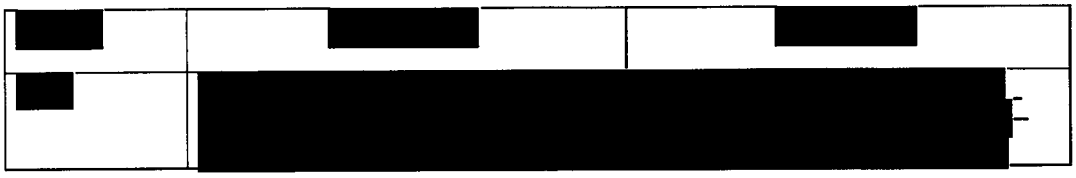

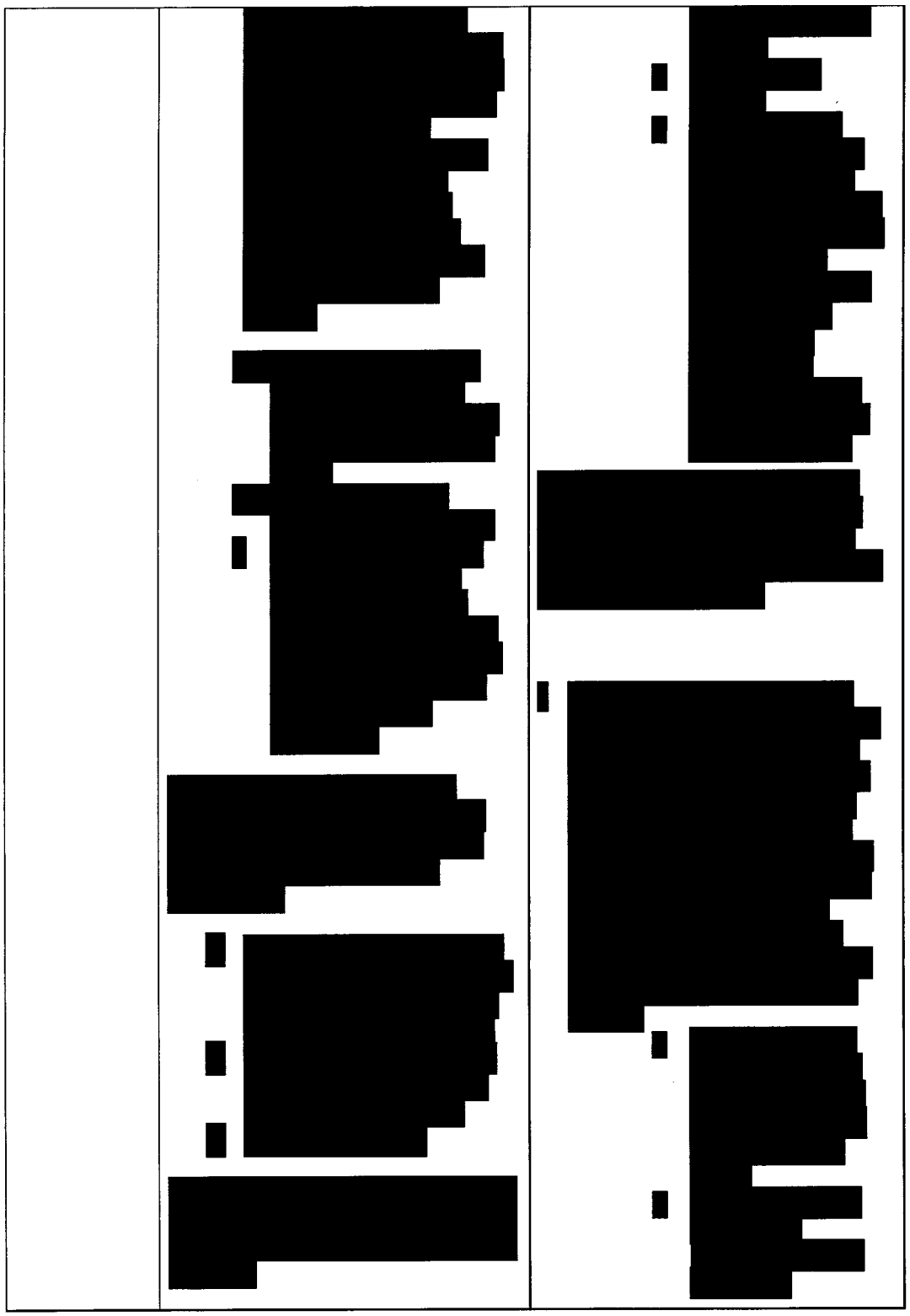

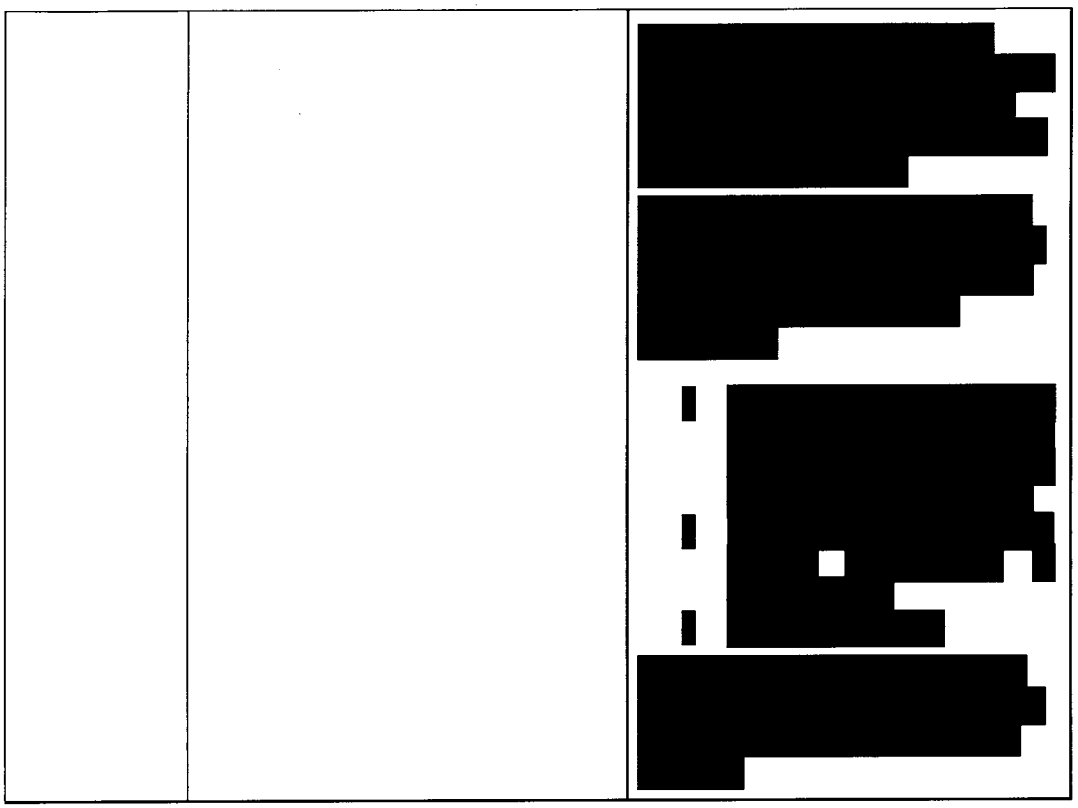

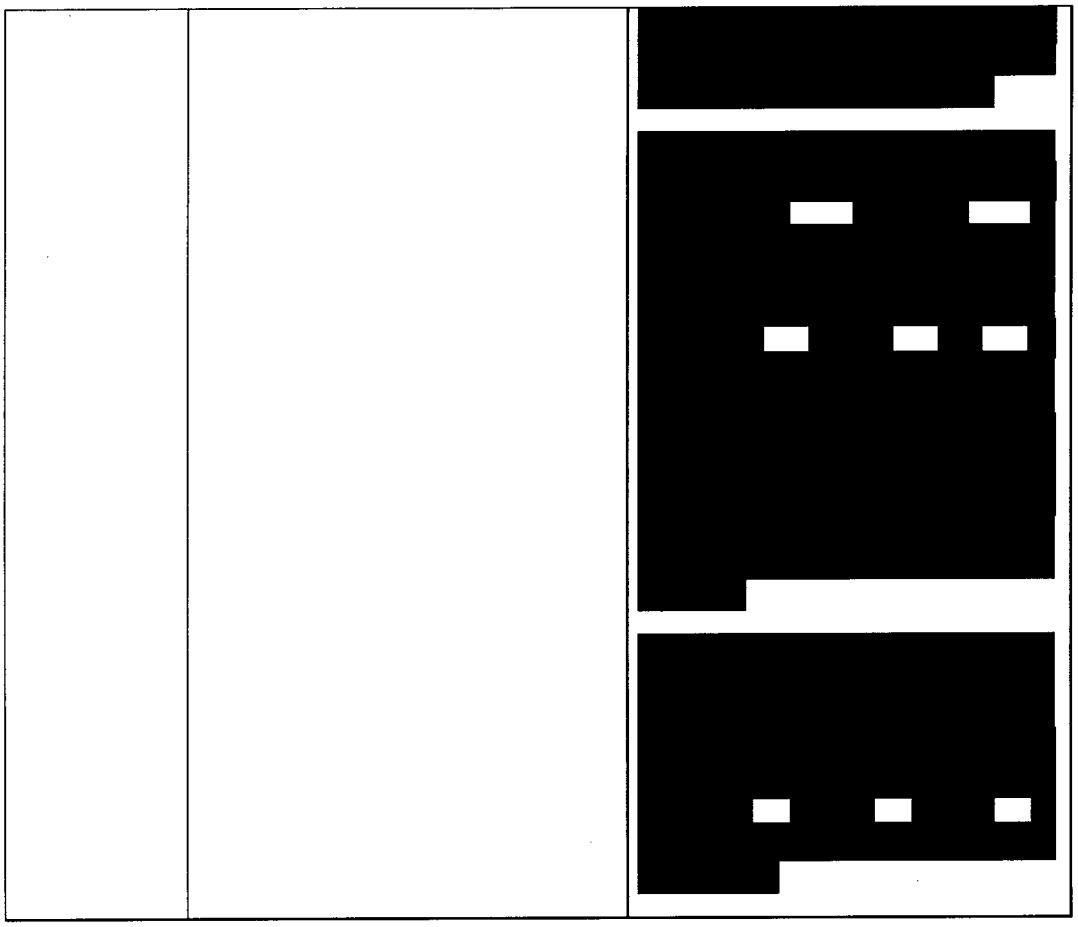

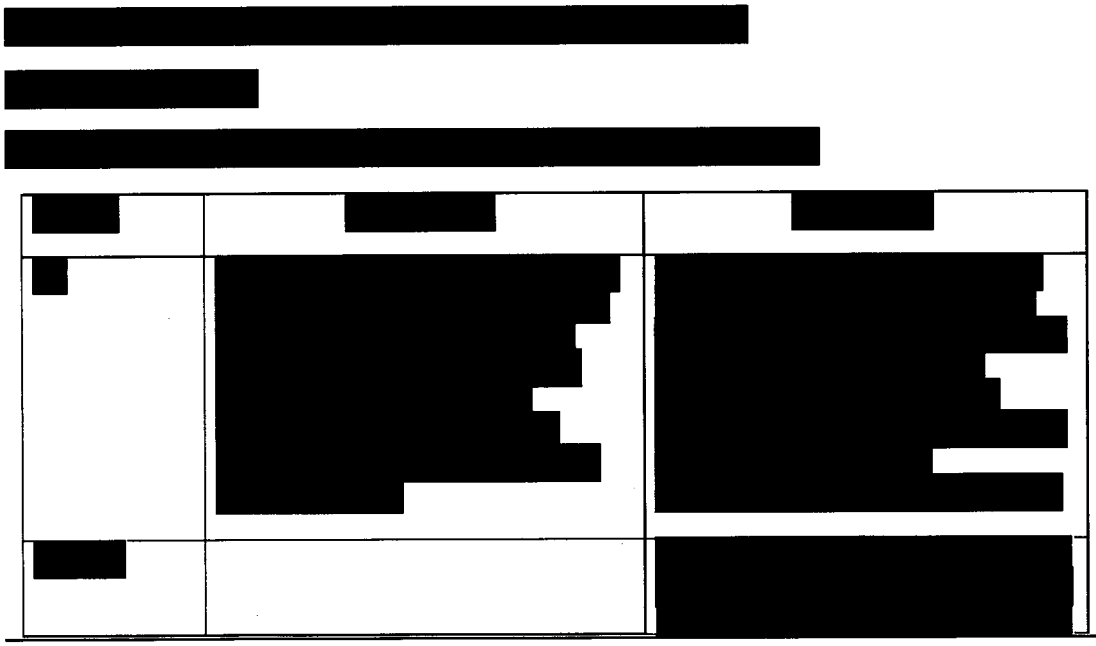

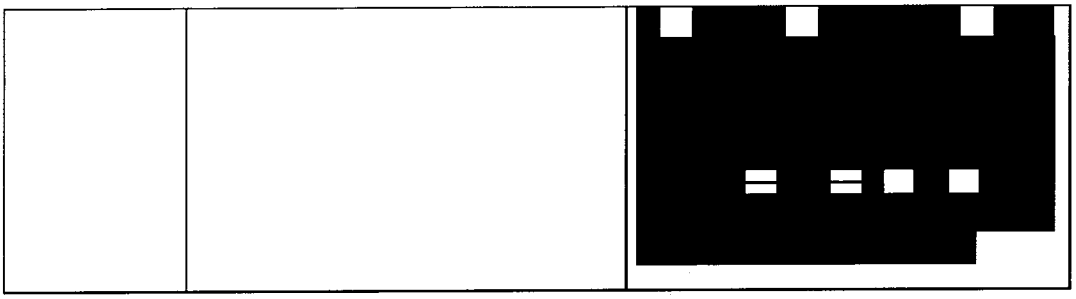

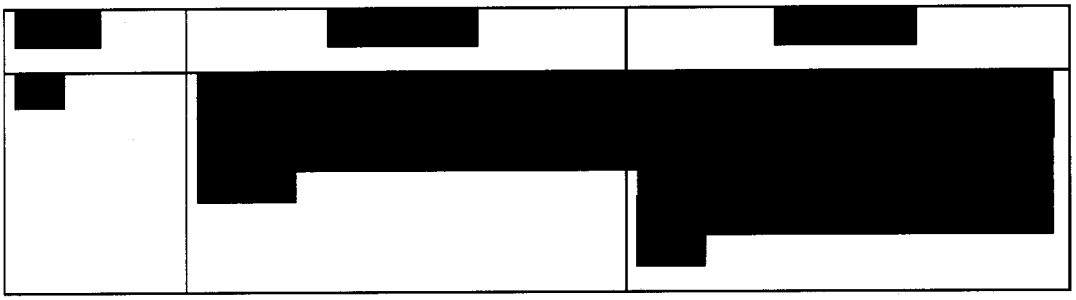

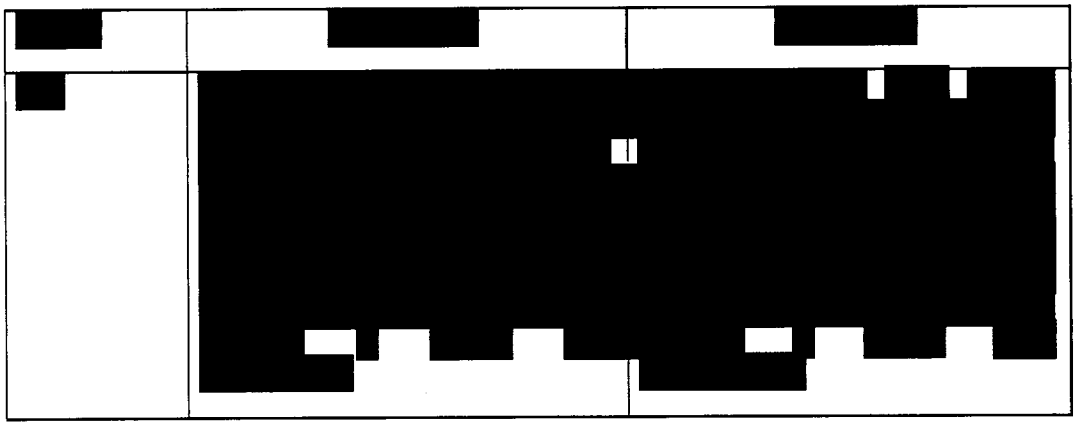

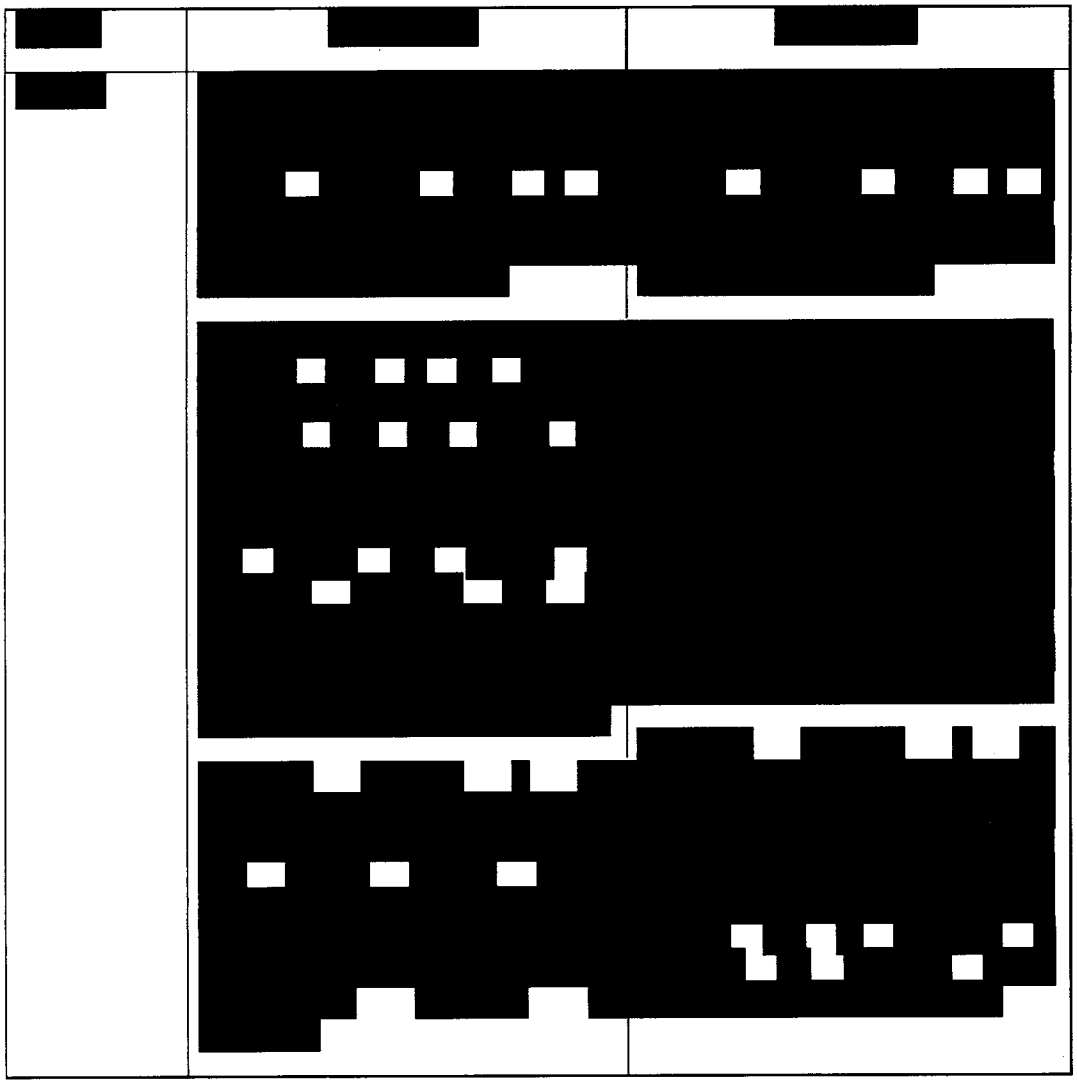

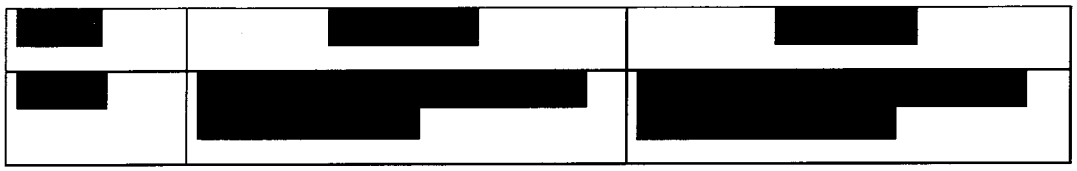

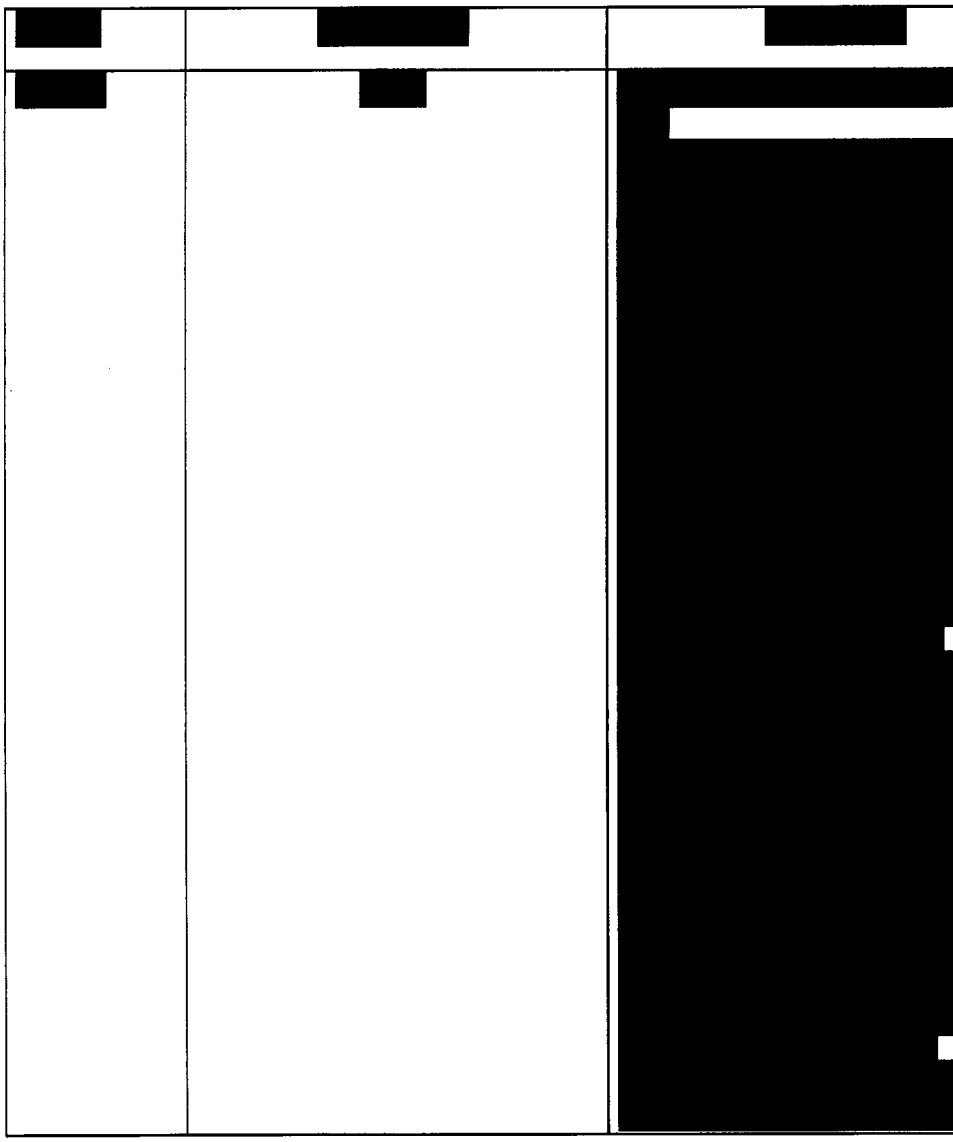

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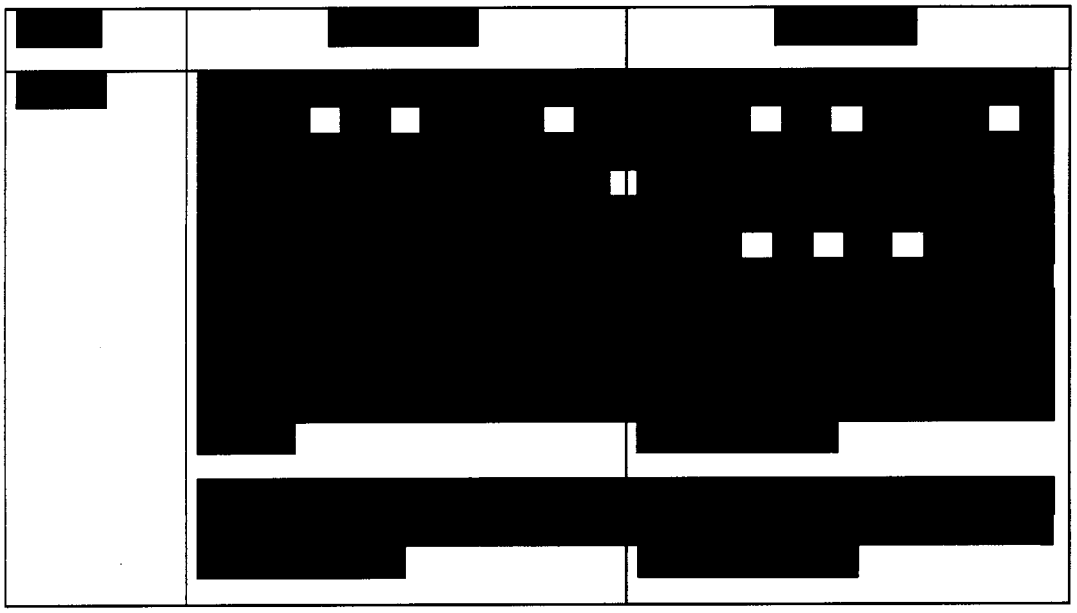

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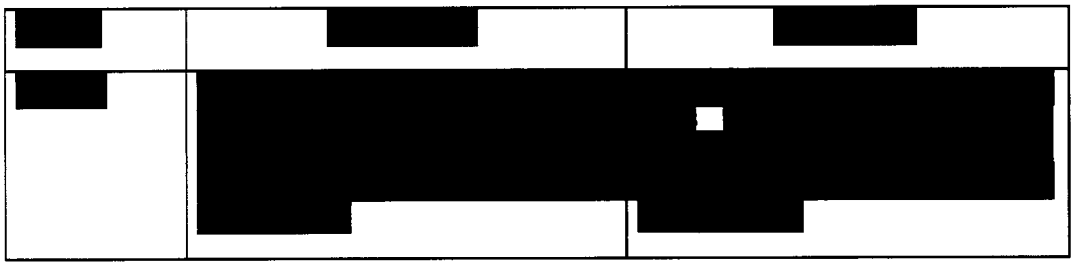

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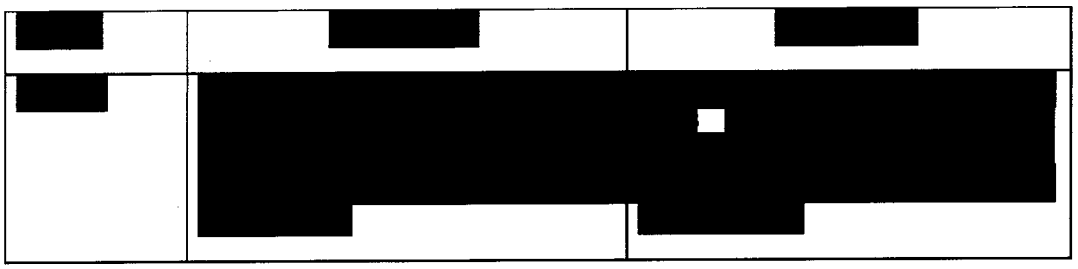

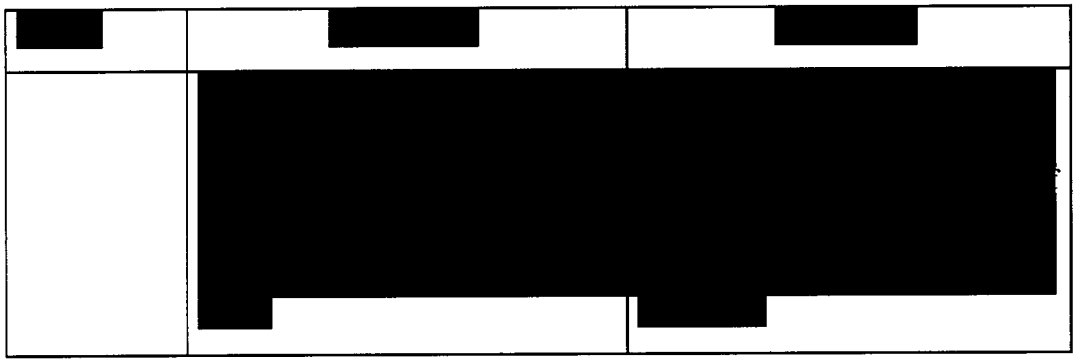

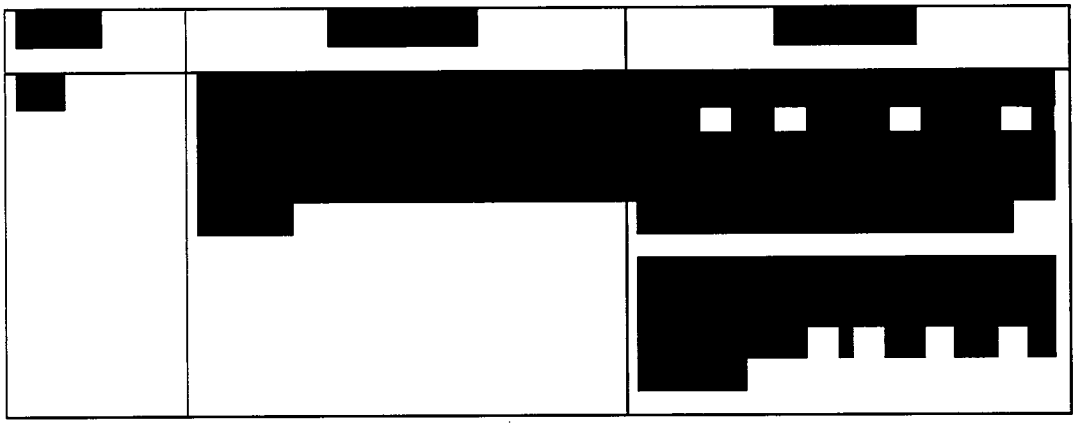

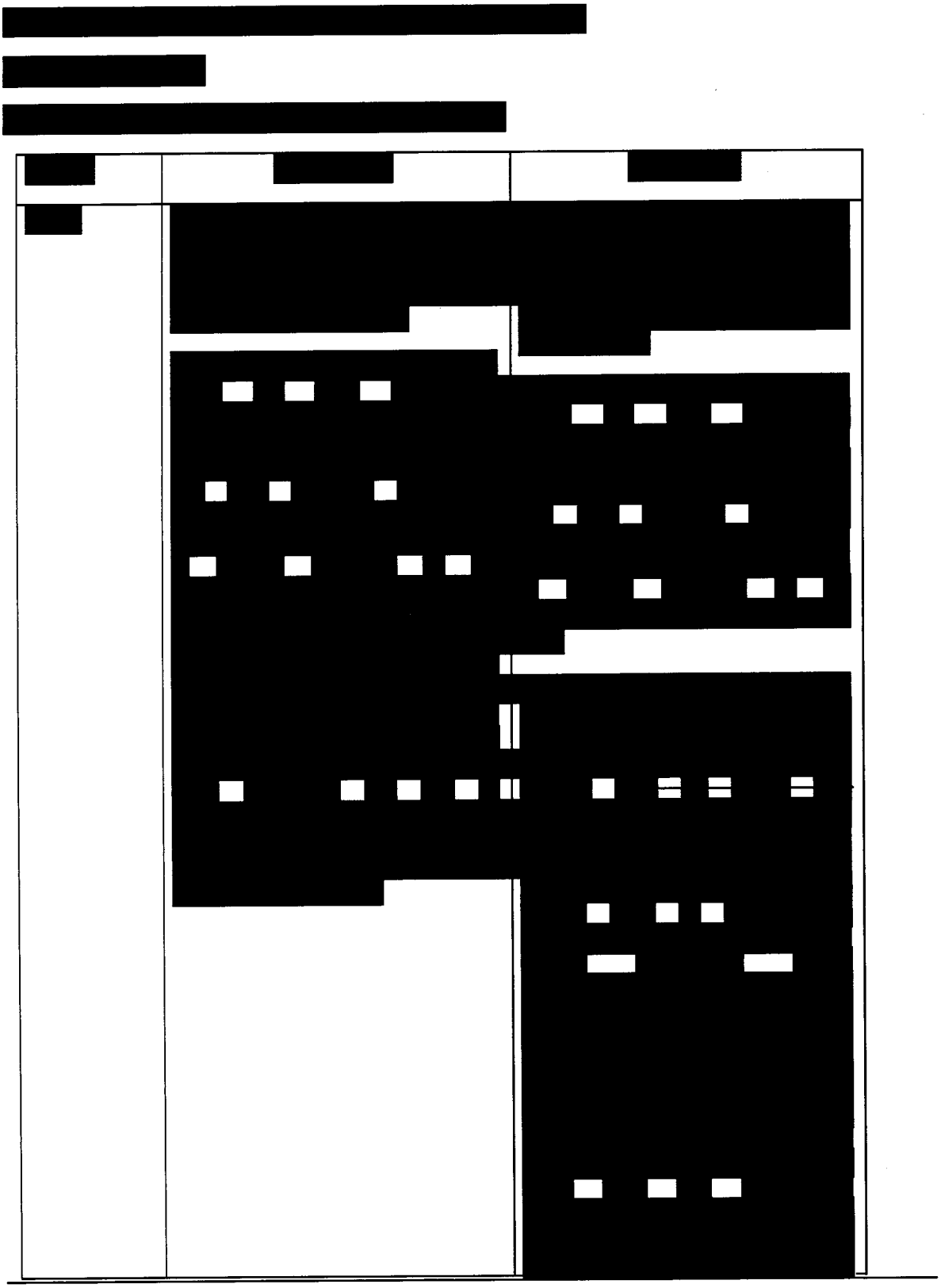

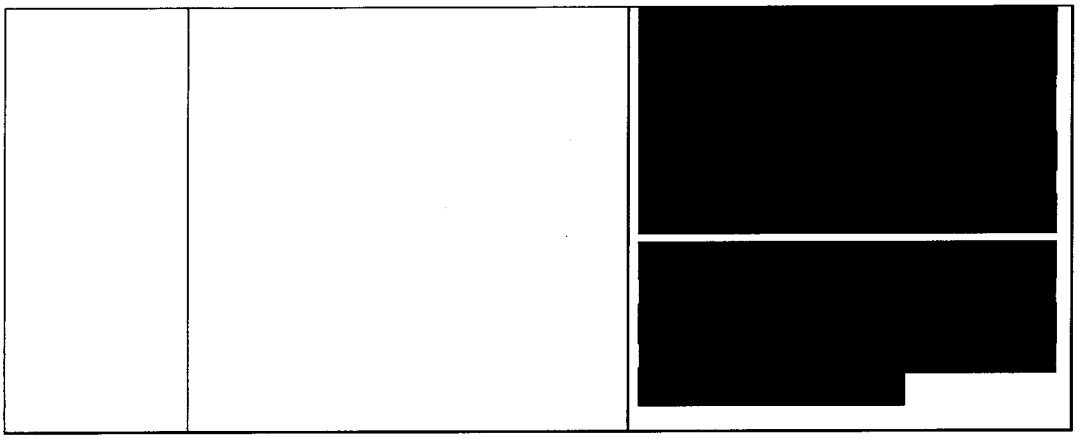

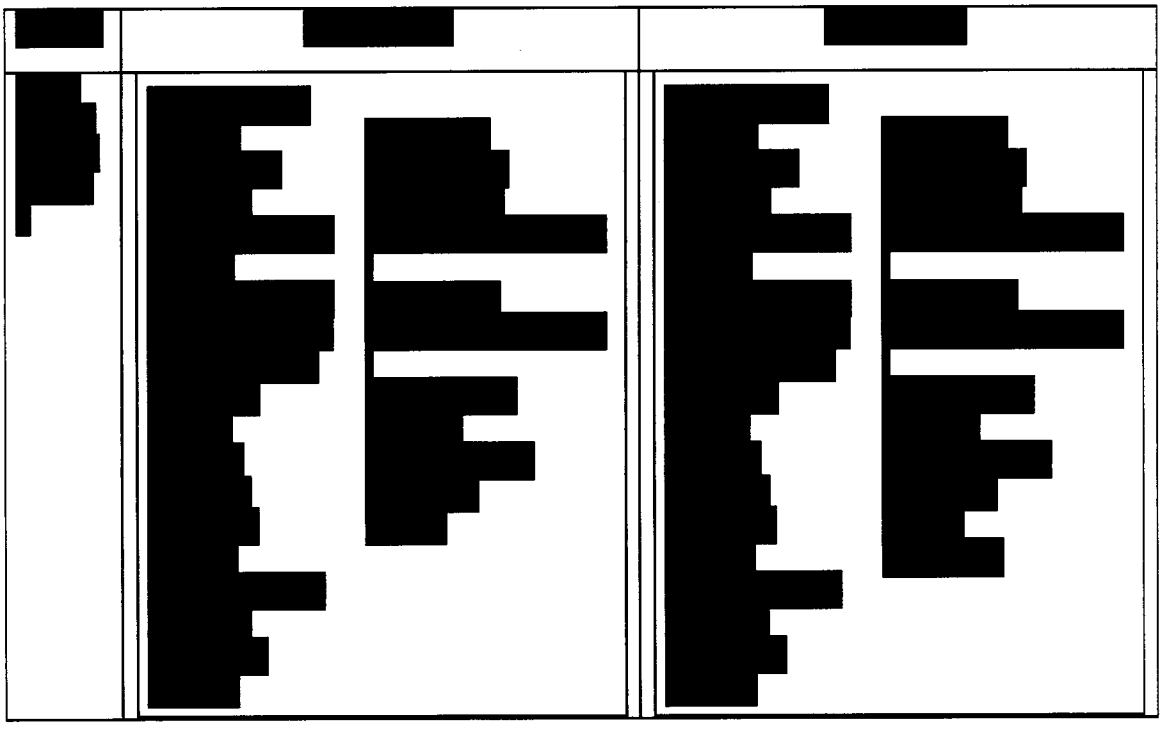

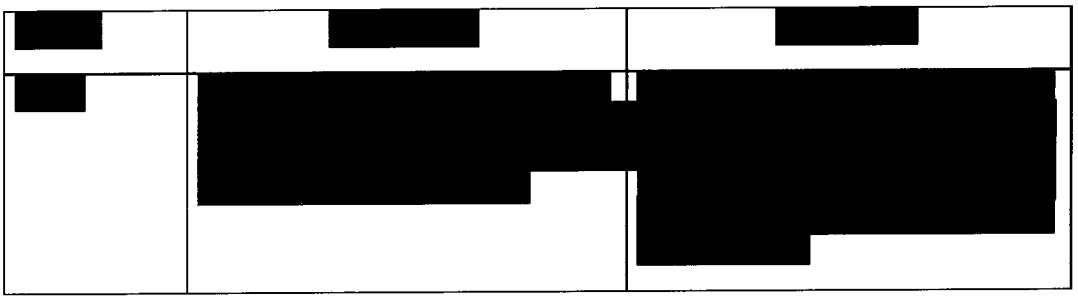

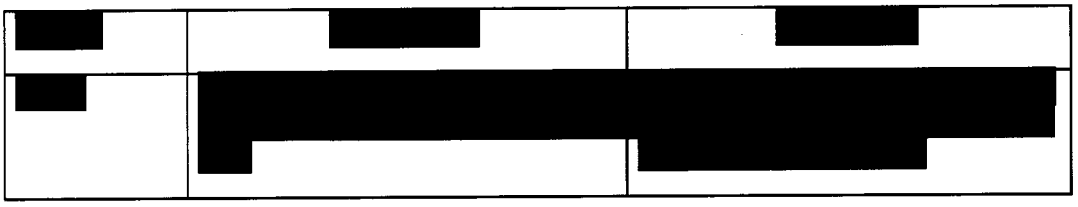

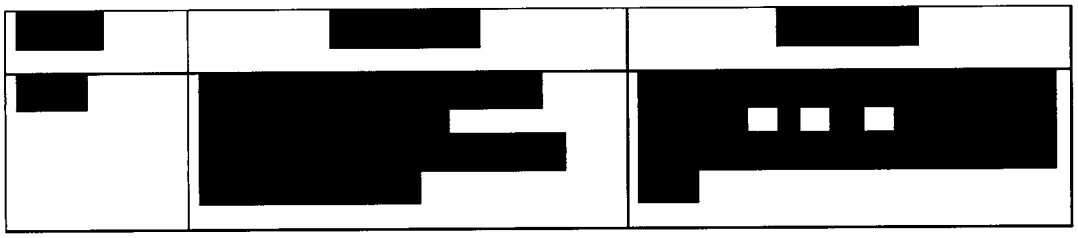

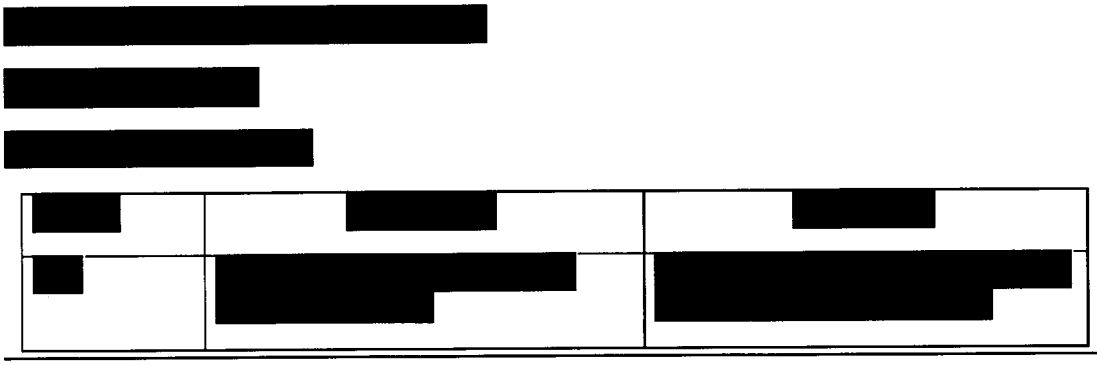

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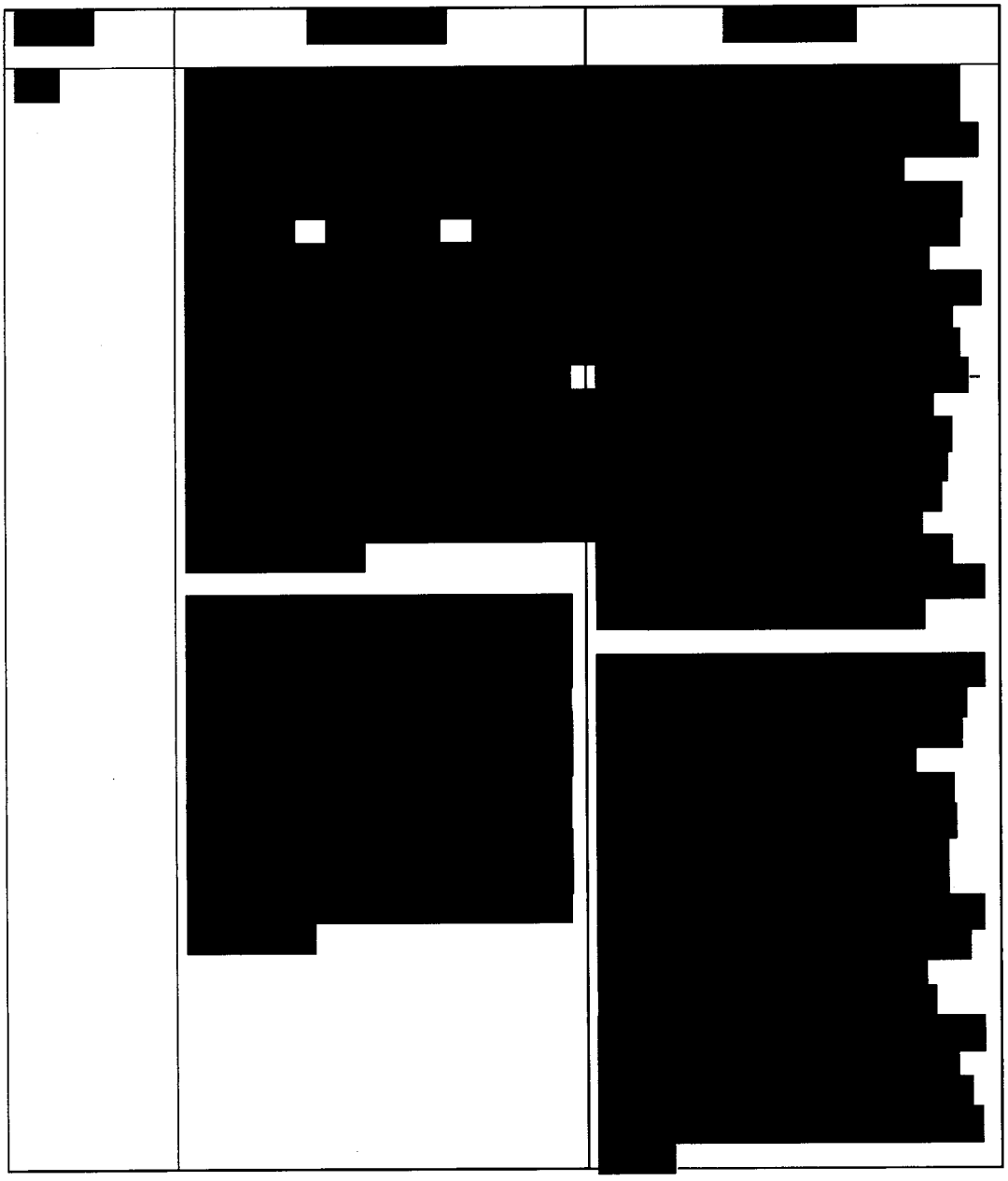

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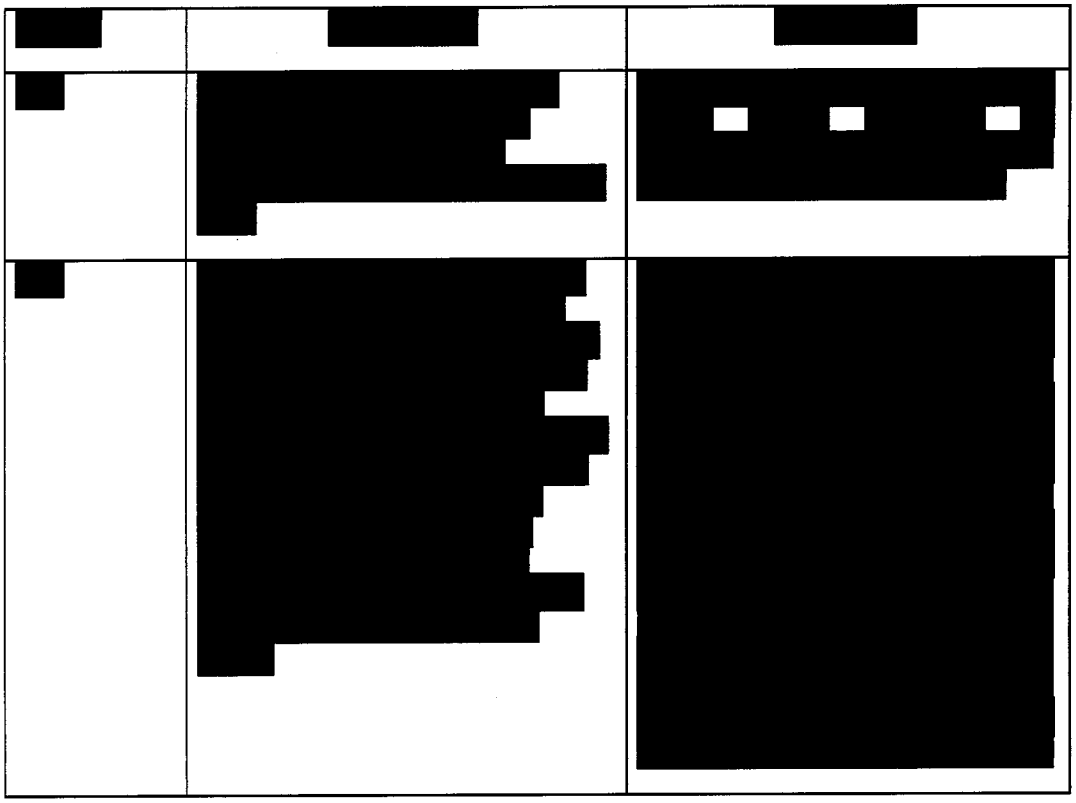

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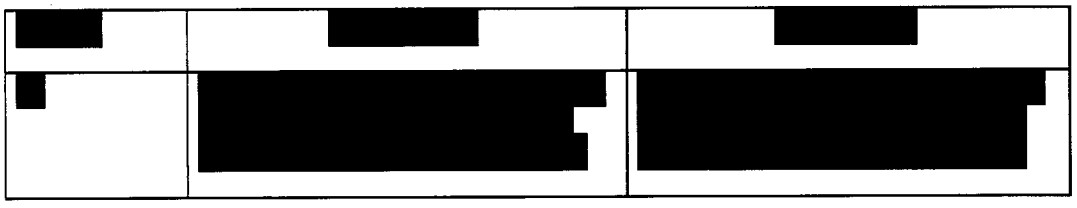

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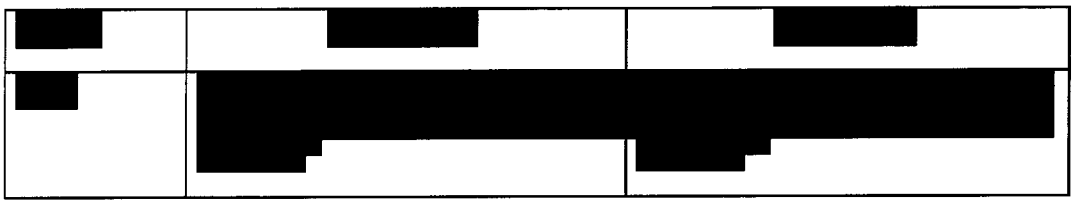

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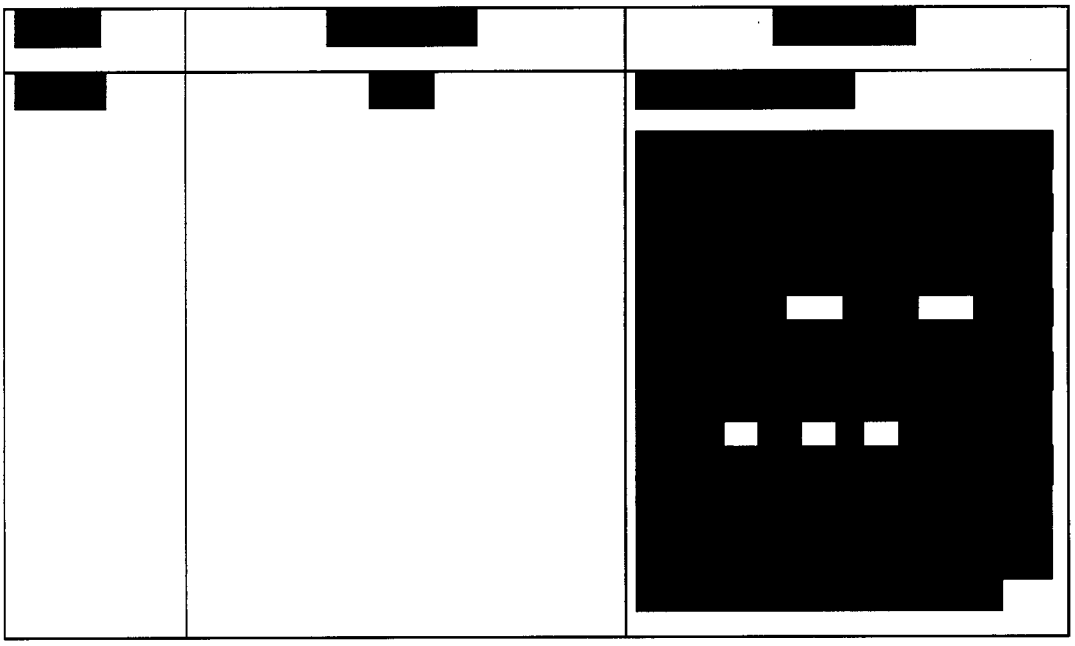

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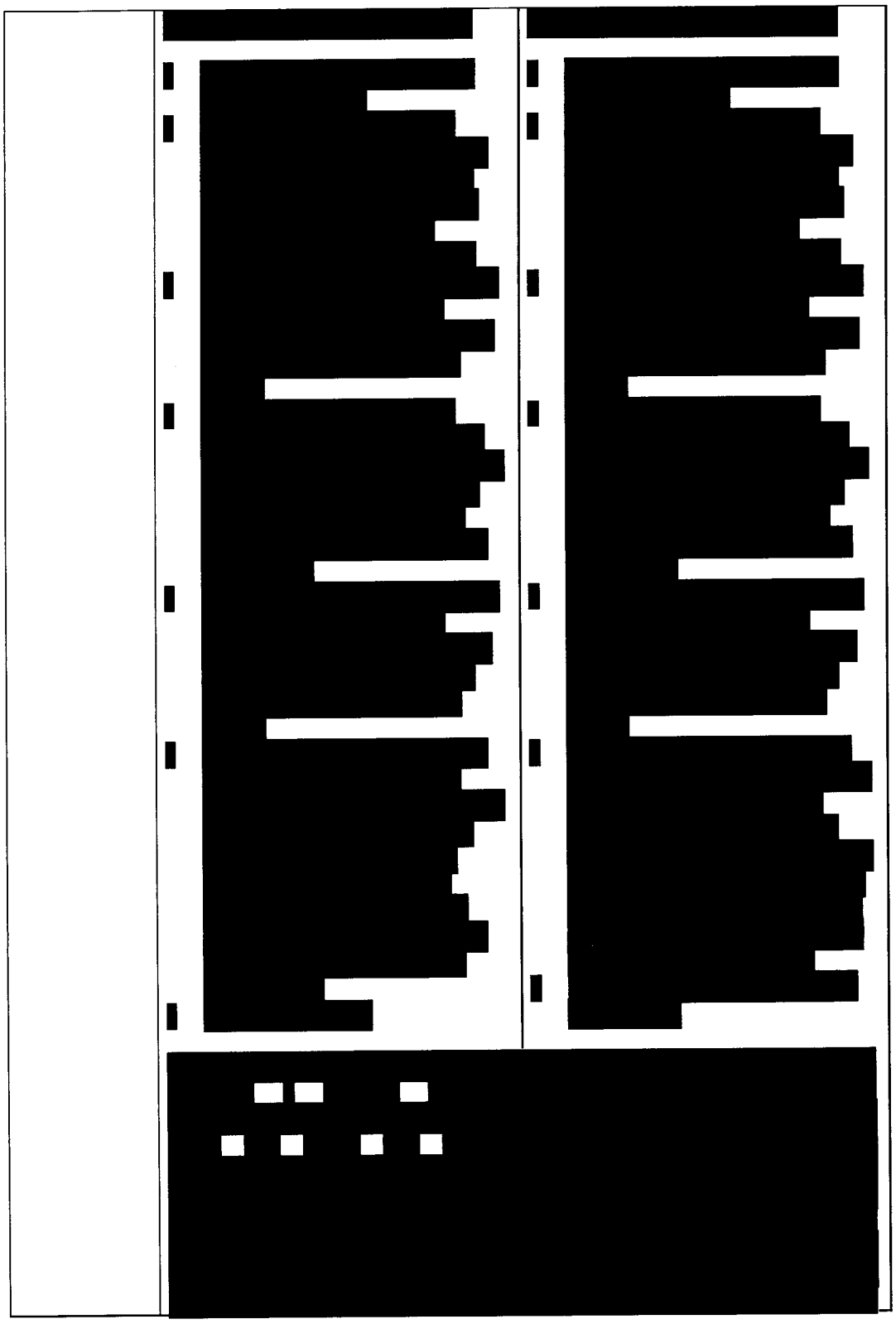

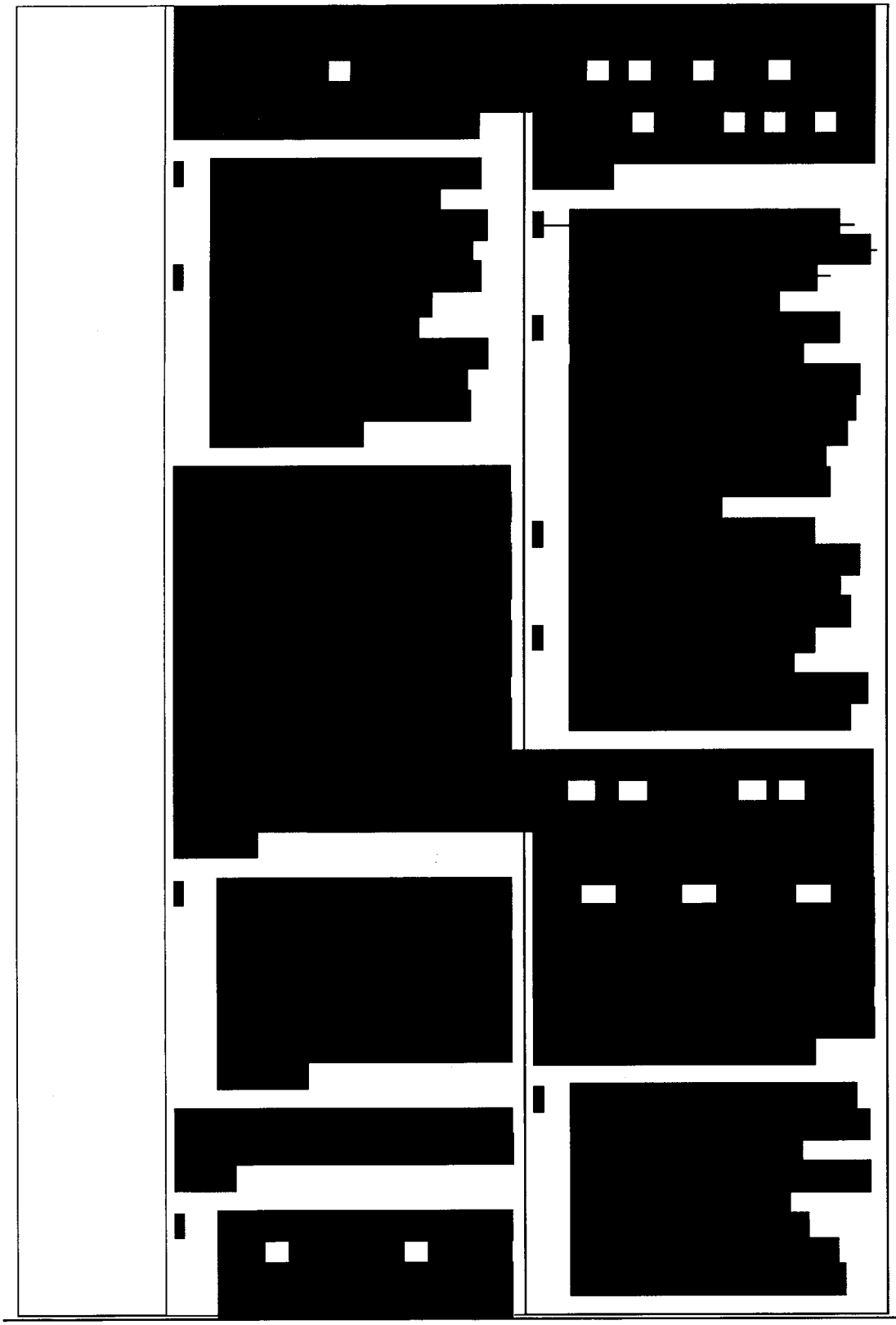

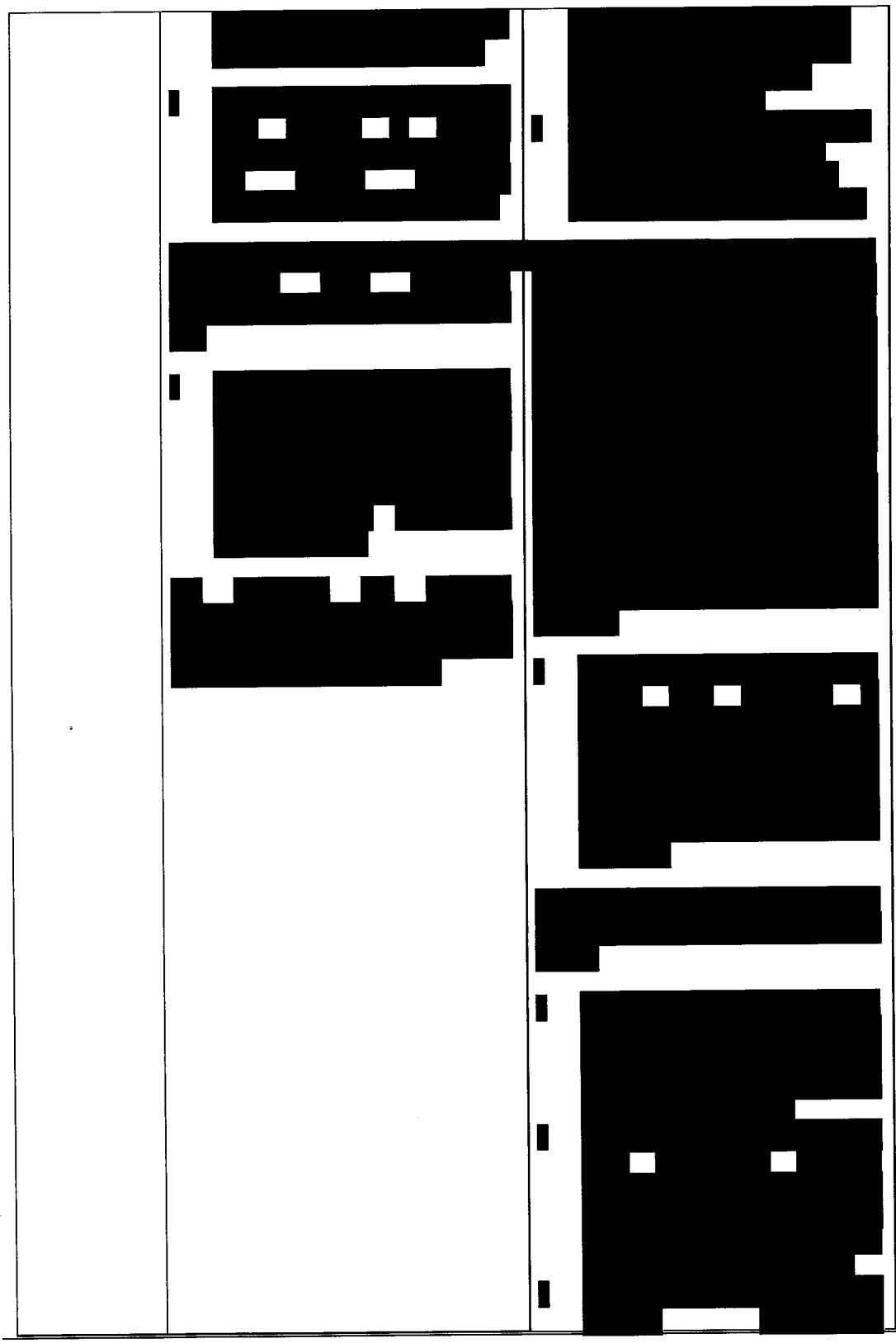

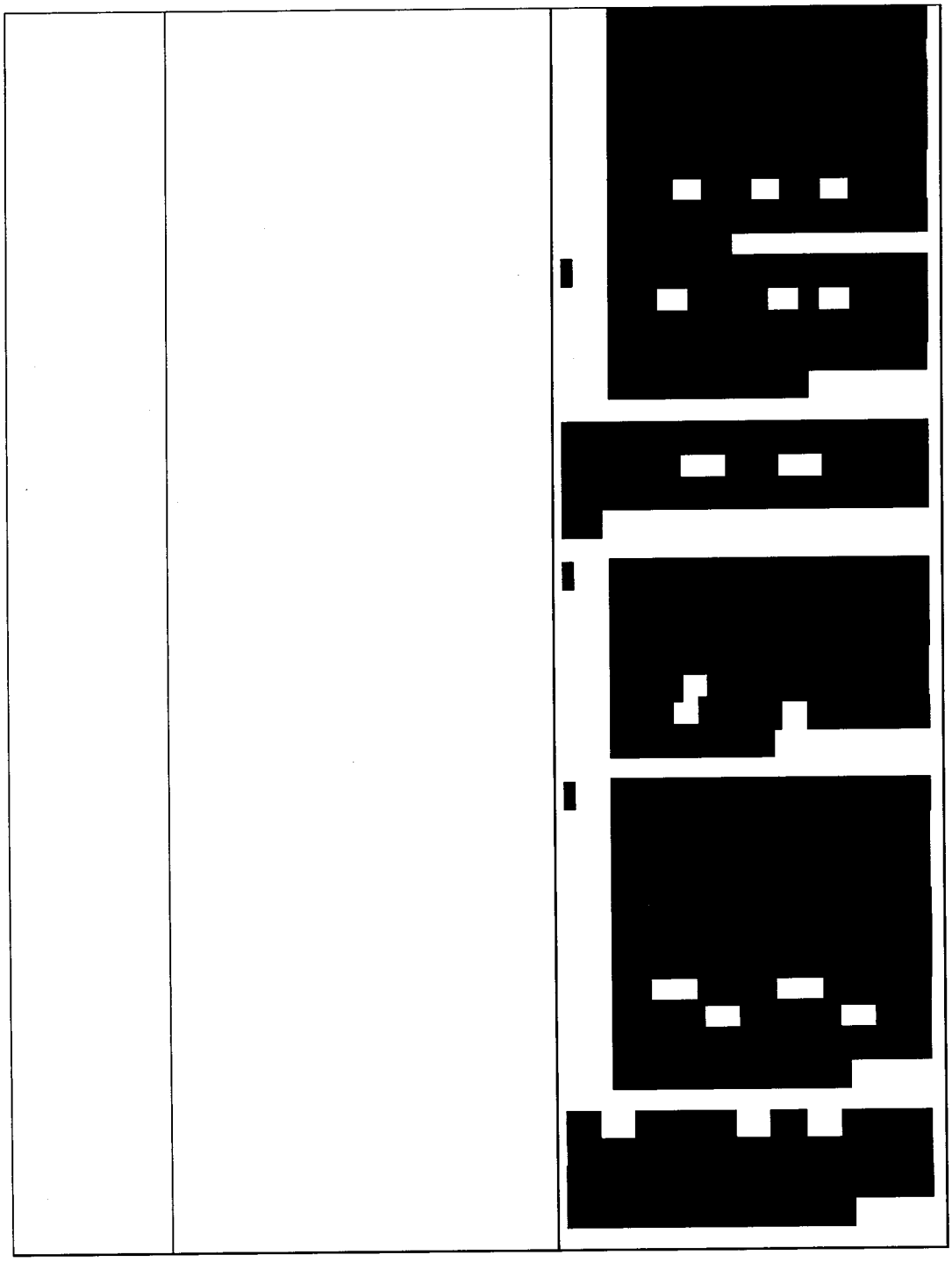

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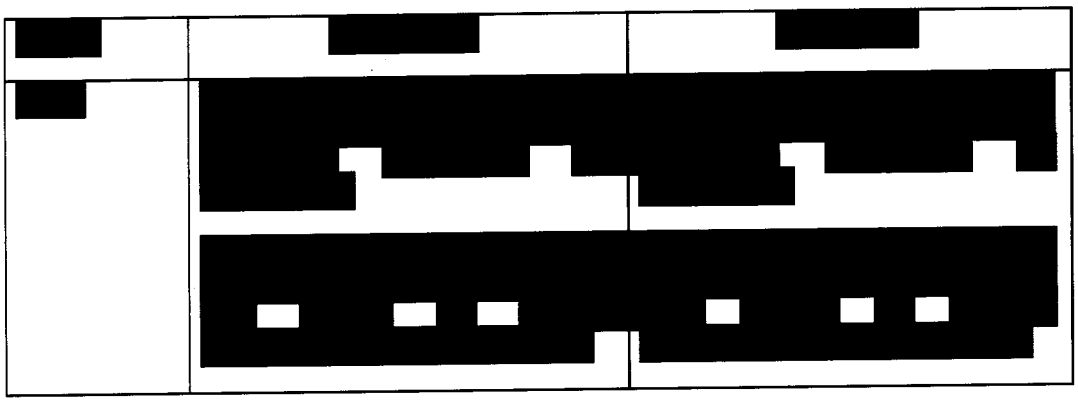

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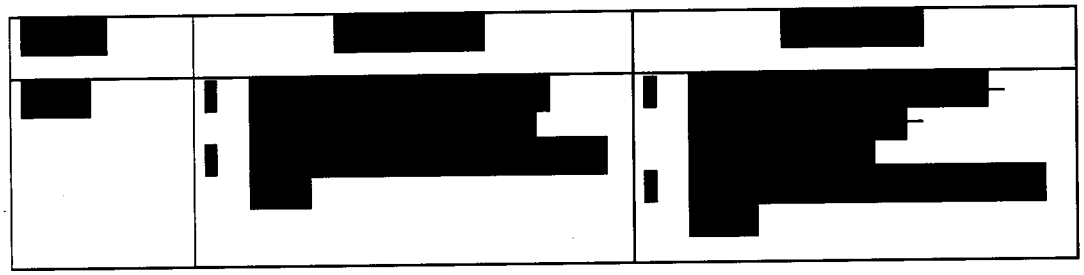

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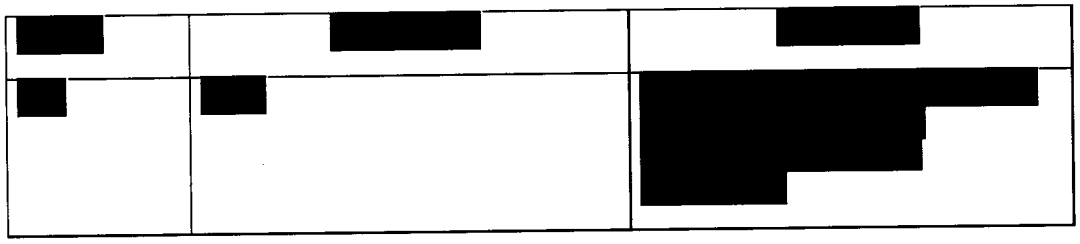

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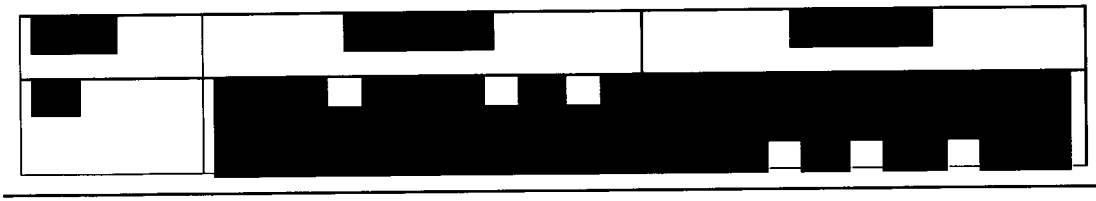

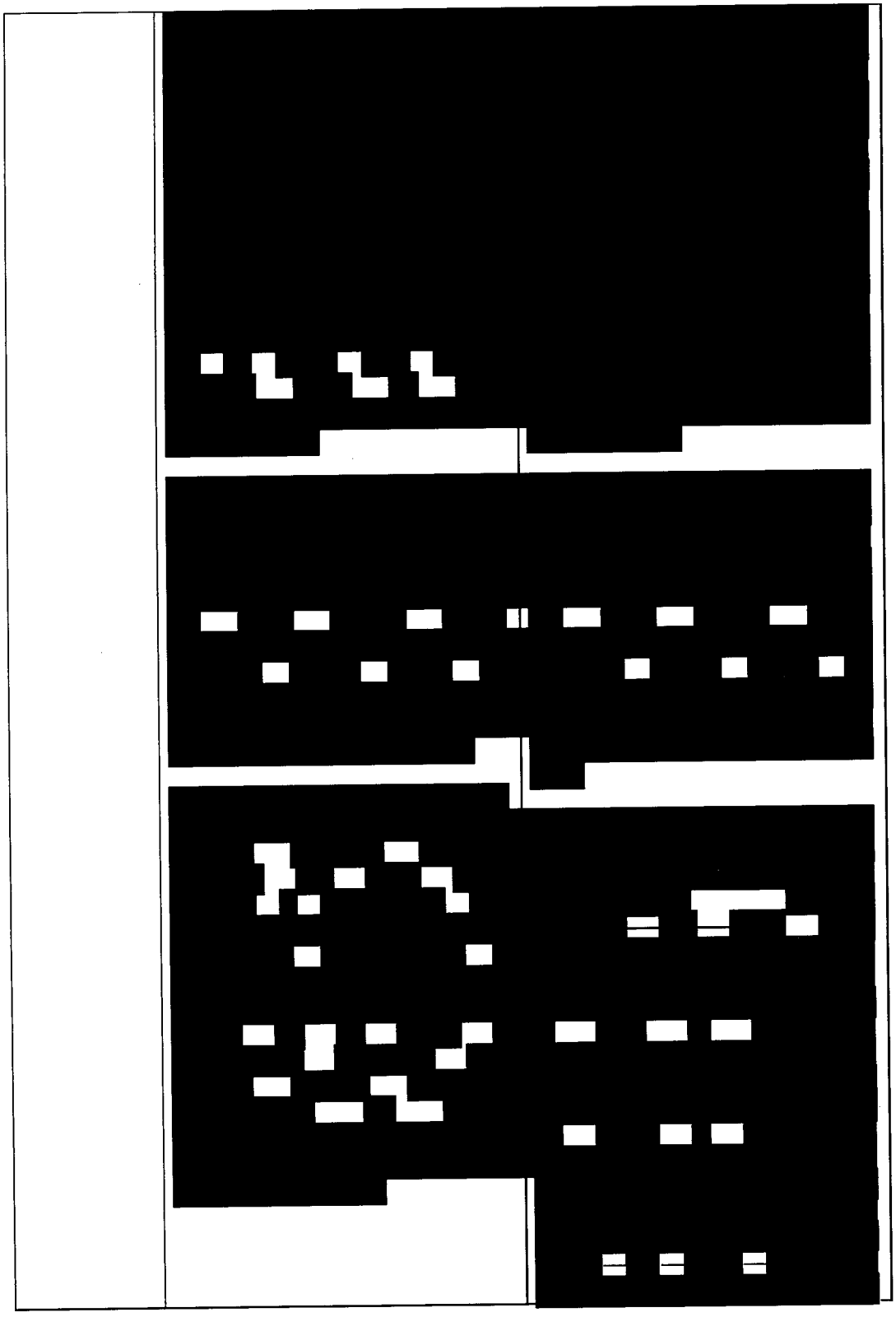

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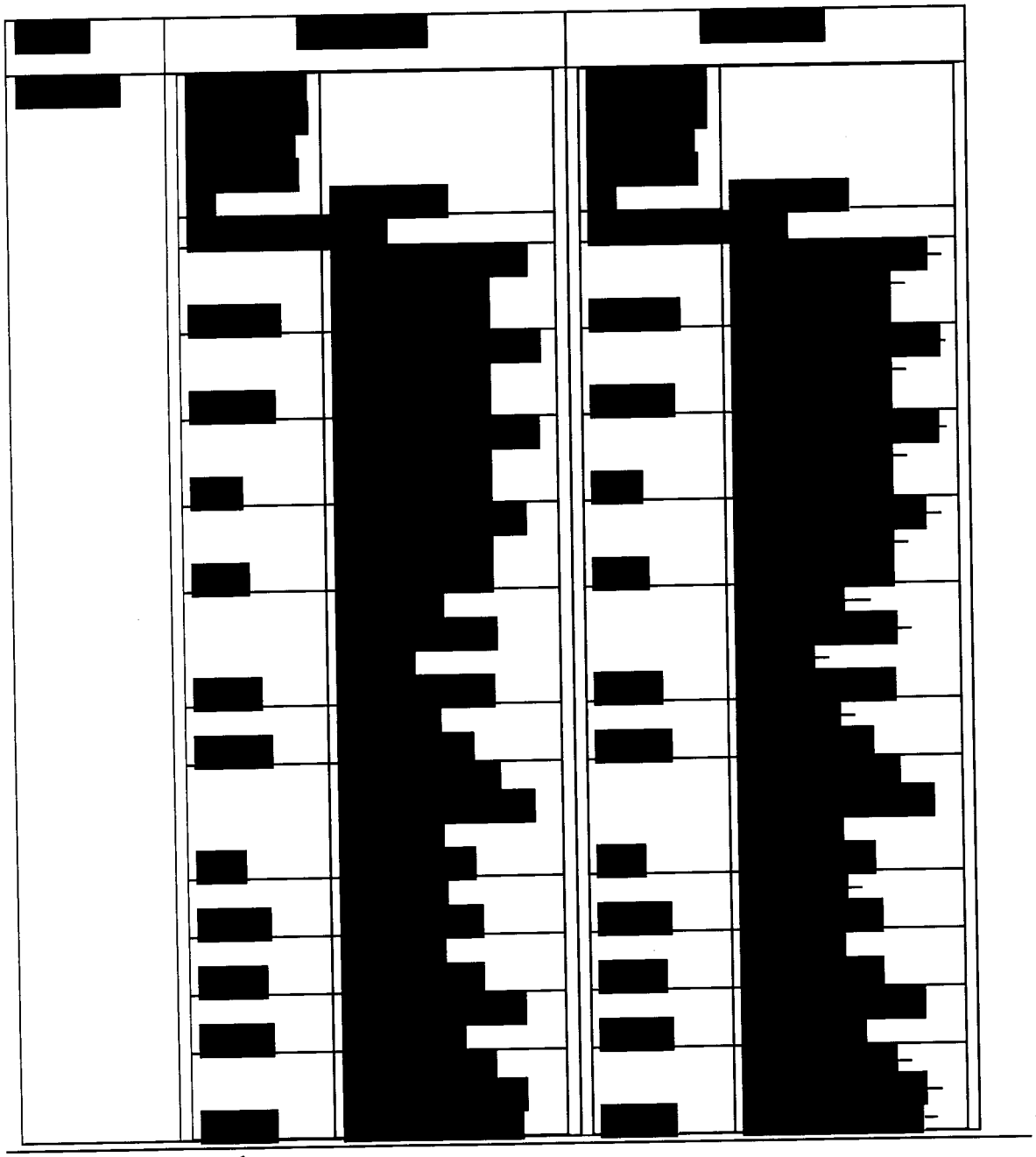

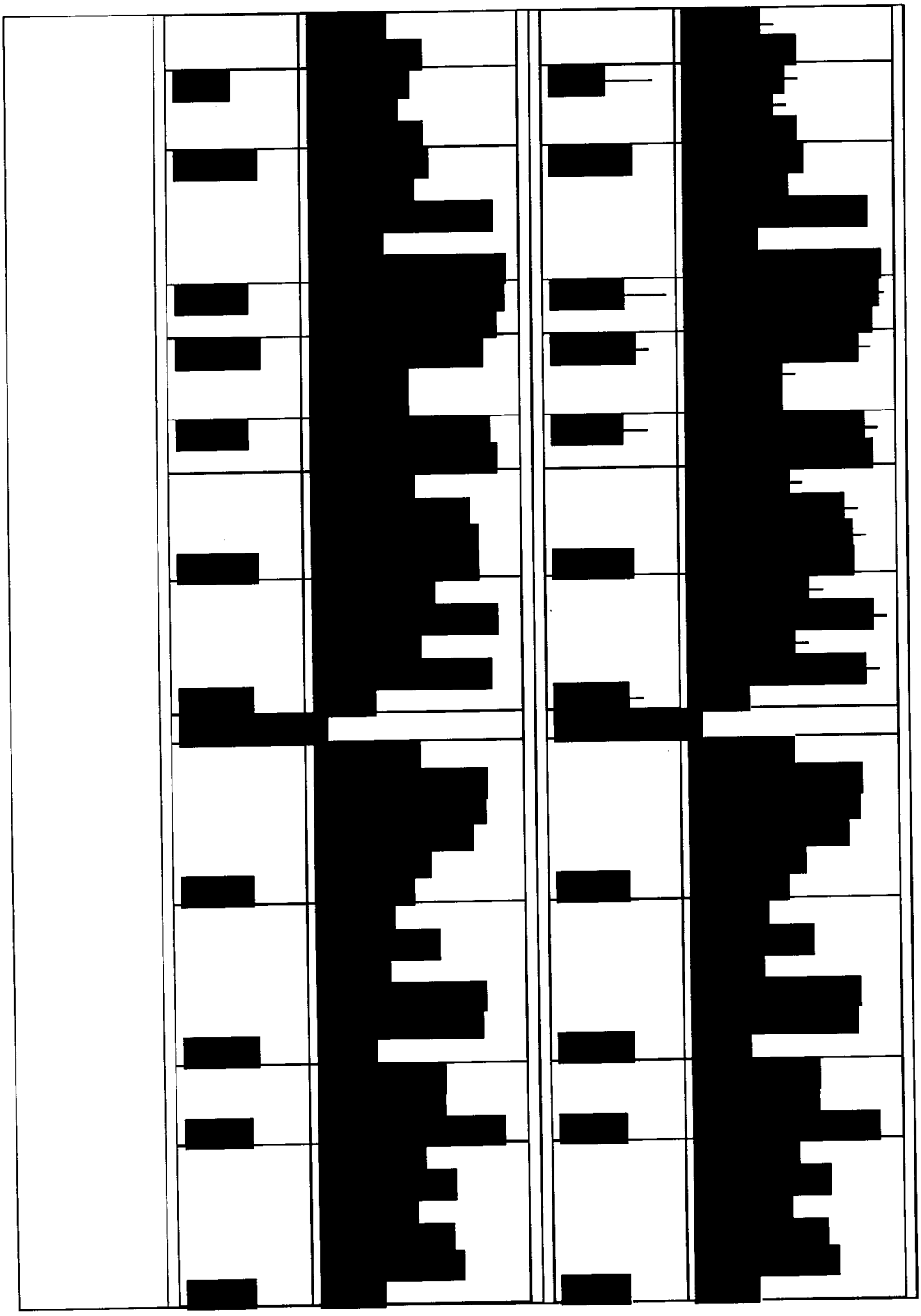

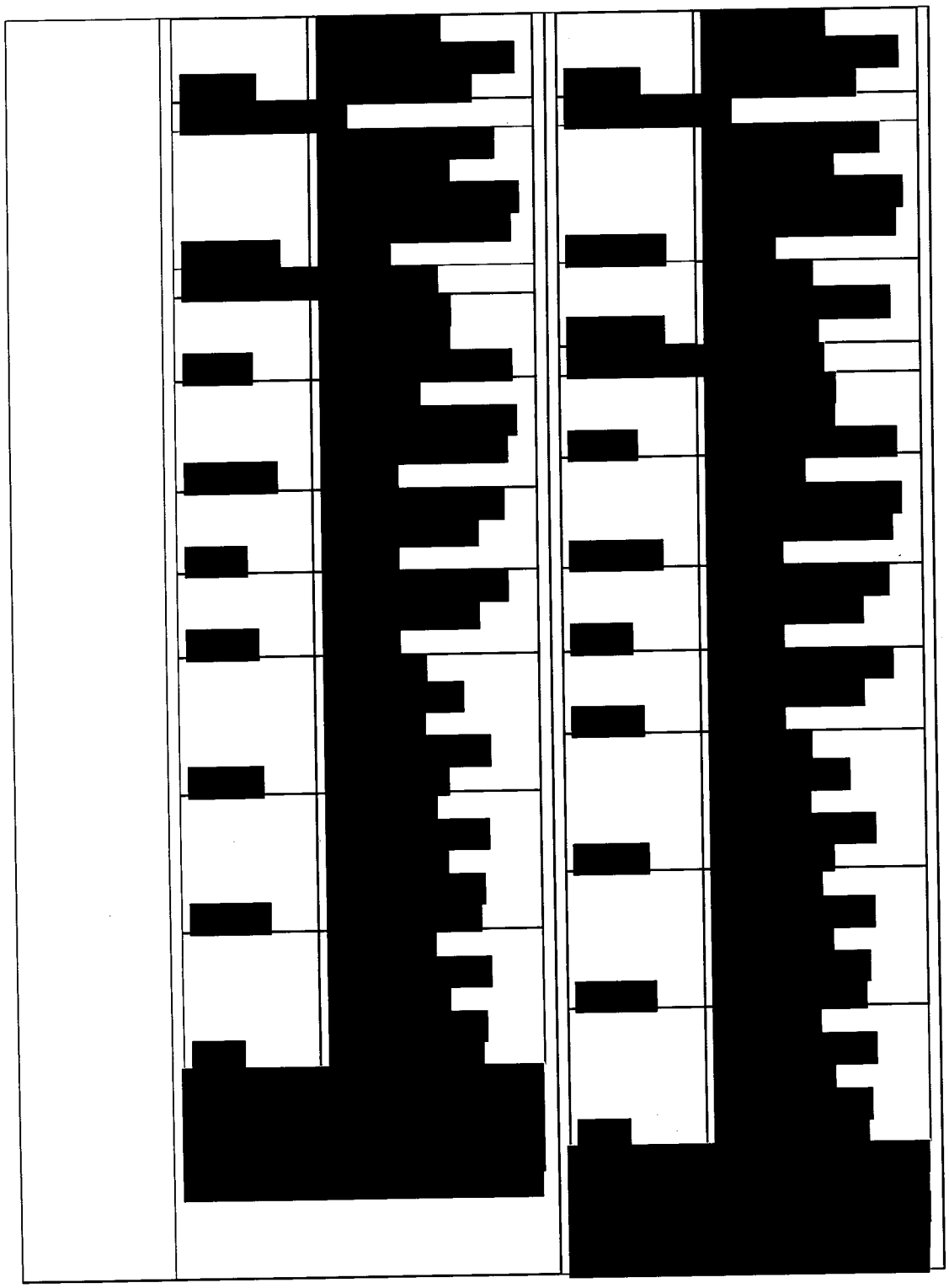

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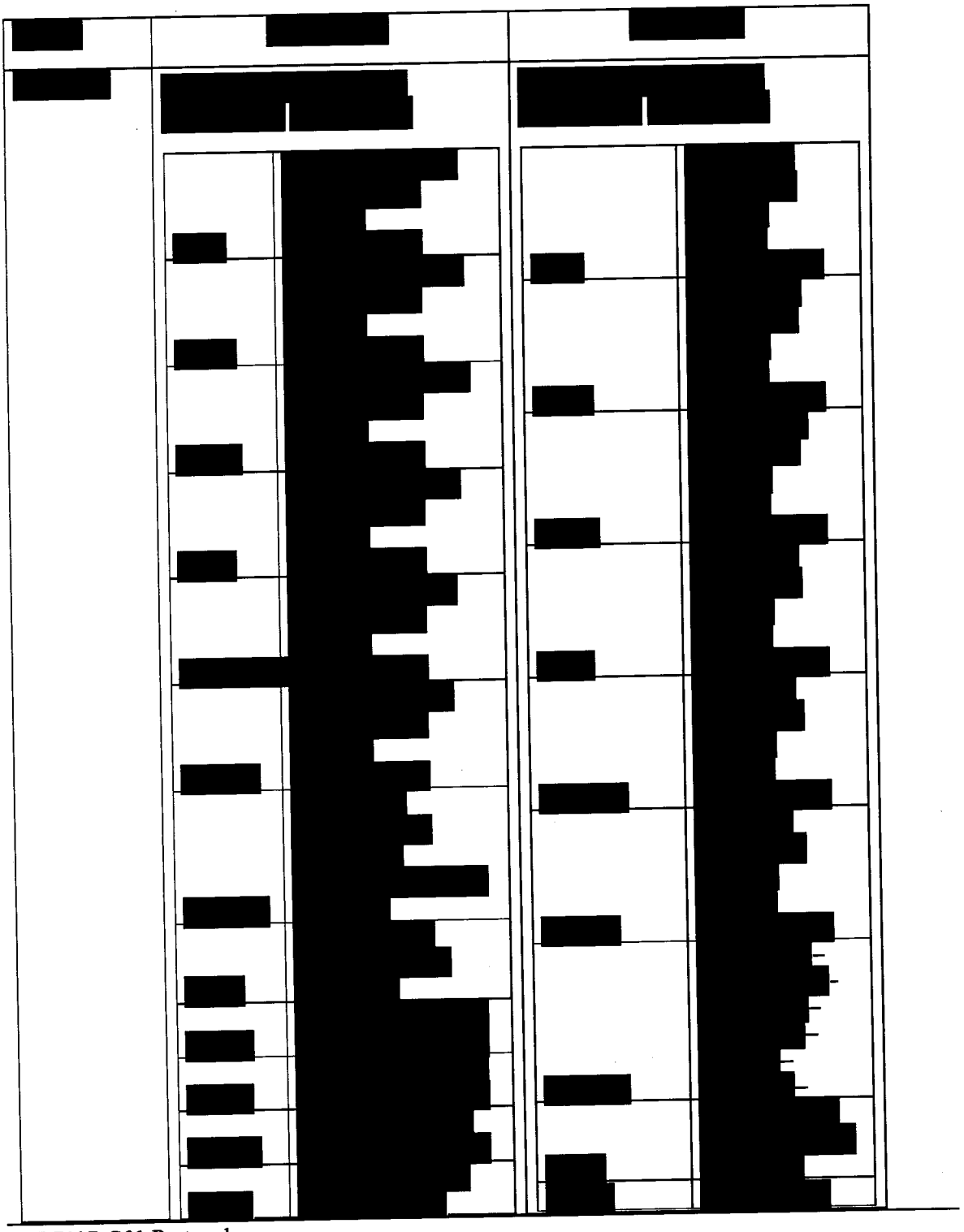

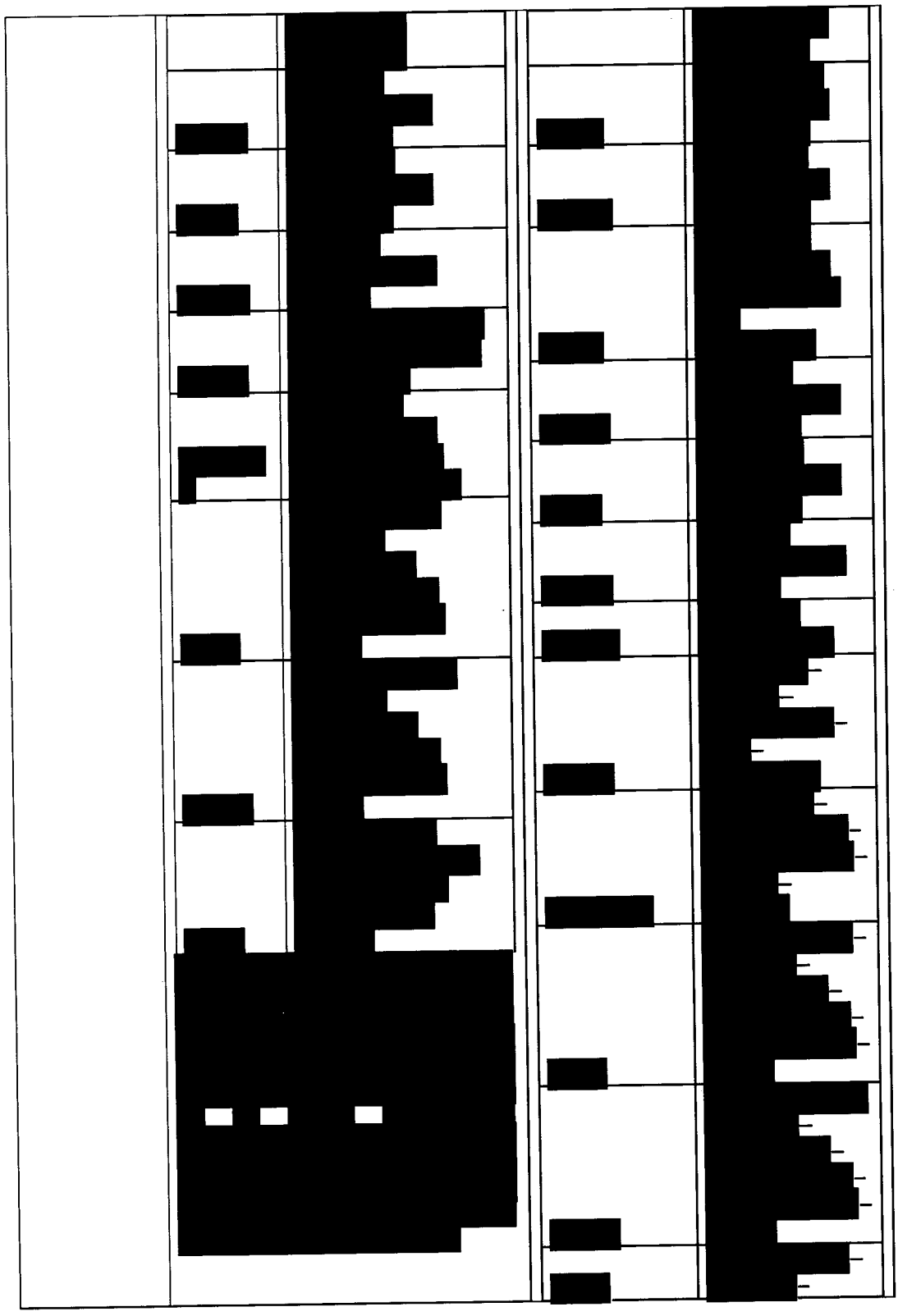

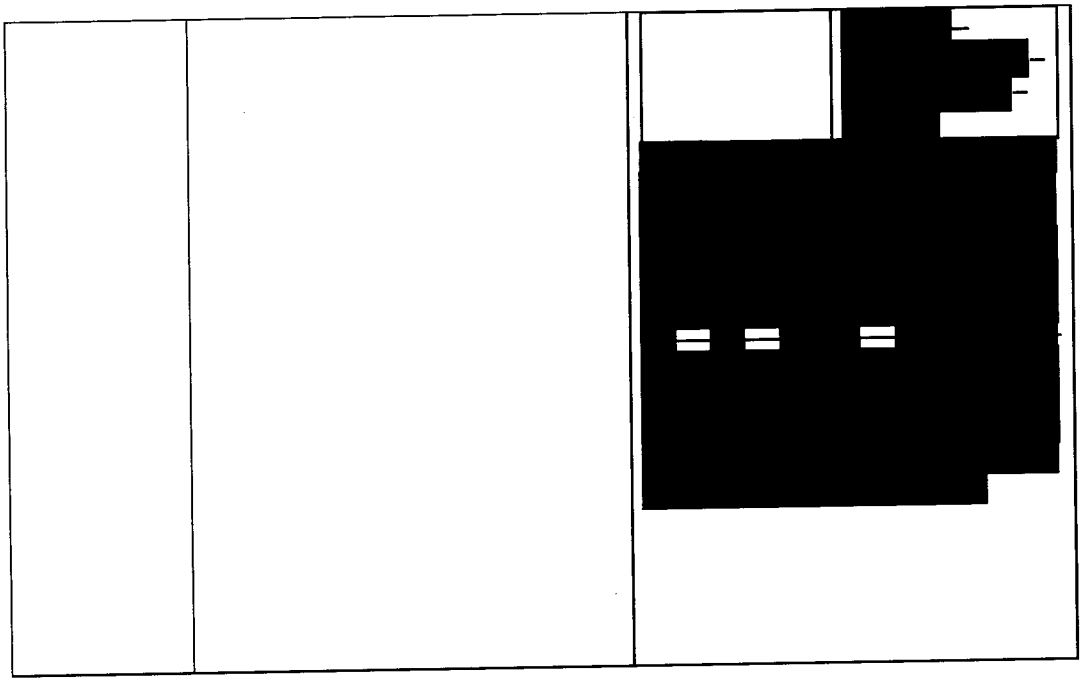

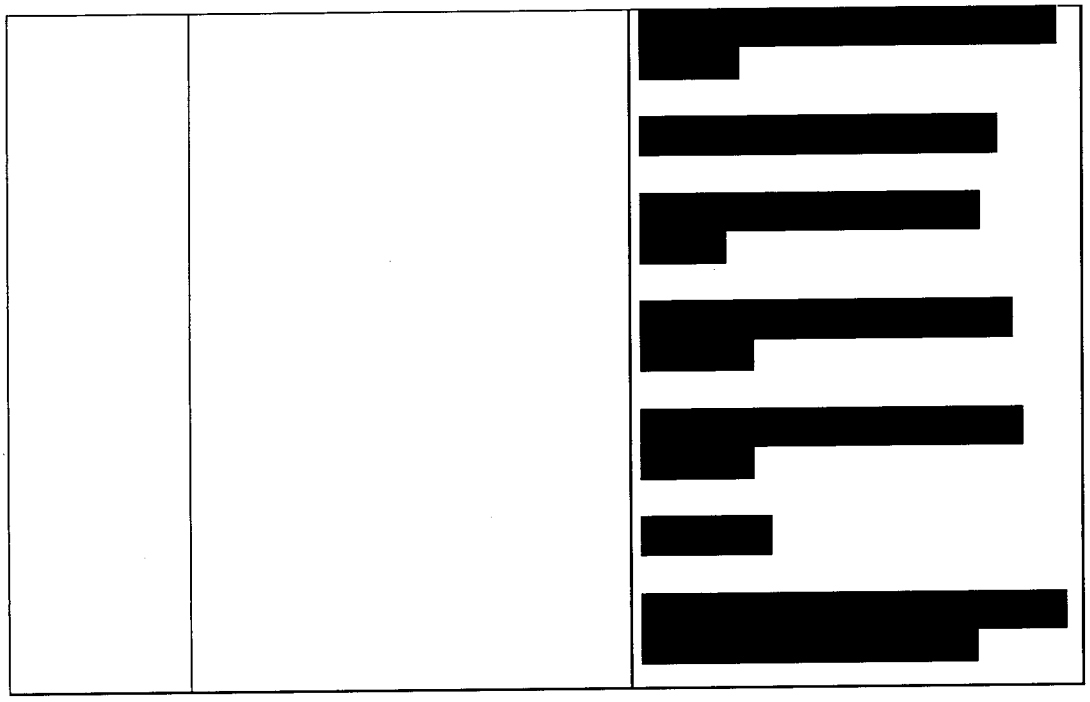

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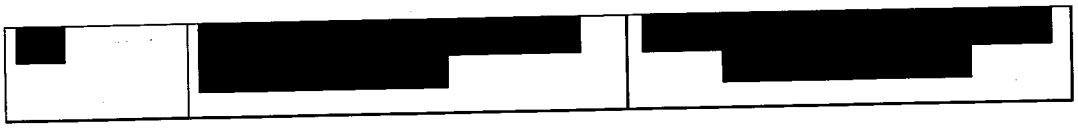

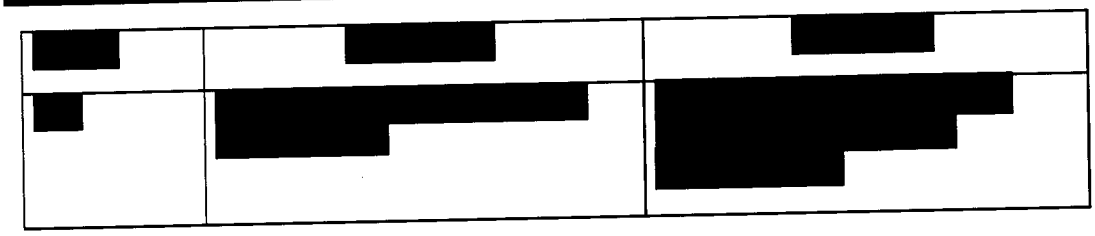

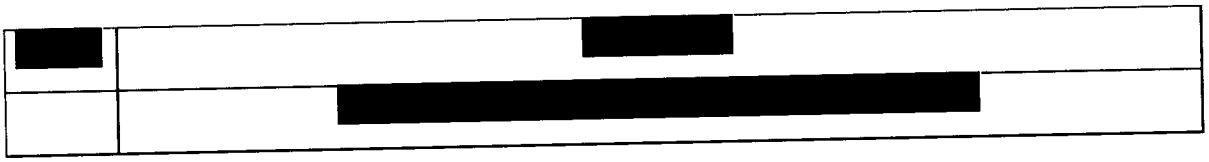

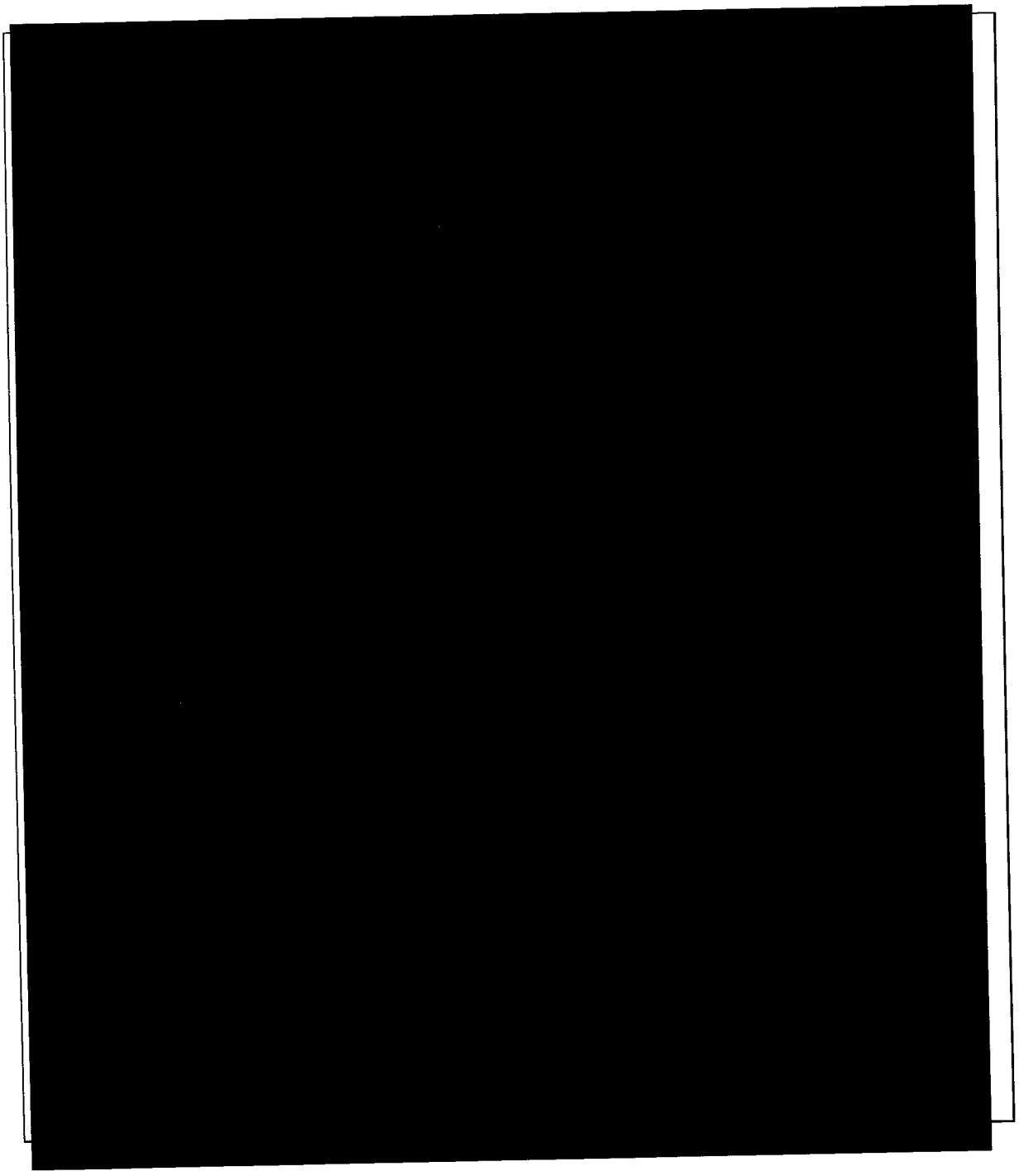

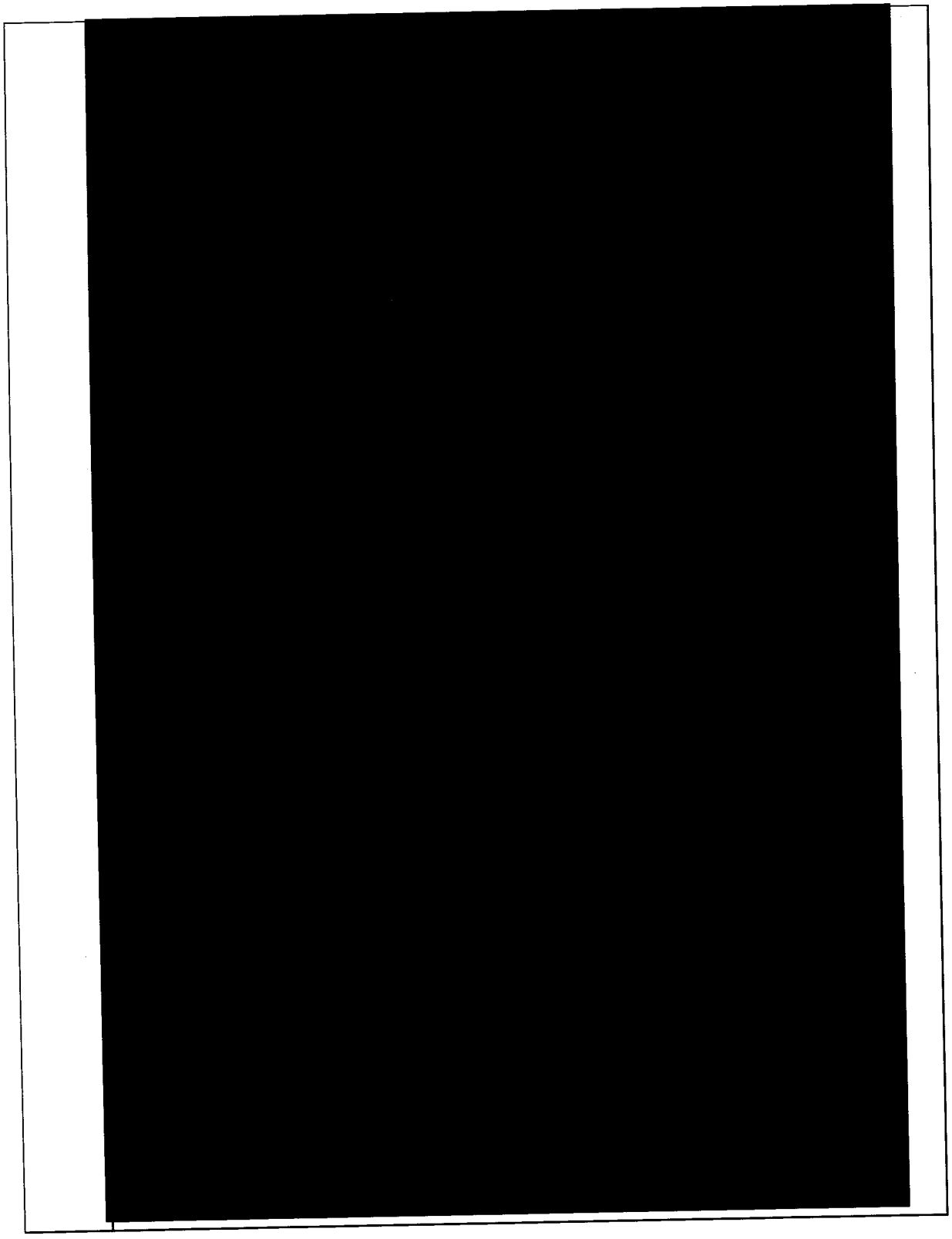

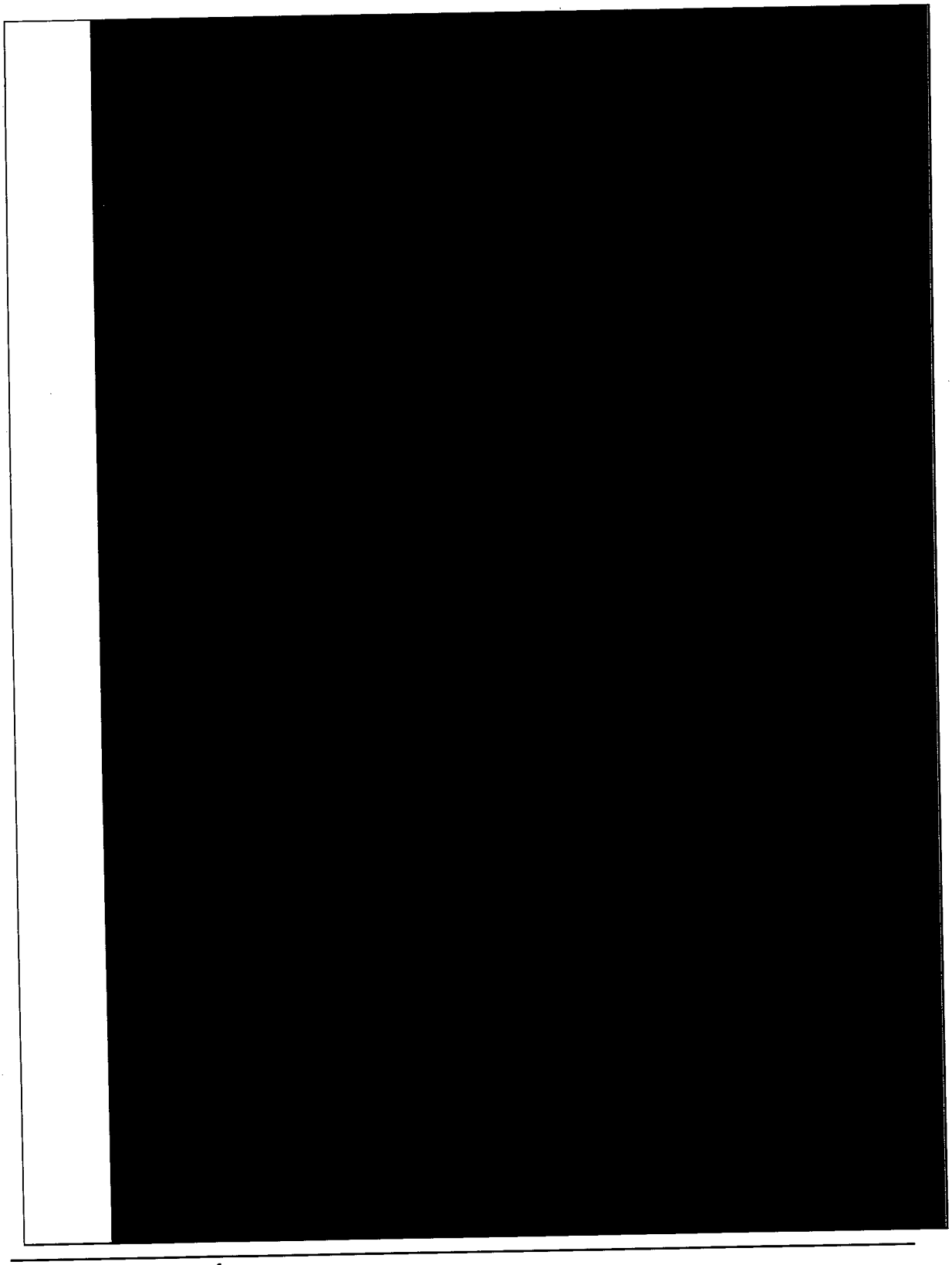

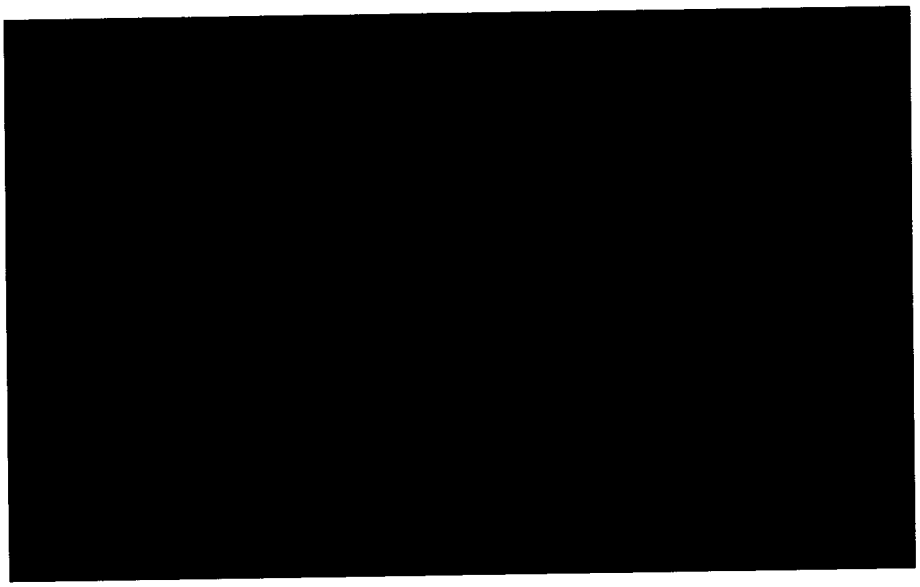

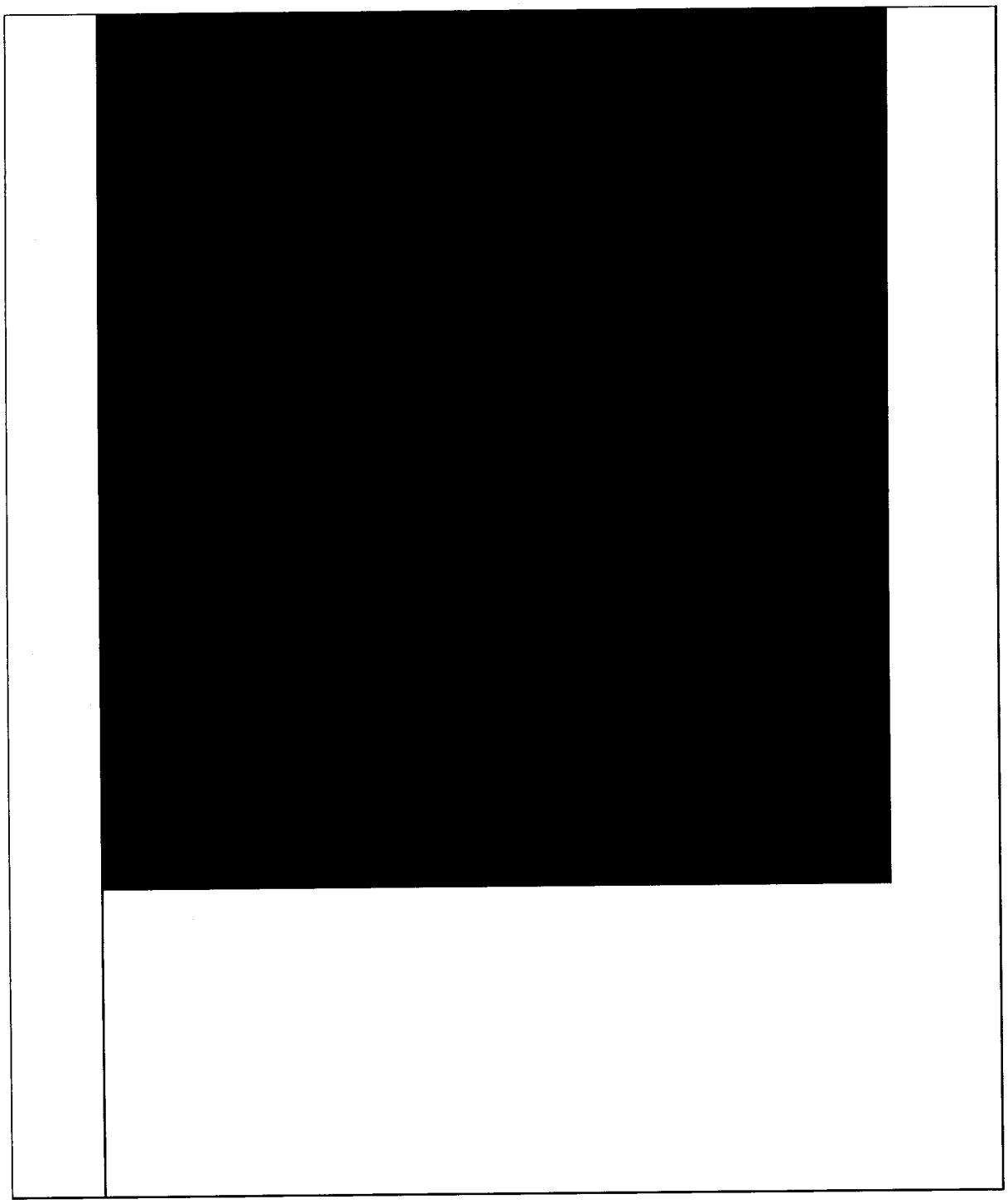

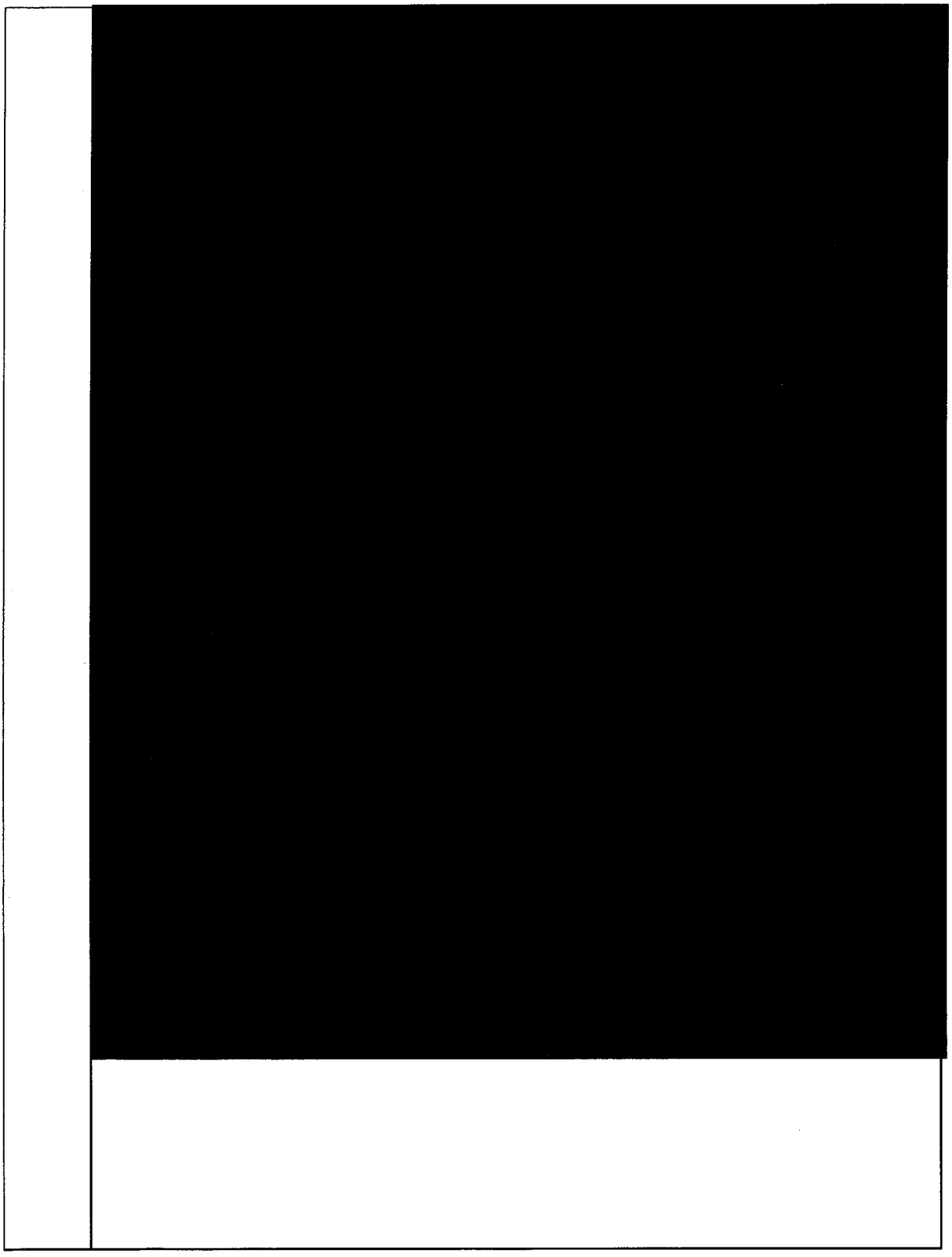

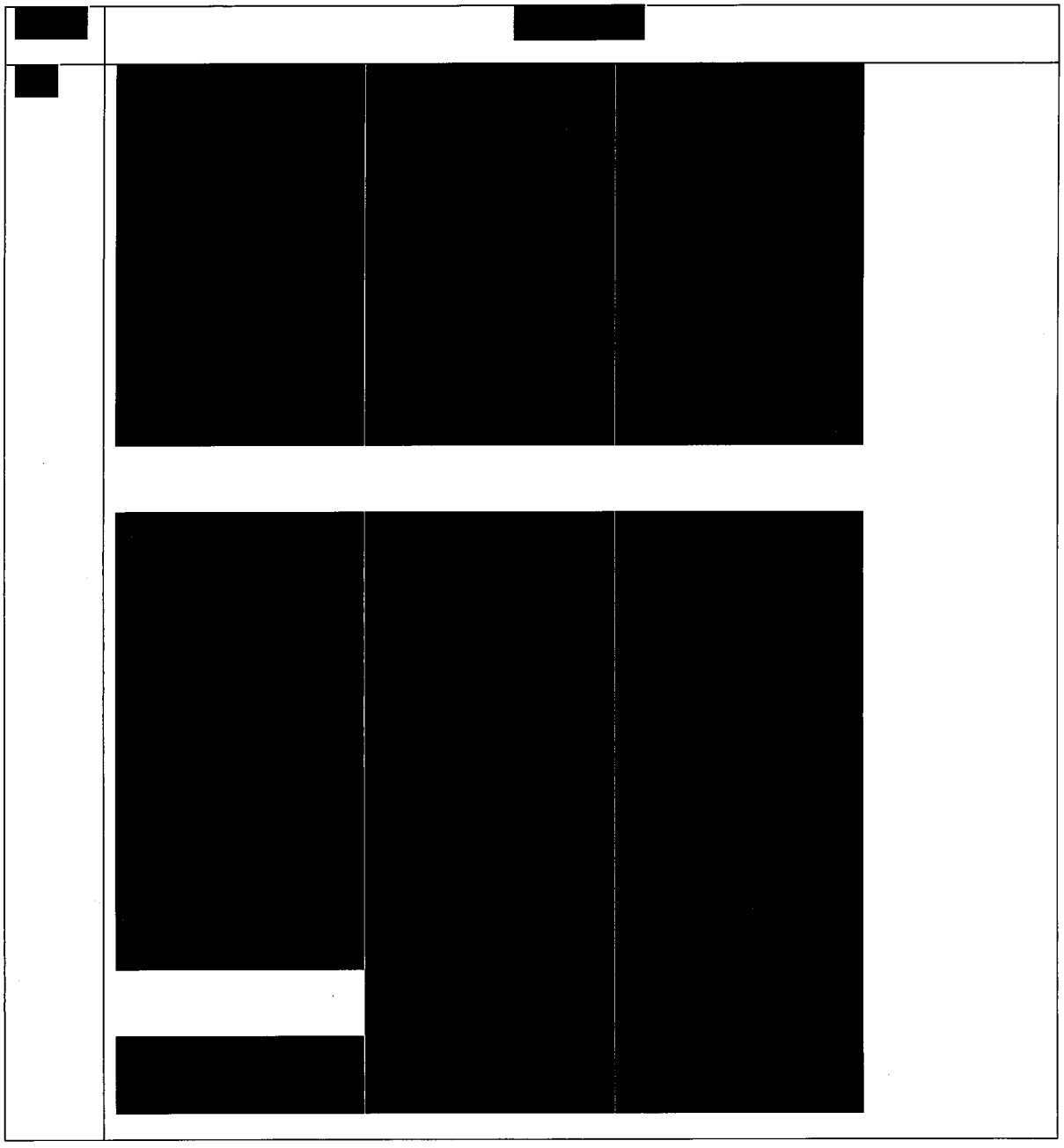

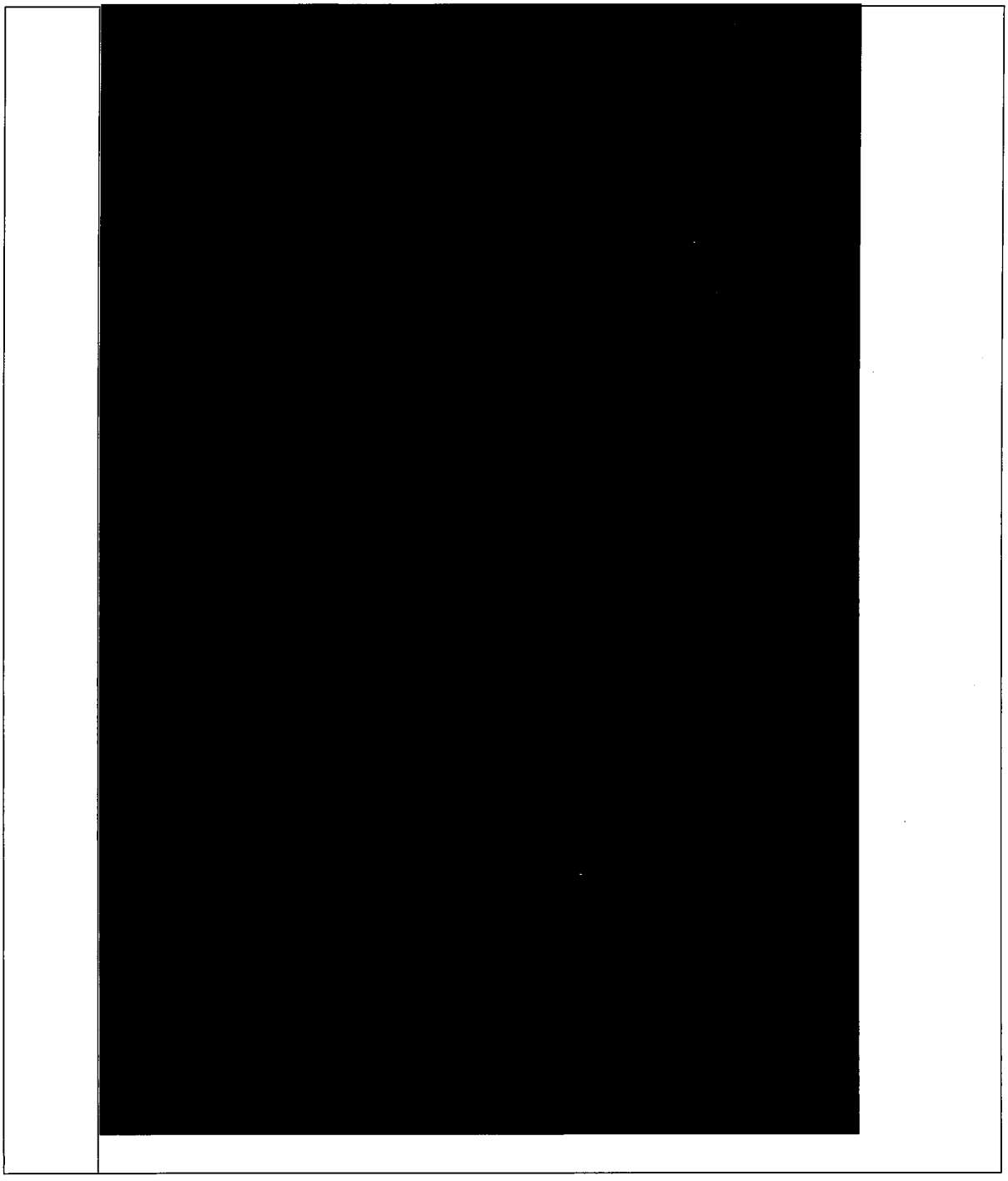

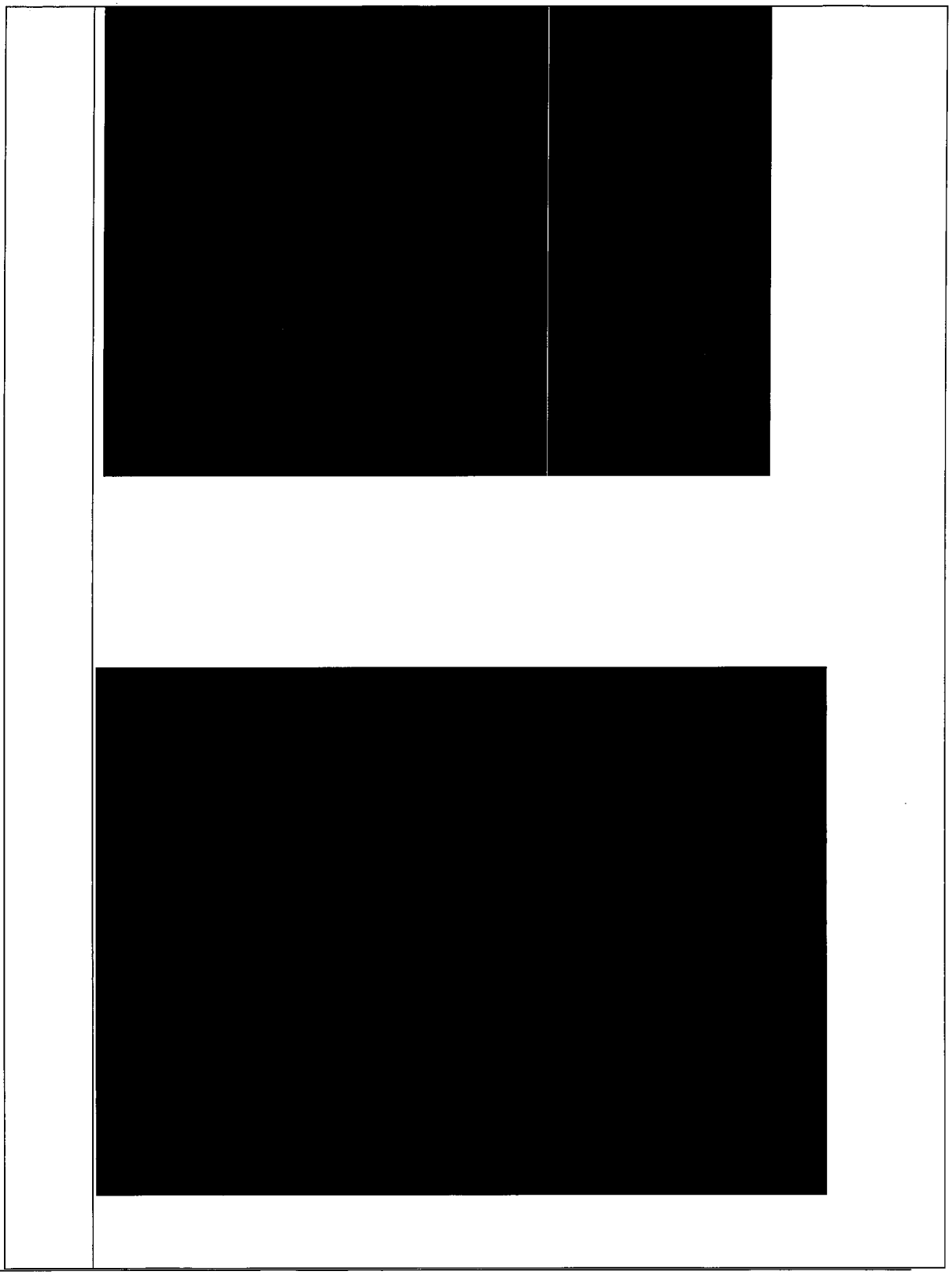

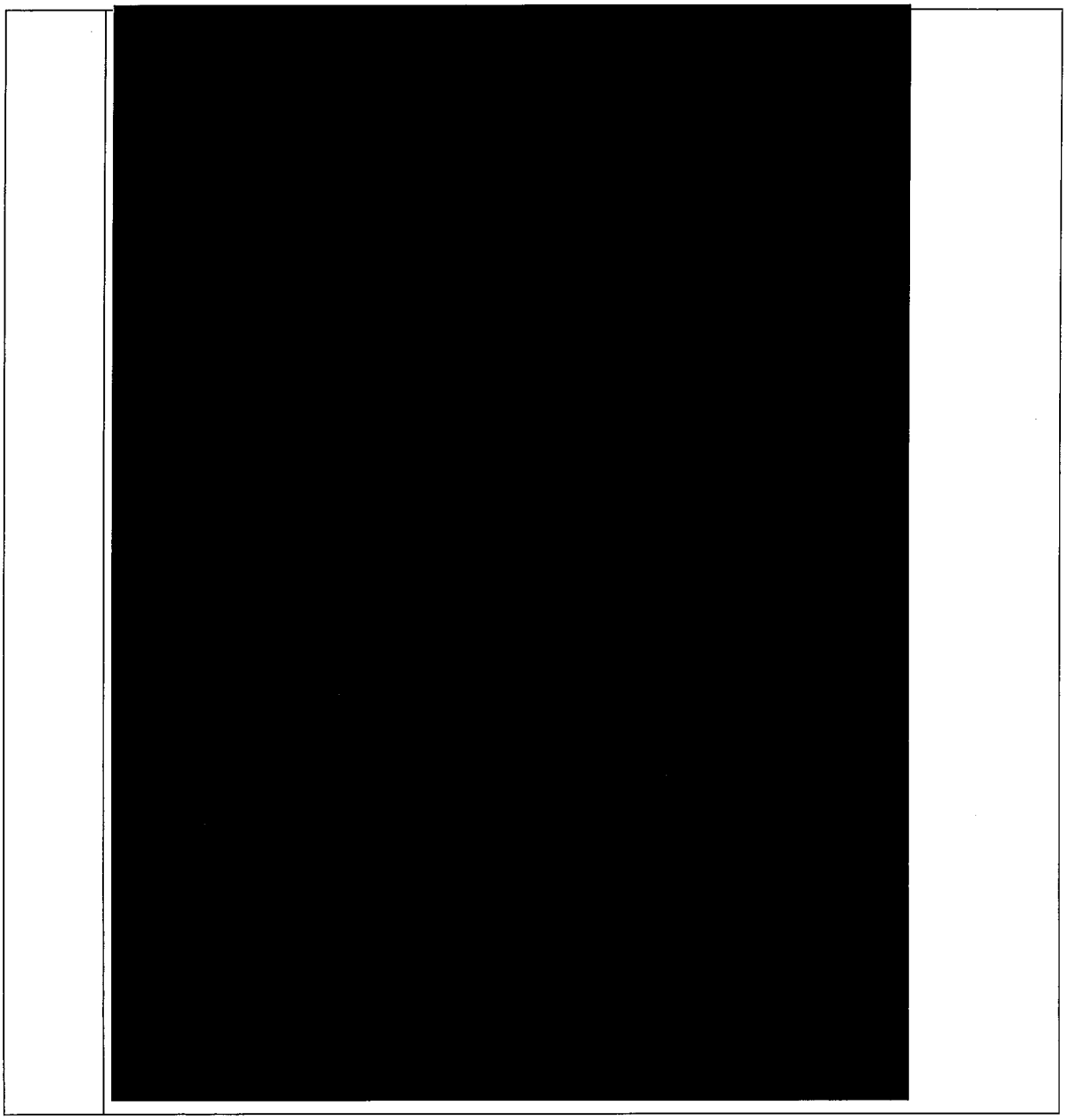

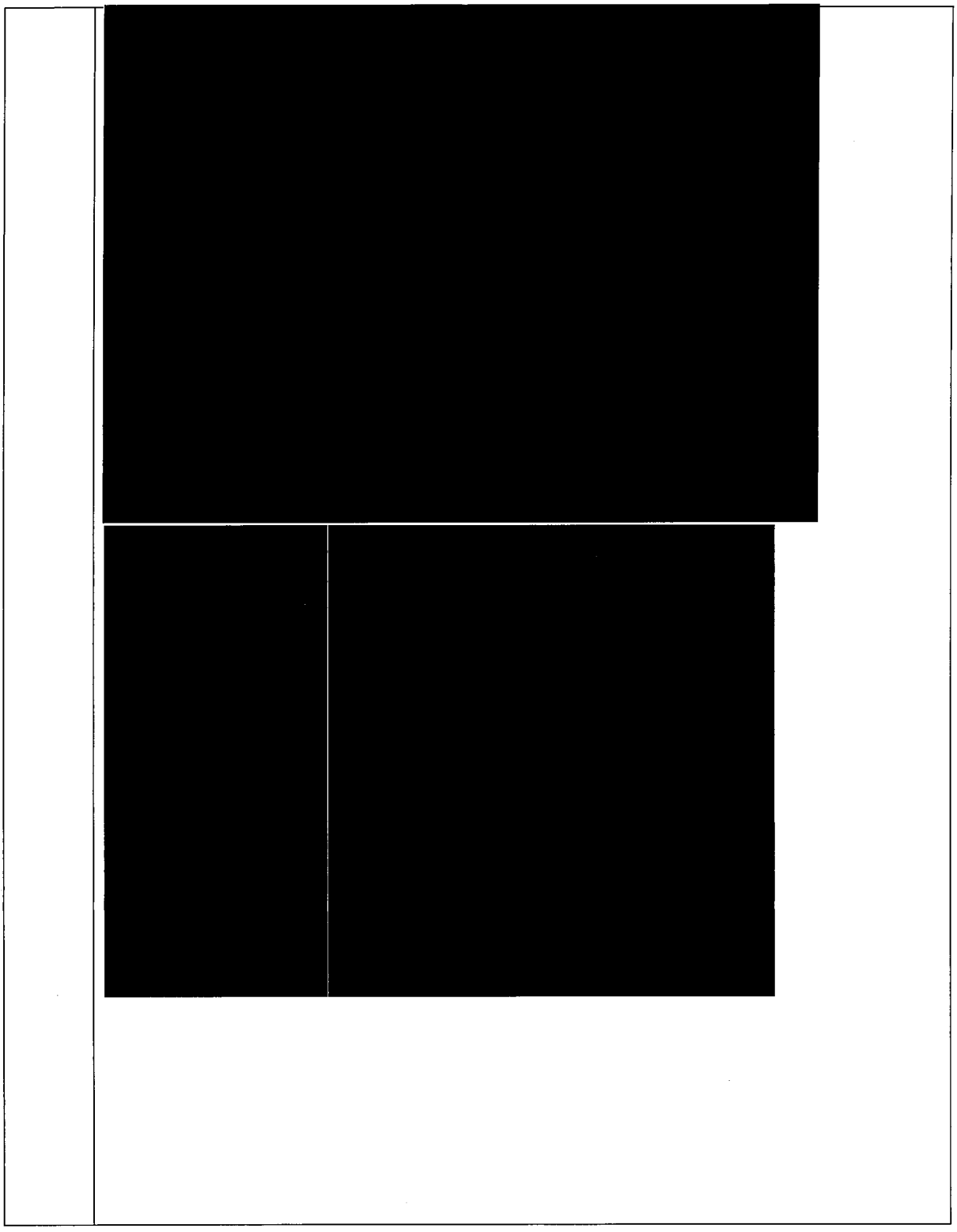

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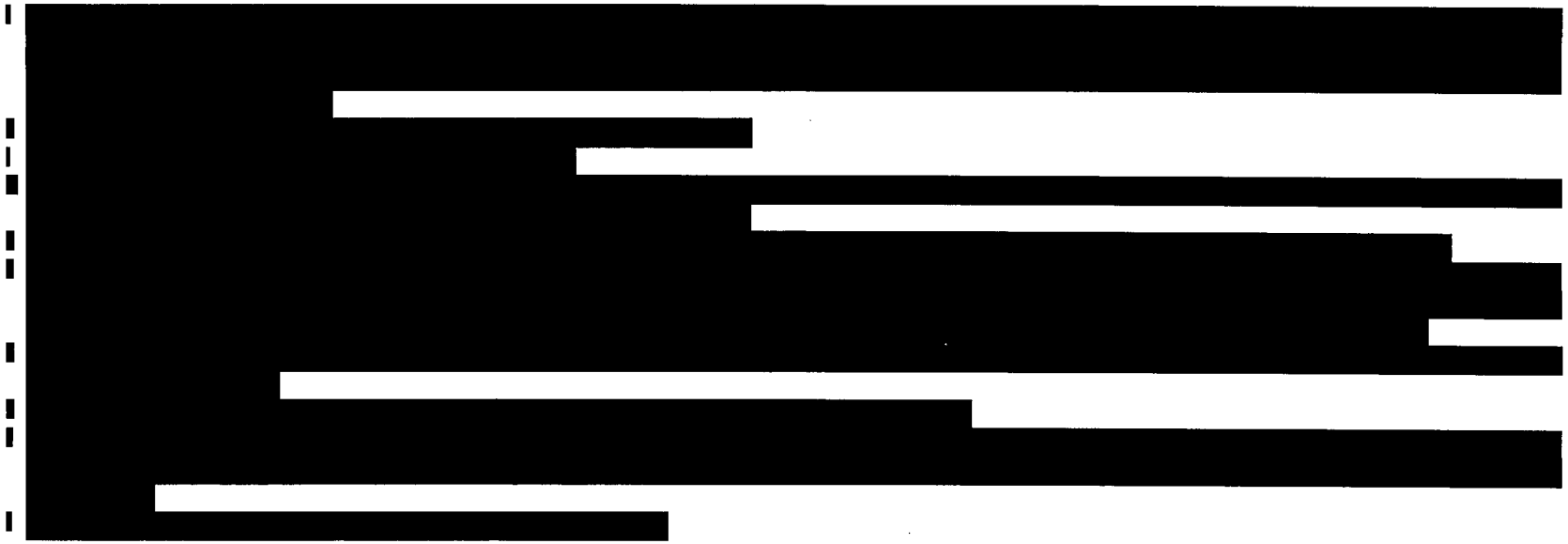

18.9 APPENDIX 9: [redacted]

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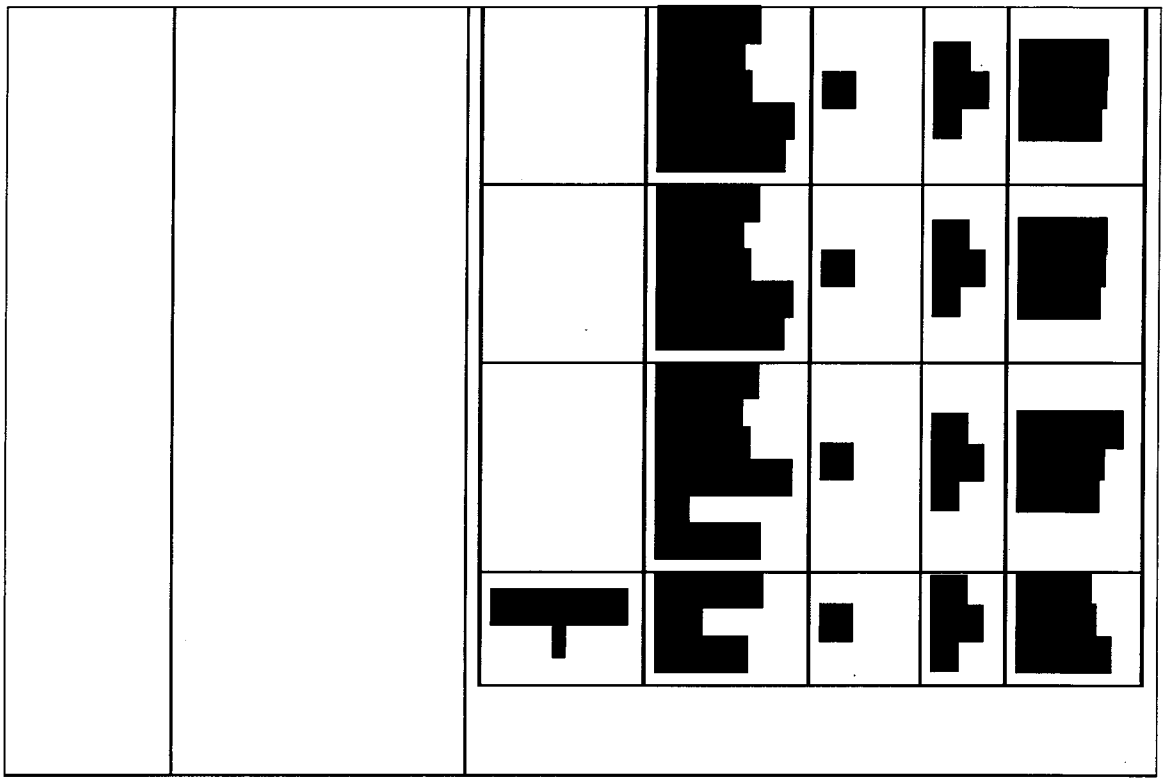

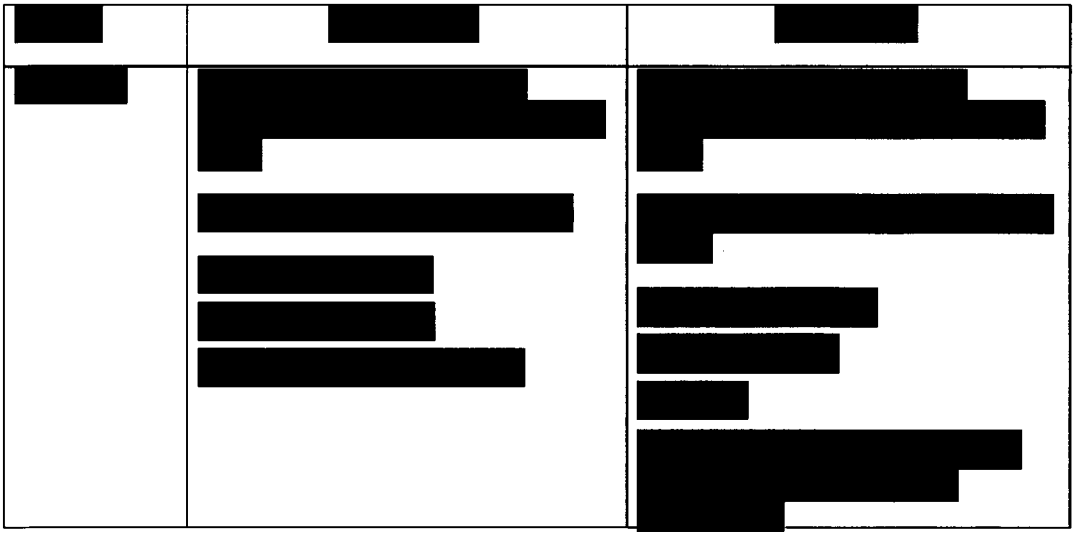

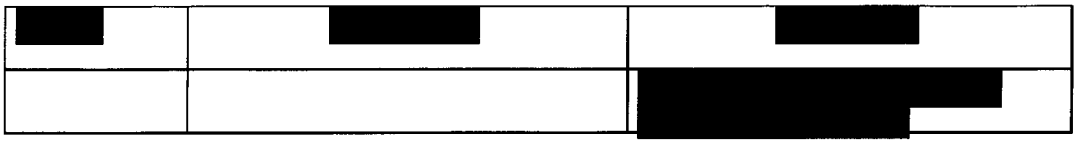

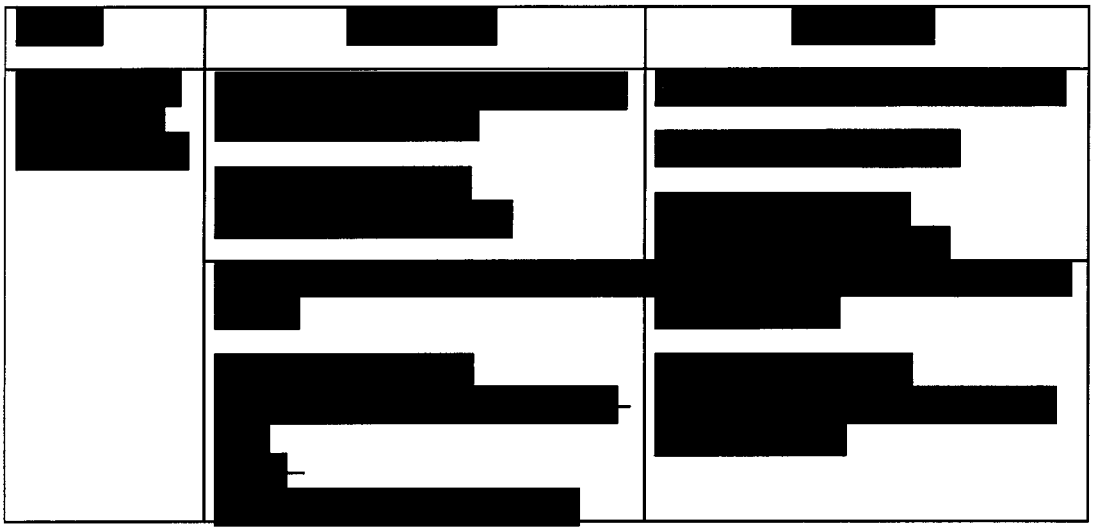

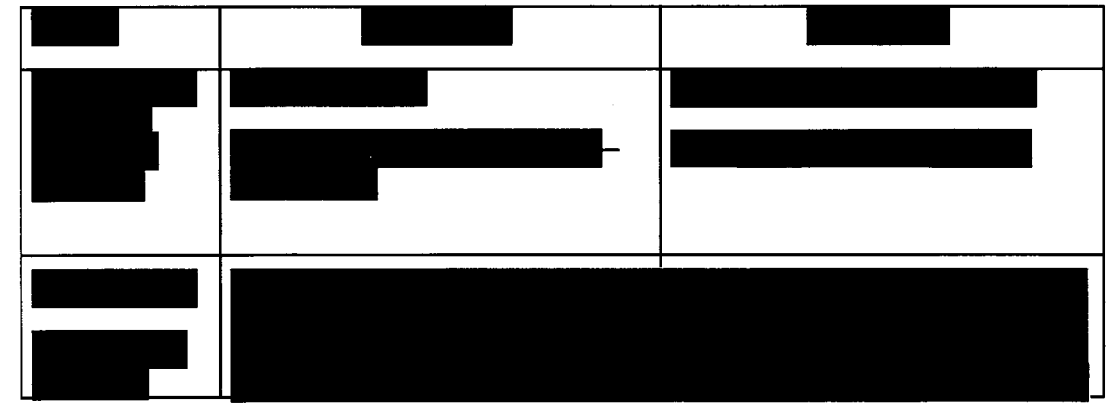

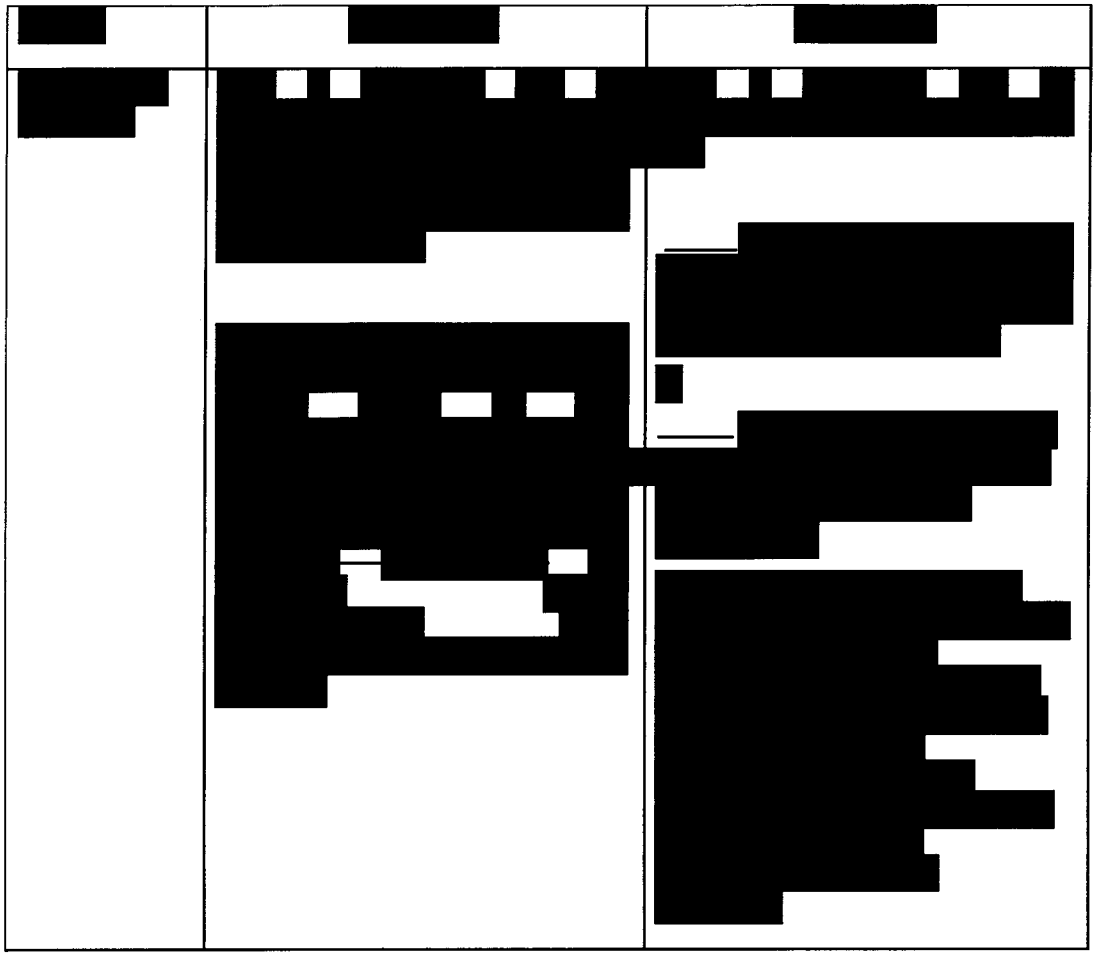

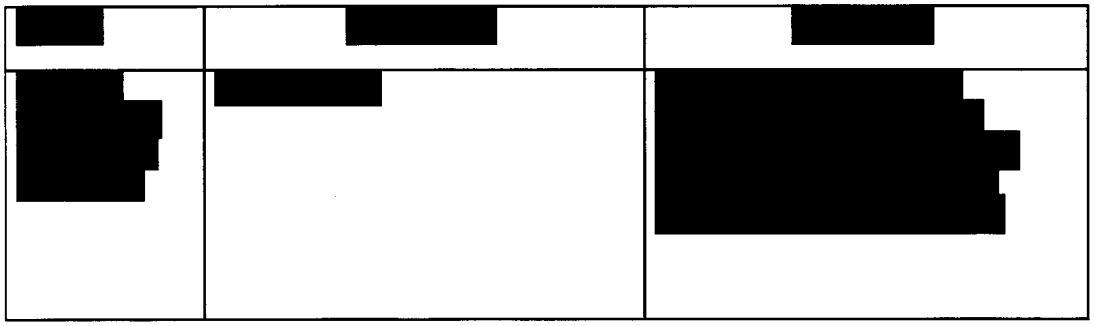

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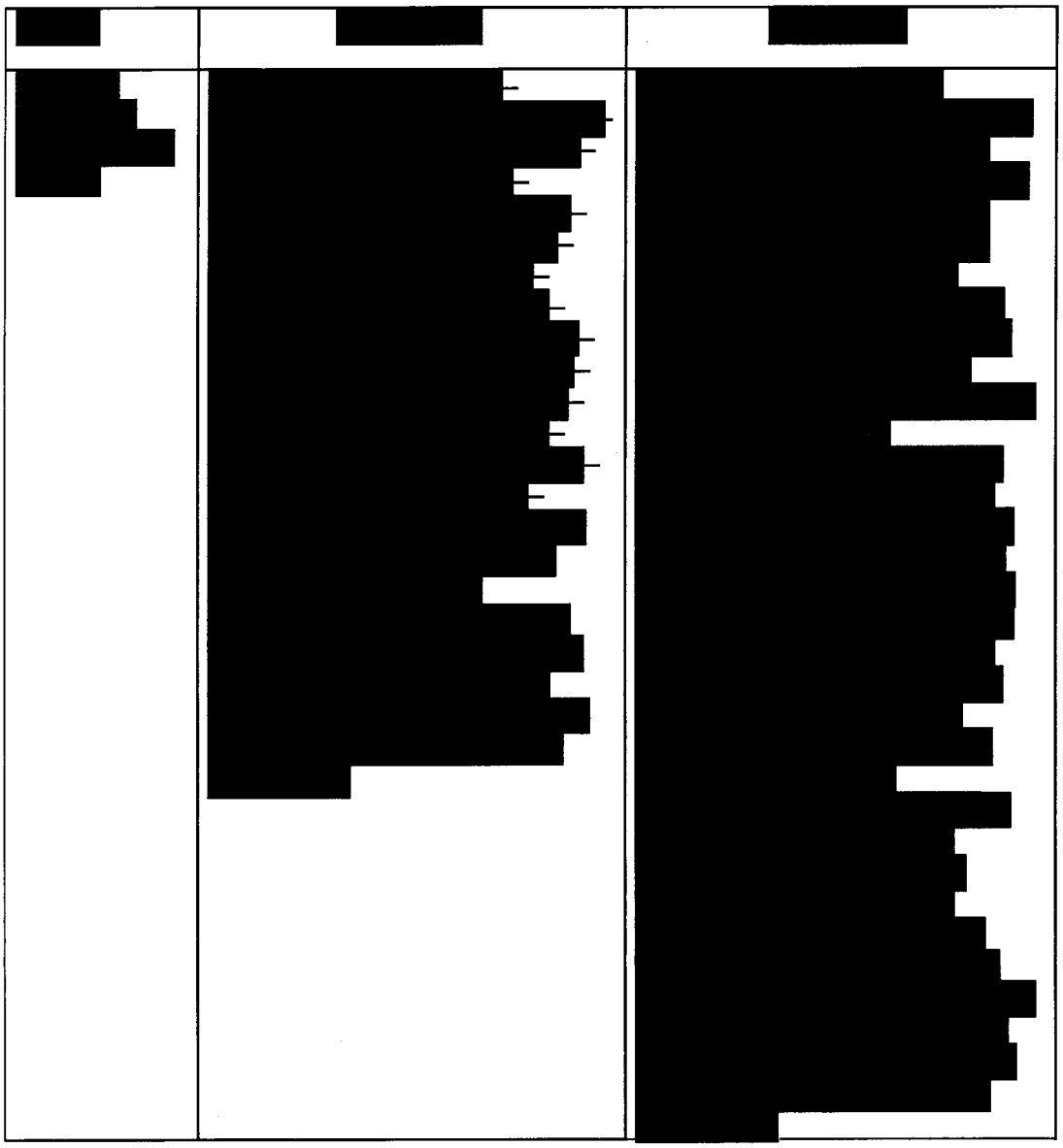

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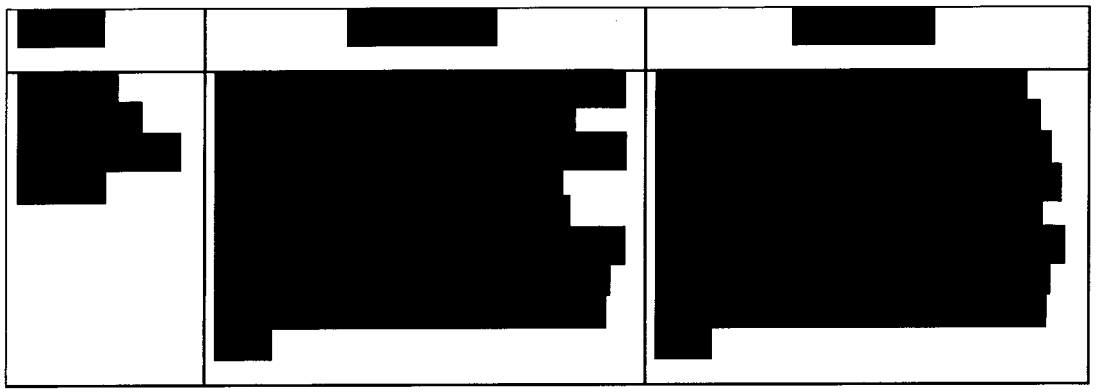

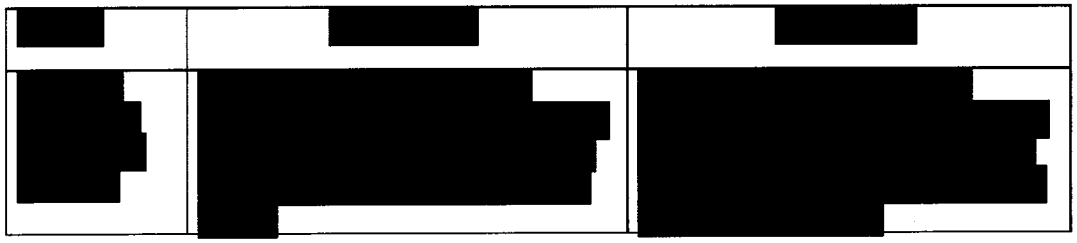

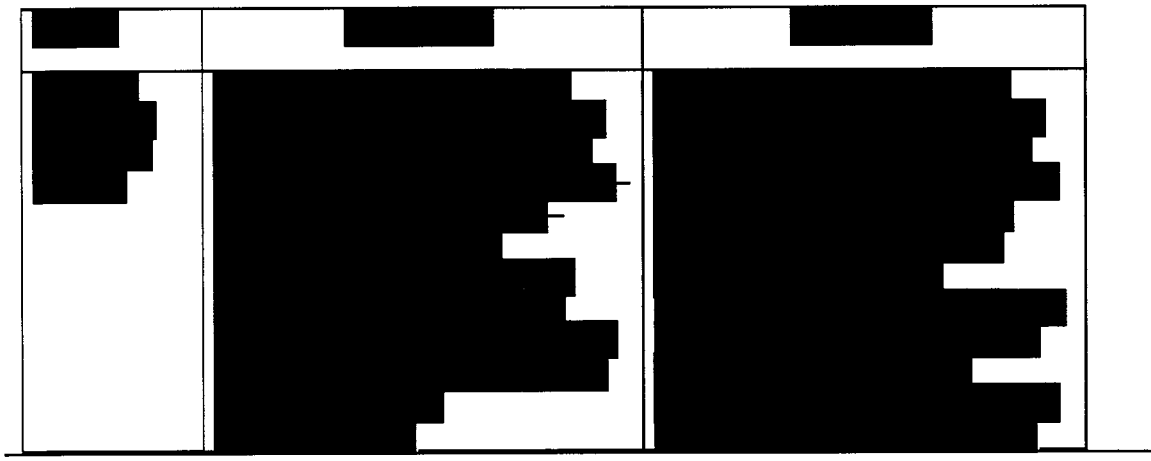

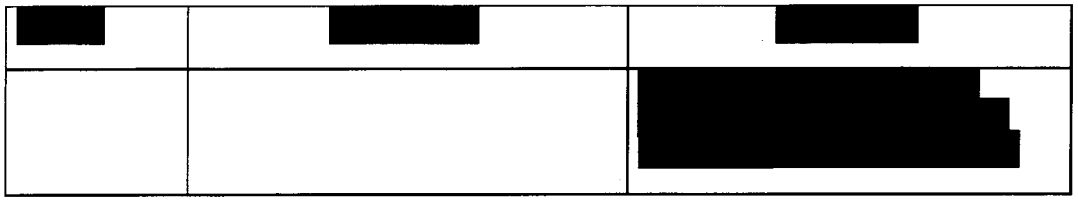

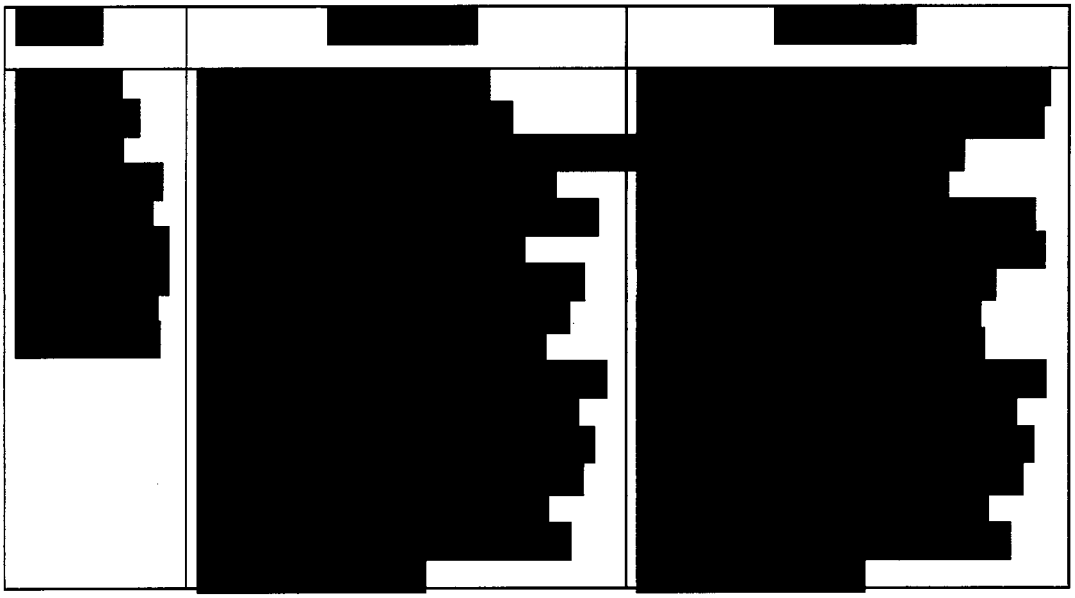

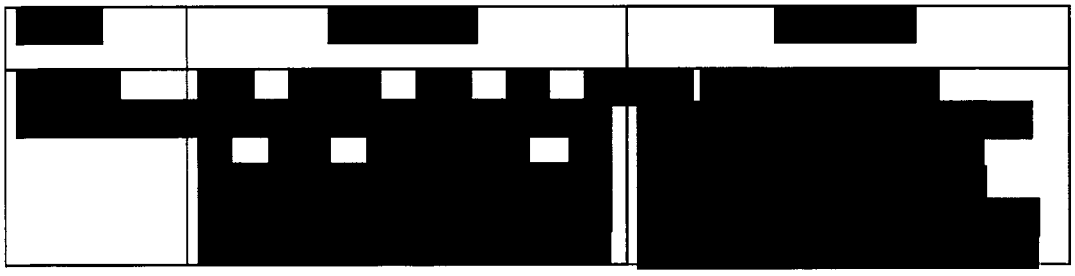

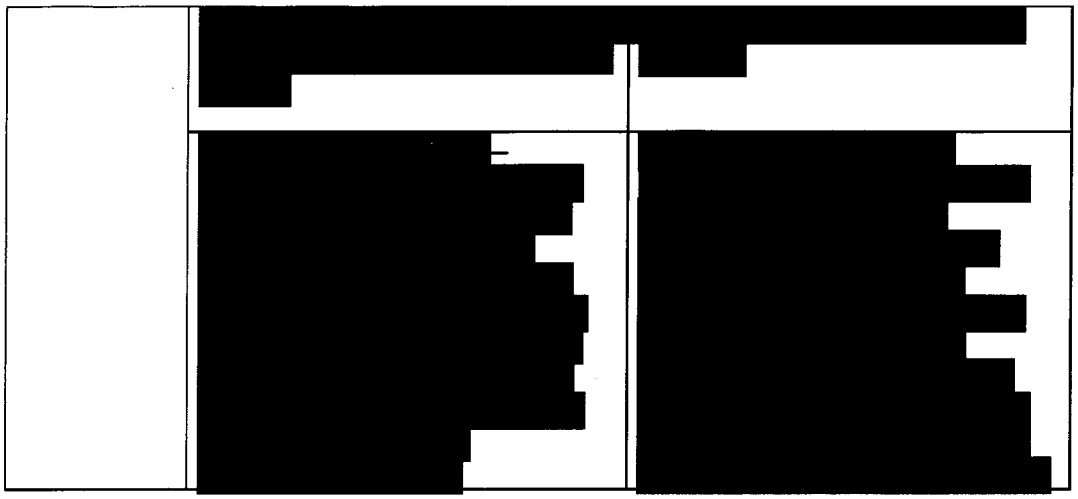

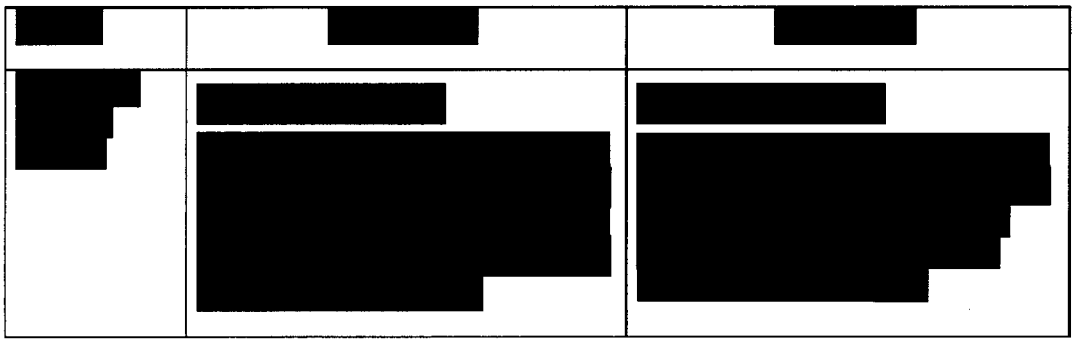

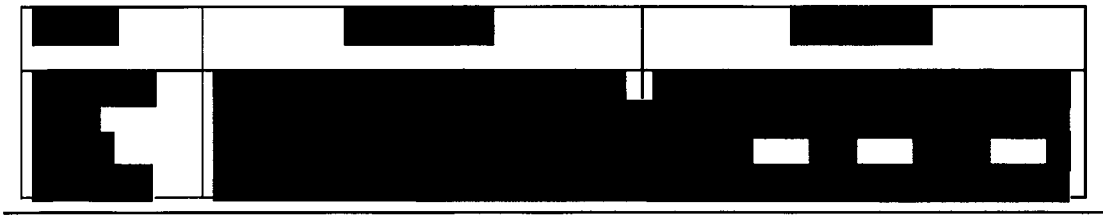

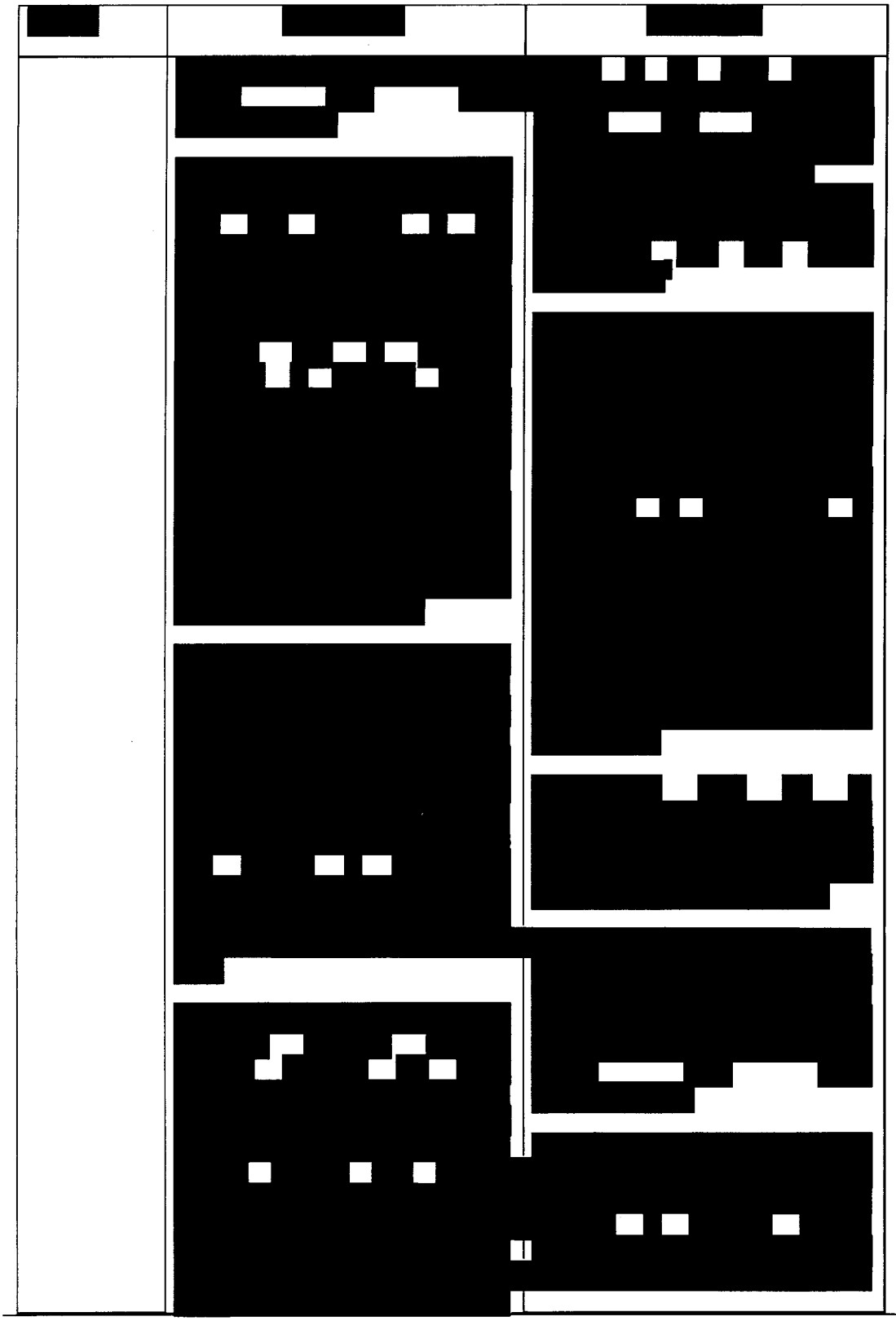

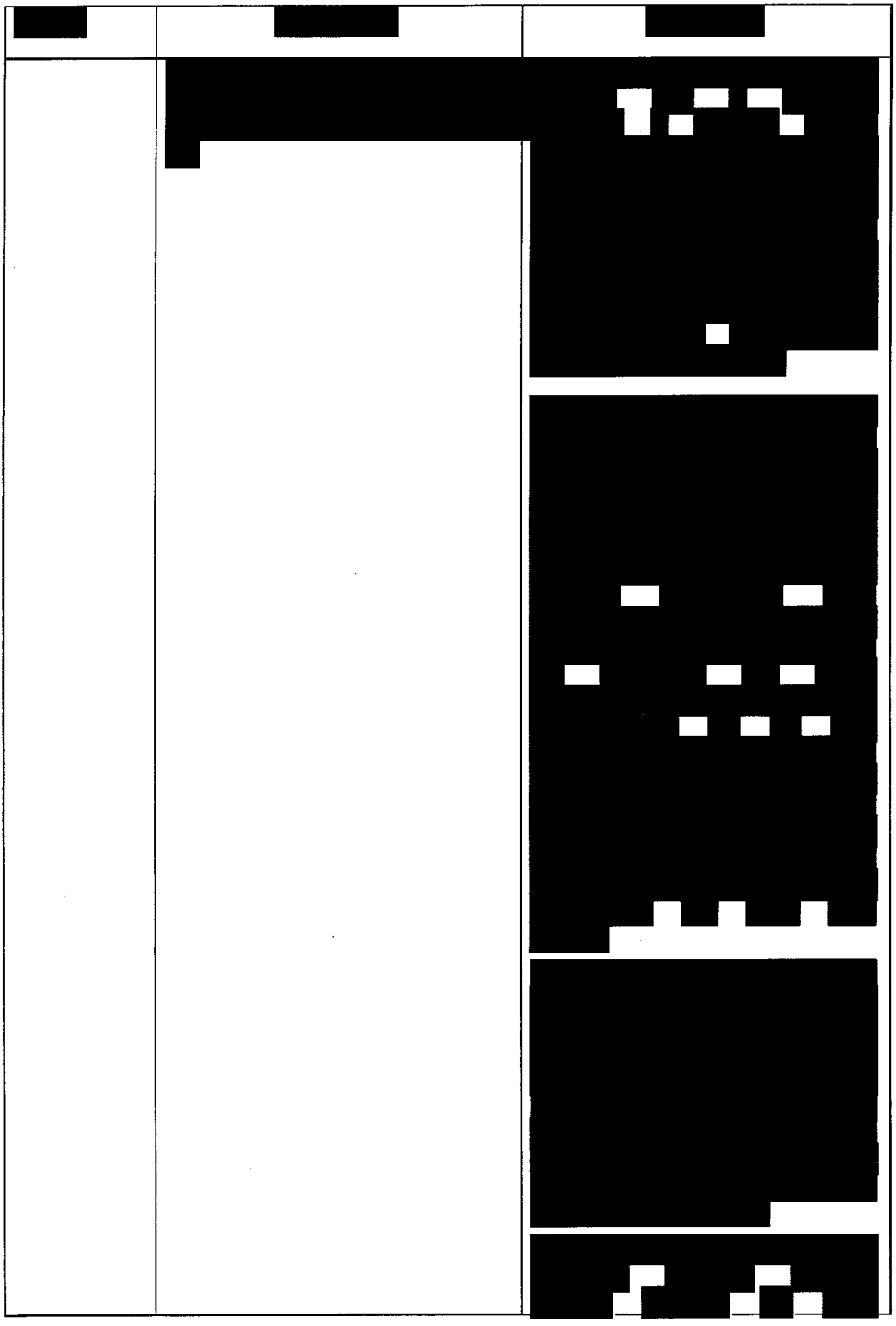

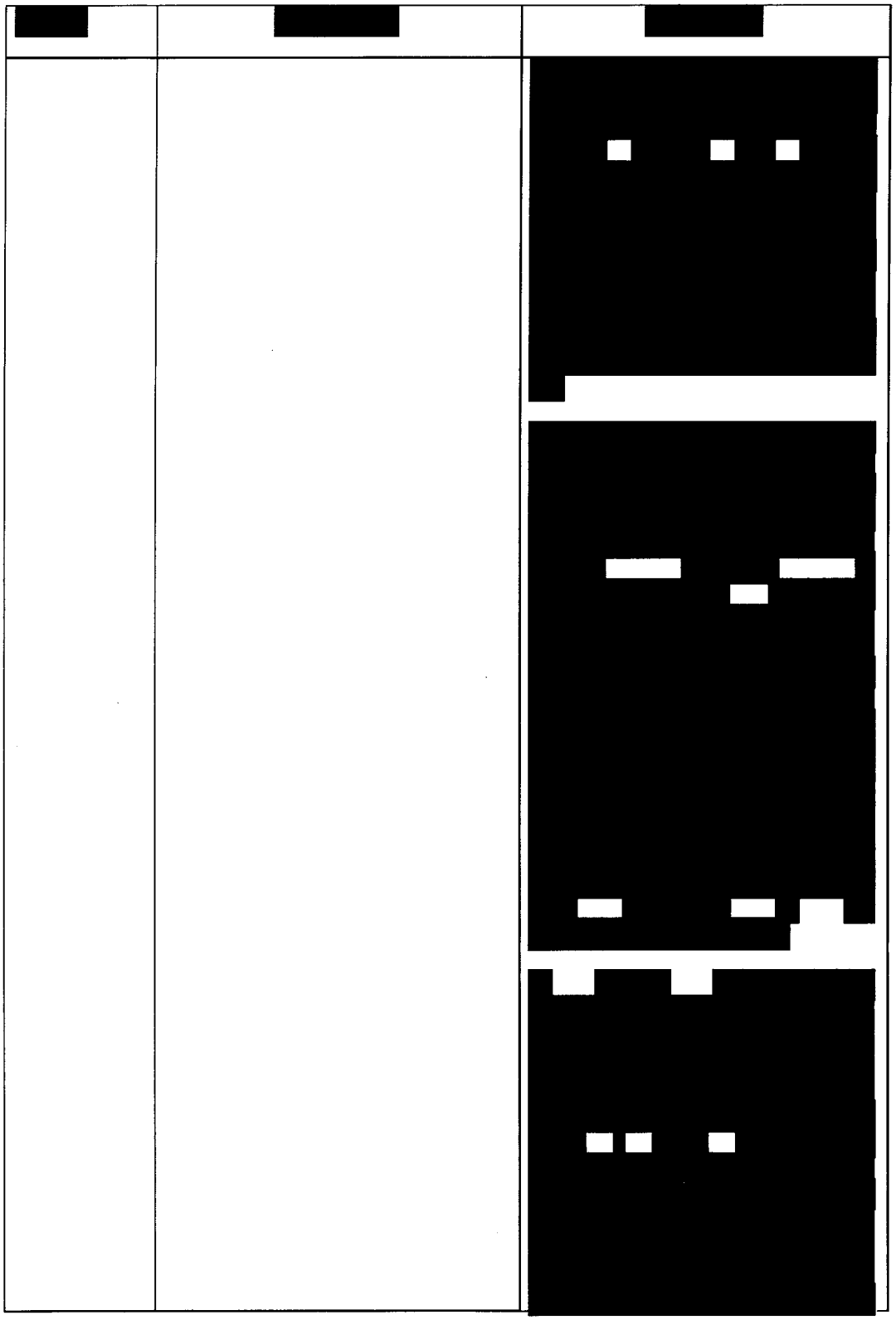

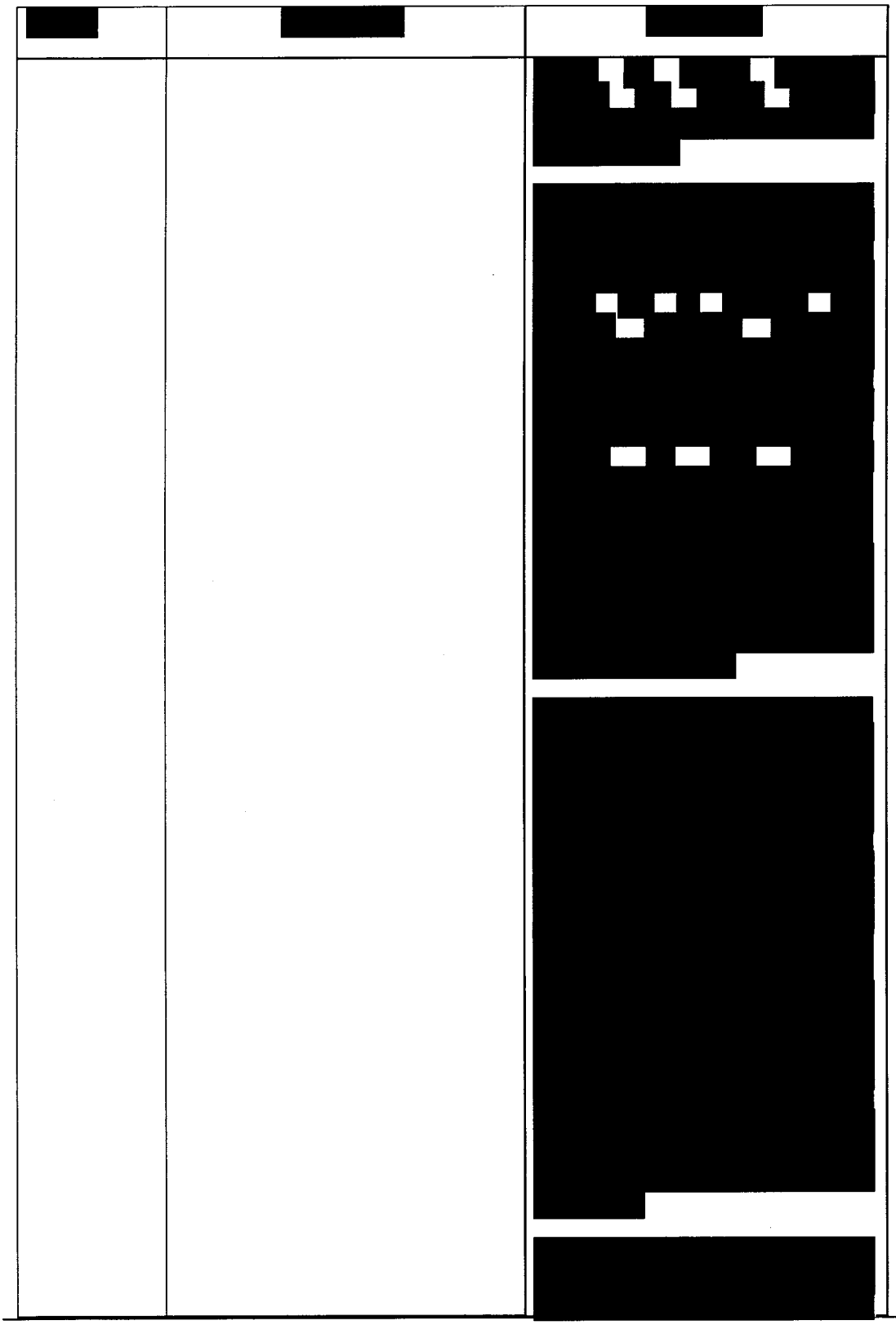

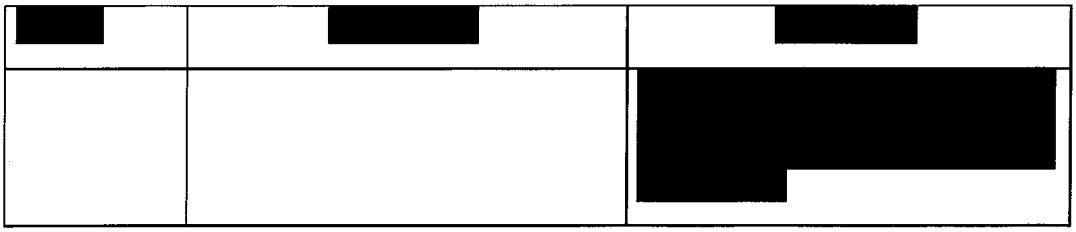

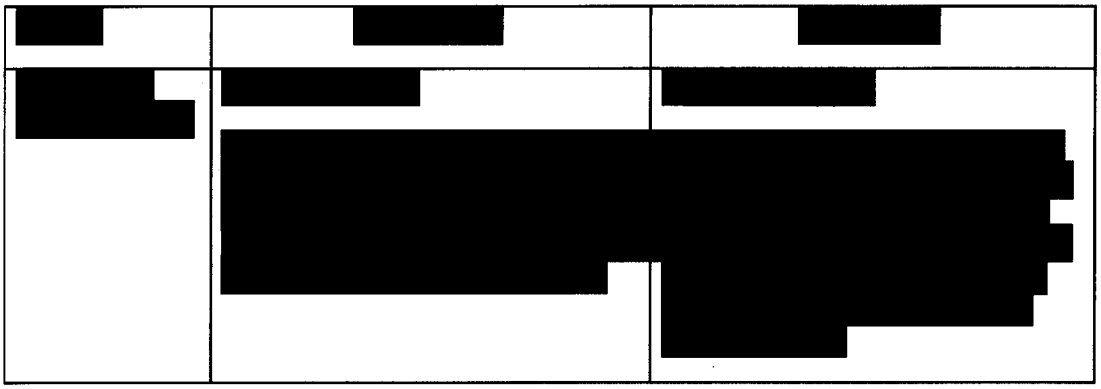

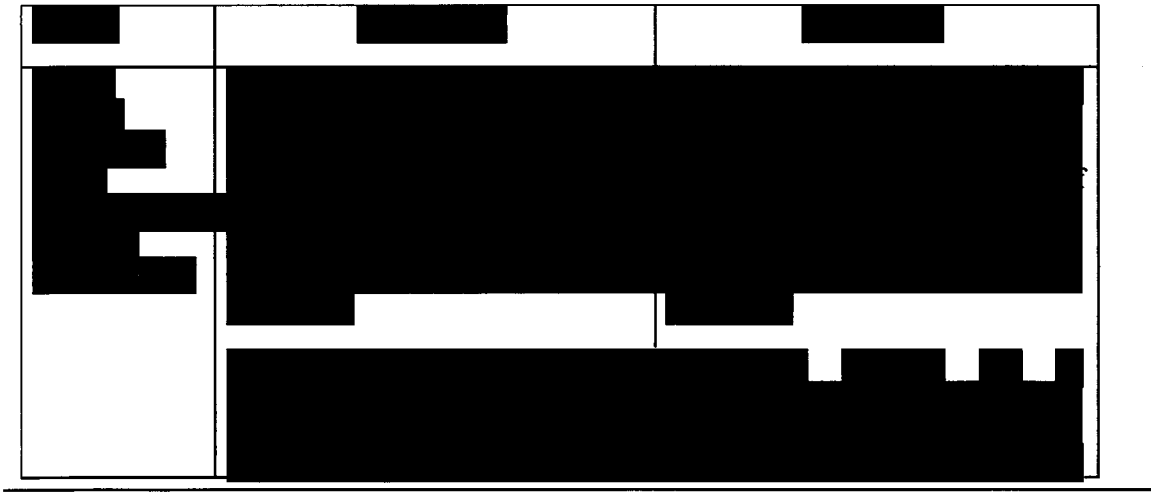

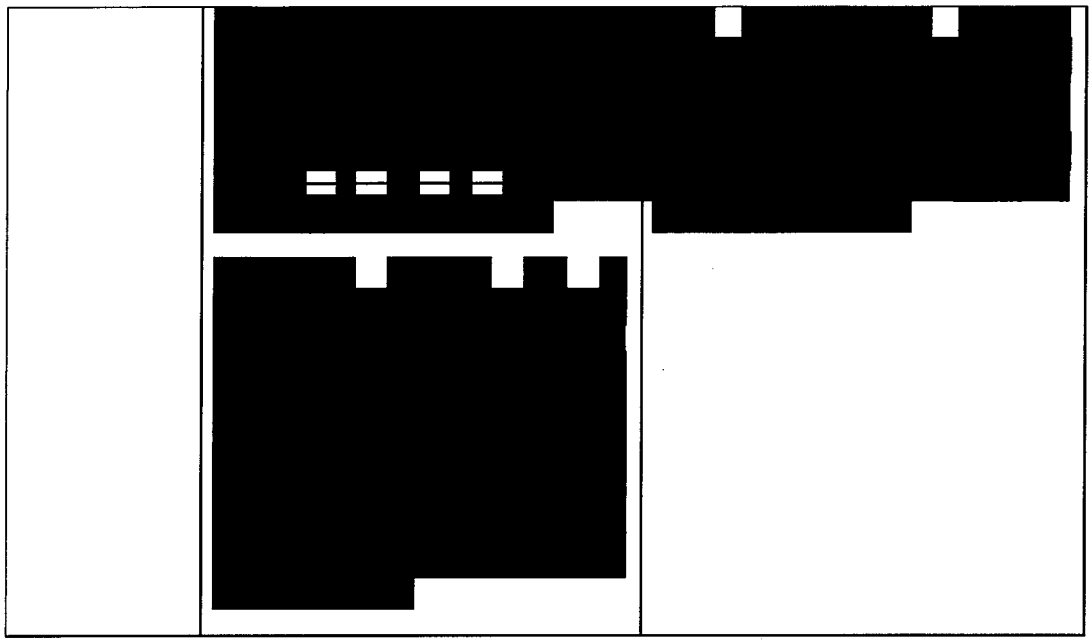

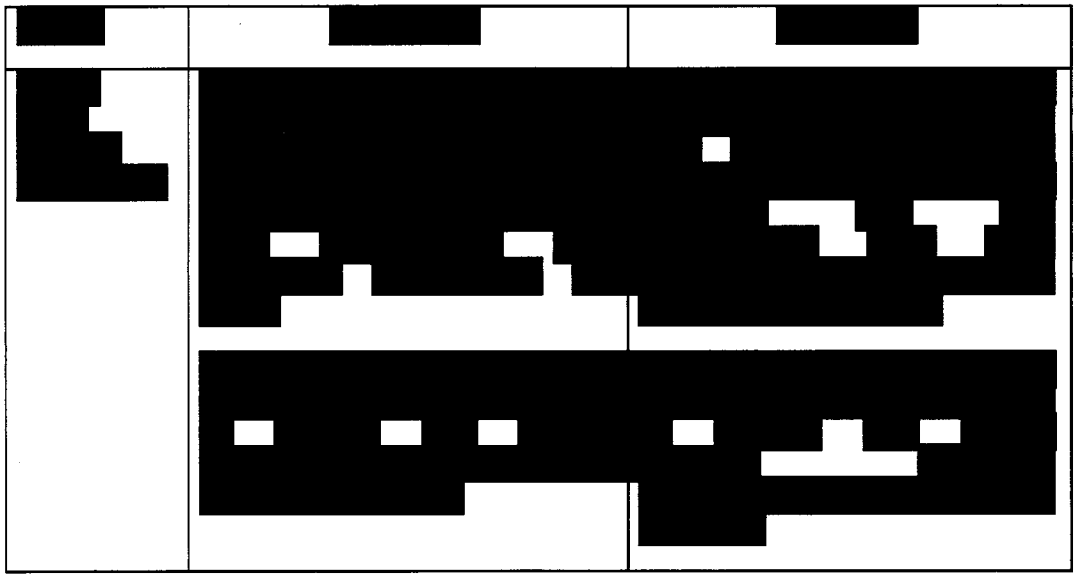

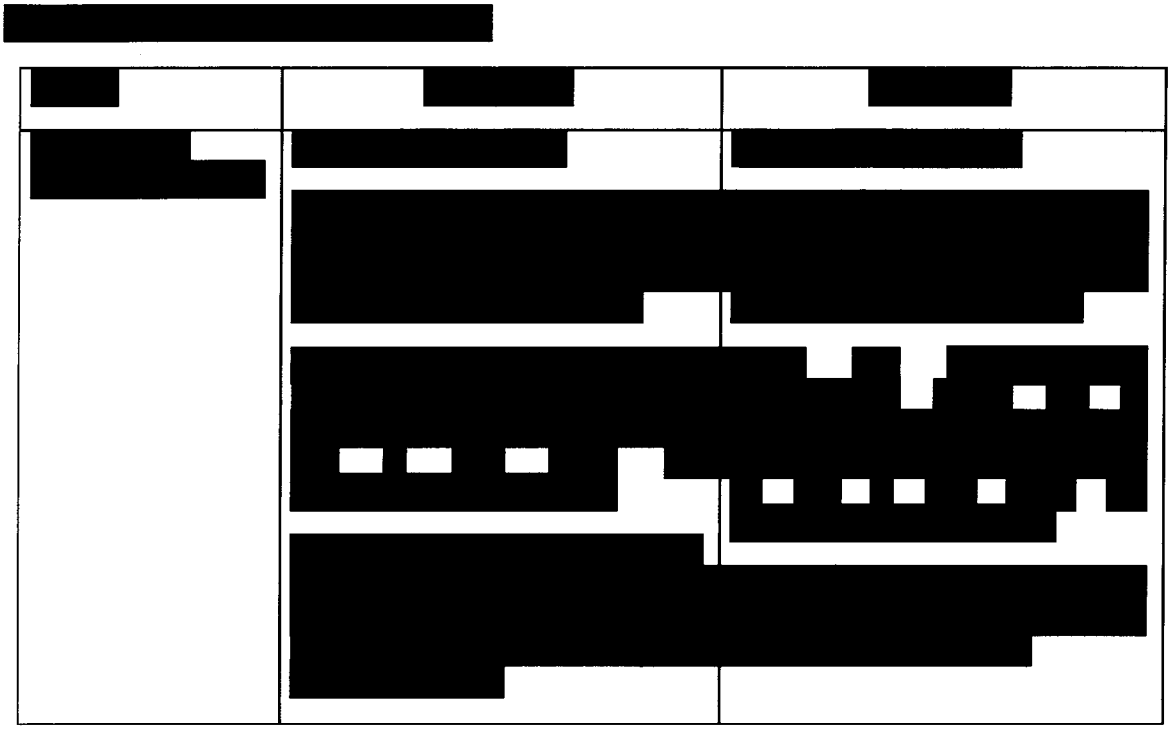

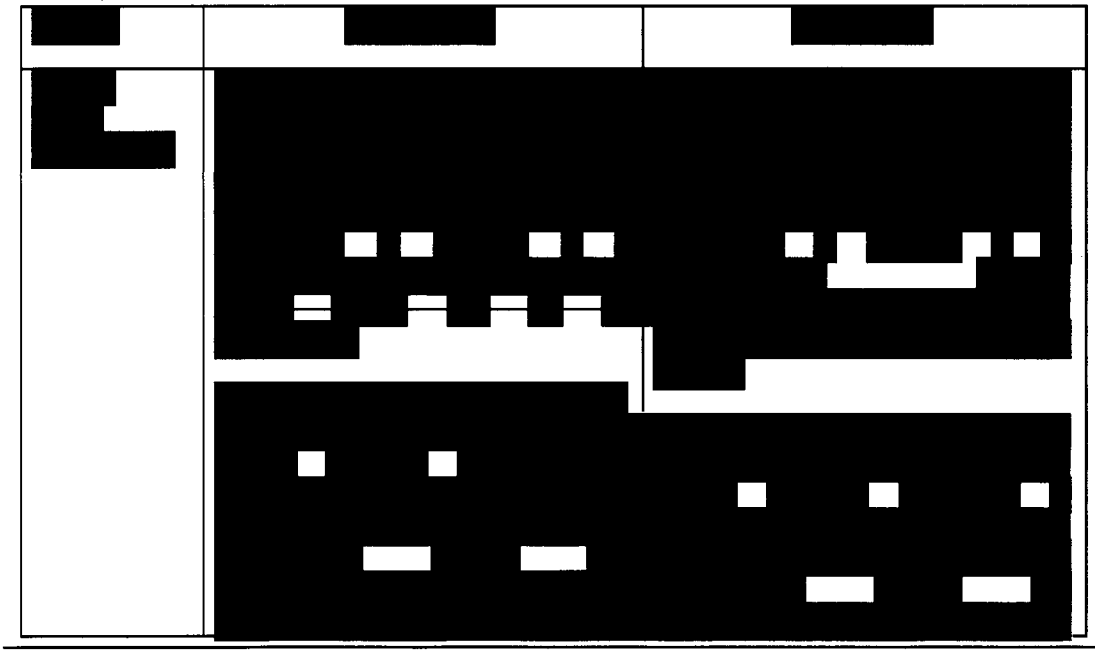

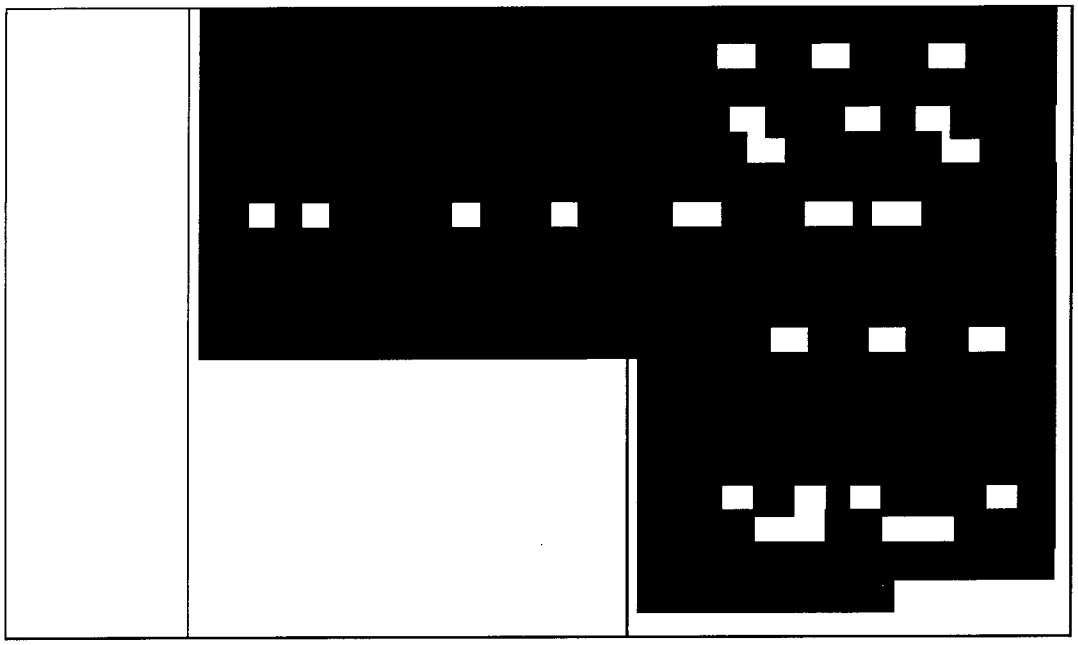

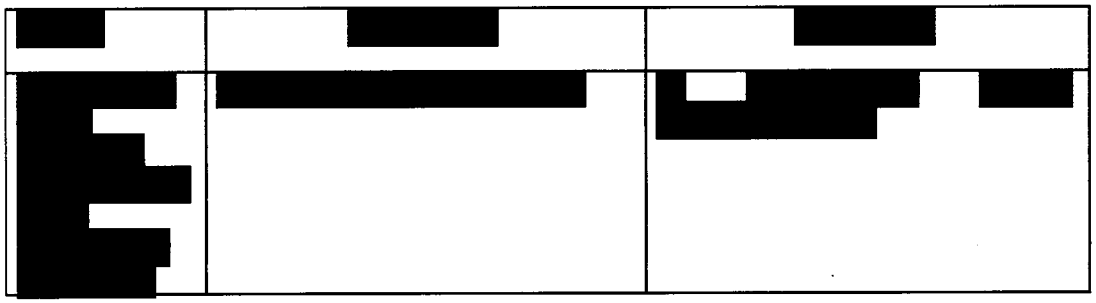

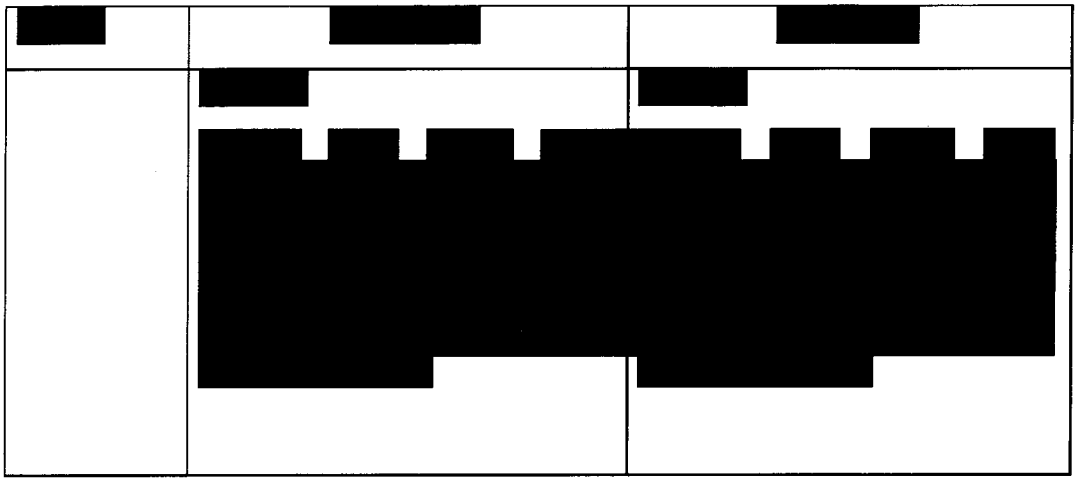

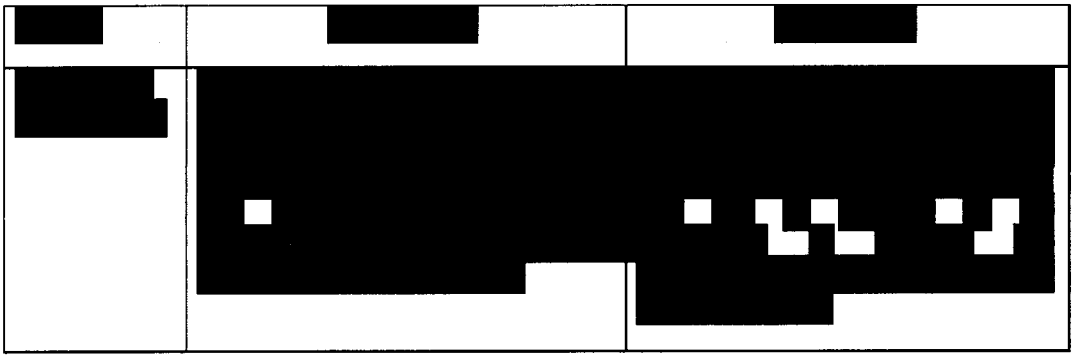

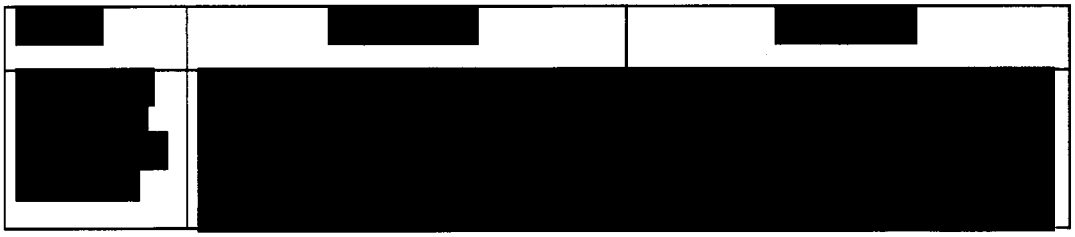

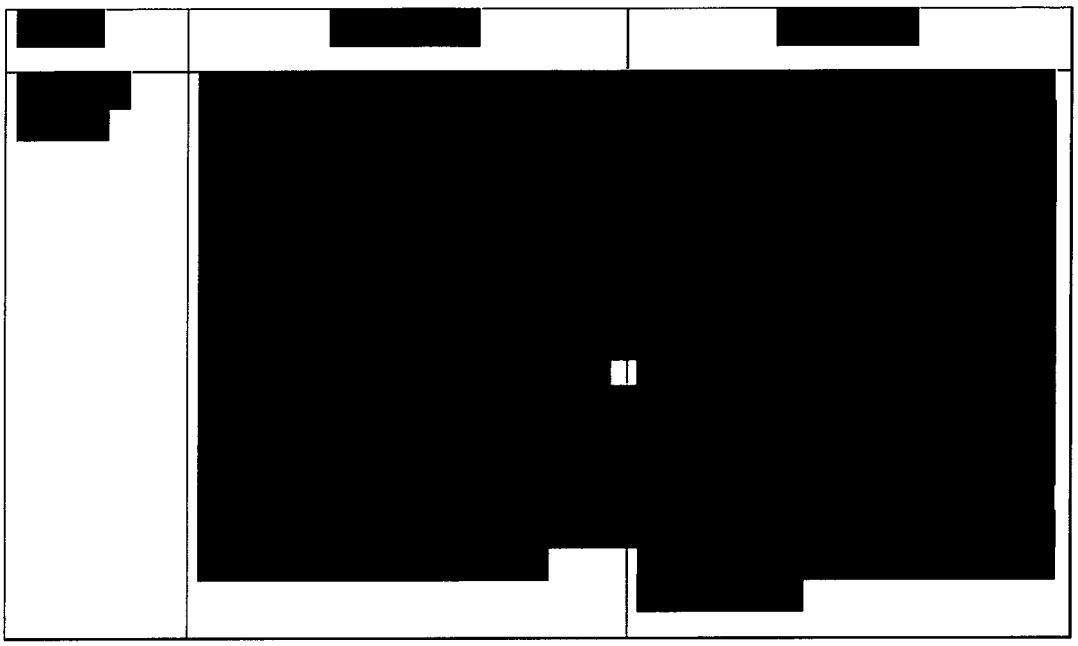

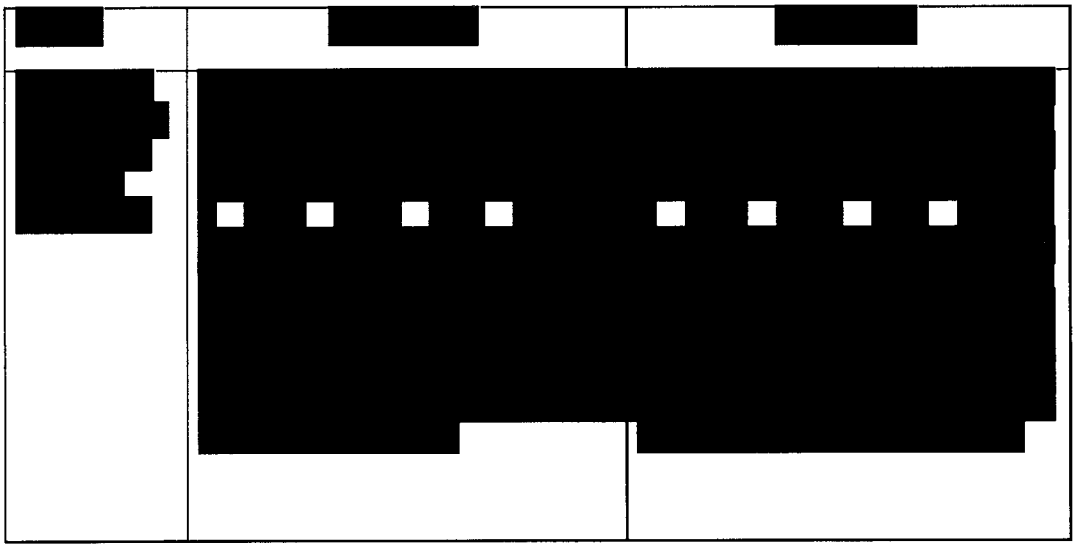

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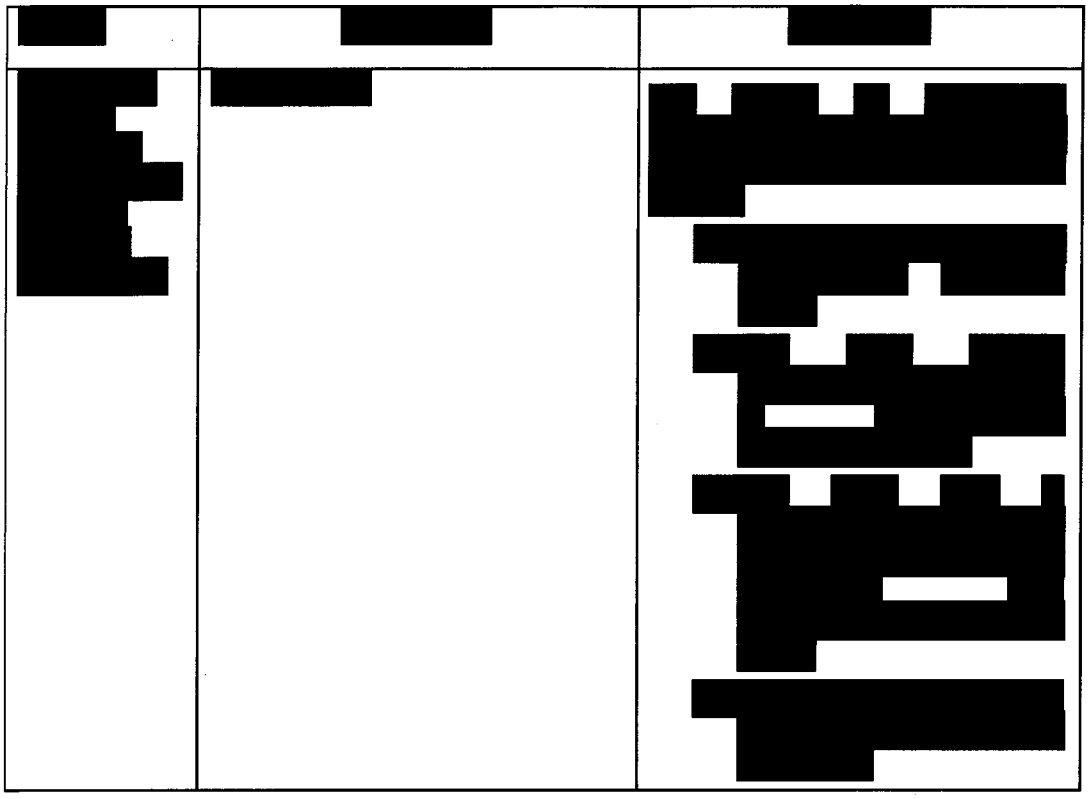

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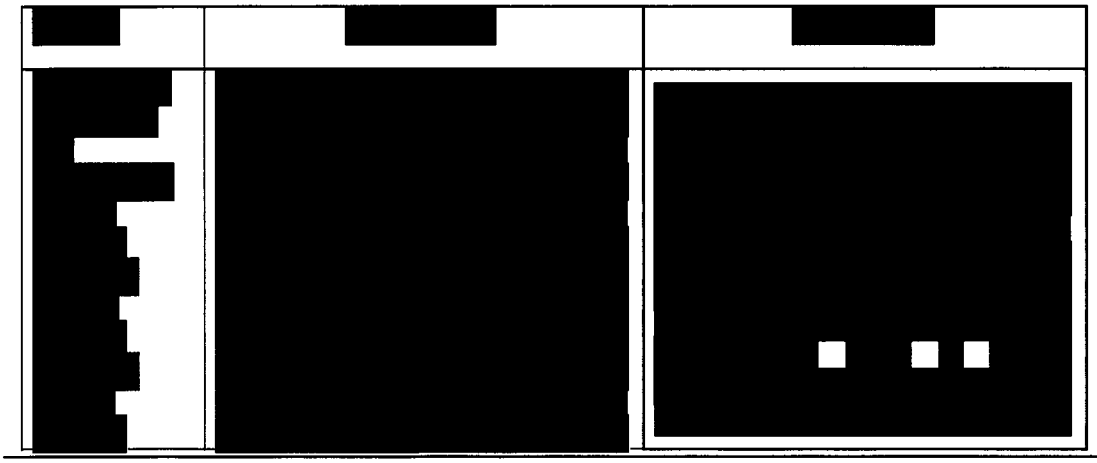

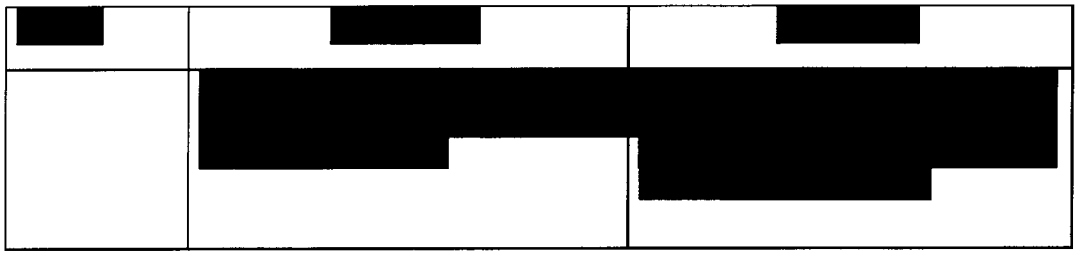

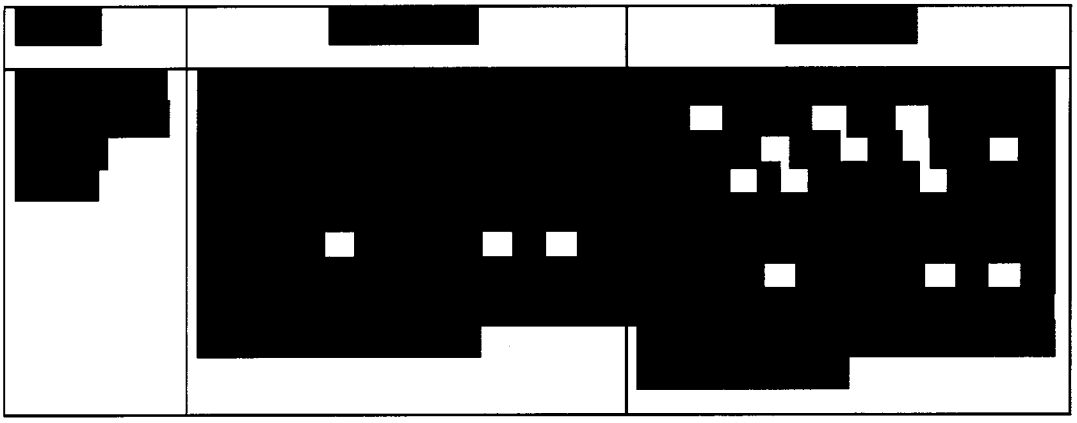

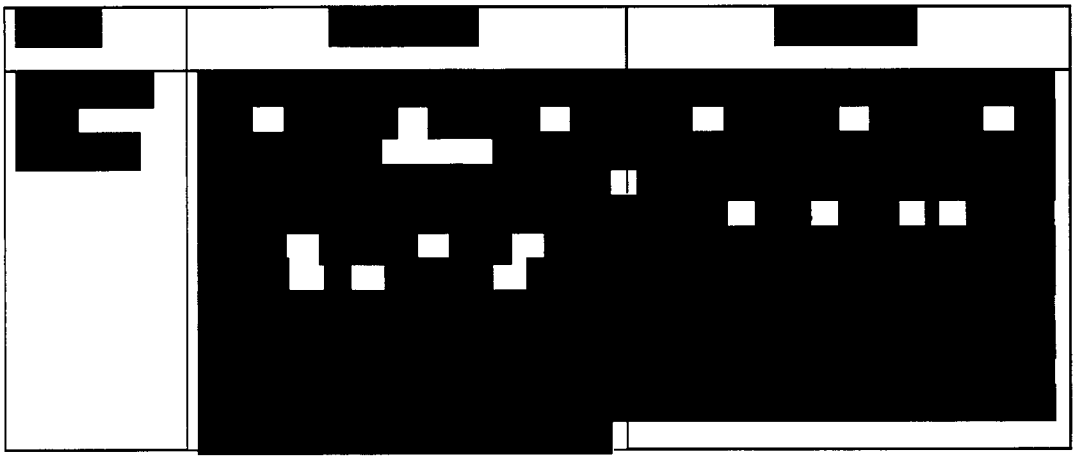

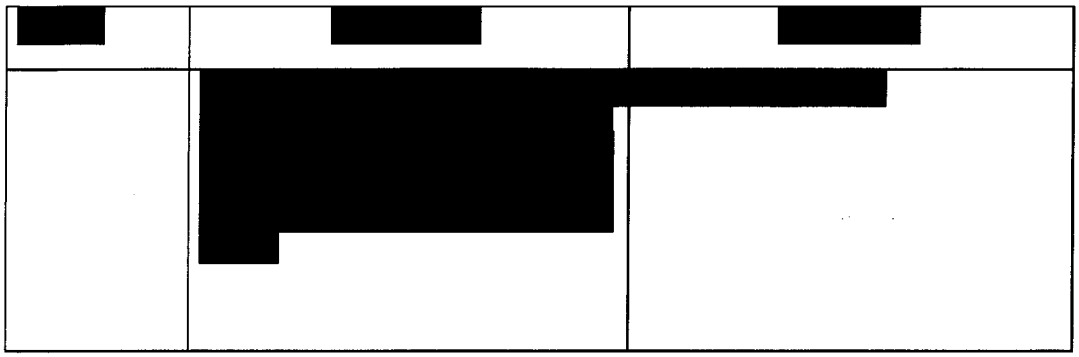

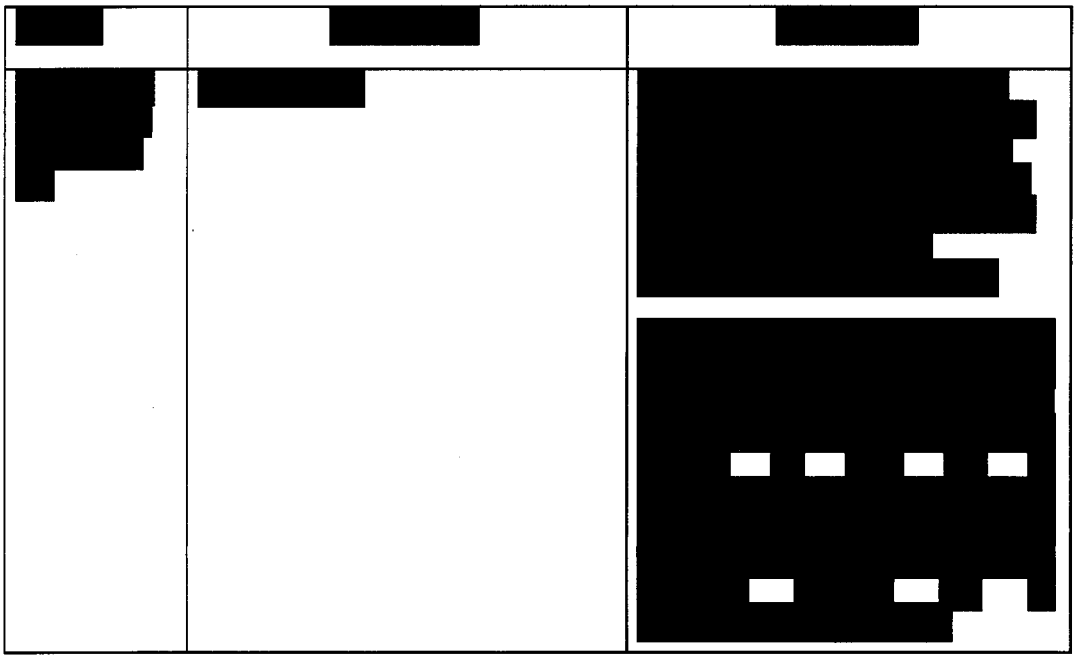

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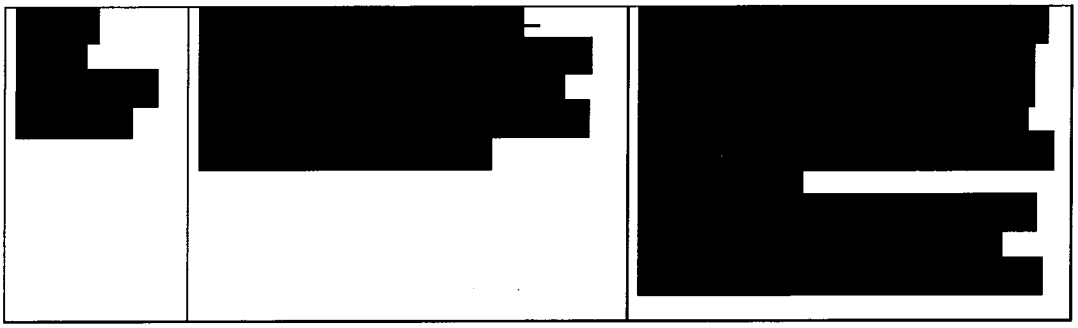

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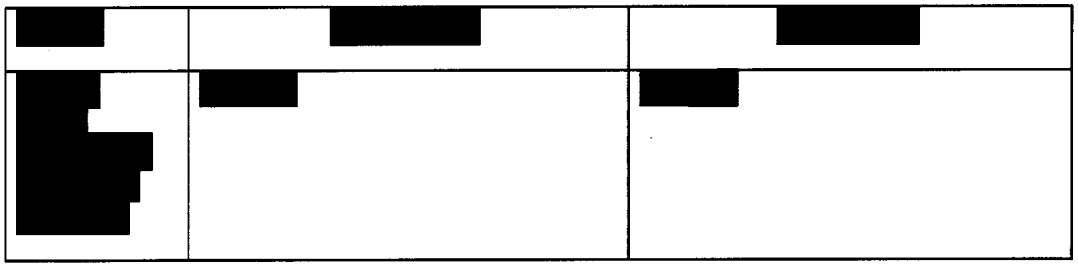

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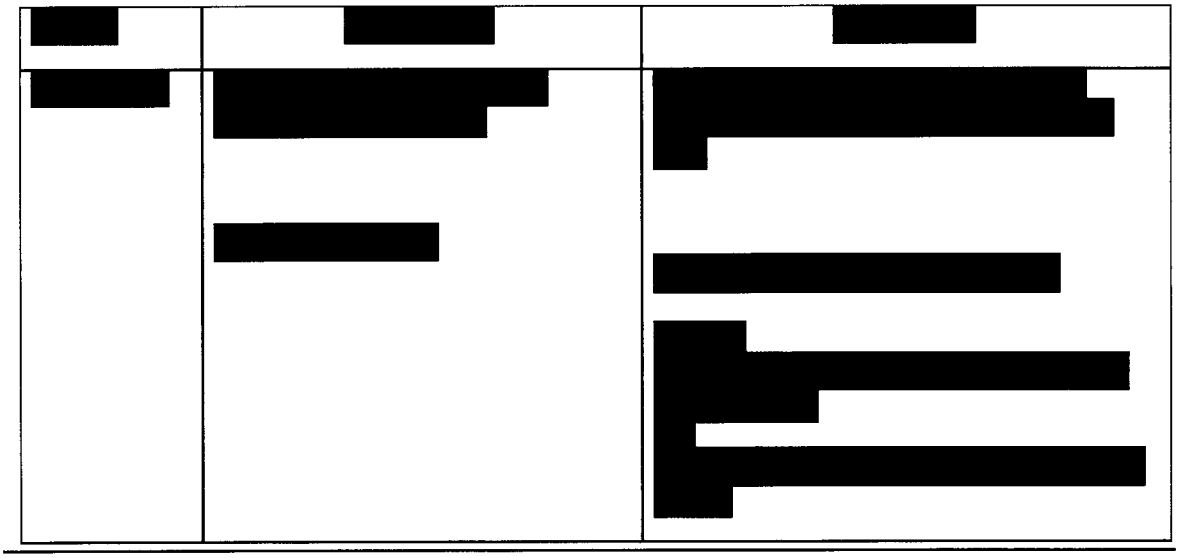

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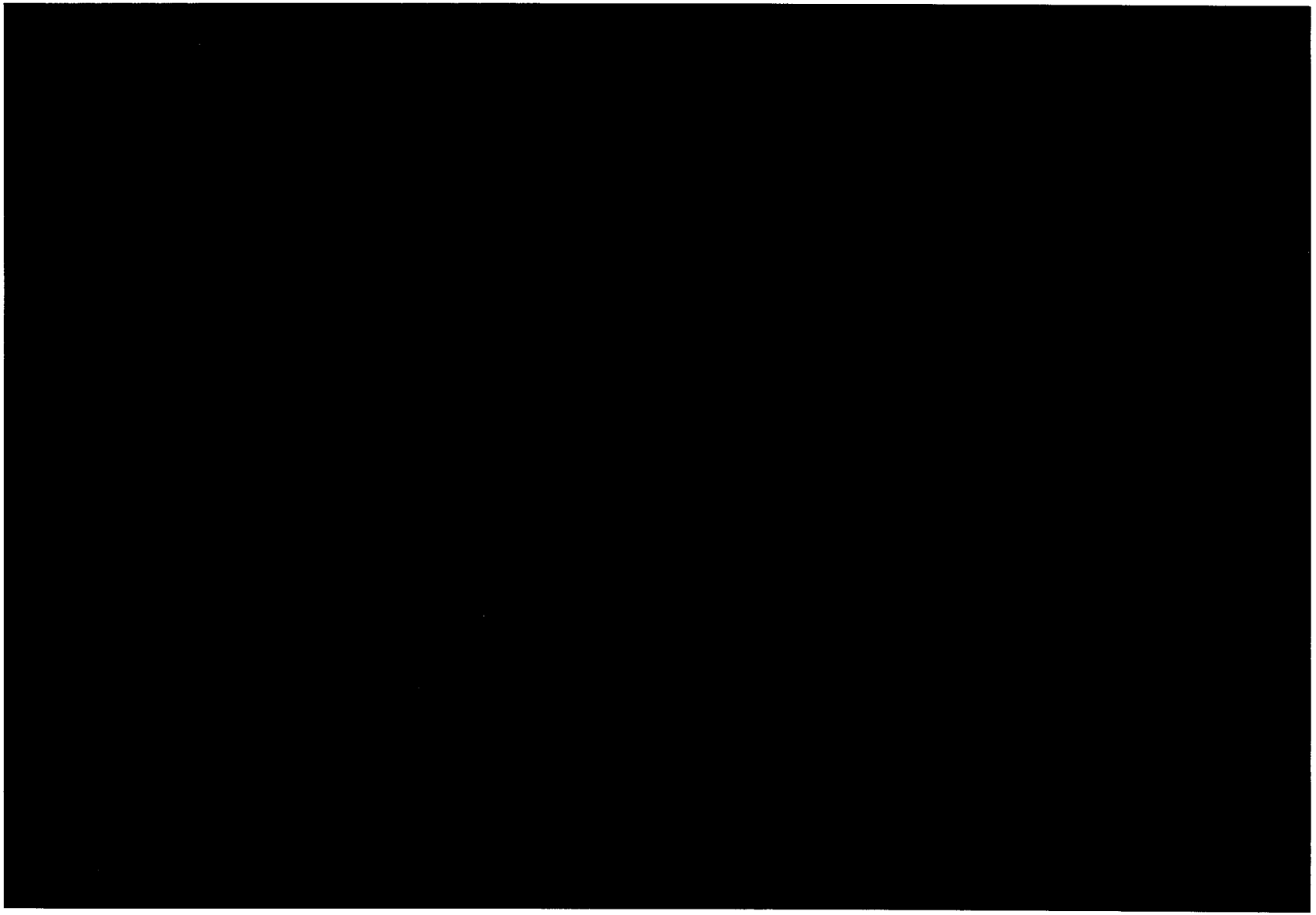

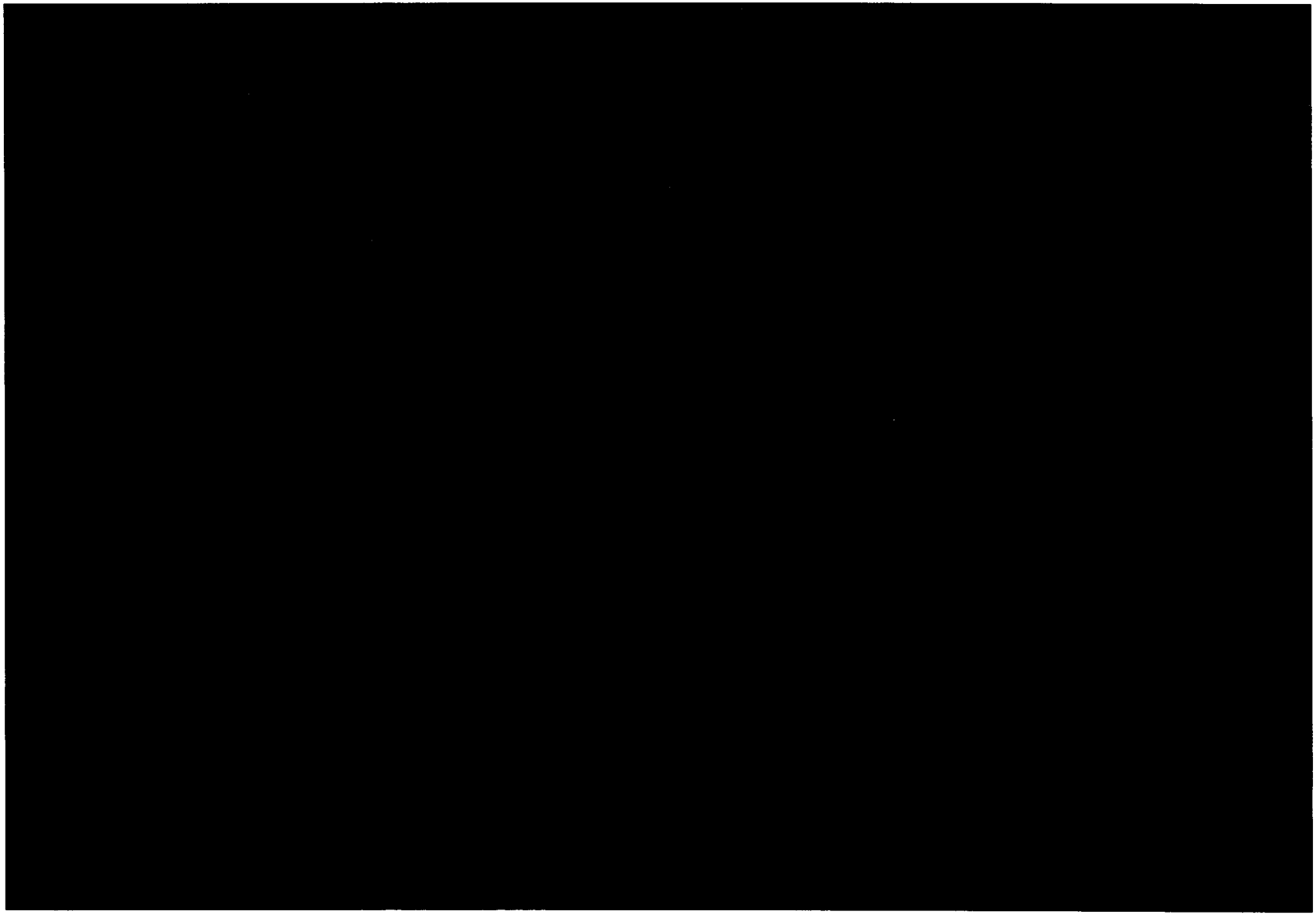

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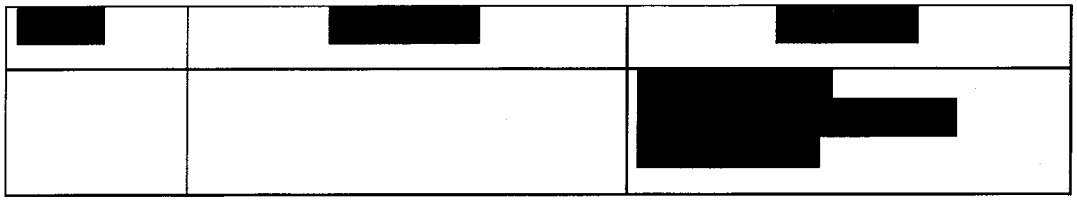

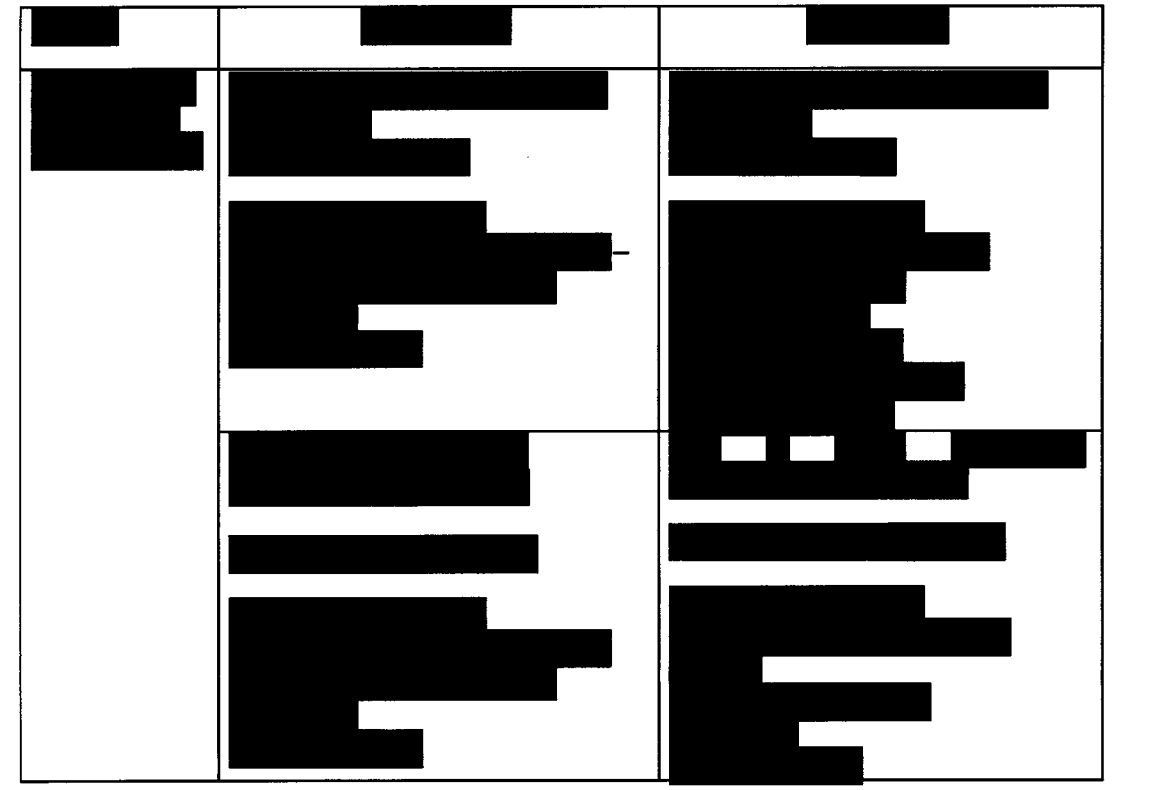

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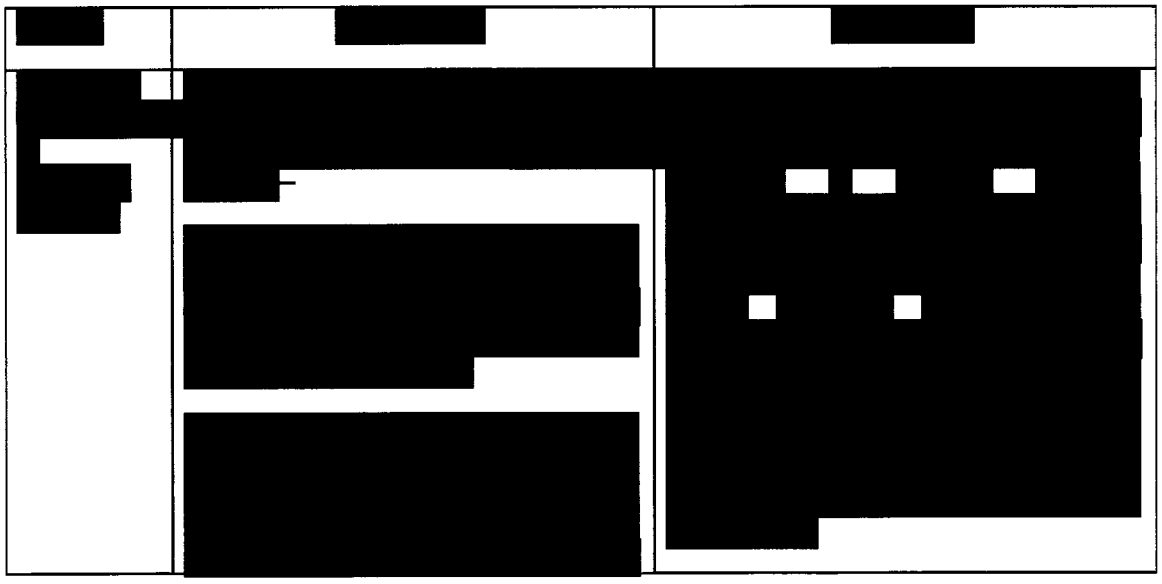

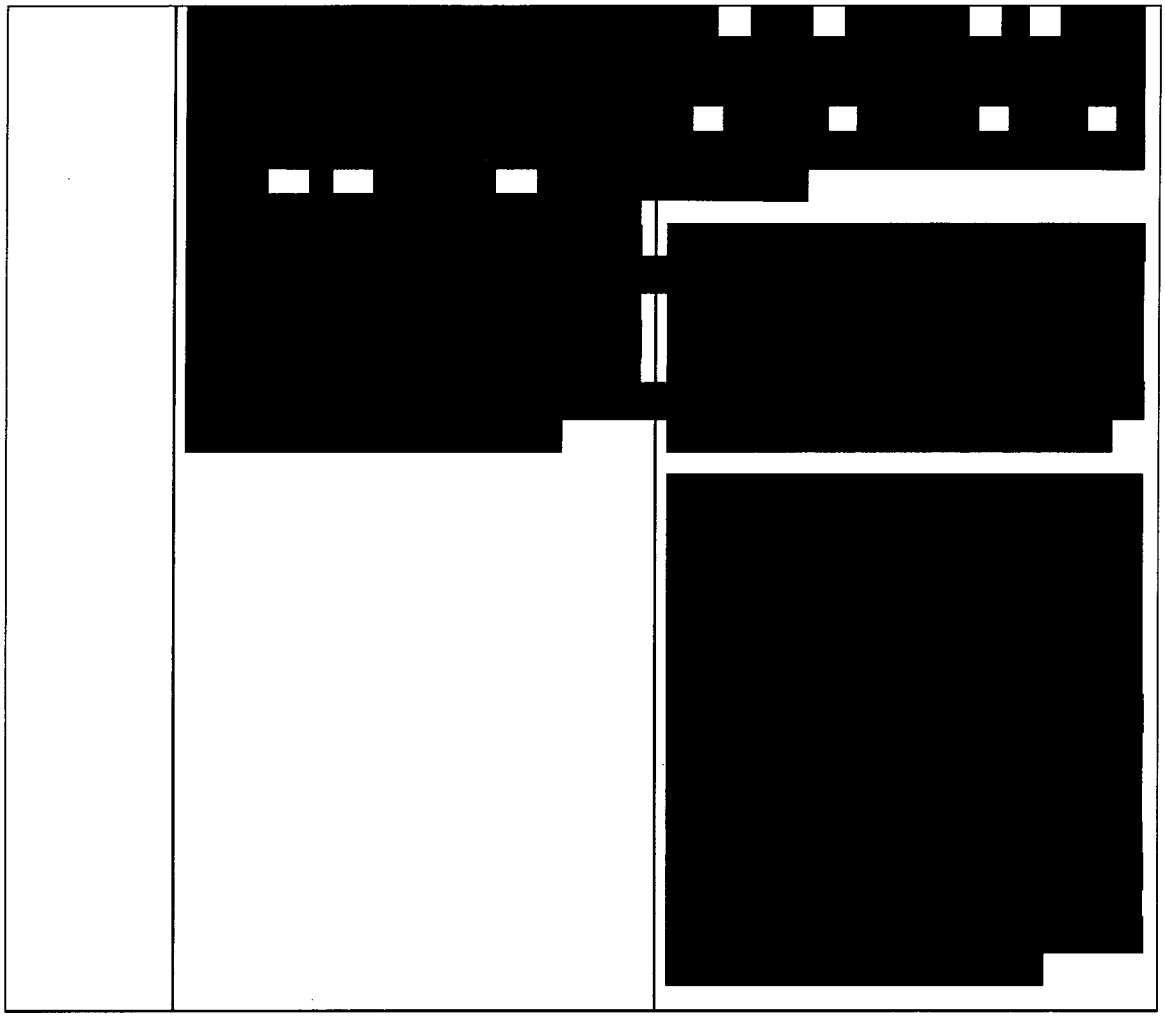

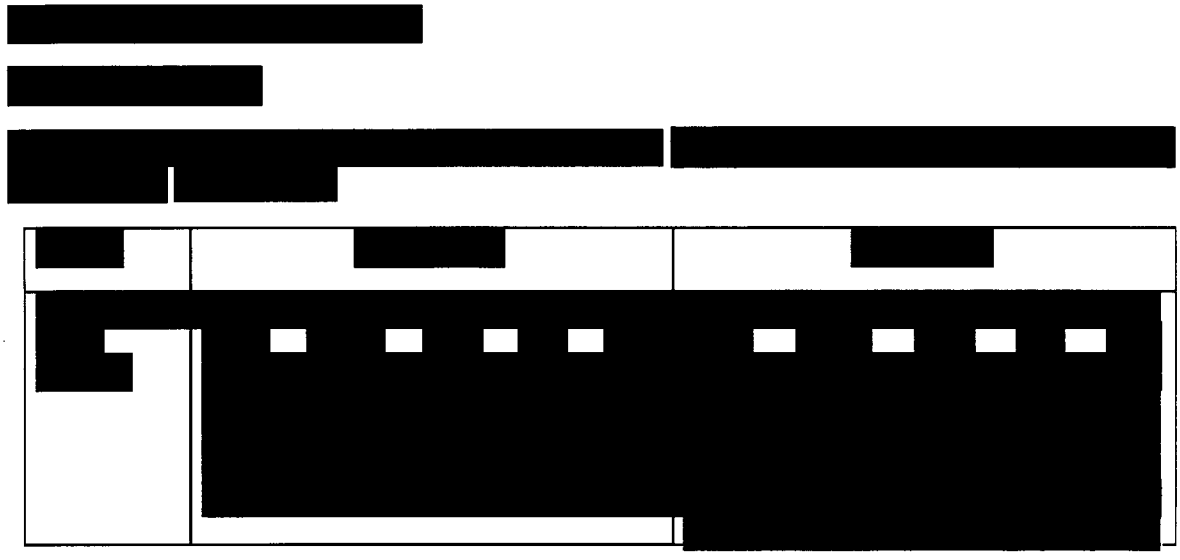

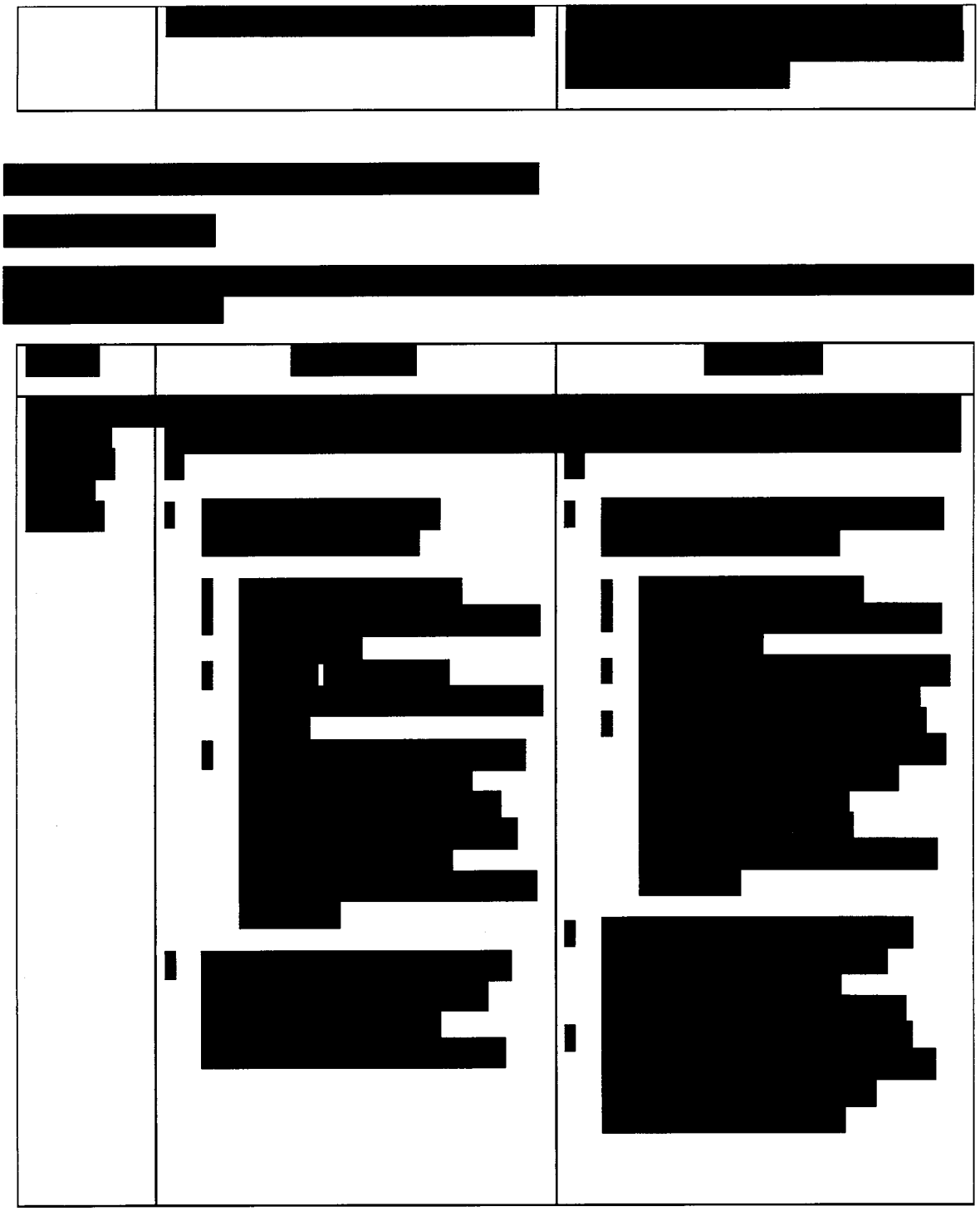

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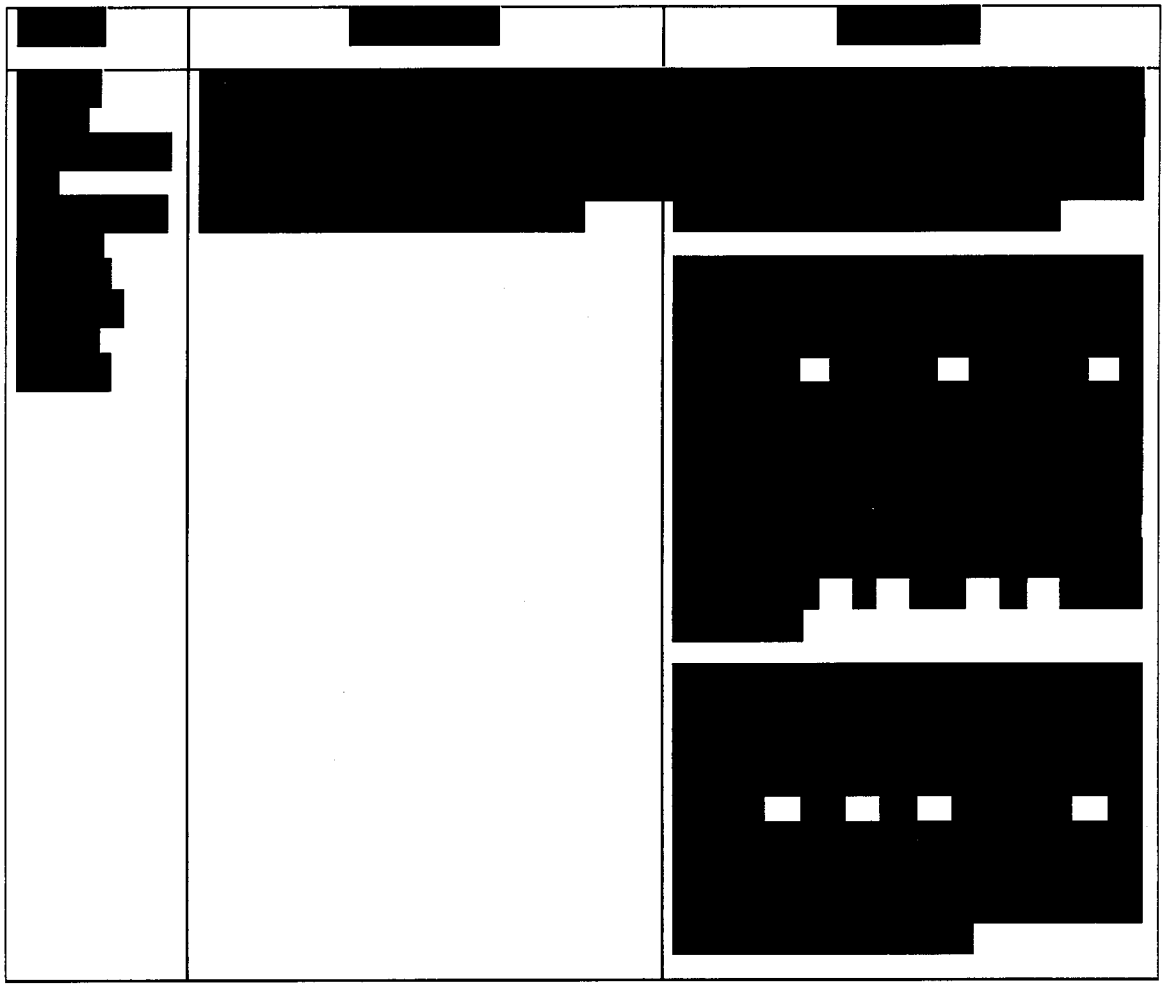

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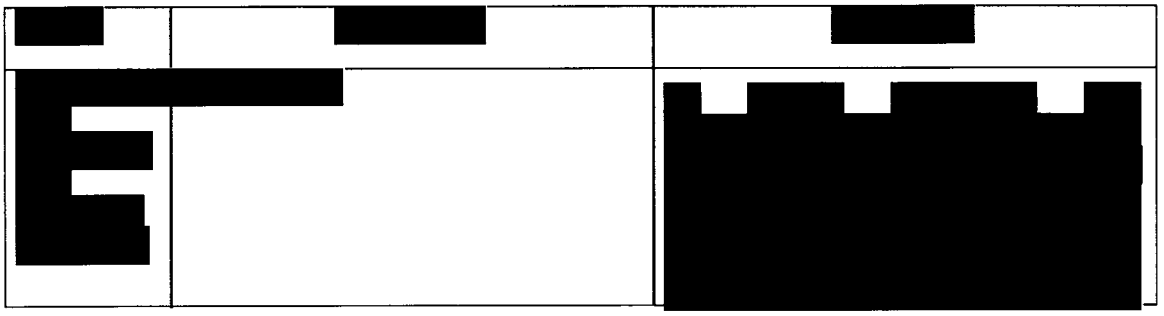

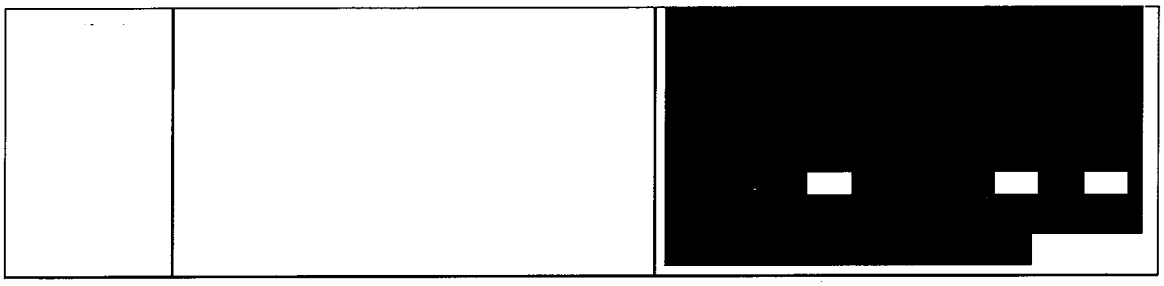

18.11 APPENDIX 11: [redacted]

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