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| Official Title: | STATISTICAL ANALYSIS PLAN:<br>A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Cream, USP, 0.01% (Prasco LLC) to Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) in the Treatment of Vulvar and Vaginal Atrophy |
| NCT Number: | NCT03332303 |
| Date: | January 17, 2018 |

[redacted]

**STATISTICAL ANALYSIS PLAN**



# STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Cream, USP, 0.01% (Prasco LLC) to Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) in the Treatment of Vulvar and Vaginal Atrophy

Protocol Number: 71759501
[redacted] Study Number: 71759501

**Sponsor:**
Prasco LLC
6125 Commerce Court
Mason, OH 45040

**Contract Research Organization:**
[redacted]

January 17, 2018

Final Version 1.0

[redacted]



## SAP FINAL VERSION APPROVALS

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Cream, USP, 0.01% (Prasco LLC) to Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) in the Treatment of Vulvar and Vaginal Atrophy

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STATISTICAL ANALYSIS PLAN

**Estradiol Vaginal Cream USP, 0.01%** **Protocol/Study Number 71759501**

**Revision History**

| VERSION | DATE | DESCRIPTION OF REVISIONS | REVISED BY |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

## List of Abbreviations and Definition of Terms

| | |
|---|---|
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| ANOVA | Analysis of variance |
| C | Celsius |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | Confidence Interval |
| CMH | Cochran-Mantel-Haenszel |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| dL | Deciliter |
| F | Fahrenheit |
| FDA | Food & Drug Administration |
| FSH | Follicle-stimulating hormone |
| Hg | Mercury |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| LOCF | Last Observation Carried Forward |
| mcg | Microgram |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| mITT | modified Intent-to-Treat |
| mL | Milliliter |
| mm | Millimeter |
| OGD | Office of Generic Drugs |
| PAP | Papanicolaou |
| pH | Measure of acidity/alkalinity |
| PP | Per-Protocol |
| RS | Reference Standard |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SDTM | Study Data Tabulation Model |
| U.S.A | United States of America |
| VVA | Vulvar and Vaginal Atrophy |

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**STATISTICAL ANALYSIS PLAN**

**Estradiol Vaginal Cream USP, 0.01%** **Protocol/Study Number 71759501**

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## 1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol 71759501 (Rev 0) dated 07-25-2017. The SAP provides details on the planned statistical methodology for the analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures.

This SAP describes the study endpoints, derived variables, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP therefore outlines in detail all other aspects pertaining to the planned statistical analyses and presentations for this study.

The following documents were reviewed in preparation of this SAP:

- Final Clinical Study Protocol 71759501 (Rev 0) dated 07-25-2017
- Case Report Form Booklet Version 1.0 for Study No. 71759501

## 2. OBJECTIVES

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of a Test product, the generic Estradiol Vaginal Cream USP, 0.01% (Prasco LLC) to the Reference product, Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) in the treatment of VVA.
2. Demonstrate the superiority of the active treatments (Test and Reference) over Placebo (vehicle) treatment in patients with VVA.
3. Compare the safety of Test, Reference and Placebo treatments in patients with VVA.

## 3. OVERALL STUDY DESIGN

This randomized, double-blind, placebo-controlled, parallel-design, multiple-site study is designed to evaluate the clinical (therapeutic) effect of a Test product, a generic Estradiol Vaginal Cream USP, 0.01% (Prasco LLC) compared to the FDA Reference Standard (RS), Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01% (Warner Chilcott) in patients with VVA. Additionally, both the Test and Reference products will be tested for superiority against a Placebo.

Before any study-specific procedures are performed, all patients will read and sign the IRB-approved informed consent form (ICF).

Approximately [redacted] eligible postmenopausal female patients, with a confirmed diagnosis of VVA will be randomized in a [redacted] to one of the three study products as follows:

- **Test**: Estradiol Vaginal Cream, USP, 0.01% (Prasco LLC)
- **Reference**: Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott)
- **Placebo**: Placebo (Test vehicle cream) Vaginal Cream (Prasco LLC)

Following a 28-day screening period, at Visit 2 patients will be instructed to self-administer 2 grams of study product once daily at approximately the same time for seven consecutive days.

During the study, patients will visit the clinical center for a total of three scheduled visits:

- Visit 1/Screening (Day -28 to Day -1)
- Visit 2/Randomization (Day 1)
- Visit 3/End of Study (Day 8 or Day 9)

Final assessments will be carried out on Day 8 or Day 9.

Vaginal cytology and vaginal pH determination will be performed by the Investigator as a part of clinical evaluation at Visits 1 and 3. The primary statistical analysis of interest is the proportion of patients in the PP population that are identified as Responders at the end of the treatment period evaluated on Day 8 or Day 9. A Responder is defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5.

**Study Schematic**

| | **Visit 1** (Day -28 to Day -1) Screening | **Visit 2** (Day 1) Randomization | **Visit 3** (Day 8 or Day 9) End of Study or Early Termination |
|---|---|---|---|
| Informed Consent | X | | |
| Medical History and Demographics | X | | |
| Review and Assessment of Concomitant Medications | X | X | X |
| Review and Assessment of Adverse Events | X | X | X |
| Vital Signs | X | X | X |
| Signs and Symptoms of VVA | X | X | X |
| Physical Exam | X | | X |
| Vaginal Cytology and pH | X | | X |
| PAP*Smear | X | | |
| Serum FSH and Fasting Triglycerides | X | | |
| Mammogram† | X | | |
| Vaginal Ultrasound‡ | X | | |
| Inclusion/Exclusion Criteria Review | X | X | |
| Collect and Review Patient Diary | | X | X |
| Provide Patient Diary | X | X | |
| Dispense Study Product | | X | |
| Collect Study Product | | | X |

*Patients with an intact uterus who do not have documentation of a PAP smear completed within the [redacted].
†Patients over the age of [redacted] who do not have documentation of a mammogram completed within the [redacted] before Screening will have a mammogram as part of the Screening evaluations.
‡Patients with an intact uterus will have a vaginal ultrasound as part of the Screening evaluations which will be reviewed before randomization.

## 4. RANDOMIZATION AND BLINDING

Patients who meet the inclusion criteria and none of the exclusion criteria at Visits 1 and 2 will be assigned a randomization number. The randomization number will [redacted]. Randomization numbers will be assigned immediately before dispensing of study product and in ascending sequential order, beginning with the lowest available number at the study site. Each patient kit and each dispensed study tube should include [redacted] on the label.

All randomized study product [redacted]

At the end of the study, after all the clinical data have been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician.

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment.

## 5. SAMPLE SIZE

For the primary endpoint analysis (proportion of patients in the PP population that are identified as Responders at the end of the treatment period evaluated on Day 8 or Day 9), sample size is estimated for therapeutic equivalence of the Test product to the Reference product and superiority of each of the active treatments groups over Placebo. [redacted]

## 6. ANALYSIS POPULATION

### Per-Protocol (PP) Population

The PP population will include all randomized patients who:

- Met the inclusion/exclusion criteria as defined in the protocol at Visit 1 and 2.
- Did not have any significant protocol deviations.
- Did not develop any concurrent vaginal infection or illness exhibiting symptoms similar to VVA, or symptoms that in the Investigator's opinion would interfere with primary and secondary endpoint assessments.
- Completed the last study visit (Visit 3) within window (Day 8 or Day 9).
- Were compliant with dosing between [redacted] of the required doses.

Any patient who withdraws from the study because of lack of efficacy will be included in the PP population as a Non-Responder, provided they did not have any significant protocol deviations that would affect treatment evaluation.

### Modified Intent-to-Treat (mITT) Population

The modified Intent-to-Treat (mITT) population will include all randomized patients who:

- Administered at least one dose of randomized study product.
- Had a post-randomization evaluation.

### Safety Population

The safety population will include all patients who are randomized and received study product.

## 7. STUDY ENDPOINTS

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients in each treatment group that are identified as Responders at the end of the treatment period evaluated on Day 8 or Day 9.

A "Responder" is defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5.

Secondary Efficacy Endpoint

The secondary efficacy endpoint is the proportion of patients in each treatment group that are considered a Treatment Success at the end of the treatment period evaluated on Day 8 or Day 9.

A "Treatment Success" is defined as a score of 0 or 1 on Day 8 or Day 9 for the symptom identified at baseline as the most bothersome. This evaluation will be based on (one) patient self-assessed symptom of VVA (vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, or vaginal pain associated with sexual activity) on a scale of 0 to 3 where 0 = none and 3 = severe. Evaluation of vaginal bleeding during sexual activity will be based on a Score of 1 (presence) if it is identified by the patient as the most bothersome symptom at baseline and a score of 0 (absent) on Day 8 or Day 9.

Baseline is defined as the symptom score at Randomization Visit 2.

## 8. STATISTICAL ANALYSIS METHODS

If not otherwise specified, statistical significance is defined as $p < 0.05$ and is two-tailed. Data will be summarized with respect to demographic and baseline characteristics, efficacy variables and safety variables.

For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, statistics will include n, mean, standard deviation, median, minimum and maximum values.

All statistical analyses will be conducted using SAS®, [redacted]

## 8.1 Baseline Characteristics

### 8.1.1 Patient Disposition

The patient disposition information will be summarized by study treatment group. The number of patients randomized, and the number of patients in each analysis population will be tabulated. In addition, completion status and primary reason for withdrawal will be summarized by study treatment group.

### 8.1.2 Demographic and Other Baseline Characteristics

Baseline comparability of all treatment groups will be evaluated separately in the PP, mITT and Safety populations. The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Gender (male/female)
- Ethnicity (Hispanic/non Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- Natural or surgical menopause
- Duration of postmenopausal status
- Baseline signs and symptoms
- Baseline % of the three major vaginal wall cell types (basal/parabasal cells, intermediate cells and superficial cells)
- Vaginal pH

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, maximum). Categorical variables will be summarized using frequencies and percentages.

Baseline treatment comparisons will be presented using Chi-Square test for the categorical variables, and Analysis of Variance (ANOVA) for the continuous variables.

All data will be listed by treatment and patient.

### 8.1.3 Medical History

At Visit 1, patients will be questioned about medical history, including acute and chronic medical history and medical history relevant to their VVA.

Medical history data will be listed by treatment and patient.

### 8.1.4 Concomitant Medications

At Visit 1, patients will be questioned about all concomitant medication use within the previous 6 months. At Visits 2 and 3, patients will be questioned about ongoing or any new concomitant medication use.

All prior and concomitant medications taken since screening until the end of the study will be listed by treatment and patient.

### 8.1.5 Physical Exam

At Visit 1, the Investigator will perform a general physical exam including pelvic exam and breast exam. At Visit 3, the Investigator will perform a general physical exam including pelvic and breast exam. Any clinically significant abnormal findings on this exam should be reported as adverse events (AEs).

Physical examination results will be listed by treatment and patient.

### 8.1.6 Laboratory Evaluations

At Visit 1, all patients will have a blood sample taken for evaluation of serum FSH levels. Serum FSH will be evaluated by a central clinical laboratory. [redacted]

All patients will have a blood sample taken for fasting triglyceride testing. These samples will be sent to the central laboratory for testing. [redacted]

Laboratory evaluation results will be listed by treatment and patient.

### 8.1.7 Dosing Compliance

Patients will be considered compliant if they take a total of at least six doses and no more than eight doses, and not more than two doses on any day. Patients taking fewer than 75% or more than 125% of the required doses will be considered non-compliant with dosing. Compliance with dosing will be verified by the use of the patient diaries. Compliance criteria are as outlined in the table below:

For patients who have completed the study:

| Study Design | | | Compliance Criteria | |
|---|---|---|---|---|
| Visit 3 | Treatment Duration | Required Doses | Not more than 125% (doses) | Not less than 75% (doses) |
| Days 8-9 | 7 days | 7 | 8 | 6 |

For patients who are early terminated, compliance will be determined from their duration in the study, up to the time they are considered early terminated. For example, if a patient is dropped after six days of participation and starts application of study product on the day of Visit 2 (i.e., Day 1) and once daily for the four of the five remaining days, then percent compliance would be 83% (4 out of 5 doses).

Drug administration and dosing compliance will be listed by treatment and patient.

## 8.2 Efficacy Analyses

### 8.2.1 Analysis of Primary Efficacy Endpoint

**Therapeutic Bioequivalence Analysis**

Therapeutic equivalence of the Test product to the Reference product based on the primary endpoint will be evaluated in the PP population after the end of treatment on Day 8 ± 1.

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment should be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

versus

where = cure rate of test treatment
= cure rate of reference treatment.

Let
= sample size of test treatment group
= number of cured patients in test treatment group
= sample size of reference treatment group
= number of cured patients in reference treatment group

, and

The 90% confidence interval for the difference in proportions between test and reference will be calculated as follows, using Yates' correction:

If the 90% confidence interval (calculated using Yates' continuity correction) for the absolute difference between the proportion of patients considered as "Responders" (at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5) in the Test and Reference groups is contained within the range [-20%, +20%] then bioequivalence of the Test product to the Reference product will be considered to have been demonstrated for the primary endpoint.

To declare therapeutic equivalence of the Test product to the Reference product, equivalence must be demonstrated for only the primary endpoints in the PP population.

**Superiority to Placebo Analysis**

The mITT population and LOCF will be used to evaluate the superiority of both the Test and Reference product to Placebo. LOCF will apply to each parameter of the endpoint.

Summary table with frequency and percentage on the proportion of responders by treatment group will be presented. If the proportion of Responders in the Test and the Reference product groups is numerically and statistically superior to that of the Placebo ($p < 0.05$; using a two-sided CMH test, stratified by clinical site) then superiority of the Test and Reference products over Placebo will be concluded.

To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population.

### 8.2.2 Analysis of Secondary Efficacy Endpoint

**Therapeutic Bioequivalence Analysis**

Similar to the analysis for primary endpoint above, therapeutic equivalence of the Test product to the Reference product based on the secondary endpoint will be evaluated in the PP population after the end of treatment on Day 8 ± 1.

Secondary analysis will compare the proportion of patients considered to be a "Treatment Success" for their most bothersome symptom. A "Treatment Success" is defined as a score of 0 or 1 at Day 8 for the symptom identified at baseline as the most bothersome). Baseline is defined as the symptom score at Randomization Visit 2. If the 90% confidence interval (calculated using Yates' continuity correction) for the absolute difference between the proportion of patients considered as "Treatment Success" in the Test and Reference groups is contained within the range [-20%, +20%] then bioequivalence of the Test product to the Reference product will be considered to have been demonstrated for the secondary endpoint.

To declare therapeutic equivalence of the Test product to the Reference product, bioequivalence must be demonstrated for only the primary endpoint. Bioequivalence testing of the secondary

endpoint will be conducted for supportive information.

**Superiority to Placebo Analysis**

The mITT population and LOCF will be used to evaluate the superiority of both the Test and Reference products to Placebo.

Summary table with frequency and percentage on the proportion of responders by treatment group will be presented. If the proportion of Responders in the Test and the Reference product groups is numerically and statistically superior to that of the Placebo ($p < 0.05$; using a two-sided CMH test, stratified by clinical site) then superiority of the Test and Reference products over Placebo will be concluded.

### 8.2.3 Treatment-by-Site Interaction and Pooling of Clinical Sites

As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population for equivalence testing. The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$, 2-sided). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the stratification of the sites in the CMH test and in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ($p < 0.05$) for the primary endpoint, then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Responder rates at each site where sample sizes per treatment may be influential in the assessment of the interaction.

## 8.3 Safety Analysis

### 8.3.1 Adverse Events

All the AEs reported will be coded and classified according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (Version 20.0 or higher). Each AE is to be evaluated for date of start and end, seriousness, severity, causal relationship with the study drug, action taken and outcome.

All AEs will be listed by patient and treatment.

The total number and percentage of patients with at least one AE, discontinued study drug due to AEs, AE severity, AEs related to investigational product, serious adverse events (SAEs), and death will be summarized by treatment groups.

A summary table of the number and percent of patients with AEs by system organ class, preferred term, and treatment group will be presented. Each patient will be counted only once within each preferred term.

A frequency summary table of the number of AEs by system organ class, preferred term, severity, and treatment group will be presented. Severity will be classified as "Mild", "Moderate", or "Severe".

Similarly, a frequency summary table of the number of AEs by system organ class, preferred term, and relationship to a study drug, and treatment group will be presented. Relationship to a study drug will be classified as "Related" or "Not Related".

Adverse event frequencies will be compared between treatments using the Fisher's exact test.

### 8.3.2 Vital Signs

The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at Visits 1, 2, and 3.

Descriptive summaries (n, mean, standard deviation, minimum, median and maximum) will be provided by treatment and visit. The summary table will be based on safety population randomized.

All data will be listed by treatment and patient.

## 8.4 Multiple Comparisons

No multiple comparison adjustment will be made in this study.

## 8.5 Methods for Handling Missing Data

For demographic and baseline characteristics, each variable will be analyzed using all available data. Patients with missing data will be excluded only from analyses for which data are not available.

Any patient who withdrew from the study because of lack of efficacy will be included in the PP population as a Non-Responder, provided they did not have any significant protocol deviations that would affect treatment evaluation. Patients who discontinue early for other reasons should be excluded from the PP population and included in the mITT population using Last Observation Carried Forward (LOCF).

## 8.6 Interim Analyses

There is no interim analysis planned in this study.

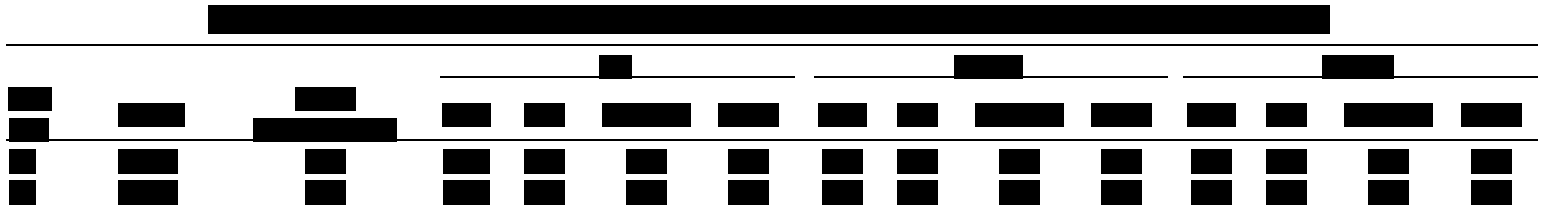
## 9. TABLE, LISTING AND FIGURE SHELLS

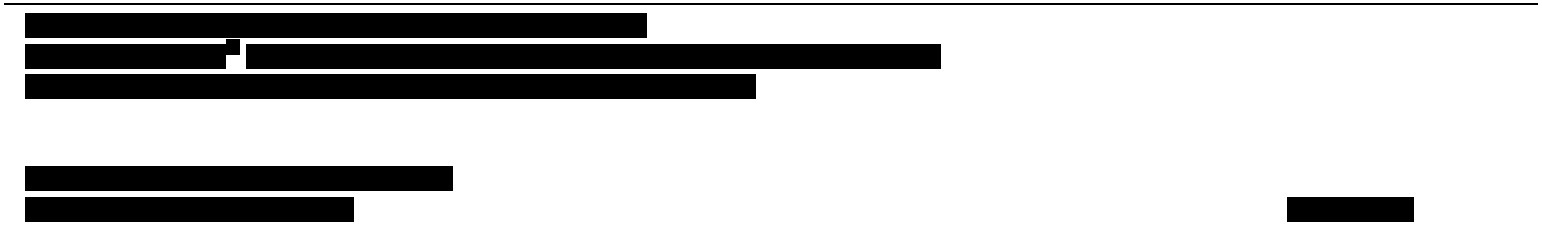
The following shells are provided in order to provide a framework for the display of data from this study. [redacted]

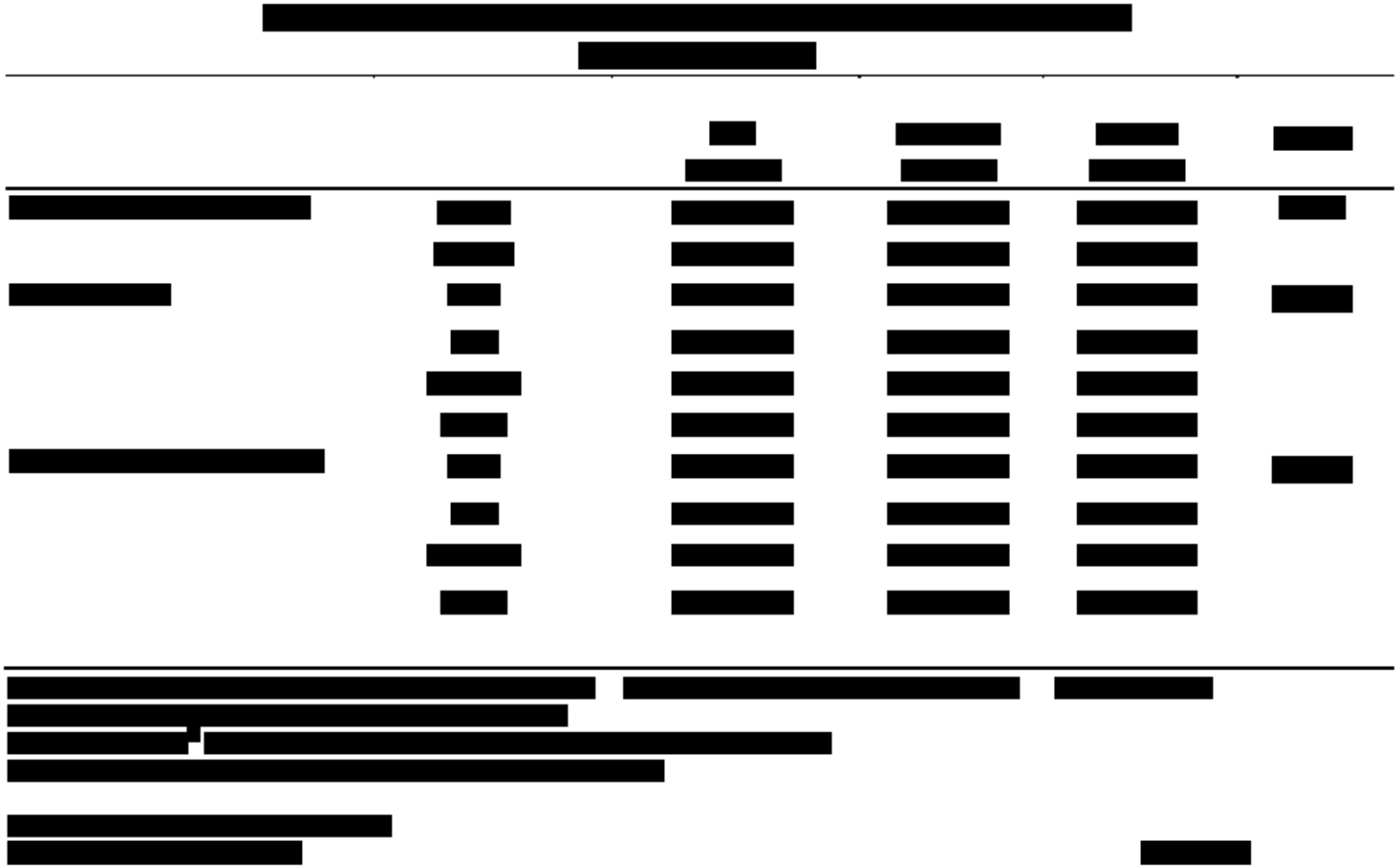
# TABLE, LISTING AND FIGURE SHELLS

[redacted]

[redacted]







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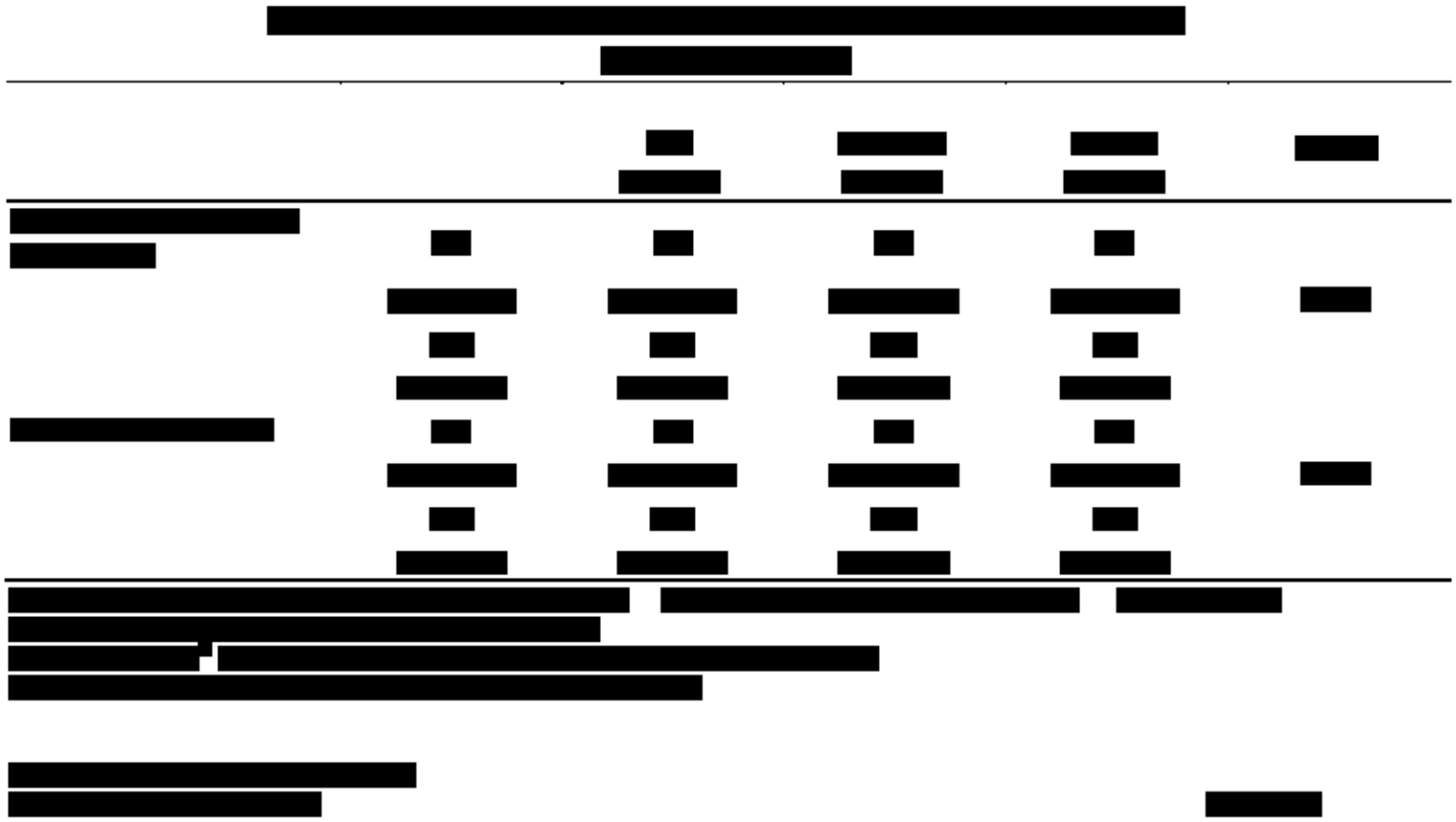

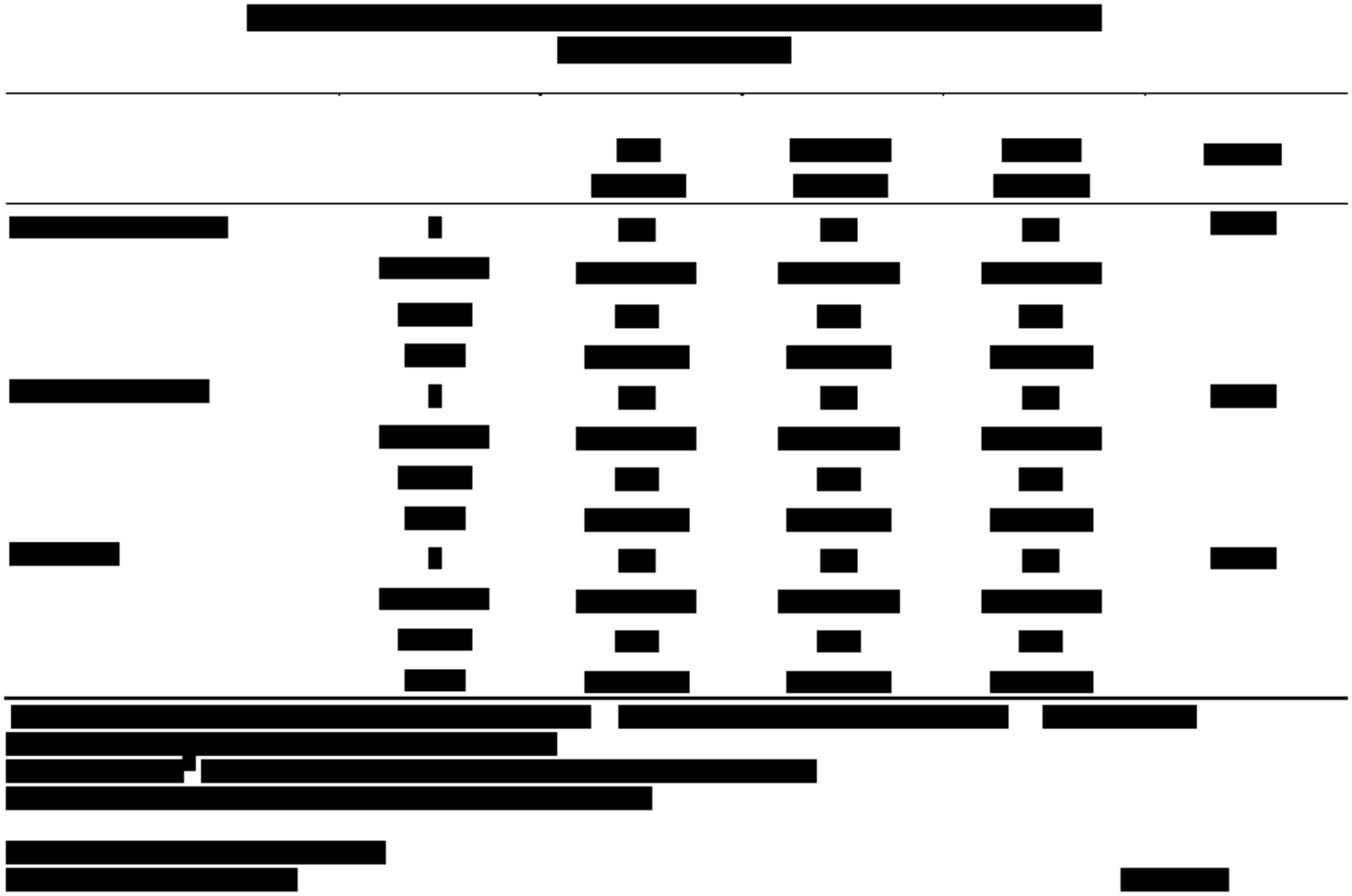

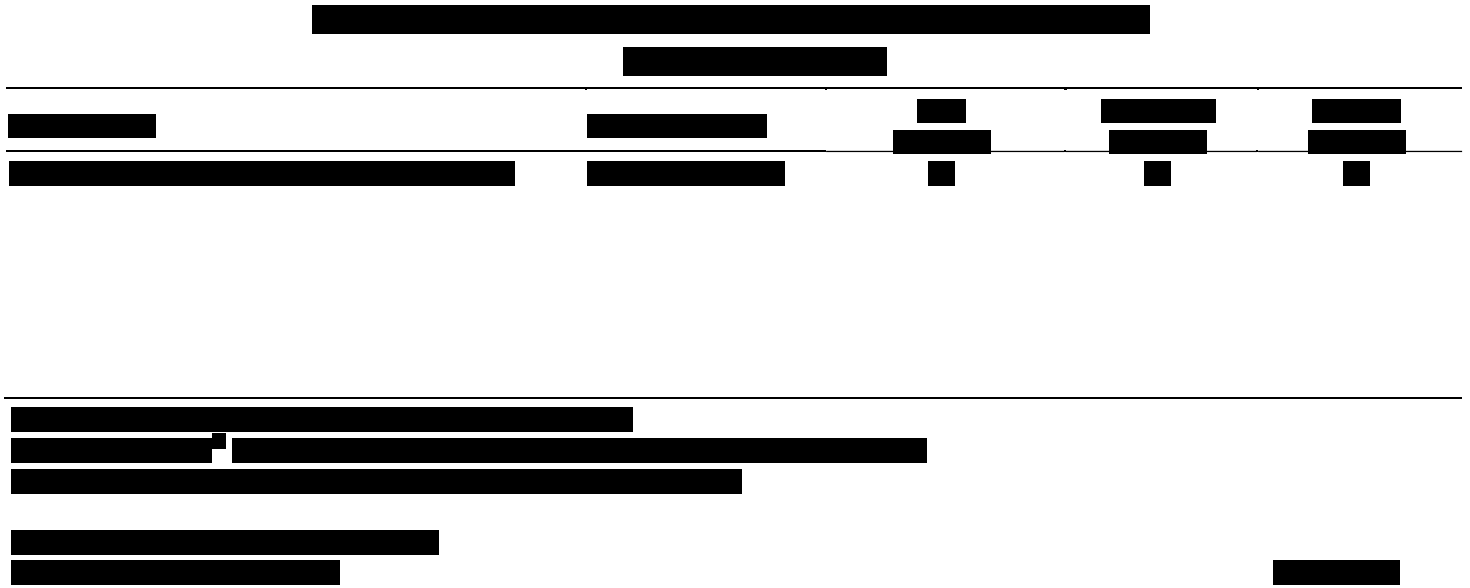

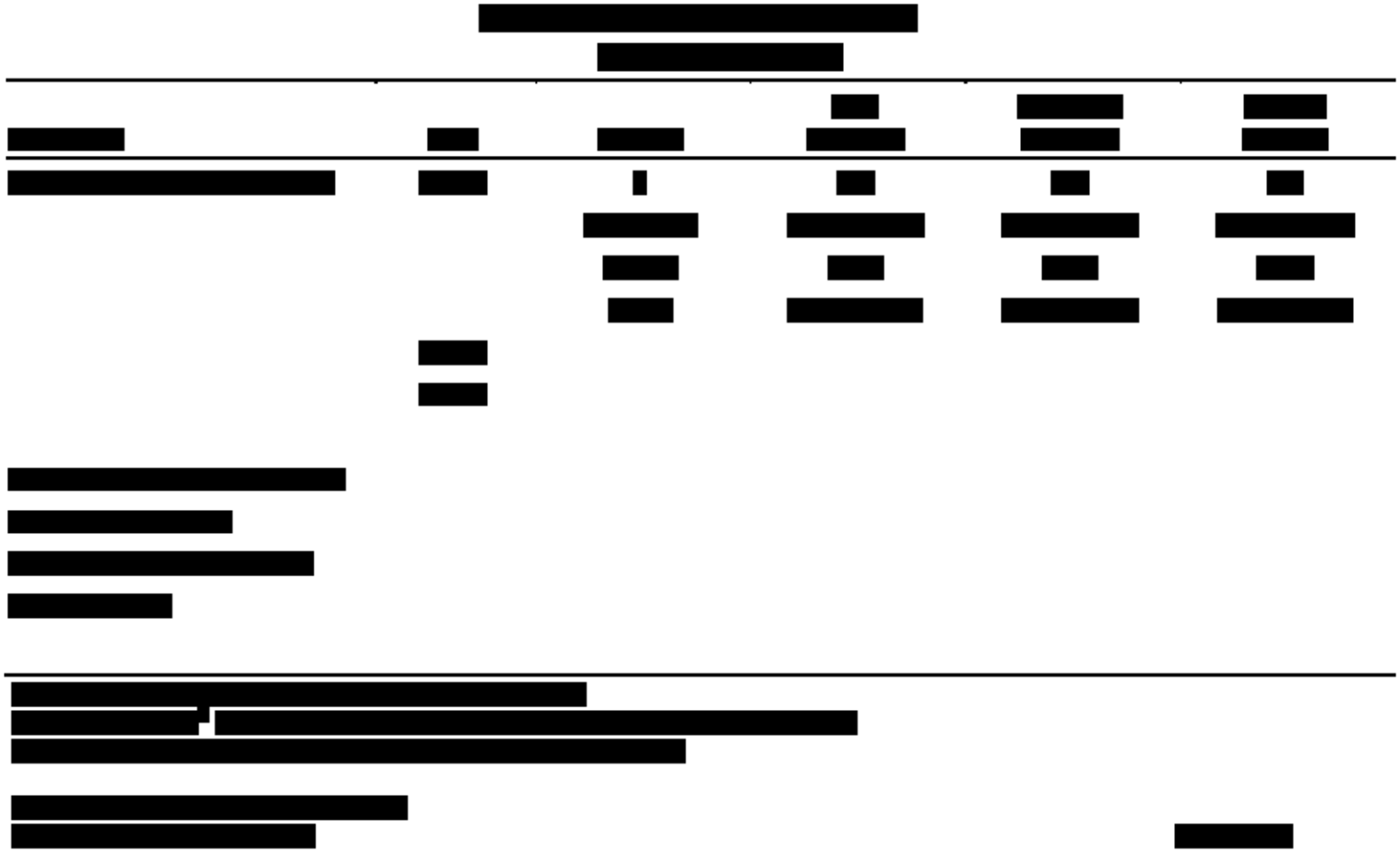

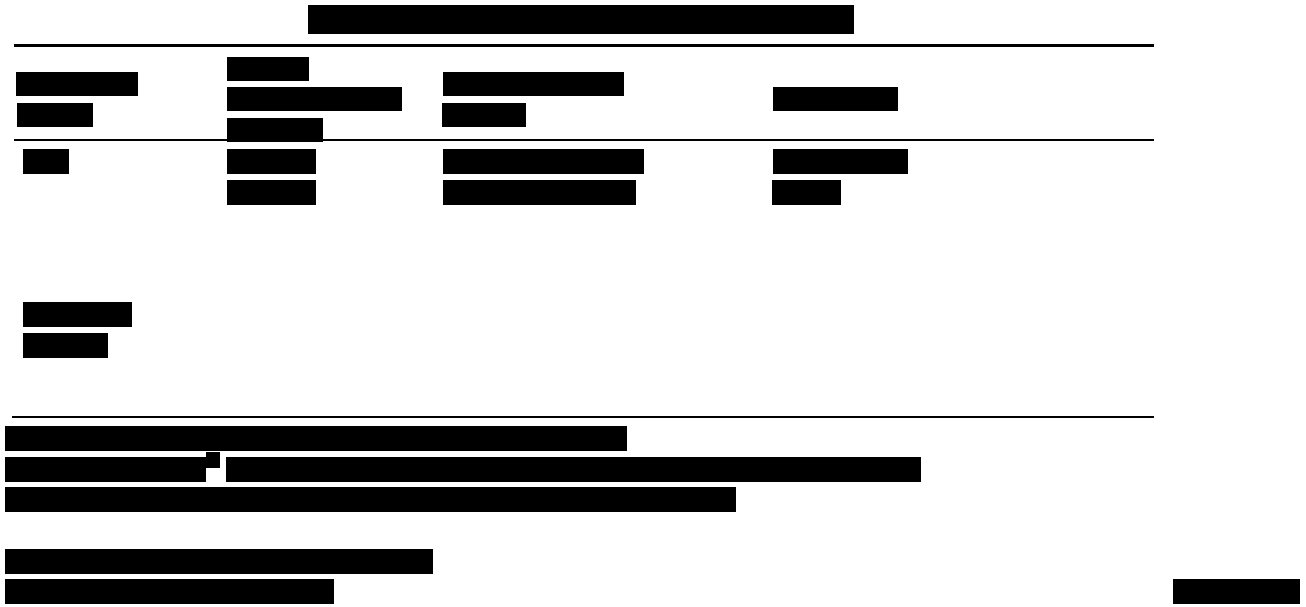

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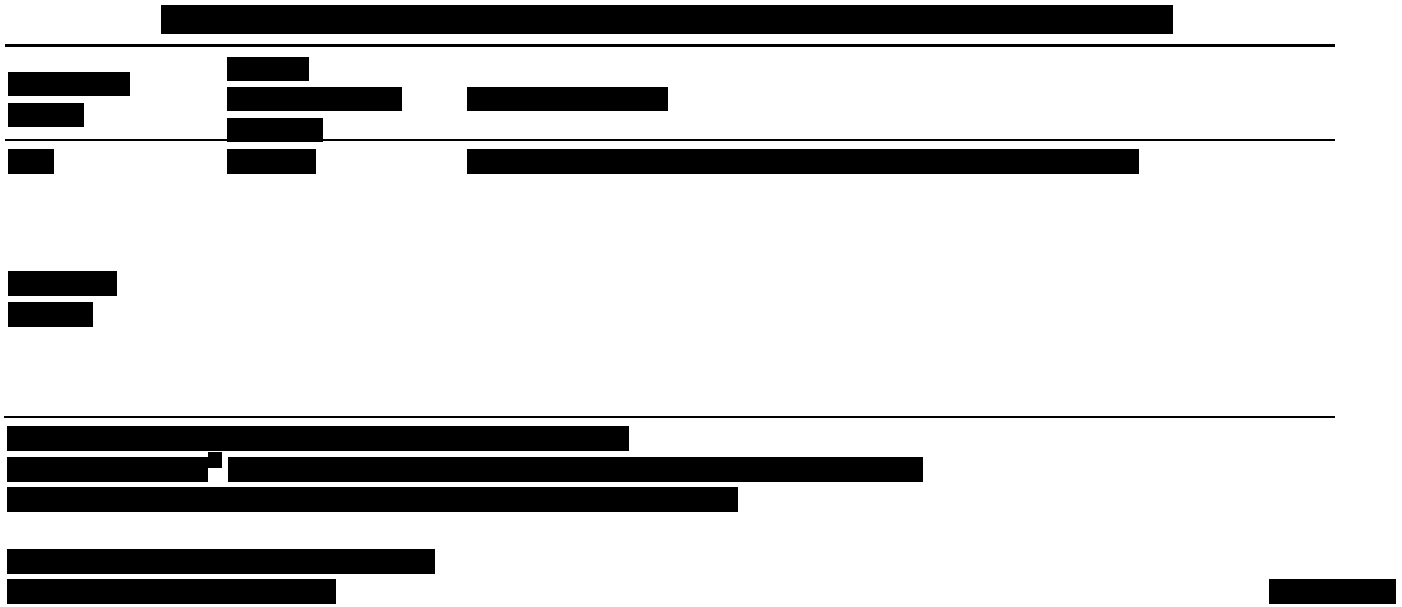

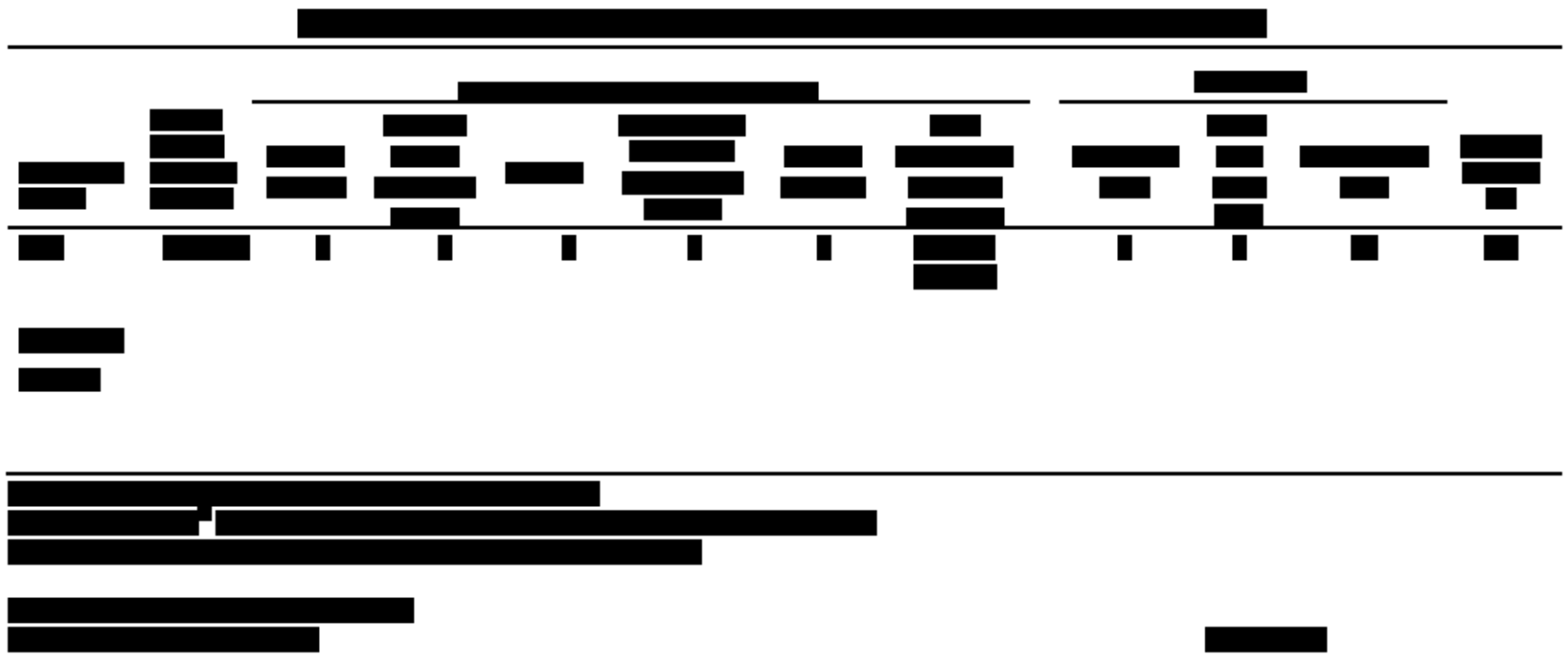

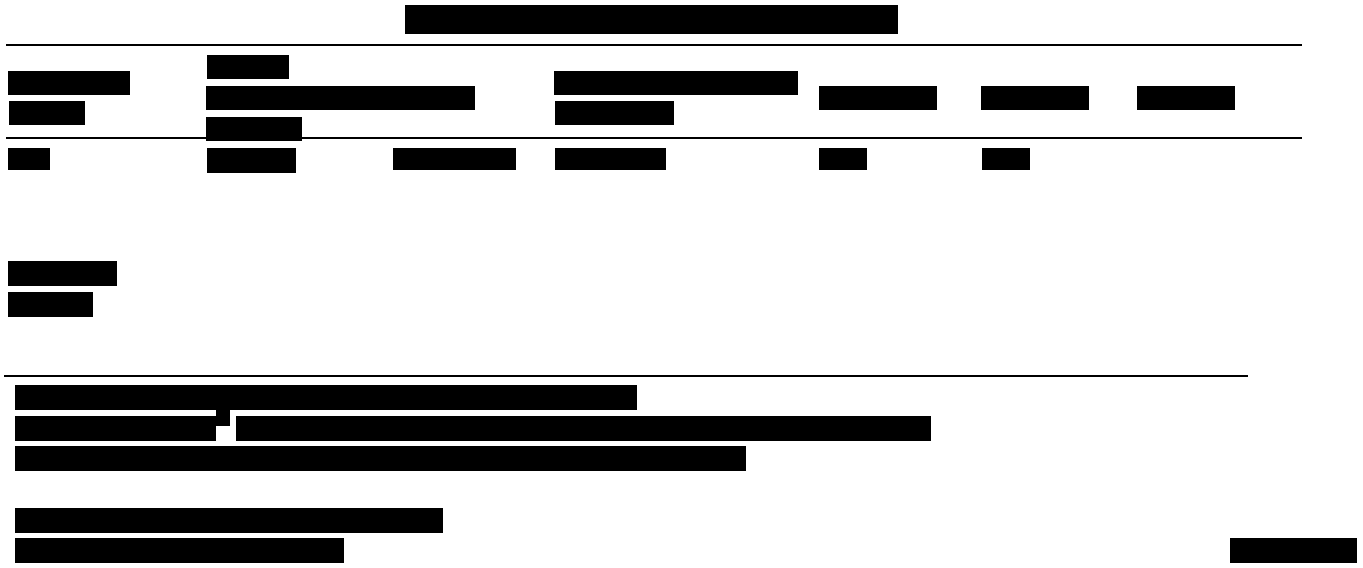

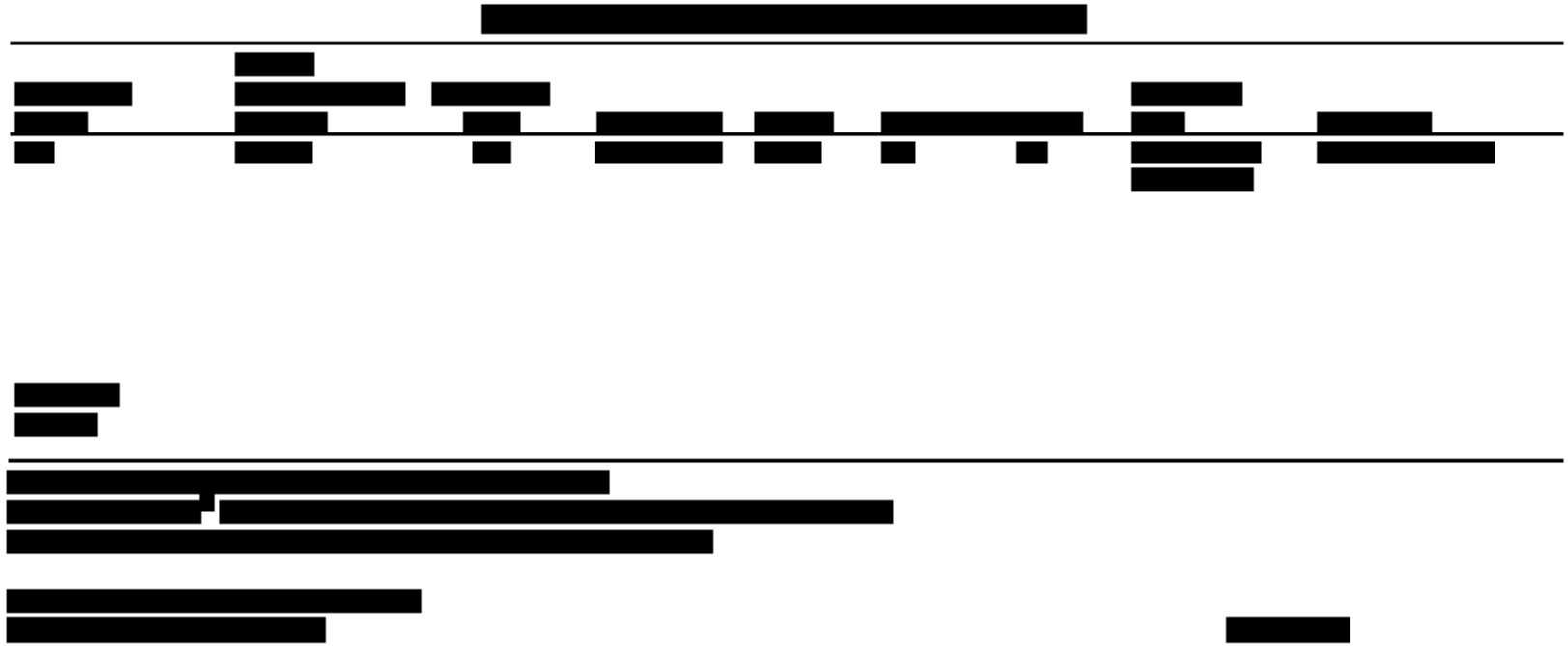

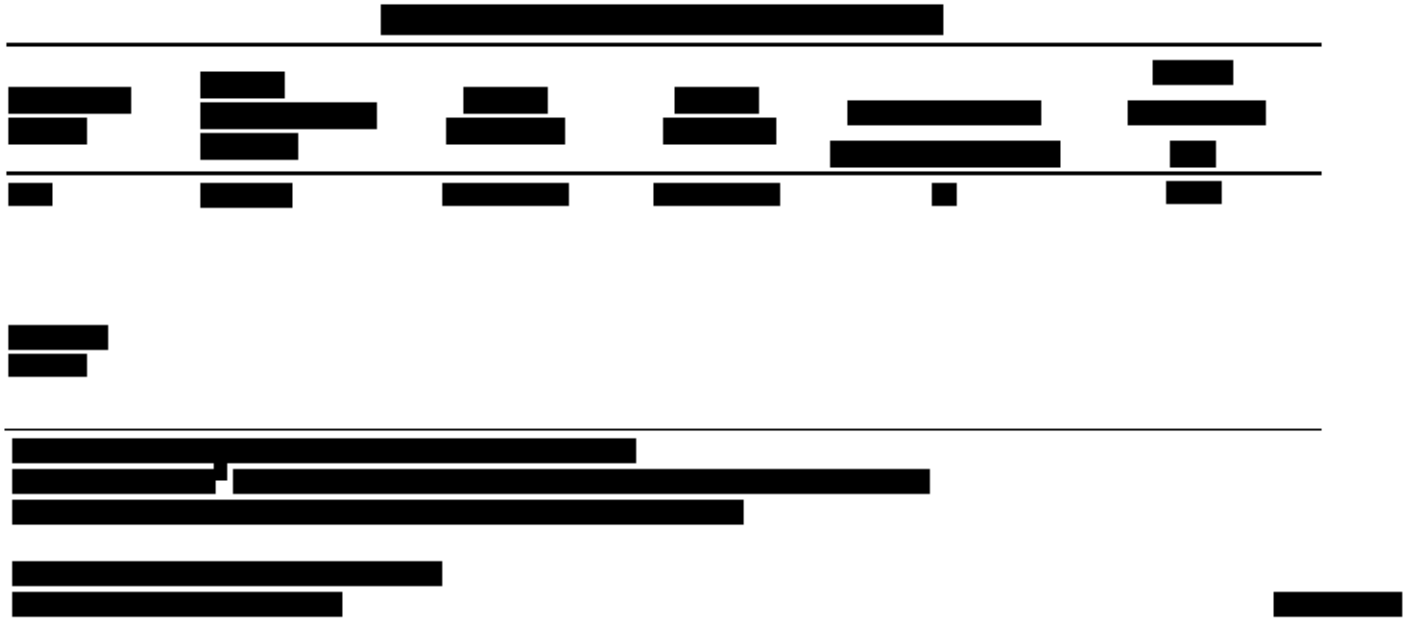

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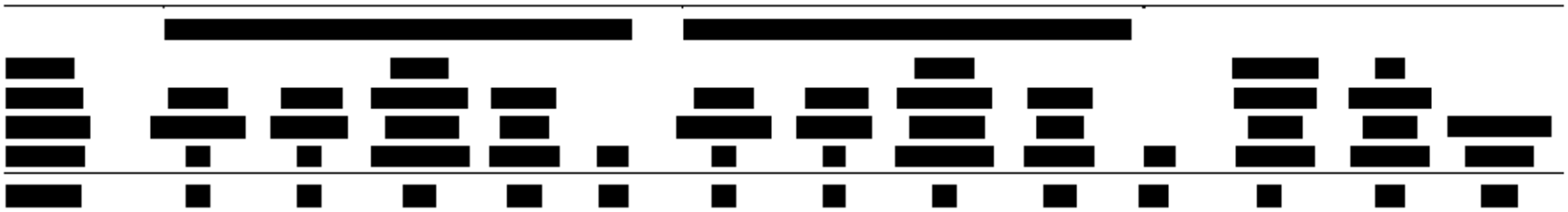

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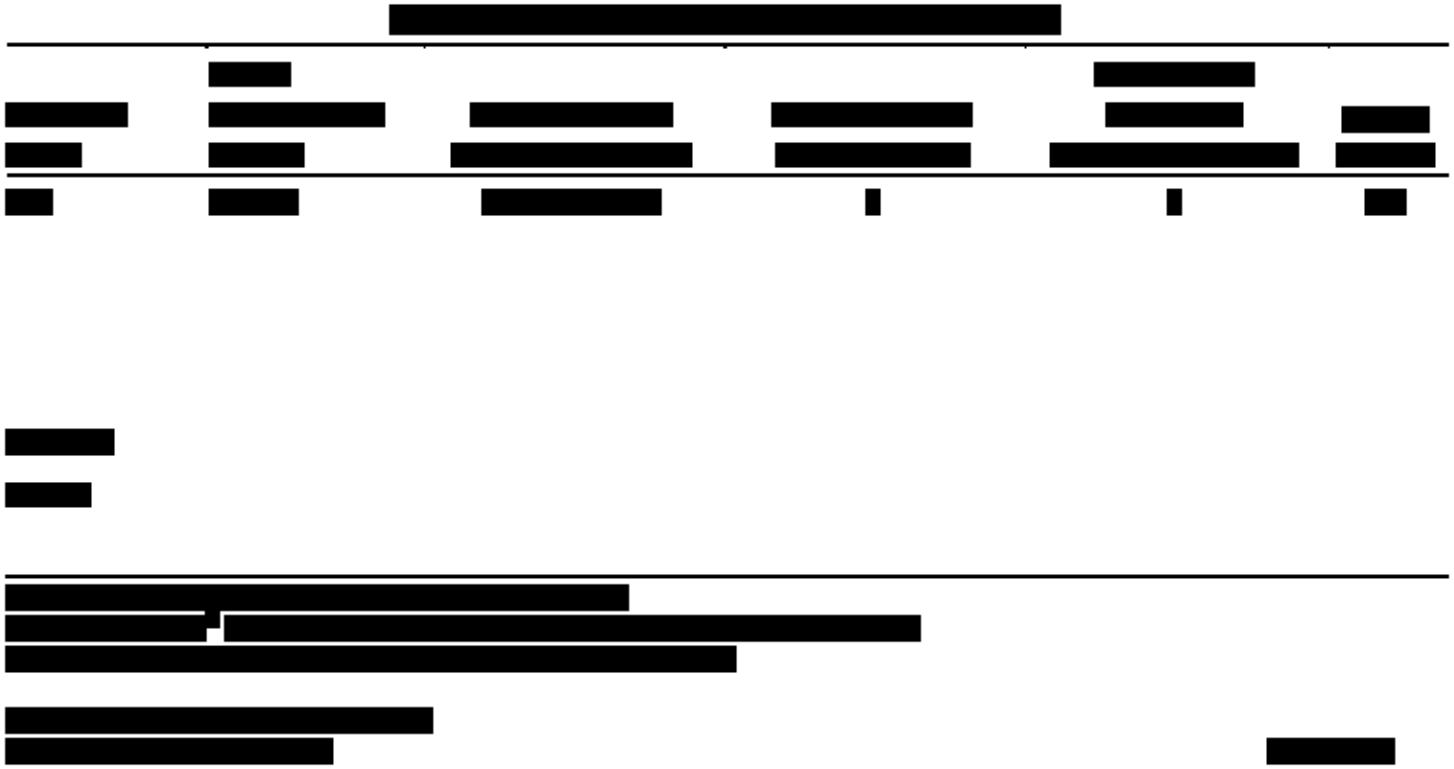

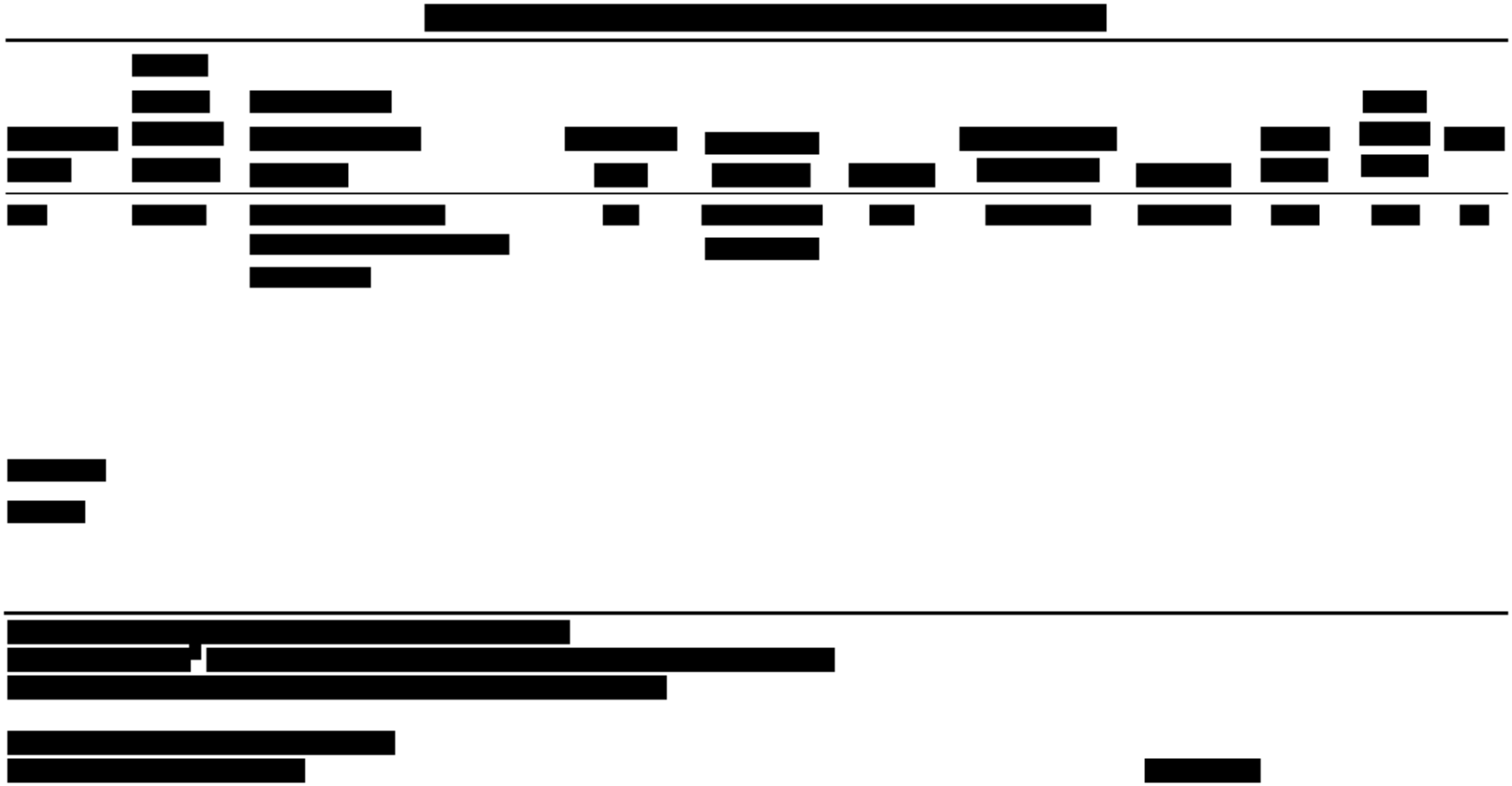

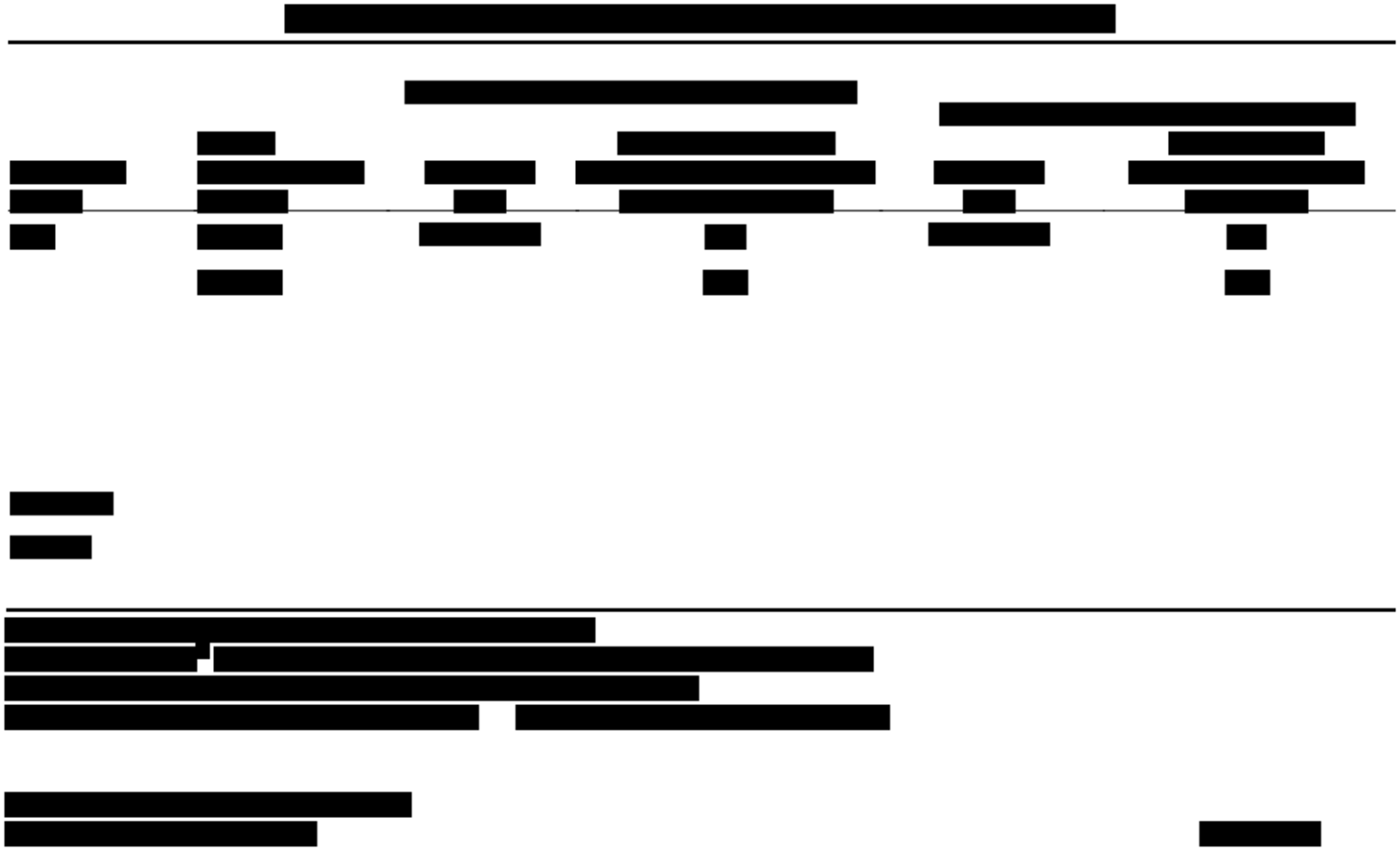

## 10. APPENDICIES

### Appendix A: Definitions and Severity Ratings For Signs and Symptoms

| **Vaginal Dryness** | | |
|---|---|---|
| No lubrication or secretions noted on perineum or after wiping; if sexually active loss of lubrication during coitus. | | |
| Score | Severity | Description |
| 0 | None | No noticeable lack of vaginal lubrication or secretions reported or observed |
| 1 | Mild | Episodic loss of lubrication/secretions or noticed some reduction in general secretions, does not interfere with daily activities |
| 2 | Moderate | Symptom present most of the time, and noticeable but overall is tolerable and does not interfere with daily activities |
| 3 | Severe | Very minimal or no natural vaginal lubrication/secretions almost all of the time and interferes with normal activities |

| **Vaginal/Vulvar Irritation/Itching** | | |
|---|---|---|
| Scratching or sand paper type feeling in vaginal/vulvar area. May feel uncomfortable with clothing or undergarments touching the perineum. | | |
| Score | Severity | Description |
| 0 | None | No irritation or itching reported. |
| 1 | Mild | Occasional irritation/itching but does not interfere with daily activities |
| 2 | Moderate | Frequent irritation/itching that can be uncomfortable but generally does not interfere with daily activities |
| 3 | Severe | Very frequent or continuous irritation/itching of the vaginal area, may interfere with daily activities. |

| **Dysuria** | | |
|---|---|---|
| Pain or discomfort during urination | | |
| Score | Severity | Description |
| 0 | None | No pain or discomfort during urination reported. |
| 1 | Mild | Occasional or slight discomfort during urination but tolerable |
| 2 | Moderate | Some discomfort during urination at least 50% of the time which can be painful but overall tolerable. |
| 3 | Severe | Urination nearly always painful, usually intolerable and causing disruption to daily activities |

| **Vaginal Pain during Sexual Activity** | | |
|---|---|---|
| Suffers discomfort or pain during sexual activity that may be restrictive. | | |
| Score | Severity | Description |
| 0 | None | No discomfort or pain |
| 1 | Mild | Some feeling of vaginal soreness or pain, during or after sexual activity. Does restrict frequency of or type of sexual activity. |
| 2 | Moderate | Vaginal pain during sexual activity such that frequency and type of sexual activity have been disrupted. Lubrication may be needed for penetration |
| 3 | Severe | Vaginal penetration very painful and impossible without vaginal lubrication. Discomfort such that frequency of sexual activity significantly reduced. |

| **Vaginal bleeding during or after sexual activity** | | |
|---|---|---|
| Score | Severity | Description |
| 0 | Absent | No vaginal bleeding observed |
| 1 | Present | Bleeding observed during or soon after vaginal activity |

At each visit each patient must also clearly identify which is the most bothersome sign/symptom to her, even if she rates two or more symptoms the same severity rating.