STATISTICAL ANALYSIS PLAN

[redacted]

A Randomized, Blinded, No-Treatment Control, Multicenter, Prospective Clinical Study of TEOSYAL® RHA Redensity for the Treatment of Moderate to Severe Perioral Rhytids

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SAP APPROVAL SIGNATURE PAGE

The following individuals approve this version of the TEO-RHA-1501 Statistical Analysis Plan.

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Signature	Date

Accepted for the Clinical Research Organization - [redacted].:

Printed Name	Title
Signature	Date

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1. INTRODUCTION

This statistical analysis plan (SAP) gives a comprehensive and detailed description of statistical techniques to be used [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.

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. HA is widely present in all animal species and does not differ from one species to another. Due to this extended compatibility, HA can be used in humans without unacceptable adverse effects. Due to its natural viscoelastic and hydrogel properties, HA is widely used as matrix in tissue regeneration and particularly in dermal defect reconstruction.

TEOSYAL® RHA Redensity 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. The formulation also contains 0.3% w/w of lidocaine hydrochloride. TEOSYAL® RHA Redensity is an investigational device that has not yet been approved by the FDA. In the current study, this device will be compared to a No-Treatment control in a superiority pivotal study designed to support a PMA application for TEOSYAL® RHA Redensity.

1.2 Hypothesis

TEOSYAL® RHA Redensity will be superior to No-Treatment control for the correction of moderate to severe perioral rhytids as determined by the PR-SRS at Week 8 after the last treatment. An improvement in the PR-SRS of ≥1-grade compared to pre-treatment will be considered clinically meaningful.

1.3 Primary Objectives

The study's primary objectives are to establish the safety and effectiveness of TEOSYAL® RHA Redensity in the treatment of moderate to severe perioral rhytids:

1. To demonstrate the superiority of TEOSYAL® RHA Redensity versus the No-Treatment control at 8 weeks for the correction of moderate to severe perioral rhytids. Assessment of superiority will be based on the Perioral Rhytids Severity Rating Scale (PR-SRS) as rated by the Blinded Live Evaluator (BLE).

   To evaluate the safety of TEOSYAL® RHA Redensity for the treatment of moderate to severe perioral rhytids. Safety will be determined by the rates of Adverse Events (AEs) associated with the use of the study device. Subjects will be observed for up to approximately 52 weeks following initial treatment or touch-up treatment with the study device. Safety will also be evaluated for 4 weeks following any retreatment.

2 OVERVIEW OF STUDY DESIGN

2.1 Study Design

This is a randomized, blinded, No-Treatment control, multicenter, prospective clinical study.

The **Treating Investigator** (TI) will evaluate subjects for eligibility of the subject for the study. The **Blinded Live Evaluator** (BLE) at screening will evaluate the subject's perioral rhytids severity using the Perioral Rhytids Severity Rating Scale (PR-SRS) in order to confirm eligibility and to establish a pre-treatment score. This will be done independently of the TI, and exact concordance between the BLE and the TI is not necessary.

Enrolled subjects will be randomized to either the TEOSYAL® RHA Redensity treatment group or the "No-Treatment" control group. The TI will administer study device, and if necessary, subjects will receive a touch-up treatment 14 days following the initial treatment to optimize the results. The TI will conduct safety and effectiveness evaluations at study subject visits, which will occur at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, and 4 weeks after a repeat treatment.

The BLE will conduct assessments of efficacy during the trial, including assessment of the primary endpoint at Week 8 after initial or touch up treatment. The BLE will conduct effectiveness evaluations at Week 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment.

Subjects will be followed for 52 weeks from initial or touch up treatment, at which point they will be offered a repeat treatment (provided that the TI deems the treatment to be appropriate, and if the subject agrees). The subject will then be followed for an additional 4 weeks after the treatment before exiting the study.

Should a subject return to his/her pre-treatment PR-SRS level before Week 52, as assessed by the TI, he/she will be eligible to receive an early repeat treatment (provided that the TI deems the treatment to be appropriate, and if the subject agrees) at Week 12, or Week 16, or Week 24, or Week 36 after initial or touch-up treatment. .

Subjects randomized to the "No-Treatment" control group will receive their first treatment after the primary endpoint evaluation (8 weeks after randomization) and will then follow the same schedule as the initial treatment group.

2.2 Sample Size

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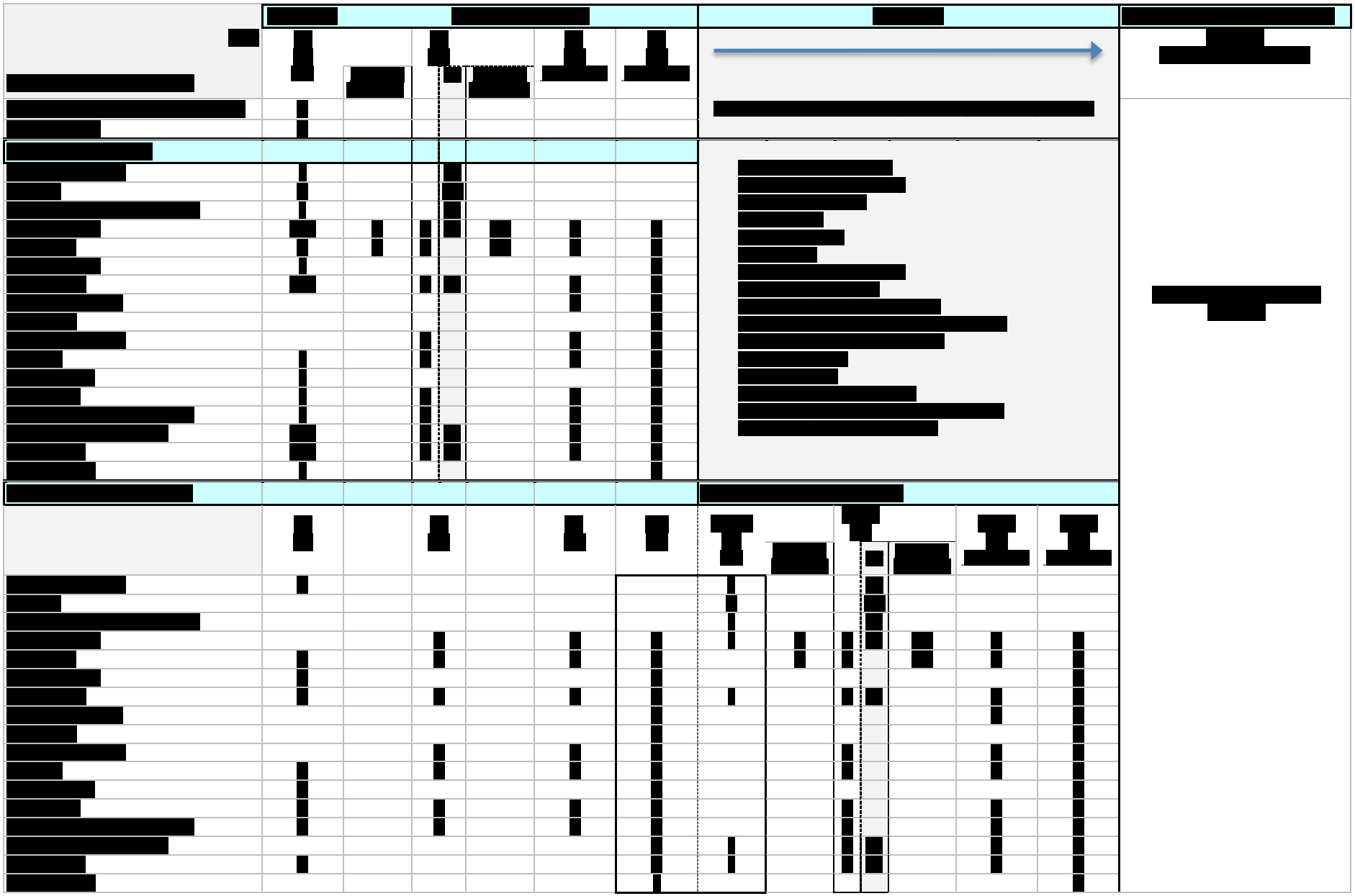

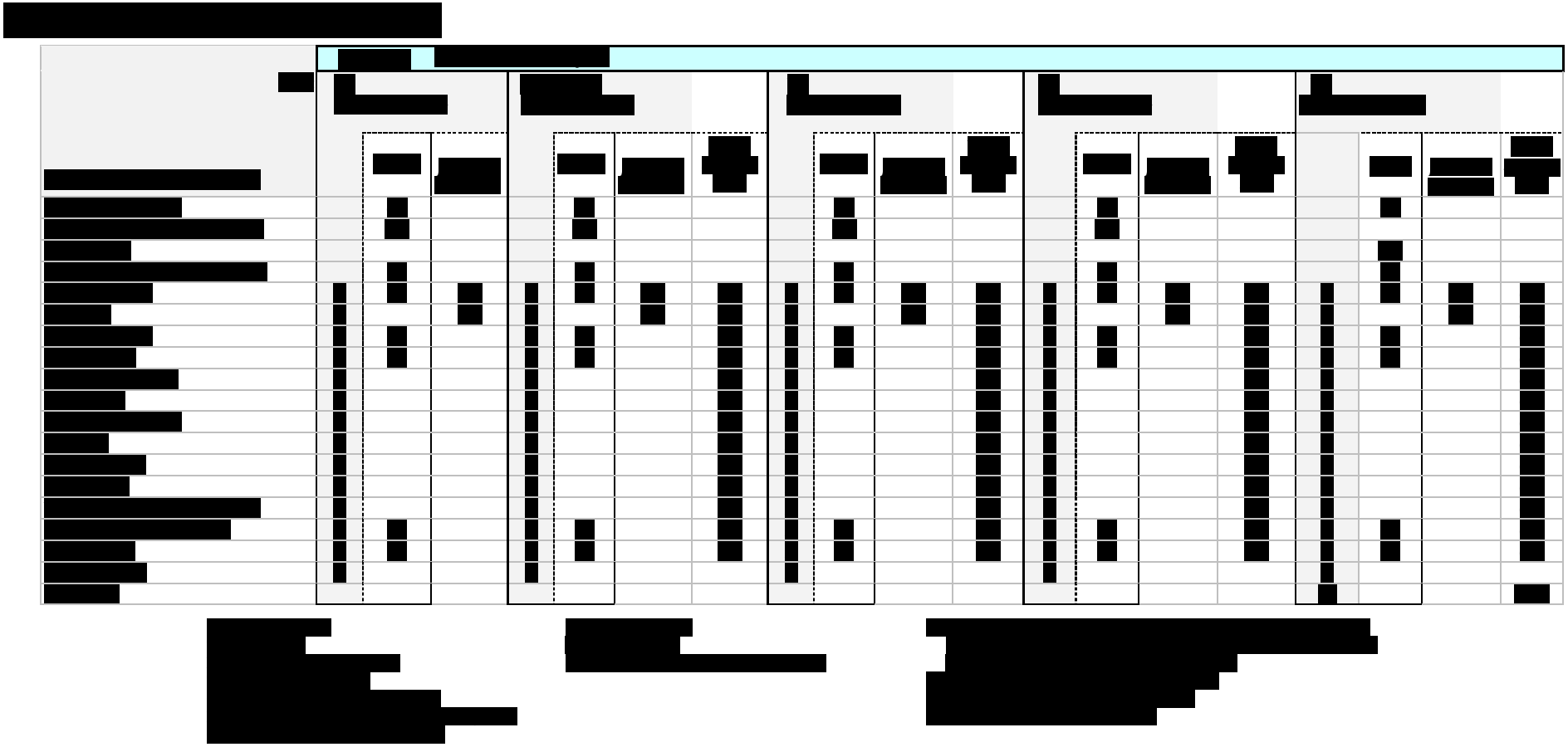

3. STUDY POPULATION

The study population includes female and male subjects with at least 25% of the population of Fitzpatrick skin IV to VI subjects.

3.1 Inclusion Criteria

1. Outpatient, male or female of any race, 22 years of age or older. Female subjects of childbearing potential must have a negative UPT at Visit 1 and practice a reliable method of contraception throughout the study.

[redacted]

4. Be able to follow study instructions and likely to complete all required visits;
5. Sign the IRB-approved ICF, Photographic Release Form and the Authorization for Use and release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed.

3.2 Exclusion Criteria

1. Female subjects that are pregnant, breast-feeding, or of childbearing potential and not practicing reliable birth control.

[redacted]

3. Use of a prohibited treatment/procedure within time periods [redacted]

5. Known susceptibility to keloid formation, hypertrophic scarring or clinically significant skin pigmentation disorders (TI discretion).

[redacted]

7. History of active chronic debilitating systemic disease that in the opinion of the investigator, would make the subject a poor candidate in the study.

[redacted]

9. Malignancy (excluding non-melanoma skin cancer) within the past 5 years.

[redacted]

11. History or presence of condition or feature that may confound the interpretation of the results in the perioral region, for example, tattoo, significant facial hair, acne scaring, prior surgery in the area, potential for active disease or infection flare up such as herpes simplex.

[redacted]

13. History of skin cancer in the treatment area.

[redacted]

15. Clinically active disease or infection in the perioral area or mouth (e.g., dental abscess).

[redacted]

17. Medical or psychiatric conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results or compliance of the subject and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study (TI discretion).

[redacted]

19. Subjects seeking lip augmentation.

[redacted]

21. Clinically significant alcohol or drug abuse, or history of poor cooperation or unreliability.

4. TREATMENT ALLOCATION AND RANDOMIZATION

Upon qualifying for treatment, subjects will be randomized to a study group utilizing a randomization algorithm embedded into the electronic Case Report Form (eCRF). Subjects will be randomized (3:1 ratio) to one of the following groups:

- TEOSYAL® RHA Redensity;
- No-Treatment (untreated control).

Subjects will be considered "enrolled" at the time of consent, and will be considered "enrolled and randomized" at the time of randomization. The required sample size is based on "enrolled and

randomized" subjects. If an enrolled subject withdraws from the study prior to being randomized, he/she may be replaced.

[redacted]

5. DEVICE APPLICATION

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subject agrees. The subject will then be followed for an additional 4 weeks before exiting the study.

6. STUDY EVALUATIONS

6.1 Efficacy Variables

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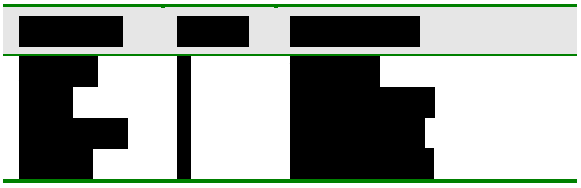

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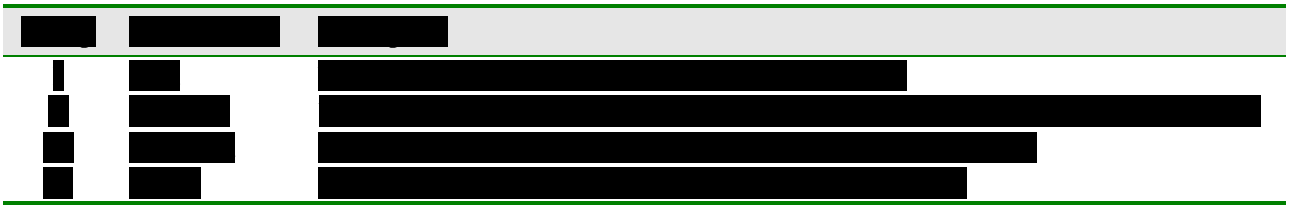

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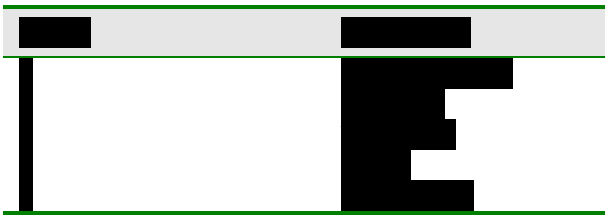

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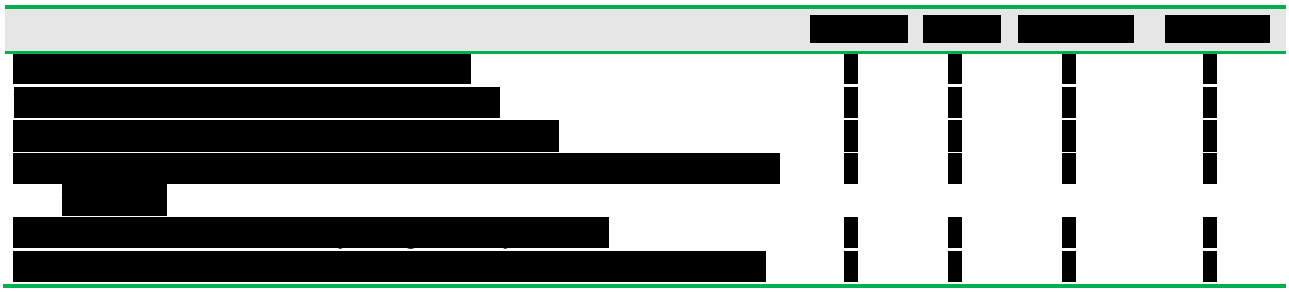

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6.2 Safety Variables

6.2.1 Common Treatment Response (CTR) Diary

Subjects will record their observations of CTRs for the first 14 days after each treatment (initial, touch-up, retreatment(s)). The CTRs to be assessed are redness, pain, tenderness, firmness, swelling, lumps/bumps, bruising, itching, discoloration, and "other" (e.g., fever, headache, changes in vision). The presence and the severity of each observed sign/symptom will be recorded as none, mild, moderate, or severe.

CTRs will also be considered as Adverse Events if the duration and/or severity are in excess of that typically observed following injection of a dermal filler, and are clinically significant as determined by the Tx Investigator. Importantly, CTRs persisting longer than 14 days and CTRs that are indicated on the last recorded day of the CTR Diary, will be recorded as AEs regardless of severity or clinical significance.

6.2.2 Assessment of Injection Site Pain

Subjects will assess injection site pain (during injection and post-injection) using a 100mm Visual Analog Scale (VAS).

6.2.3 Lip Functionality

Lip functionality testing will include the following Yes/No evaluations:

- Lip function: Yes or No with the following question: "Can the subject drink/suck through a straw effectively?"
- Lip Sensation:
    1. monofilament test (i.e., three points on the upper lip and three points on the lower lip);
    2. cotton wisp test (i.e., three points on the upper lip and three points on the lower lip).
- Lip Movement: Yes or No with the following question and based on a list of 10 words, "Can the subject effectively pronounce the following words?"

6.2.4 Adverse Events (AEs)

The Treating Investigator will assess AEs and record details of seriousness, severity, duration, and action taken with the study device, and relationship to the study device. AEs will be reported from the time of consent until the final visit, or to 1 month following the last treatment.

6.2.5 Concomitant Medications and Procedures

Any medication or procedure (including OTC preparations) that the subject takes during the study protocol period will be considered concomitant medication and will recorded.

7. ANALYSIS POPULATIONS

7.1 Populations

Three analysis populations will be defined: Intent-to-Treat (ITT), Per Protocol (PP), and Safety (SAFT). All populations will be defined and determined prior to unblinding for the final analysis.

7.1.1 Intent-to-Treat (ITT) Population

[redacted]

7.1.2 Per Protocol (PP) Population

[redacted]

7.1.2.1 Safety (SAFT) Population

The SAFT Population will consist of all subjects in the No-Treatment control group, and all subjects in the Redensity treatment group that are randomized and received at least one treatment with a study device. Subjects in the SAFT Population will be analyzed in the group of the treatment they actually received, whether or not it is the group to which they are randomized.

8. SAMPLE SIZE JUSTIFICATION

[redacted]

The study will ensure that enrolled subjects are representative of U.S. population ethnicity and will be comprised of at least 25% subjects of Fitzpatrick skin IV to VI. In order to be able to detect a sufficient AE rate (i.e., maximum 2.5% in the sub-population of subjects of Fitzpatrick skin type IV to VI), the number of subjects must be increased beyond that required for achieving statistical power for the primary efficacy outcome; specifically:

[redacted]

9. STATISTICAL METHODS

9.1. Efficacy Analyses

[redacted]

9.1.1 Primary Endpoint

The primary endpoint will be a co-primary endpoint. A responder will be defined as a subject who has a ≥1-grade improvement on the **PR-SRS** as assessed by the **BLE** at Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the BLE. Only data from the first 8-week phase will be taken into account. The No-Treatment control group after treatment will not be pooled for the primary endpoint.

The effectiveness of TEOSYAL® RHA Redensity will be demonstrated if:

- The responder rate for subjects treated with TEOSYAL® RHA Redensity is statistically superior to the responder rate for the No-Treatment control , and;
- The responder rate for subjects treated with TEOSYAL® RHA Redensity is ≥70%, and;
- The difference between the responder rate for subjects treated with TEOSYAL® RHA Redensity and the No-Treatment group is ≥50 points.

9.1.2 Secondary Endpoints

Statistical inference tests will be performed using two-sided tests, with a 0.05 significance level. Data will be summarized descriptively. For the Secondary Endpoints, like for the Primary Endpoint, only data from the first 8 week phase will be taken into account, and will compare TEOSYAL® RHA Redensity to No-Treatment (the No-Treatment control group after treatment will not be pooled for the secondary endpoints):

- **FACE-Q** at Week 4 and Week 8 after initial or touch-up treatment.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by **subject** at Week 4 and Week 8 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (**GAI**) scale.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by **BLE** at Week 8 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (**GAI**) scale.
- Proportion of subjects "satisfied" or "very satisfied" at Week 8 after initial or touch-up treatment, using the 5-point scale assessing **Subject Satisfaction** with study treatment.

9.1.3 Exploratory Endpoints

For the following Exploratory Endpoints, like for the Primary Endpoint, only data from the first 8 week phase will be taken into account and will compare TEOSYAL® RHA Redensity to No-Treatment (the No-Treatment control group after treatment will not be pooled for these exploratory endpoints):

- Proportion of subjects with ≥1-grade improvement from pre-treatment on the **PR-SRS** as assessed by the **Treating Investigator**, at Week 4 and Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the Treating Investigator.
- Proportion of subjects with ≥1-grade improvement from pre-treatment on the **PR-SRS**, as evaluated by the Independent Photographic Reviewers (**IPR**) at Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the IPR. For a given subject to be considered a responder, at least 2 of the 3 readers must have confirmed a 1-point improvement for that subject.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by **Treating Investigator** at Week 4 and Week 8 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (**GAI**) scale.
- Proportion of subjects with ≥1-grade improvement from pre-treatment of dynamic perioral rhytids on the 1-4 Modified **Glogau** classification of wrinkling as assessed by the **BLE** at

Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the BLE.

- Proportion of subjects with ≥1-grade improvement from pre-treatment of dynamic perioral rhytids on the 1-4 Modified **Glogau** classification of wrinkling as assessed by the **Treating Investigator** at Week 4 and Week 8 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the Treating Investigator.

For the following Exploratory Endpoints, unlike for the Primary and Secondary Endpoints, data from the TEOSYAL® RHA Redensity group and from the No-Treatment control group after treatment **will be pooled** (if deemed comparable).

- Proportion of subjects with a ≥1-grade improvement based on the **PR-SRS** assessed by the **BLE** at Weeks 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the BLE.
- Proportion of subjects with a ≥1-grade improvement based on the **PR-SRS** assessed by the **Treating Investigator** at Weeks 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the Treating Investigator.
- Proportion of subjects with a ≥1-grade improvement, based on the **PR-SRS** as evaluated by the Independent Photographic Reviewers (**IPR**) at Week 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the IPR. For a given subject to be considered a responder, at least 2 of the 3 readers must have confirmed a 1-point improvement for that subject
- Proportion of subjects with ≥1-grade improvement of their dynamic perioral rhytids on the 1-4 Modified **Glogau** classification of wrinkling as assessed by the **BLE** at Week 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the BLE.
- Proportion of subjects with ≥1-grade improvement of dynamic perioral rhytids on the 1-4 Modified **Glogau** classification of wrinkling as assessed by the **Treating Investigator** at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, compared with the pre-treatment assessment (baseline) by the Treating Investigator.
- **FACE-Q** at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by **subjects** at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (**GAI**) scale.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by **Treating Investigators** at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (**GAI**) scale.
- Proportion of subjects with a Global Aesthetic "improved" or "much improved", as assessed by **BLE** at Week 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using the 5-grade Global Aesthetic Improvement (**GAI**) scale.
- **Subject satisfaction** at Weeks 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using the 5-point scale assessing subjects' satisfaction with study treatment.
- Proportion of subjects with a **natural look and feel** ≥7 assessed by subjects at Week 4, 8, 12, 16, 24, 36, and 52 after initial or touch-up treatment, using an 11-point scale.

9.2 Safety Analyses

Safety data will be presented as listings and summary tables based on the SAFT Population (unless otherwise specified).

9.2.1 Adverse Events (AEs)

Safety outcomes will be incidence rate of AEs, including UADEs, types of AEs and relationship to study treatment (i.e., Treatment-Emergent Adverse Events [TEAEs]; Treatment-Related-Adverse Events [TRAEs]). TEAEs will include all reported AE since the time of informed consent. Any AEs that occur in the No-Treatment control group since the time of informed consent will be considered to be TEAEs. TRAEs will include all reported AEs that were deemed by the Treating Investigator to be possibly, probably or definitely related to study treatment.

Safety data will be tabulated with descriptive group statistics (mean, standard deviation, minimum, maximum). Severity and relationship to study treatment will be assessed.

AEs will be coded using MedDRA. [redacted]

[redacted]

9.3 General Statistical Considerations

9.3.1 Statistical Testing

For specific information regarding the statistical tests to be used in this study, please refer to [redacted] Statistical testing will be conducted using parametric and non-parametric processes as appropriate. Continuous variables that are normally distributed will be tested using the Student t-test, while testing will be conducted with the Mann-Whitney test if not normally distributed. Normality of the observed distribution will be confirmed using a Shapiro-Wilk test. Quantitative (i.e., nominal/categorical) variables in 2x2 tables will be tested using Fisher test. For larger tables (i.e., more than 2x2), Chi-2 test will be used if expected cell counts are all $\geq$5.

All tests will be performed on a two-sided basis. A p-value of less than 5% will be considered statistically significant. First level risk error for secondary criteria will not been adjusted for multiplicity.

9.3.2 Comparison of Treatment Groups

Comparisons will be made between TEOSYAL® RHA Redensity and the control.

9.3.3 Descriptive Statistics

Descriptive statistics (i.e., frequency and percent) will be calculated for each treatment group. Quantitative variables will be presented by way of number of observations, number of missing values, mean, standard deviation, extreme values (minimum and maximum), median, and 95% confidence internal. Categorical data will be presented by way of number of observations, number of missing values, and for each observed category, the number of occurrences and its corresponding percentage.

[redacted]

9.3.5 Discontinuation and Drop-Outs

A dropout rate of up to 20% is assumed. Dropouts will not be replaced. All available data from dropouts will be included in the ITT analysis. The disposition of subjects will summarize the number of subjects enrolled and discontinued.

9.3.6 Multiple Comparisons

No methods will be used to accommodate multiplicity (unless otherwise specified).

9.3.7 Multicenter Data

The data will be pooled across centers for analysis. Additionally, data for each center will be provided in data listings.

9.3.8 Pooling of Data from US and Canadian Sites

In order to establish if safety and efficacy data from the the US and Canada can be combined, homogeneity of various baseline characteristics across the two countries will be explored (i.e., age, BMI, smoking history, alcohol history, sun exposure, and surgical/procedure history*).

** Surgical/procedure history limited to any previous facial and/or cosmetic surgery/procedures (e.g., facial aesthetic procedures such as laser/toxin/filler, rhytidectomy, blephrospasm, dental surgery, breast enhancement, etc.).*

Ethnicity, race and Fitzpatrick Skin Type do not need to be proportionately balanced between US sites and Canadian sites; however, the predefined minimal sample of subjects with Fitzpatrick Skin Types IV, V and VI must still be obtained in the subject population overall.

Testing will be performed with the null hypotheses being the absence of differences between the US and Canada. All observed two-sided p-values must be >0.05 to pool data; if the two-sided p-value is ≤0.05, data collected from subjects of both countries will not be pooled unless further argumentation could be provided to support such pooling. Percentages of each characteristic will be compared using a Fischer's exact test, and continuous data will be compared using a Student t-test (or Mann-Whitney test if not normally distributed).

9.3.9 Visit Windows

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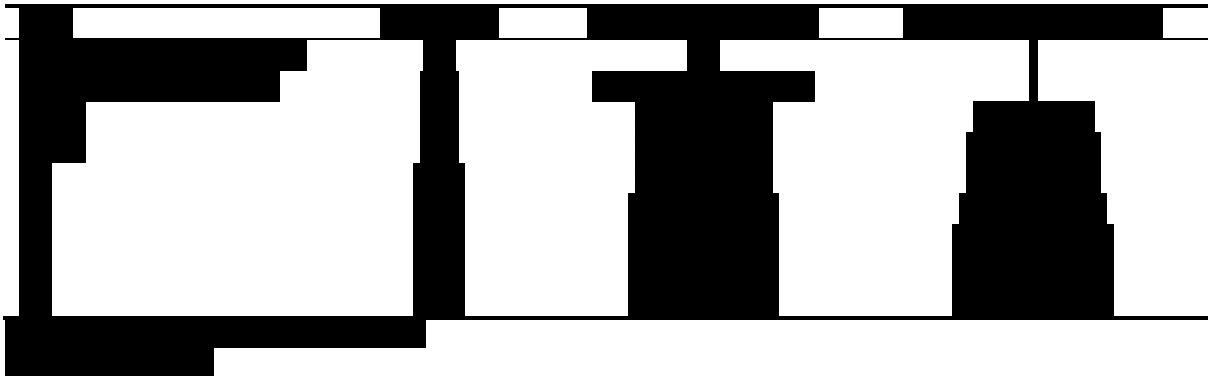

9.3.10 Dates

Partial dates will be imputed to the lowest available element of time (e.g., month or year). Missing dates will not be imputed. In case of adverse events duration, if the month is missing, the 15 of the month will be used in the calculation of the duration while the 01 of July will be used in case of a missing year.

9.3.11 Interim Analysis

There will be no interim efficacy analysis.

9.3.12 Outliers

No method to process outliers will be used. Data will be analyzed as reported in the database.

9.3.13 Software Documentation

All summaries and statistical analyses will be performed using SAS® 9.3 or higher.

APPENDIX A: SUMMARY OF STATISTICAL TESTS

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EFFICACY ANALYSIS

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SAFETY ANALYSES

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APPENDIX B: STATISTICAL TABLES

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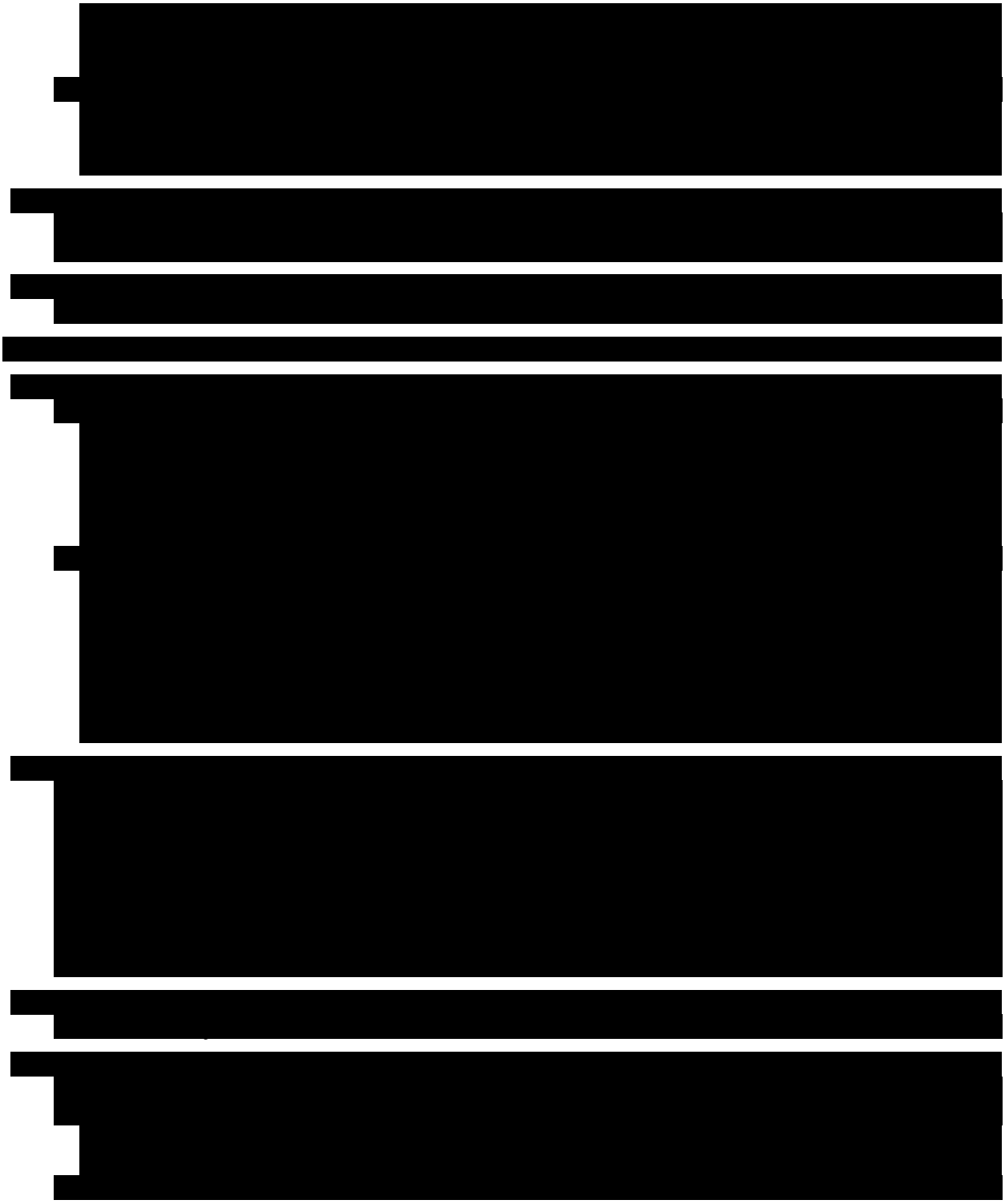

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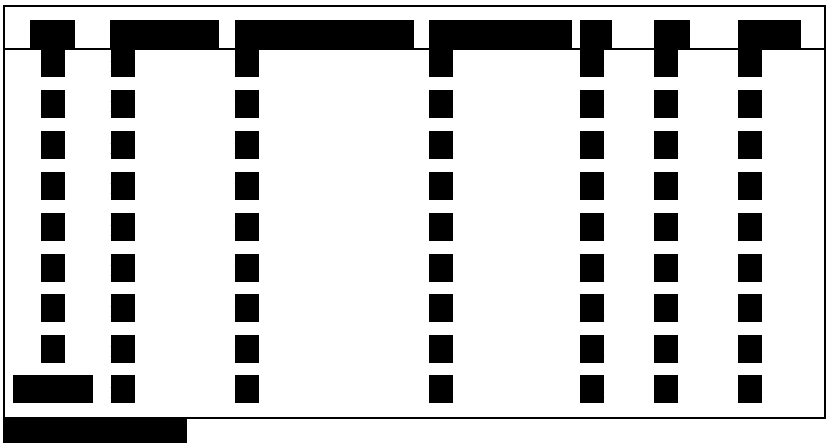

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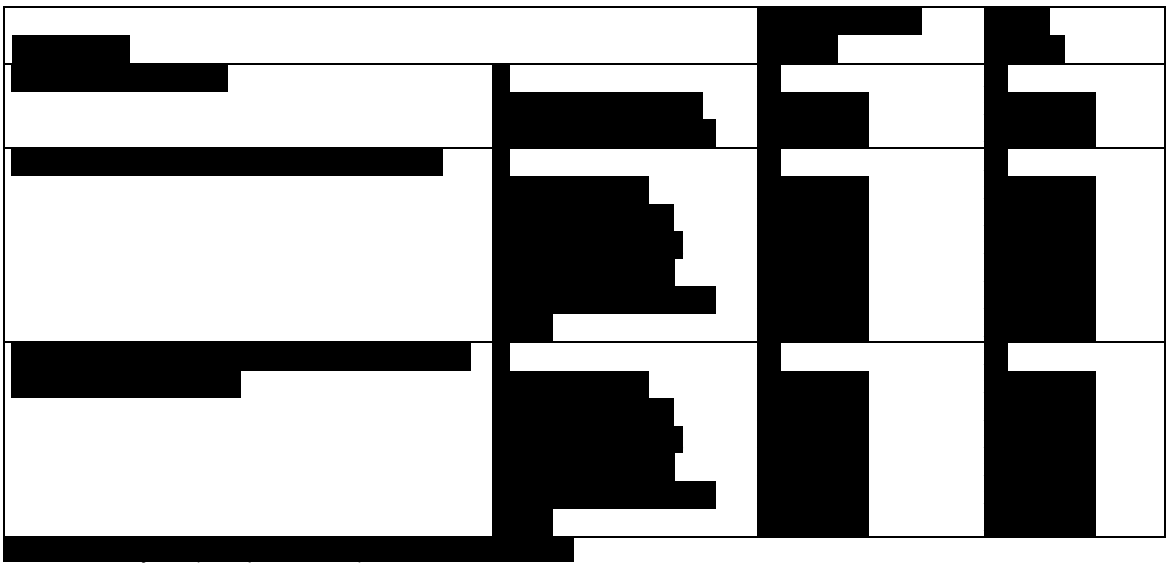

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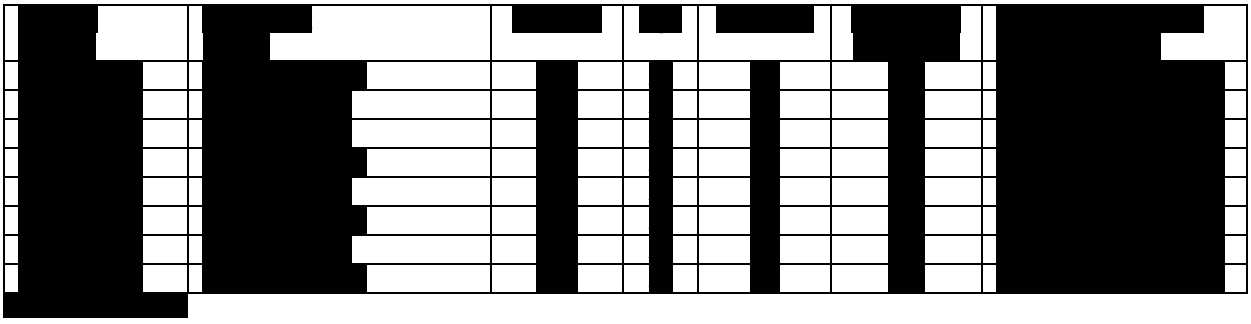

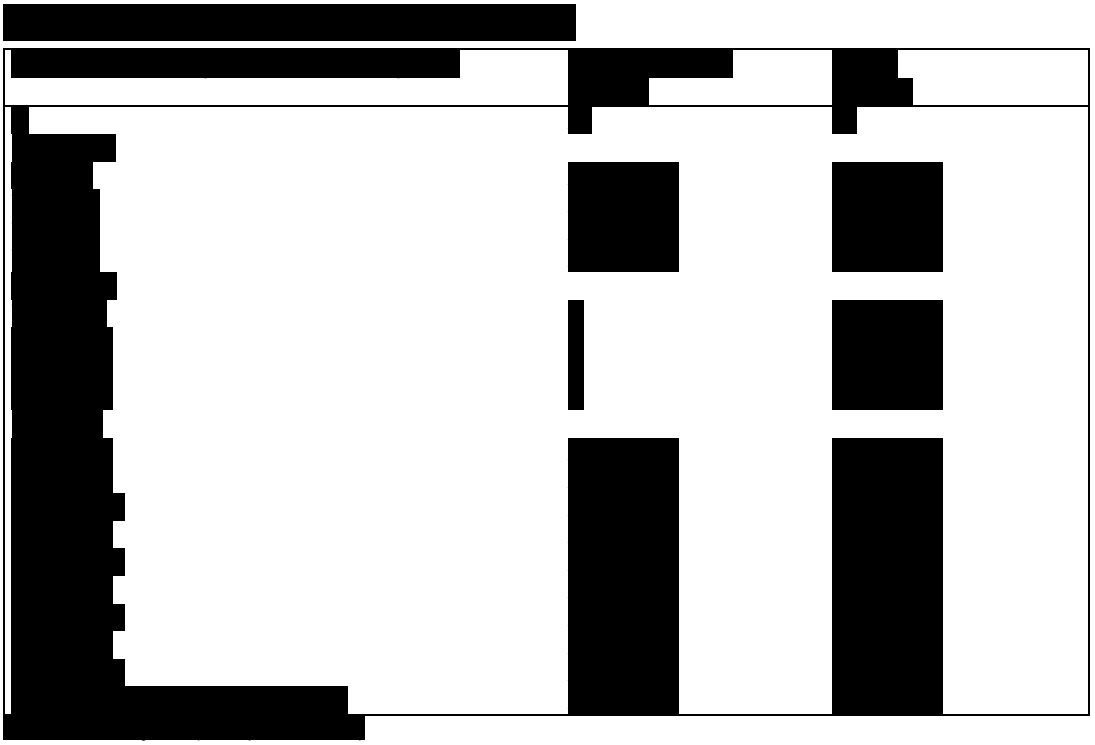

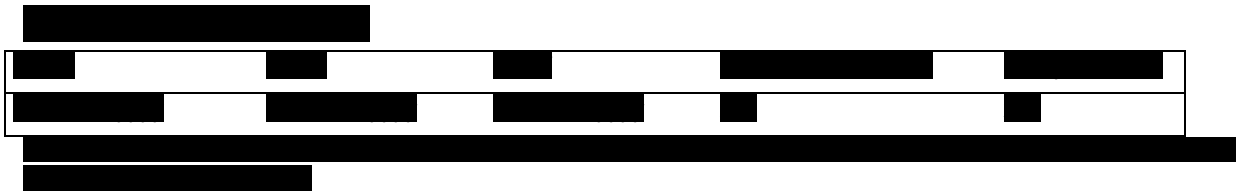

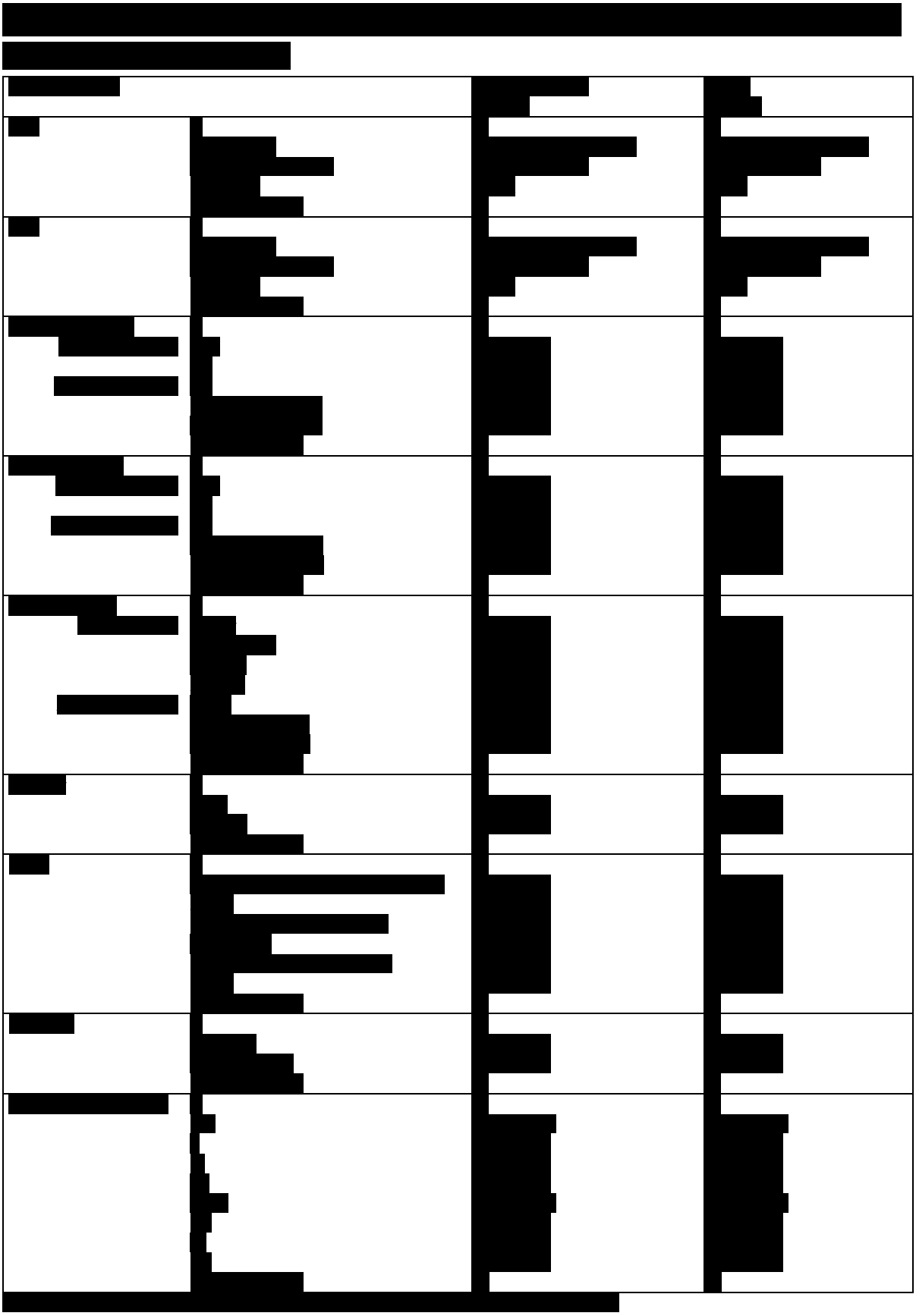

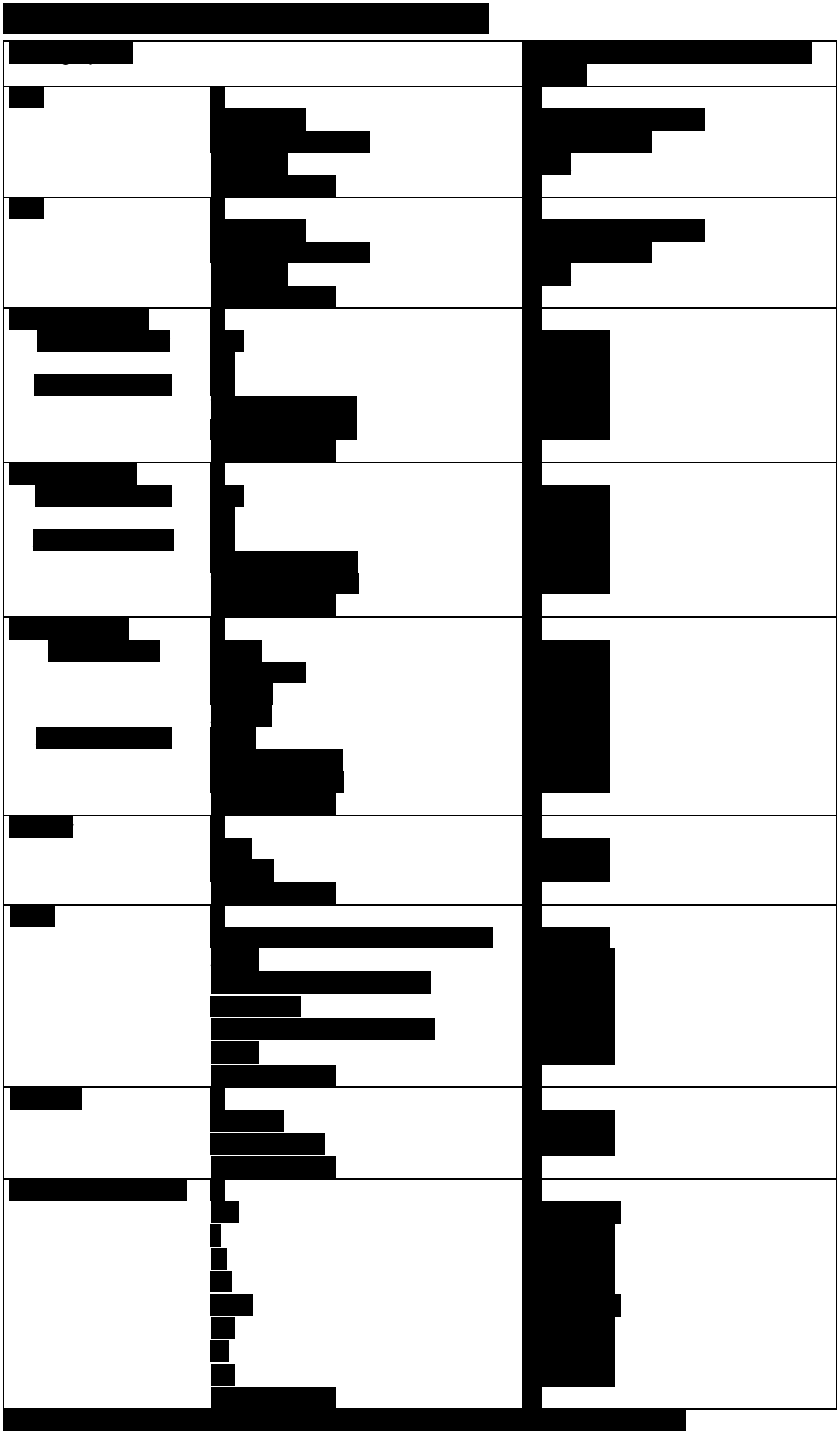

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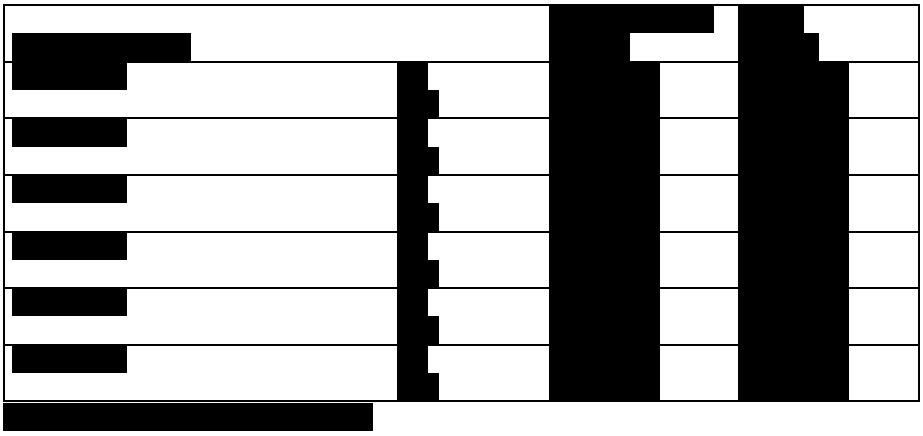

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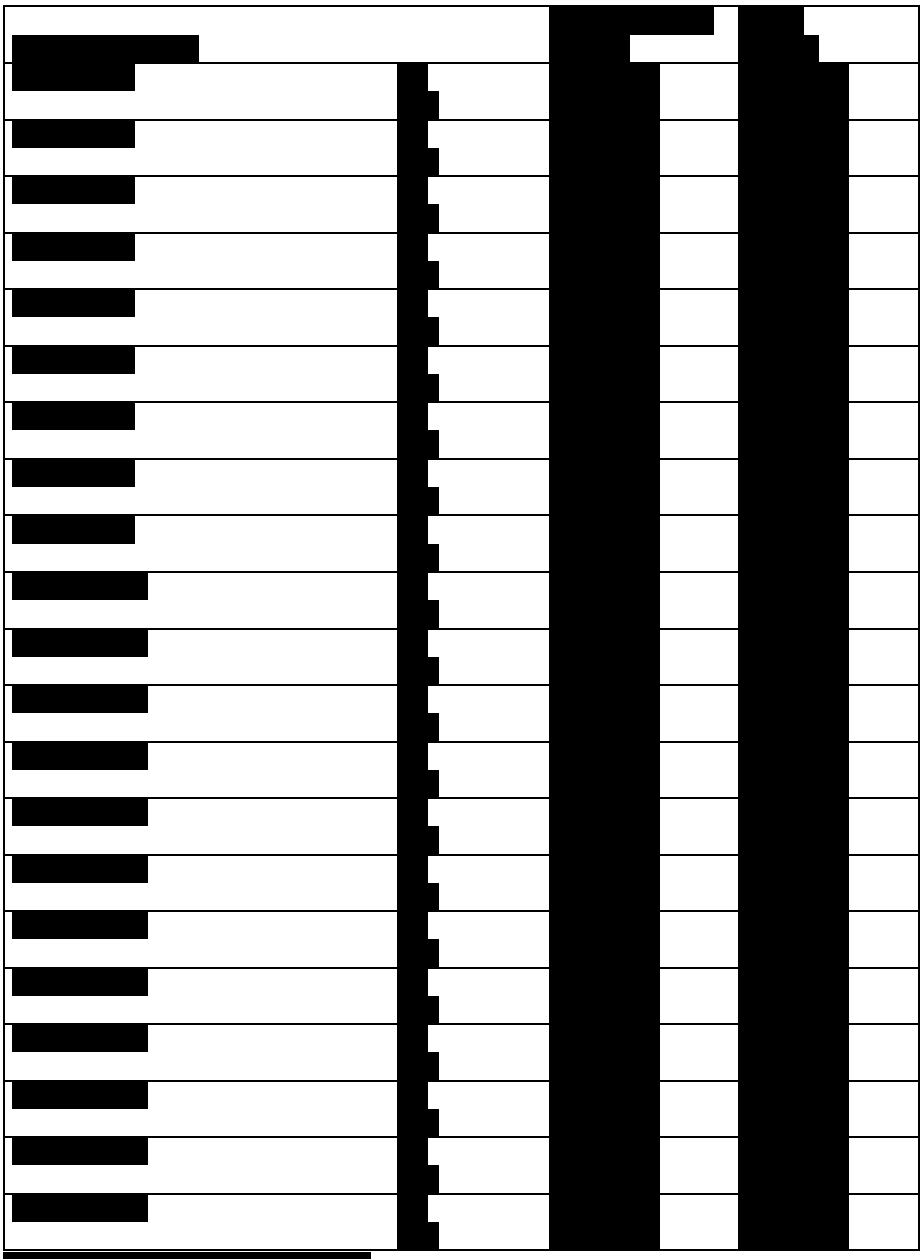

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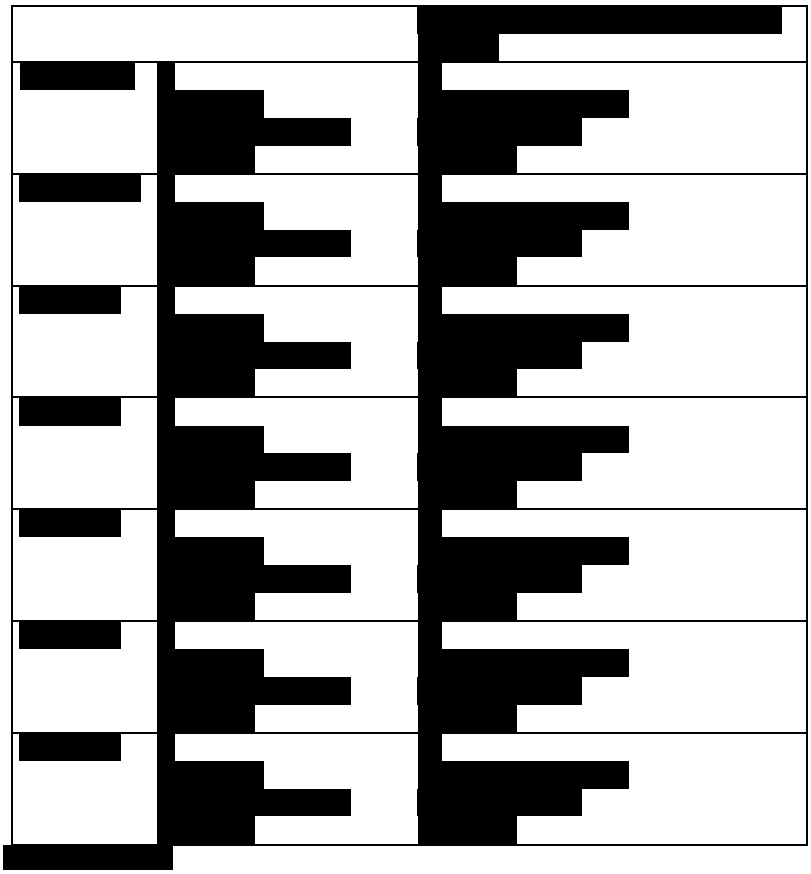

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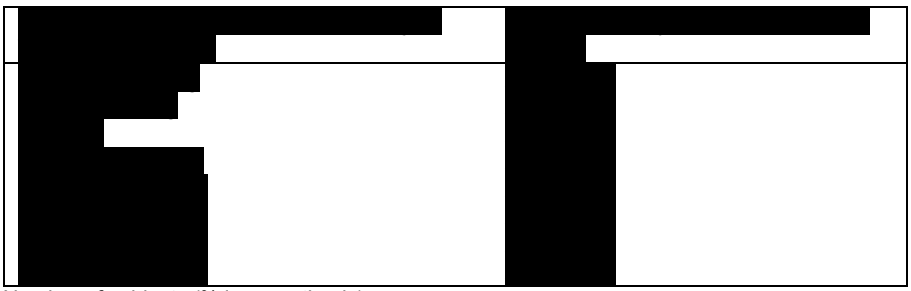

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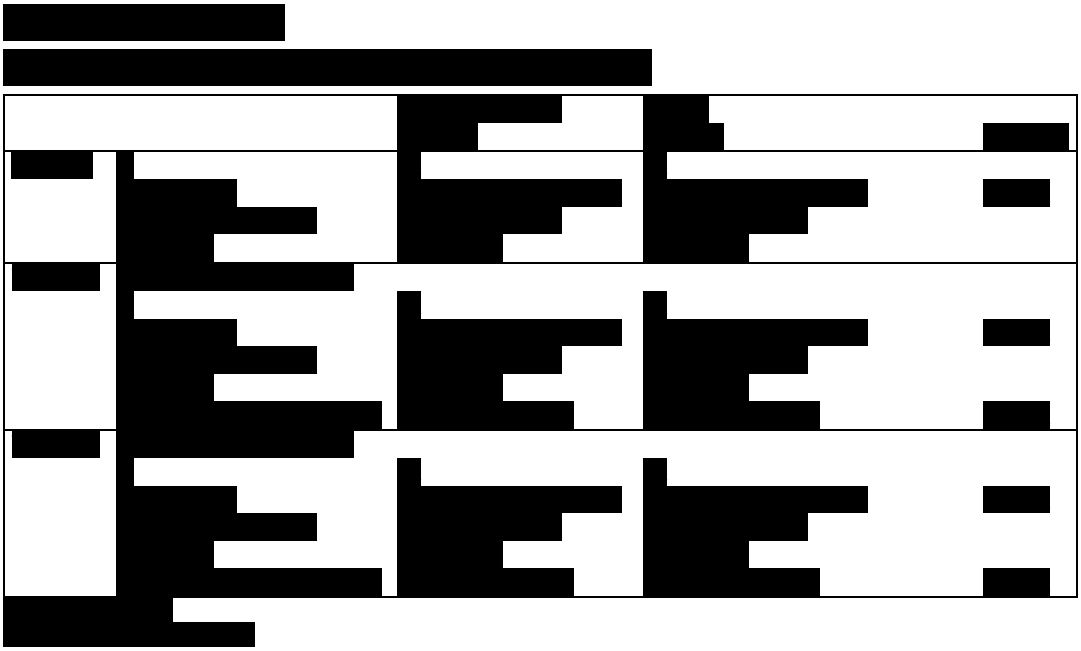

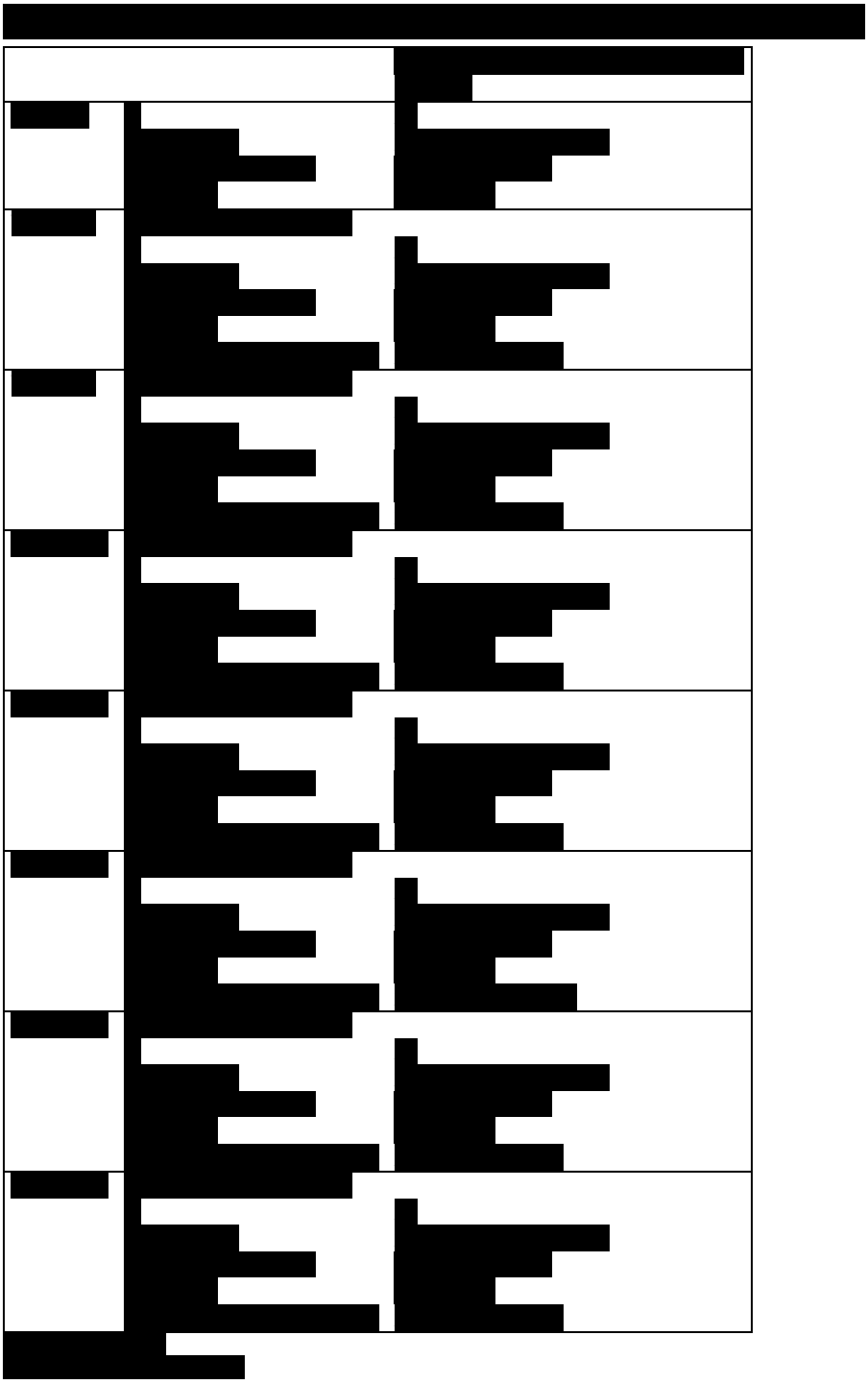

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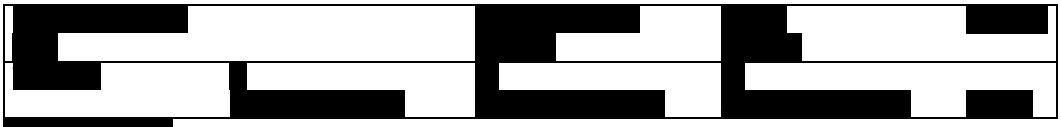

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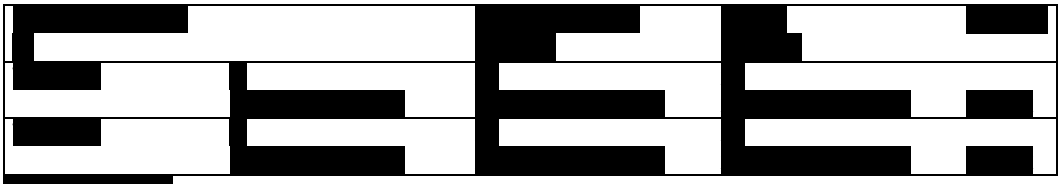

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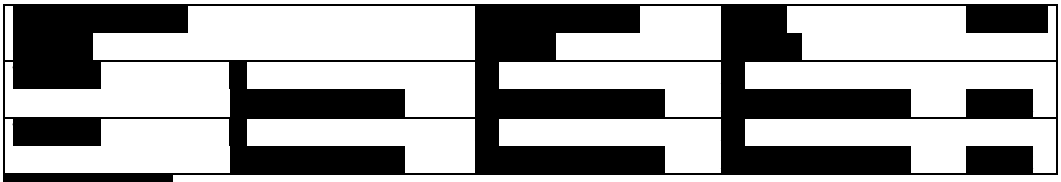

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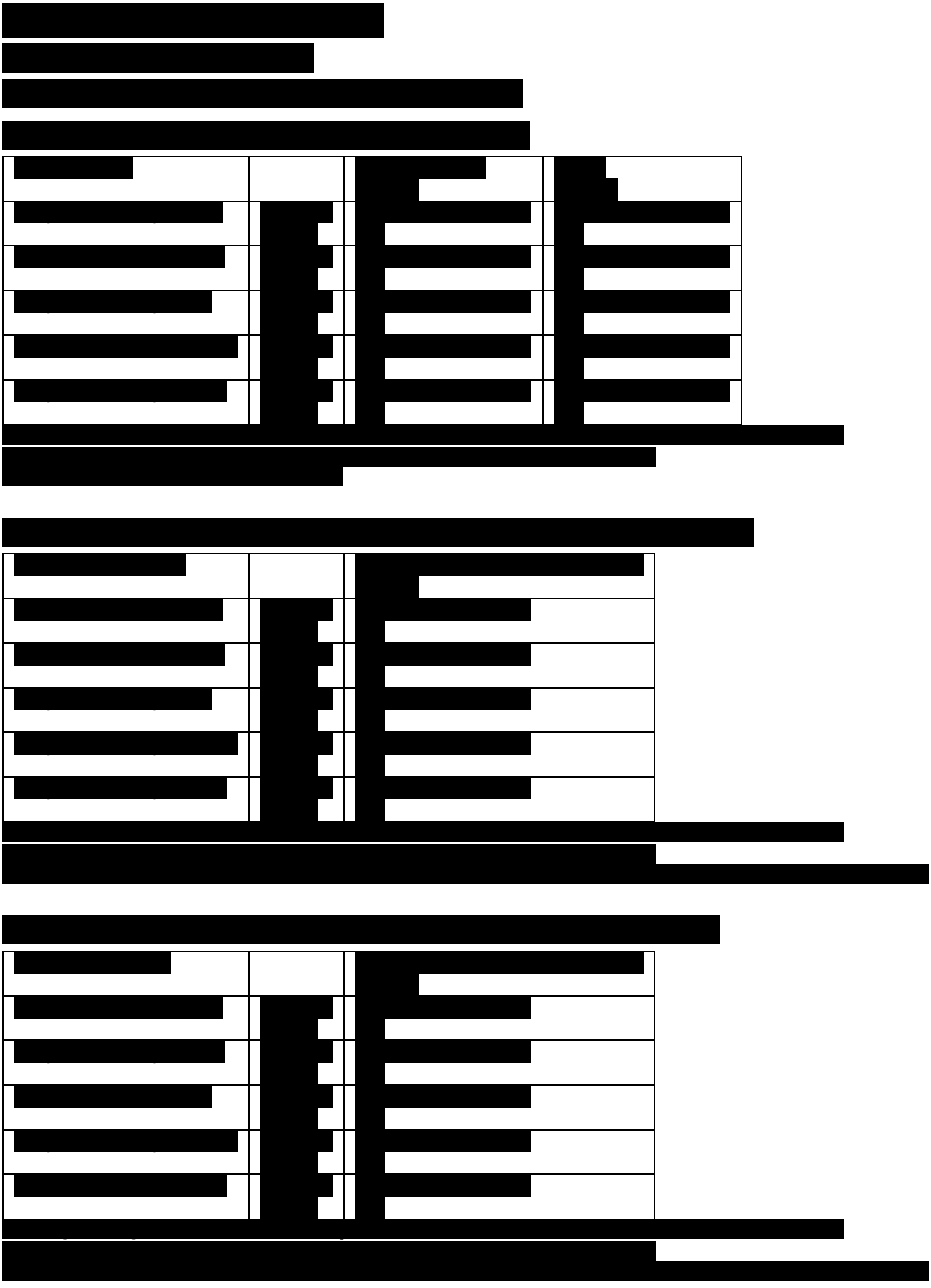

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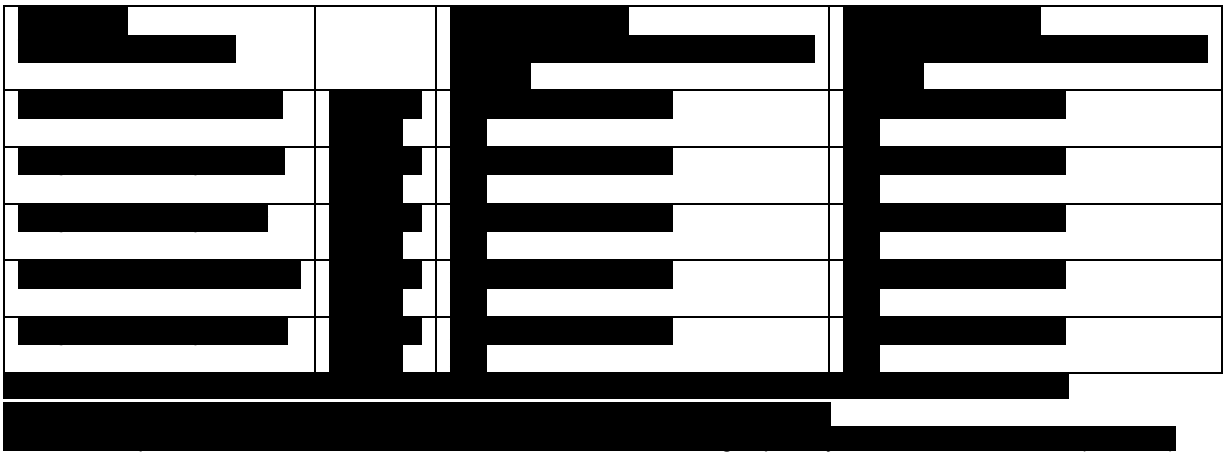

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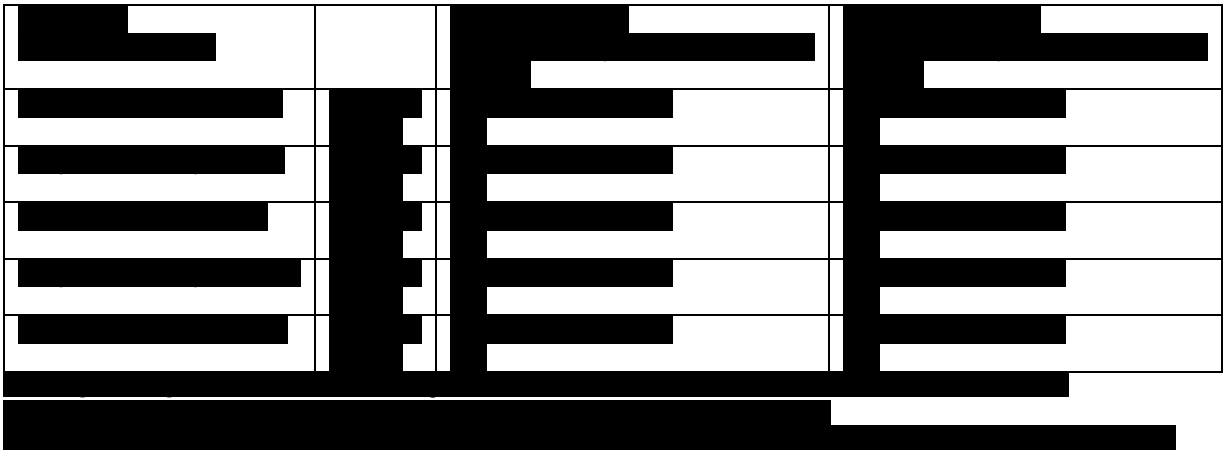

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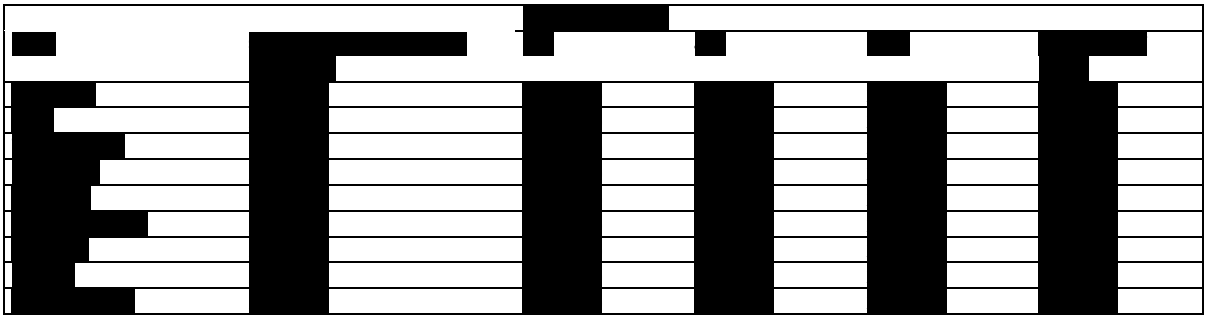

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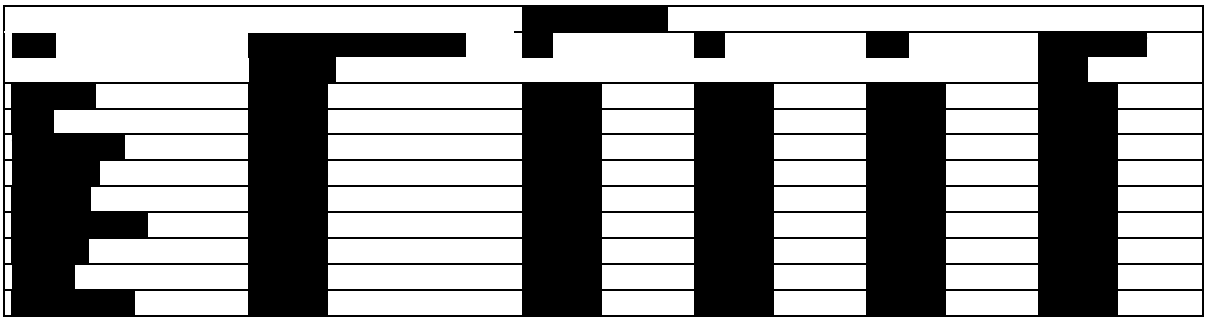

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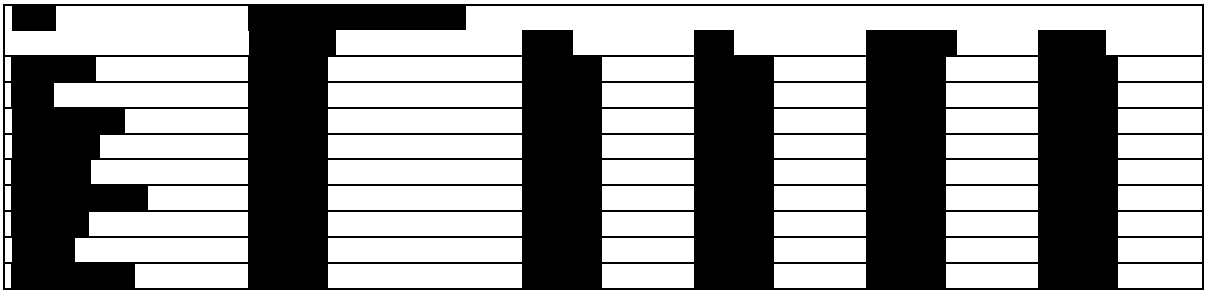

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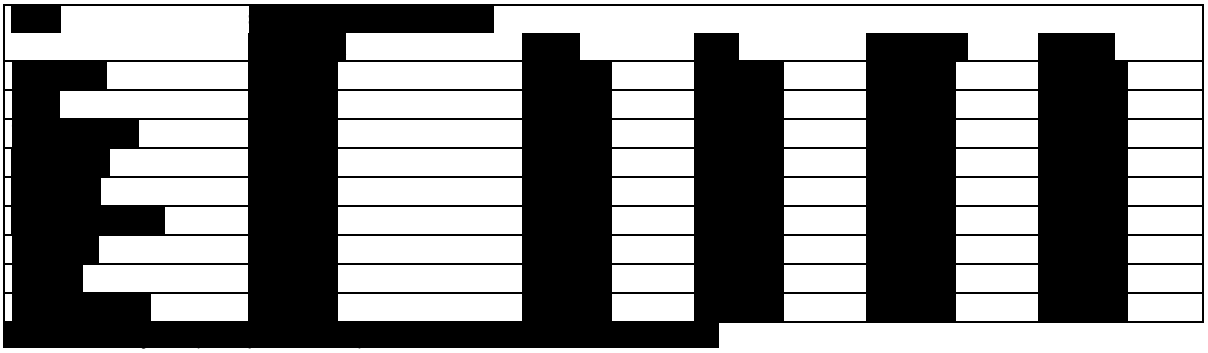

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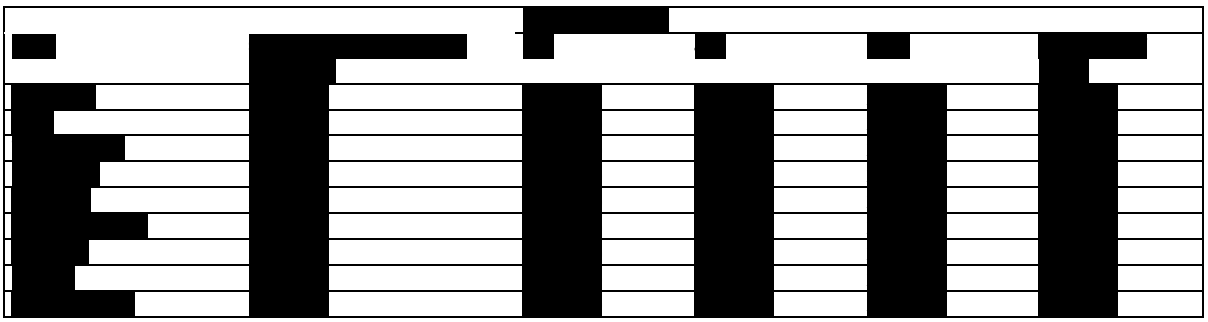

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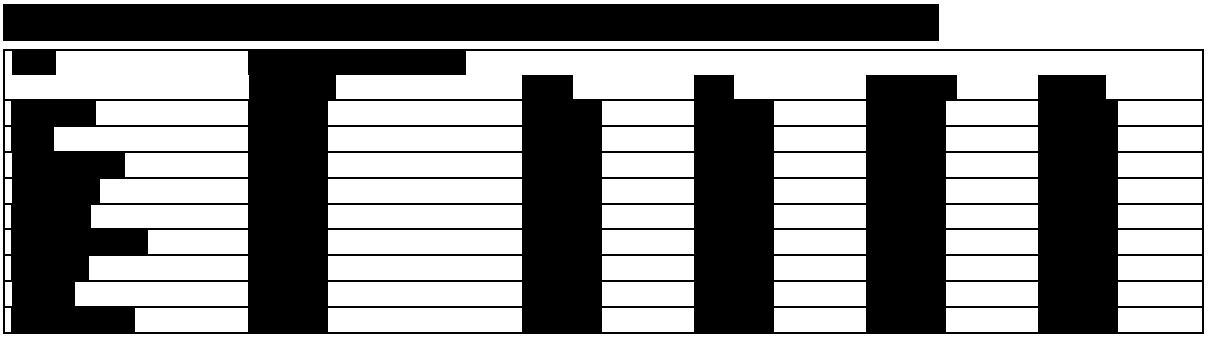

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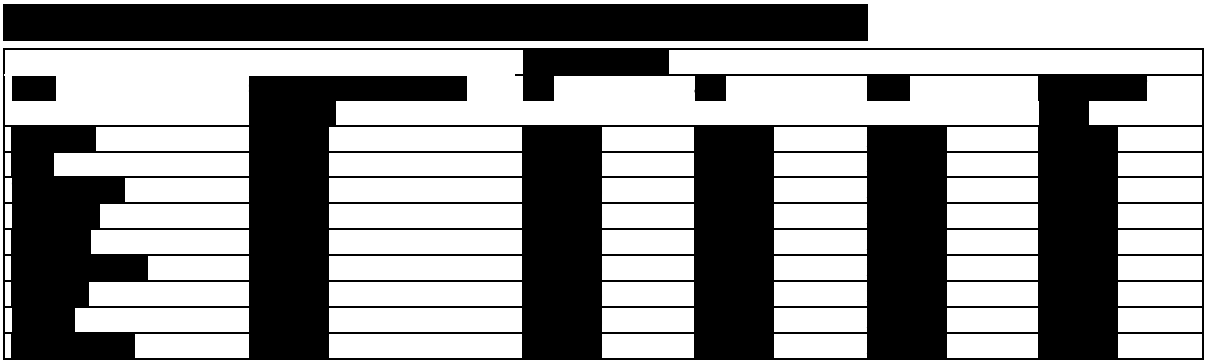

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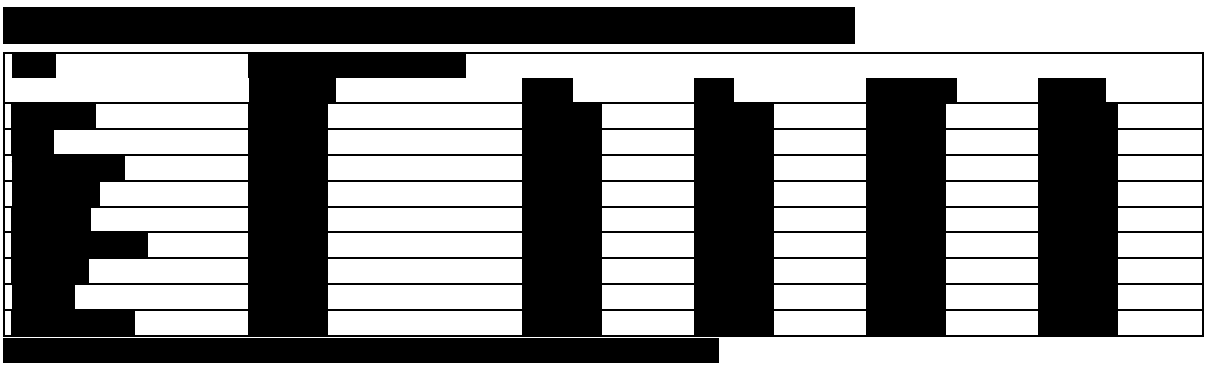

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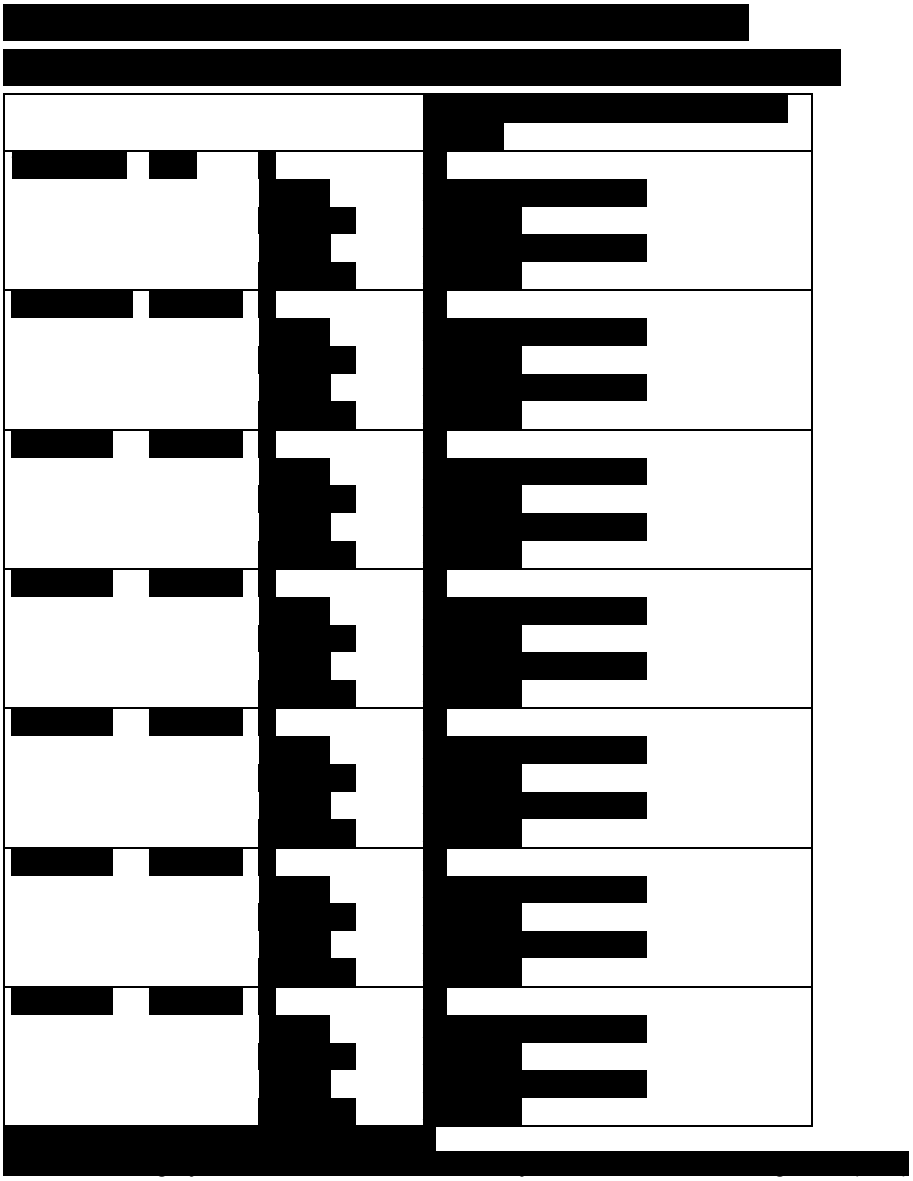

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