Statistical Analysis Plan (SAP) for NCT Number: NCT02047461

SAP Date: 03 May 2019

Certain information within this protocol has been redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems.
- Other information as needed to protect confidentiality of BridgeBio Pharma, Sentynl Therapeutics, Inc., or their partners, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

A PHASE 2, MULTICENTER, MULTINATIONAL, OPEN LABEL, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ORGN001 (FORMERLY ALXN1101) IN PEDIATRIC PATIENTS WITH MOLYBDENUM COFACTOR DEFICIENCY (MOCD) TYPE A CURRENTLY TREATED WITH RECOMBINANT ESCHERICHIA COLI-DERIVED CYCLIC PYRANOPTERIN MONOPHOSPHATE

Protocol Number: ALXN1101-[redacted]

Name of Test Drug:	ORGN001 (formerly ALXN1101)
Sponsor:	Origin Biosciences [redacted]
Sponsor Medical Officer:	[redacted] Chief Medical Officer
Document Date:	03 May 2019
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SIGNATURE PAGE

Protocol Title: Statistical Analysis Plan of ORGN001 (formerly ALXN1101) for Protocol ALXN1101-[redacted]

Sponsor: Origin Biosciences

Author: [redacted]

Author Signatory:

[redacted]
Biostatistician

Signature: [redacted]

Date: 06MAY2019

Sponsor Approval:

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatories:

[redacted]
Chief Medical Officer

Signature: [redacted]

Date: 5/6/2019

1. TABLE OF CONTENTS AND LIST OF TABLES

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this SAP.

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration-time curve
Bayley-III	Bayley Scales of Infant Development-Third Edition
BMI	Body mass index
BP	Blood pressure
BQL	Below quantification level
CDC	Centers for Disease Control and Prevention
C_{max}	Maximum observed plasma concentration
CSR	Clinical Study Report
CT	Computed tomography
DMC	Data Monitoring Committee
DQ	Developmental quotient
EEG	Electroencephalogram
FAS	Full Analysis Set
GMFCS–E&R	Gross Motor Function Classification System–Expanded and Revised
HR	Heart rate
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MoCD	Molybdenum Cofactor Deficiency Type A
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
PD	Pharmacodynamics
PK	Pharmacokinetics
PI	Principal Investigator
PT	Preferred term
PTAE	Pre-treatment adverse events
rcPMP	Recombinant *Escherichia coli*-derived Cyclic Pyranopterin Monophosphate
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SAS	Statistical Analysis Software
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SRC	Safety Review Committee
[redacted]	[redacted]

Abbreviation or Acronym	Explanation
t½	Terminal half-life
TEAEs	Treatment-emergent adverse events
t_{max}	Time to maximum observed plasma concentration
WHO	World Health Organization
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

3. DESCRIPTION OF THE PROTOCOL

Protocol Number: ALXN1101-MCD-[redacted]

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Title: A Phase 2, Multicenter, Multinational, Open-label, Dose-Escalation Study to Evaluate the Safety Efficacy of ORGN001 (formerly ALXN001) in Pediatric Patients with Molybdenum Cofactor Deficiency (MoCD) Type A Currently Treated with Recombinant *Escherichia coli*-derived Cyclic Pyranopterin Monophosphate (rcPMP).

This Phase 2, multinational, multicenter, open-label, dose-escalation study is designed to evaluate the safety and efficacy of ORGN001 (formerly ALXN1101) administered to infants and children with MoCD Type A currently treated with rcPMP. Eligible subjects will be identified through [redacted] use with rcPMP. This study will include a screening period (Days -21 to Day -1), a 6-month study period that includes escalating doses of ORGN001 after the first 2 months of treatment with ORGN001 (Day 1 [first dose of study drug] to Day 180), and a [redacted] extension period (after Day 180).

Screening evaluations will be performed at any time during the screening period before the first dose of ORGN001. Enrolled subjects will attend at least 2 study visits in order for baseline data to be obtained. During the screening period, subjects will continue to receive daily IV infusions of current rcPMP treatment. During the 6-month initial treatment period, starting on Day 1, subjects will begin IV infusions of ORGN001 at the same dose as their current dose of rcPMP approximately 24 hours after their last treatment with rcPMP. No further treatments with rcPMP will be allowed during the study. Subjects [redacted] will continue to receive daily infusions of ORGN001 at home [redacted] and will attend multiple study visits for safety, efficacy, pharmacodynamic (PD), and pharmacokinetic (PK) assessments through Month 6 of the initial treatment period and [redacted] the extension period. After the first 2 months of treatment with ORGN001, if the subject's clinical, PK, and safety assessments permit (including the absence of signs and symptoms of drug-related toxicity), dosing with ORGN001 will increase every month [redacted] based on the subject's clinical response, safety labs, and when appropriate, exposure data. [redacted]. After the 6-month study period, subjects will enter the [redacted] extension period and continue to receive uninterrupted daily dosing of ORGN001 at their final tolerated dose based on the dose escalation. After dose escalation is complete, the subject can be returned to the prior dose based on the subject's clinical status at the discretion of the treating physician after consultation with the Safety Review Committee (SRC). Subjects who prematurely discontinue from the study will attend a safety follow-up visit [redacted] and return to the care of their treating physician.

The study objectives are as follows:

Primary Objective:

The primary objective of this clinical study is to evaluate the safety of ORGN001.

Secondary Objectives:

The secondary objectives of this clinical study are to:

- Characterize the PK of increasing doses of ORGN001
- Evaluate the effect of ORGN001 on urine and blood [redacted] levels
- Evaluate the effect of ORGN001 on neurologic, motor, and cognitive functions
- Evaluate the effect of ORGN001 on central nervous system structure
- Evaluate the long-term safety of ORGN001

[redacted]

Additional information about the study can be found in the protocol.

Results from this study will be summarized in a clinical study report (CSR).

3.1. Changes from Analyses Specified in the Protocol

Not applicable.

[redacted]

4. DEFINITIONS

4.1. Efficacy

There is no pre-specified primary efficacy endpoint in this study. The secondary efficacy endpoints at all key study timepoints include:

- Change from baseline in urine and blood [redacted] levels
- Change from baseline in clinical findings from neurologic examination
- Change from baseline in age-appropriate motor and cognitive assessments (Bayley Scales of Infant Development-Third Edition [Bayley-III], The expanded and revised Gross Motor Function Classification System [GMFCS-E&R], Wechsler Preschool and Primary Scale of Intelligence [WPPSI])
- Change from baseline in seizure frequency
- Change from baseline in neuroimaging
- Changes in growth parameters (body weight, body length, head circumference)
- Change from baseline in feeding patterns

[redacted]

4.1.1. Neurologic Examinations

Neurologic examination includes, but is not limited to, assessment of mental status, cranial nerves, motor strength and tone, sensory examination, deep tendon reflexes and primitive reflexes, if present.

4.1.2. Bayley Scales of Infant and Toddler Development-Third Edition

The Bayley-III will be administered to assess changes in gross motor, language, fine motor, and cognitive development. The Bayley-III will be administered to children under 3 years of age and to subjects with severe developmental delay for whom the WPPSI is not an appropriate assessment.

The Bayley-III is a standardized and norm-referenced instrument that assesses the developmental functioning of infants and children 1 month to 42 months of age. The Bayley-III consists of 3 administered scales: the Cognitive Scale, the Language Scale (administered only to native English speakers in English-speaking countries and includes the Receptive Communication and Expressive Communication subtests), and the Motor Scale (including the Fine Motor and Gross Motor subtests).

From the raw scores, scaled scores can be calculated for the cognitive scale and the 2 combined language scales and motor scales.

These scores can then be used to determine composite scores, percentile ranks and confidence intervals, development age equivalents, and growth scores.

Scaled scores range from 1 to 19, with a mean of 10 and a standard deviation (SD) of 3.The composite score is scaled to a metric with a mean of 100, a SD of 15, and range from 40 to 160.

Percentile ranks indicates percentage of individuals in standardization sample, at a given age, who obtained scores less than or equal to a given scaled score or composite score. Percentile ranks range from 1 to 99, with 50 as the mean and median.

Developmental age equivalents represent the average age in months at which a given total raw score is typical.

The developmental age equivalent raw score can be used to calculate the developmental quotient (DQ). The DQ is the age equivalent score divided by chronological age.

- DQ = age equivalent scores/chronological age × 100
    - Example: $\frac{12\ month\ developmental\ age\ equivalent\ score}{24\ months\ chronological\ age} \times 100\ = 50\ DQ$

Raw scores are also mapped into growth scores, with a mean of 500 and a SD of 100 for each subtest. Growth scores provide an equal-interval scale by which progress can be measured over time.

4.1.3. The Gross Motor Function Classification System

The GMFCS–E&R is a 5-level classification system that describes the gross motor function of children and youth (up to 18 years of age) on the basis of their self-initiated movement with particular emphasis on sitting, walking, and wheeled mobility for children with impaired motor skills.

Distinctions between levels are based on functional abilities, the need for assistive technology, including hand-held mobility devices (walkers, crutches, or canes) or wheeled mobility, and to a much lesser extent, quality of movement.

Children who have motor functions similar to those classified in “Level I” can generally walk without restrictions but tend to be limited in some of the more advanced motor skills. Children whose motor function has been classified at “Level V” are generally very limited in their ability to move themselves around even with the use of assistive technology.

The Investigator or designee will assess the subject according to the levels of the GMFCS–E&R. GMFCS-E&R will be assessed [redacted].

4.1.4. Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition

The WPPSI is an intelligence measure designed for children ages 2 years, 6 months to 7 years, 7 months. The WPPSI consists of 14 subtests from which the composite scores are derived. For subjects with severe developmental delay, the WPPSI may not be an appropriate assessment, and therefore, the Bayley-III may be administered instead. WPPSI assessments will be performed following the GMFCS-E&R assessment schedule where WPSSI is more appropriate than Bayley-III.

Most subjects completed WPPSI 4th edition, however, one subject followed the 3rd edition and was not included in the study database and listed as a protocol deviation.

4.1.5. Seizure Diary

At screening, the subject's parent or legal guardian will be asked to recall the frequency of seizures over the prior month and the subject's history of seizure medication including the start and stop dates, dose, and frequency of each seizure medication. If the subject does have seizures, the subject's parent or legal guardian will be given a diary to be used to record data regarding the frequency of seizures and any changes in seizure medication for the entire duration of the study.

4.1.6. Neuroimaging

Magnetic resonance imaging (MRI) scans are the preferred imaging modality and should be performed [redacted] if the subject's clinical condition allows. [redacted] A previous MRI scan may be provided in lieu of a scan during the screening period if the previous scan was performed within 6 months prior to enrollment and the subject has remained stable; [redacted].

If, in the opinion of the Principal Investigator (PI), an MRI is not possible due to the subject's clinical condition, a computed tomography (CT) scan without contrast should be performed.

4.1.7. Growth Parameters

Growth parameters (body weight [kg] and length [cm] and head circumference) will be measured [redacted].

World Health Organization (WHO) growth charts only provide information on children up to 5 years of age.[1] Applicable Centers for Disease Control and Prevention (CDC) growth charts will be used for children older than 5 years.[2]

4.1.8. Feeding Pattern Assessment

The feeding pattern assessment will be performed to record if a subject is able to feed orally or through a nasogastric or gastronomy feeding tube and any changes in the feeding pattern.

4.1.9. Pharmacodynamics

Blood and urine samples will be evaluated for [redacted] of the MoCD pathway, [redacted]

[1] Additional WHO growth chart information and methodology can be found at http://www.who.int/childgrowth/publications/technical_report_2/en/index.html.

[2] Additional CDC growth chart information and methodology can be found at https://www.cdc.gov/growthcharts/clinical_charts.htm.

[redacted]

Pharmacodynamic sampling will be measured [redacted].

4.2. Pharmacokinetic Assessments

Pharmacokinetic parameters of ORGN001 will include, but not be limited to, maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve (AUC) and if possible, terminal half-life ($t_{½}$), and dose linearity.

4.3. Safety

The safety of ORGN001 (formerly ALXN1101) will be assessed based on:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of clinical laboratory abnormalities
- Change from baseline in clinical laboratory assessments
- Change from baseline in clinical findings from physical examination
- Change from baseline in vital sign measurements
- Change from baseline in electroencephalogram (EEG) results

In order to monitor subject safety, data will be reviewed daily by the PI or designee during the first 2 weeks following initiation of ORGN001. [redacted] The SRC [redacted] will review all available clinical data [redacted] prior to each subject's scheduled dose escalations in conjunction with the data monitoring committee (DMC) [redacted] and at any other time during the study as requested by the PI or Sponsor.

Based on the review of the available data, [redacted] the SRC, in consultation with the DMC, may recommend stopping, increasing, decreasing, or maintaining (current dose) the dose of ORGN001.

In addition to the scheduled dose escalations, the PI may also convene the SRC for unscheduled dose adjustments based on drug-related AEs and changes in clinical parameters. The SRC chair will also convene the DMC if a dose escalation is being considered or will notify the DMC if the dose is decreased. Blood and urine samples will be collected for PD and PK assessments on the first day the adjusted dose is administered. PD and safety laboratory assessments will be repeated [redacted] at the [redacted] follow-up visit.

4.3.1. Adverse Events

An AE is defined as any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product or procedure, whether or not considered related to the medicinal product or procedure that occurs during the course of the clinical study. Adverse events are defined in Protocol Section 15.5.

4.3.2. Vital Signs

Vital signs will be measured [redacted] and will include assessments of heart rate (HR), respiratory rate (RR), BP, and temperature.

4.3.3. Physical Examination

A complete physical examination will be performed [redacted].

Ascites and hepatic encephalopathy scores will be recorded [redacted] and the Child-Pugh score will be calculated.

4.3.4. Laboratory Assessments

Blood samples will be collected for analysis of hematology (complete blood count, including platelet count, red blood cell (RBC) count, white blood cell (WBC) count and automated differential, hemoglobin, hematocrit, and RBC indices); serum chemistry (sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, serum osmolality and total serum albumin); coagulation (prothrombin time and international normalized ratio). Urine samples will be collected for urinalysis (specific gravity, pH, glucose, protein, blood and ketones, urine protein to creatinine ratio). Clinical laboratory evaluations will be performed [redacted] and will be measured [redacted]

4.3.5. Electroencephalogram

Standard EEGs [redacted] will be performed [redacted]. However, additional EEGs may be performed at the discretion of the Investigator. Results from a previous EEG may be provided in lieu of performing an EEG during the screening period if the previous assessment was performed within 6 months prior to enrollment and the subject's seizure frequency has not changed significantly since that study.

5. DATA SETS ANALYZED (STUDY POPULATIONS)

Efficacy analyses will be performed on the Full Analysis Set (FAS). Due to the small number of subjects, a Per-Protocol population will not be utilized for this study. Subject disposition will include all subjects.

The FAS will include all subjects who were MoCD Type A and received at least 1 dose of ORGN001.

Safety analysis set will be performed on the Safety Analysis Set, defined as all subjects who received at least 1 dose of ORGN001.

6. STATISTICAL ANALYSIS

No formal statistical hypothesis testing will be performed. Efficacy data will be analyzed using descriptive statistics. All data collected during the study will be presented in summary tables, figures, or by-subject data listings. Continuous variables will be summarized using mean, SD, median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency distributions. Graphical displays will be produced as appropriate.

6.1. Study Subjects

6.1.1. Disposition of Subjects

A summary of subject disposition for all treated subjects will be presented and will include a summary of the number of subjects enrolled and percentage of subjects who completed the study through Month 6 or discontinued/withdrew from the study prior to Month 6, along with reason for discontinuation/withdrawal.

A summary of the number and percentage of subjects who consented to the extension study, the number and percentage of subjects who completed [redacted] or discontinued/withdrew from the study, along with reason for discontinuation/ withdrawal.

The number and percentage of subjects in each analysis set will be tabulated.

By-subject data listings with disposition will be provided as well as a listing of subjects who did not meet the inclusion/met the exclusion criteria.

6.1.2. Protocol Deviations

All protocol deviations will be listed for all subjects.

6.1.3. Demographics, Prenatal and Antenatal History, and Disease Characteristics

All demographic information, family history, disease characteristics, and medical history will be summarized for the FAS. By-subject data listings of all demographic, family history, disease characteristics and medical history information will be produced for all subjects.

6.1.3.1. Demographics

The following demographic variables will be summarized:

- Gender
- Race
- Ethnicity
- Age (months) at first ORGN001 infusion

6.1.3.2. Disease Characteristics

The following disease characteristics will be summarized:

- Age at onset of first MoCD signs/symptoms (days)
- Age at genetic diagnosis (days)
- MoCD Presenting signs and symptoms

6.1.3.3. MoCD Family History

The following family history, if available will be summarized:

- Parental consanguinity
- Number of living or deceased siblings with suspected or confirmed MoCD type A
- Parental genotype

6.1.3.4. Prenatal and Antenatal History

The following prenatal and antenatal history, if available will be summarized:

- Gestational age (weeks)
- Any complications during pregnancy
- Delivery type
- Placental condition
- History of in utero seizures
- Apgar scores

6.1.4. Medical/Surgical History

Medical/surgical history information will be summarized using the number (%) of subjects who have a specific medical history.

Previous vision and hearing assessments will be displayed in by-subject data listings.

6.1.5. Prior and Concomitant Medications and Seizure Medications/Therapies

Prior and concomitant medications will be summarized using the Safety Set. Prior medications are defined as medications taken prior to the first study infusion. Concomitant medications are defined as medications received by the subjects on/after first study infusion.

Medications will be coded using the WHO Drug Dictionary (September 2018). Medication summaries, i.e., number (%) of subjects using prior and concomitant medications as well as seizure medications, will be presented by WHO Anatomical Therapeutic Chemical (ATC) and by generic name.

A listing of prior and concomitant medications will be produced. A separate listing of antiseizure prior and concomitant medications will be produced, including the start and stop dates and total number of antiseizure medications per subject.

6.2. Efficacy Analyses

All efficacy analyses will be conducted on the FAS. When applicable, summaries will be presented by study visit. All endpoints will be presented in listings.

6.2.1. Primary Analysis

There is no pre-specified primary efficacy endpoint in this study.

6.2.1.1. Handling of Dropouts or Missing Data

In general, missing or invalid observations will not be replaced or imputed. The following imputation rules apply to partially missing start and end dates:

- Any imputed dates need to be logical.
- Imputation of start date:
  - Missing day and month:
    - If partial date year < year of the first dose date, then impute December 31.
    - If partial date year = year of the first dose date, then impute to first dose date.
    - If partial date year > year of the first dose date, then impute to January 1.
  - Missing day only:
    - If the partial month and year < month and year of the first dose date, then impute last day of the start date month.
    - If the partial month and year = month and year of the first dose date, then impute the day of first dose.
    - If the partial month and year > month and year of the first dose date, then impute first day of the start date month.
  - If the imputed start date is after the stop date, the start date will be imputed to be equal to the stop date.
- Imputation of end date:
  - Missing day and month:
    - If partial date year < year of the last dose date, then impute December 31.
    - If partial date year = year of the last dose date, then impute to last dose date.
    - If partial date year > year of the last dose date, then impute to January 1.
  - If partial date has missing day only:
    - If the partial month and year < month and year of the last dose date, then impute last day of the start date month.
    - If the partial month and year = month and year of the last dose date, then impute the day of last dose.

- If the partial month and year > month and year of the last dose date, then impute first day of the start date month.

- If the imputed stop date is before the start date, the stop date will be imputed to be equal to the start date.

For subjects continuing treatment at time of analysis, the data cut-off will be used.

6.2.1.1.1. Missing Data: Efficacy and Developmental Assessments

Missing data for efficacy and developmental assessments will be handled as specified in the instructions for each instrument. [redacted]

6.2.1.1.2. Missing Data: Medical/Surgical History and Prior Medications (Including Antiseizure Medication) Date Imputation

For start date partial (month and year are available), then impute day as "01."

For start date partial (year only is available), then impute day and month as "01JAN."

For end date partial (month and year are available), then impute day as last day of the month.

For end date partial (year only is available), then impute day and month as the last day of the year.

No overlap between medical history/prior medications and study drug will be allowed. The end date of medical history/prior medications will be imputed to the first dose date of study drug – 1 if there is overlap due to imputation of partial dates.

6.2.1.1.3. Missing Data: Concomitant Medications Date Imputation

Start dates of medications that have a missing day will be considered as prior medication if the month and year are before the month and year of the first dose of study drug, unless the stop date of the medication is after the date of the first dose of study drug, then it is considered both a prior and concomitant medication.

If a medication has a missing month, the medication will be considered to be prior medication unless by reference to the stop date that it is concomitant, then it will be both a prior medication and concomitant medication.

If a medication has a completely missing start date and either the stop date is after the first dose of study medication or the stop date is completely missing, the medication will be considered both a prior and concomitant medication. If the medication has a completely missing start date and the stop date is prior to the first dose of study medication, the medication will be considered to be a prior medication.

6.2.1.1.4. Missing Data: Adverse Event Date Imputation

Follow the general rules outlines in Section 6.2.1.1.

6.2.1.2. Subgroup Analysis

No subgroup analyses are planned due to the expected small sample size.

6.2.1.3. Multicenter Studies

This is a multicenter study; however, the expected sample size is not sufficient to perform any meaningful efficacy summaries by center.

6.2.1.4. Hypothesis Testing and Significance Level

No statistical hypothesis testing will be performed. Efficacy data will be analyzed using descriptive statistics.

6.2.1.5. Sensitivity Analyses

No sensitivity analyses will be performed.

6.2.2. Secondary Analyses

6.2.2.1. Neurologic Examination

A summary of the frequency and percentage of subjects with neurologic examination findings [redacted] will be presented by visit.

6.2.2.2. Developmental Assessments

Changes from baseline to post-treatment assessments in the Bayley-III will be summarized using descriptive statistics. The raw, scaled, age-equivalent, and DQ scores will be summarized for the Cognitive Scale and Fine Motor and Gross Motor subtests. Additionally, the composite score for cognitive and motor scales will be summarized for subjects up to 42 months in age or subjects with severe disability and the Bayley assessment is more appropriate. Language Scale results will be displayed in a by-subject data listing.

A summary of the frequency and percentage of subjects at each level of the 5-level classification system of the GMFCS–E&R will be presented by visit.

Changes from baseline to post-treatment assessments in the WPPSI will be summarized using descriptive statistics. A by-subject data listing of all WPPSI IV assessments will be produced.

6.2.2.3. Seizures

The number and frequency of subjects with seizures prior to treatment with ORGN001 and over each 6-month period on study will be summarized. In addition, the number of subjects with medication changes due to seizures will be summarized. A by-subject data listing of seizure data and changes in medications since the last visit, along with reasons for the change will be produced.

Seizures collected as AEs will be summarized as AEs.

6.2.2.4. Neuroimaging

Shifts from baseline [redacted] in findings from MRI or CT scan, if MRI/CT scan is contraindicated, will be presented for the different visits. A summary of the abnormal findings [redacted] will be provided, as will the number and frequency of subjects with changes since previous neuroimaging.

[redacted]

6.2.2.5. Feeding Patterns

The number and frequency of subjects able to feed orally will be summarized by visit. For subjects that are not feeding orally, the feeding method will be summarized by visit. Results will also be included in by-subject listings.

6.2.2.6. Growth Parameters

Body weight, length, head circumference, and body mass index (BMI) will be analyzed by converting each parameter to age-adjusted z-scores and age percentiles and descriptive statistics will be presented for each parameter, as well as, for the change from baseline. The 5th, 25th, 50th, 75th, 90th, and 95th percentiles will be calculated.

Weight, length, head circumference, and BMI data including age-adjusted z-scores and percentile for each growth parameter-for-age will be presented in a by-subject data listing.

In addition, the following individual subject's growth charts will be produced with a flag for start of ORGN001 infusion and will include a symbol representing dose changed, if applicable: weight-for-age percentiles, length-for-age percentiles, head circumference-for-age percentiles, and BMI-for-age percentiles.

6.2.2.7. Pharmacodynamic Assessments

[redacted] Levels of biochemical markers that are measured in urine will be normalized to urine creatinine levels. [redacted] The actual value, change, and percentage change from baseline in MoCD-associated urine and blood biomarker levels will be summarized by visit.

All [redacted] levels (plasma and urine) will be graphically displayed for each subject over time.

In addition, by subject plots will be graphically displayed, [redacted].

The percentage of change from baseline of each [redacted] (example: ([Month x – Baseline] / Baseline × 100)) will be plotted on the same figure.

[redacted]

6.2.3. Other Efficacy Analyses

Not applicable.

6.3. Pharmacokinetic Analyses

All PK analyses specified in the protocol will be performed [redacted].

6.4. Pharmacokinetic and Pharmacodynamic Analyses

The relationship between PK and plasma and urine SSC levels will be explored using graphic methods or PK/PD modeling.

[redacted]

6.5. Safety Analyses

All safety analyses will be conducted on the Safety Set. All safety data available at the time of database lock will be provided in subject listings. All AEs will be coded in the Medical Dictionary for Regulatory Activities (MedDRA) (version 22.0) and no formal hypothesis testing will be performed.

6.5.1. Study Duration, Treatment Compliance, and Exposure

Summary statistics (mean, SD, median, minimum, and maximum) will be produced for the following, using the FAS:

- Number of ORGN001 infusions
- Proportion of the number of infusions by expected number of infusions
- Number of make-up doses
- Number of missed doses
- Duration (days) of study participation from informed consent
- Total time (days/weeks/months) on ORGN001

By-subject listings will be produced for study duration, treatment compliance, and exposure, as well as, for study drug administration.

6.5.2. Dose Modification

The proportion of patients with dose modification (dose interruption, dose reduced, dose increased, dose stopped) will be listed and summarized using descriptive statistics. [redacted]

By-subject listings will be produced for dose modifications.

6.5.3. Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) using of MedDRA (version 22.0). The severity/relationship will be assessed.

The AEs will be determined as occurring prior to treatment with ORGN001 (pre-treatment), or as on or after first treatment (treatment-emergent), as described in Section 8.3. Analyses of pre-treatment adverse events (PTAEs) and treatment-emergent adverse events (TEAEs) will be tabulated and presented separately. An incomplete date of AE onset will be compared to treatment start date, if unable to determine AE onset date is prior to treatment start, then AE will be considered a TEAE.

Subjects having multiple AEs within a category (e.g., overall, SOC, PT) will be counted once in that category. For severity/relationship tables, the subject's most severe/most related event within a category will be counted. Missing relationship to study drug will be considered treatment-related.

Percentages will be based on the total number of treated subjects in the Safety Set. Tables will be sorted by descending frequency of SOC and by descending frequency of PT within SOC. Listings will be provided for all TEAEs and PTAEs for the Safety Set. TEAEs with missing severity will not be included in the counts of patients within a SOC or PT; however, the event will be reported in listings.

AEs will include the displays described in the following sub-sections.

6.5.3.1. Overall Summary of Adverse Events

All PTAEs and TEAEs will be presented using summary statistics (n, %). The number of subjects with events (n, %) will be displayed.

Table 2: Treatment-Emergent Adverse Events

Relationship	Severity
Related AEs (possibly, probably, or definitely related, missing/unknown) Not related AEs (not related or unlikely related)	Mild AEs Moderate AEs Severe AEs

Additionally, the number and percentage of subjects who withdrew from the study due to an AE, discontinued treatment due to an AE, or who died on study will be presented. These statistics will be presented for all TEAEs and separately, for SAEs.

6.5.3.2. Adverse Events and Serious Adverse Events by System Organ Class and Preferred Term

The number of PTAEs and TEAEs and the number and percentage of subjects with events will be presented by SOC and PT.

6.5.3.3. Adverse Events and Serious Adverse Events by System Organ Class, Preferred Term, and Relationship

The number and percentage of subjects with TEAEs will be presented by SOC and PT as described above by relationship (related, not related). If a patient has more than 1 occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. SAEs will be summarized similarly.

6.5.3.4. Adverse Events and Serious Adverse Events by System Organ Class, Preferred Term, and Severity

The number and percentage of subjects with TEAEs will be presented by SOC and PT as described above by severity (mild, moderate, severe). If a subject has more than one occurrence of an AE, the most severe occurrence will be used in the summary table. SAEs will be summarized similarly.

6.5.3.5. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All SAEs will be presented in subject listings. All AEs leading to study treatment withdrawal will be listed. A listing of subject deaths will be produced, if applicable.

6.5.4. Other Safety Analyses

6.5.4.1. Analyses for Laboratory Tests

Descriptive statistics by visit will be presented for each laboratory parameter and for changes from baseline.

Serum Chemistry	Hematology	Coagulation	Urinalysis
Sodium	Red blood cell count	Prothrombin time	Specific gravity
Potassium	Mean corpuscular volume	International Normalized Ratio	pH
Bicarbonate	Mean corpuscular hemoglobin		Glucose
Chloride	Mean corpuscular hemoglobin concentration		Protein
Blood urea nitrogen	White blood cell count		RBC (by dipstick)
Creatinine	Neutrophils (absolute and percentage)		Ketones (by dipstick)
Calcium	Lymphocytes (Absolute and percentage)		Urine protein to creatinine ratio
Alanine aminotransferase	Monocytes (absolute and percentage)		
Aspartate aminotransferase	Eosinophils (absolute and percentage)		

Serum Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	Basophils (absolute and percentage)		
Total bilirubin	Platelet count		
Serum osmolality	Hemoglobin		
Total Serum Albumin	Hematocrit		

For purposes of analyses, laboratory results based upon standardized units will be used. All laboratory values, where applicable, will be classified as normal, below normal, or above normal, and shift tables will be presented over time.

Scatter plots of all chemistry and hematology lab test values [redacted] by baseline values will be plotted. For hematology, the following tests will be plotted: RBC, WBC count, platelet count, hemoglobin, and hematocrit. All data will be presented in by-subject listings and flag for abnormal result will be included.

6.5.4.2. Vital Signs

Vital signs (systolic and diastolic BP, temperature, RR and HR) change from baseline, and percent change from baseline in vital signs will be summarized by visit and time point. Individual plots of systolic and diastolic BP measurements conducted [redacted] will be graphically displayed separately. Listings of vital signs will be produced and flag for abnormal result will be included.

6.5.4.3. Physical Examination

Physical examination results and Child Pugh scores (A[a score of 5 to 6], B[a score of 7 to 9], C[a score of 10 or above]) will be summarized by visit. Listings of physical examination and Child Pugh scores results will be produced.

6.5.4.4. Electroencephalogram

The number and frequency of subjects with EEG findings will be summarized by visit. All data from local interpretation of EEGs will be presented in by-subject listings.

Central EEG readings will be summarized in a separate report, if determined to be applicable.

7. REFERENCES

Bayley N. Technical & Administration manuals for Bayley scale of infant and Toddler Development (third edition). PsychCorp, a brand of Harcourt Assessment; 2006.

8. APPENDICES

[redacted]

8.3. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

Age

Age will be presented as the number of days or months between date of birth and the reference date and will be calculated as follows:

Age in days: (Visit date – date of birth) + 1 day

Age in months: ((Visit date – date of birth) + 1 day)/30.4375

The following ages in Table 3 may be computed, with reference dates indicated.

Table 3: Age and Reference Date

AGE	REFERENCE DATE
Age at study enrollment (months)	• Date of signing ICF
Age at first symptom (days)	• Date of first symptoms
Age at first ORGN001 infusion (days)	• Date of first infusion
Age at each developmental assessment (months)	• Date of developmental assessment

If the reference date is not complete, then age at reference date will be determined by the month and/or year of date of birth and reference date.

Weight and Height

Weight in pounds will be multiplied by 0.4536 to be converted to kilograms; and height in inches will be multiplied by 2.54 to be converted to centimeters.

The BMI will be calculated by dividing the subject's weight in kilograms by the subject's height in meters squared. The units are kg/m^2.

BQL and LLOQ Values for Clinical Laboratory [redacted] Parameters

For all clinical laboratory [redacted] parameters, values that are reported as below quantification level (BQL) or lower limit of quantification (LLOQ) will have numeric values set equal to the BQL or LLOQ lower limit (e.g., if BQL <2, then value will be set equal to 2). However, the original value will be displayed in by-subject data listings.

Date of Infusion

Date of first ORGN001 infusion, as well as date of last ORGN001 infusion will be derived.

Time from First Infusion to Applicable Assessments (Days)

For all applicable assessments, time on treatment from first infusion will be calculated as follows:

- If visit date is on or after first infusion = (Visit date – Day 1 Infusion date) + 1 day
- If visit date is prior to first infusion = (Visit date – Day 1 Infusion date)

Time from First Infusion to Applicable Assessment (Months)

For all applicable assessments, time on treatment from first infusion will be calculated as follows:

- If visit date is on or after Day 1 infusion = ((Visit date – Day 1 Infusion date) + 1 day)/30.4, rounded to 1 decimal place
- If visit date is prior to Day 1 infusion = (Visit date – Day 1 infusion date)/30.4, rounded to 1 decimal place

Time on Study (Days)

For each subject, time on study from informed consent to last visit, study completion, termination or withdrawal (days) will be calculated as follows:

- For subjects who completed Month [redacted] = (date of Month [redacted] visit date – date of informed consent) + 1 day
- For subjects who withdrew prior to Month [redacted] = (date of study exit – date of informed consent) + 1 day

Additionally, for each subject, time on study from informed consent to last infusion will be similarly calculated.

Time on Study (months)

For each subject, time on study from informed consent to last visit, study completion, termination or withdrawal (months) will be calculated as follows:

- For subject who completed Month [redacted] = ((date of Month [redacted] visit date – date of informed consent) + 1 day)/30.4375, rounded to 1 decimal place
- For subjects who withdrew prior to Month [redacted] = ((date of study exit – date of informed consent) + 1 day)/30.4375, rounded to 1 decimal place

Additionally, for each subject, time on study from informed consent to last infusion will be similarly calculated.

Definition of Baseline Values

Baseline is defined as the last available assessment prior to treatment with ORGN001, except for growth parameters and blood and urine [redacted] whereby baseline is defined as the average of all available assessments on or prior to the date of first infusion with ORGN001.

Change from Baseline

Change from baseline will be calculated as follows:

Change of Baseline = Assessment Value – Baseline Assessment Value

Percent Change in Assessments from Baseline

Percent change in values from Baseline will be calculated as follows:

$$\% \text{ Change in Value} = \frac{\text{Change in Value}}{\text{Baseline value}} \times 100$$

where Change in Value = (Assessment value – Baseline Assessment value), given that the baseline value is non-missing and non-zero and the subsequent value is non-missing.

Adverse Events

The analysis of AEs is described in detail in Section 6.5.3. Subject percentages are based on the total number of treated subjects in the Safety Set.

Related AEs are defined as possible, probable, definitely related or unknown/missing. Unrelated AEs are defined as unlikely or not related.

A pre-treatment AE refers to an AE that occurred prior to first ORGN001 infusion. Treatment-emergent AEs are events with start dates and start times on or after the date and time of the first ORGN001 infusion. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first infusion, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study drug infusion, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first study drug infusion and
  - the start month is missing, then the AE is treatment emergent; else if
  - the start month is present and is the same or after the month of the first study drug infusion, then the AE is treatment-emergent; else.
- If the start date is completely missing, then the AE is treatment-emergent.

All other AEs are considered PTAEs.

Child-Pugh Score

Child-Pugh score will be calculated as follows:

The total of the clinical or biochemical measurement scores (1, 2 or 3) according to Table 4 determines the Child-Pugh score as Grade A (5-6), Grade B (7-9), or Grade C (10-15).

Table 4: Criteria for Child-Pugh Classification

Clinical or Biochemical Measurements	Points Scored for Increasing Abnormality		
	1	2	3
Hepatic encephalopathy (grade)	Absent	1 and 2	3 and 4
Ascites	Absent	Mild	Moderate
Total bilirubin (mg/dl)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time INR	<1.7	1.7-2.3	>2.3

8.4. Z-Score

Definition: Z-scores (or SD scores) are widely used in anthropometry to quantify a measurement's distance is from the mean. For example, a measurement that is 1.645 SDs from the mean (z-score of 1.645) would be at the 95th percentile of a normal (0,1) distribution; 95% of the distribution would be less than this measurement.

8.4.1. World Health Organization Growth Chart

The WHO growth charts only provide information on children up to 5 years of age.[1]

The WHO Antro have developed SAS macros to facilitate data analysis and calculate the indictors of the attained growth standards (length-for-age, weight-for-age, head circumference-for-age, and body mass index-for age). Calculate using the WHO growth chart for patients up to 5 years of age.[2]

8.4.2. Centers for Disease Control and Prevention Growth Chart

The CDC growth charts will be used for children older than 5 years.[3]

The CDC has developed SAS macros to facilitate data analysis and calculate the indictors of the attained growth standards (length-for-age, weight-for-age, head circumference-for-age, and body mass index-for age). Calculate using the WHO growth chart for patients over 5 years of age.[4]

8.5. Visit Windows

Visits will be assigned to visit windows. Data is summarized according to the visit windows reported in the following table when appropriate (e.g., laboratory parameters, vital signs,

[1] Additional WHO growth chart information and methodology can be found at http://www.who.int/childgrowth/publications/technical_report_2/en/index.html.

[2] The SAS macro and user instructions can be found at https://www.who.int/childgrowth/software/en/.

[3] Additional CDC growth chart information and methodology can be found at https://www.cdc.gov/growthcharts/clinical_charts.htm.

[4] The SAS macro and user instructions can be found at https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm.

developmental assessments, etc.). If multiple assessments occur within a visit window, the assessment closest to the target day will be used. In case of ties, with an equal number of days on either side of the target day, the value from the day before the target day shall be used.

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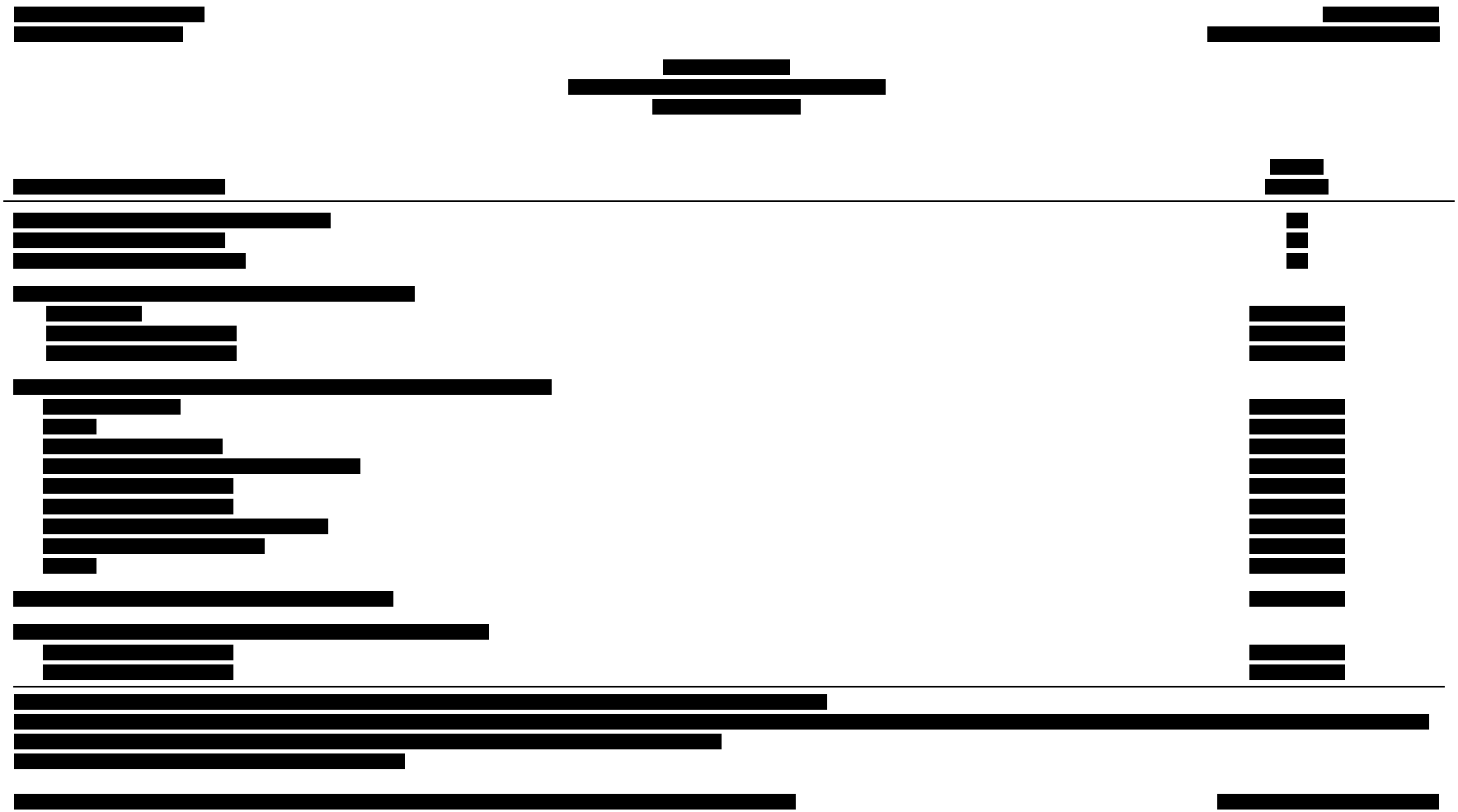

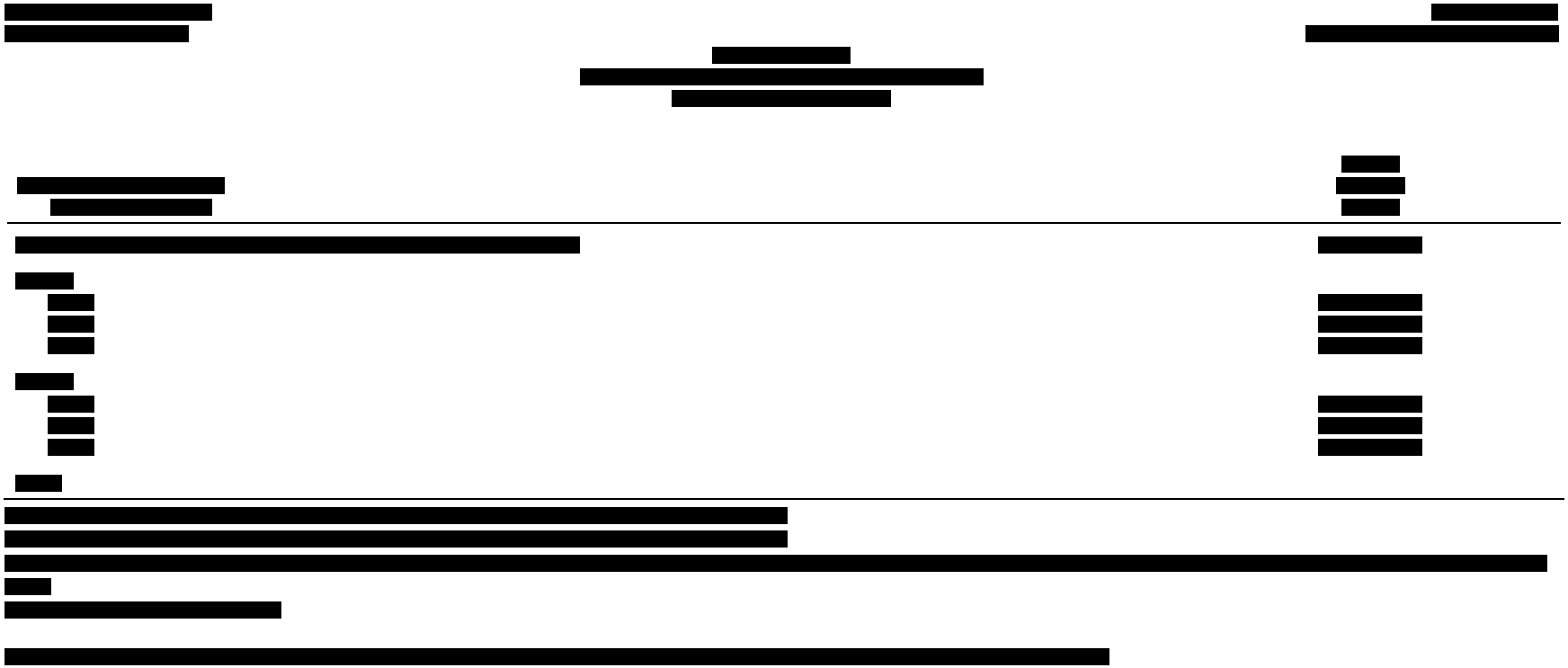

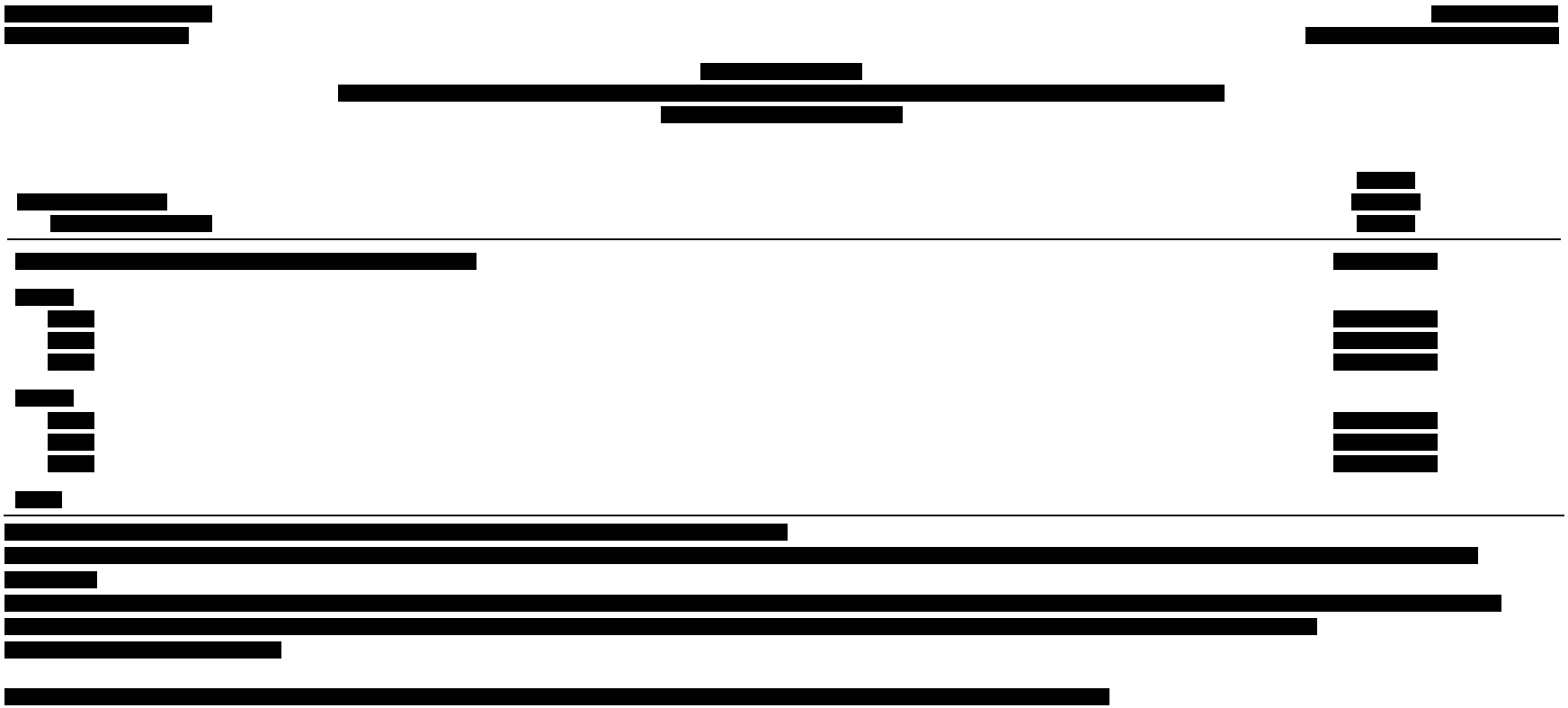

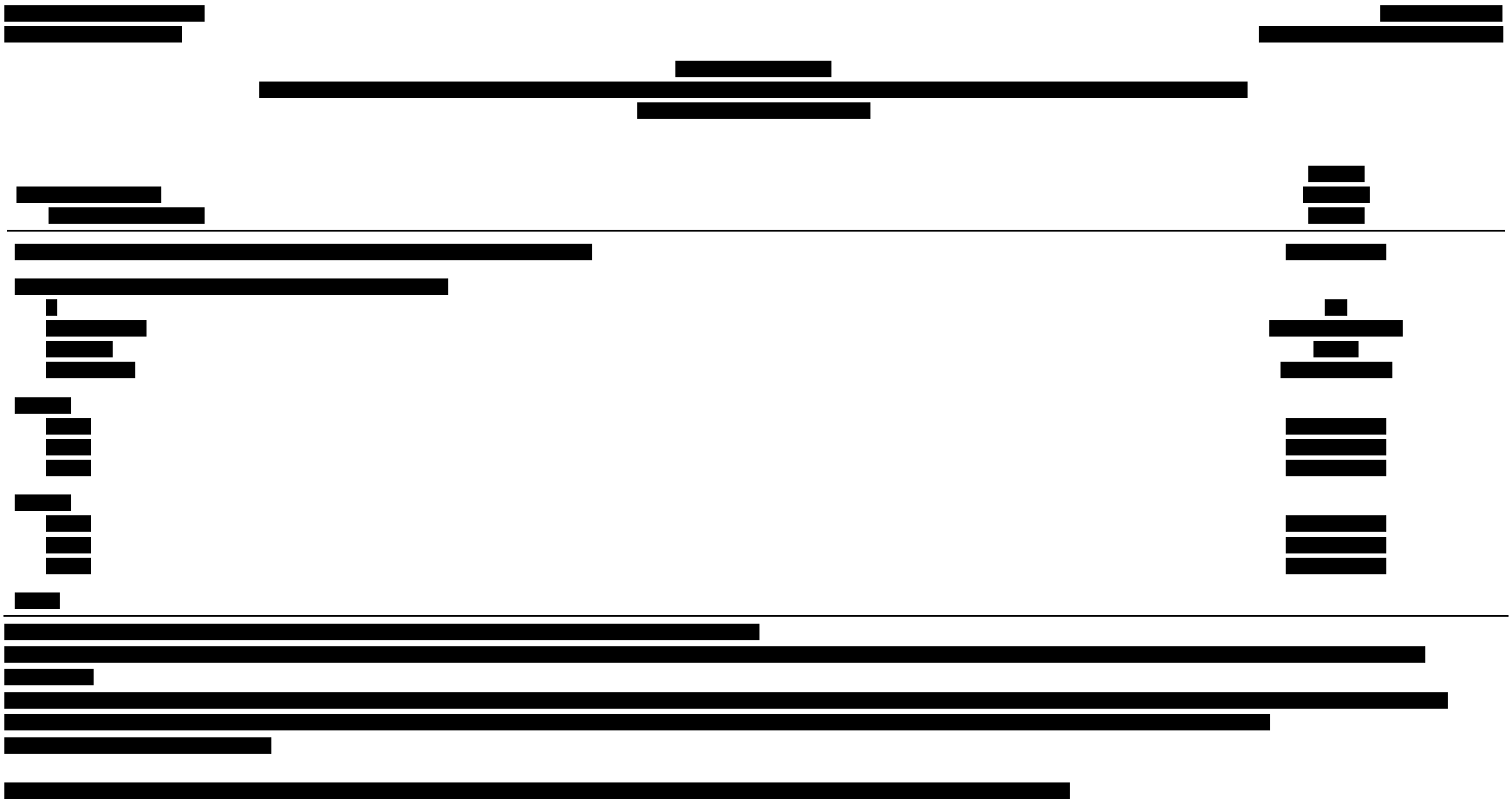

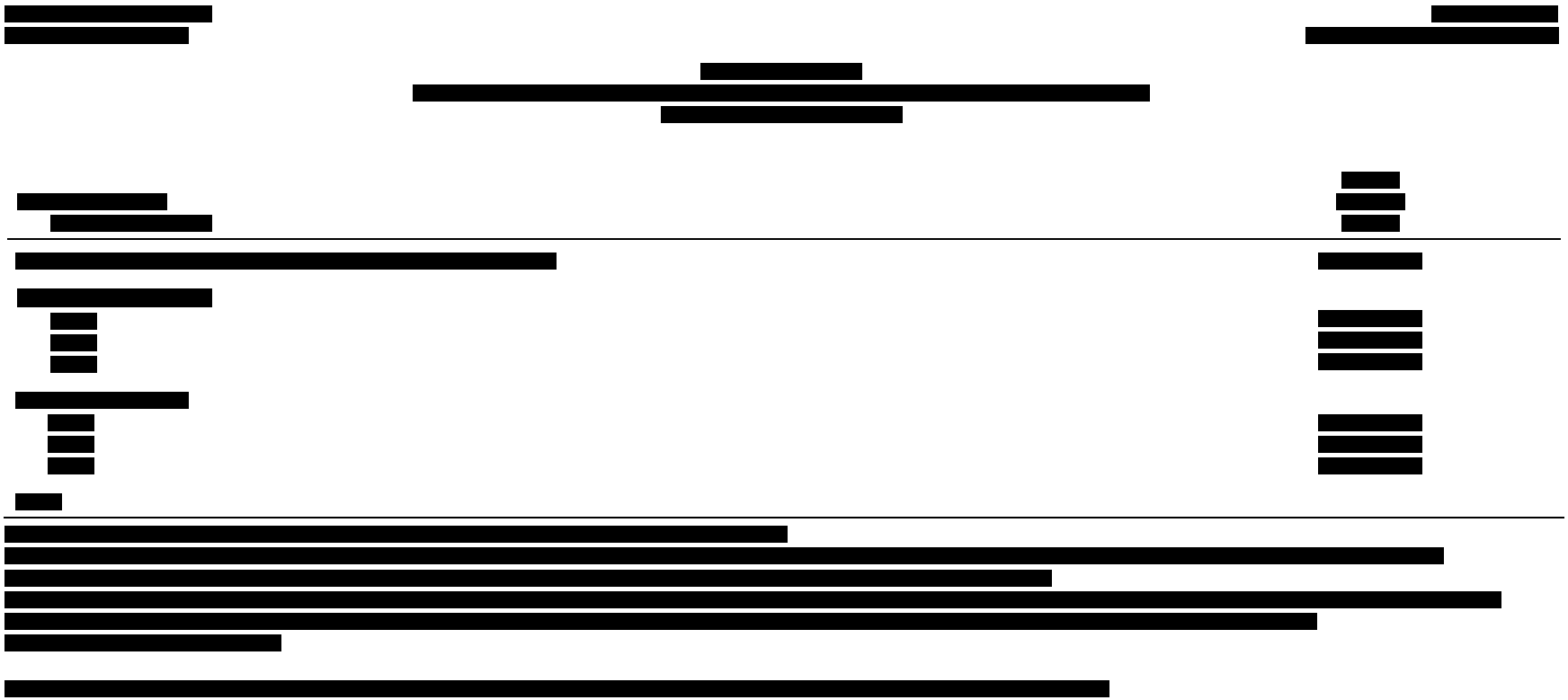

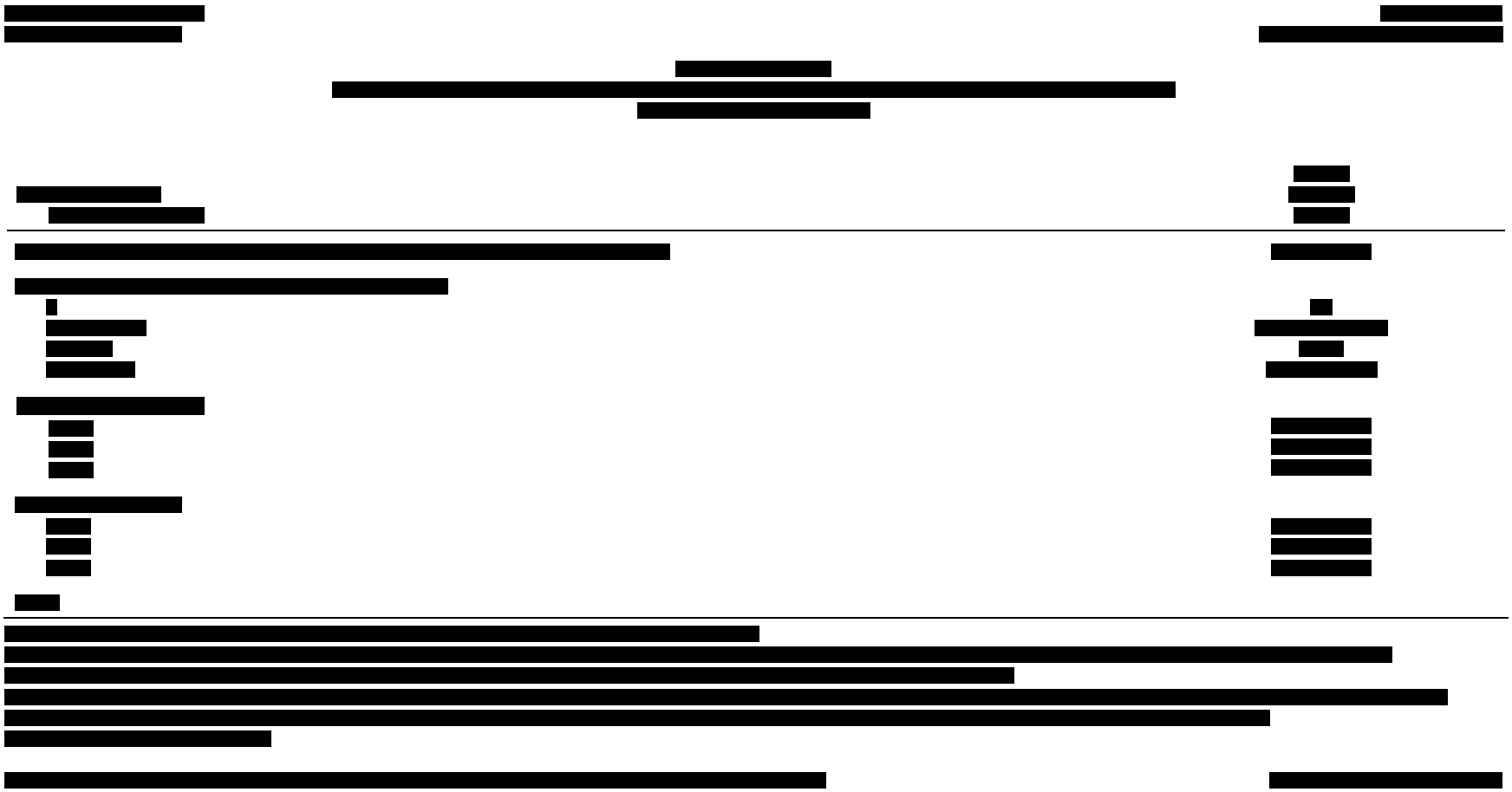

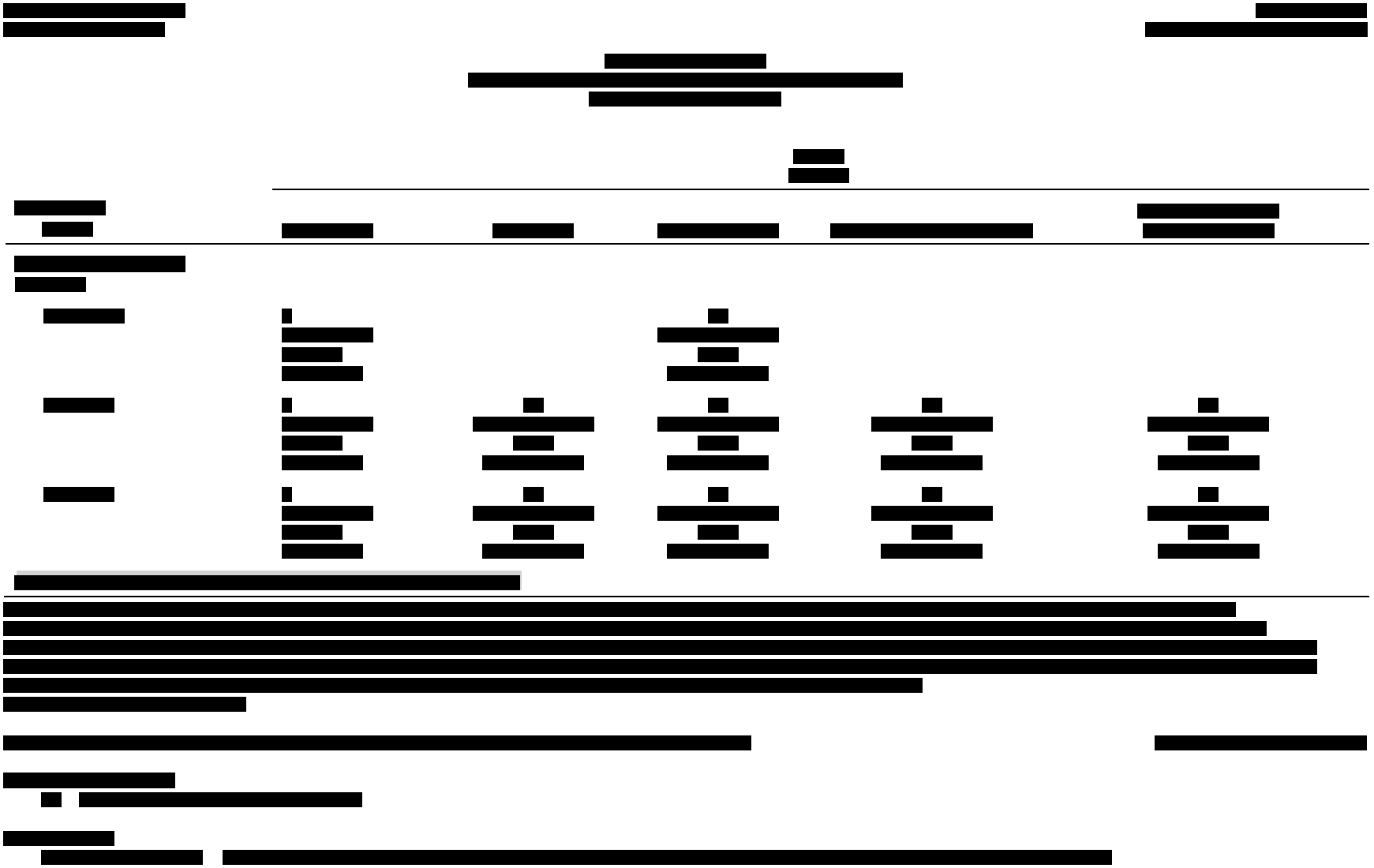

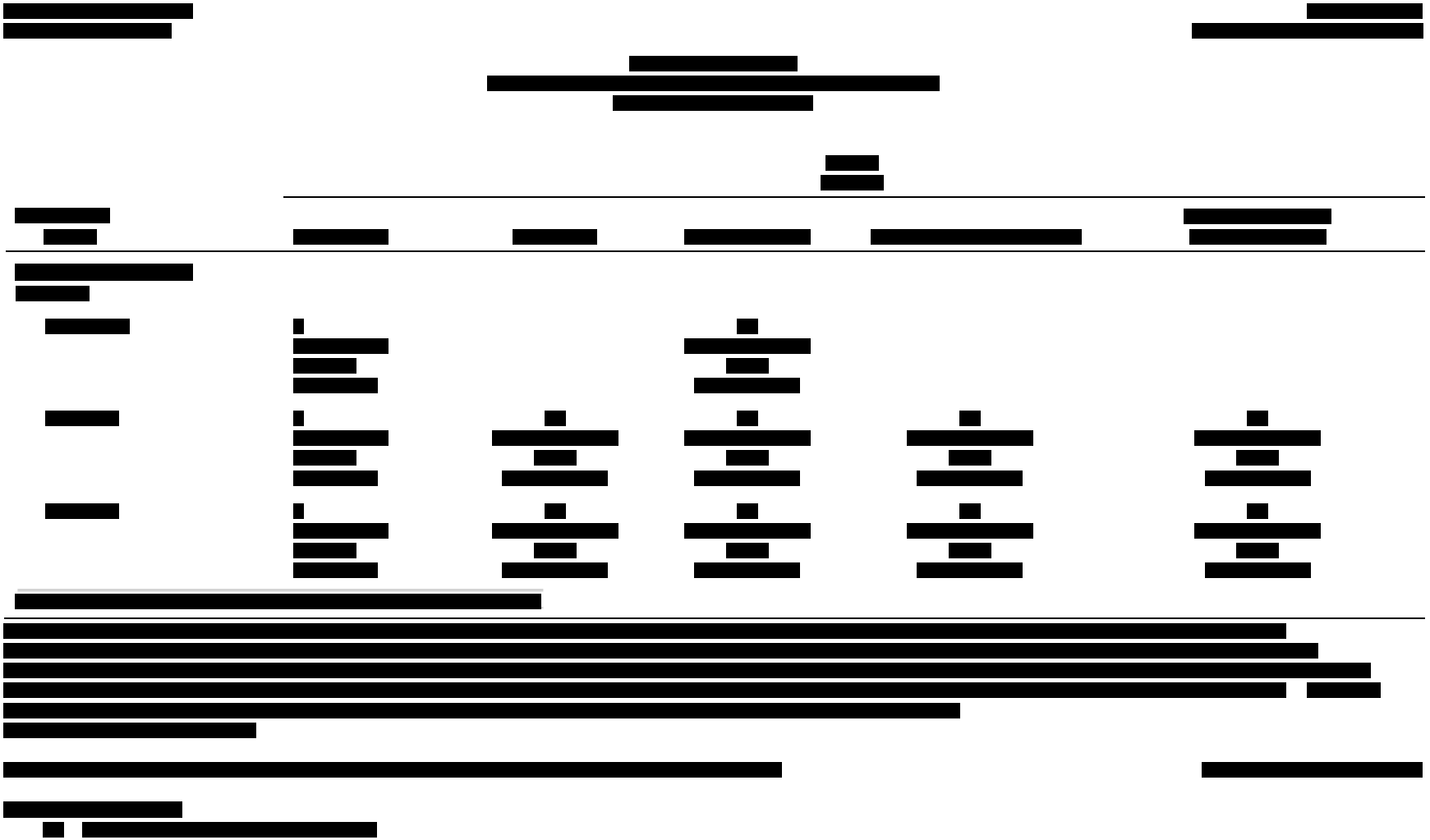

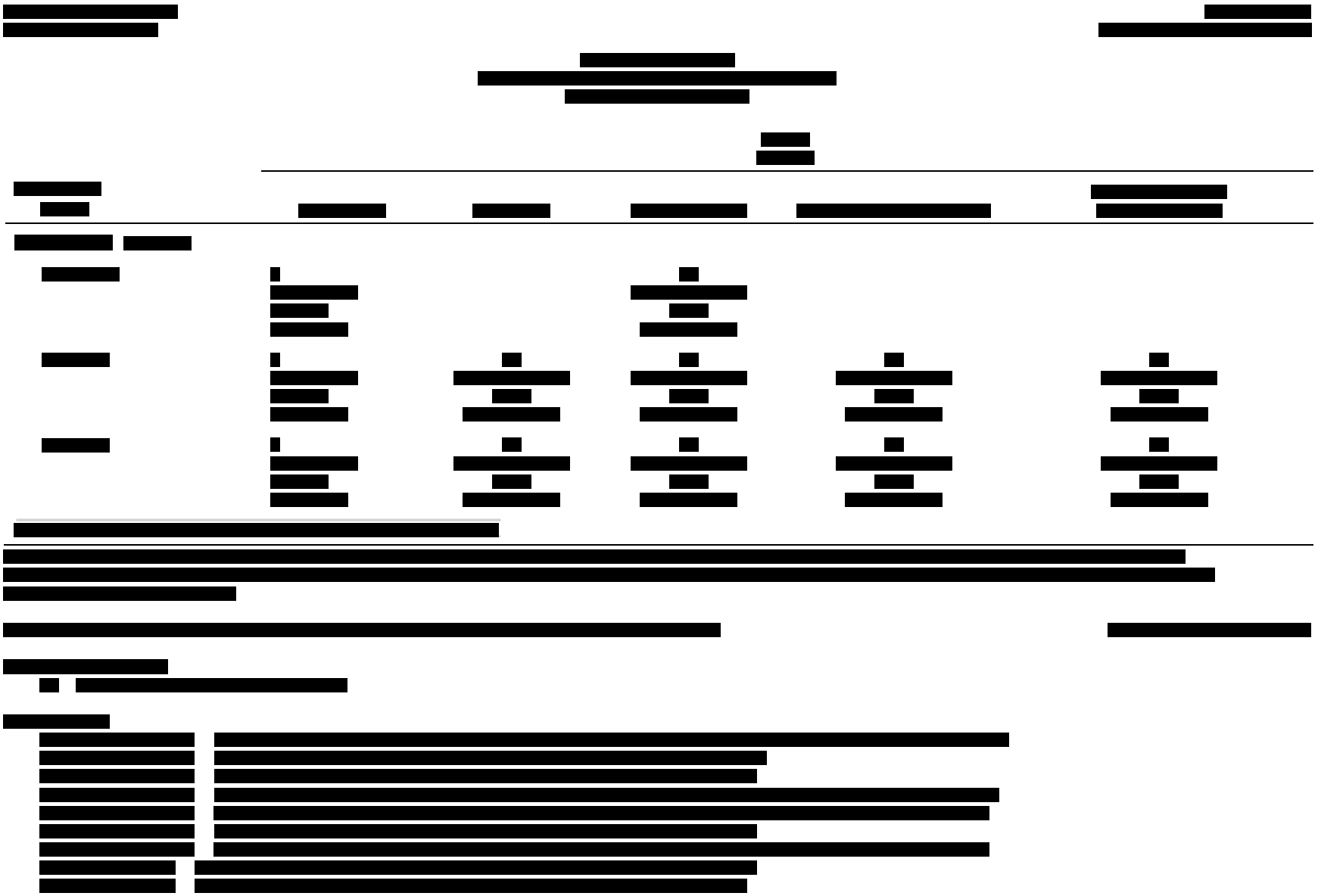

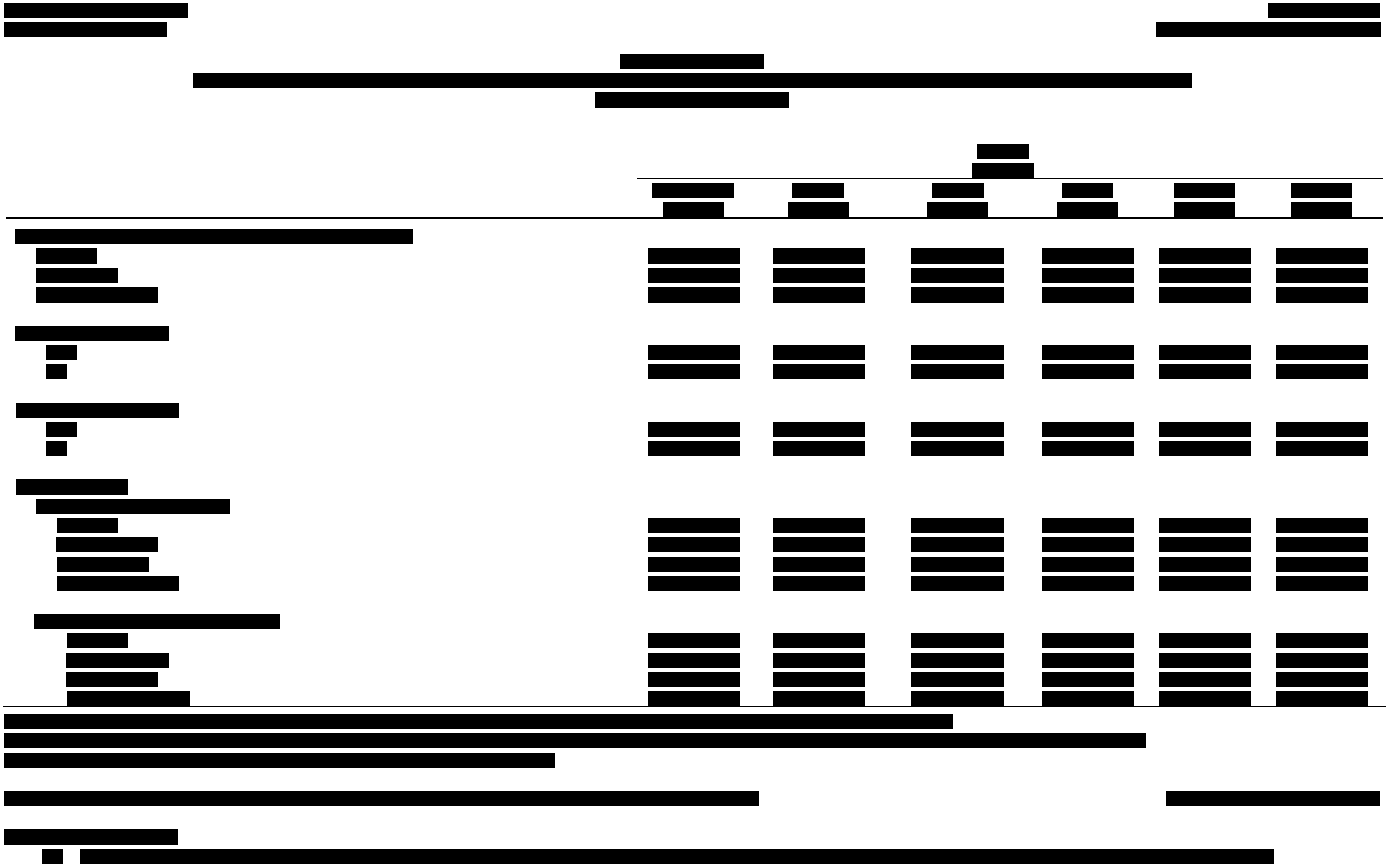

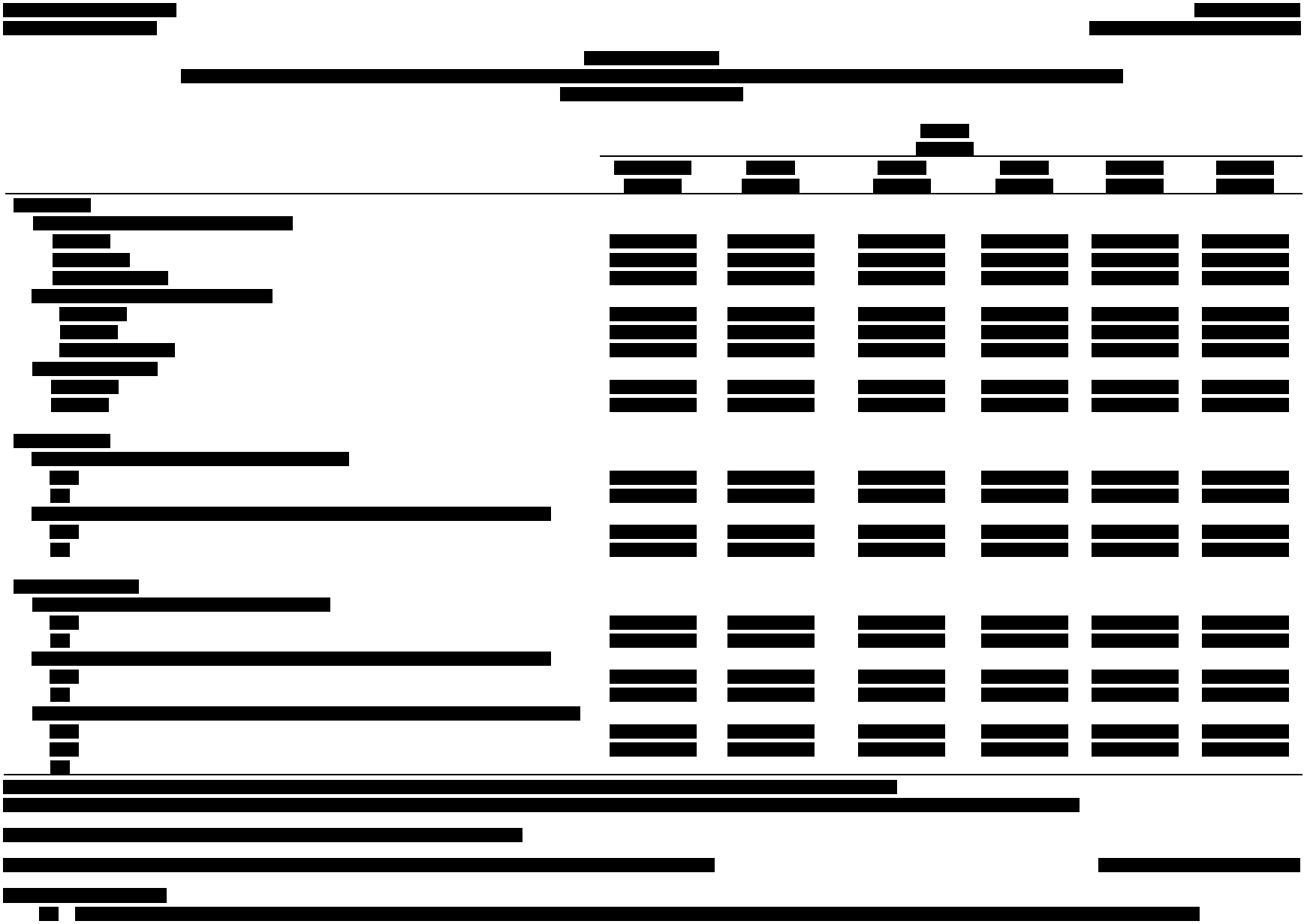

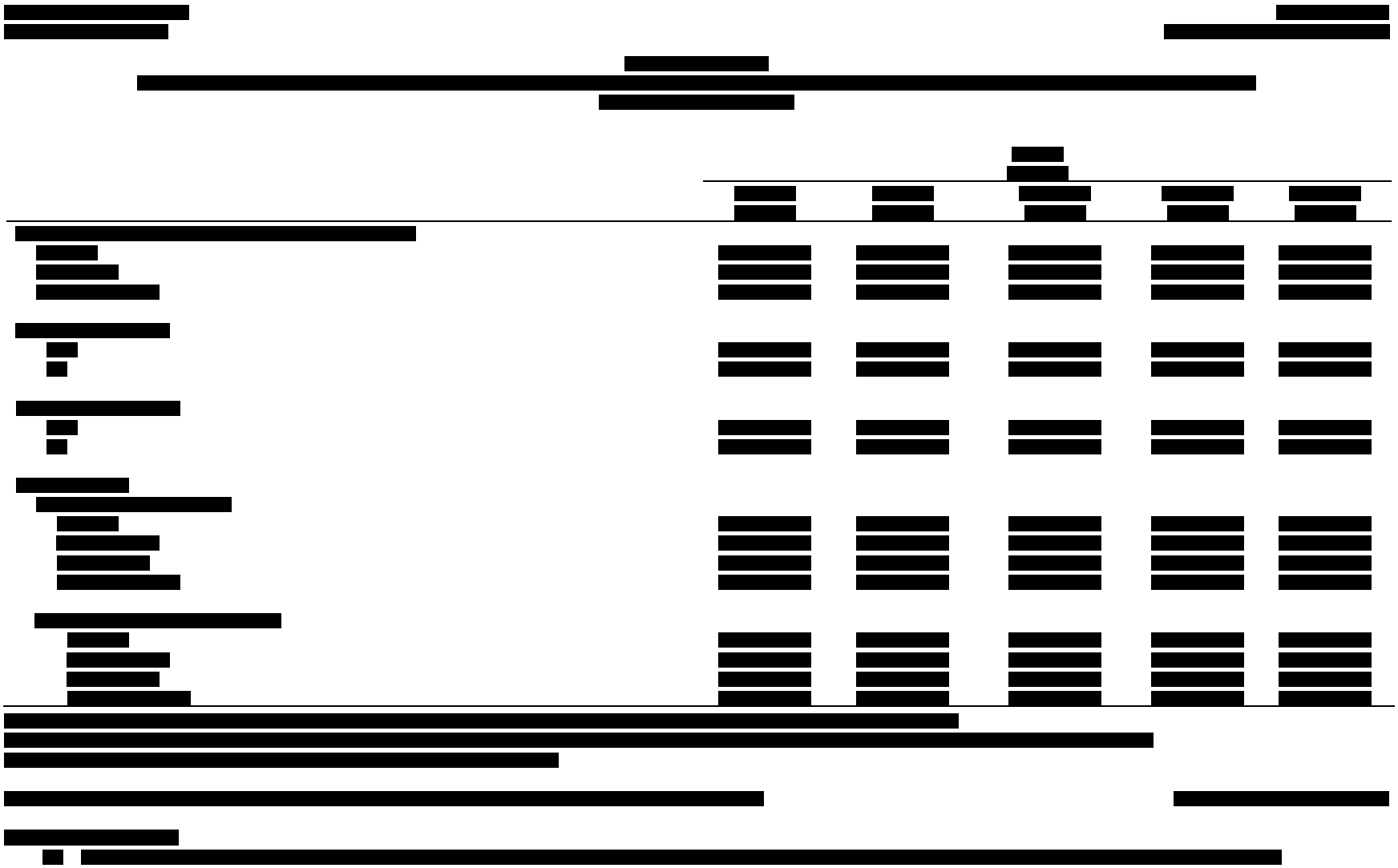

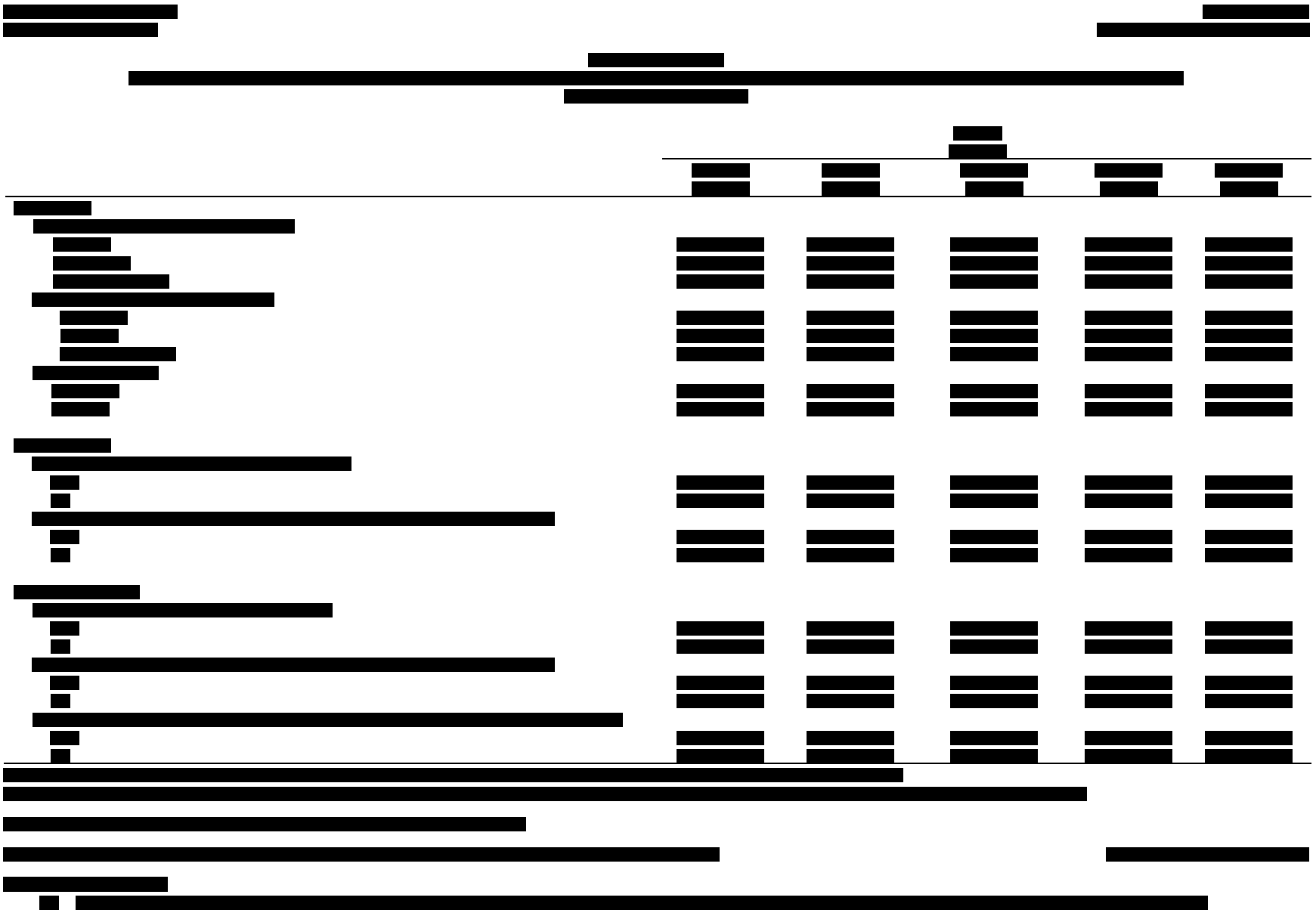

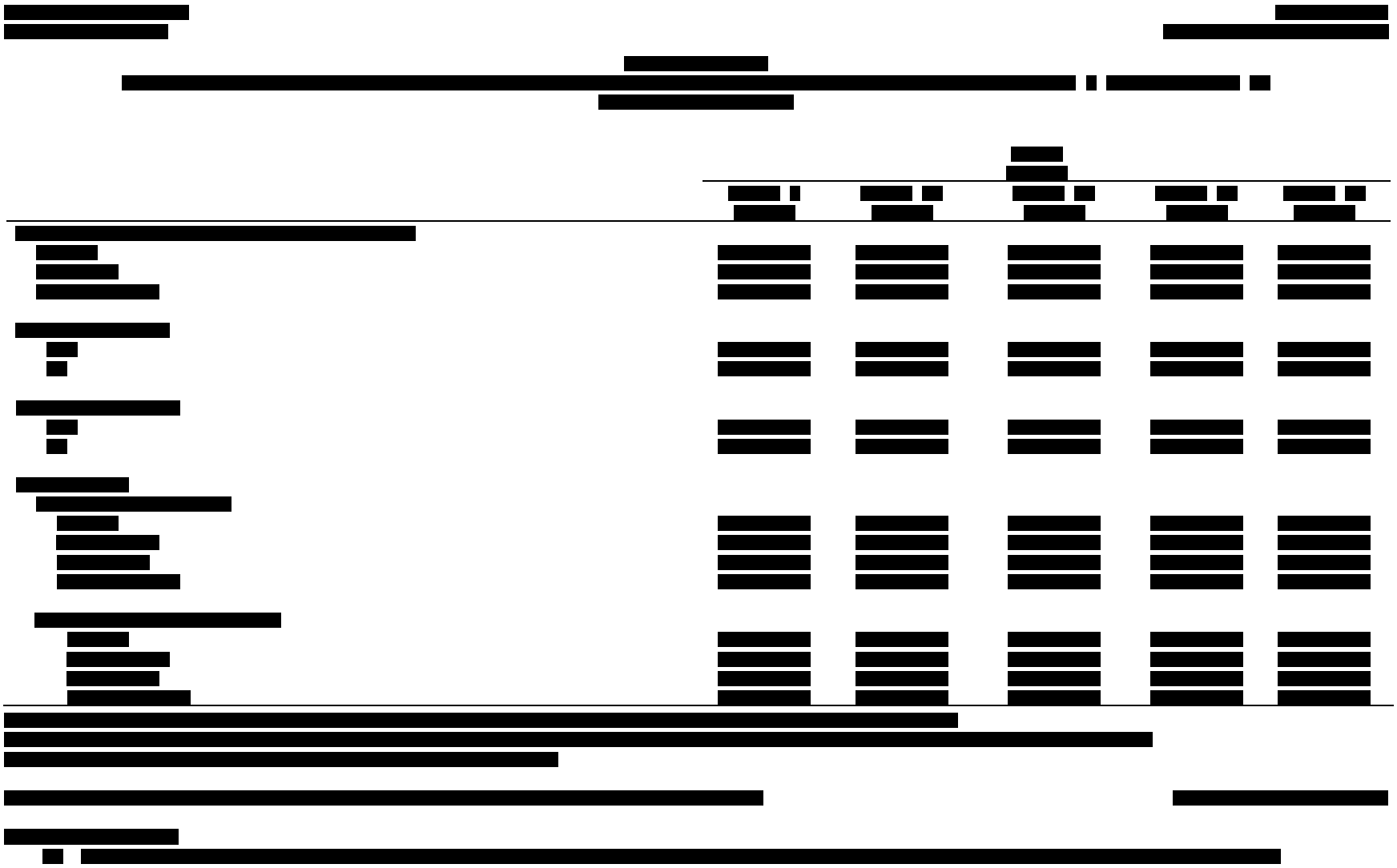

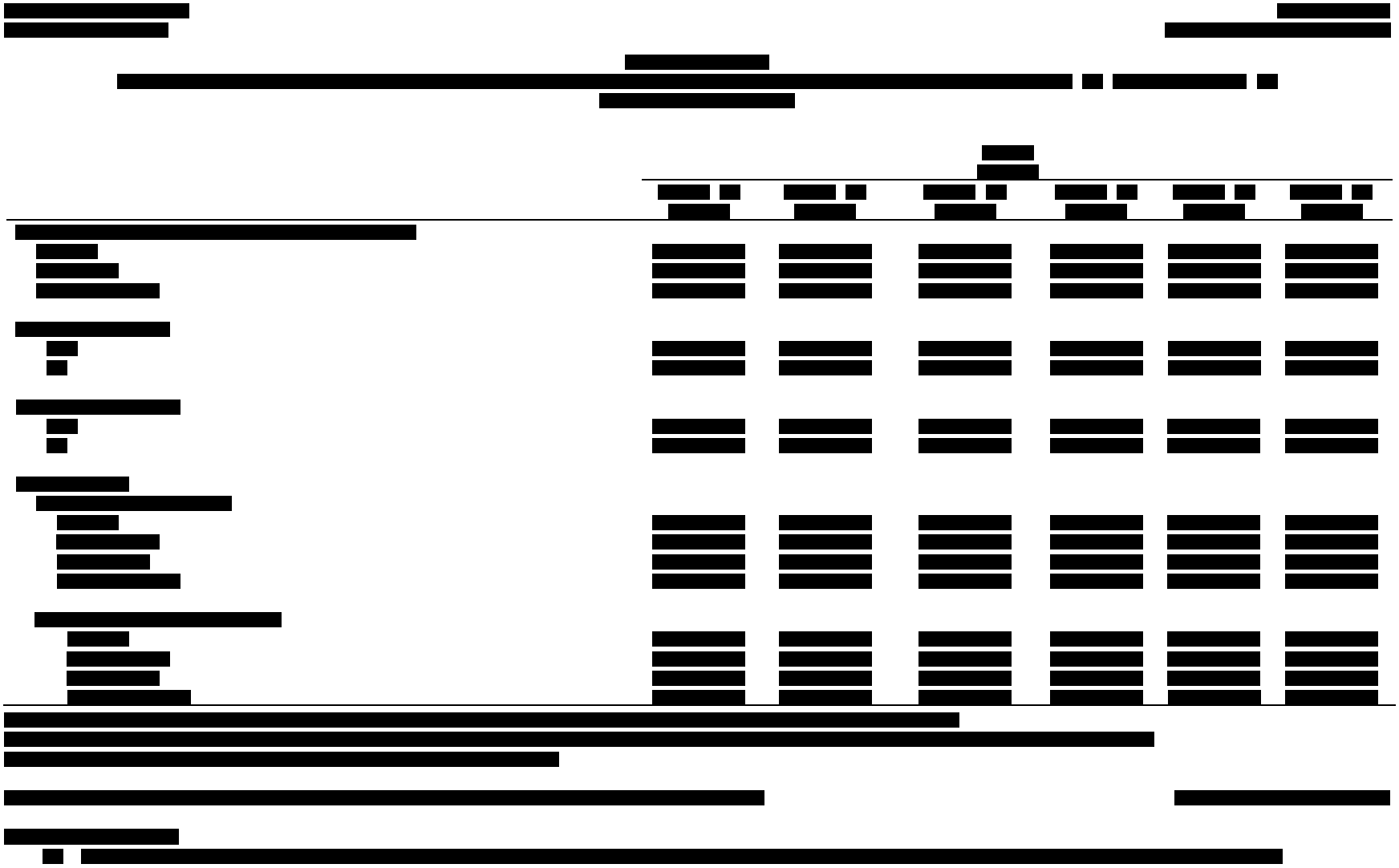

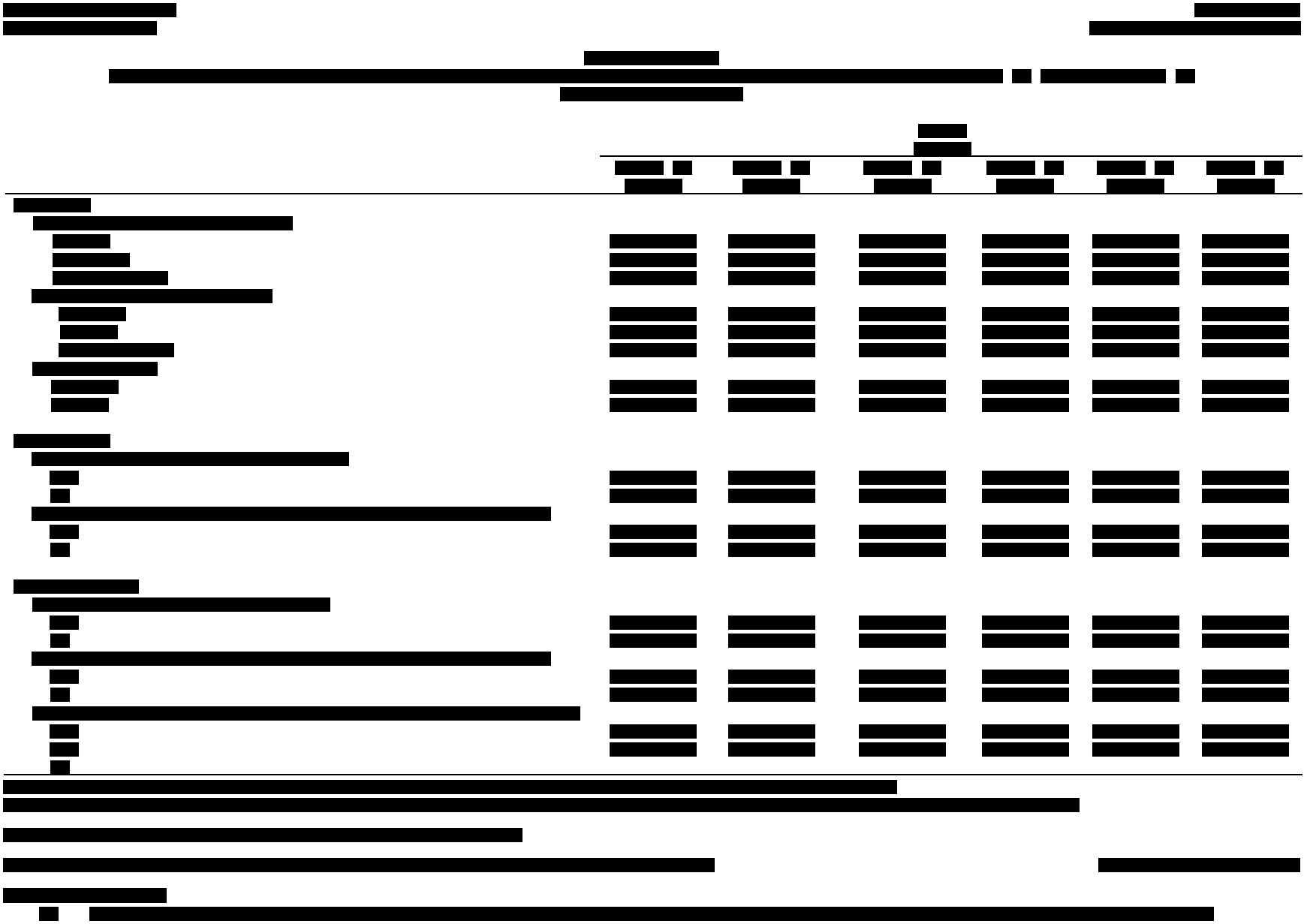

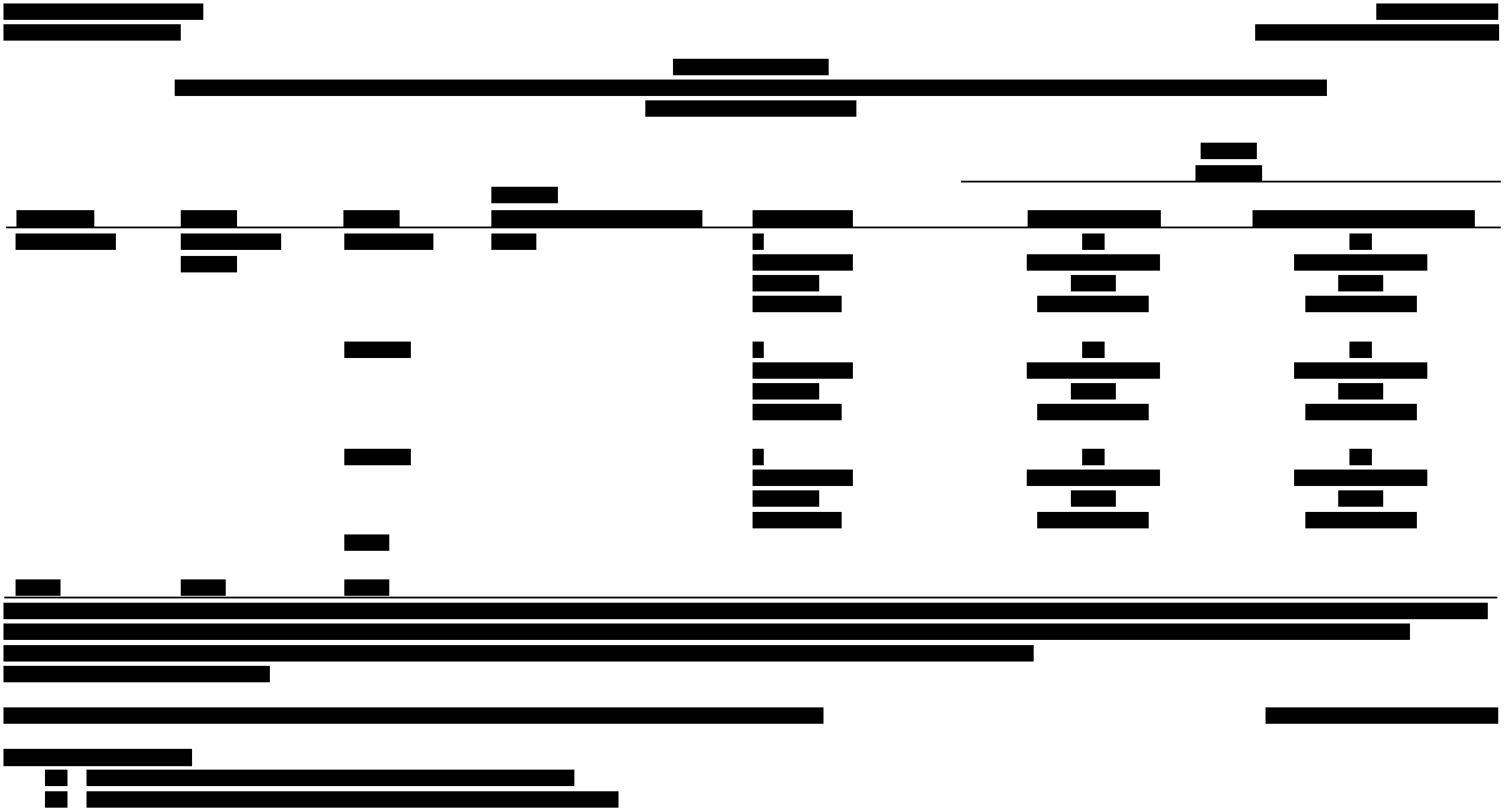

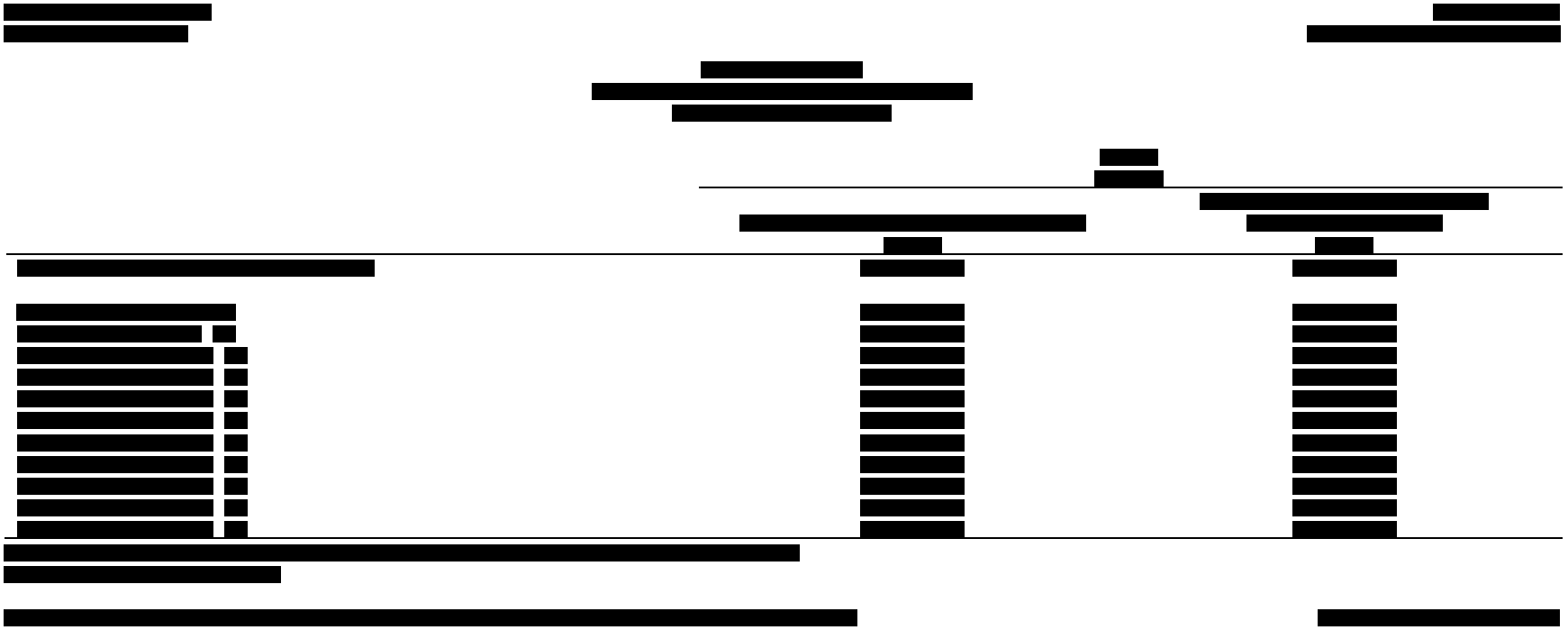

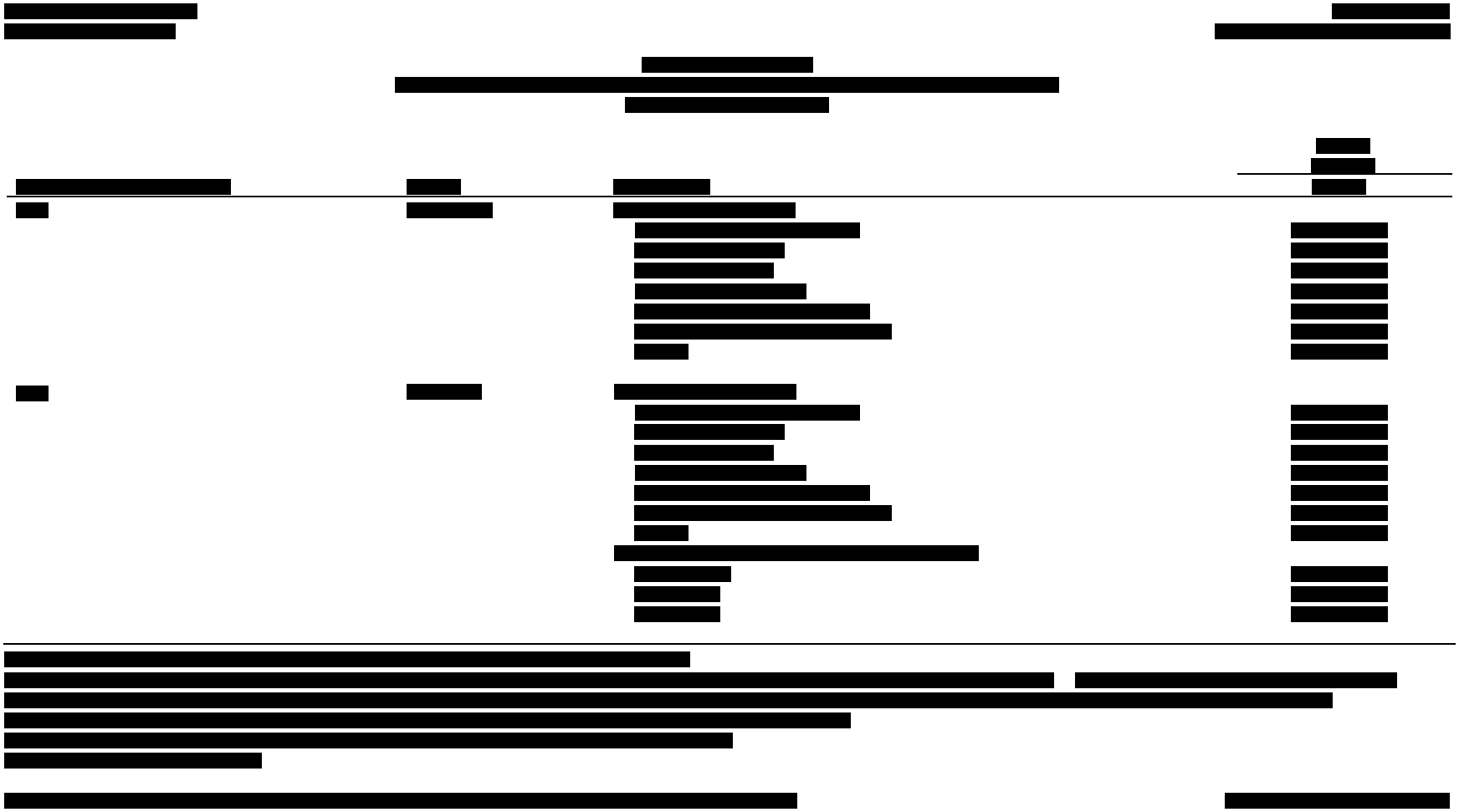

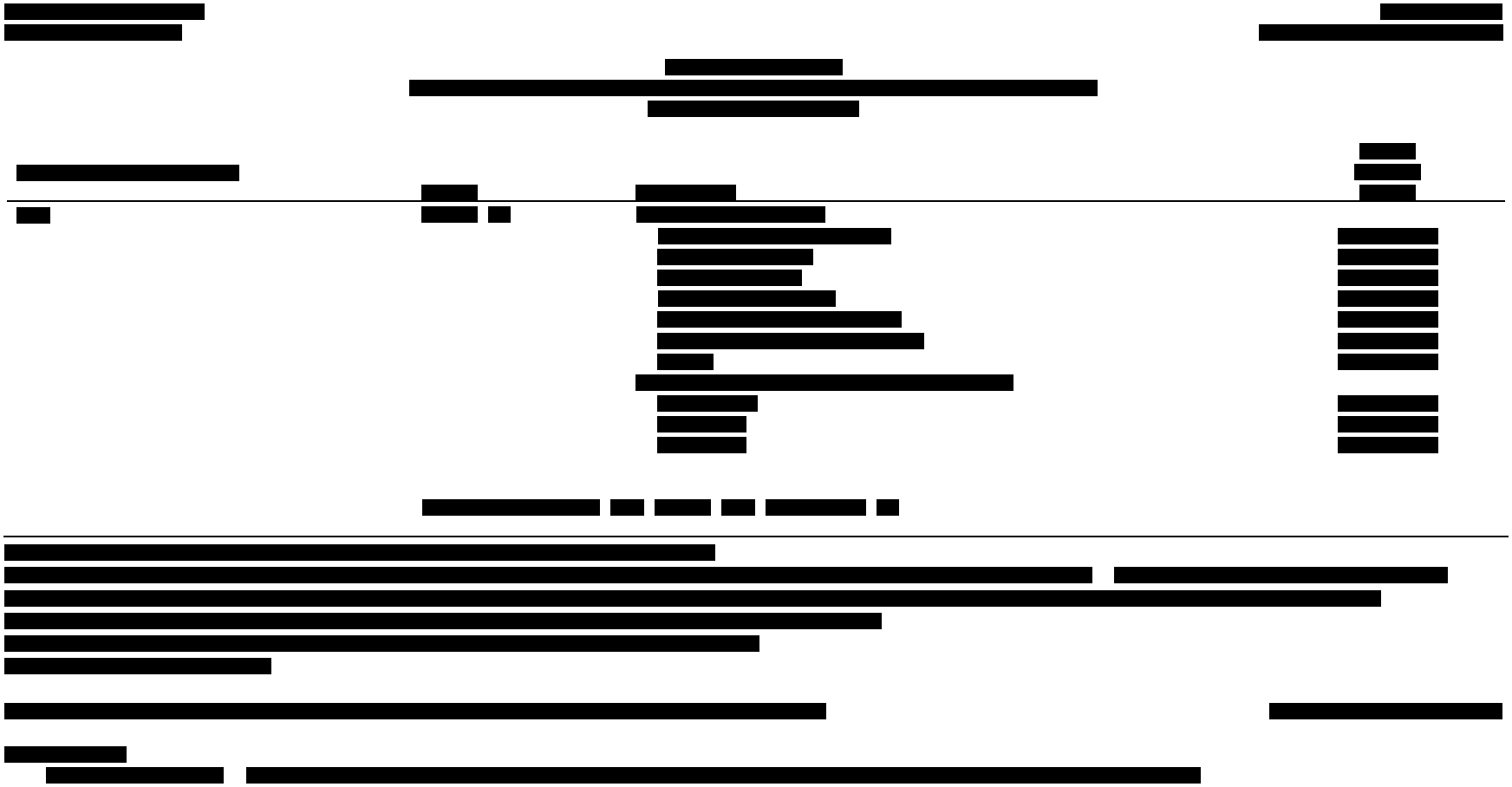

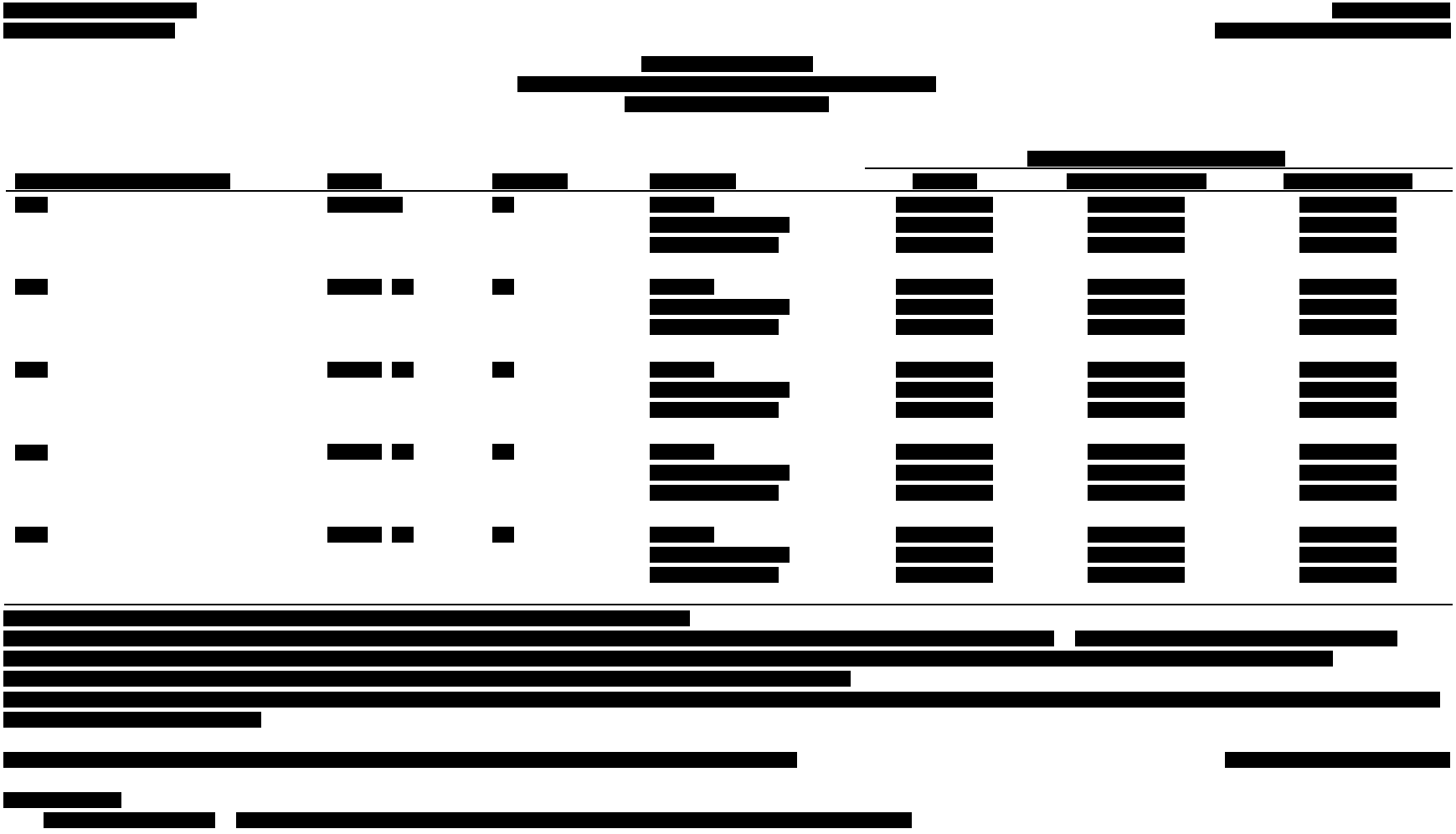

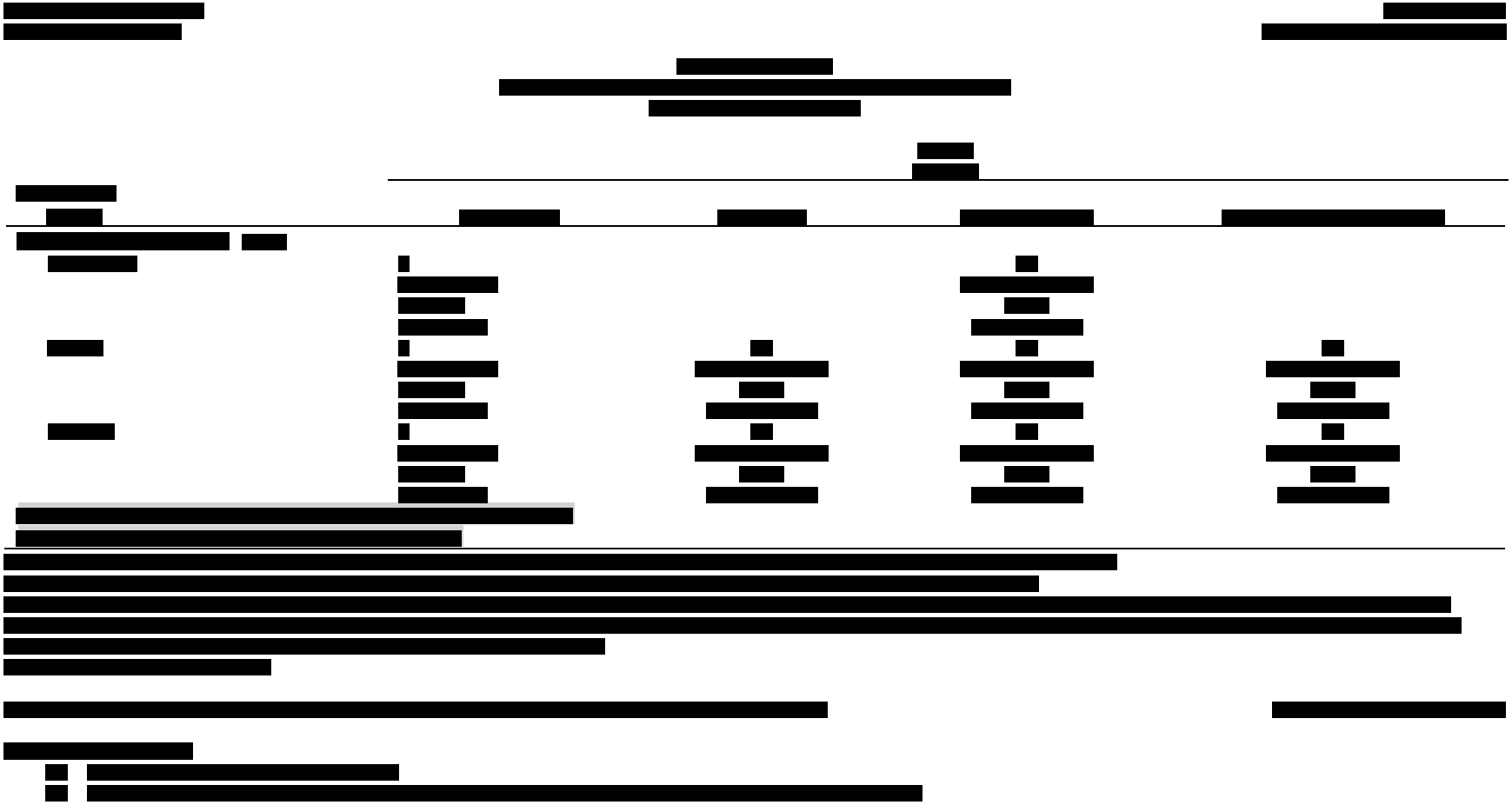

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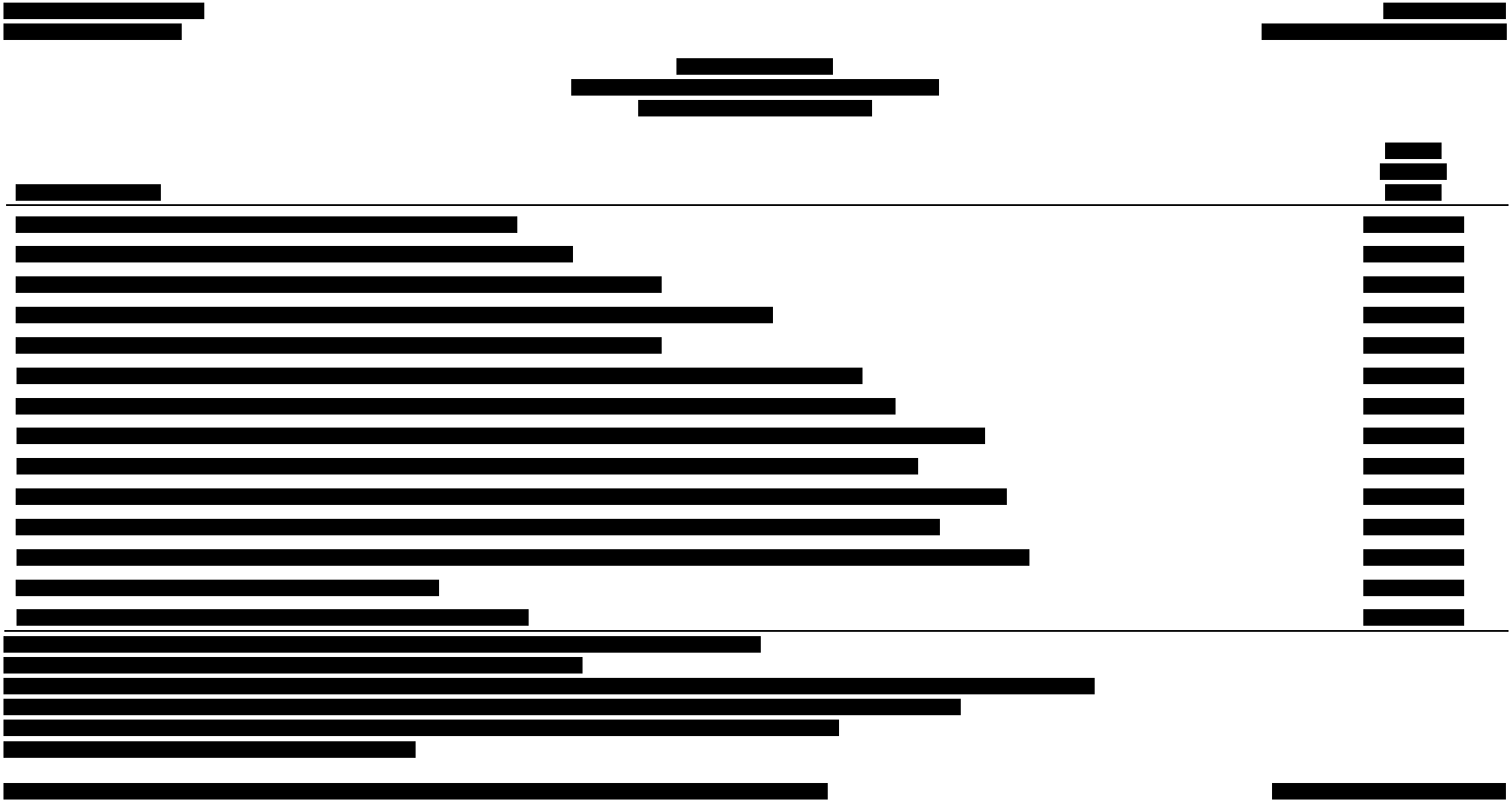

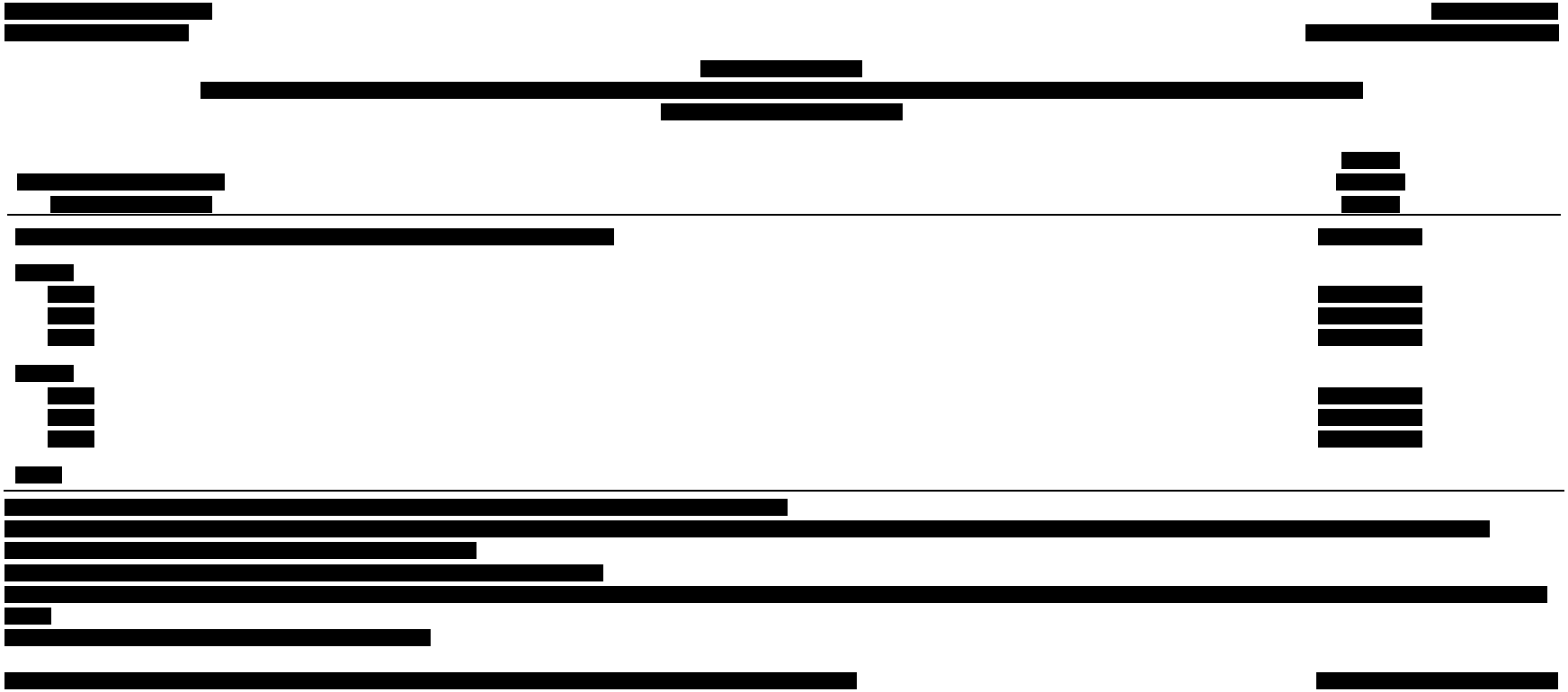

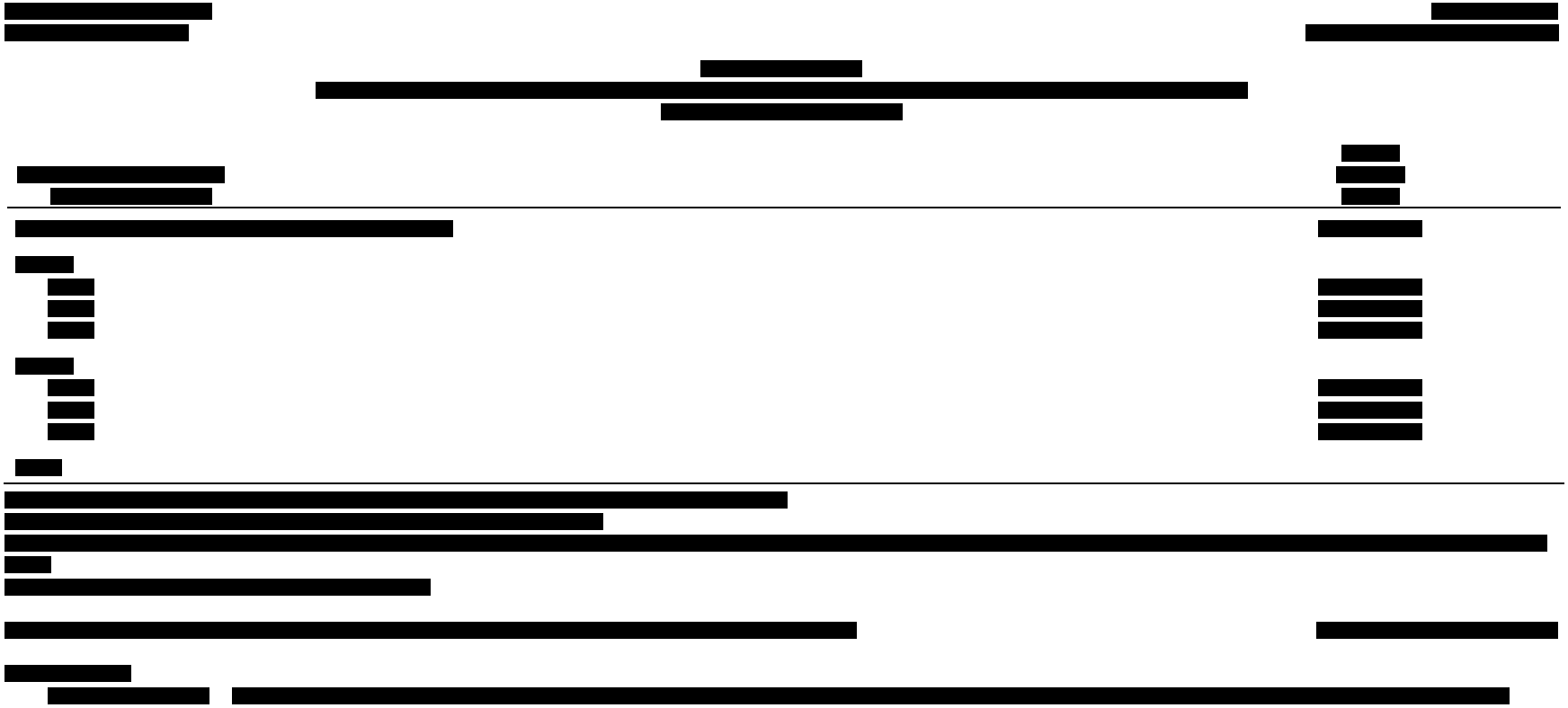

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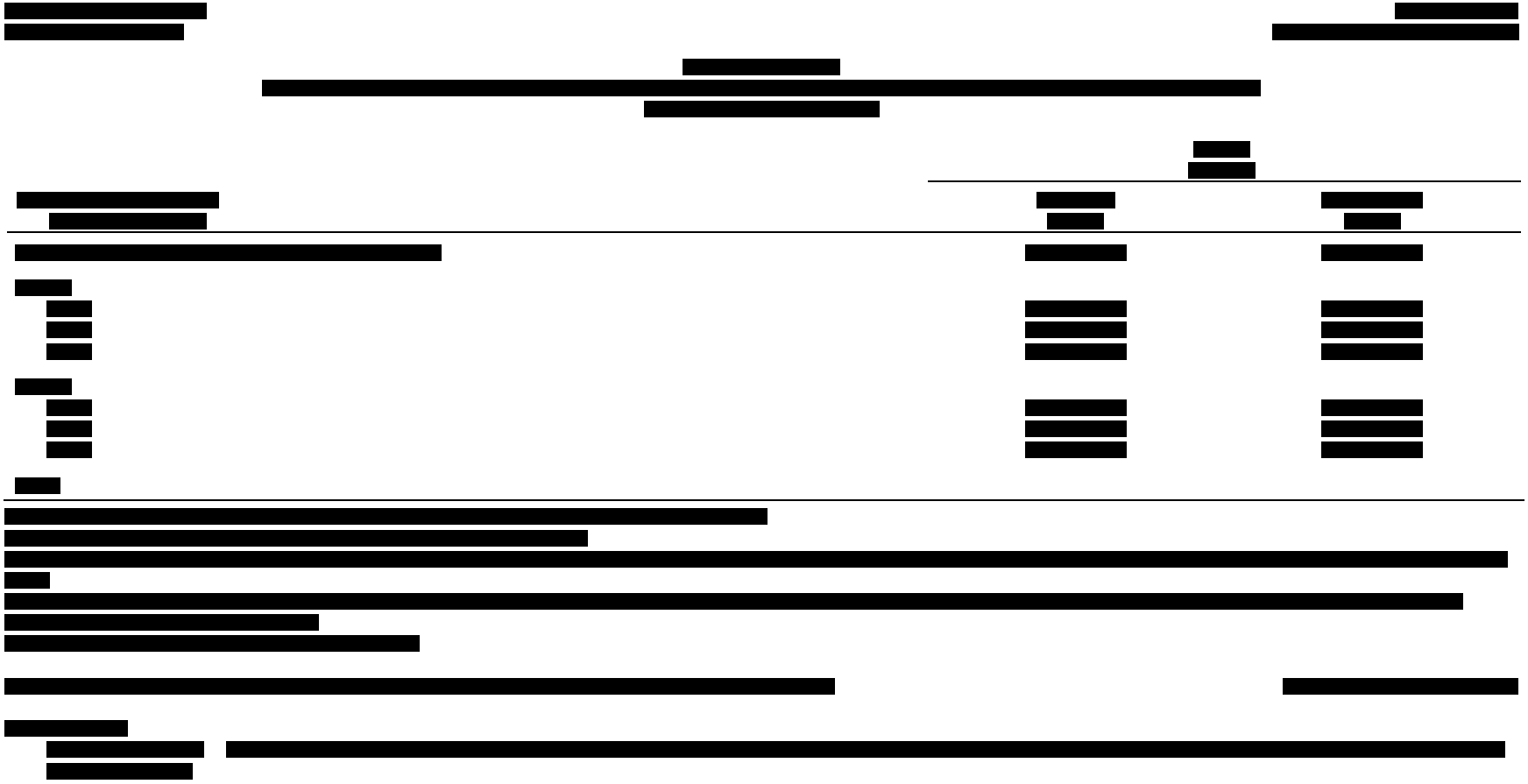

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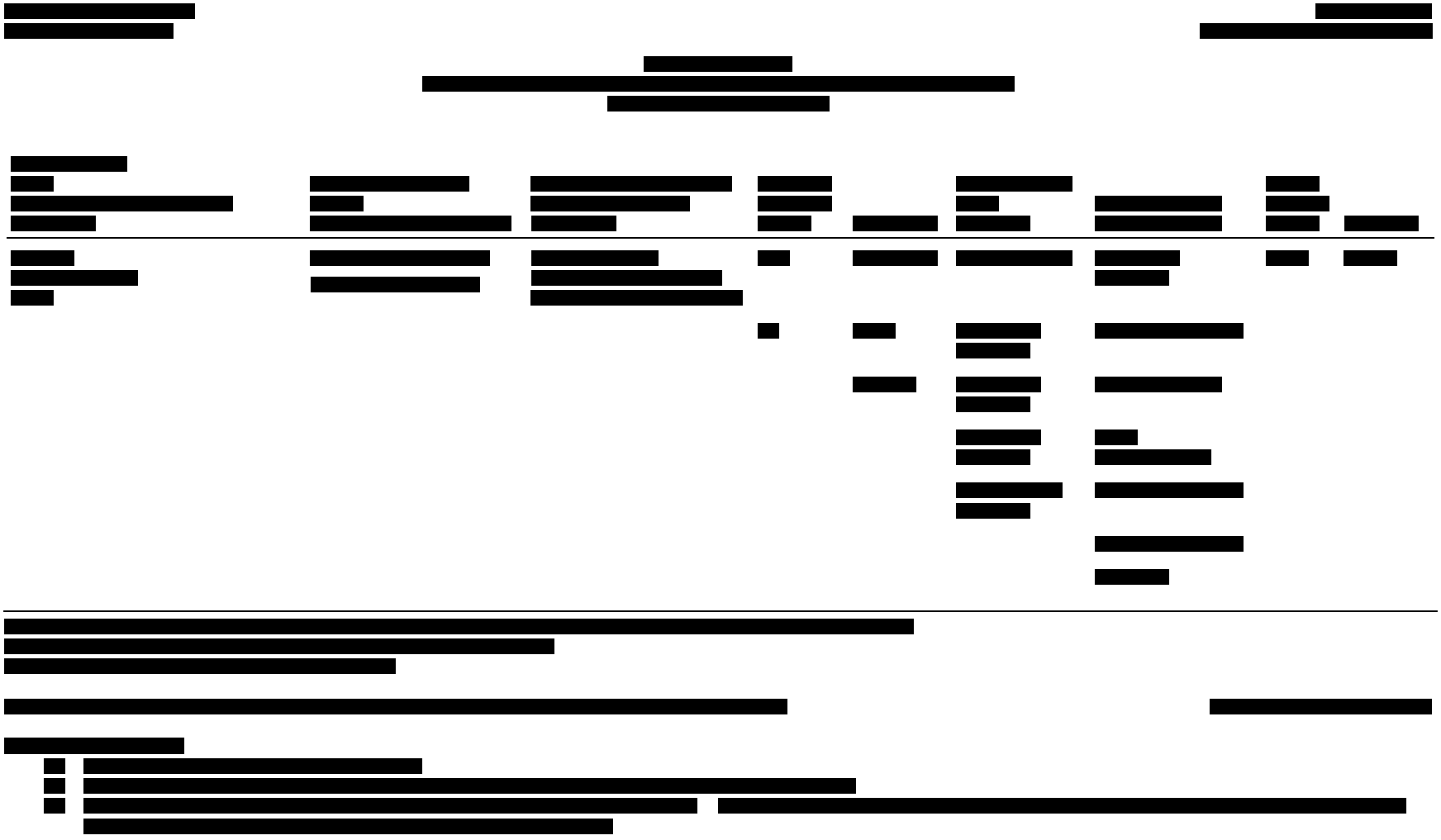

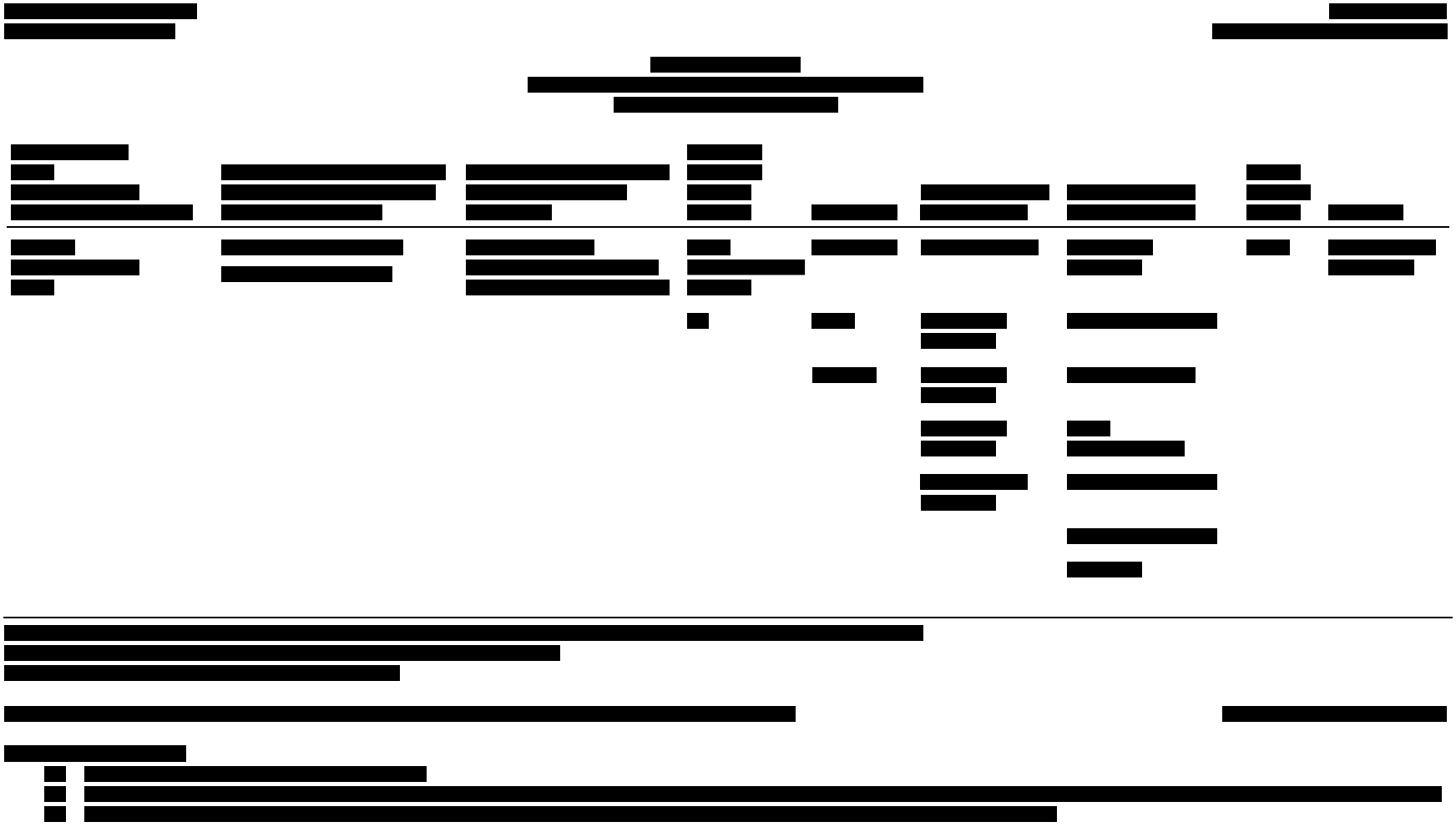

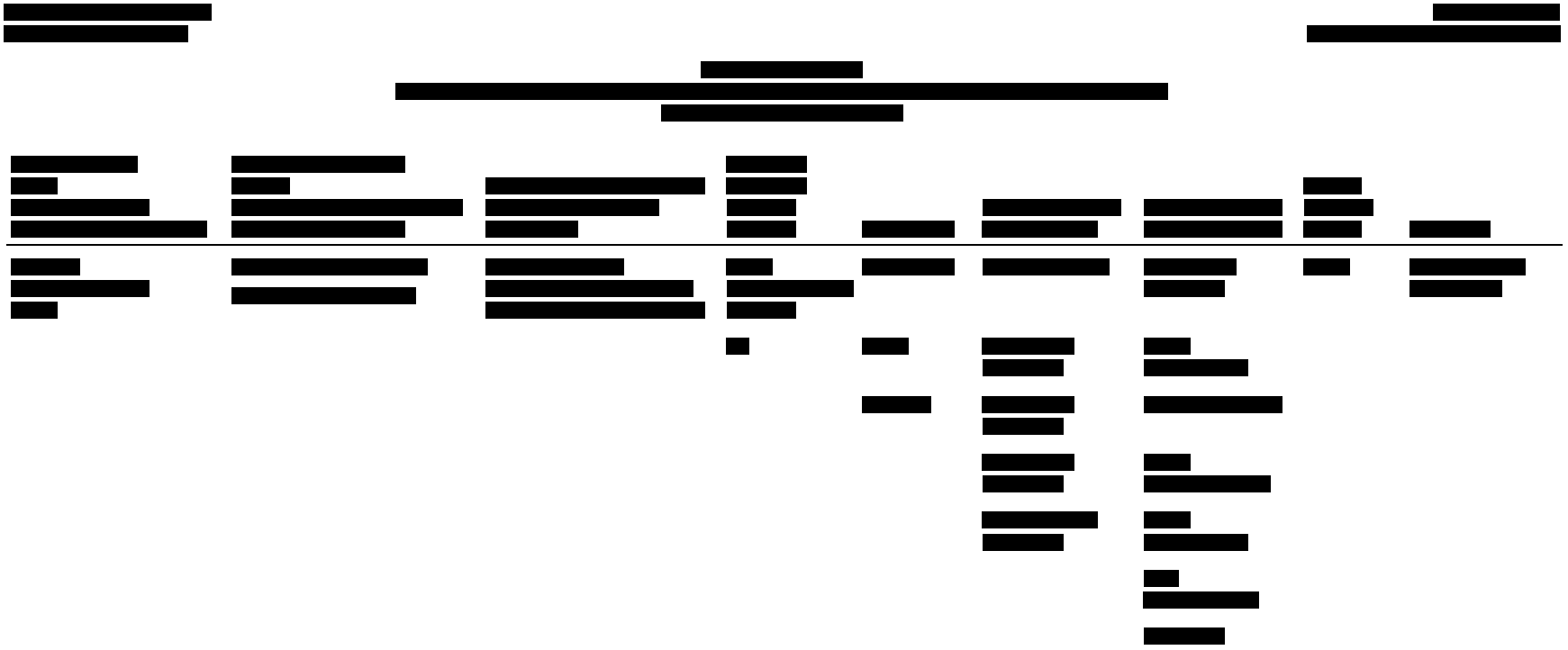

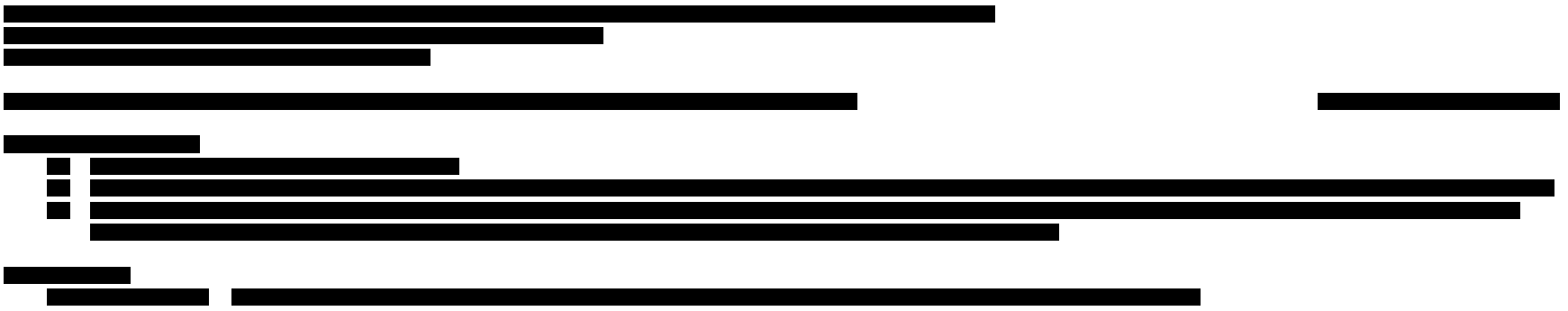

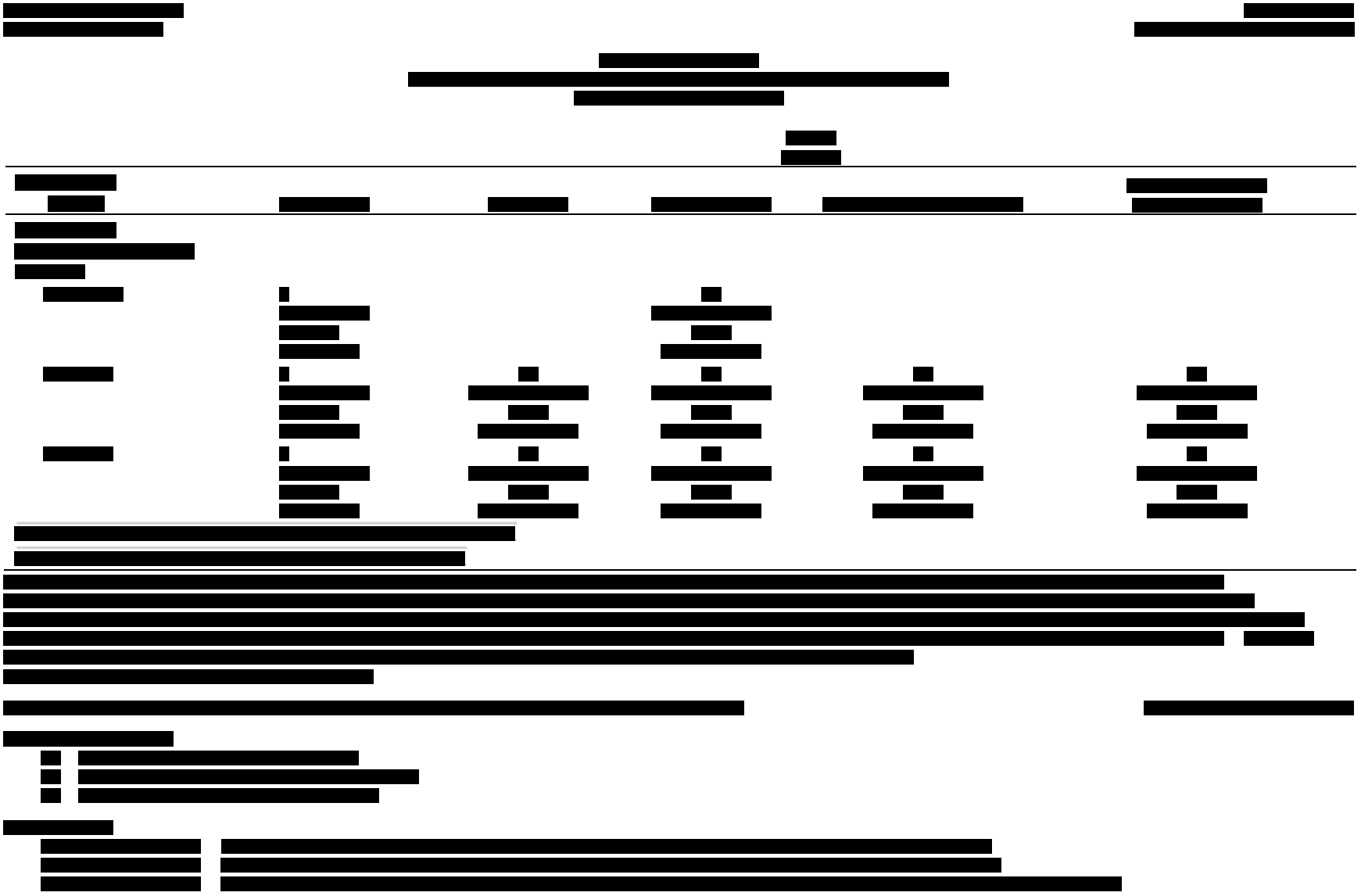

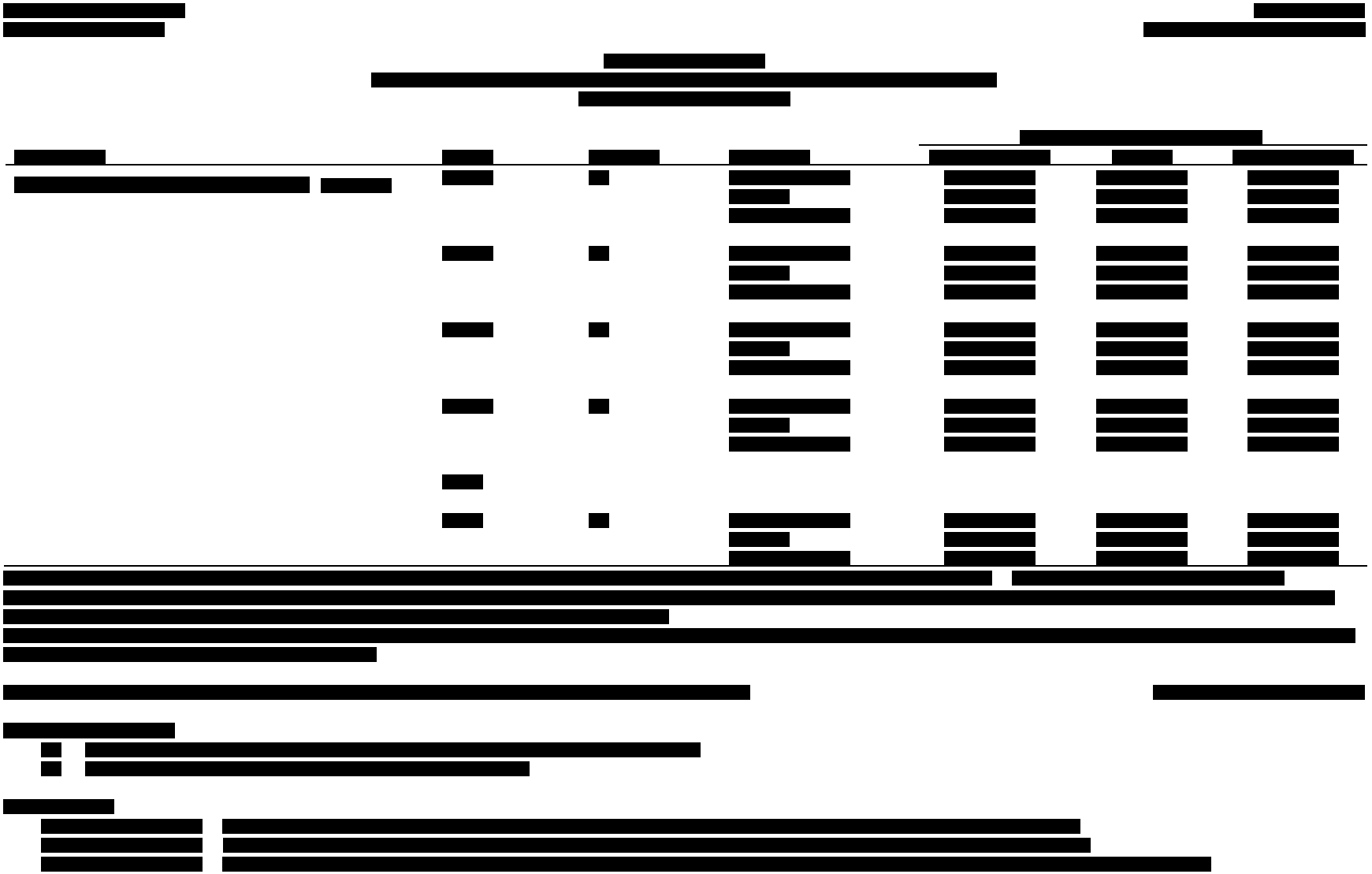

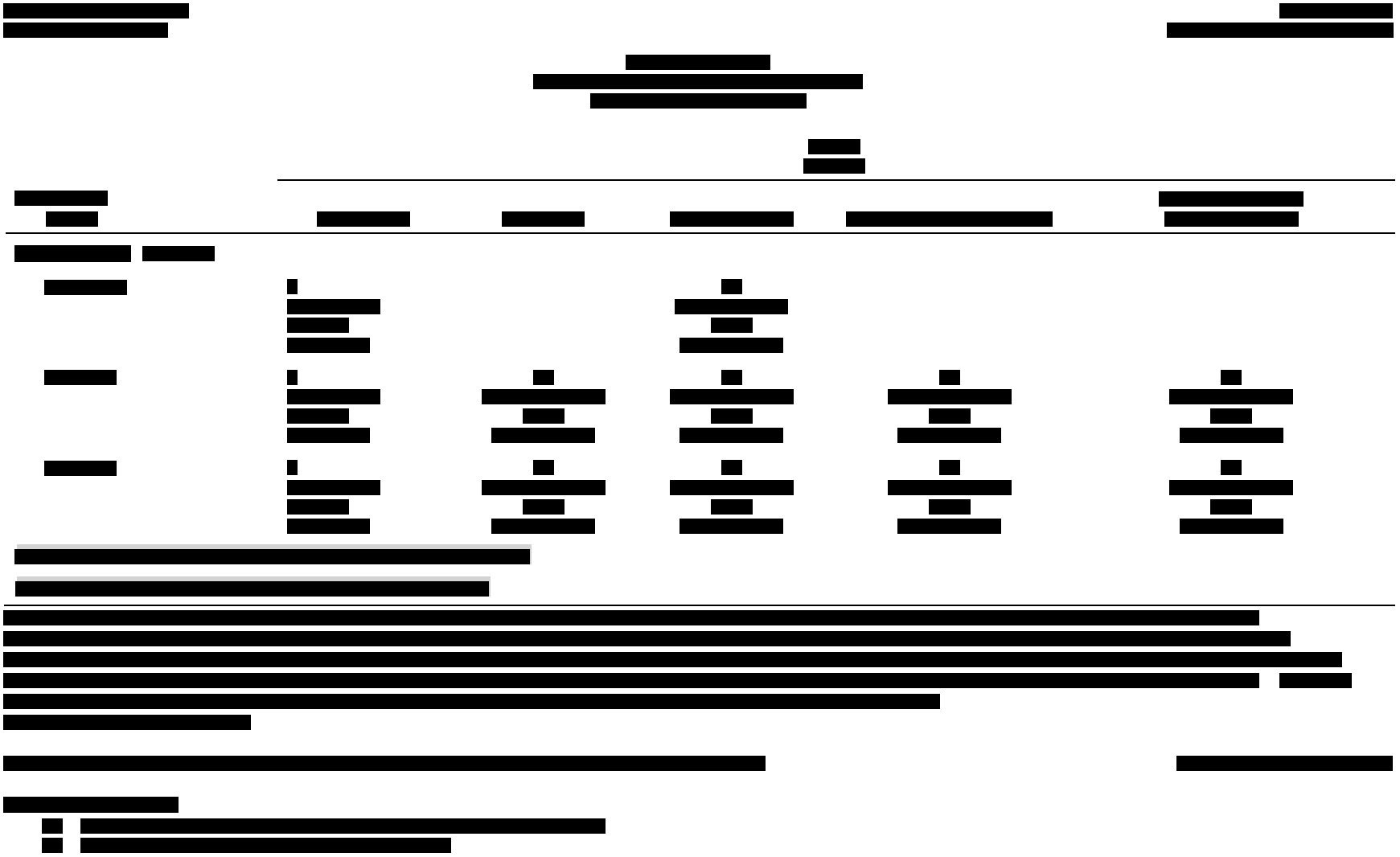

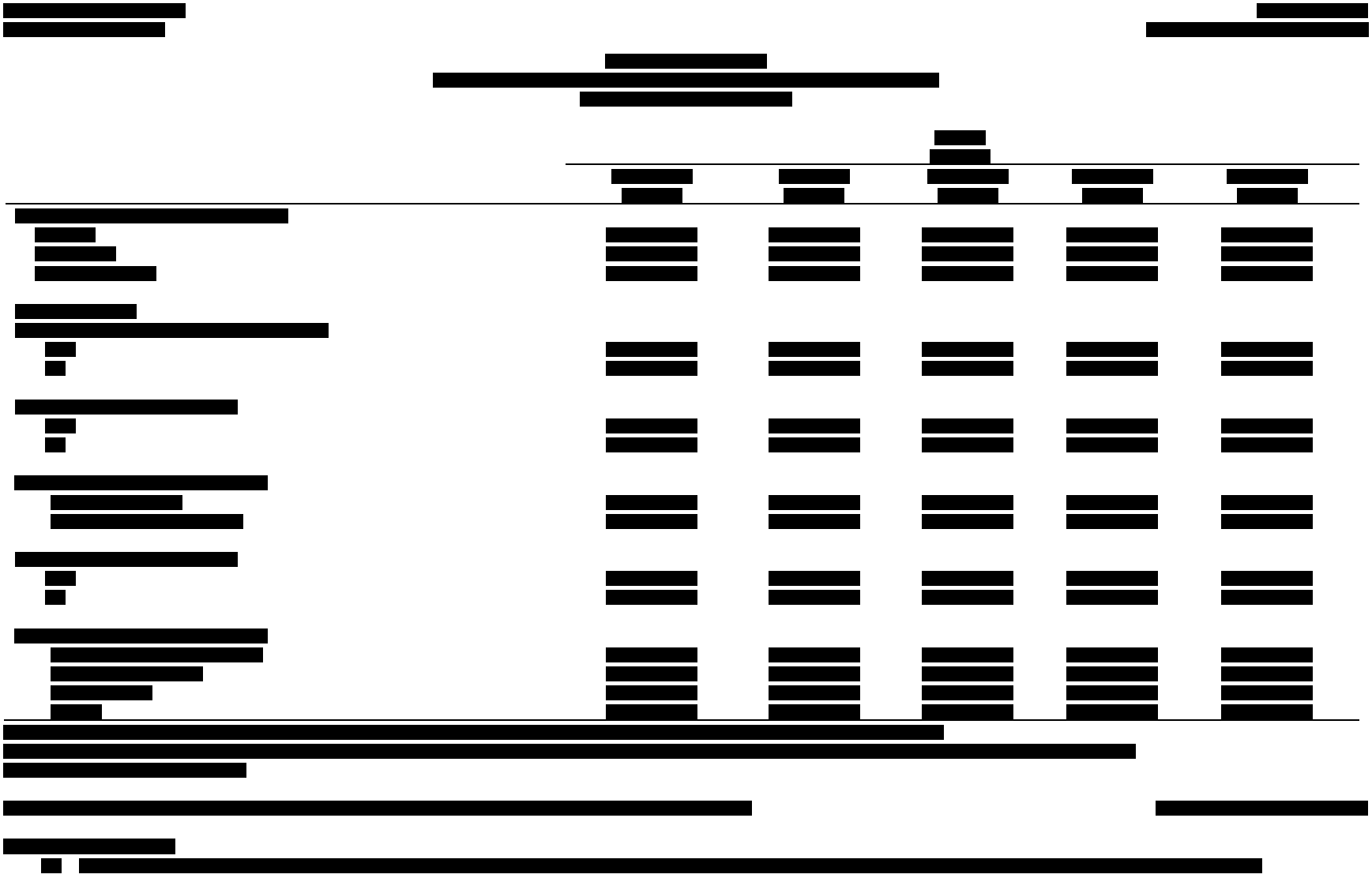

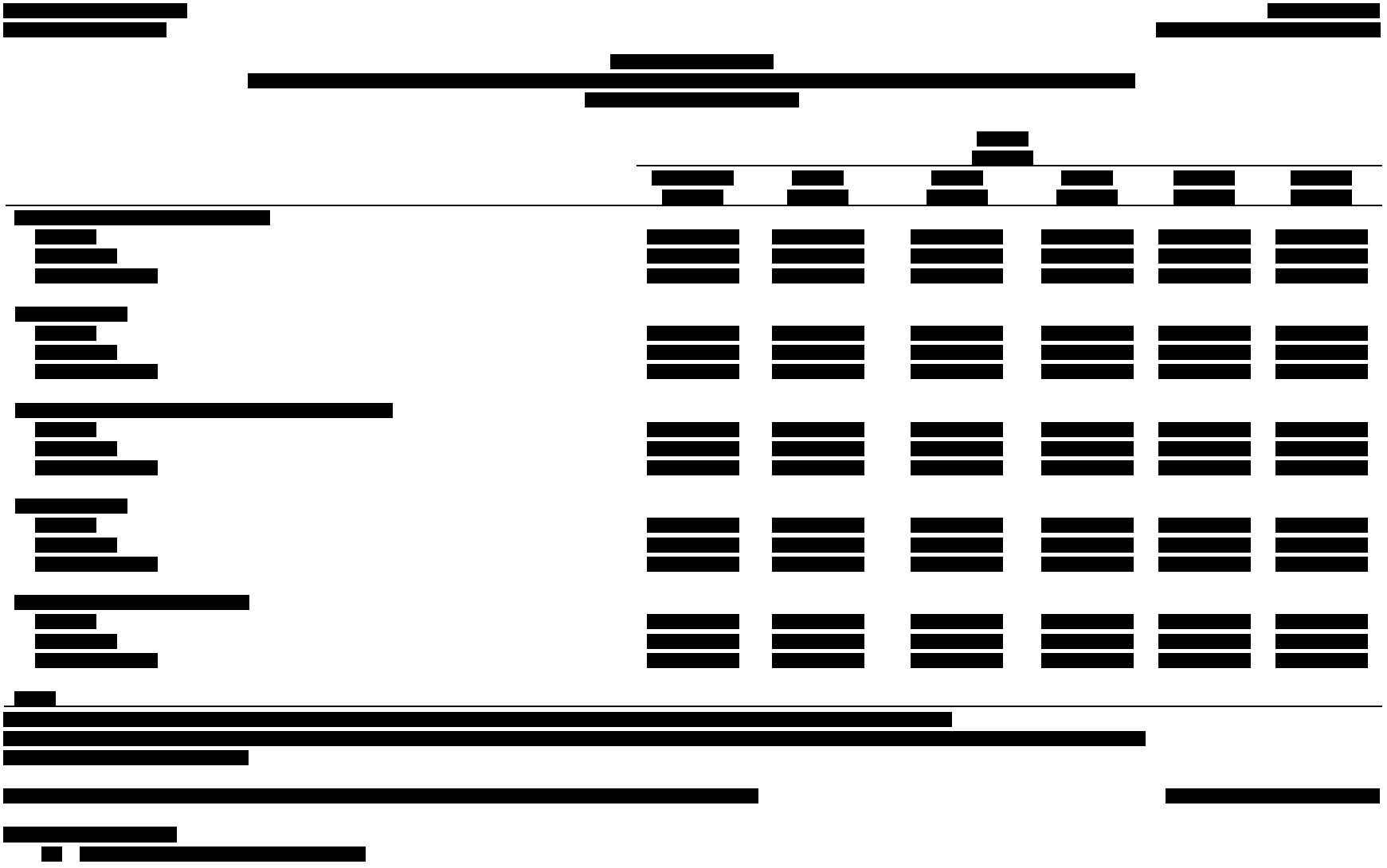

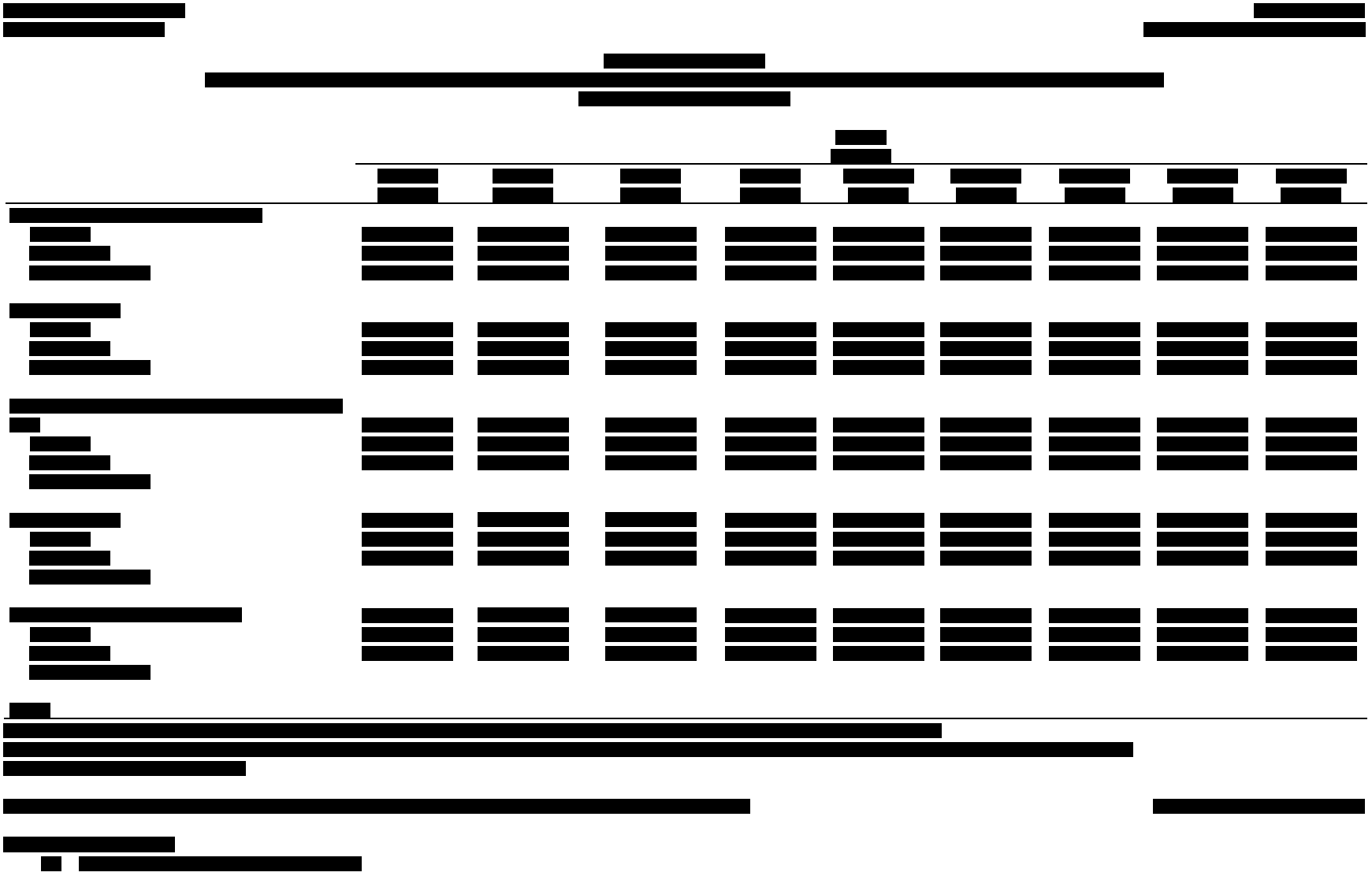

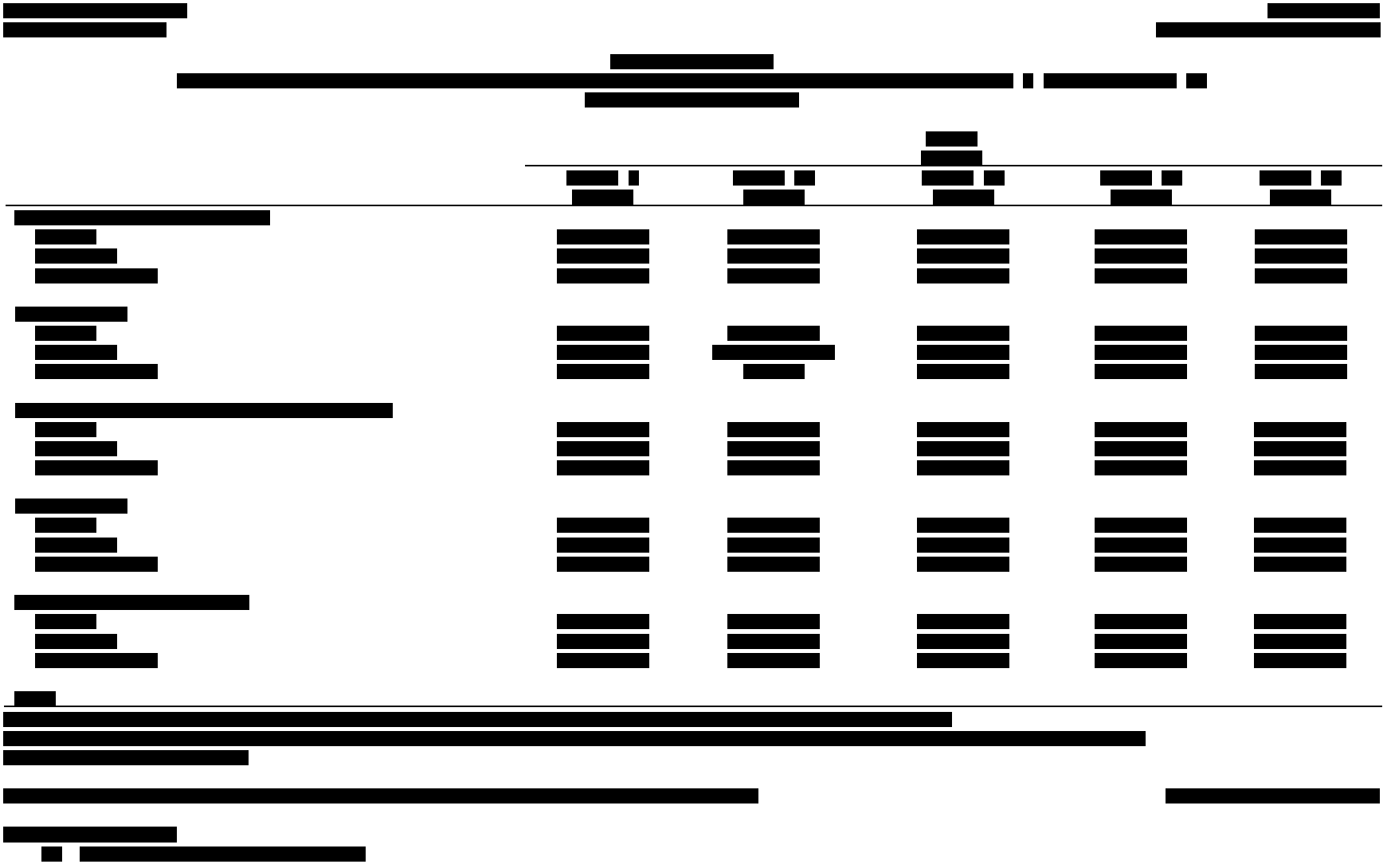

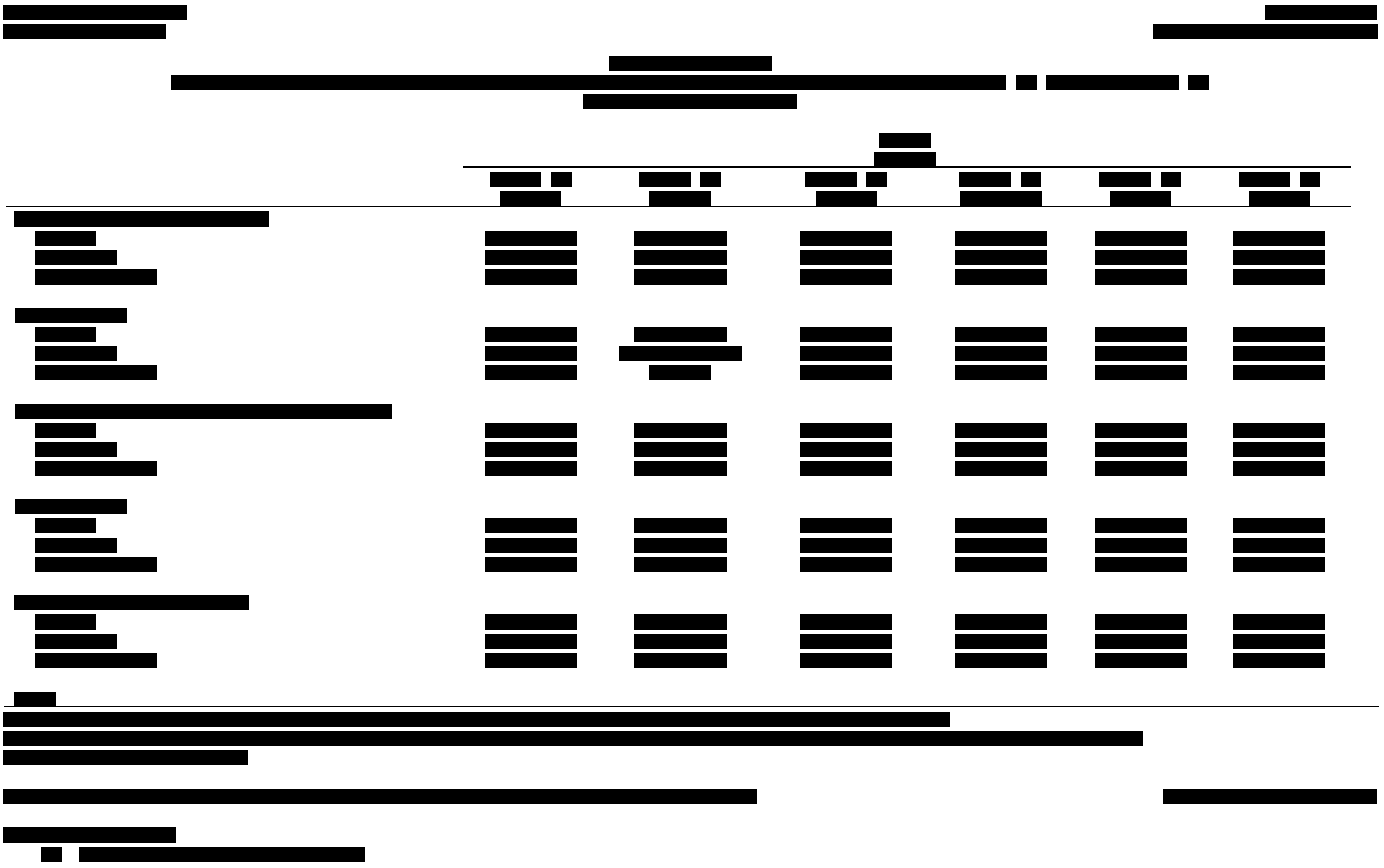

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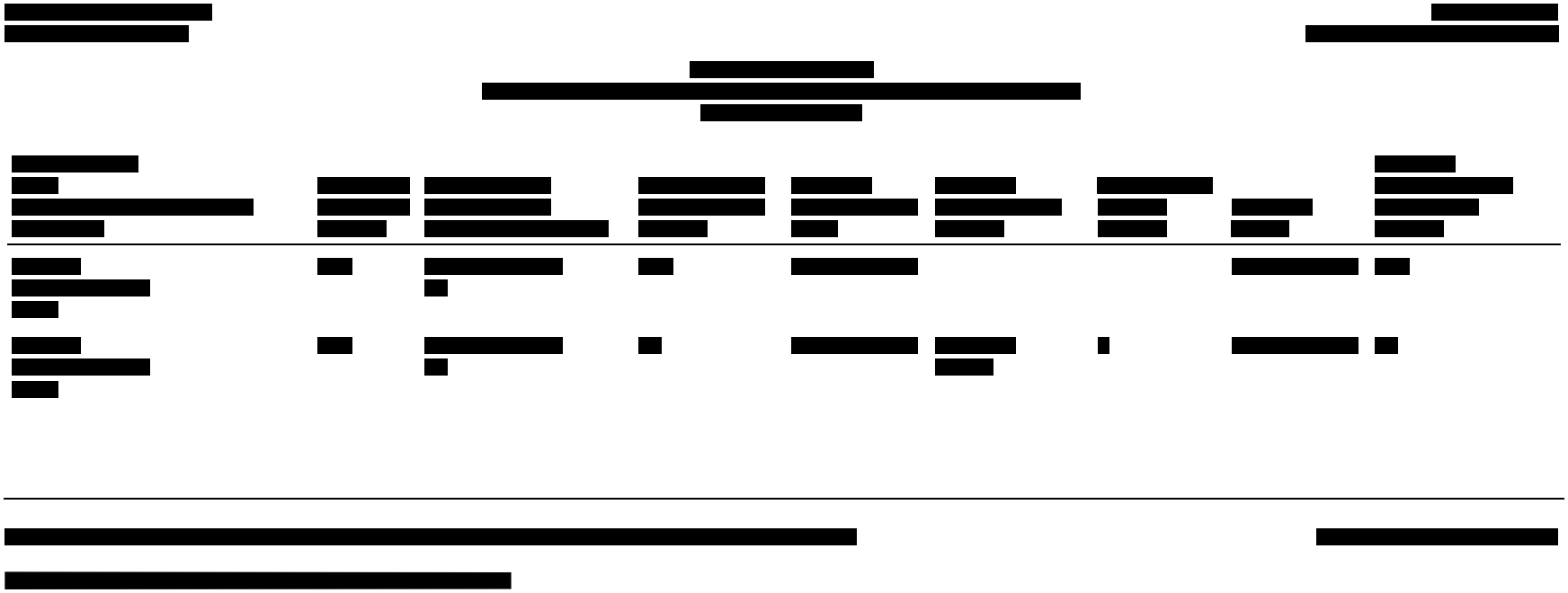

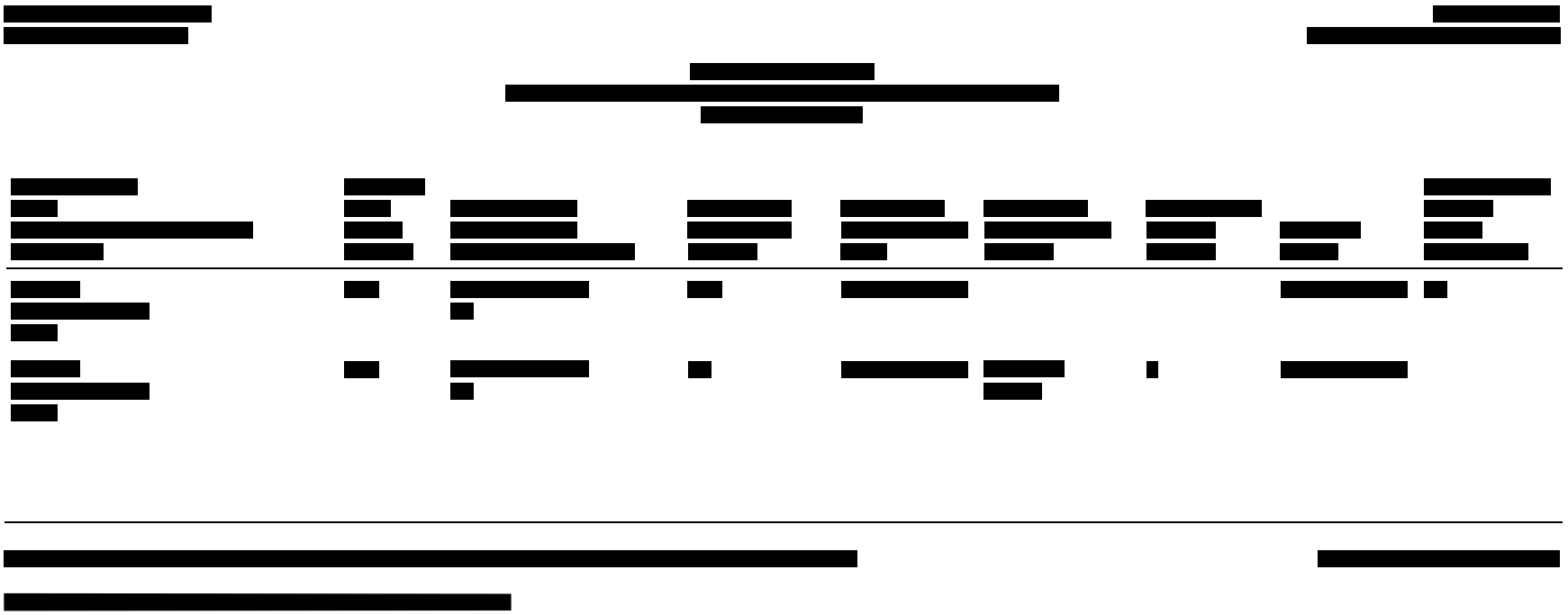

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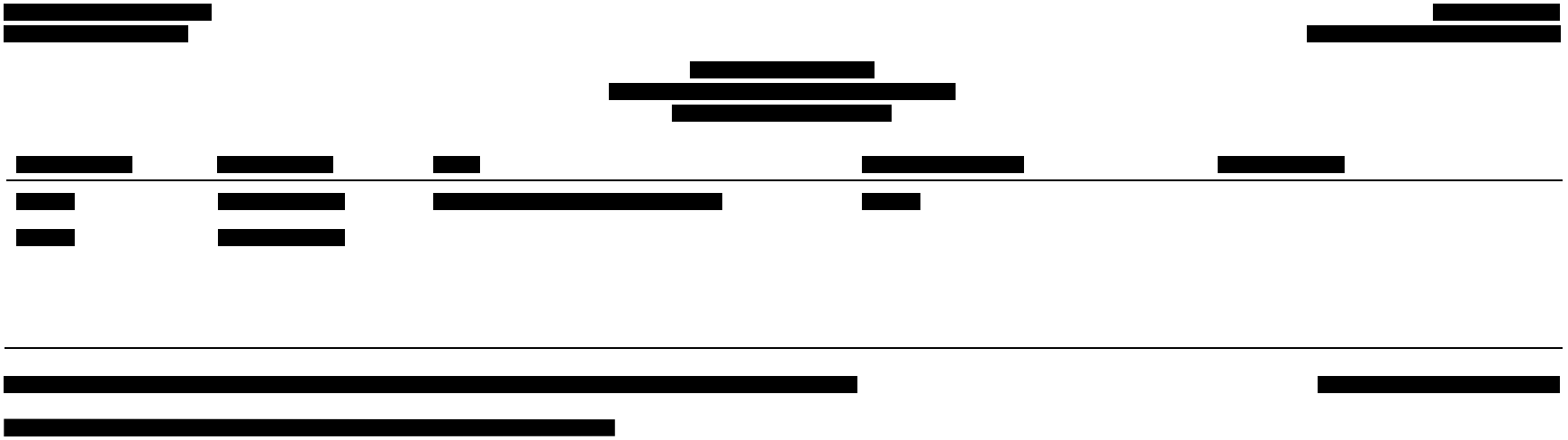

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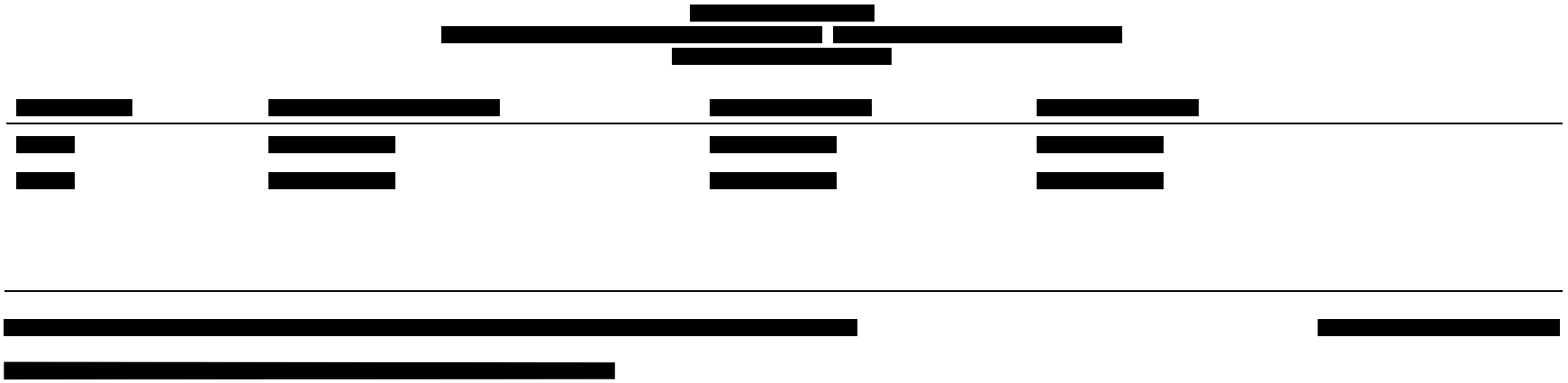

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