STATISTICAL ANALYSIS PLAN

Date: 06-May-2021

A randomized, controlled, single-blinded, within-subject (split-face), multicenter, prospective clinical study to evaluate the effectiveness and safety of using the dermal filler RHA® injected with a cannula or with a needle for the treatment of moderate to severe nasolabial folds

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SAP APPROVAL SIGNATURE PAGE

The following individuals approve this version of the [redacted] Statistical Analysis Plan.

Sponsor – TEOXANE SA:

[redacted], Clinical Program Manager DATE

Clinical Research Organization - [redacted]

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1. INTRODUCTION

This statistical analysis plan (SAP) gives a comprehensive and detailed description of statistical techniques to be used for [redacted]. The purpose of this SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches for the analysis of study data prior to database lock. This SAP provides additional details concerning the statistical analyses outlined in the protocol. Whenever differences exist in descriptions or explanations provided in the protocol and SAP, the SAP prevails.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc analyses not identified in this SAP may be performed to further examine study data. Any post hoc or unplanned analysis performed will be clearly identified as such in the final CSR.

1.1 Background

Hyaluronic acid (HA) is a long-chain, repeated dimer, N-acetyl glucosamine and D-glucuronic acid polymer and is a major component of the extracellular matrix. Due to its natural viscoelastic and hydrogel properties, HA is widely used as matrix in tissue regeneration and particularly in dermal defect reconstruction.

RHA® [redacted] dermal filler is a device containing colorless, biodegradable, sterile, biocompatible, crosslinked HA of non-animal origin (i.e., bacterial fermentation using *Streptococcus zooepidemicus*). Crosslinking is performed using 1,4-butanediol diglycidyl ether (BDDE) to form a gel. RHA® [redacted] contains 0.3% w/w of lidocaine hydrochloride, a drug substance widely used for its anesthetic properties (i.e., it blocks the origin and transmission of nervous influx at the point of injection by stabilizing the neuronal membrane). [redacted].

1.2 Rationale for Study

[redacted]

1.3 Hypothesis

RHA® [redacted] injected in NLFs with a small cannula is non-inferior to RHA® [redacted] injected in the NLFs with a needle for the correction of moderate to severe NLFs as determined by the NLF-WSRS (validated NLF Wrinkle Severity Rating Scale) at [redacted] from last treatment.

A change from Baseline in the NLF-WSRS of ≥1-grade will be considered clinically meaningful, and the non-inferiority margin for change in NLF-WSRS between needle and cannula will be 0.5 grade. The formal hypothesis set to be tested is as follows:

H_o: $\mu_{\Delta(\text{needle} - \text{cannula})} \geq 0.5$
H_a: $\mu_{\Delta(\text{needle} - \text{cannula})} < 0.5$

where $\mu_{\Delta(\text{needle} - \text{cannula})}$ represents the mean difference in change from Baseline between needle and cannula.

1.4 Study Objectives

The study is designed to achieve the following objectives:

1. Demonstrate the non-inferiority of RHA® injected in the NLFs with a cannula versus the control (RHA® injected in NLF with a needle) from last treatment for the correction of moderate to severe NLFs. Assessment of non-inferiority will be based on the change from Baseline in NLF-WSRS as rated by the Blinded Live Evaluator (BLE) at each investigative site.
2. Evaluate the safety of RHA® injected in NLF with a cannula versus the control up to from last treatment.

2. OVERVIEW OF STUDY DESIGN

2.1 Study Design

This is a randomized, controlled, single-blinded, within-subject (split-face), multicenter, prospective study to investigate whether RHA® injected in NLFs with a small cannula is non-inferior to RHA® injected in NLFs with a needle for the correction of moderate to severe NLFs as determined by the Blinded Live Evaluator (BLE) using the NLF-WSRS (validated NLF Wrinkle Severity Rating Scale) following last .

[redacted]

2.2 Study Design Rationale

2.2.1 Study Population

[redacted]

2.2.2 Primary Endpoint

The primary effectiveness endpoint will be aesthetic improvement from pre-injection as assessed by the NLF-WSRS (BLE) at [redacted] following last treatment (initial or touch-up). The primary hypothesis is that RHA® [redacted] used in conjunction with cannula is non-inferior to RHA® [redacted] with needle. An NLF-WSRS change from Baseline of ≥1-grade will be considered clinically significant. [redacted]

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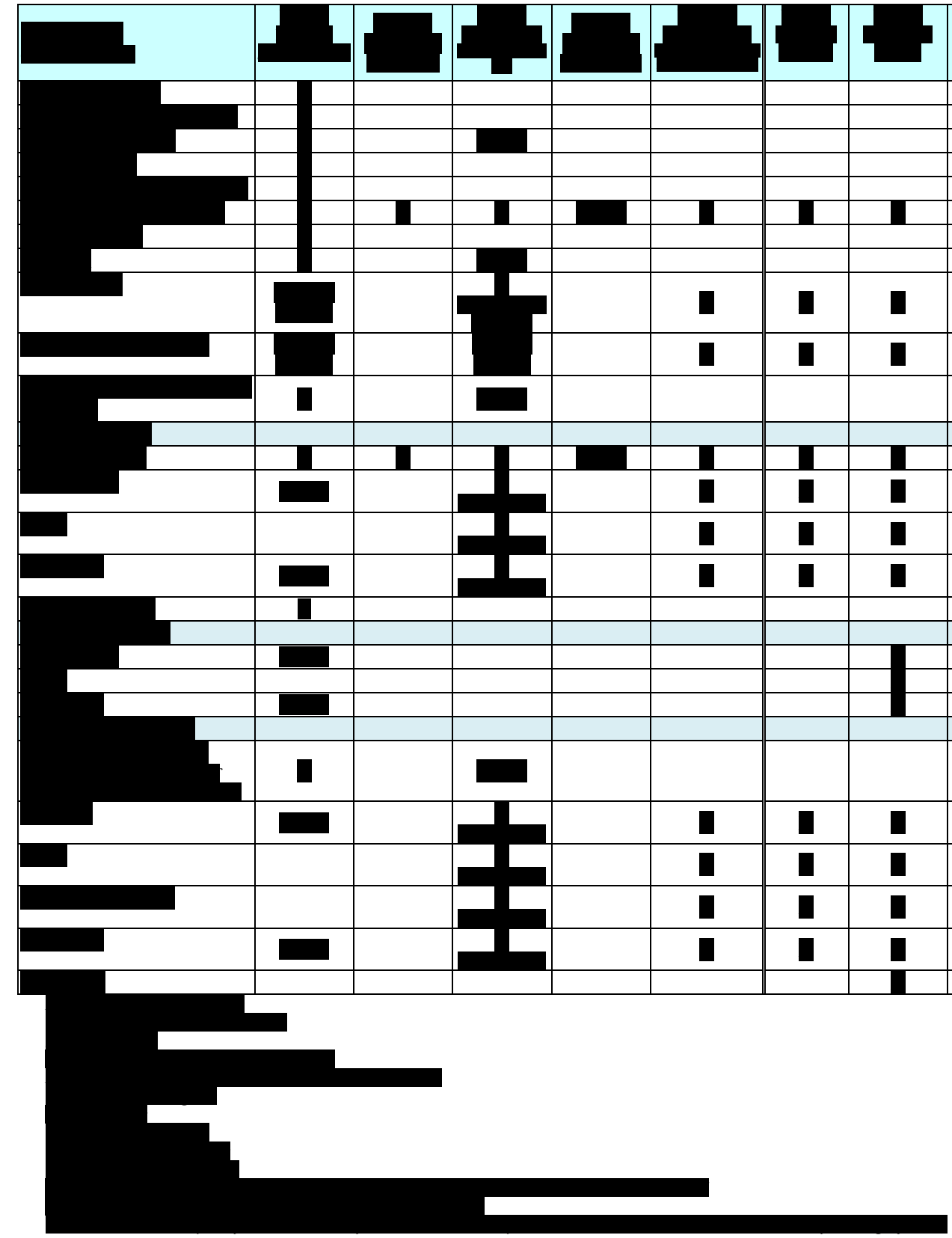

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3. TREATMENT ALLOCATION, RANDOMIZATION AND BLINDING

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4. DEVICE ADMINISTRATION

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4.1 Injection of Study Devices

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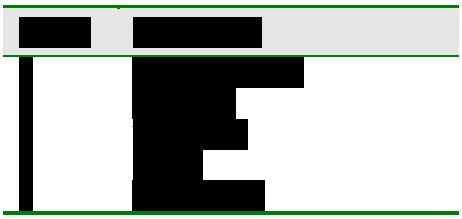
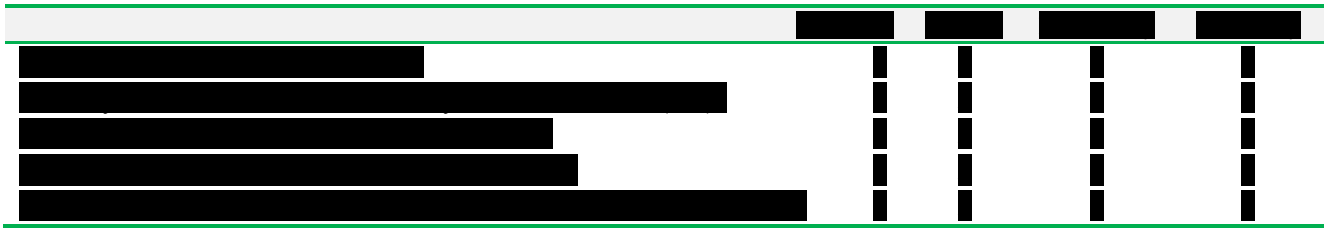
5. STUDY EVALUATIONS

5.1 Effectiveness Variables





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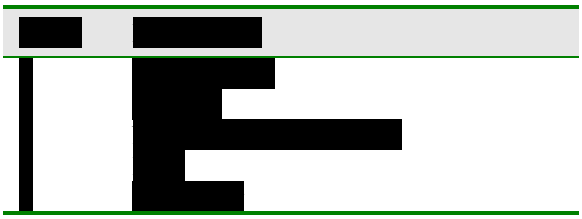

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5.2 Safety

[redacted]

5.2.1 Adverse Events

The Treating Investigator will assess AEs [redacted]

5.2.2 Patient Common Treatment Response Diary

The study coordinator will provide subjects with instructions for daily recording of his/her observations of the CTRs of the study treatments into an electronic diary for the first 4 weeks after each treatment. The diary will be activated after treatment and will be discussed during the 3-day post-injection telephone follow-up. [redacted]

[redacted]

6. STATISTICAL METHODS

6.1 Analysis Populations

[redacted]

6.2 Primary Effectiveness Endpoint

The primary endpoint of NLF-WSRS change from Baseline [redacted] as rated by the BLE will be analyzed in a non-inferiority statistical model using the PP population with a 0.5 margin for the difference between cannula and needle. A sensitivity analsyis will be done using the ITT population. Expressing the difference between treatment groups as the mean of change from Baseline in RHA®[redacted] injected with needle minus change from Baseline in RHA®[redacted] injected with cannula, the one-sided 97.5% confidence limit must be < 0.5 to conclude non-inferiority. A paired t-test will be used to calculate the confidence interval to account for dependence. The formal hypothesis set to be tested is:

H_o: $\mu_{\Delta(\text{needle} - \text{cannula})} \geq 0.5$
H_a: $\mu_{\Delta(\text{needle} - \text{cannula})} < 0.5$

where $\mu_{\Delta(\text{needle} - \text{cannula})}$ represents the mean difference in change from Baseline between needle and cannula.

[redacted]

6.3 Secondary Effectiveness Endpoints

All statistical inference tests will be performed at the same significance level (α) of 0.05. For categorical and continuous variables, the two groups will be compared using two-sided parametric or non-parametric tests for paired data, as appropriate. For continuous variables, the Shapiro-Wilk test will be used to assess normality. If data are normally distributed, testing will be conducted using the Student t-test, while testing will be conducted with the Wilcoxon signed-rank test if not normally distributed.

[redacted]

[redacted]

6.4 Safety Endpoints

The SAFT Population will be used to summarize the safety of the study devices and will consist of all treated subjects. The primary safety analysis is the calculation of the incidence of CTRs and adverse events in the study period. Point estimates for all CTRs, AEs and SAEs will be presented and two-sided exact 95% confidence intervals will be calculated for the overall incidence of AEs and SAEs. Tables will be generated which summarize AEs by investigator assessments of both relationship to treatment and severity.

[redacted]

[redacted]

6.4.1 Safety (SAFT) Population

[redacted]

6.5 Sample Size Considerations

[redacted]

6.6 General Considerations

Data will be listed by treatment group and subject number. Safety and efficacy data will be summarized by treatment group. Descriptive statistics will consist of mean, standard deviation, median, minimum/maximum for **continuous variables** (quantitative), and frequency and percent for **discrete variables** (qualitative), and 95% CIs will be provided for select data. Missing values will be presented for all variables.

All programs for data output and analyses will be written in SAS version 9.4 or higher (SAS Institute, Inc., Cary, NC).

Missing Values

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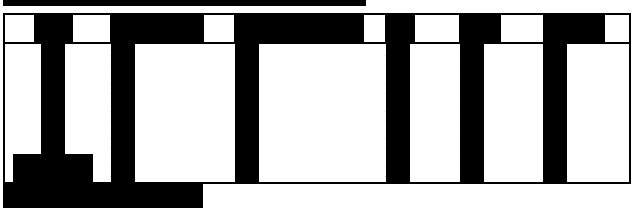

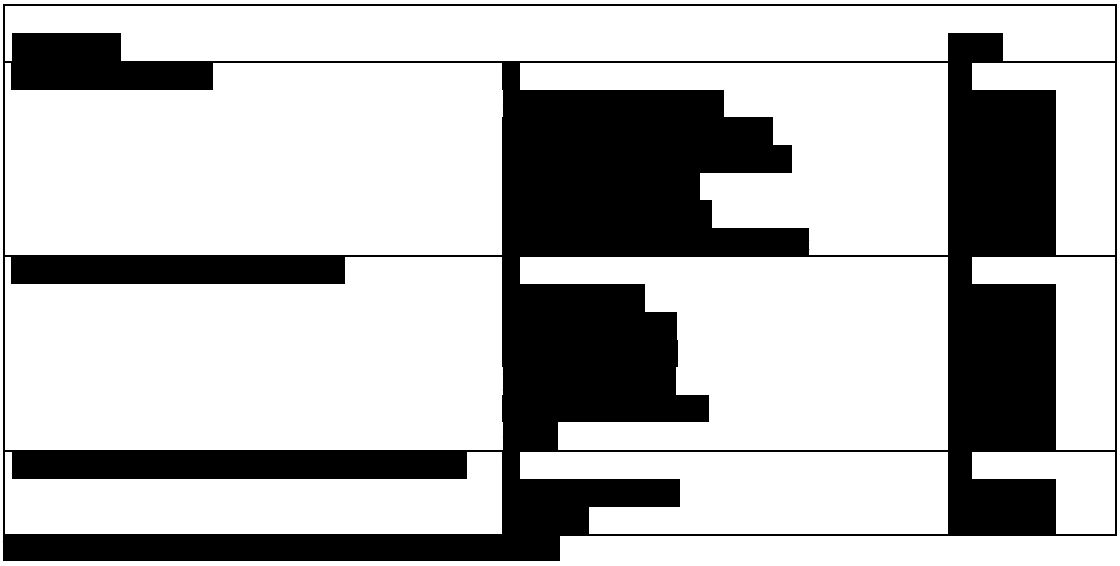

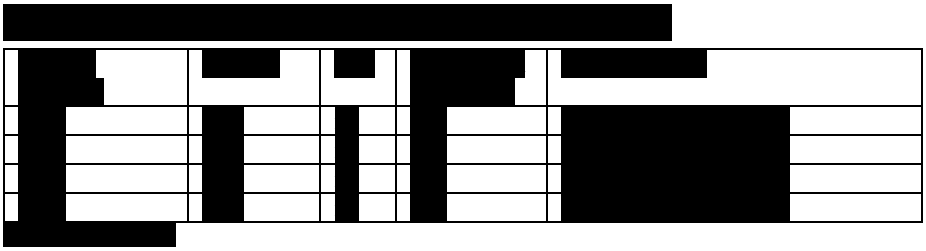

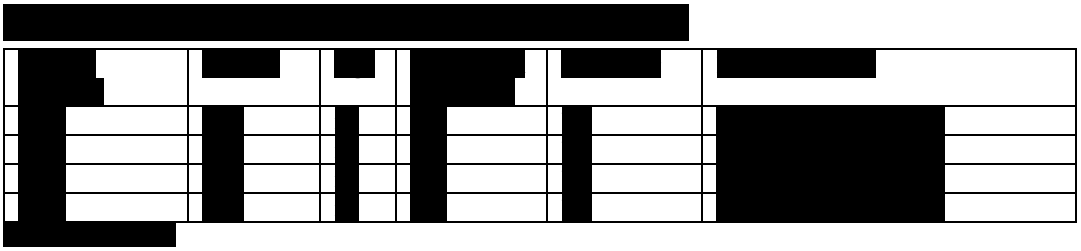

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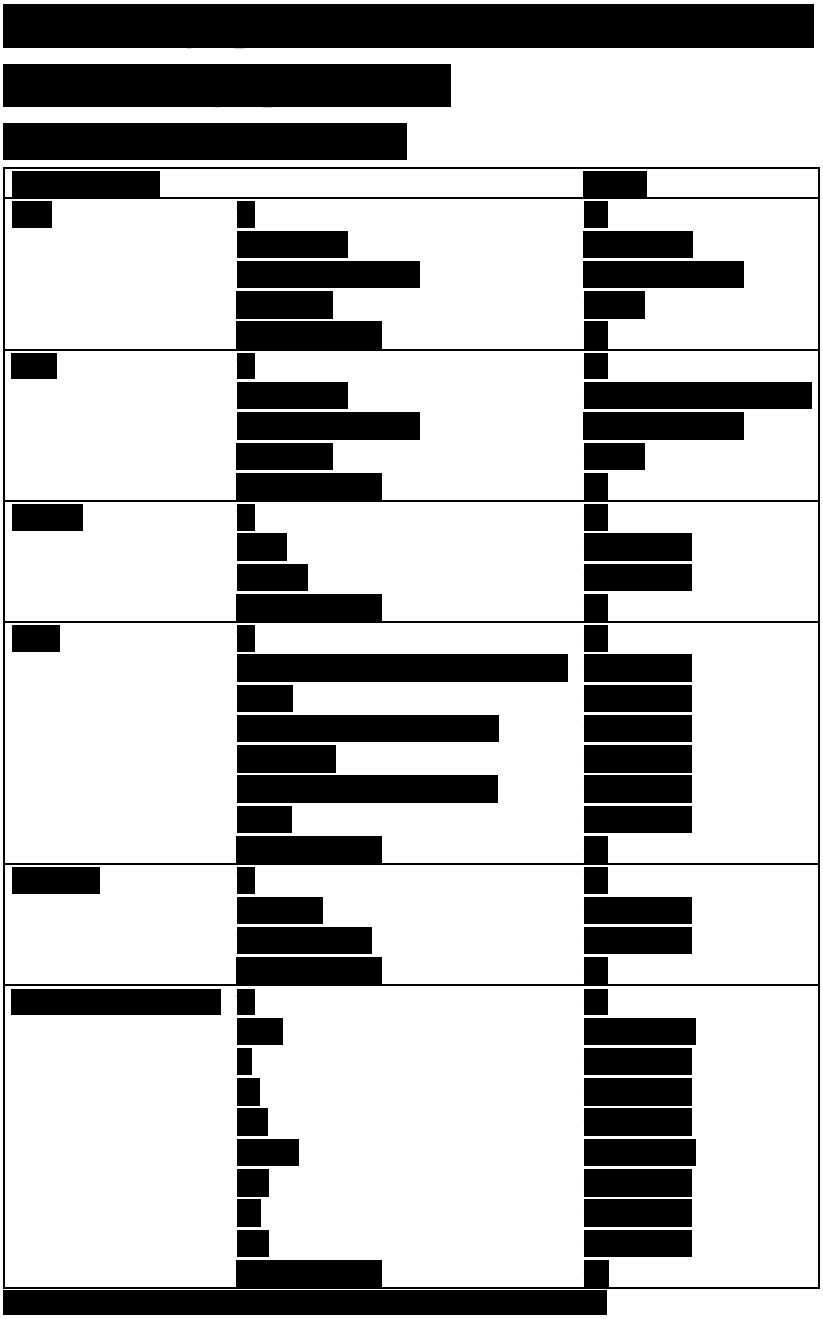

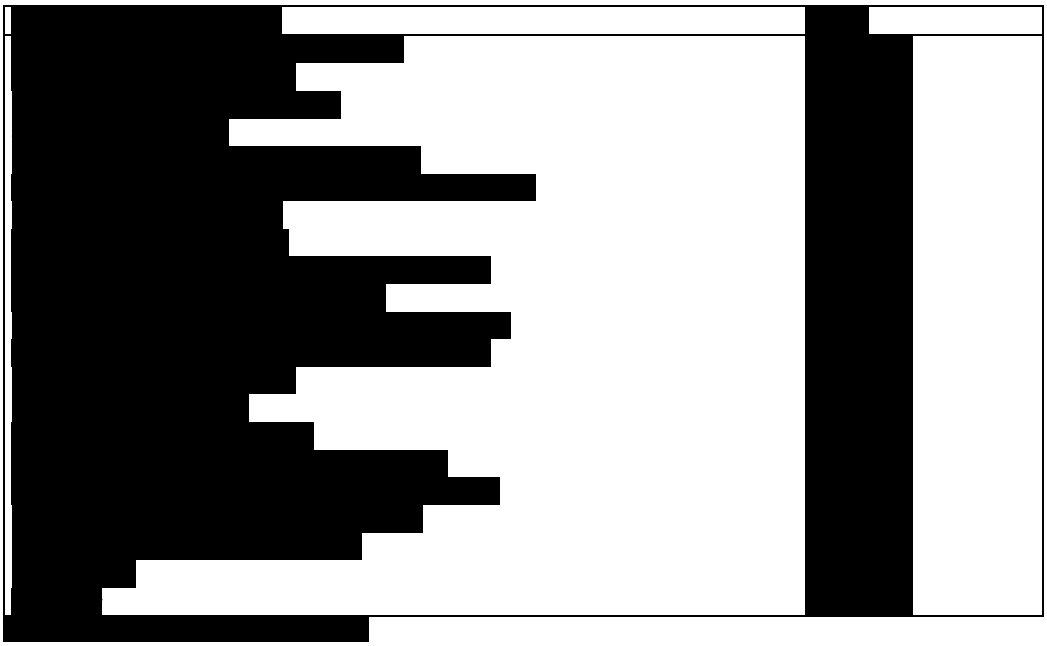

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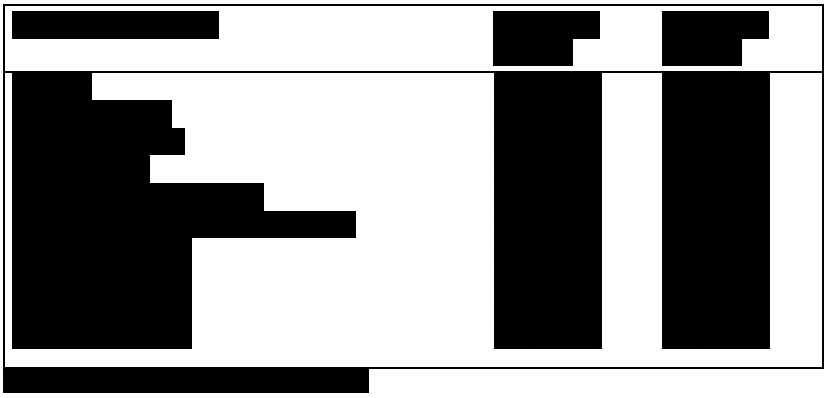

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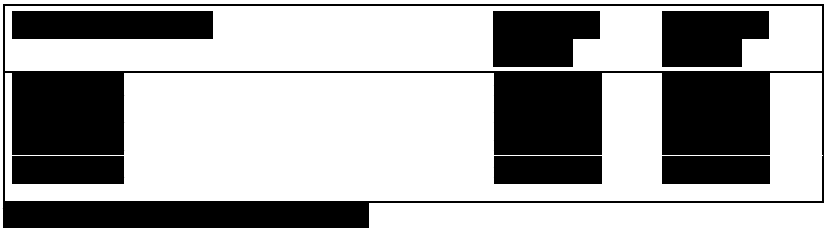

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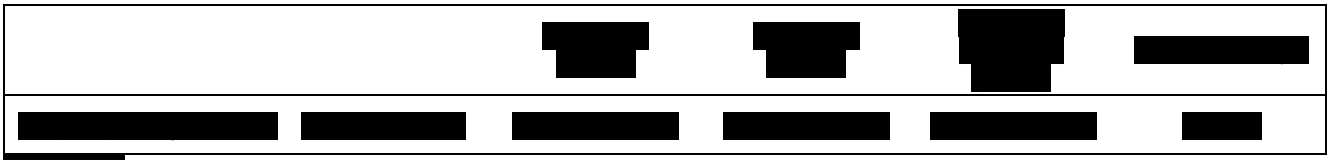

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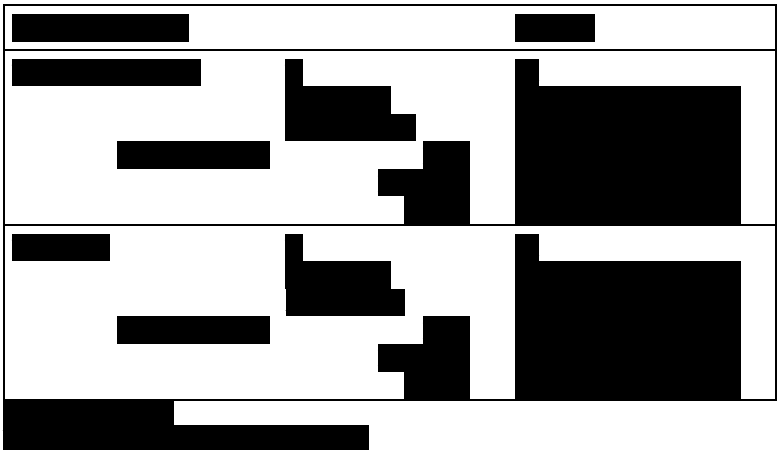

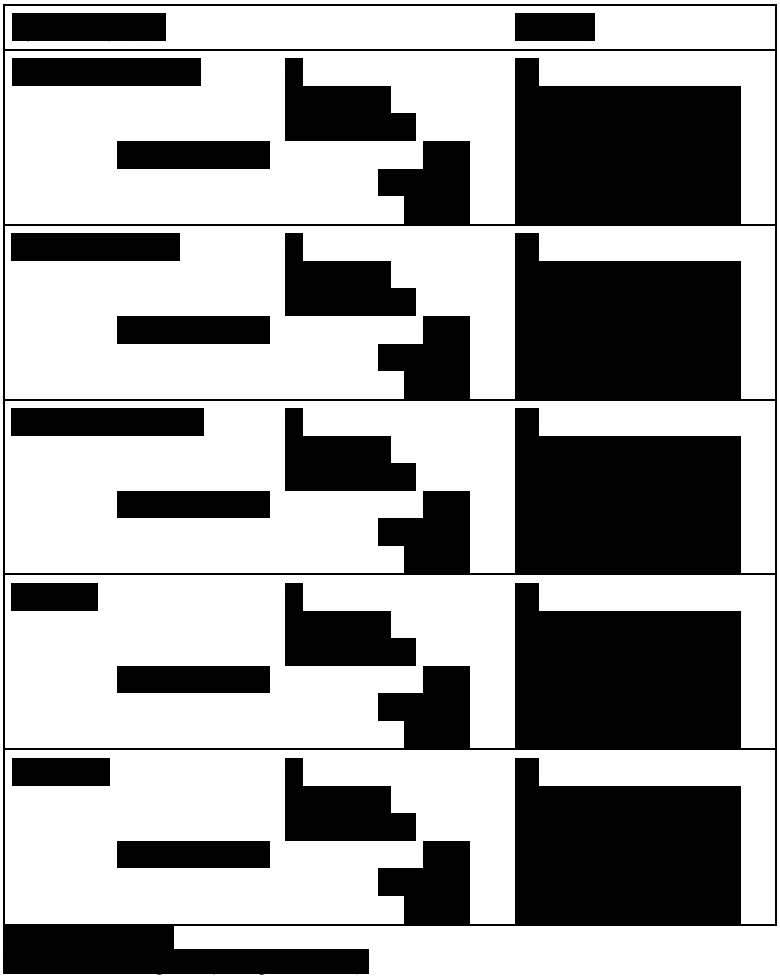

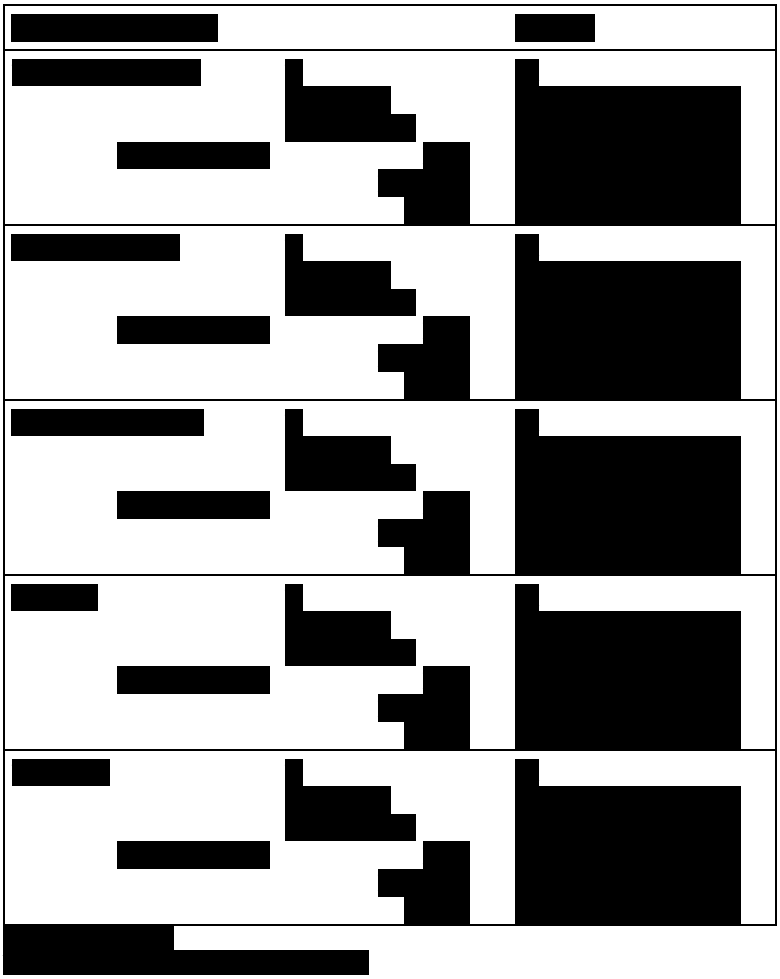

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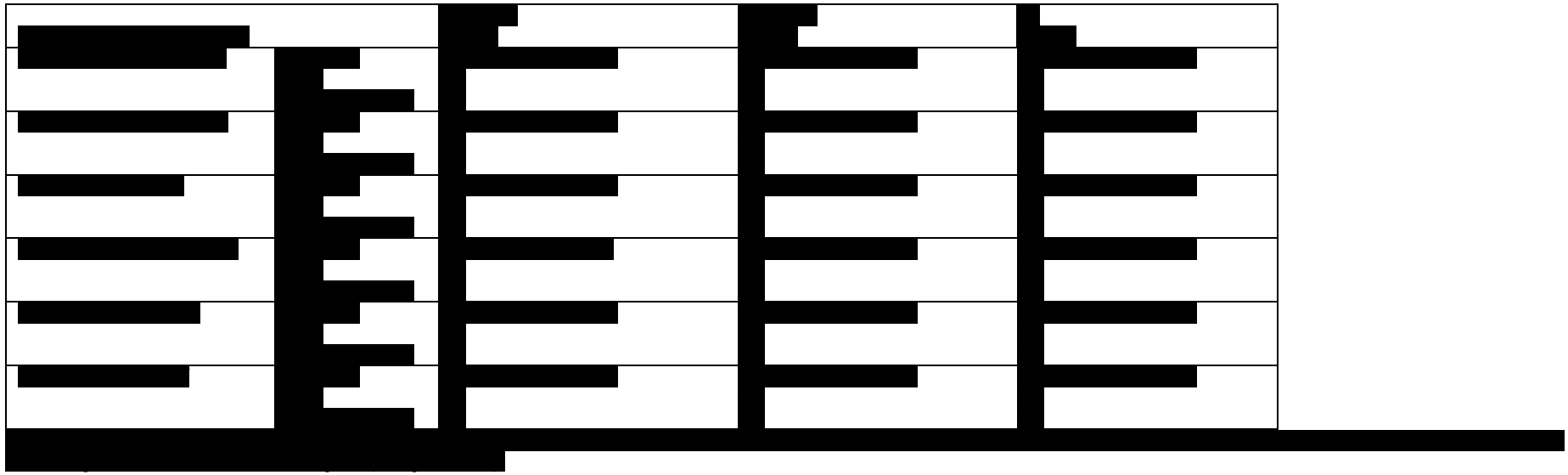

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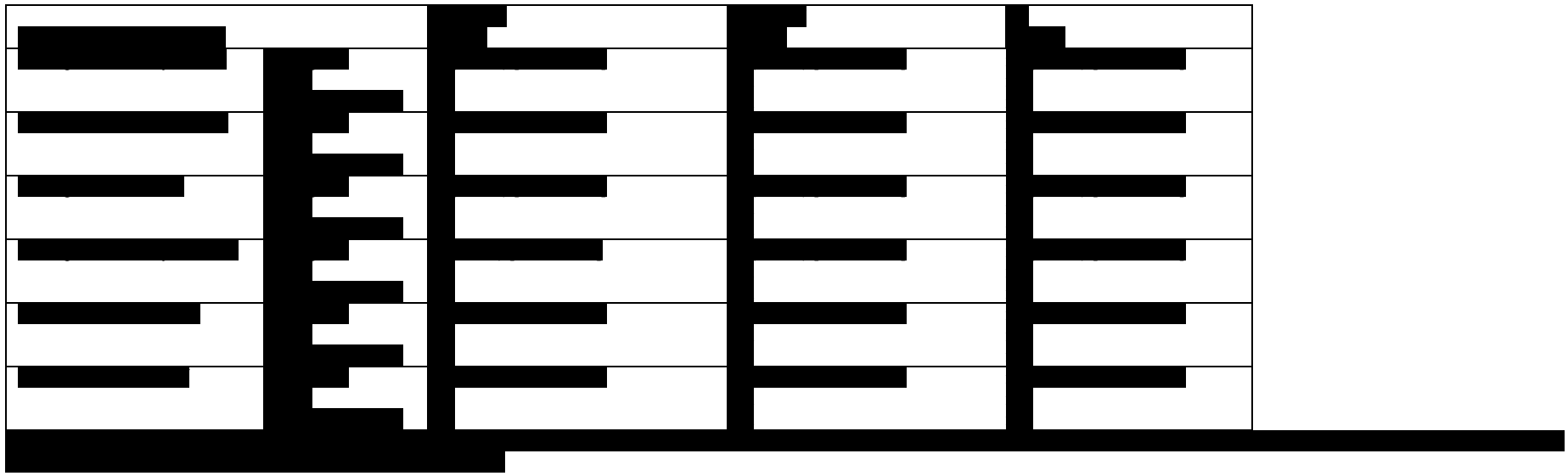

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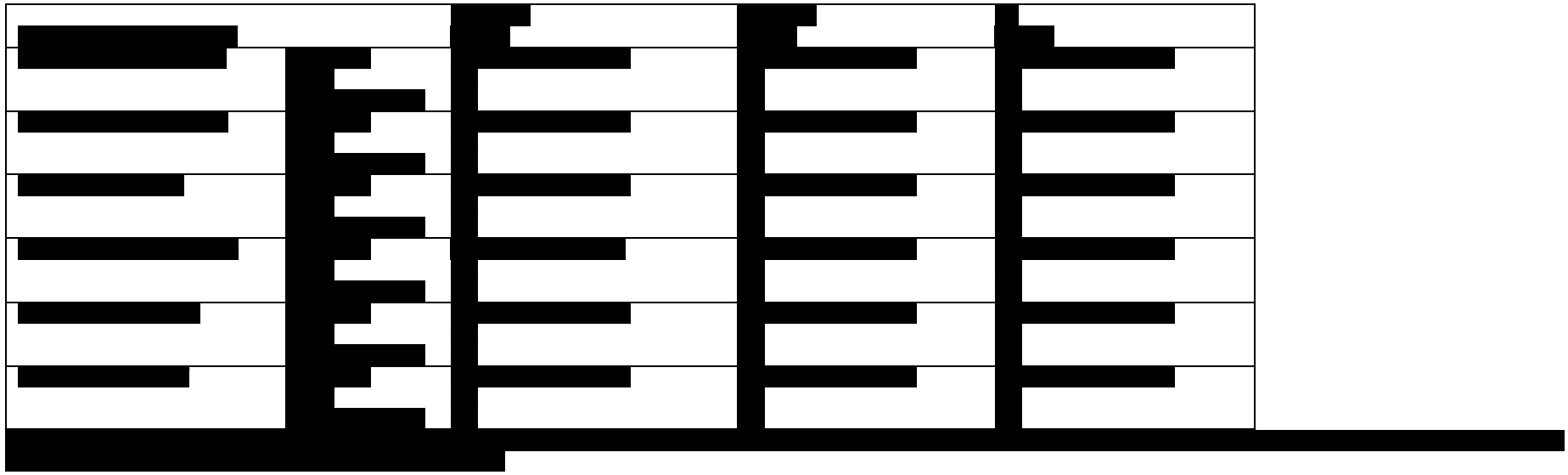

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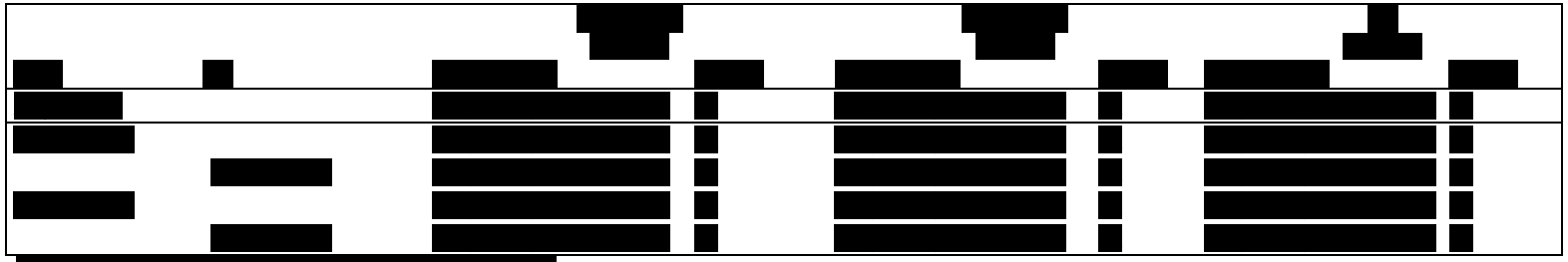

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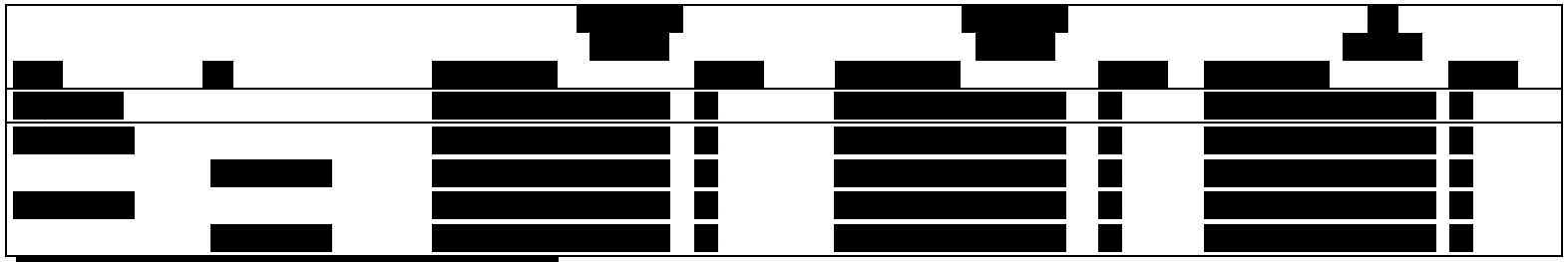

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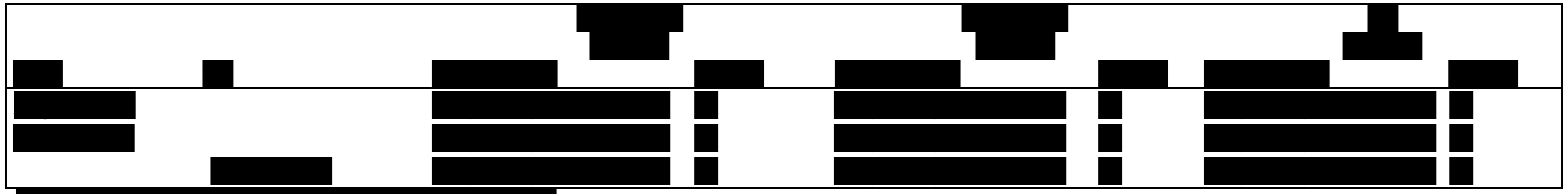

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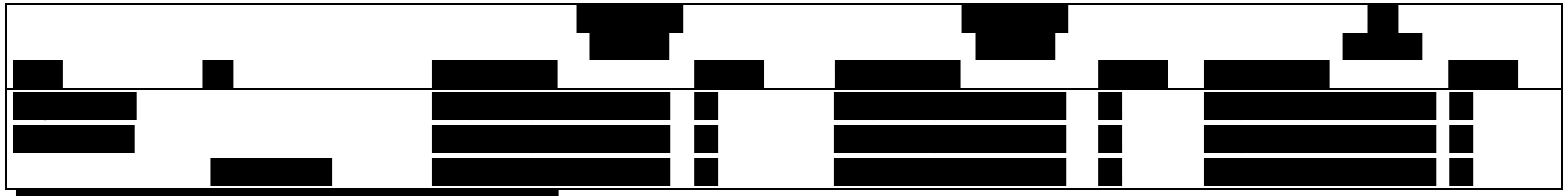

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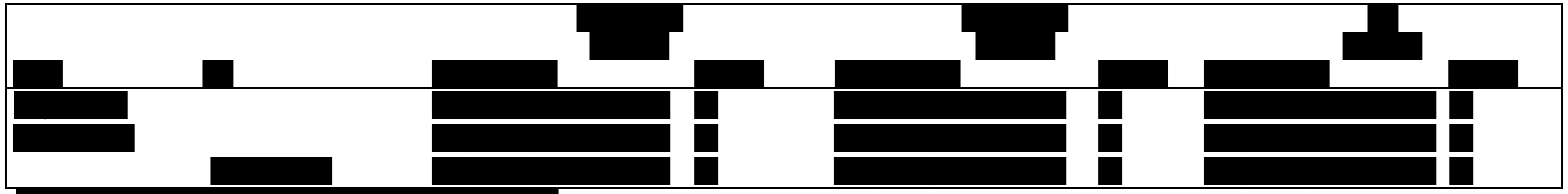

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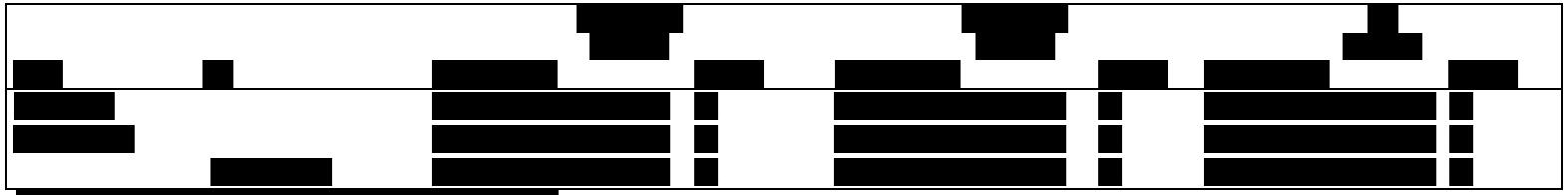

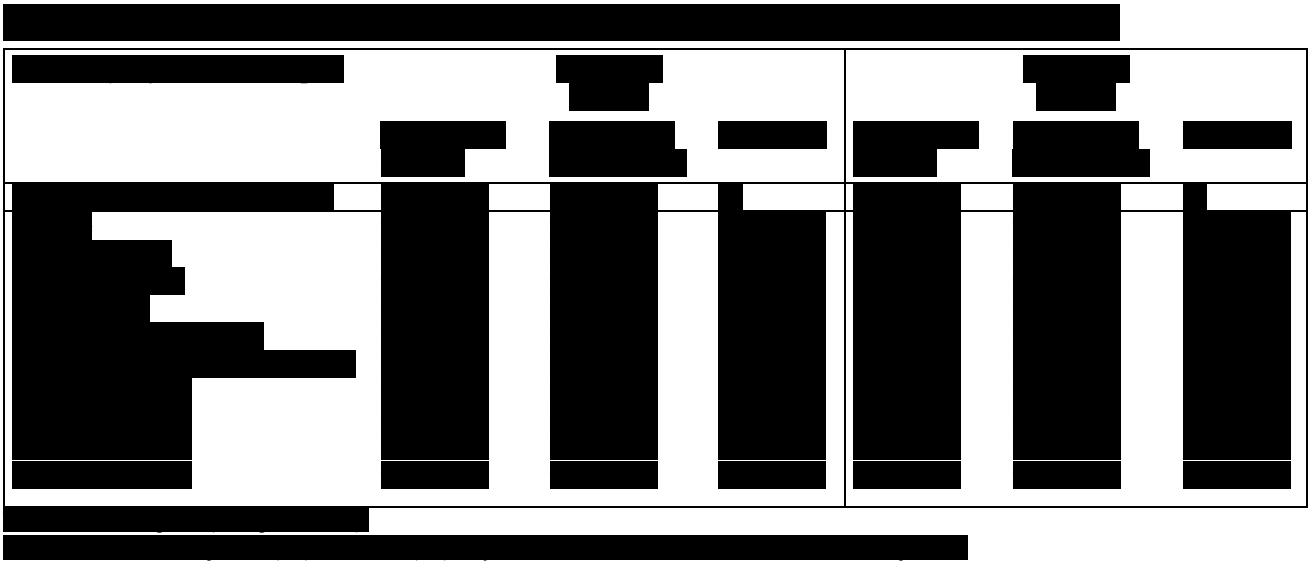

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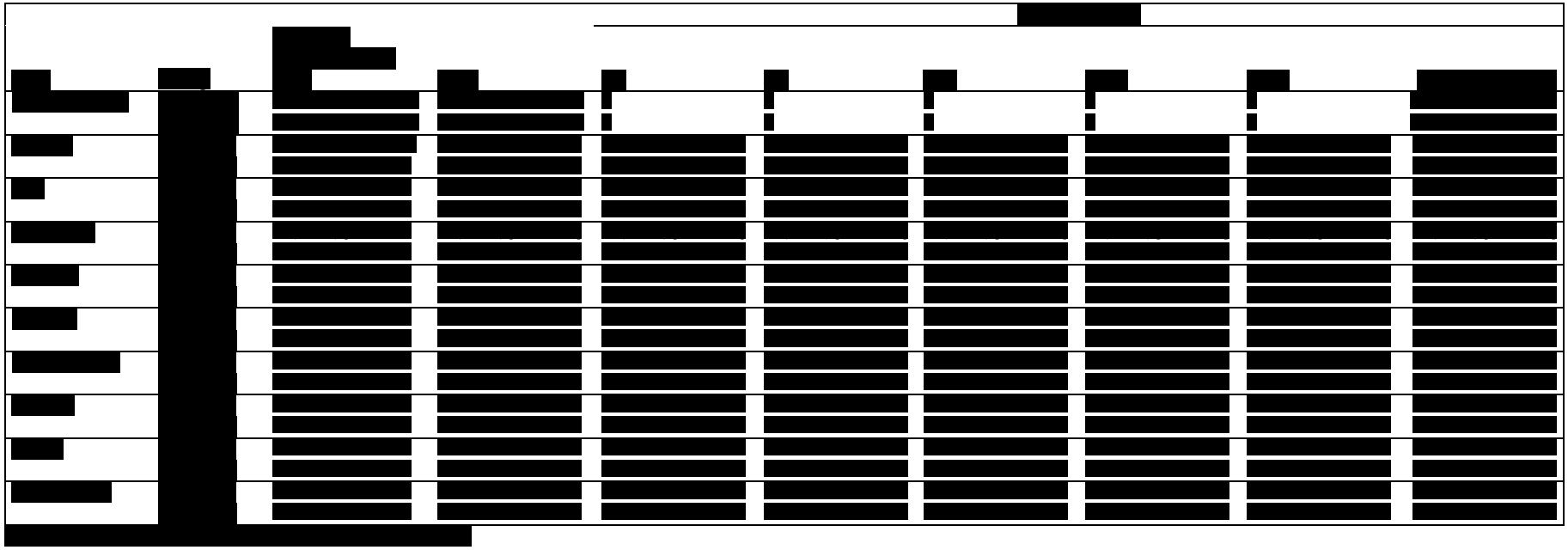

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