STATISTICAL ANALYSIS PLAN

V. 2.0 29-MAY-2019

[redacted]

SPONSOR:	**Achieve Life Sciences, Inc.**
PREPARED BY:	[redacted]
PROTOCOL TITLE:	A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2b Trial of Cytisine in Adult Smokers (**ACH-CYT-09**)
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APPROVAL SIGNATURES:

[redacted]

GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
ADaM	Analysis Data Model
AE	Adverse Event
ANOVA	Analysis of Variance
BMI	Body Mass Index
CI	Confidence Interval
CM	Concomitant Medication
CRF	Case Report Form
CSR	Clinical Study Report
DMP	Data Management Plan
ECG	Electrocardiogram
EOT	End of Treatment
FTND	Fagerstrom Test of Nicotine Dependence
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonization
LS Mean	Least Squares Mean
mg	milligrams
MH	Medical History
NMR	Nicotine Metabolite Ratio
RTF	Rich Text Format
SAP	Statistical Analysis Plan
SBQ-R	Suicidal Behaviors Questionnaire-Revised
SDTM	Study Data Tabulation Model
SEQ-12	Smoking Self Efficacy Questionnaire
SE	Standard Error
SI	Système International
SOC	MedDRA System Organ Class
SV1	Screening Visit #1
SV2	Screening Visit #2
TEAE	Treatment Emergent Adverse Event
tid	Three Times Daily

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a thorough description of statistical methods and presentation of the study data to be used for the analysis of data generated from the clinical trial described in protocol ACH-CYT-09: "A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2b Trial of Cytisine in Adult Smokers", Version 2.0 (26-September-2018).

This SAP was prepared by [redacted] under the direction of the study sponsor, Achieve Life Sciences Inc. (Achieve). It includes details of data handling procedures and statistical methodology. The final statistical analyses will proceed in accordance with this SAP as approved by both Achieve and [redacted] Any deviation from this SAP will be documented in the final CSR. Any deviations from methods described in the protocol are also detailed and explained in this SAP.

For this study, [redacted] is responsible for programming of datasets. [redacted] will provide to Achieve the Study Data Tabulation Model (SDTM) as well as Analysis Data Model (ADaM) dataset specifications based on:

- SDTM Model 1.4 and SDTM Implementation Guide (SDTM IG) version 3.2.
- ADaM Model 2.1 and ADaM Implementation Guide (ADaM IG) version 1.1.

In addition to the protocol, the following documents were reviewed in preparation of this SAP:

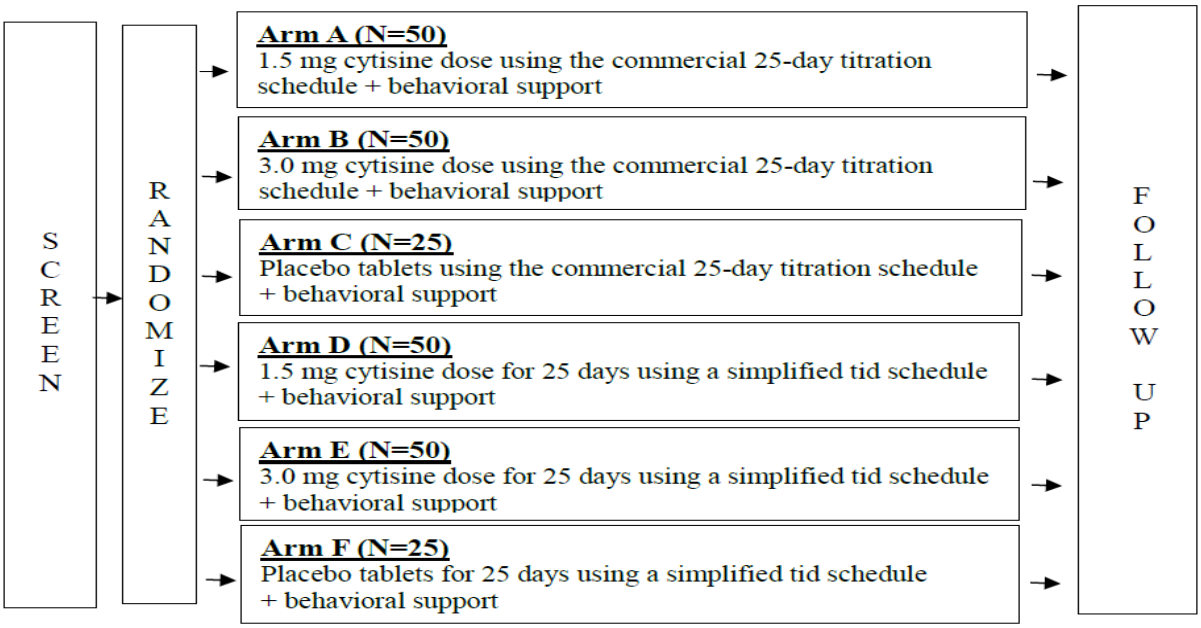
- Electronic Case Report Form (eCRF) version 2.1, 27-Feb-2019
- eCRF Completion Guidelines version 1.1, 28-Feb-2019
- Data Management Plan version 1.0, 05-Sep-2018
- Study Design Specification version 2.1, 27-Feb-2019

2. STUDY DESCRIPTION

2.1. Study Design

This Phase 2b study is a six-arm, multicenter, randomized, double-blind, placebo-controlled, and parallel-design trial of the safety and efficacy of cytisine in adult cigarette smokers who are willing to set a quit date that is 5-7 days after being randomized on the study. A total of 250 subjects are planned to be randomized at the ratio 2:1 to cytisine treatment and the respective placebo treatment as designated by the protocol defined schedule (i.e. the commercial titrated schedule vs the simplified three times daily (tid) schedule) for 25 days. Subjects will be stratified at randomization based on BMI class (18.5 to <25 kg/m^2; 25 to <30 kg/m^2; 30 to <35 kg/m^2) as defined in the protocol. The six treatment arms will be:

Figure 1: Study Design Overview



The study will be comprised of a pre-study screen, followed by twenty-five (25) days of study treatment, an end-of-treatment visit at Week 4 (Day 27 ± 2 days), and weekly post-treatment follow up visits from Week 5 to Week 8 post-randomization.

Blinding

- The study will be double-blinded to dose (1.5 mg cytisine, 3.0 mg cytisine, placebo) but not to the administration schedule (commercial titration schedule, simplified tid schedule).
- Sponsor and contract research personnel responsible for collecting, monitoring and analyzing the study data will also be blinded to dose but not to administration schedule.
- In order to blind the study treatment dose, all subjects will take 2 tablets at every scheduled dosing. Subjects randomly assigned to Arm A or Arm D will take one 1.5 mg cytisine tablet and one placebo tablet at each dosing. Arm B or Arm E subjects will take two 1.5 mg cytisine tablets at each dosing. Arm C and Arm F subjects will receive two placebo tablets at each daily scheduled dosing to correspond to cytisine dosing.

Randomization

- Eligible subjects will be randomized 2:1 in a blinded manner to either Arm A or Arm B vs Arm C (2:1 randomization) or Arm D or Arm E vs Arm F (2:1 randomization)

- Subjects will be stratified at randomization by BMI class (18.5 to <25 kg/m^2; 25 to <30 kg/m^2; 30 to <35 kg/m^2).
- Unique subject number and randomization code will be assigned to each study subject
- Parallel group design

Multicenter Trial

- This study will be conducted at multiple sites across the US

Type of Comparison

- Superiority in favor of cytisine

2.2. Treatment Schedules

For the 25-day commercial titration schedule, study drug will be administered according to the following schedule:

Treatment Day	Daily Administration	Approximate Interval
1-3	6 times daily	2 hours
4-12	5 times daily	2.5 hours
13-16	4 times daily	3 hours
17-20	3 times daily	4-5 hours
21-24	2 times daily	6 hours
25	1 time only	-

For the tid schedule, study drug will be administered according to the following schedule:

Treatment Day	Daily Administration	Approximate Interval
1-20	3 times daily	4-5 hours
21-24	2 times daily	6 hours
25	1 time only	-

All subjects will receive 2 tablets for each dose according to their randomization arm.

Subjects that work overnight will potentially be taking their daily administered dose over two calendar days. This is accounted for in the CRF and the date of their first dose taken will be recorded as the dosing start date.

2.3. Study Population

Approximately 250 subjects who are daily cigarette smokers intending to make a quit attempt during the study will be enrolled at multiple study sites within the US. Based on the planned 2:1 (cytisine:placebo) randomization, it is expected that 200 subjects will be randomized to receive

cytisine (50 subjects at each cytisine treatment arm) and 50 subjects will be randomized to receive placebo (25 subjects per treatment schedule).

3. STUDY OBJECTIVES

3.1. Primary Efficacy Objectives

The primary efficacy objectives of this study are:

1. Assess whether subjects randomized to cytisine, administered using the commercial titration schedule, have a greater overall reduction in cigarette smoking during the study treatment period (Day 1 – 25) compared to subjects randomized to the same titration schedule of a placebo.
2. Assess whether subjects randomized to cytisine, using a simplified tid schedule, have a greater overall reduction in cigarette smoking during the study treatment period (Day 1 - 25) compared to subjects randomized to the same tid schedule of a placebo.

3.2. Other Efficacy Objective(s)

Each of the following will include comparisons for 1.5 mg or 3.0 mg doses versus placebo when given as the commercial 25-day titration schedule and for the tid treatment schedule (as well as comparisons between the commercial 25-day titration versus tid treatment schedules). The other efficacy objectives are:

1. Assess the probability of abstinence from Week 5 to Week 8 post-randomization in subjects randomized to cytisine as compared to subjects randomized to placebo.
2. To compare cytisine and placebo arms on initial quit rates during study treatment, at Week 4 (End of Treatment) and on 7-day point prevalence abstinence at Week 5, Week 6, Week 7, and Week 8.
3. Among subjects abstinent at Week 4 (End of Treatment), compare time to failure to maintain abstinence through Week 8 between arms.
4. To explore potential relationships between subject-reported outcomes (e.g. anxiety, withdrawal symptoms, depression, tobacco craving, alcohol use) with the reduction in cigarette smoking during the study treatment period, as well as smoking cessation outcomes at Week 4 (End of Treatment) and from Week 5 to Week 8 post-randomization.
5. To explore a potential correlation for subject's nicotine metabolite ratio (NMR) with the reduction in cigarette smoking and smoking cessation outcomes.

3.3. Safety Objective(s)

To evaluate overall safety profiles of cytisine when administered at 1.5 mg or 3.0 mg, using the commercial 25-day titration or simplified tid schedules, compared to placebo.

3.4. Subject Selection

Only adult subjects (aged at least 18 years old) who are daily smokers (10+ cigarettes daily) with intention to quit smoking during the study, in addition meeting all the inclusion criteria and none of the exclusion criteria in the protocol will be enrolled in this study.

3.5. Determination of Sample Size

The sample size was computed based on data from a previous Phase 1/2 trial and for achieving narrow confidence intervals (CI) for the primary comparison estimates in this trial.

The trial size was based on projected realization of the effect size estimate for the primary outcome based on data from a Phase 1/2 study in adult smokers. The primary outcome standard deviation from this study was found to be approximately 17. Based on this standard deviation, the estimated between-arm differences in the primary comparisons can be estimated with a 95% CI that is ±8.3.

The trial size will not have sensitivity for a dichotomous outcome (e.g. smoking cessation as one of the other efficacy outcomes), other than for possibly large differences. For example, if the control arm outcome is 12% (3/25 defined as successes), then the experimental arm will have a two-sided 95% CI for the probability difference that excludes zero when the success probability is 36% (8/50) or more (computation based on exact CI).

3.6. Treatment Assignment

A total of approximately 250 subjects who meet the inclusion/exclusion criteria will be randomized at 2:1 ratio to the cytisine treatment and the respective placebo treatment as designated by the defined schedule, commercial titration vs simplified tid schedule.

3.7. Administration of Study Medication

All subjects will receive 2 tablets at each dosing according to the commercial titration schedule or to simplified tid schedule. For details, refer to the protocol.

4. EFFICACY AND SAFETY ENDPOINTS

4.1. Efficacy Endpoints

Efficacy endpoints will be based on cigarette consumption data. Subjects will record their cigarette consumption in a daily diary for 7 consecutive days during the screening period, and each day during the 25-day treatment period (i.e. on Day 1 through Day 25, inclusive). After Day 25, subjects will attend a Day 27 End of Treatment (EOT) clinic visit and post-treatment follow-up visits at Week 5, Week 6, Week 7 and Week 8. At each visit clinic staff will ask subjects whether they have smoked since the previous clinic visit and/or over the past 7 days, and the number of cigarettes smoked in the past 7 days.

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be based on the daily cigarette consumption data recorded in the subject diary. The primary efficacy endpoint is defined as the percent of expected cigarettes smoked computed for each subject, at end of treatment. This percent is designated by Y, Y is calculated as below:

$$\mathbf{Y} = \frac{\mathbf{100}\times\boldsymbol{N}}{\boldsymbol{T}\times\boldsymbol{R}}$$

where N represents total number of cigarettes smoked each day over the treatment period from Day 1 to Day 25; T represents number of post-randomization days where number of cigarettes smoked is recorded; and R represents the average number of cigarettes smoked daily over the 7-day screening period as baseline. T*R represents the total number of cigarettes that would have been smoked without intervention over the number of recorded days.

If a subject has no cigarette-count data collected post-randomization, then the primary endpoint will be imputed to a value of 100 (i.e., no change from baseline cigarette consumption). This is equivalent to imputing the total number of post-randomization days with data recorded (T) is 25 and the total number of cigarettes smoked over the treatment period (N) is the average number smoked daily at baseline (R) times 25.

The primary comparisons for this endpoint will be comparisons of active arms to the associated placebo arm, refer to Figure 1:

Arm A (1.5 mg cytisine commercial schedule) versus Arm C (placebo commercial schedule),

Arm B (3.0 mg cytisine commercial schedule) versus Arm C (placebo commercial schedule),

Arm D (1.5 mg cytisine tid schedule) versus Arm F (placebo tid schedule), and

Arm E (3.0 mg cytisine tid schedule) versus Arm F (placebo tid schedule).

4.1.2. Other Efficacy Endpoints

The endpoints associated with the other efficacy objectives are:

Abstinence from Week 5 to Week 8 is a binary endpoint (success, failure). Success is defined for a subject as having reported smoking abstinence (no cigarettes since the last clinic visit and over the past 7 days) at each clinic assessment from Week 5 to Week 8 with biochemical verification at each assessment. Biochemical verification will be defined by a CO concentration in exhaled breath of less than 10 ppm. Subjects will be allowed only 1 missed visit (smoking status and/or biochemical verification status unknown) between Week 5 and Week 8 (i.e. one of Week 6 or Week 7 visits only) for analysis of the abstinence from Week 5 to Week 8 endpoint.

Any outcome other than success will be regarded as a failure. There are therefore two types of failure for subjects: (1) subjects with adequate data that they were smoking at any time from Week 5 to Week 8 (either by the subject's self-report of smoking or CO ≥10 ppm) and (2) subjects having insufficient data to be determined as a success for abstinence from Week 5 to

Week 8 endpoint (e.g., subjects lost to follow-up, missing the Week 5 and/or Week 8 clinic visit, or missing both the Week 6 and Week 7 visits).

All subjects will have a realization of this endpoint, thereby enabling analyses that follow the intent-to-treat (ITT) principle without imputation.

Initial quit rate is a binary endpoint (success, failure) at Week 4 (Day 27 EOT). Success is defined for a subject as having reported smoking zero cigarettes in the subject diary at Day 25, with biochemical verification by an expired-air CO reading <10 ppm at the Day 27 EOT clinic visit. Any other outcome will be regarded as a failure. This endpoint is defined at the End of Treatment visit so that subjects have approximately a 2½-week grace period after the Day 5-7 quit date. All subjects will have a realization for this endpoint, thereby enabling analyses that follow the ITT principle without imputation.

7-day point prevalence is a binary endpoint (success, failure) at each of the following visits: Week 5, Week 6, Week 7 and Week 8. At each visit, success is defined for a subject as having reported not smoking any cigarettes over the past 7 days with biochemical verification by an expired-air CO reading <10 ppm. Any other outcome will be regarded as a failure. All subjects will have a realization of this endpoint, thereby enabling analyses that follow the ITT principle without imputation.

Time to failure to maintain abstinence through Week 8 will be evaluated for the subgroup of subjects who were classified as a success for the initial quit rate endpoint (see previous definition). Time to failure to maintain abstinence (days) will be calculated as end date of abstinence minus start date of abstinence + 1. The start date of abstinence will be defined as the date of the Week 4 (Day 27 EOT) visit. The end date of abstinence will be defined as the earliest date that the subject was known to have resumed smoking. Specifically:

- At a visit, if a subject reported not smoking in the past 7 days but has smoked since the last visit (either by the subject's self-report or CO ≥10 ppm), the end date of abstinence will be the date of that last visit.
- At a visit, if a subject reported not smoking since the last visit but has smoked in the past 7 days (either by the subject's self-report or CO ≥10 ppm), the end date of abstinence will be defined as the date of the visit minus 7 days.
- Subjects who have not resumed smoking at the final (Week 8) visit will have end date of abstinence censored at the date of the Week 8 visit.

Relationship between Outcome Variables and Smoking Reduction and Cessation Endpoints: The relationships between subject-reported outcomes (e.g. anxiety, depression, withdrawal symptoms, tobacco craving, alcohol use) and the following smoking efficacy endpoints will be evaluated:

- The primary efficacy endpoint, which measures reduction in smoking during the study treatment period.
- Initial quit rate, which evaluates smoking cessation at Week 4 (Day 27/EOT).

- Abstinence from Week 5 to Week 8.

It is expected that the relationship between each of these efficacy variables and the following subject-reported outcome variables will be evaluated for this objective:

- Change during the treatment period, in self-reported number of cigarettes smoked over the previous 24 hours.
- Total scores and change from baseline for the following questionnaires: HADS-Anxiety, HADS- Depression, Tobacco Craving (TC).
- TC subscores for Emotionality, Expectancy, Compulsivity, and Purposefulness.
- Responses on the Alcohol Use questionnaire.
- Adverse event outcomes such as whether the subject experienced any adverse events, any serious adverse events.
- Compliance outcomes such as percent of study drug taken, number of behavioral support sessions attended.

The potential correlation for subjects' nicotine metabolite ratio (NMR) with both reduction in cigarette use and smoking cessation will be explored during the study treatment period and at Week 8.

4.2. Safety Endpoints

The safety endpoints are:

- Adverse events.
- Laboratory assessment
  - Hematology
  - Chemistry
- Vital signs
- ECG results
- Concomitant medications

4.3. Pharmacokinetic and Pharmacodynamic Evaluations

None planned.

5. TRIAL CONDUCT CONSIDERATIONS

5.1. Changes in Inclusion and Exclusion Criteria

No changes are planned.

5.2. Interim Analysis and Early Stopping

None planned.

5.3. Sample Size Adjustment

Not applicable.

6. DATA ANALYSIS CONSIDERATIONS

6.1. General Considerations

The overall goal of the study is to obtain estimates of effect size for efficacy and safety endpoints that will be used to inform the design of future studies. As stated in the protocol, this study will be analyzed without specific statistical criteria. That is, no formal statistical hypothesis testing will be conducted and consequently a level of significance (α level) is not specified in this Statistical Analysis Plan. There will be statistical testing with P values and confidence intervals computed. The P values will be interpreted as an assessment of consistency with the play of chance (small P values indicating a small likelihood the observed effect is due to chance) and will be used qualitatively in decisions concerning next steps.

Statistical analyses will be performed at the conclusion of the study once all data have been collected, cleaned, and the database has been locked.

Medical history events and adverse events will be coded to standard “preferred terms” and “system organ classifications (SOC)” using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG) Version Sep-2017 B2.

All statistical programming will be done using SAS® version 9.4 (SAS® Institute, Cary, North Carolina). All tables, figures and listings will be produced in landscape format.

In general, all data will be listed by treatment arm, subject and visit/time point where appropriate. The summary tables will have columns corresponding to, or be stratified by, treatment arm. The 6 treatment arms are: 1.5 mg Cytisine – Commercial Schedule, 3.0 mg Cytisine – Commercial Schedule, Placebo – Commercial Schedule and 1.5 mg Cytisine – tid Schedule, 3.0 mg Cytisine – tid Schedule, Placebo – tid Schedule.

The total number of subjects under the stated analysis set in each treatment arm (N) will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. In case of n<2, where n indicates the number of evaluable subjects at the particular time point, the standard deviation will be empty. The statistic "Missing" will also be presented as the number of missing entries/subjects, if any at that visit/timepoint, and presented as a summary statistic only when non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be used. The count [n] indicates the actual number of subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects with non-missing value of the variable or event [M]. Percentage will be obtained by: % = (n/M)*100. Unless otherwise stated, all percentages will be expressed to one decimal place.

In by-visit summary tables only scheduled visits/timepoints will be summarized. In listings all visits and timepoints with any data collected, including both scheduled and unscheduled ones, will be included.

All dates in tables, figures and listings will be displayed in DDMMMYYYY format.

All outputs will be sent to Achieve as electronic files in RTF format documents.

6.2. Definition of Analysis Timepoints

- **Baseline:** The last non-missing observation prior to the first dose of study drug (cytisine and/or placebo), unless otherwise specified. If both a planned assessment and repeat assessment (e.g., retest) meet the above criteria and were collected on the same date and time, the repeat assessment will be used as baseline.
- **Change from Baseline:** The change from baseline values will be derived for each subject as the post-baseline value minus the baseline value.
- **Pre-treatment Period:** Prior to first dose of study drug on Day 1.
- **Study Treatment Period:** Starts on the date of the first dose of study drug (Day 1), continues through the last dose of study drug (Day 25) and ends on the date of the Week 4 (Day 27 EOT) visit.
- **Smoking Cessation Period:** Includes the weekly visits at Week 5, Week 6, Week 7, and Week 8.
- **Follow-up Period:** Includes the weekly visits at Week 5, Week 6, Week 7, and Week 8.

- **Study Day:** Study day will be calculated for safety endpoints relative to the first dose of study drug (cytisine and/or placebo). The first dose of study treatment will be Day 1, and the date preceding Day 1 will be Day –1 which is consistent with the Submission Data Standards (Version 3.1) from Clinical Data Interchange Standards Consortium (CDISC).

6.3. Data Handling Rules

Dropouts (ICH E3/11.4.2.2) will not be replaced during the study, but will be included in the data analysis to the extent that evaluable data are present.

For qualitative parameters, a category with the number of subjects with missing values will be presented where applicable.

6.3.1. Missing Dates

Partial or missing dates will be imputed only if a date is required to derive a study endpoint (e.g. time to failure, duration of AE). Otherwise no date imputation will be done. Date imputation will follow the rules below.

Efficacy Related Dates

Partial or missing dates required to computing efficacy endpoints will be imputed as follows:

- Missing day only: For partial dates with only the day of the month missing, the day will be imputed as the 15th day of the month, provided that a preceding date of interest does not occur in the same month. If the preceding date does occur in the same month, then the missing day will be imputed as half the distance between the preceding date and the end of the month.
- Missing month and day: For partial dates with the month and day missing, the month and day will be imputed as July 1st, provided that a preceding date of interest does not occur in the same year. If the preceding date occurs in the same year, then the month and day will be imputed as half the distance from the preceding date to the end of the known year.
- Missing month, day, and year: Missing dates will be imputed as the date of first dose.
- In situations where the above rules result in an illogical time (e.g., negative study day, negative time to failure, etc) the date will be imputed as the date half the distance between the preceding date of interest and the partial date.

Safety Related Dates

For safety data where the date of onset is during or after administration of the first dose of study drug, missing or partial start dates will be imputed as the earliest possible date that is on or after the date of the first dose of study drug. For events occurring prior to first dose of study drug, missing or partial dates will not be imputed.

- Missing day only: If the start date and date of first dose share the same month and year, the missing start day will be imputed as the day of first dose. If the start date month is after the month of first dose, day will be imputed as the 1st (i.e., 01-Jan-2019).
- Missing month and day: If the start date and date of first dose share the same year, day and month will be imputed as the day and month of first dose. If the start date year is after the year of first dose, the month and day will be imputed as January 1st (i.e., 01-Jan-2019).
- Missing month, day, and year: Missing start dates will be imputed as the date of first dose.

6.4. Analysis Sets

Three analysis sets will be used.

Screening Analysis Set: all subjects who give written informed consent and have entered screening. The Screening Analysis Set consists of two mutually exclusive subgroups:

- subjects who were not randomized at completion of screening, generally due to failure of one or more of the study entry criteria (i.e., the inclusion/exclusion criteria) and
- subjects who were randomized at completion of screening

Safety Analysis Set: all randomized subjects who take at least one dose of study drug. Subjects will be evaluated by their randomized treatment arm ('intent-to-treat' analysis) unless otherwise specified. The Safety Analysis Set will be the primary set for safety summaries. Safety summaries may also be provided based on the treatment actually received.

All Randomized Analysis Set: all randomized subjects. Subjects will be evaluated by their randomized treatment arm ('intent-to-treat' analysis) unless otherwise specified. The All Randomized Analysis Set will be the primary set for efficacy analyses.

Achieve will approve the list of subjects to be excluded from the Safety and All Randomized analysis sets after database lock. Achieve must approve this list before any analysis to be performed.

6.5. Key Study Endpoints

Achieve has identified the following endpoints as key study endpoints:

- Percent of expected cigarettes smoked (primary efficacy endpoint, see Section 4.1.1)
- Abstinence from Week 5 to Week 8 (other efficacy endpoint, see Section 4.1.2)
- Adverse events (serious adverse events, adverse events that resulted in dose reduction or discontinuation of study drug, all adverse events)

- Exposure to study drug, including study drug compliance

6.6. Sensitivity Analyses

Sensitivity analyses will include the assessment of the contribution of interaction terms and effect modification analyses.

Unless otherwise indicated, the sensitivity and effect modifier analyes will be conducted by an independent statistician ([redacted]) who will document the results of those analyses in a statistical report that will be included as an appendix to the clinical study report.

The sensitivity analyses outlined in this Statistical Analysis Plan will be performed for both the primary efficacy endpoint (see Section 10.1.2) and the abstinence from Week 5 to Week 8 endpoint (see Section 10.2.2).

6.7. Interactions and Covariates

Interactions: Assessment of the effect of interaction between treatment (1.5 mg cytisine, 3.0 mg cytisine, placebo) and the BMI stratification factor (18.5 to <25 kg/m^2; 25 to <30 kg/m^2; 30 to <35 kg/m^2) will be included in the sensitivity analyses.

Covariates: Baseline cigarettes smoked, defined as the average number of cigarettes smoked daily over the 7-day screening period.

7. SUBJECT DISPOSITION

The number of subjects who were screened, failed screening, randomized and treated will be summarized overall. The reason for failing screening will also be summarized.

The number of subjects screened, randomized, treated, discontinuing and completing study drug, completing and withdrawing from the study, as well as the number of subjects in each analysis set will be summarized for each treatment arm. In addition, the number of subjects screened, randomized and treated will be summarized by investigational site for each treatment arm.

For subjects who discontinued study drug, the reasons for discontinuation (e.g. adverse event, withdrawal by subject, physician decision) will be summarized for each treatment arm. The list of subjects who discontinued study drug will be reported, along with the reason for discontinuation.

For subjects who did not complete the study, the reasons for withdrawal (e.g. adverse event, withdrawal by subject, physician decision) will be summarized for each treatment arm. The list of subjects who withdrew from the study will be reported, along with the reason for withdrawal. Reasons will also be reported for why subjects were excluded from each analysis set. The list of subjects who are excluded from the Safety Analysis Set (subjects randomized but who never

took any study drug before discontinuing from the study) will be reported only if those subjects had safety information collected.

Attendance at each study visit will be reported with the number and percentage of subjects who attended each visit (i.e. Screening #1, Screening #2, Randomization, Treatment Day 1, etc.). Similarly, the last study visit attended will be reported with the number and percentage of subjects having their last study visit at Week 8, Week 7, etc.

The number and percentage of subjects who completed the Treatment Period (i.e., attended the Day 27 EOT) and Follow-up Assessment Period (i.e., attended the Week 8 visit) will be reported.

A Kaplan-Meier figure will be produced by treatment arm of time to last recorded data related to the abstinence endpoints (i.e., time from date of randomization to date of last smoking cessation data recorded at or prior to the Week 8 visit). Smoking cessation data includes the self-reports of cigarette smoking [number of cigarettes smoked in previous 24 hours, whether any cigarettes were smoked since the last clinic visit (yes, no) or over the past 7 days (yes, no)] and expired CO levels.

7.1. Protocol Deviations

Protocol deviations will be reported as outlined in the ACH-CYT-09 Monitoring Plan and documented in the CRF. Each deviation will be classified as either “major” or “minor”. Major deviations were defined in the monitoring plan as those requiring direct/immediate escalation to the Sponsor/Medical Monitor in order to determine if the subject can continue with his/her study participation. These included deviations in the following categories:

- Inadequate informed consent procedures,
- Violations of inclusion/exclusion criteria,
- Errors in randomization/stratification,
- Missing results from screening assessments used for determining subject eligibility.

The number and percentage of subjects with at least one deviation (major or minor) and with at least one major deviation will be summarized by treatment arm. For major deviations, the number and percentage of subjects with each type of deviation (e.g., informed consent, inclusion/exclusion criteria, etc.) will be summarized by treatment arm.

8. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be listed and summarized.

8.1. Demographics

Demographic data (gender, age, race, ethnicity, body weight, height, and BMI) will be summarized for each of the subgroups in the Screening Set, and overall.

Demographic data will also be summarized by treatment arm and overall for both the All Randomized Analysis Set and the Safety Analysis Set.

8.2. Medical and Psychiatric History

A medical and psychiatric history summary will be provided for the All Randomized Analysis Set. The number and percentage of subjects with events will be summarized for each treatment arm by MedDRA SOC and preferred term. Multiple occurrences of the same event within a subject will be counted only once.

8.3. Prior Medications

Per protocol, concomitant medications will be recorded beginning at the Screening #1 (SV1) visit. Prior medications are defined as medications with a stop date prior to the first dose of study drug. Prior medications will be summarized for the All Randomized Analysis Set. The number and percentage of subjects with each prior medication will be summarized for each treatment arm by highest available Anatomical Therapeutic Chemical (ATC) class and preferred name. Multiple occurrences of the same medication within a subject will be counted only once.

8.4. Smoking History

At SV1 the following subject-reported smoking history variables will be summarized by treatment arm.

- Duration of smoking (years)
- Average number of cigarettes the subject reported smoking per day over the past 30 days
- Number (%) of subjects who attempted to quit in the past
- Number of previous quit attempts
- Time from last quit attempt to date of SV1 visit

In addition, the number (%) of subjects reporting past use of various smoking cessation treatments will be summarized for both the most recent quit attempt and all quit attempts. For each of these summaries, multiple occurrences of the same treatment within a subject will be counted only once.

8.5. Baseline Smoking and Nicotine Testing

The following baseline data related to smoking will be summarized by treatment arm:

- Average number of cigarettes smoked per day over 7 consecutive days, as reported in the subject diary
- Expired CO (ppm) at SV1
- Expired CO (ppm) at Day 0
- Nicotine metabolism ratio (NMR) at SV1. NMR will be derived as the ratio of the results for 3-hydroxycotinine (3-OH cotinine) and cotinine (i.e., 3-OH cotinine / cotinine).

8.6. Baseline Questionnaires

Subjects will complete the Suicidal Behaviors Questionnaire – Revised (SBQ-R) and Hospital Anxiety and Depression (HADS) questionnaires at SV1 and the Fagerstrom Test of Nicotine Dependence (FTND), Self-efficacy Questionnaire (SEQ-12), Tobacco Craving Questionnaire (TCQ) and Alcohol Use Questionnaire at Day 0, prior to randomization. The following scores will be derived and summarized at baseline by treatment arm:

- SBQ-R: total score
- HADS: scores for depression and anxiety (see Appendix 5, study protocol)
- FTND: total score
- SEQ-12: internal stimuli score (items 1-6), external stimuli score (items 7-12) and total score (items 1-12)
- TCQ: scores for emotionality, expectancy, compulsivity and purposefulness (see Appendix 4, study protocol), as well as a total score.

In addition, the number and percentage of subjects with each item response on the baseline Alcohol Use Questionnaire will be summarized by treatment arm.

8.7. Other Baseline Characteristics

Vital signs (body temperature, heart rate, and systolic and diastolic blood pressure) will be assessed at two timepoints prior to randomization: SV1 and Day 0. Baseline vital signs will be summarized by treatment arm.

Serum chemistry and hematology testing will be performed at SV1. Baseline laboratory test results will be summarized by treatment arm. Separate summaries will be provided for hematology tests (hemoglobin, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets), serum chemistry tests (total protein, albumin, total bilirubin, aspartate aminotransferase (ALT), alanine aminotransferase (AST), alkaline phosphatase, glucose, sodium, potassium, calcium, creatinine and urea) and creatinine-clearance.

A 12-lead ECG will be performed at SV1. Baseline ECG findings (normal, abnormal – not clinically significant, abnormal – clinically significant) will be summarized by treatment arm.

9. EXPOSURE TO STUDY TREATMENT

Study treatment consisted of administration of study drug in combination with behavioral support.

9.1. Duration of Study Drug Treatment

The time (days) from randomization to first dose of study drug will be derived and summarized by treatment arm for the Safety Analysis Set.

Duration of study drug treatment (days) will be calculated as date of last dose of study drug minus date of first dose of study drug + 1. Duration of study drug treatment will be summarized by treatment arm for the Safety Analysis Set. The number (%) of subjects who had duration of 25 days will be summarized by treatment arm.

9.2. Study Drug Compliance

A dose of study drug consisted of 2 tablets. Subjects assigned to the 25-day commercial schedule will be prescribed a total of 100 doses of study drug. Subjects assigned to the tid schedule will be prescribed a total of 69 doses.

Each dose of study drug taken by the subject will be recorded in a subject diary. For each dosing day (Day 1 to Day 25), the dosing date will be recorded as well as each of the dosing times and, for each dosing time, whether the dose was taken by the subject or missed. The total dose of study drug taken over the 25-day treatment period will be derived for each subject.

The following variables will be summarized by treatment arm for the Safety Analysis Set:

- total dose of study drug,
- total number of missed doses,
- percentage of doses missed: (# missed doses/ # doses prescribed) * 100
- study drug compliance: [(# doses prescribed - # missed doses) / # doses prescribed] * 100.

Compliance with study drug will be summarized both as a continuous variable and as a categorical variable (<80%, 80-<90%, 90-<100%, 100%). In addition to summary tables, details of study drug administration and compliance will be listed. The listing will include the total number of doses taken by the subject, total number of doses missed, percentage of doses missed, and percentage of doses taken (i.e. compliance with study drug) in addition to the details of each dose (date of administration, time of administration and whether dose was taken or missed).

9.3. Behavioral Support Compliance

Per protocol, subjects will receive a total of 13 behavioral support sessions at visits: SV2, Day 0, Day 2, Day 3, Day 6, Day 12, Day 16, Day 20, Day 27 EOT, Week 5, Week 6, Week 7 and Week 8.

The total number of behavioural support sessions received will be calculated for each subject and summarized by treatment arm for the Safety Analysis Set. Summaries will also be provided for compliance with behavioral support [(# behavioral support sessions received) / (# behavioral support sessions planned] * 100.

10. EFFICACY ANALYSIS

The efficacy analyses will be conducted using subjects in the All Randomized Analysis Set, as defined in Section 6.4. Subjects will be evaluated by their randomized treatment arm ('intent-to-treat' analysis).

For qualitative endpoints, summary tables will present the number and percentage of subjects for each class of the endpoint. Quantitative endpoints will be summarized by presenting the mean, SD, minimum, median and maximum values. All summary statistics will be presented by treatment arm.

The planned figures for efficacy endpoints are displayed in Section 15.

10.1. Analyses of Primary Efficacy Endpoint

10.1.1. Primary Efficacy Analysis

The two primary objectives, one for each administration schedule (commercial, tid), are stated in Section 3.1. The primary efficacy endpoint, percent of expected cigarettes smoked computed for each subject at end of treatment, is defined in Section 4.1.1.

The distribution of the primary efficacy endpoint for each treatment arm will be displayed by treatment arm using side-by-side box plots. There will be one plot for each administration schedule. Side-by-side box plots will also be provided by treatment arm and BMI class (3 level stratification).

The primary comparisons will compare active arms to the associated placebo arm as follows:

1. 1.5 mg Cytisine – Commercial Schedule vs Placebo – Commercial Schedule
2. 3.0 mg Cytisine – Commercial Schedule vs Placebo – Commercial Schedule
3. 1.5 mg Cytisine – tid Schedule vs Placebo – tid Schedule
4. 3.0 mg Cytisine – tid Schedule vs Placebo – tid Schedule

The primary comparisons will be conducted using an analysis of variance model with fixed effect terms for treatment arm (3 level categorical variable: placebo, 1.5 mg, and 3.0 mg) and BMI class (3 level stratification), and a covariate of baseline cigarettes. There will be one analysis for each administration schedule. The least squares means (LS Means), differences of the LS Means, and their respective 95% CIs will be reported. Forest plots will be used to display 95% CIs for the differences of the LS Means.

10.1.2. Sensitivity Analyses

Sensitivity analyses will include the assessment of the contribution of interaction terms and effect modification analyses.

The following sensitivity analyses will be performed by [redacted]

- For each of the primary comparisons, an analysis of variance model will be fit that adds an arm-by-BMI interaction term to the model. That is, the sensitivity model will include treatment arm, BMI class, arm-by-BMI-class interaction, and a covariate of baseline cigarettes. If there is evidence of an interaction then each of the primary comparisons will be repeated within each level of the BMI class variable.
- The placebo treatment arms (Placebo – Commercial Schedule, Placebo – tid Schedule) will be compared using an analysis of variance model with fixed effects for treatment arm (2 levels) and BMI class (3 levels) and a covariate of baseline cigarettes. The Least Square (LS) Means, LS Means Differences, and their respective 95% CIs will be reported.
- If the placebo treatment arms are similar then the primary efficacy analysis will be repeated using the pooled placebo arms. The sensitivity analysis described in the previous paragraph will also be repeated.

Additional sensitivity analyses for the primary comparisons will be conducted by an independent statistician ([redacted]). These include a sensitivity analysis that computes the standard error (SE) for each subject of the cigarette-count data collected post-randomization and uses $1/(SE^2)$ as a weight.

Exploratory analyses will also be conducted by [redacted] as described below in order to identify effect modifiers. The objective of these analyses is to assess the homogeneity of treatment effect within strata (subgroups) defined by each potential effect-modifying variable. Strata for continuous effect modifiers will be defined by either logical considerations (e.g., age >65 years) or statistical criteria (e.g., quantile (median, tertile) split). The variables (factors) that will be evaluated as effect modifiers include, but are not limited to:

- demographic charateristics (e.g., sex, age, race, BMI),
- smoking history variables (e.g., duration of smoking, average number of cigarettes the subject reported smoking per day over the past 30 days, number of previous quit attempts),
- baseline smoking variables (e.g. average number of cigarettes smoked per day over 7 consecutive days as reported in the subject diary, baseline CO (ppm)),
- baseline questionnaire scores (see Section 8.6),
- clinical site.

Each factor will be evaluated in a two-arm analysis of variance model with fixed effect terms for treatment arm (experimental arm, control arm), the factor, and arm-by-factor interaction, and the covariate of baseline cigarettes. The following summary statistics will be reported for each level of a factor: the number of subjects overall and within each treatment arm, the mean difference between treatment arms in the primary endpoint (percent of expected cigarettes smoked), and the 95% CI for the difference. Forest plots will be used to display the 95% Cis for all factors.

The sensitivity analyses described above will be repeated using an analysis of variance model that does not include the covariate of baseline cigarettes, and for models with BMI class as a stratifier and without BMI as a stratifier.

10.1.3. Smoking Diary Compliance

Subjects will record their cigarette consumption in a daily diary for 7 consecutive days during the screening period, and each day during the 25-day treatment period (i.e. on Day 1 through Day 25, inclusive). For each period (screening, treatment), compliance with diary reporting requirements will be derived as:

[(# diary days entered by subject) / (# diary days expected for subject] * 100.

The number of diary days expected is 7 days for the screening period and 25 days for the treatment period. The number of diary days and compliance will be summarized for each period by treatment arm. Compliance will be summarized both as a continuous variable and as a categorical variable (<80%, 80-<90%, 90-<100%, 100%).

Other elements of protocol-compliance are described in Section 9.2 (study drug compliance) and Section 9.3 (behavioral support compliance).

10.2. Analyses of Other Efficacy Endpoints

The other efficacy objectives are stated in Section 3.2. The other efficacy endpoints are defined in Section 4.1.2. The results for each endpoint will be displayed graphically by treatment arm. Side-by-side bar charts will be used to display categorical endpoints, Kaplan-Meier figures will be used for time-to-event endpoints. For binary endpoints, forest plots will be used to display 95% CIs for the odds ratio.

The other efficacy analyses will be conducted using subjects in the All Randomized Analysis Set described in Section 6.4.

For each of the other efficacy endpoints identified below, 4 within-schedule comparisons of cytisine vs placebo will be performed:

1. 1.5 mg Cytisine – Commercial Schedule vs Placebo – Commercial Schedule
2. 3.0 mg Cytisine – Commercial Schedule vs Placebo – Commercial Schedule
3. 1.5 mg Cytisine – tid Schedule vs Placebo – tid Schedule

4. 3.0 mg Cytisine – tid Schedule vs Placebo – tid Schedule

The statistical analyses that will be performed for the other efficacy endpoints are described below.

10.2.1. Abstinence from Week 5 to Week 8

Abstinence from Week 5 to Week 8 is a binary (success, failure) endpoint. For each of the comparisons listed above, the two treatment arms will be compared in terms of the proportion of subjects classified as a success. Following is template SAS code for doing each of the statistical comparisons where s is the stratification factor (BMI, 3 levels), x is the treatment arm (2 levels, each comparison), and y is the efficacy endpoint (success vs failure).

```
proc freq data=data;
  exact fisher or comor eqor;
  table s*x*y / nopercent nocol;
run;
```

The effect size estimate of each comparison will be based on the common odds ratio estimate using exact computations for stratified 2x2 frequency tables.

Homogeneity of odds ratios will be assessed using Zelen's Exact Test. If there is evidence of odds ratio heterogeneity across the strata (p-value ≤ 0.10) then the analysis will be performed separately for each level of the stratification factor and stratum-specific estimates of the odds ratios and CIs for those odds ratios will be reported.

10.2.2. Sensitivity Analyses for Abstinence from Week 5 to Week 8

The following sensitivity analyses will be performed for the Abstinence from Week 5 to Week 8 endpoint by [redacted]

- The placebo treatment arms (Placebo – Commercial Schedule, Placebo – tid Schedule) will be compared. If the proportion of subjects classified as a success is similar for the two placebo arms then each of the cytisine treatment arms will be compared to the pooled placebo arms.

All other sensitivity analyses for the Abstinence from Week 5 to Week 8 endpoint will be conducted by an independent statistician ([redacted]). These analyses will include exploratory analyses to identify effect modifiers. The variables that will be evaluated as effect modifiers are identified Section 10.1.2. The relationship between treatment arm and the proportion of subjects with abstinence will be evaluated within stratum defined by the effect modifier. For each stratum, the number (%) of subjects within each stratum with abstinence will be reported for each treatment arm. Odds ratios (1.5 mg cytisine vs. placebo, 3.0 mg cytisine vs. placebo) and their 95% CIs will also be reported. Forest plots will be used to display the stratum-specific 95% CIs.

A tipping point analysis will be performed.[1]

10.2.3. Initial Quit Rates

The initial quit rate endpoint is binary (success, failure) defined at Week 4 (Day 27 EOT). For each comparison (see Section 10.2), the treatment arms will be compared in terms of the proportion of subjects classified as a success (Section 4.1.2). The effect size estimate of each comparison will be based on the common odds ratio estimate using exact computations for stratified 2x2 frequency tables.

If there is evidence of odds ratio heterogeneity across the strata (p-value for Zelen's Exact Test ≤ 0.10) then the analysis will be performed separately for each level of the stratification factor and stratum-specific estimates of the odds ratios and their 95% CIs will be reported.

10.2.4. 7-day Point Prevalence

The 7-day point prevalence endpoints are binary (success, failure) endpoints defined at each of the following visits: Week 5, Week 6, Week 7 and Week 8.

For each comparison (see Section 10.2), the treatment arms will be compared in terms of the proportion of subjects classified as a success (Section 4.1.2). The effect size estimate of each comparison will be based on the common odds ratio estimate using exact computations for stratified 2x2 frequency tables.

If there is evidence of odds ratio heterogeneity across the strata (p-value for Zelen's Exact Test ≤ 0.10) then the analysis will be performed separately for each level of the stratification factor and stratum-specific estimates of the odds ratios and their CIs will be reported.

10.2.5. Time to Failure to Maintain Abstinence Through Week 8

Time to failure to maintain abstinence through Week 8 (Section 4.1.2) will be evaluated for the subgroup of subjects who were classified as a success on the initial quit rate endpoint. Time to failure (days) will be calculated for individual subjects as described in Section 4.1.2. Subjects who are still abstinent at Week 8 will have time to failure censored at the date of the Week 8 visit.

Time to failure will be summarized by treatment arm; the minimum, maximum, median and 95% confidence interval for the median time to failure reported by the LIFETEST procedure will be reported. Two Kaplan-Meier figures of treatment arm by time to failure will be produced, one figure for each schedule (commercial, tid).

10.2.6. Relationship Between Outcome Variables and Smoking Cessation

This objective will explore relationships between subject-reported outcomes and smoking cessation outcomes during the study treatment period (primary efficacy endpoint), as well as smoking cessation endpoints at Week 4 (initial quit rate endpoint) and from Week 5 to Week 8 (abstinence from Week 5 to Week 8 endpoint). It is expected that the relationship between each

of these endpoints and each of the following subject-reported outcome variables will be evaluated for this objective:

- Change during the treatment period, in self-reported number of cigarettes smoked over the previous 24 hours.
- Total scores, and change from baseline scores, for the following questionnaires: HADS, SBQ-R, Tobacco Craving, and Alcohol Use.
- Adverse event outcomes such as whether the subject experienced any adverse events, any serious adverse events.
- Compliance outcomes such as percent of study drug taken, number of behavioral support sessions attended.

10.2.7. Relationship Between Outcome Variables and Nicotine Metabolite Ratio (NMR)

The correlation of NMR with reduction in cigarette use (primary efficacy endpoint), initial quite rate and abstinence from Week 5 to Week 8 will be explored. Descriptive statistics for NMR, reduction in cigarette use and the cessation endpoints will be produced.

10.2.8. Questionnaires

The HADS, SBQ-R, Tobacco Craving and Alcohol Use questionnaires will be administered at Section 8.6.

The HADS, SBQ-R and Tobacco Craving questionnaires will be summarized using descriptive statistics. For each questionnaire score, the actual value, change from baseline and percent change from baseline will be summarized by treatment arm and visit. Only subjects with non-missing results at both baseline and the post-baseline visit will be summarized at each time point.

The individual items on the Alcohol Use questionnaire will be summarized categorically by treatment arm and visit.

11. SAFETY ANALYSIS

All safety analyses described below will be presented for each treatment arm using the Safety Analysis Set defined in Section 6.4. No statistical comparisons between treatment arms are planned for safety endpoints; thus, no statistical test results will be reported.

11.1. Adverse Events

Per the study protocol all adverse events (AE) occurring during the study, whether or not attributable to study drug, will be recorded in the subject's source documents and CRF. Adverse event reporting will start at the date of informed consent and continue through the end of study (Week 8 visit).

AE severity will be assessed by the Investigator as mild, moderate or severe. The Investigator will also assess the relationship of each AE to study drug (none, unlikely, possible, probable, definite). Treatment-related AEs are defined as events the Investigator considers to be possibly, probably, or definitely related to study drug, as well as events with "unknown" relationship.

Adverse event summaries will present data by treatment arm.

An overall summary of adverse events will be provided that reports, for each treatment arm, both the number (%) of events meeting a specific criterion and the number (%) of subjects with at least one event meeting that criterion. Events meeting the following specific criteria will be presented in this table:

- Any reported adverse event (i.e., both pre-existing and treatment-emergent events)
- For treatment-emergent AEs:
  - Any TEAE
  - Any serious TEAE
  - TEAEs by severity (mild, moderate, severe)
  - TEAEs by relationship (none, unlikely, possible, probable, definite)
  - TEAEs by relationship (not related, related)
  - TEAEs by action taken with study drug (dose increased, dose not changed, dose reduced, dose interrupted, drug withdrawn, not applicable, unknown)
  - TEAEs by outcome (recovered no sequelae, recovered with sequelae, ongoing, death)

In addition to the overall summary, the following summaries of the number (%) of subjects with at least one TEAE will be produced:

- Incidence by SOC and PT, in alphabetical order of SOC and PT, for both all TEAE and related TEAE
- Incidence by PT, in decreasing frequency of PT, for both all TEAE and related TEAE
- Incidence of TEAEs that resulted in dose reduction or discontinuation of study drug (i.e., action taken with study drug reported as dose reduced, dose interrupted, or drug withdrawn), in decreasing frequency of PT
- Incidence of TEAE by PT and severity (mild, moderate, severe), in alphabetical order of SOC and PT
- Incidence of TEAE by PT and relationship (yes, no), in alphabetical order of SOC and PT
- Kaplan-Meier figure of time to first treatment-emergent adverse event (i.e., time from date of randomization to earliest TEAE start date) by treatment arm.

In these summaries, if a subject experiences the same AE (preferred term) multiple times that subject will be counted only once for that preferred term. Similarly, if a subject experiences multiple AEs (preferred terms) within the same SOC then that subject will be counted only once for that SOC. When summarizing by severity and relationship, only the AE with the highest severity or relationship will be counted.

In addition to summary tables, the following listings will be produced.

- All AEs
- AEs which resulted in dose reduction or discontinuation of study drug (i.e., action taken with study drug reported as dose reduced, dose interrupted, or drug withdrawn)

Pre-existing AEs will be flagged in the listing of all AEs.

11.2. Serious Adverse Events

Serious adverse events (SAEs) will be summarized by preferred term and SOC for each treatment arm using counts and percentages. The followings summaries of SAEs will be produced.

- Incidence by SOC and PT, in alphabetical order of SOC and PT
- Incidence by PT, in decreasing frequency of PT

In addition to summary tables, a listing of SAEs will be produced.

11.3. Definition of Treatment Emergent Adverse Events and Serious Adverse Events

A treatment-emergent AE (TEAE) is any AE that is new in onset or was aggravated in severity or frequency following the first dose of study drug, up to and including the last visit of the study. Treatment emergence will be determined by comparing the AE start date/time with the actual date/time of first dose of study drug. TEAEs are defined as events with start date/time on or after the date/time of first dose of study drug. If either the AE start date or start time is unknown, treatment-emergent events will be defined based on a "Yes" response to the CRF item "Did the AE start after the first dosing?"

A Serious Adverse Event (SAE) is defined as an AE that:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongs existing inpatient hospitalization.
- Results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.

- Is an important medical event that requires medical intervention to prevent any of the above outcomes.

11.4. Laboratory Data

Routine laboratory safety samples will be collected at SV1, each clinic visit during the Treatment Period, and Week 8. The protocol-specified serum chemistry tests are total protein, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, glucose, sodium, potassium, calcium, creatinine, creatinine clearance/glomerular filtration rate and blood urea nitrogen (BUN). The protocol-specified hematology tests are hemoglobin, red blood cells (erythrocytes), platelets, white blood cells (leukocytes), and absolute counts for neutrophils, lymphocytes, monocytes, eosinophils and basophils. Samples will be analyzed by a central laboratory. If the central laboratory does not provide results in Système International (SI) units then [redacted] will convert all laboratory results to SI units prior to analysis.

The following laboratory summaries will be provided for the protocol-specified tests by treatment arm:

- Actual value and change from baseline will be summarized using descriptive statistics, by laboratory test and visit.
- Shift tables will be used to summarize the number (%) of subjects with changes from baseline in normal range flag (L=low, N=within normal limits, H=high), by laboratory test and visit.

Separate summary tables will be produced for serum chemistry tests and hematology tests. In addition to summary tables, separate listings of protocol-specified laboratory test results will be produced.

11.5. Vital Signs and Weight

Vital signs, including weight, will be assessed at SV1, Randomization, each clinic visit during the Treatment Period and each clinic visit during the Follow-Up Period.

For each test (oral temperature, pulse rate, systolic and diastolic blood pressure, weight), the actual value and change from baseline will be summarized by treatment arm and visit (baseline, Day 2 through Day 27 EOT, Week 5 through Week 8) using descriptive statistics. For change from baseline, only subjects with non-missing results at both baseline and the post-baseline visit will be summarized at each time point.

The number and percentages of subjects reporting potentially clinically significant (PCS) vital signs at any time post-baseline will be summarized by treatment arm, where PCS are defined as follows:

	PCS – Low if:			PCS – High if:		
	Observed Value is:	**AND**	**Decrease from Baseline is:**	**Observed Value is:**	**AND**	**Increase from Baseline is:**
Systolic Blood Pressure	<85 mmHg		≥20 mmHg	>160 mmHg		≥20 mmHg
Diastolic Blood Pressure	<40 mmHg		≥10 mmHg	>90 mmHg		≥10 mmHg
Heart Rate	<35 bpm		≥15 bpm	>100 bpm		≥15 bpm

11.6. 12-Lead ECG Interpretation

A 12-lead ECG was done at SV1, Day 12 and Day 27 EOT. An overall interpretation (normal, abnormal – not clinically significant, abnormal – clinically significant) was recorded in the CRF.

The number and percentage of subjects with at least one shift from normal at baseline to abnormal – clinically significant at any time post-baseline will be summarized by treatment arm.

In addition, an ECG listing will be provided.

11.7. Concomitant Medications

Concomitant medications will be defined as any medication (other than study drug) taken during the course of treatment, i.e. with medication start date on or after the date of the first dose of study drug. Additionally, medications will be considered concomitant if the medication started during the screening period and the stop date of the medication is either missing (not available) or reported as ongoing. The number and percentage of subjects with each concomitant medication will be summarized for each treatment arm by highest available ATC class and preferred name. Multiple occurrences of the same medication within a subject will be counted only once.

12. PHARMACOKINETIC ANALYSES

None planned.

13. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Changes that might need to be made to this document after database lock will be documented in the Clinical Study Report.

14. REFERENCES

1. Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. Journal of biopharmaceutical statistics 2009;19:1085-98.

15. TABLE, LISTING AND FIGURES

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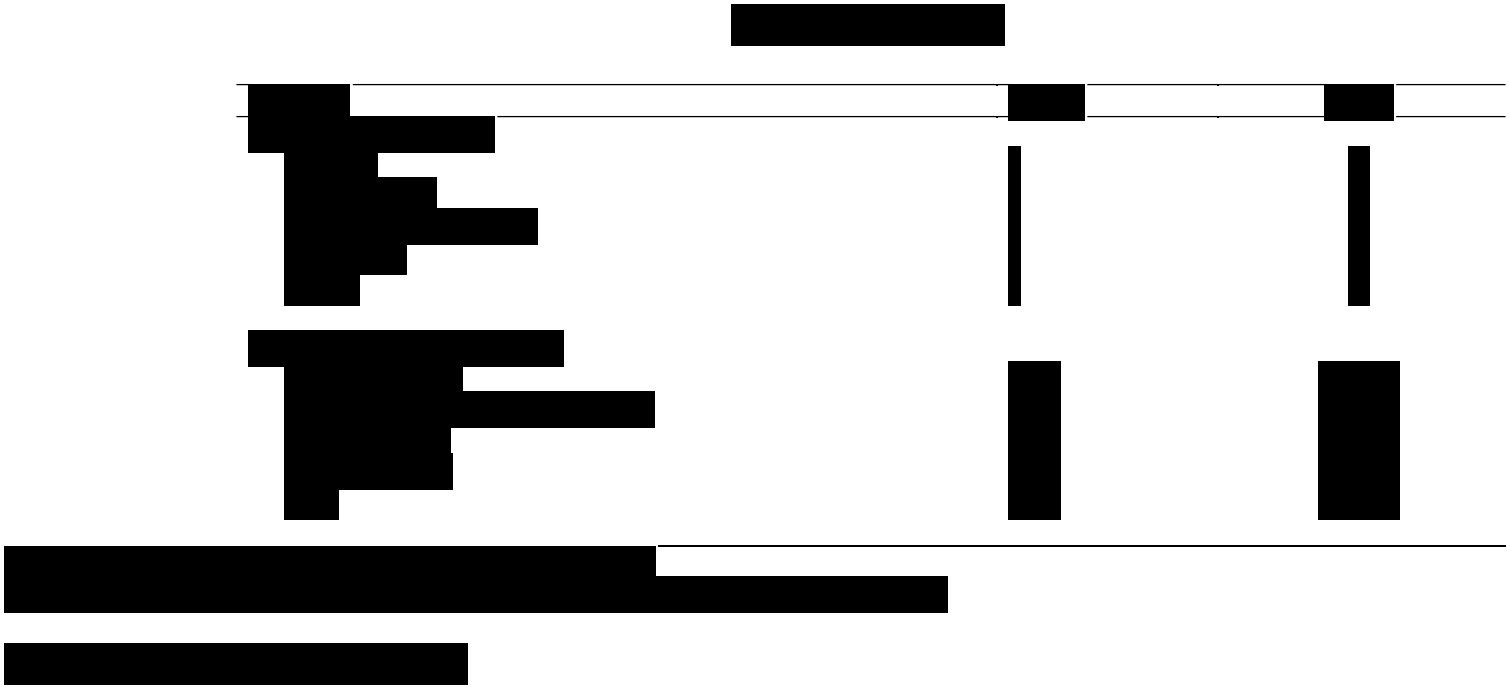

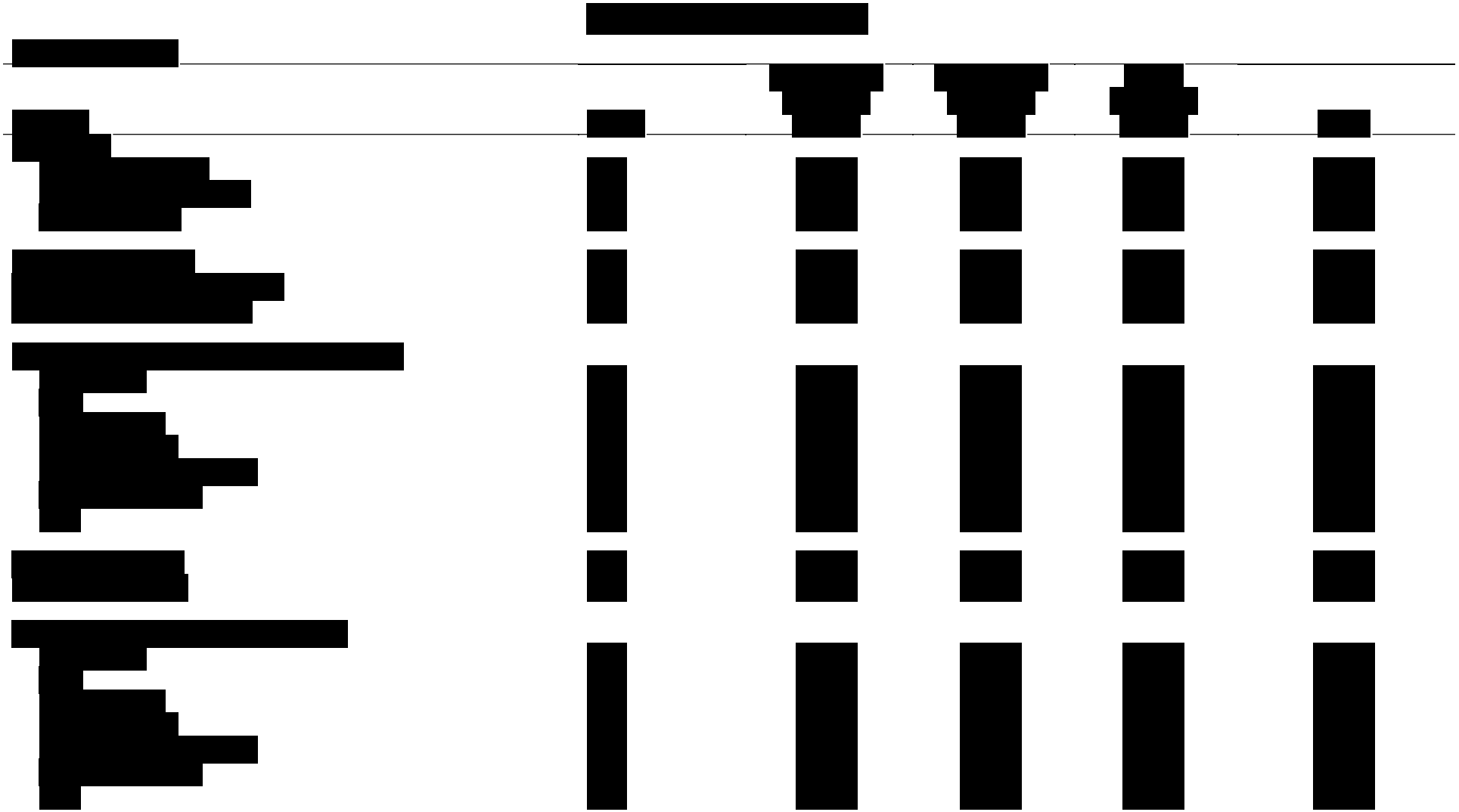

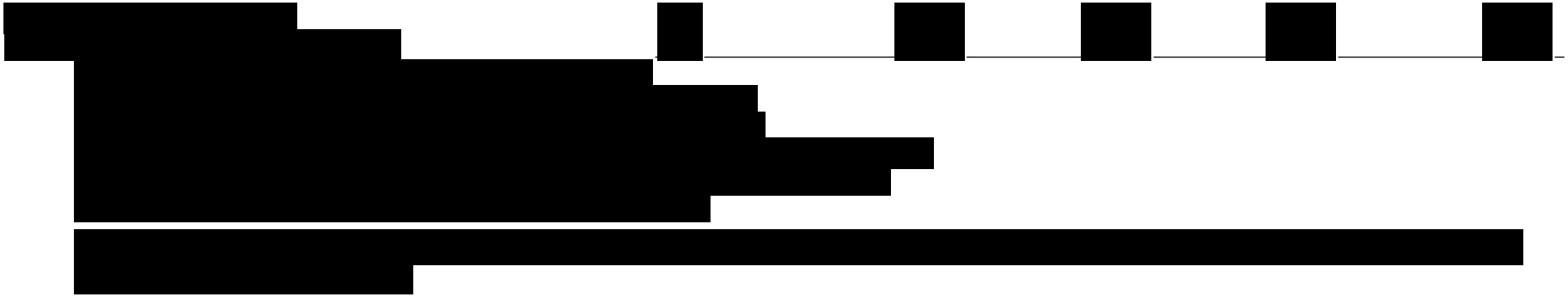

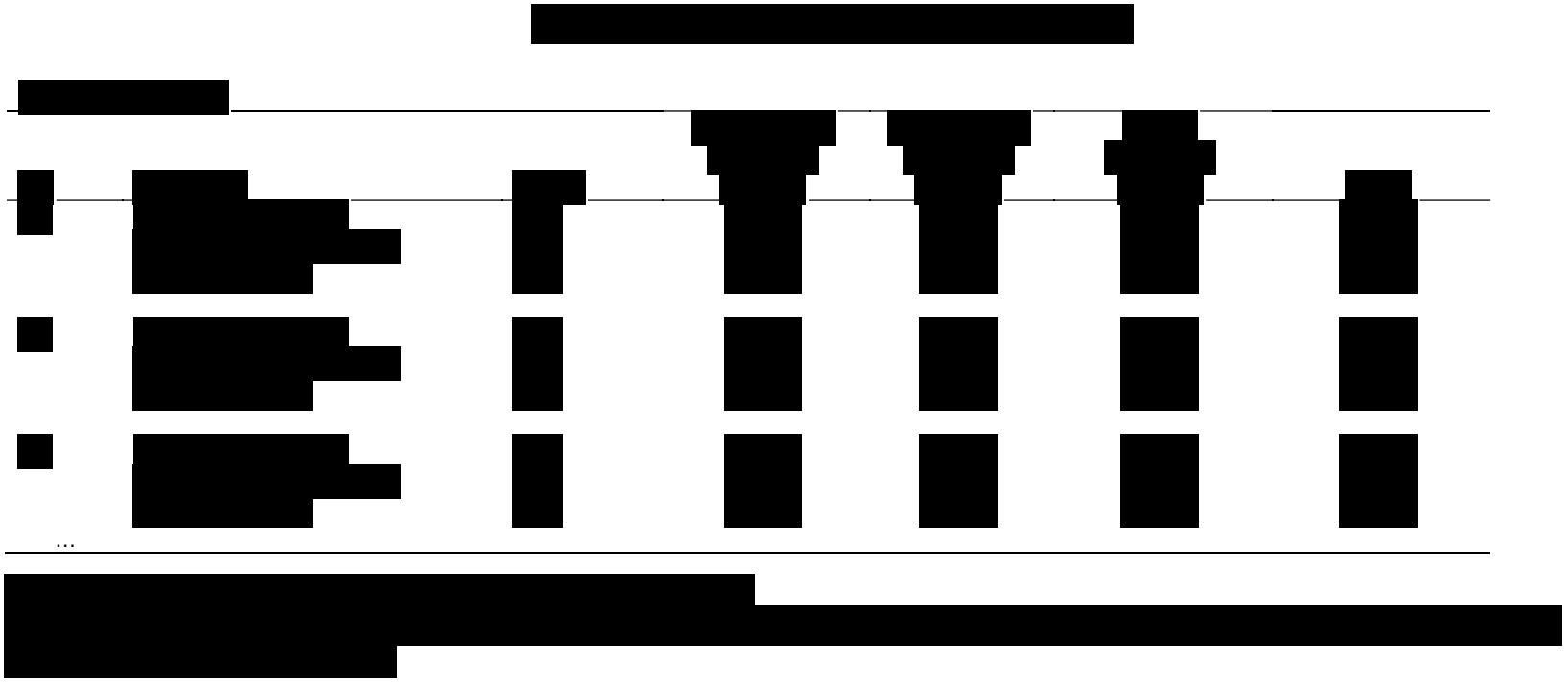

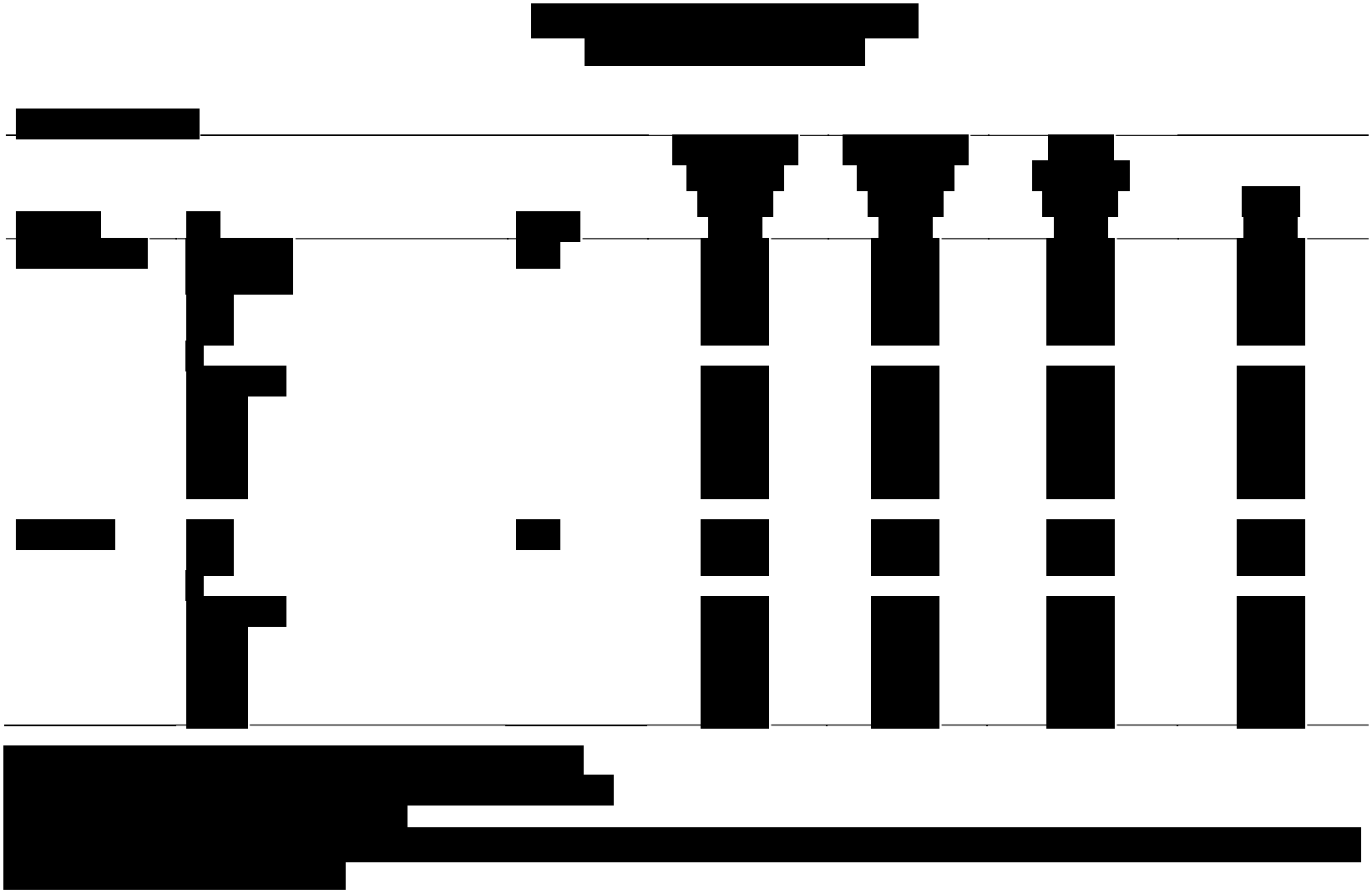

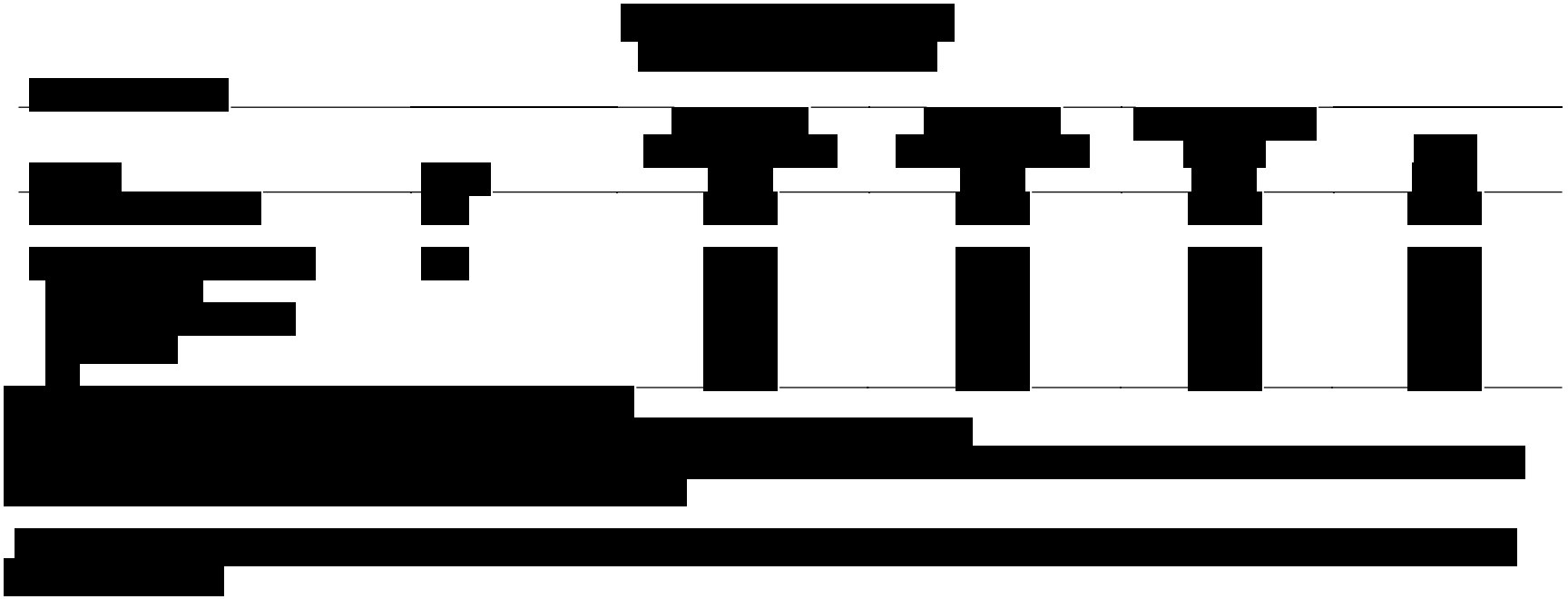

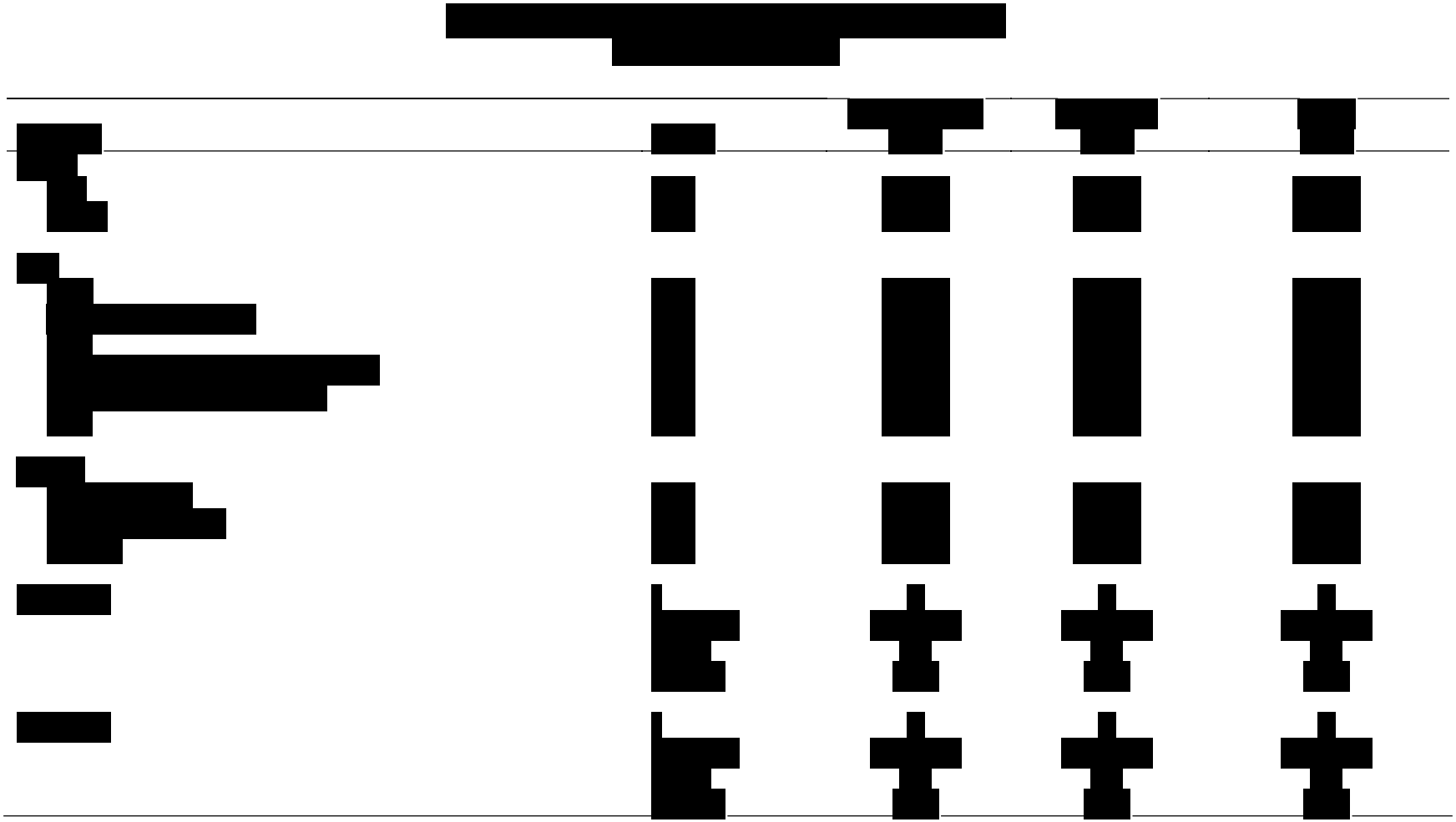

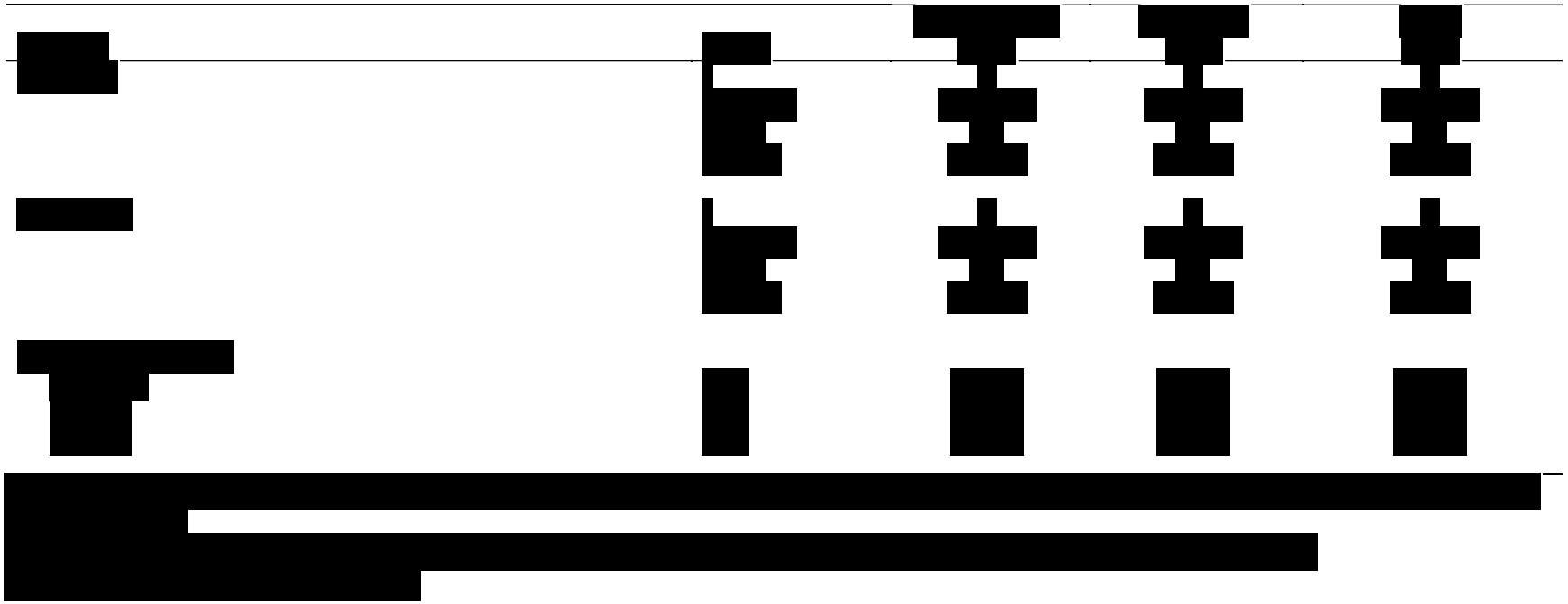

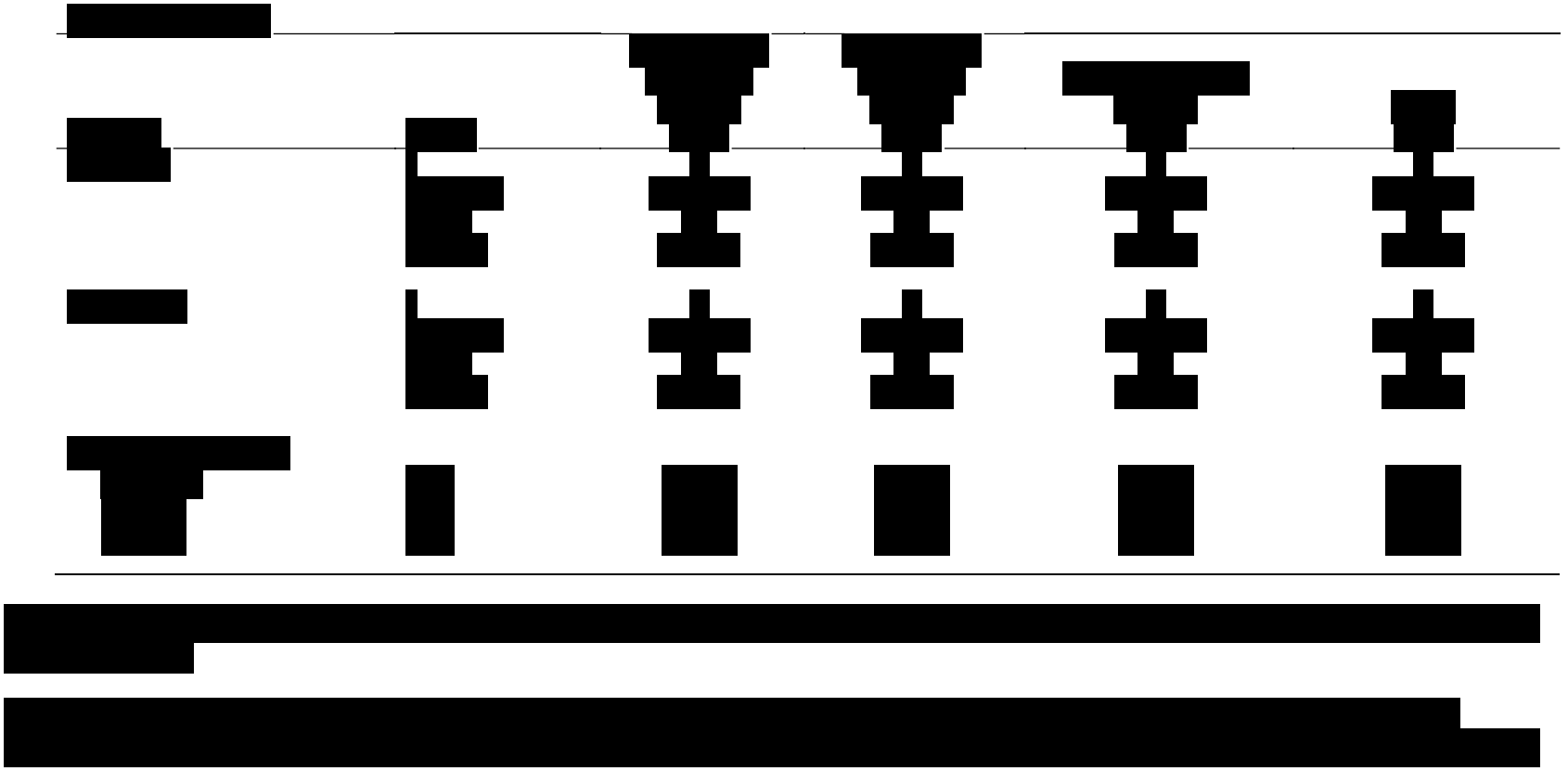

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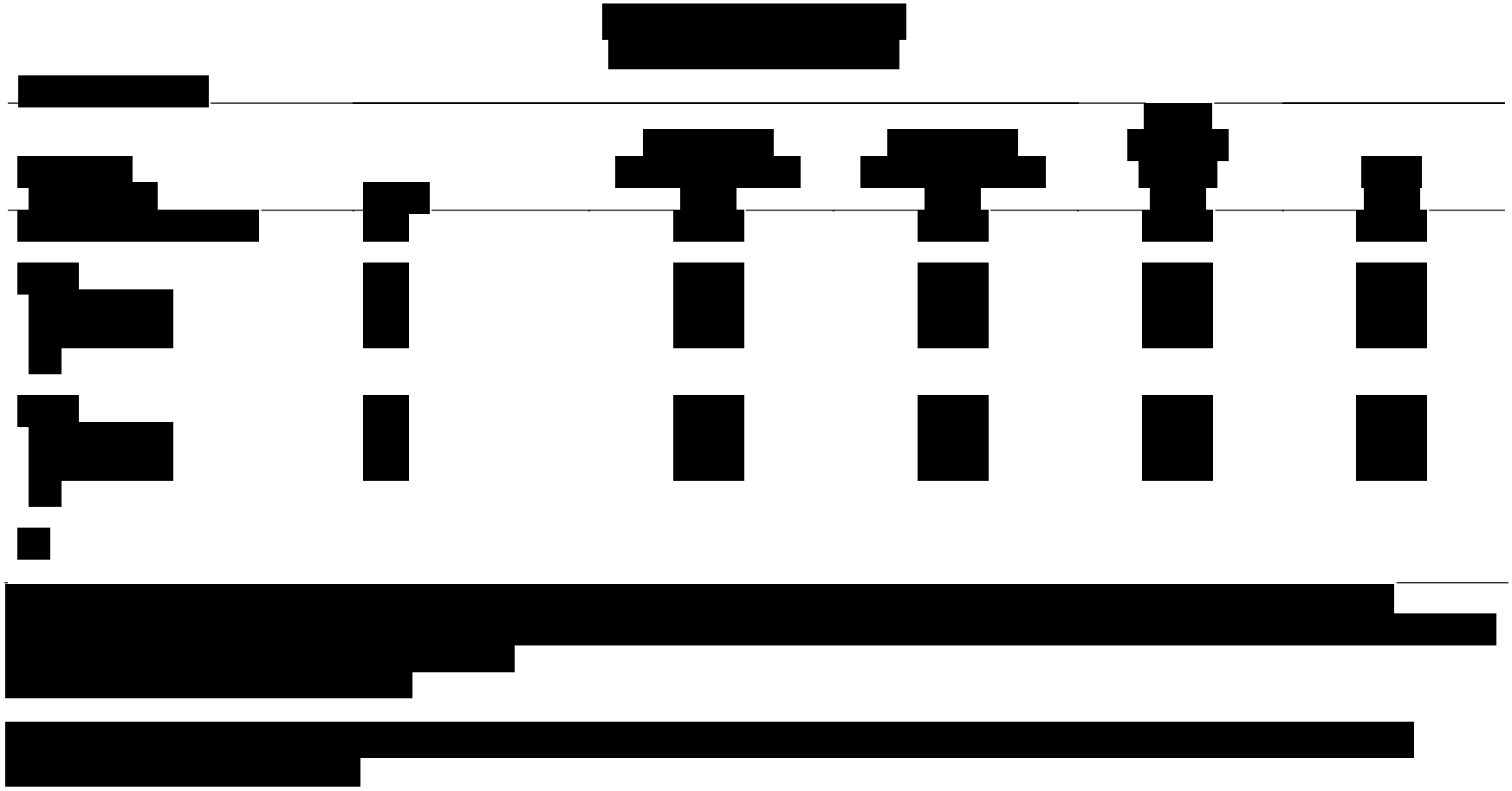

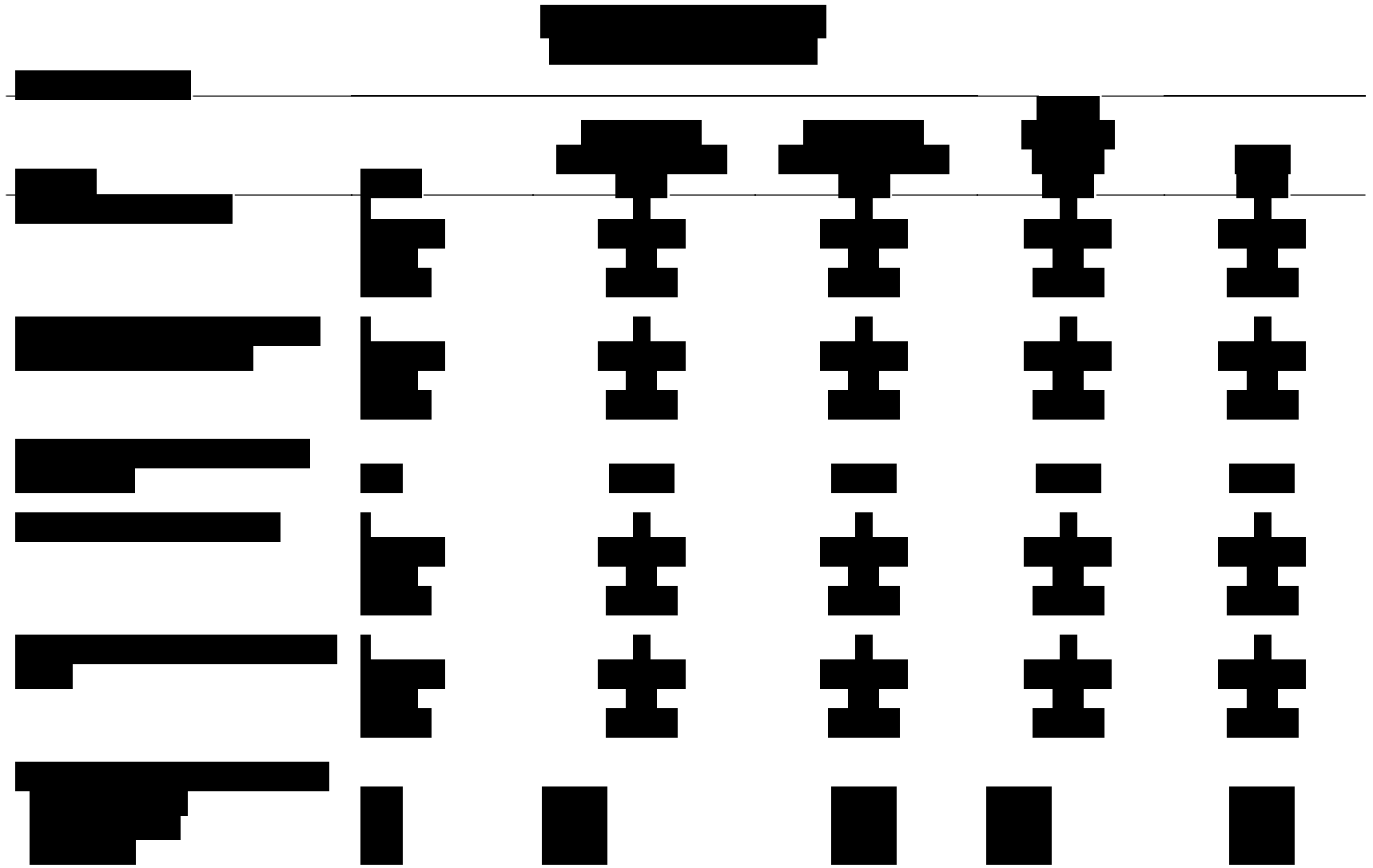

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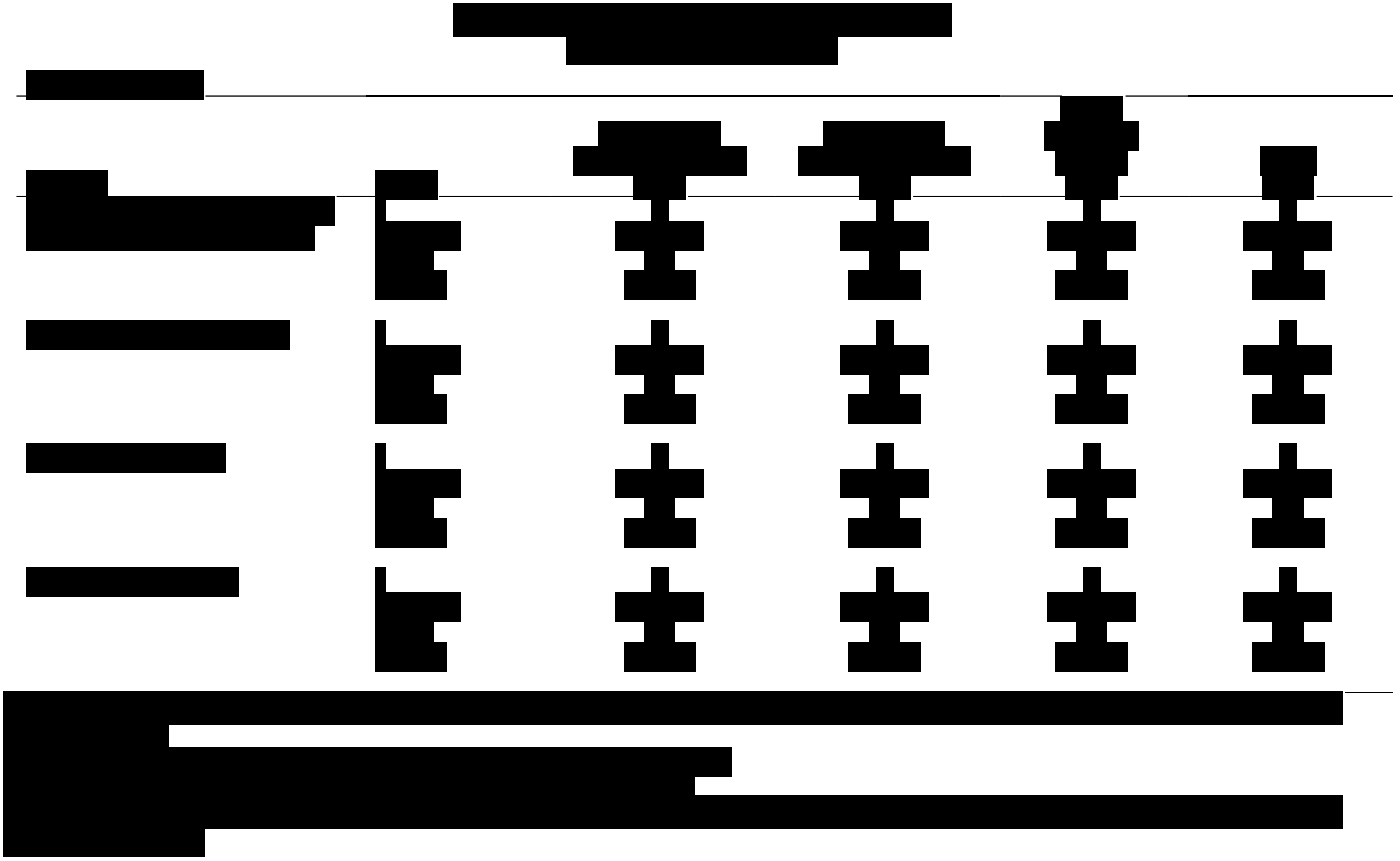

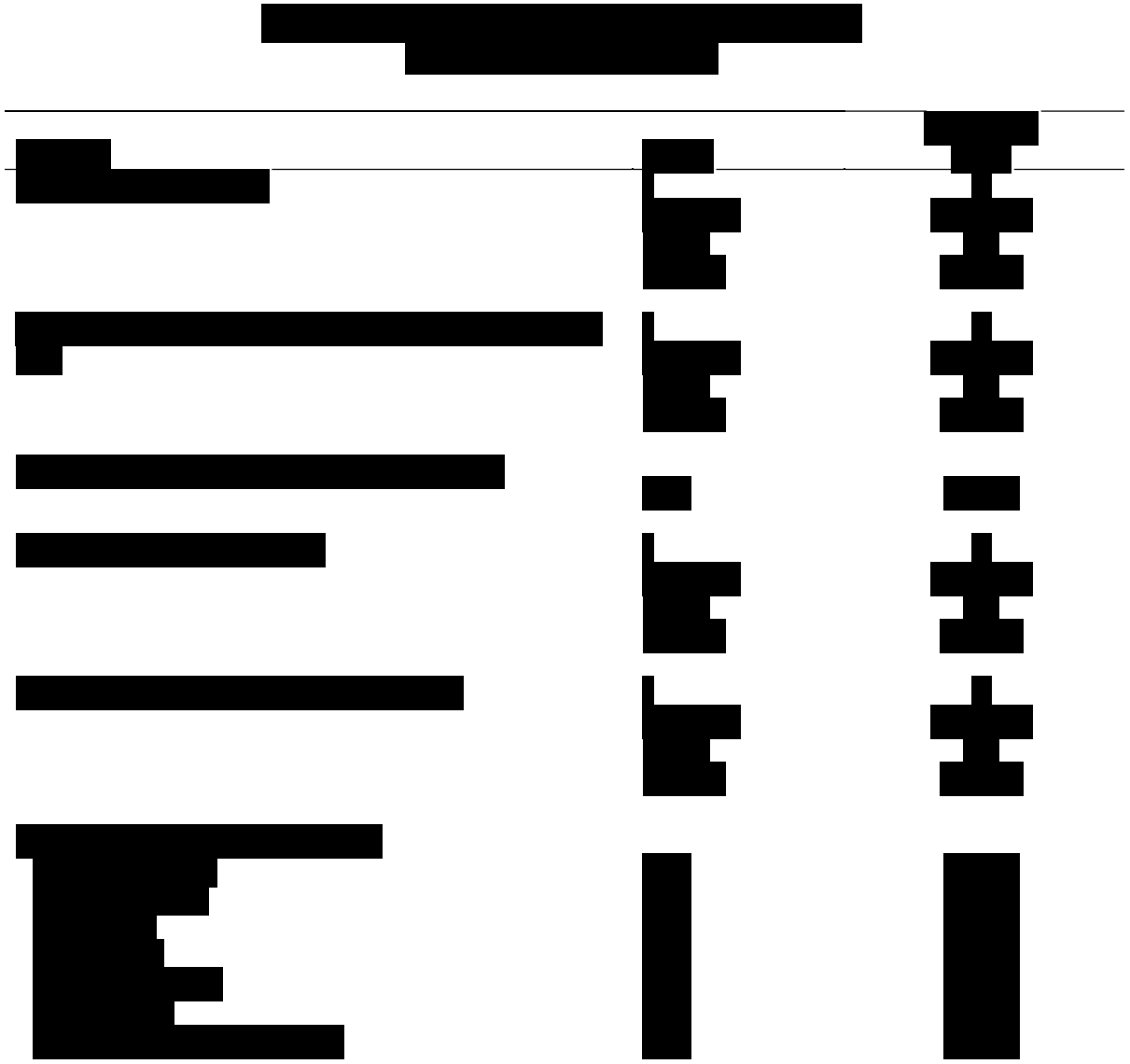

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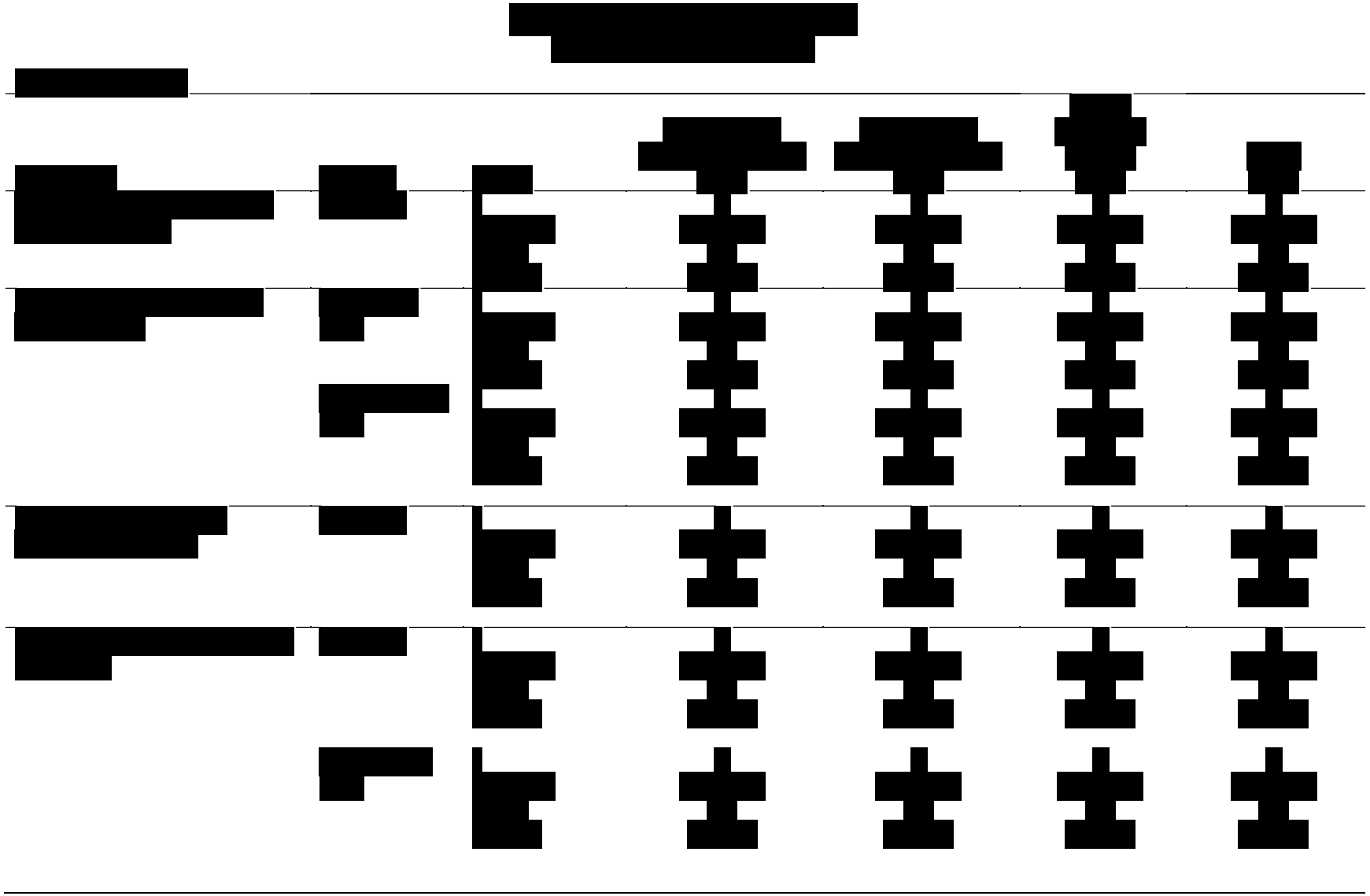

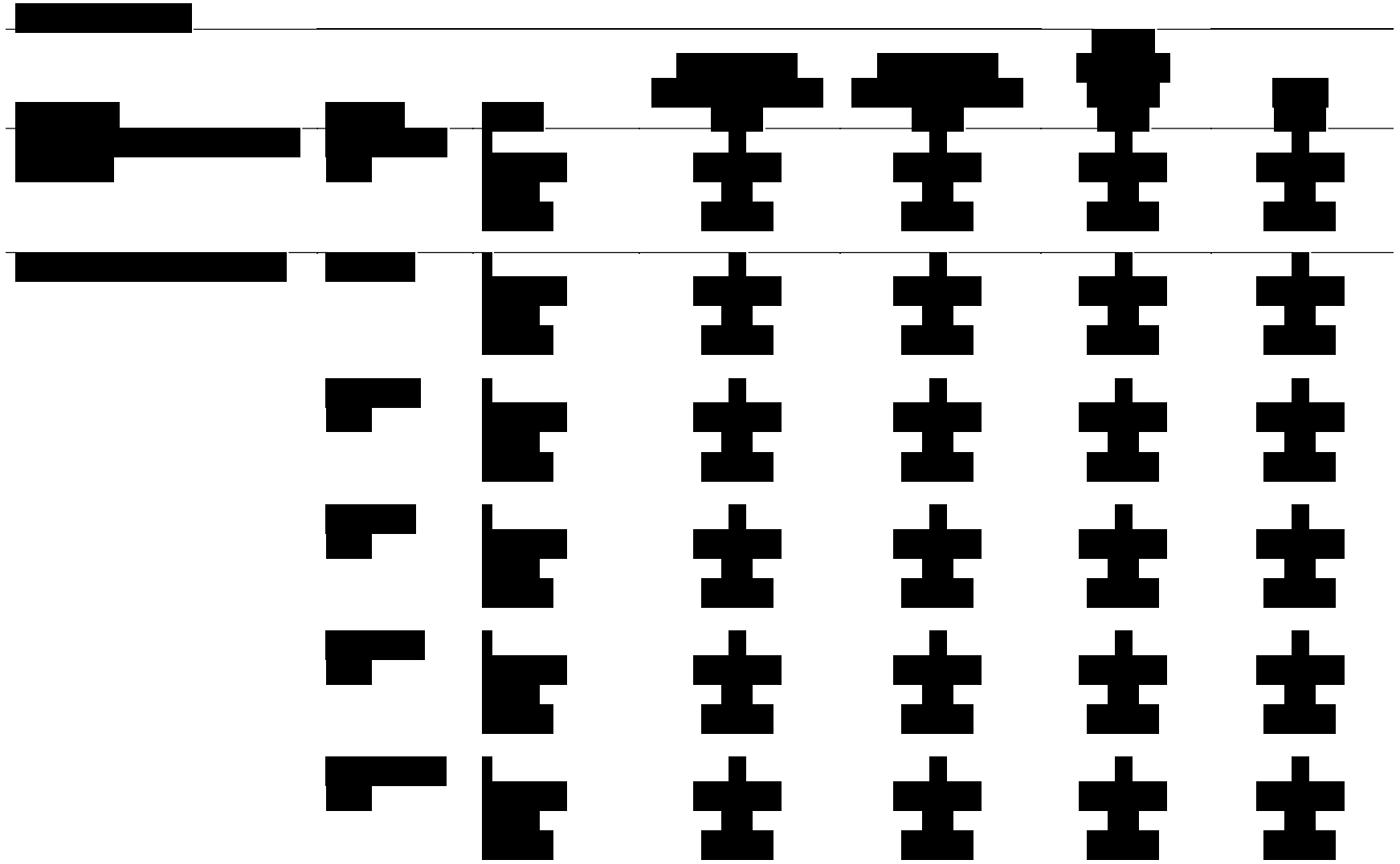

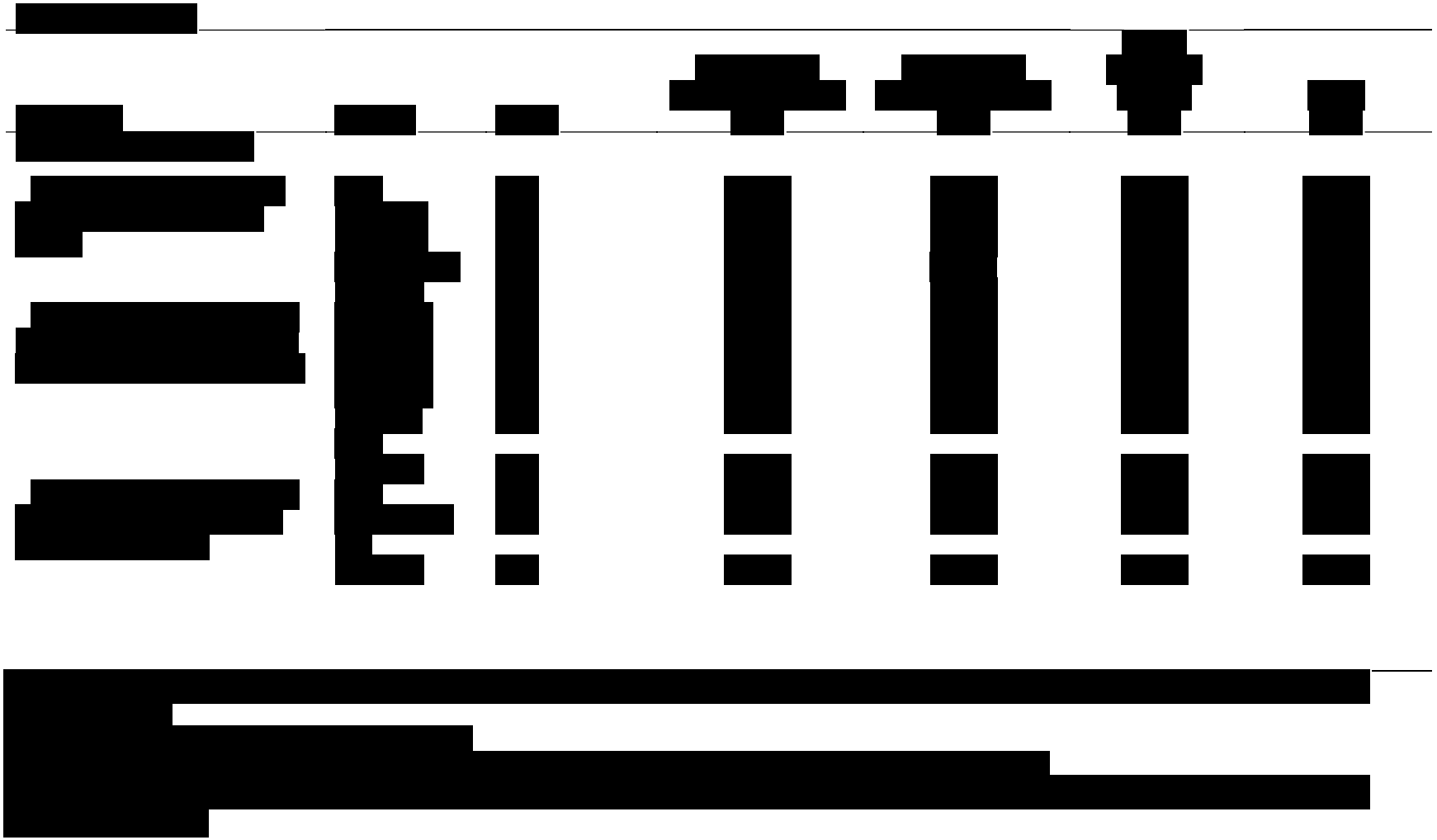

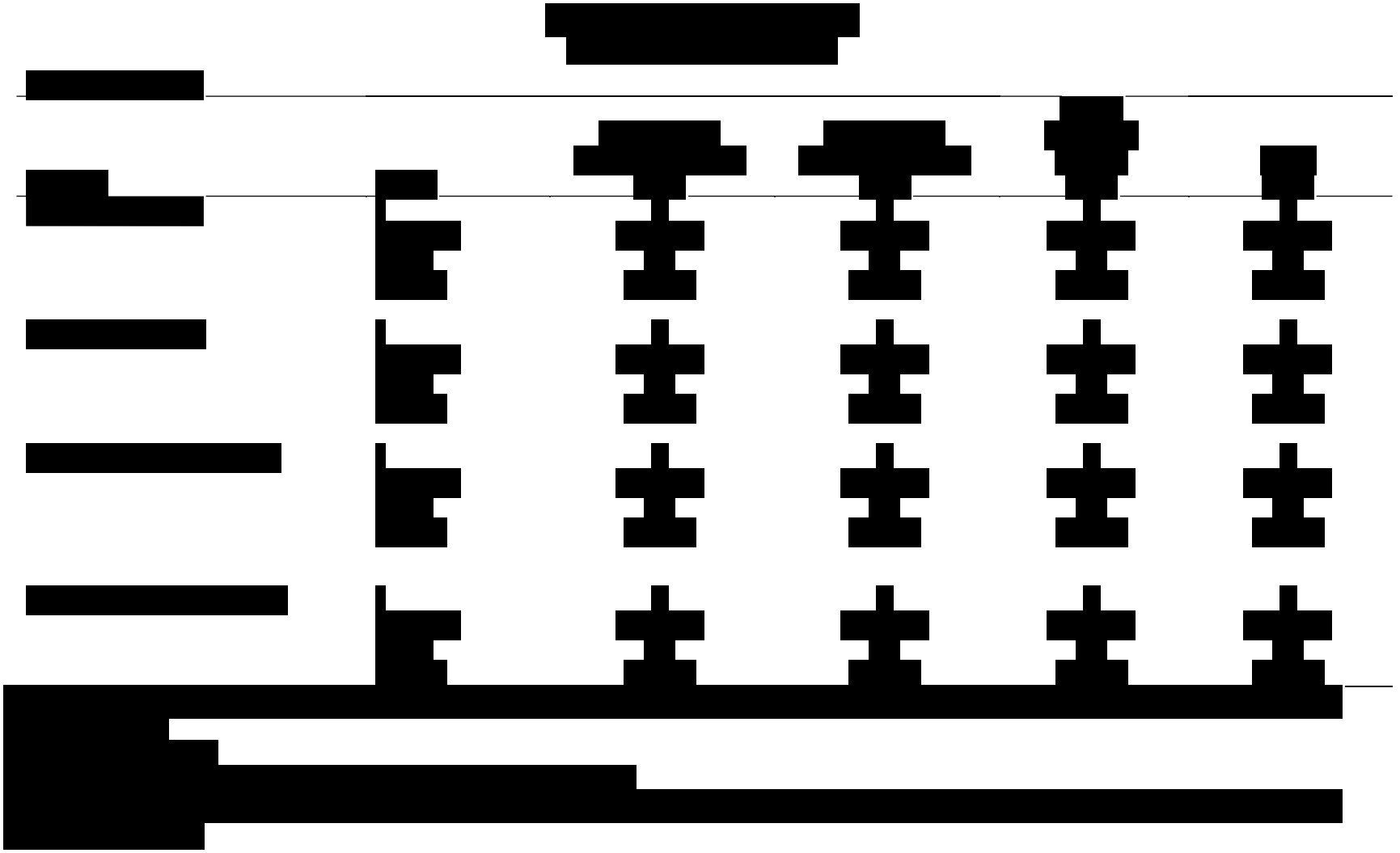

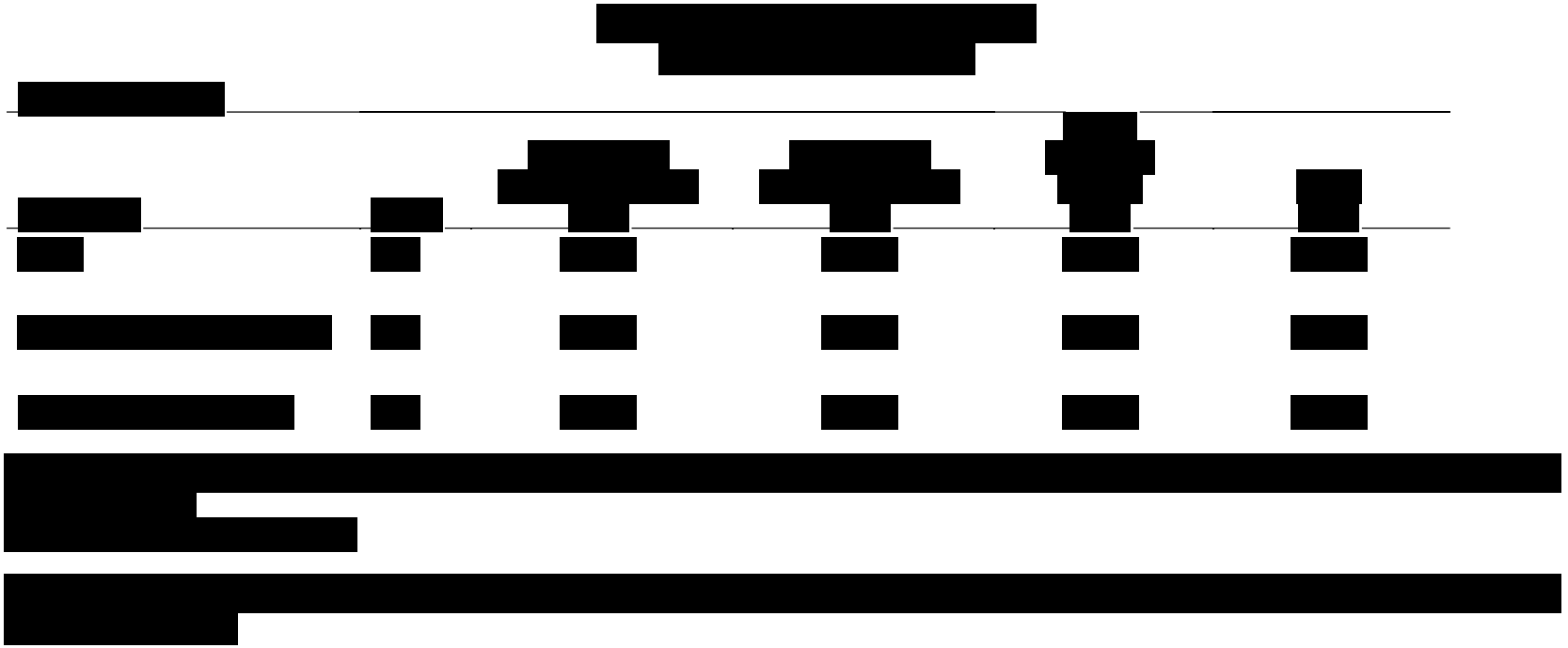

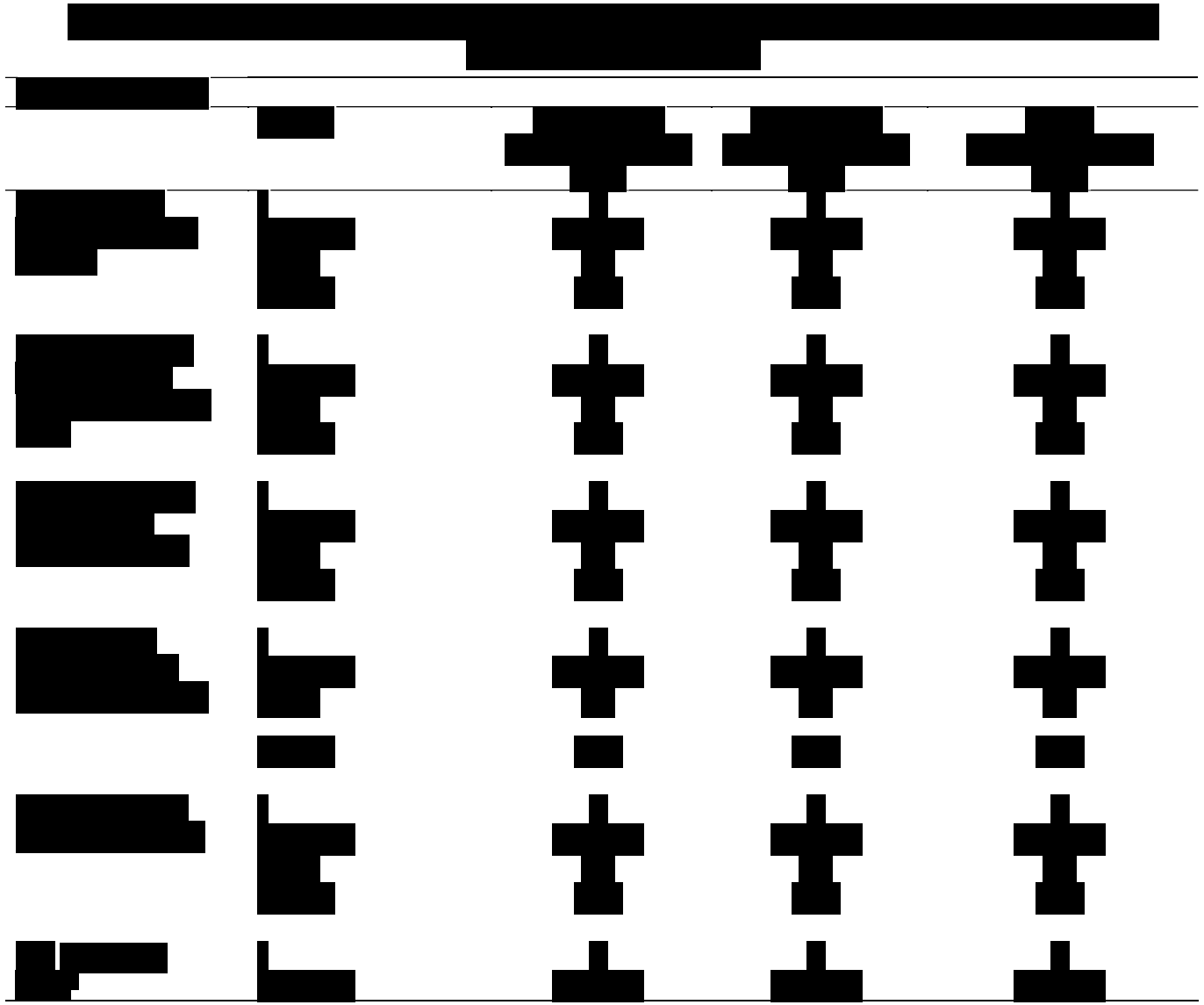

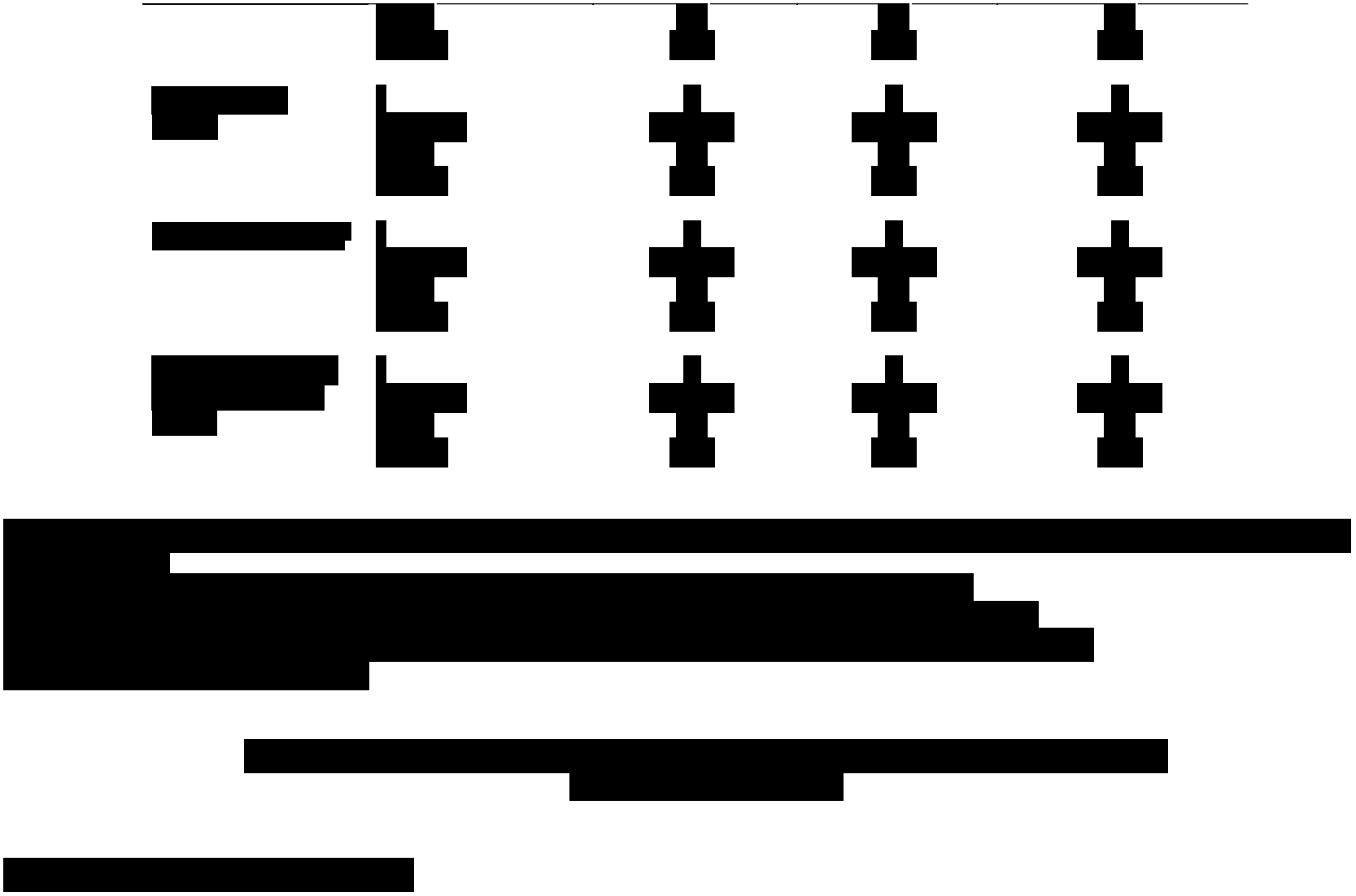

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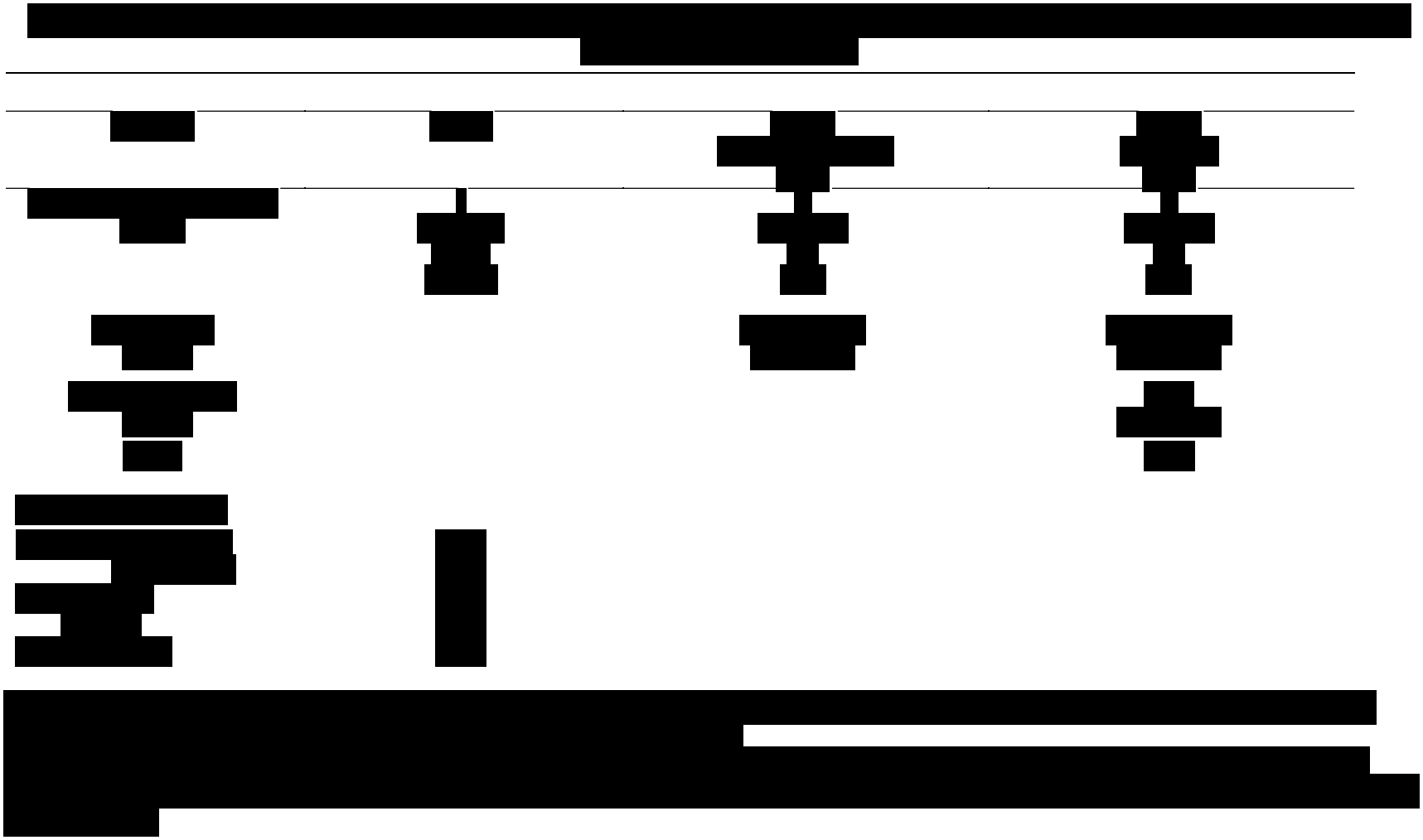

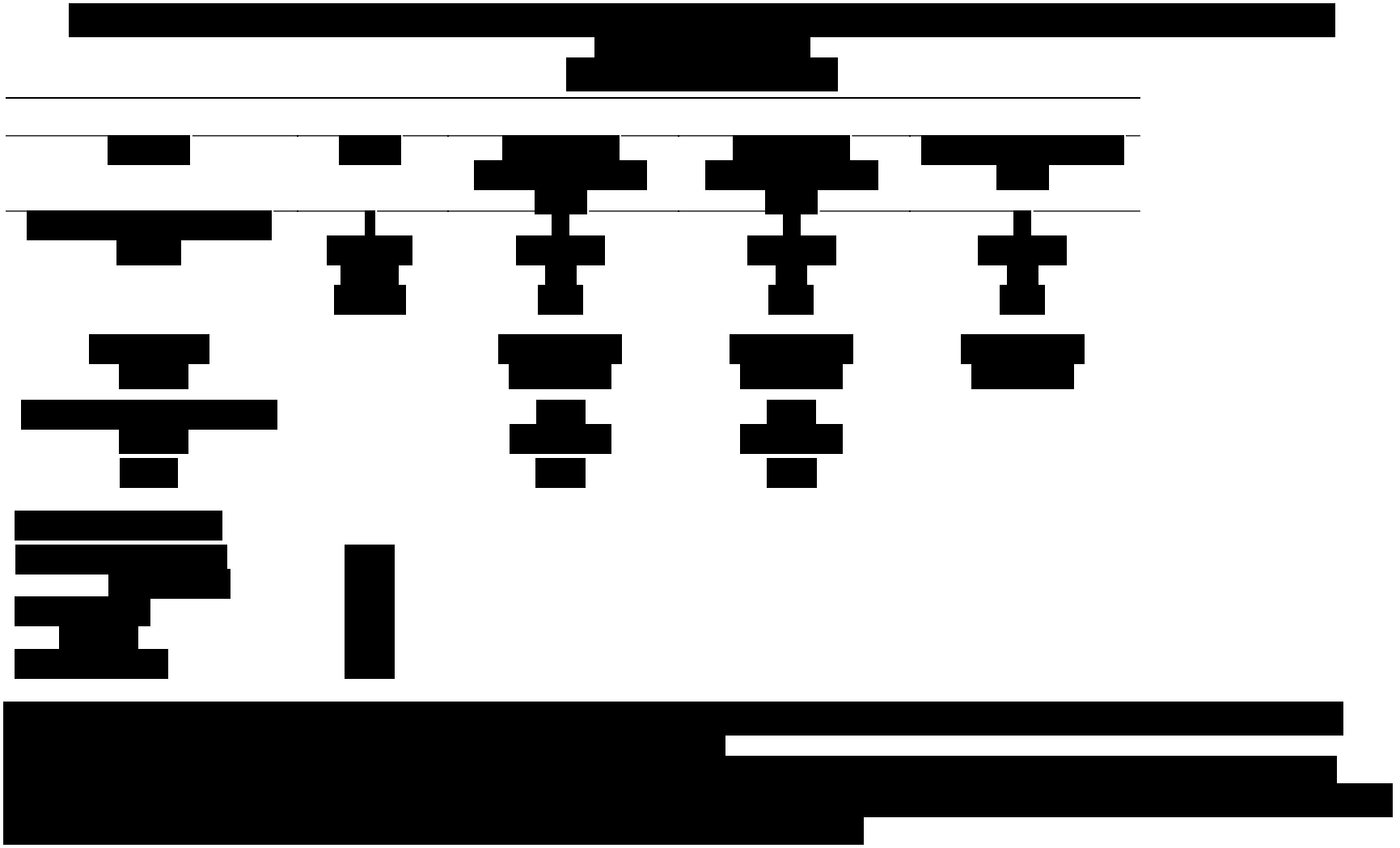

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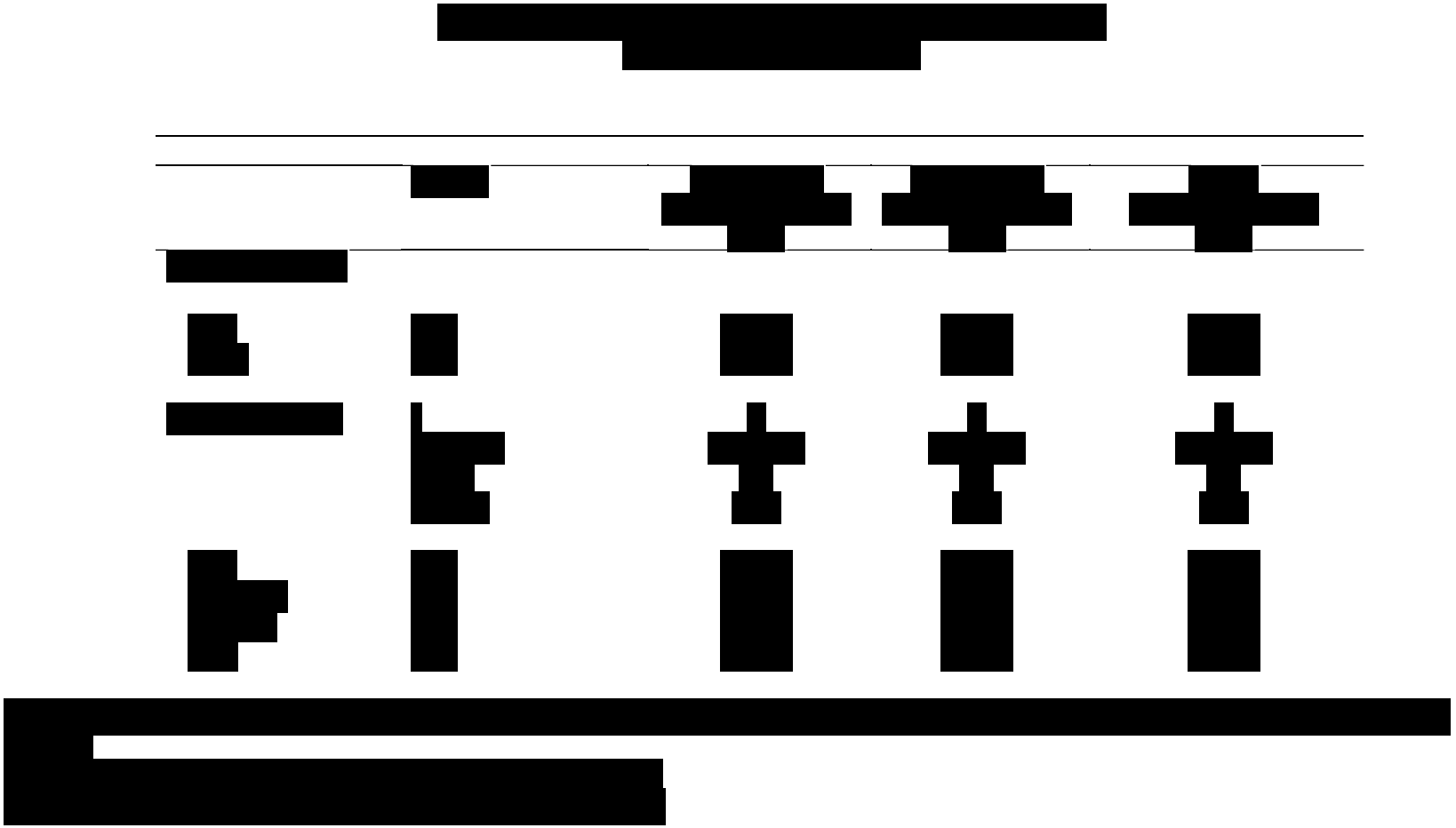

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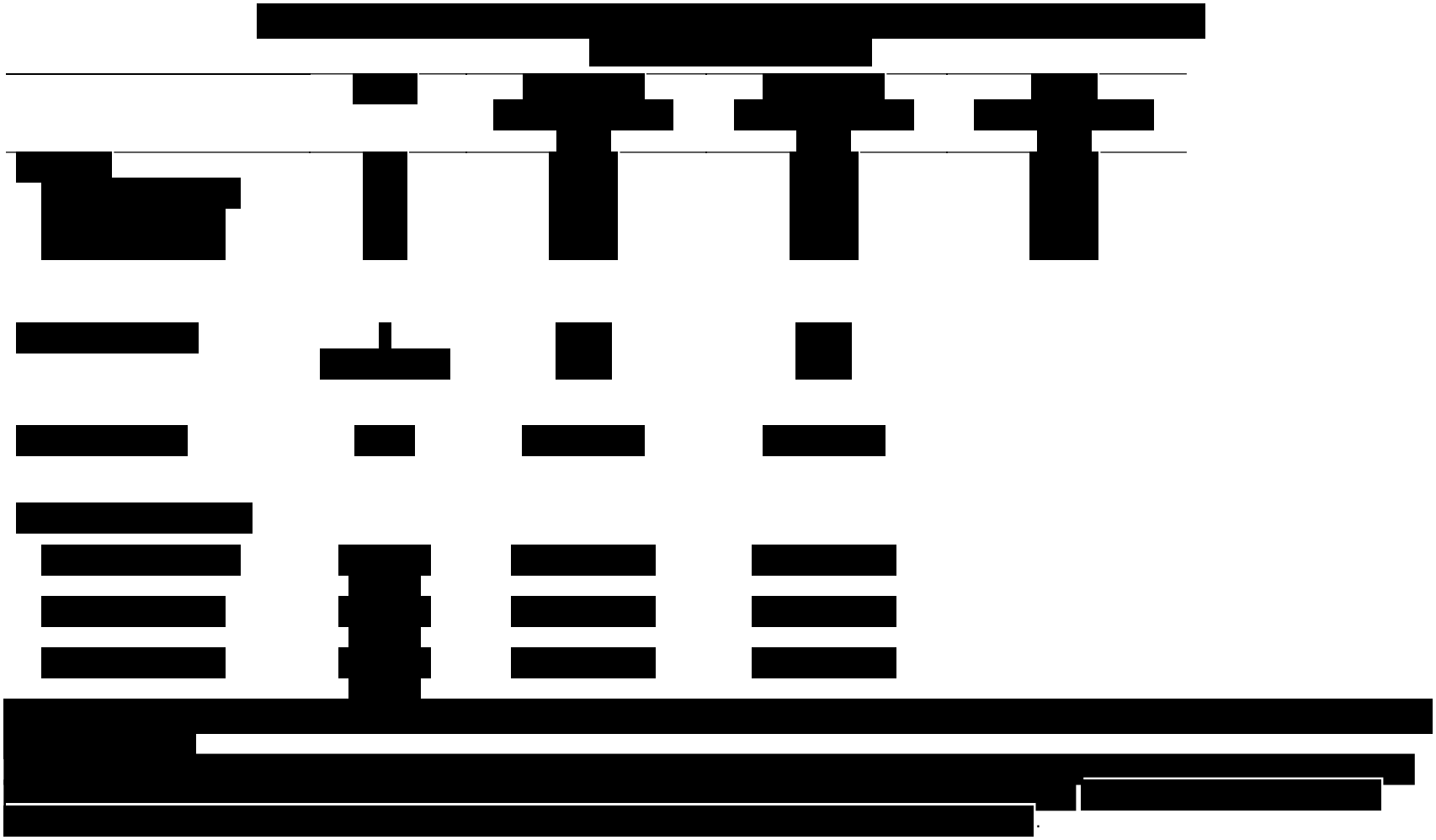

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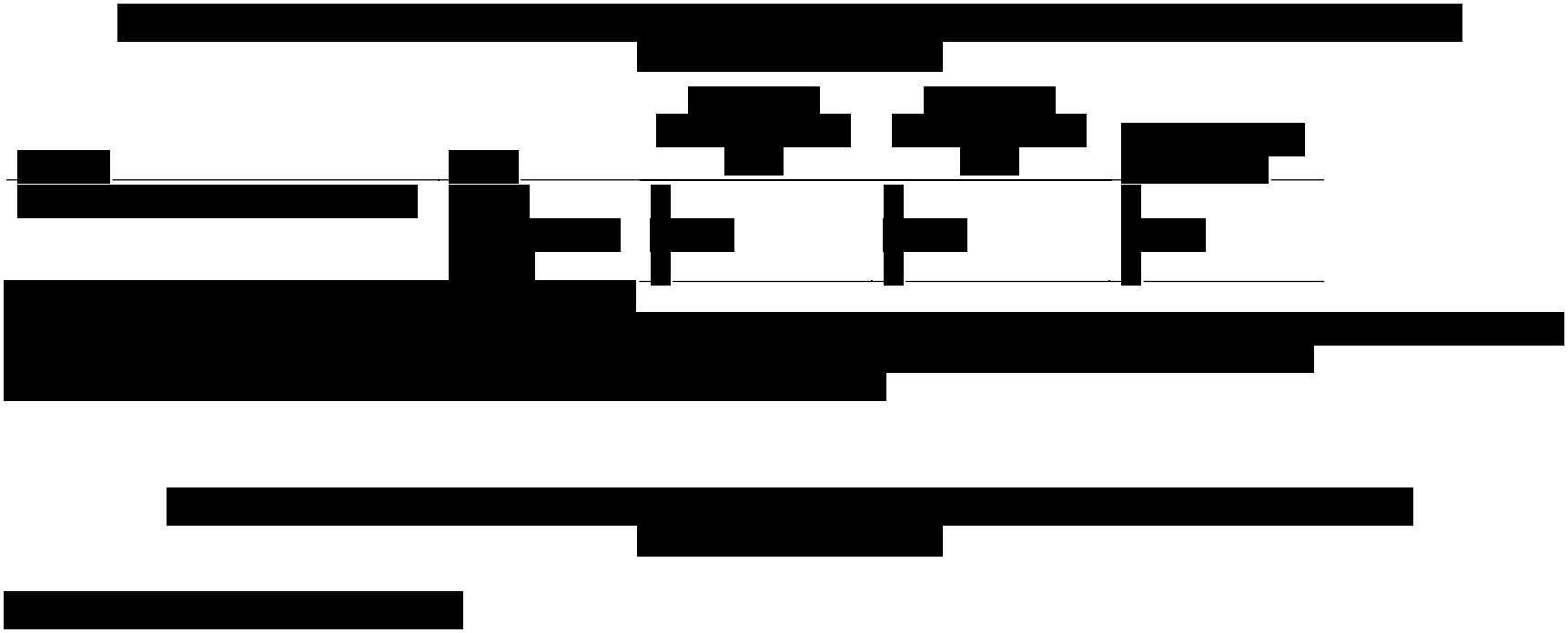

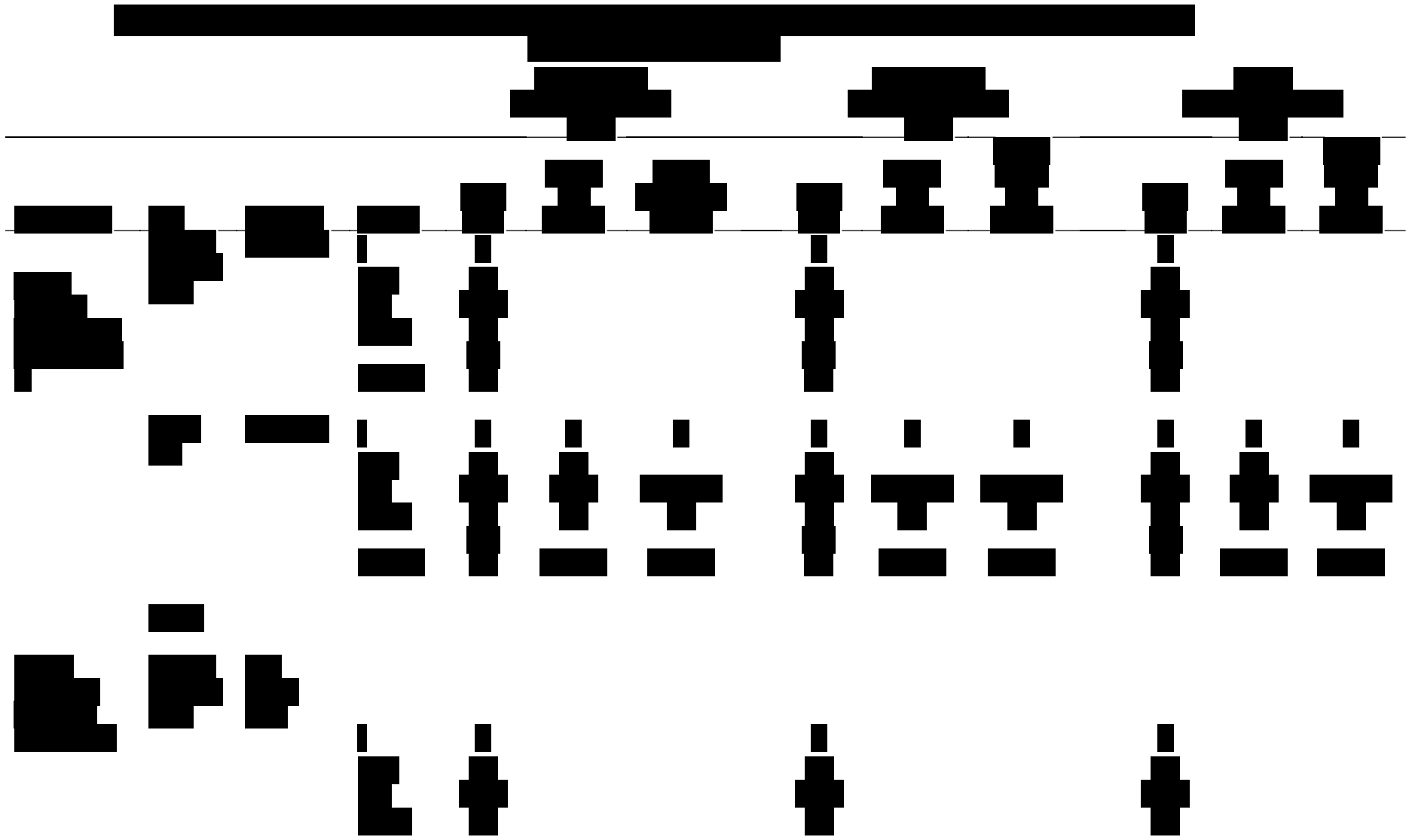

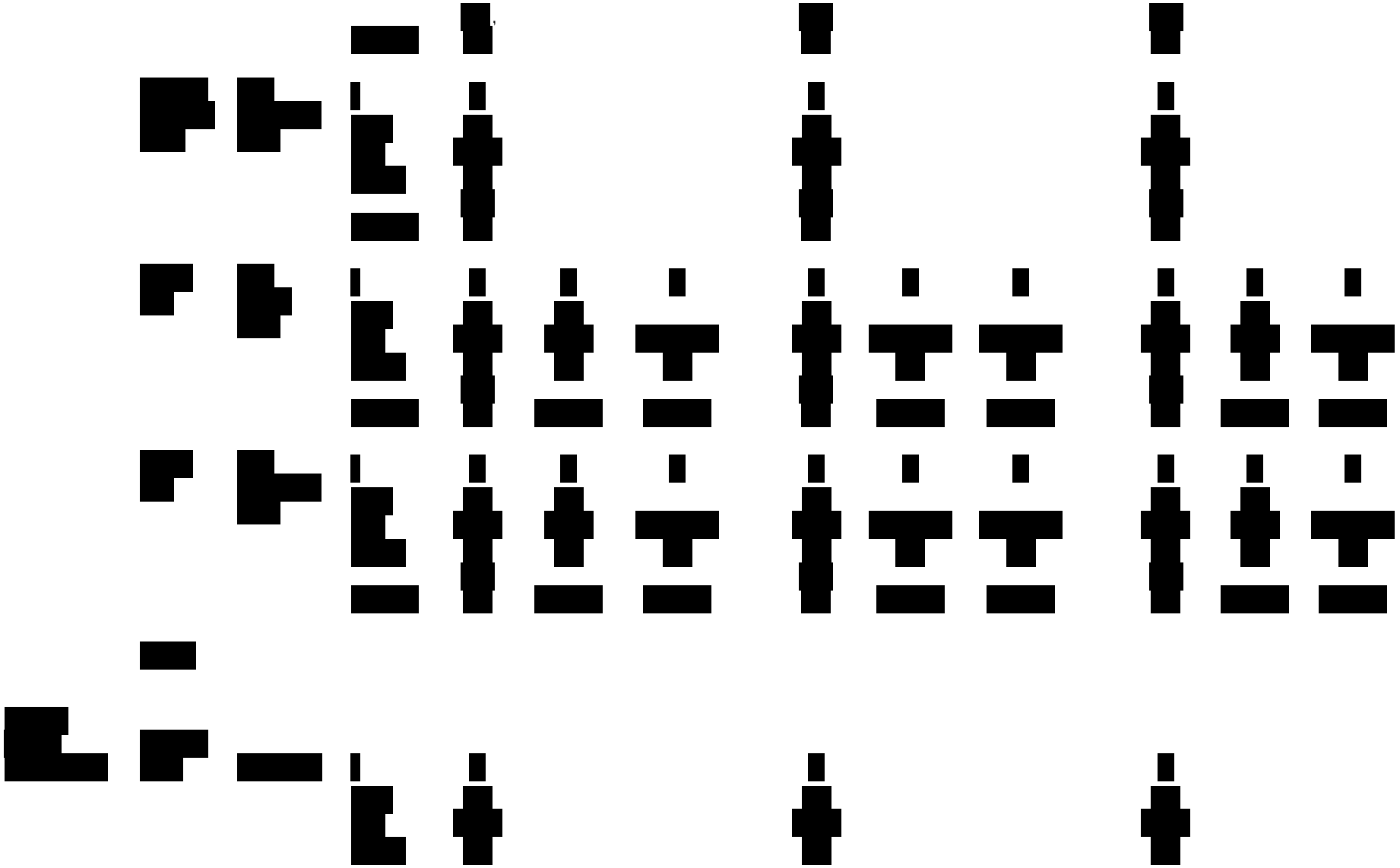

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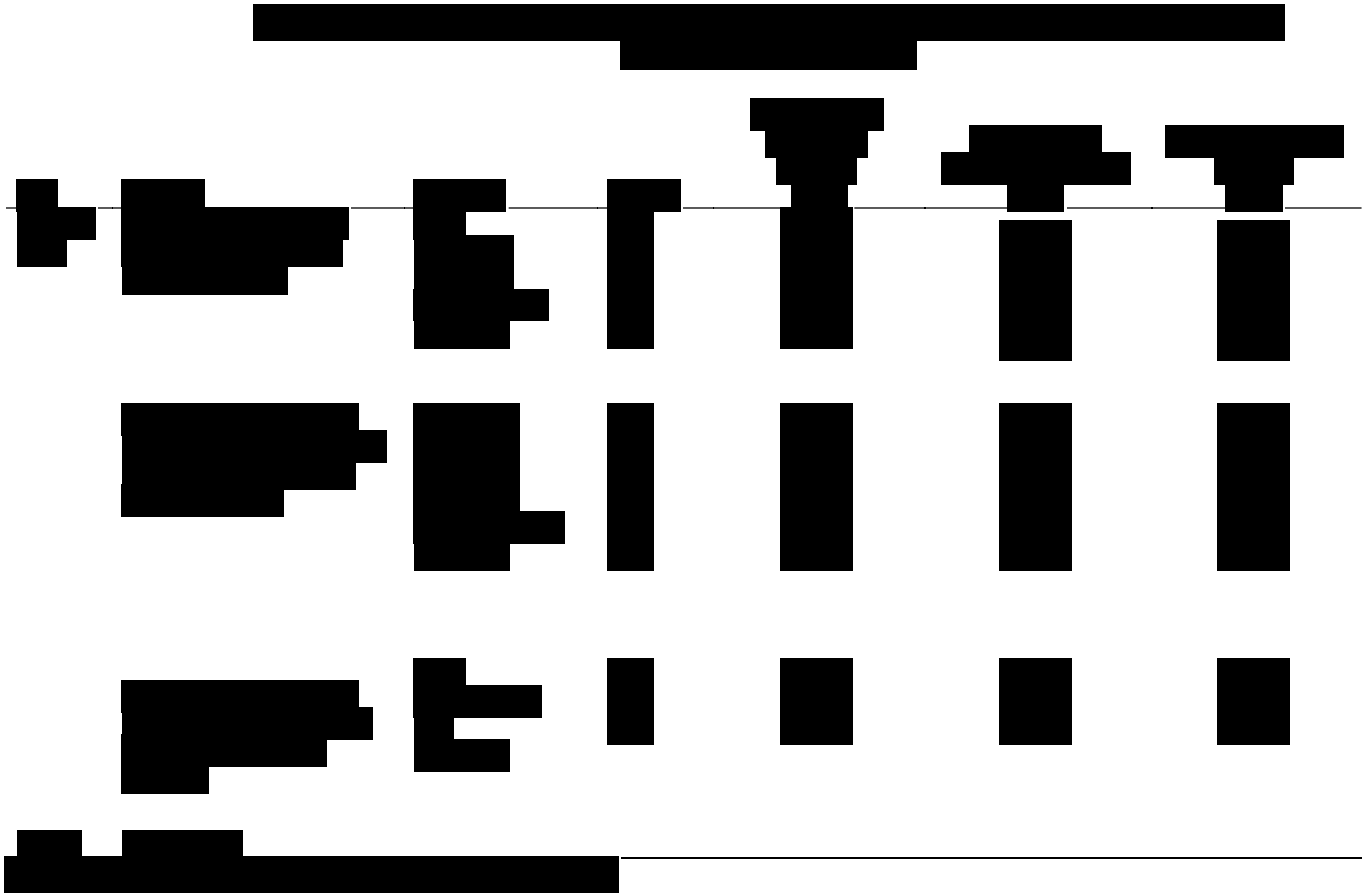

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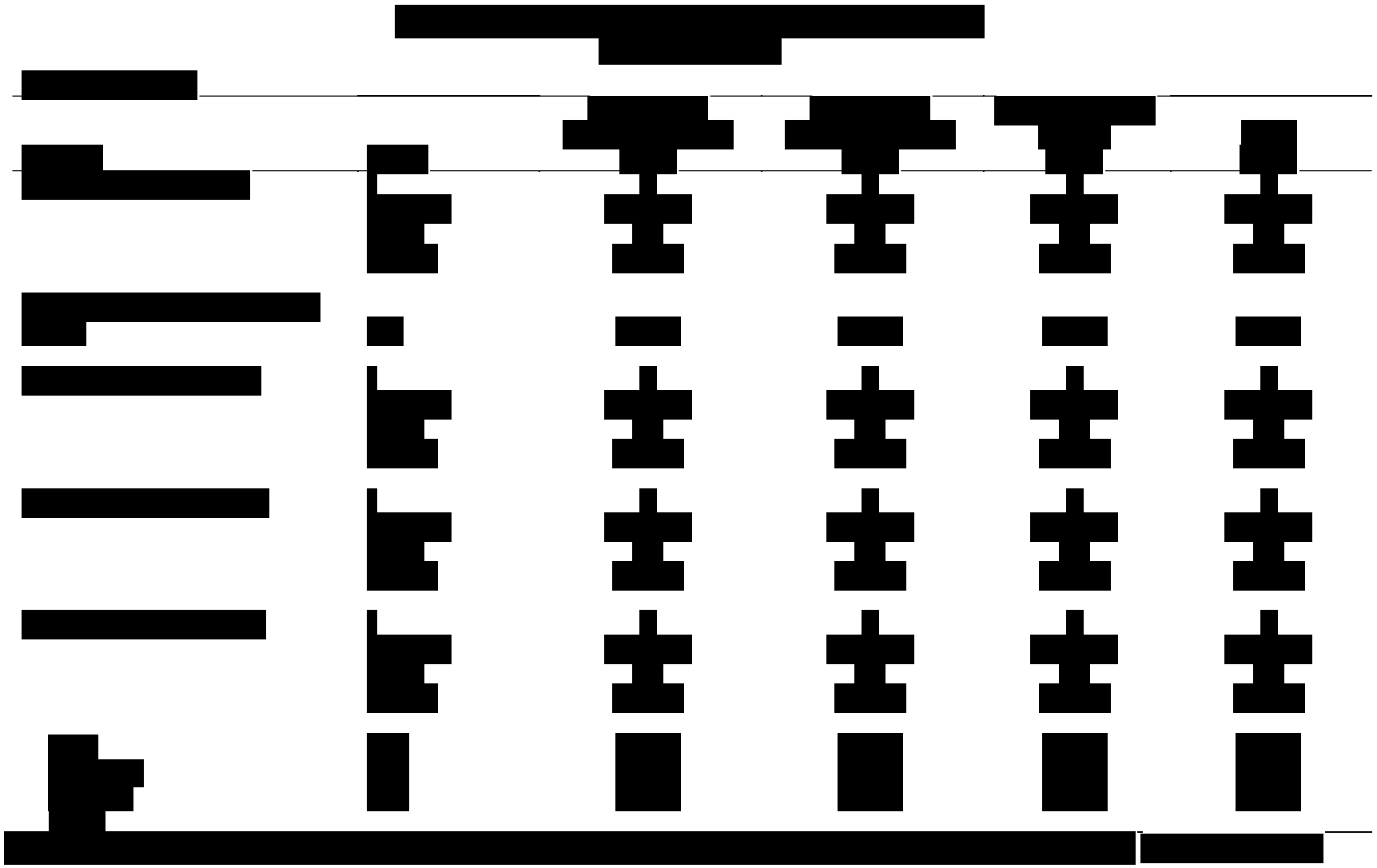

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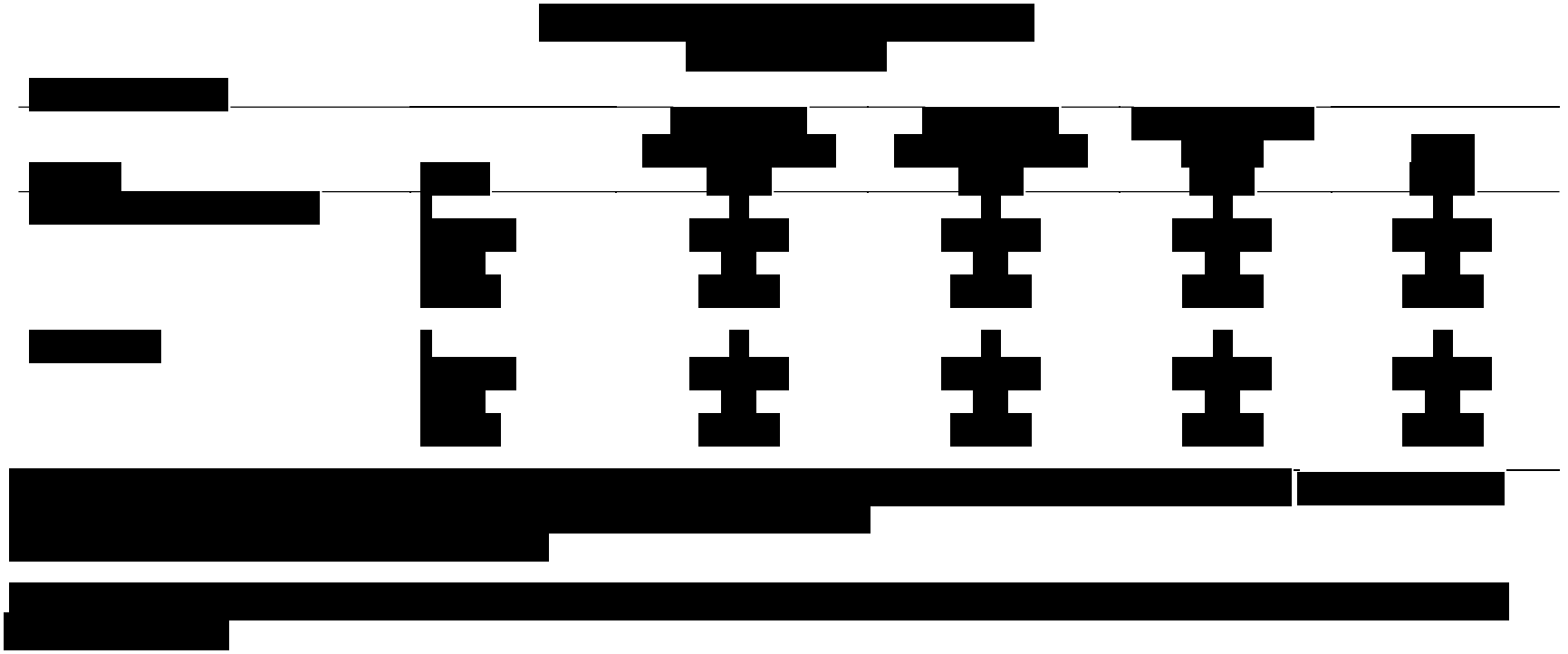

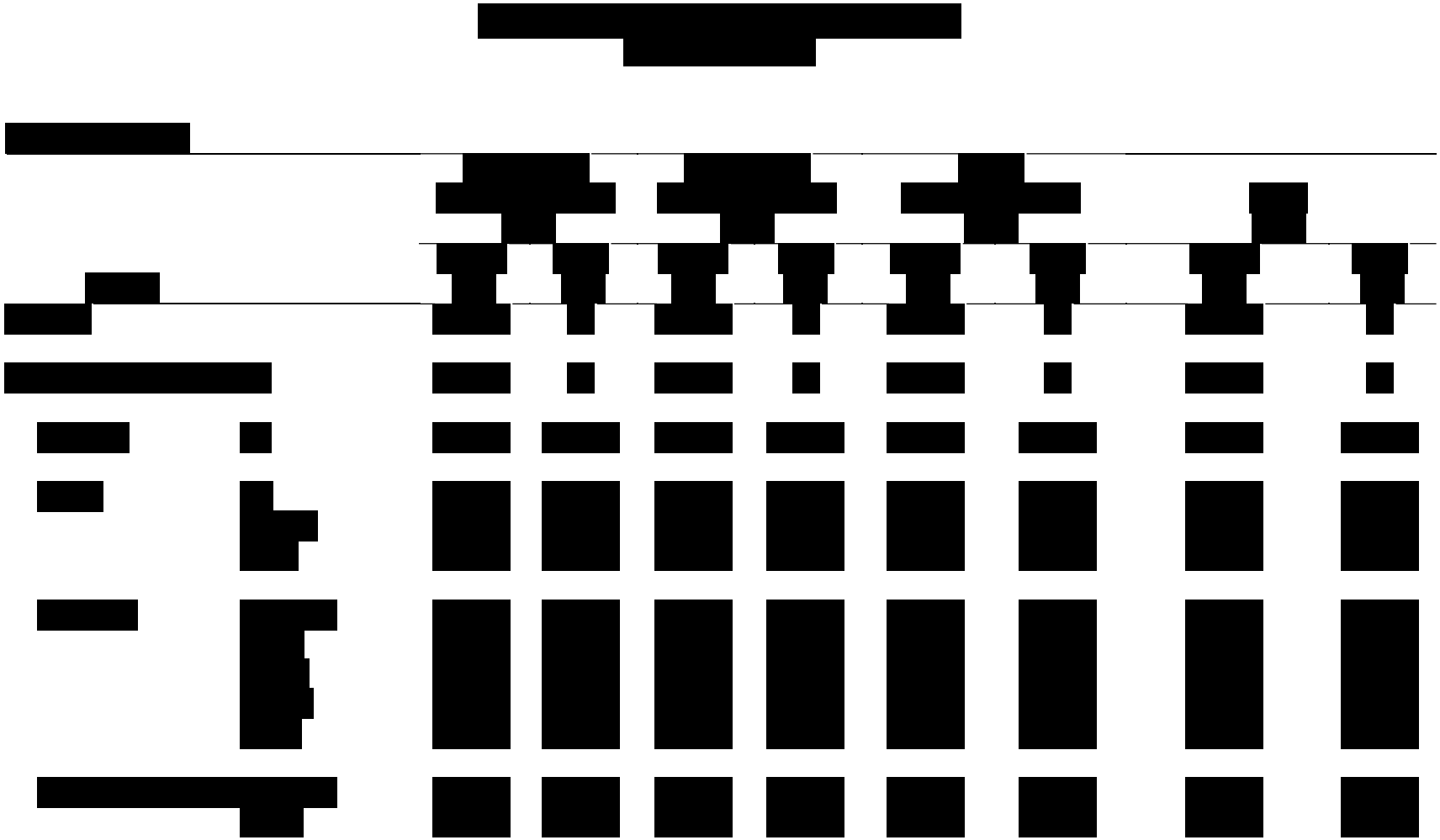

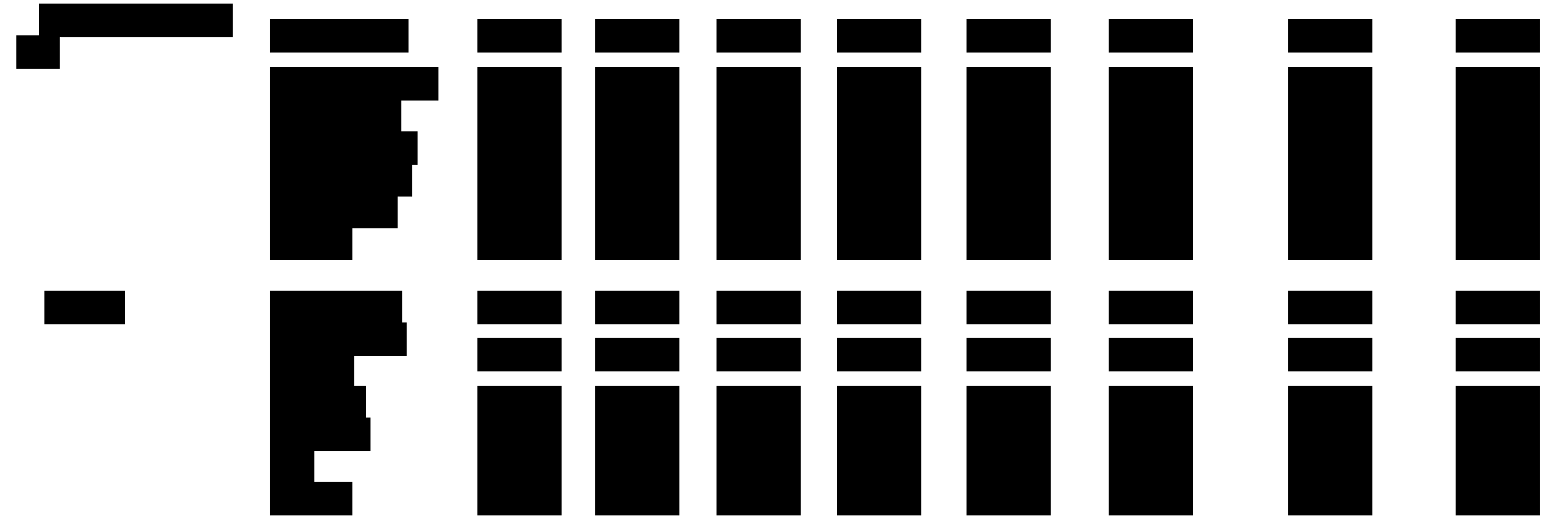

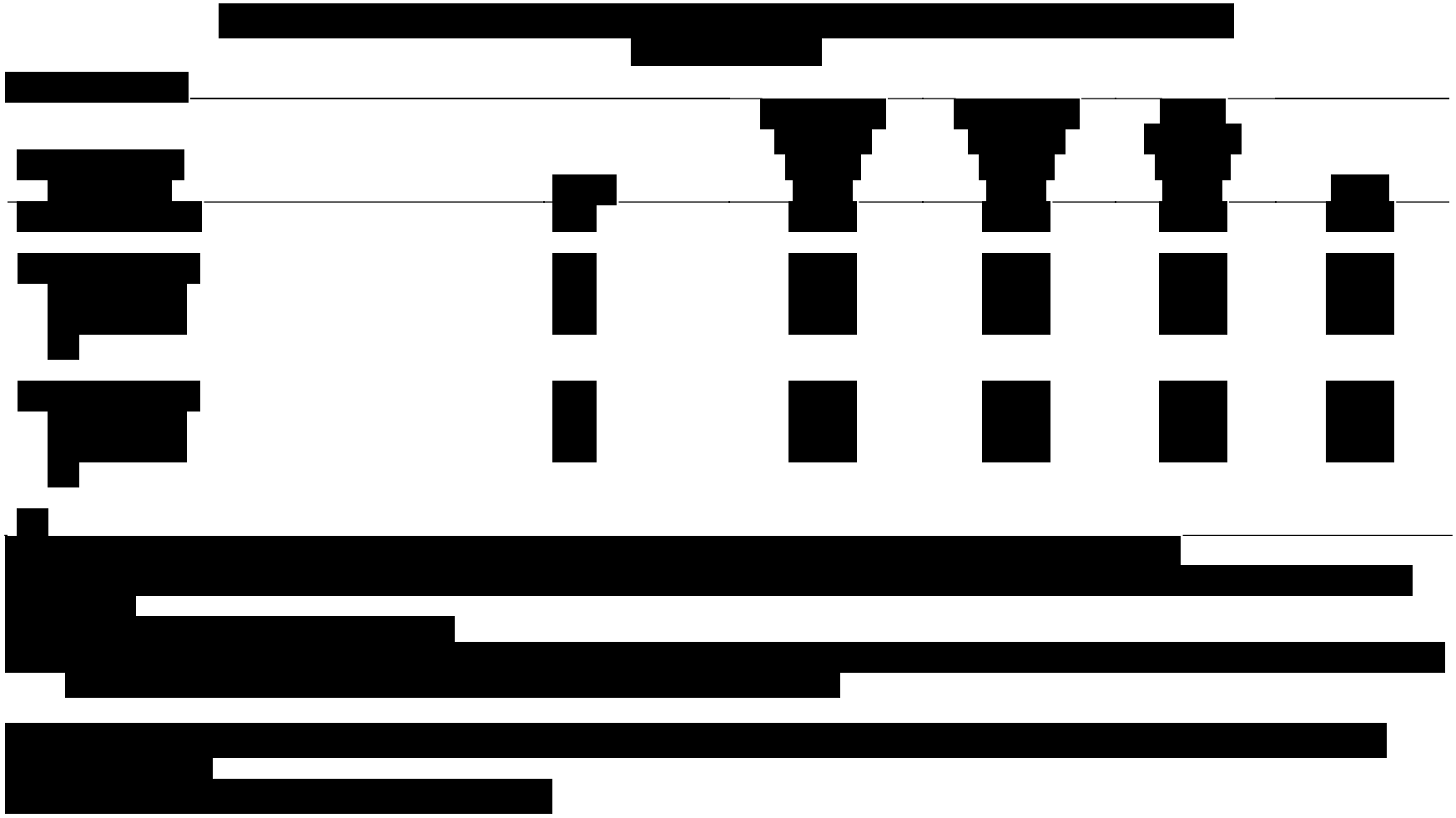

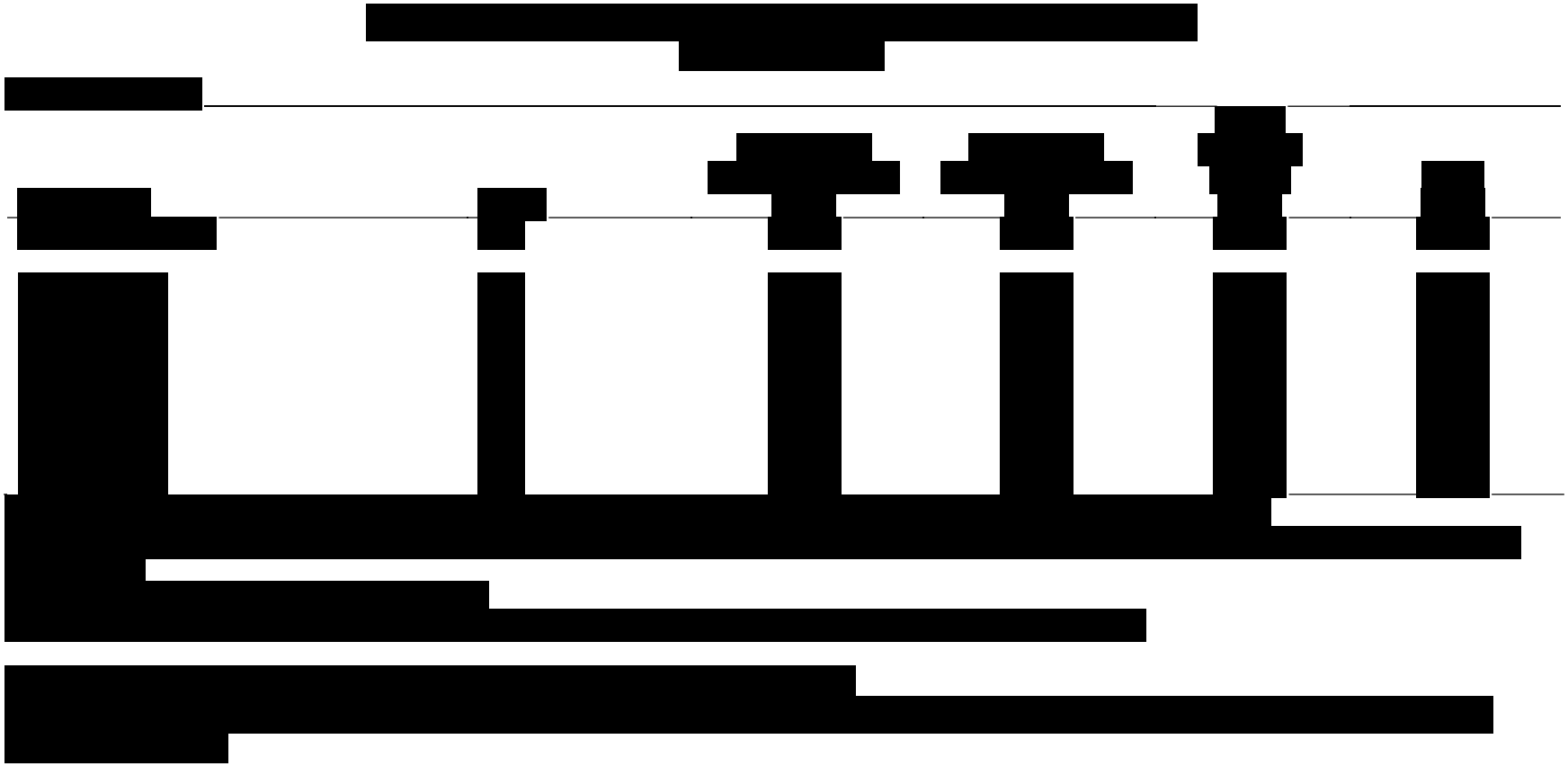

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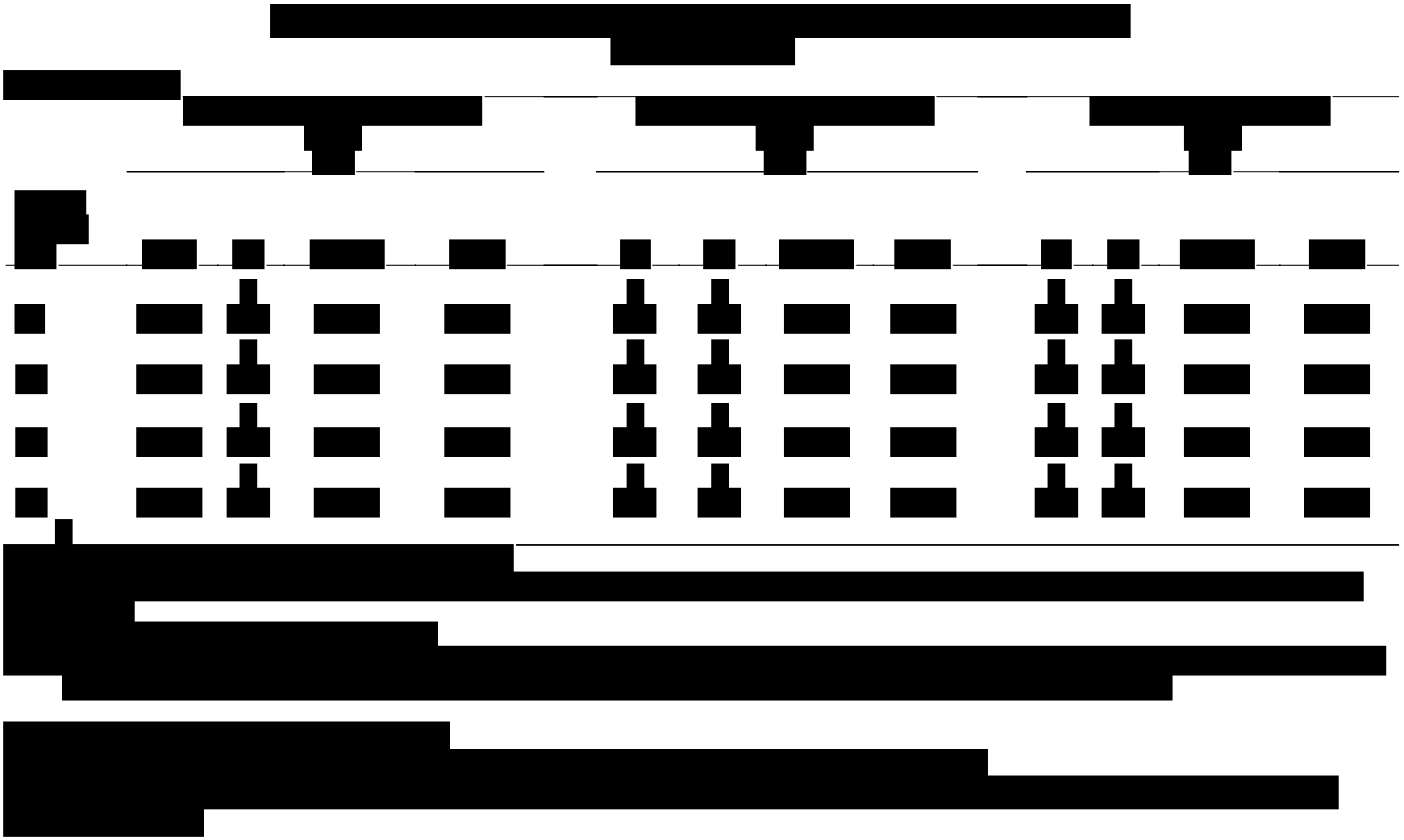

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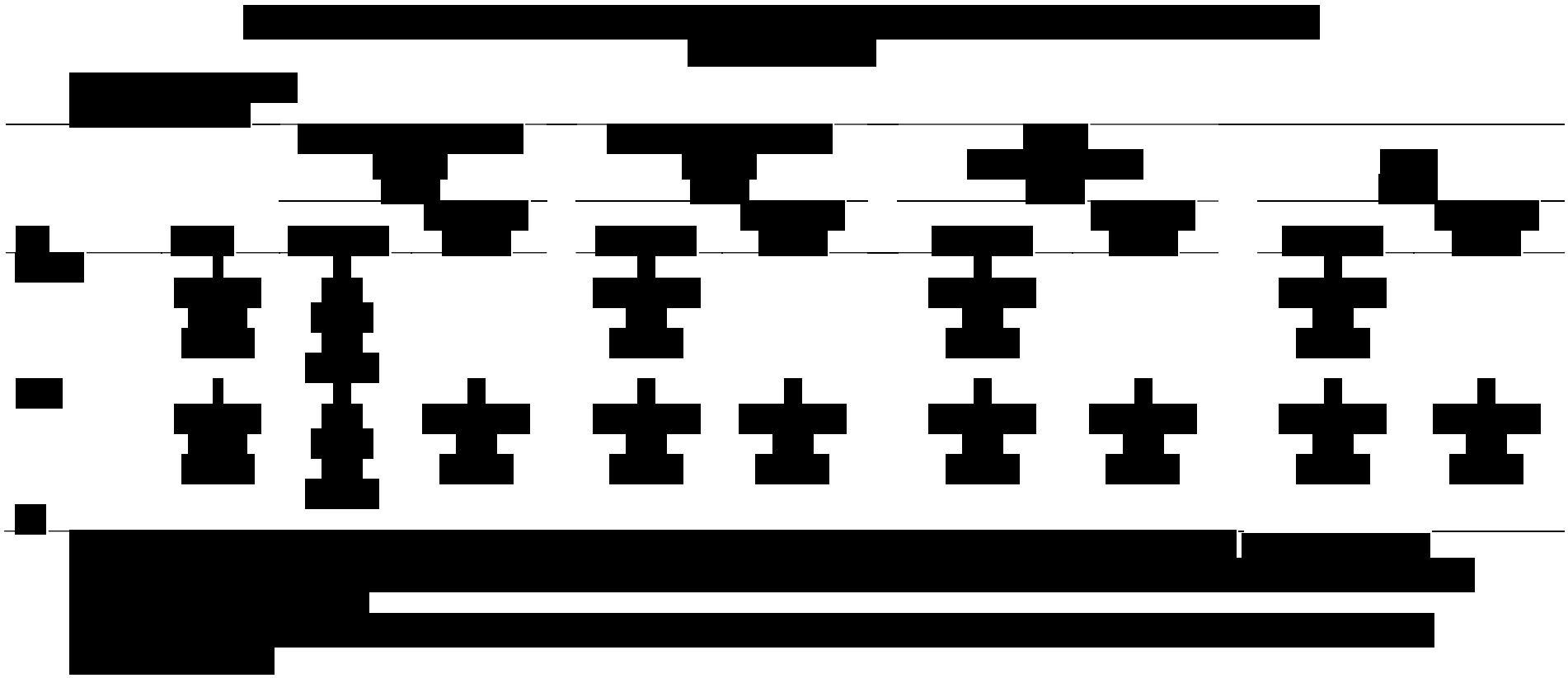

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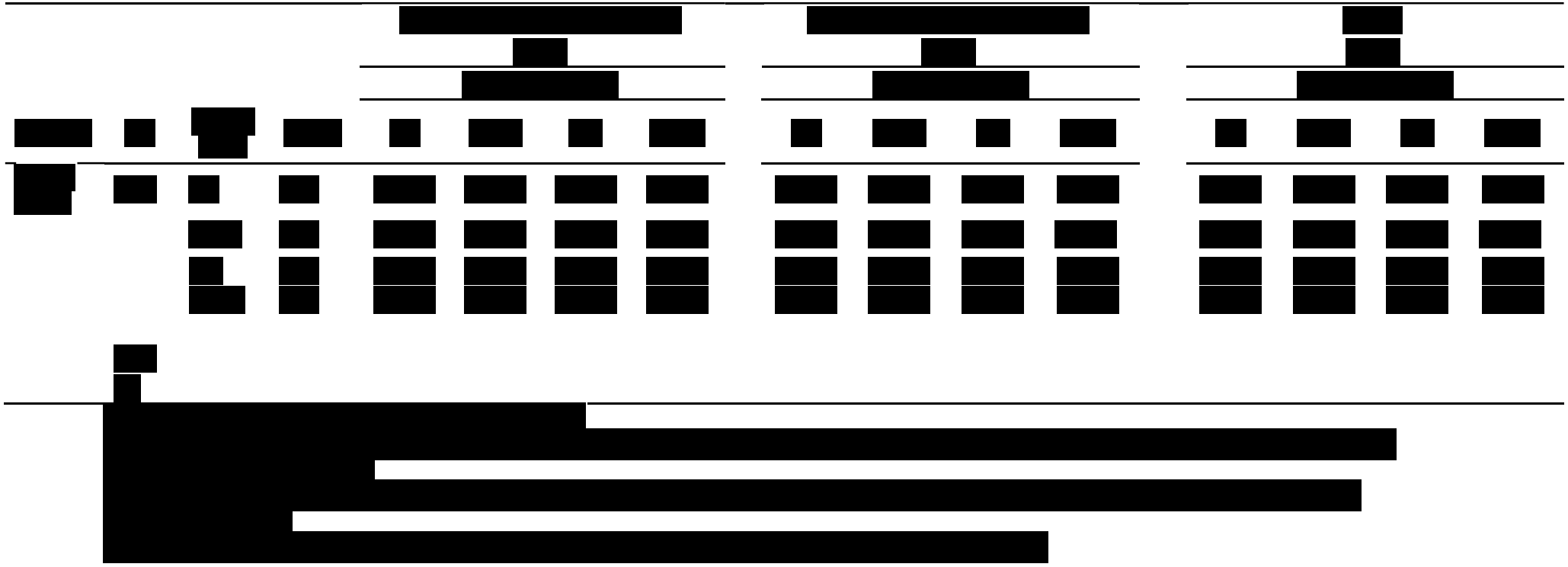

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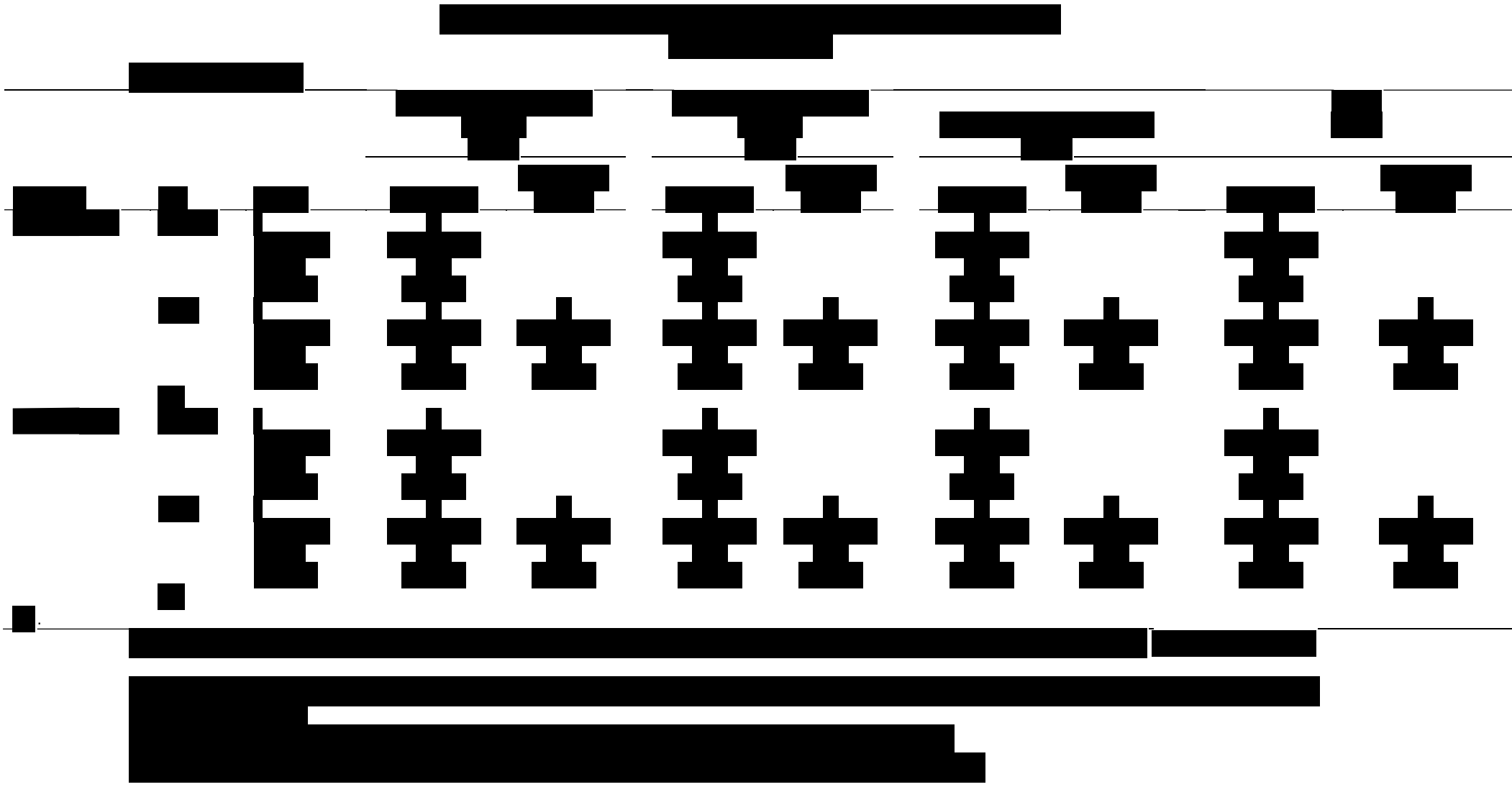

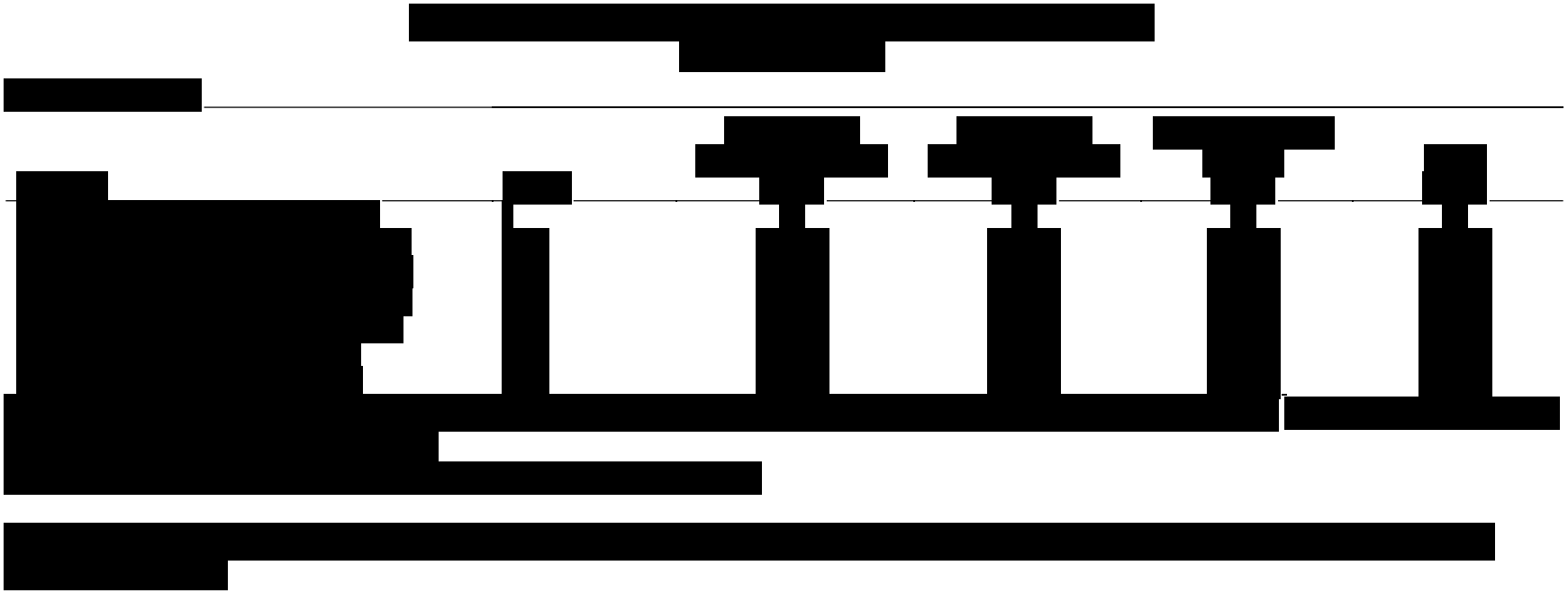

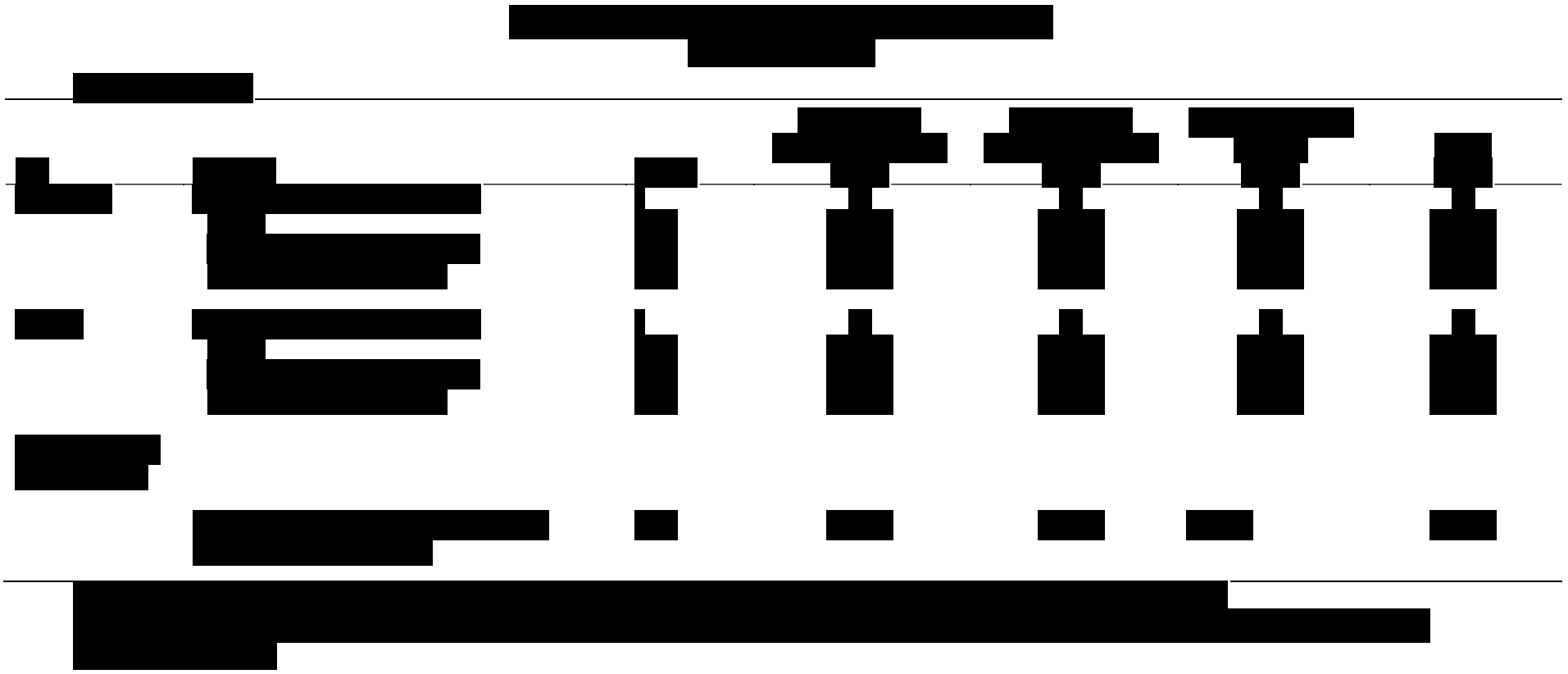

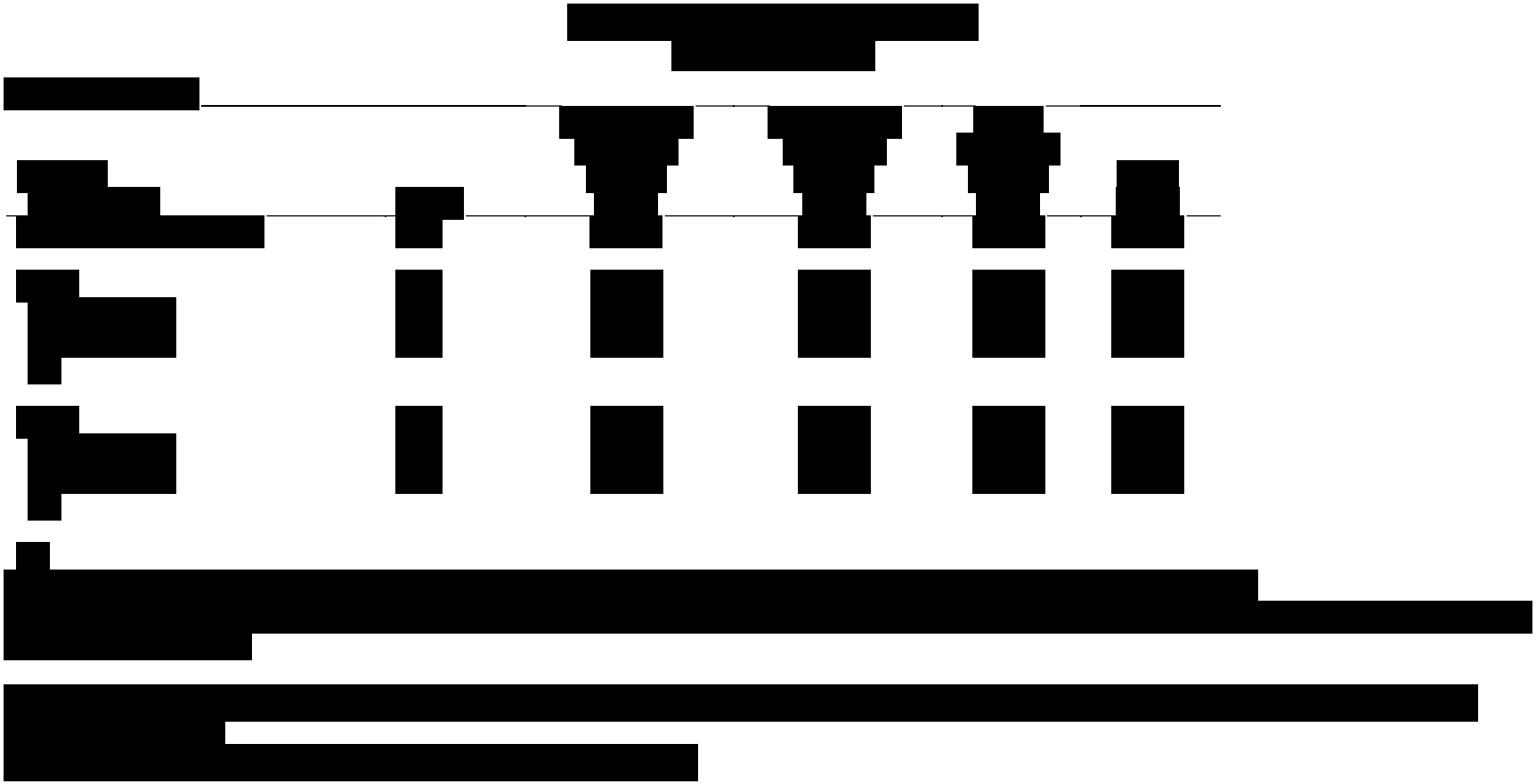

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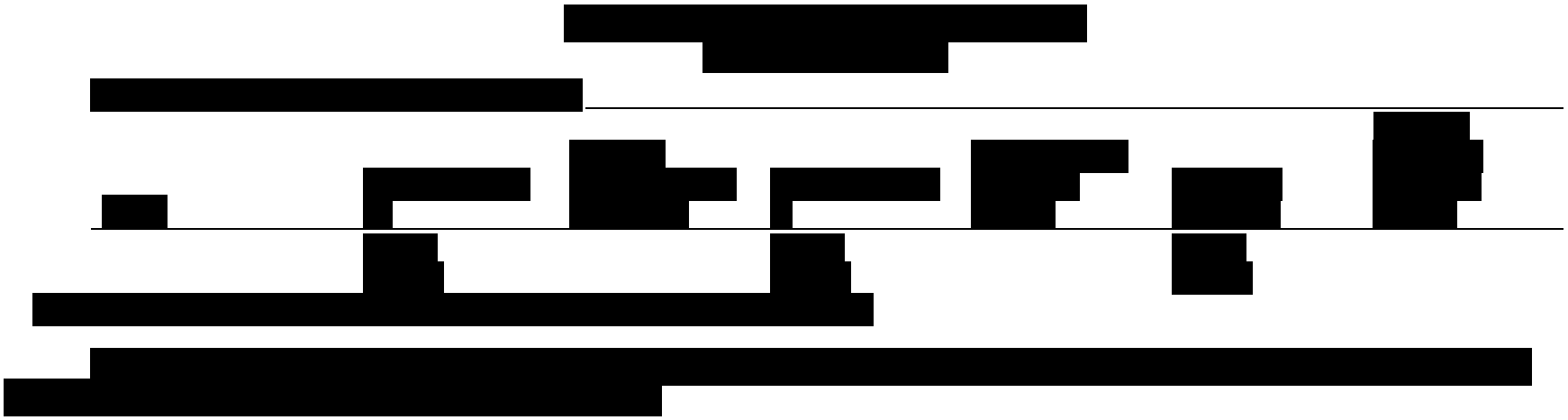

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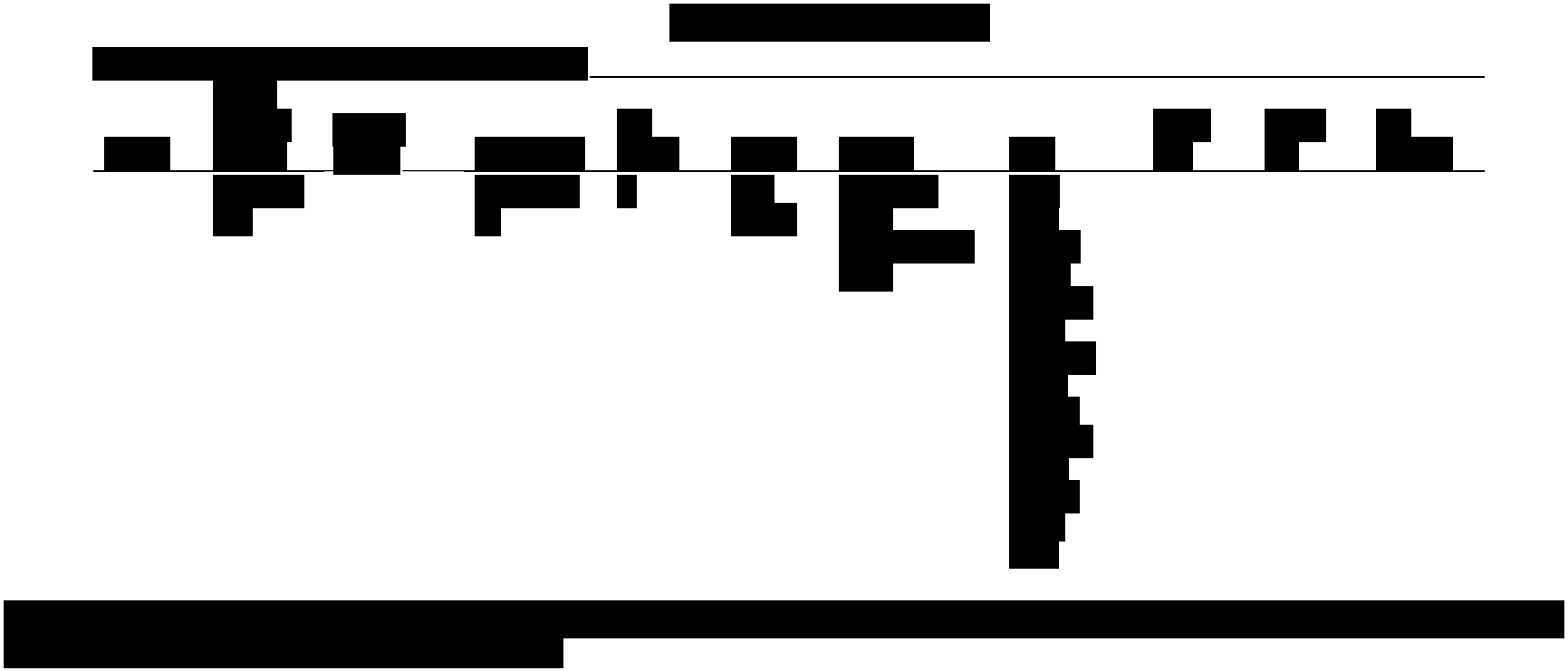

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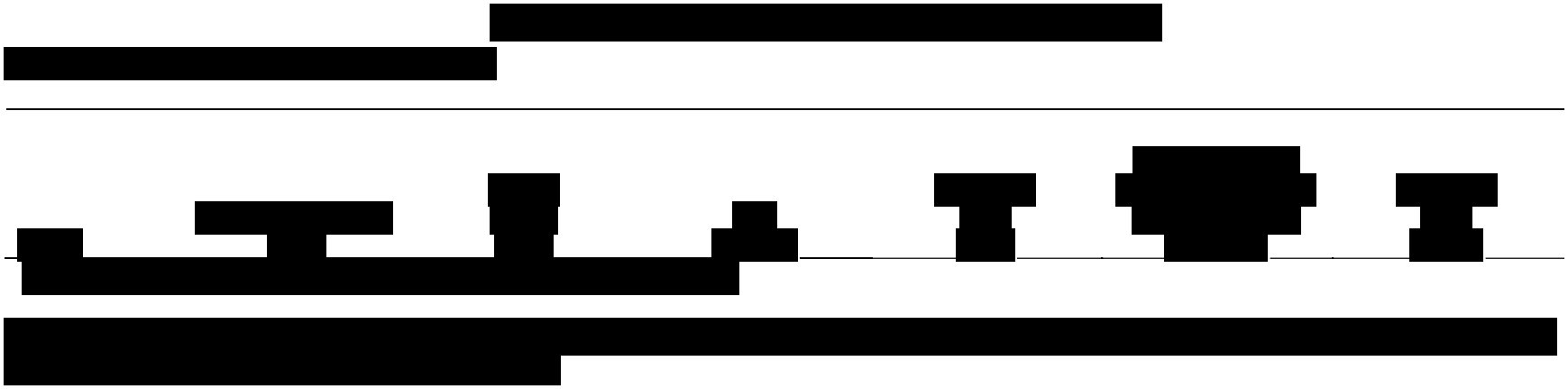

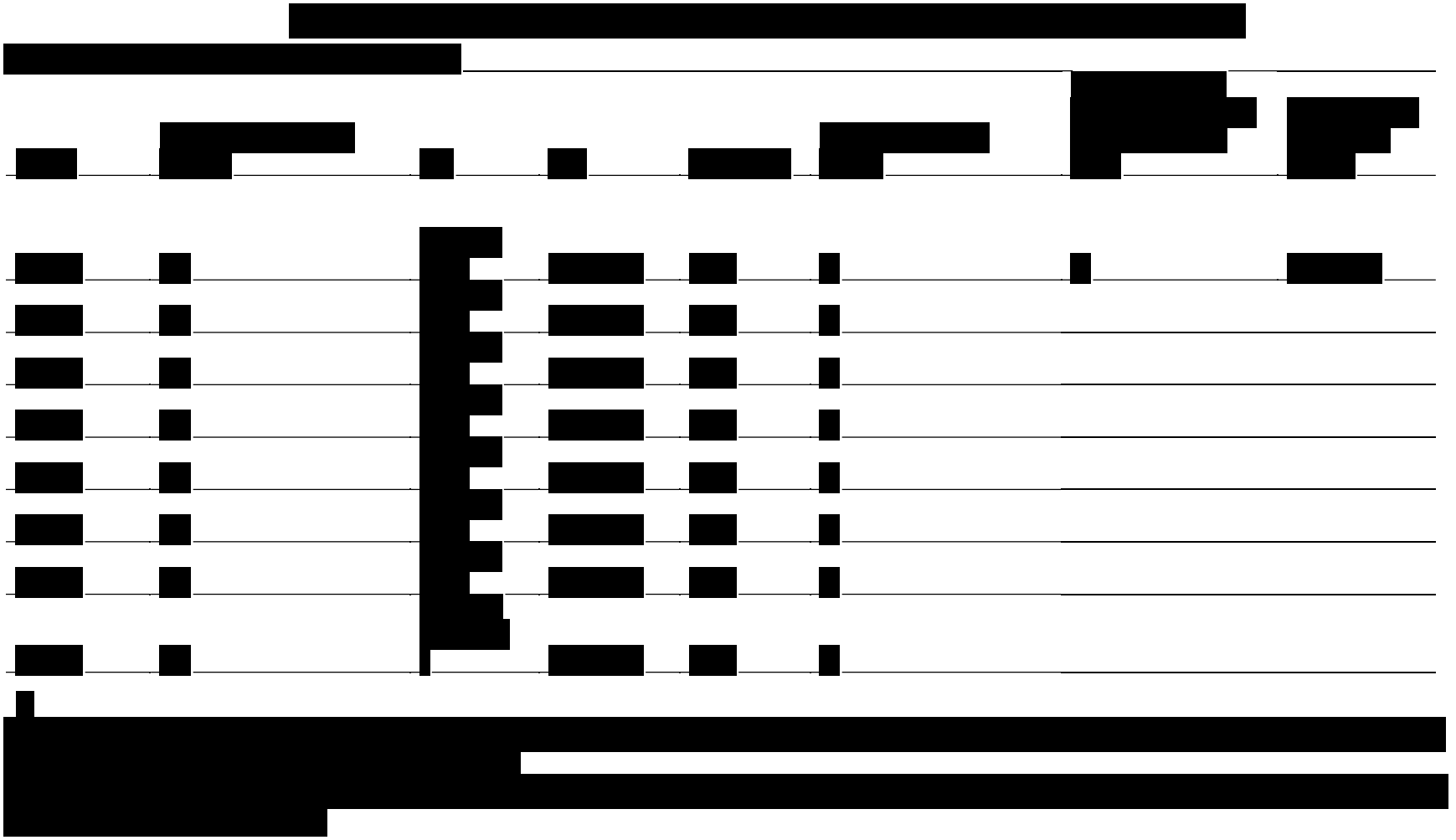

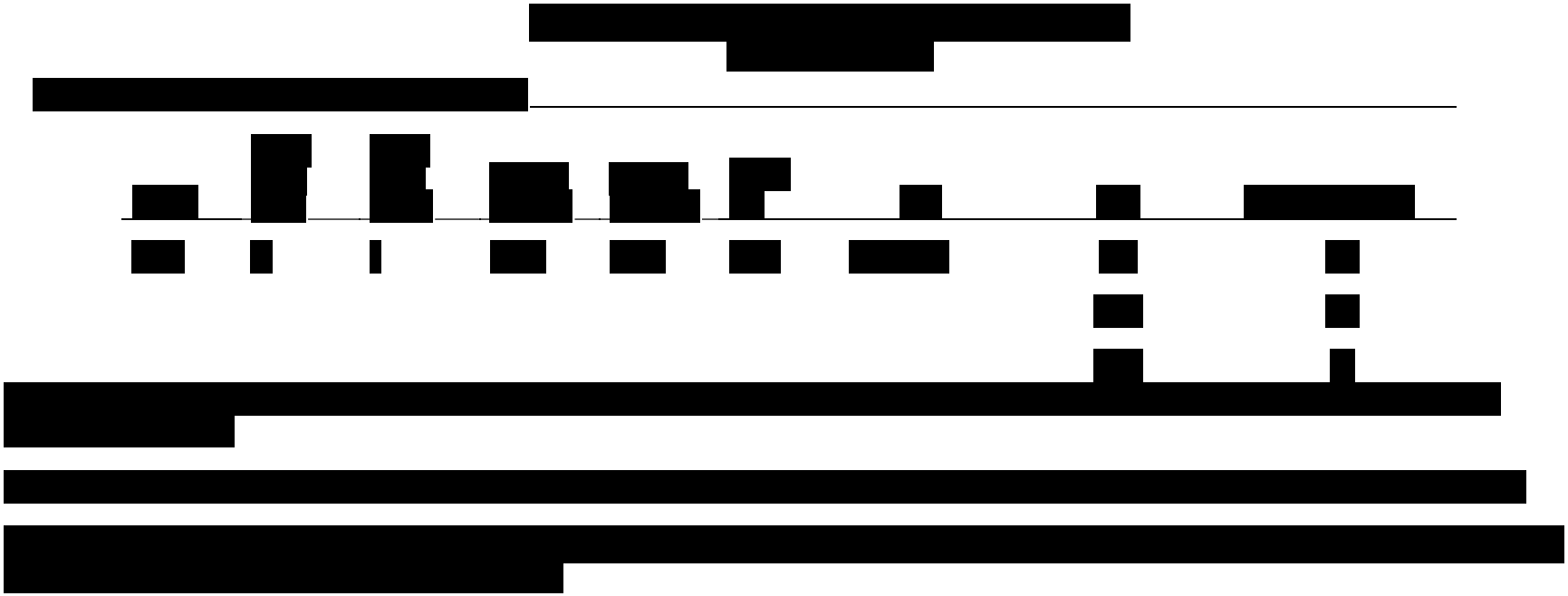

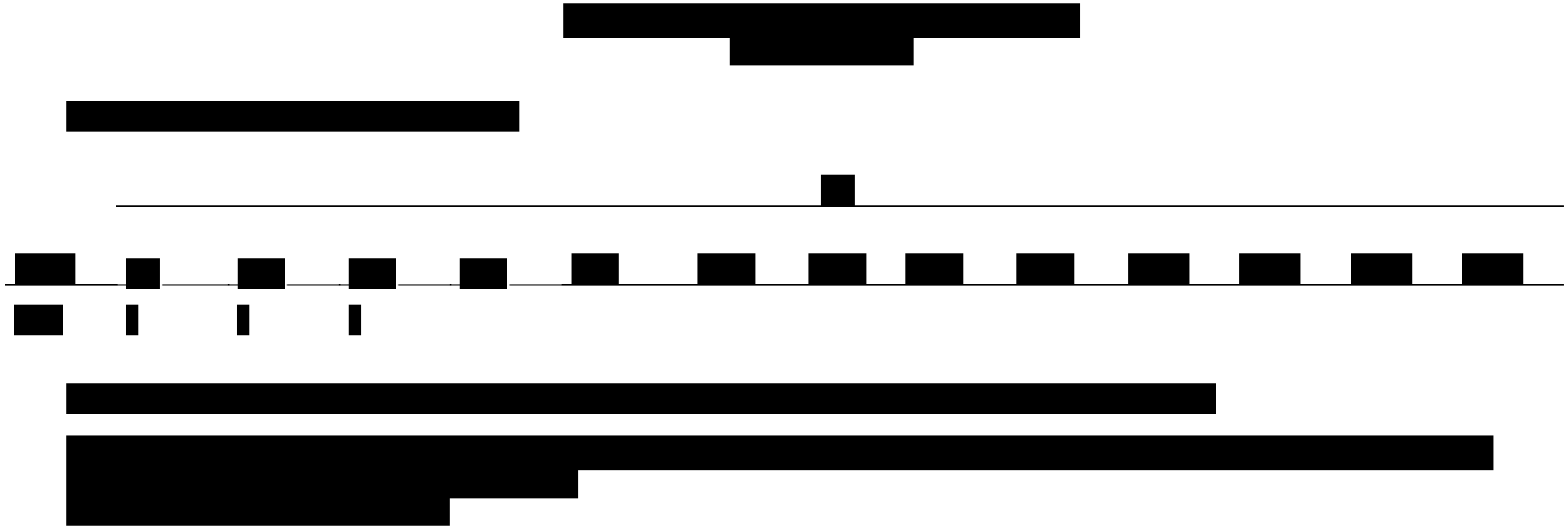

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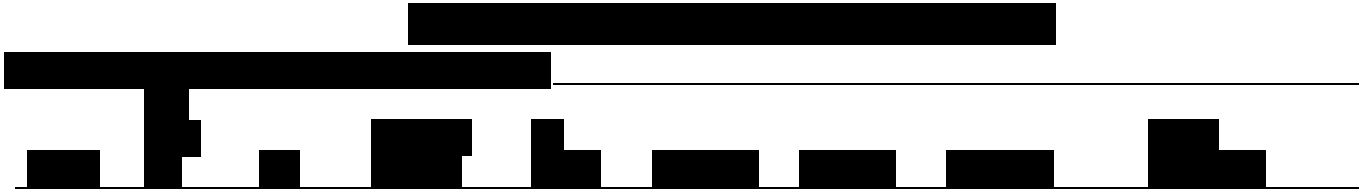

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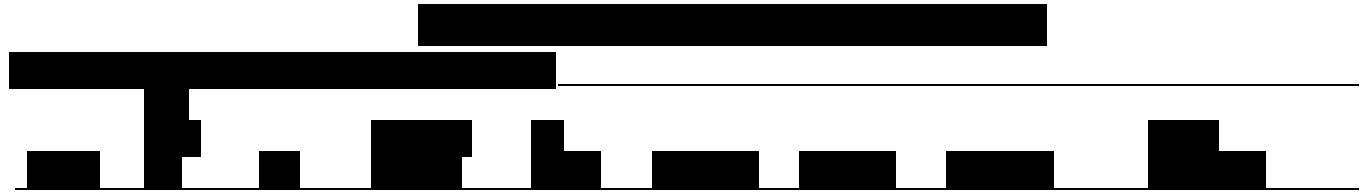

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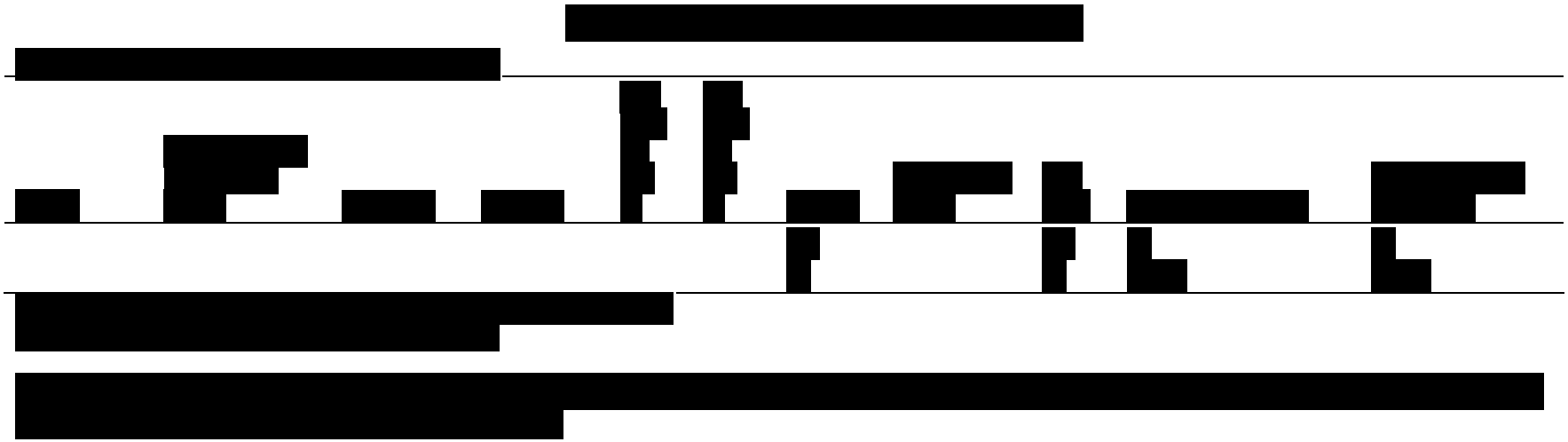

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