Title: A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

NCT Number: NCT03961308

SAP Approve Date: 05 July 2018

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: VedolizumabSC-1022
CCI STUDY NUMBER: CA23621

A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects

Vedolizumab SC PFS+AI Pharmacokinetic Study

PHASE 1

Version: Final

Date: 05 July 2018

Prepared by:
PPD

Based on:

Protocol Dated: 11 December 2017
Protocol Clarification Letter Dated: 14 February 2018
Protocol Clarification Letter Dated: 25 April 2018
Protocol Clarification Letter Dated: 24 May 2018

1.1 Approval Signatures

Study Title: A Phase 1, Open-Label, Randomized, Parallel Group Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Autoinjector in Healthy Subjects - Vedolizumab SC PFS+AI Pharmacokinetic Study

Approvals:

PPD

Date

Date

Date

Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the curve
AUC_{∞}	area under the serum concentration-time curve from time 0 to infinity
AUC_{last}	area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{Week2}	area under the serum concentration-time curve from time 0 to Week 2.
AVA	antivedolizumab antibodies
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed serum concentration
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
GCV	geometric coefficient of variation
Geo. Mean	geometric mean
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ln	natural log
LSM	least-square means
LTFU	long-term follow-up
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
PFS	prefilled syringe
PFS+AI	prefilled syringe in autoinjector
PI	Principal Investigator
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy

RAMP	Risk Assessment and Minimization for PML
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{½}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures and listings
t_{max}	time to first occurrence of C_{max}
VNS	Visual Numeric Scale
WHO	World Health Organisation

4.0 OBJECTIVES

4.1 Primary Objectives

- To compare the pharmacokinetics (PK) of single dose of vedolizumab subcutaneous (SC) 108 mg administered as prefilled syringe (PFS) versus prefilled syringe in autoinjector (PFS+AI).

4.2 Secondary Objectives

Not applicable.

4.3 Additional Objectives

- To evaluate the safety and tolerability of single dose of vedolizumab SC 108 mg administered as PFS and PFS+AI.
- To evaluate the development of antivedolizumab antibodies (AVA) and neutralizing AVA following single dose of vedolizumab SC 108 mg administered as PFS and PFS+AI.
- To evaluate the PK of single dose of vedolizumab SC 108 mg administered at 3 different injection sites (arm, abdomen, and thigh).

4.4 Study Design

This is an open-label, randomized, parallel-group study to compare the PK of a single dose of vedolizumab SC 108 mg for injection administered in 2 different device delivery presentations (2 treatments) in healthy subjects. A minimum 204 subjects (102 per group) will be randomized to 1 of 2 device presentations (Group A or B).

A summary of the treatment groups is presented in Table 4.a.

Table 4.a Summary of Treatment Groups

Group	Approximate Number of Subjects	Treatment (a)
A	102	Single dose of vedolizumab SC 108 mg delivered by PFS (reference)
B	102	Single dose of vedolizumab SC 108 mg delivered by PFS+AI (test)

(a) Subjects randomized to each device (1:1 ratio) were also randomized for the injection site (abdomen, thigh, or arm) (1:1:1 ratio). Thus, within each treatment group, there are 3 injection sites (abdomen, thigh, or arm) randomly assigned, for a total of 6 treatment combinations.

For the initial randomization 102 subjects were randomized to each Group in a 1:1 ratio using 51 blocks of 2. Within each Group subjects were randomized to injection site in a 1:1:1 ratio using 17 blocks of 3. No stratification factors were used in the randomization. However, at least 40% of each sex will be enrolled. When the study was increased to 204 subjects (see Section 6 below) this randomization process was repeated for an additional 102 subjects using 51 blocks of 2. The additional subjects within each Group were randomized to injection site in a 1:1:1 ratio as

described above. Subjects will be screened up to 28 days prior to dosing, to determine eligibility before randomization. Eligible subjects will return to the clinic at Check-in (Day -1). On Day 1, all doses will be administered by a health care professional. A schematic of the study design is included as Figure 4.a.

Figure 4.a Schematic of Study Design

<table>
<tr><th colspan="2">Screening</th><th>Treatment</th><th colspan="5">Follow-up</th></tr>
<tr><td rowspan="2">Days
-28 to -2</td><td rowspan="2">Day -1
(Check-in)</td><td>Day 1</td><td>Day 2</td><td>Days 3-8</td><td>Days 10, 15, 29, 43, 64, 85, 106</td><td>Final Visit/ Early Termination Day 127 (a)</td><td>Day 168 Follow-up Phone Call (b)</td></tr>
<tr><td>Dosing, PK, and safety</td><td colspan="4">PK and safety assessments</td><td></td></tr>
<tr><td></td><td colspan="2">←----------Confinement ----------→</td><td colspan="4"></td></tr>
</table>

(a) In the case that abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the clinic for re-evaluation per investigator's discretion.
(b) Subjects will be followed poststudy by telephone to administer a questionnaire, which will include progressive multifocal leukoencephalopathy (PML) questions at Day 168 (±3 days).

Subjects for all treatment groups will be kept in the study unit from Day -1 Check-in until at least 24 hours after dosing (Day 2) for safety and PK assessments before discharge. The minimum confinement will be 2 nights (Days -1 to 2, inclusively). Subjects can stay longer at the discretion of the investigator. Subjects will return to the study unit periodically according to the schedule for PK sampling and safety assessments. Subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone on Day 168; data from Day 168 are not recorded in the case report form (CRF) and will be presented in a separate report.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following serum PK parameters will be analyzed for each treatment (PFS and PFS+AI) following a single dose of vedolizumab SC:

- Maximum observed serum concentration (C_{max}).
- Area under the serum concentration-time curve (AUC) from time 0 to time of the last quantifiable concentration (AUC_{last}).
- AUC from time 0 to infinity (AUC_{∞}).

5.2 Additional Endpoints

5.2.1 Safety Endpoints

The following safety variables will be used to characterize the safety and tolerability of vedolizumab SC:

- Physical examination findings, treatment-emergent adverse events (TEAEs), clinical laboratory test results, vital sign measurements, and 12-lead electrocardiograms (ECGs).
- Percentage of subjects who are positive for AVA during the study.
- Percentage of subjects who have positive neutralizing AVA during the study.

5.2.2 PK Endpoints

- Percent of AUC_{∞} extrapolated ($AUC\%_{extrap}$).
- Terminal disposition phase half-life ($t_{½}$).
- Time to first occurrence of C_{max} (t_{max}).
- Apparent clearance after extravascular administration (CL/F).
- Apparent volume of distribution during the apparent terminal phase after extravascular administration (V_z/F).
- Apparent terminal elimination rate constant (Lambda_z).

6.0 DETERMINATION OF SAMPLE SIZE

Based on the results of the pilot study VedolizumabSC-1021, a sample size of 102 subjects per group for a total of 204 subjects was computed. Assuming a true test/reference ratio of approximately (~)119% with an intersubject CV of ~20%, a sample size of 102 (93 + 9 extra for dropouts) subjects per group would provide ~51.7% power for determining that the 90% CIs for the ratios of geometric LSMs for AUC_{last}, AUC_{∞} (if data permits) and Cmax between the 2 different device delivery presentations are between 80.00 – 125.00%. A ~8.8% dropout rate was assumed for the sample size calculation. This sample size is updated from the Final Protocol (11DEC2017) in a protocol clarification letter (PCL; 25APR2018).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All PK analyses will be conducted using Phoenix® WinNonlin® Version 7.0, or higher. All statistical analyses will be conducted using SAS® Version 9.3, or higher.

Arithmetic mean (mean), median, and geometric mean (Geo. Mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values.

Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (GCV%) will be presented to 1 decimal place.

Geometric least-squares means (LSMs) will be presented with 1 more level of precision than the recorded data. Geometric LSMs are least-squares means derived from analysis of covariance model with weight as a covariate, and then exponentiated to provide estimates on the original scale. Ratios of geometric LSMs (presented as a %) and 90% confidence intervals (CIs) about a parameter estimate will be reported as 2-sided and presented using 2 decimal places.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group, site of injection, and overall, where applicable. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

Concentration values below the limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are obvious outliers (e.g. BLQ value between 2 measurable values), in which case they will be treated as missing.

For the calculation of PK parameters, if actual times are missing, nominal times will be used instead.

A subject's PK parameter data will be included in the listings but excluded from the descriptive statistics and statistical evaluation if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that subject's C_{max} value in that period (e.g. single dose BE studies).
- A subject did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and CCI Pharmacokinetic Scientist).
- A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and CCI Pharmacokinetic Scientist).

See Clinical Pharmacology Analysis Plan (CPAP) for details on the PK parameter calculations and data presentation including specifics on the following:

- Insufficient data to determine a reliable $t_{½}$ value and other terminal elimination rate constant dependent parameters.
- PK parameters presented by treatment and by injection site within each treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables.

- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables.
- Concentration data file used for PK analysis.
- PK parameter WinNonlin® output file used to generate the tables, figures, and listings (TFLs).
- Analysis of covariance (ANCOVA) results including all subjects and excluding AVA-positive subjects (sensitivity analysis) presented in in-text and end-of-text tables.
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures.
- Individual concentration-time figures presented in Appendix 16.2.6.
- AUC and C_{max} scatter plots presented by treatment and by injection site within each treatment as in-text and end-of-text figures.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to Day 1 with Day -1 being the day prior to Day 1. Study day prior to the first dose of treatment will be calculated as: date of assessment/event-date of treatment; study day on or after the date of first dose will be calculated as: date of assessment/event-date of treatment +1.

7.2 Analysis Sets

Safety Set:

The Safety Set will consist of all subjects who are enrolled and received 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

PK Set:

The PK Set will consist of all subjects who receive study drug and have at least 1 measurable serum concentration.

7.3 Disposition of Subjects

Disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized for each treatment and overall. Study completion status, including reason for discontinuation, will also be listed by subject. A separate listing will be generated for screen failures.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall. Summary statistics (number of subjects [n], mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [calculated from the date of signed Informed Consent Form [ICF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). For height the screening measurement will be reported but for weight and BMI the check-in value will be reported. The demographics listing will also include the date each signed the ICF. A separate listing will be generated for screen failures.

7.5 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing the ICF. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug will be classified as an adverse event. The medical history listing will include whether the event was medical or surgical, the body system or organ class involved, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

7.6 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 14 days prior to signing the ICF. Concomitant medications are recorded on the CRF and include any medication other than study drug taken at any time between time of signing the ICF through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Dictionary Version 01-Sep-2017 and listed. The listing will include the medication name, dosage, route of administration, start date and time (if known), end date and time, or whether it continued after study completion, and indication for use.

7.7 Study Drug Exposure and Compliance

Not applicable.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Blood samples (one 5 mL sample per scheduled time) for PK analysis of vedolizumab will be collected as specified in Table 7.a even if the vedolizumab SC is discontinued before the complete dose is administered to the subject.

Table 7.a Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Vedolizumab	Serum	1	Within 0.5 hours before the SC injection (predose), 2, 8, 24, 72, 120, and 168 hours after Day 1 dosing, and on Days 10 (Hour 216), 15 (Hour 336), 29 (Hour 672), 43 (Hour 1008), 64 (Hour 1512), 85 (Hour 2016), 106 (Hour 2520), and Final Visit Day 127 (Hour 3024)/Early Termination (a)

(a) If a subject experiences a serious adverse event (SAE), a blood sample for PK analysis should also be obtained at the unscheduled visit. PK samples will be collected at Early Termination at the discretion of the investigator.

The actual date and time of sample collection will be recorded on the source document and electronic case report form (eCRF).

Samples collected outside 10% of the nominal time will not be considered a protocol deviation as long as the exact date and time of PK sampling is recorded in the eCRF.

The PK parameters of vedolizumab listed in the CPAP for this study will be determined from the concentration-time profiles for all evaluable subjects using a noncompartmental analysis method. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If actual sample times are missing, nominal times may be used.

Concentrations will be listed and summarized descriptively by PK sampling time. Summary will be done by treatment using the summary statistics listed in the CPAP. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive summary. Individual subject and arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear and semi-log scales. For summary statistics and arithmetic mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

PK parameters will be summarized descriptively by treatment and by injection site within each treatment using the summary statistics listed in the CPAP. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the descriptive summary. Scatter plots of the individual AUC_{last}, AUC_{∞}, and C_{max} values, including the median values, will be plotted by treatment and by injection site within treatment.

Natural log (ln)-transformed AUC_{last}, AUC_{∞} (if data permits), and C_{max} will be analyzed using an ANCOVA model. Because treatments were administered in multiple groups the statistical model will include Group, Treatment, and injection site (Inj_Site) as fixed-effects and weight as a continuous covariate. The following SAS® code will be used for the analysis:

```
PROC MIXED DATA=XXXX;
CLASS Group Treatment Inj_Site;
MODEL <PK_Parameter> = Group Treatment Inj_Site Weight;
```

ESTIMATE 'Treatment PFS+AI vs PFS' Treatment -1 1 / CL ALPHA = 0.10 E;
LSMEANS Treatment*Inj_Site;
Run;

Estimates of the covariate adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Single doses of 108 mg of vedolizumab SC administered as PFS+AI (test treatment) will be compared versus PFS (reference treatment). Comparability between the test and reference treatments will be concluded if the 90% CIs for AUC_{last}, AUC_{∞} (if data permits), and C_{max} are contained within the range of 0.8 and 1.25.

In addition to the analysis described above using all subjects, a sensitivity analysis will be performed excluding subjects that are AVA-positive.

If the two devices are not found to be bioequivalent, additional analysis including a Group x Treatment interaction term may be performed if deemed necessary.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, changes from baseline in the subjects' clinical laboratory results, vital signs, and ECG's using the safety set. Reasons for discontinuation will be tabulated. Exposure to study drug will be presented in by-subject listings. All clinical safety data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.11.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (mild, moderate or severe), relationship to vedolizumab SC and to study procedures (related or unrelated) and action relative to the study drug. All AEs occurring during this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 20.1. However, only TEAEs occurring after administration of the first dose of study drug and through the end of the study (127 days after the last dose of study drug) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. If an AE increases in severity, that AE will be given a resolution date and time, and a new AE will be entered with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution.

For each treatment, TEAEs will be coded using MedDRA® Version 20.1 and tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of safety set by treatment. The most commonly reported TEAEs (i.e., those events reported by >5% of all subjects) will also be summarized.

In addition, TEAEs will be summarized as number of AEs and percentage of AEs for each treatment. Additional summary tables will be presented by severity and relationship to vedolizumab SC and relationship to study procedure. If a subject has multiple AEs with different severity levels within the same term, the subject will be counted in the most severe category only. If a subject has both related and unrelated AEs with the same term, the subject will be counted as having related TEAEs.

Adverse events of special interest (AESI) will be summarized by treatment and injection site using AESI definitions presented in Table 7:2.

Table 7.b Adverse Events of Special Interest

Adverse Event	MedDRA Terms or definitions
Hypersensitivity Reactions	Anaphylactic/anaphylactoid shock conditions SMQ (broad).
	Angioedema SMQ (broad).
	Hypersensitivity SMQ (broad).
PML	Human polyomavirus infection PT.
	JC virus infection PT.
	JC virus test positive PT.
	Leukoencephalopathy PT.
	Polyomavirus test positive PT.
	Progressive multifocal leukoencephalopathy PT.
Liver injury	Cholestasis and jaundice of hepatic origin SMQ (Broad)
	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (Broad)
	Hepatitis, non-infectious SMQ (Broad)
	Liver related investigations, signs and symptoms SMQ (Narrow)
	Liver infections SMQ (Broad)

Should any SAEs occur they will be summarized the same way as TEAE. In addition, all SAEs, AEs leading to discontinuation, and AEs resulting in death that may occur during this study will be listed by subject. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the study report.

7.11.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) and Days 8, 29, 85 and 127 postdose. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI).

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by treatment and assessment time points. Change from baseline will be summarized using last assessment including rechecks taken prior to dosing as the baseline value.

For each laboratory test, a shift table will be developed comparing the frequency of the results at treatment baseline (above normal (H), normal (N), or below normal (L)) with those postdose time points for each regimen. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a clinically significant (CS) range. If the value falls within the CS range, it will be noted as “N” for not clinical significant. If the value fails the CS range, it will be flagged with a “Y” which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. All clinically significant lab tests and the corresponding values will be listed by subject. All clinical laboratory data will be presented in by-subject data listings.

7.11.3 Vital Signs

Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at screening, check-in (Day -1), Day 1 (predose, postdose), Days 8, 106, and Final Visit Day 127/Early Termination. For Day 1, heart rate and blood pressure will be measured after 5 minutes in the supine position and at 1 and 3 minutes after standing. For Days 8, 106, and 127/Early Termination, heart rate and blood pressure will be measured after 5 minutes supine only.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital sign results and change from baseline by treatment and time point. Baseline is defined as the last assessment including rechecks taken prior to dosing. Vital signs will also be displayed in a data listing by subject.

7.11.4 12-Lead ECGs

Standard 12-lead ECGs will be recorded at screening, check-in (Day -1), Day 1 (predose; within 0.5 hours before dosing the SC injection), and Final Visit Day 127/Early Termination. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from baseline by treatment and time point. Baseline is defined as the last assessment including rechecks taken prior to dosing. ECG data will also be displayed in a data listing by subject.

7.11.5 Other Observations Related to Safety

7.11.5.1 Standardize immunogenicity analysis for AVA data

Definitions of AVA negative, positive and positive neutralizing:

- AVA Negative: defined as a sample that was evaluated as negative in the AVA screening assay. Samples that were determined to be positive in the AVA screening assay but the result was not confirmed in the AVA confirmatory assay were considered negative.
- AVA Positive: defined as a sample that was evaluated as positive in both the AVA screening and confirmatory assays.
- Neutralizing AVA Positive: defined as a sample that was evaluated as positive in the neutralizing AVA assay.

Subject AVA status will be grouped into 3 categories as follows:

- Negative: defined as subjects who did not have confirmed AVA results
- Positive: defined as patient who had at least 1 positive AVA result
  - Transiently positive: defined as subjects with confirmed positive AVA in 1 sample.
  - Persistently positive: defined as subjects with confirmed positive AVA in 2 or more consecutive positive AVA samples.

Subject AVA positive at baseline is defined as a positive AVA sample at Day 1 (predose).

The proportion and percentage of subjects that are AVA negative, AVA positive, and neutralizing AVA positive will be presented for each visit by treatment (all injection sites combined = overall), by each injection site separately within each treatment, and in total for both treatments combined. The proportion and percentage of subjects that are AVA positive will be presented for each titer for each visit by treatment (all injection sites combined = overall), by each injection site separately within each treatment, and in total for both treatments combined. The frequency and percentage of subjects that are AVA negative, AVA positive, transiently AVA positive, persistently AVA positive, and neutralizing AVA positive will be presented for each visit by treatment (all injection sites combined = overall), by each injection site separately within each treatment, and in total for both treatments combined.

7.11.5.2 Progressive Multifocal Leukoencephalopathy Checklist

The PML subjective checklist will be administered at Screening Visit, on Day 1 before dose, Day 127/Early Termination Visit, and at any unscheduled visits. Any subjects reporting signs and/or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation, as described in the Risk Assessment and Minimization for PML (RAMP) algorithm. PML checklist responses and algorithm results will be displayed in a data listing by subject.

7.11.5.3 Visual Numerical Scale

The Visual Numeric Scale (VNS) for self-reported pain assessment at the injection site will be completed by each subject on Day 1 immediately following the SC injection and a second assessment will be performed between 15 and 30 minutes following the injection. Subjects will be presented with the pain scale and instructed to assess their pain on a scale of 0 to 10, with 0=no pain and 10=severe pain. Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for pain scale assessments. Pain scale assessment responses will be displayed in a data listing by subject.

7.11.5.4 Subject Self-Reporting

Subjects will self-report any pain, pruritus, erythema, swelling, hematoma, discoloration, warmth, or bruising at the injection site of study drug. In addition, the location of the reaction (arm, abdomen, thigh), laterality (right or left) and maximum diameter of the reaction will be recorded. Injection site reactions will be graded on a 1 to 4 scale. If there are any hypersensitivity reactions, a hypersensitivity reaction assessment will be completed. Injection site reaction and hypersensitivity reaction (if any) results will be displayed in a data listing.

7.12 Interim Analysis

No interim analysis was performed.

7.13 Preliminary Analysis

Analysis will be completed as described in the CPAP and Section 7.9.1, with the following changes: 1) QCed data will be used (not QAed); 2) nominal times will be used for the calculation of PK parameters (not actual sampling times); 3) tables and figures will be created using Phoenix® WinNonlin® Version 7.0, or higher (not SAS® Version 9.3 or higher) and; 4) a sensitivity analysis will not be provided at this preliminary stage.

7.14 Changes in the Statistical Analysis Plan

The protocol specified median profiles of the concentration-time data will be plotted by treatment; however, arithmetic mean profiles will be generated instead.

The protocol stated that single doses of 108 mg of vedolizumab SC administered as PFS will be compared versus PFS+AI, however single doses of 108 mg of vedolizumab SC administered as PFS+AI (test treatment) will be compared versus PFS (reference treatment) instead.

A sensitivity analysis using the same model as described in Section 7.9.1 will also be performed excluding subjects that are AVA-positive.

The protocol states that values of subjects with markedly abnormal values for laboratory tests, vital signs and ECG results will be tabulated and mapped. However, after discussions between CCI and Takeda, it was decided that these would not be presented.

In addition to the 2 additional PK endpoints described in the protocol (t½ and t_{max}), $AUC\%_{extrap}$, CL/F, V_z/F and Lambda_z were also included as additional endpoints.

In the Final Protocol (11DEC2017), the determination of the sample size was expected to provide 90% probability (power) that ratios of central values for AUC or Cmax between the 2 treatment device presentations would meet the BE criteria of 80.00-125.00% and a drop-out rate of 18% was assumed. Based on the preliminary results from the pilot study VedolizumabSC1021, a PCL (25APR2018) revised the sample size calculation to meet the BE criteria of 80.00-125.00% with an expected power of ~51.7% and a ~8.8% drop-out rate was assumed. Details are provided in Section 6.0.

In the Final Protocol the statistical analysis did not include Clinic or Group fixed-effects or interaction terms. However, in order to recruit sufficient subjects to meet the increased sample size an additional clinic had to be added and the subjects were dosed in multiple groups. To account for any potential added variation of an additional clinic and a group effect, and to determine whether a Clinic x Treatment or Group x Treatment effect was present in the study, Clinic and Group main effects and interaction effects with Treatment were included in the model.

8.0 REFERENCES

Not applicable.

9.0 SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the International Conference on Harmonisation (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the clinical study report (CSR). Please note that PK and safety summary tables and figures will be generated using SAS® Version 9.3 or higher.

The following are lists of TFL numbers and titles that will be included within the CSR.

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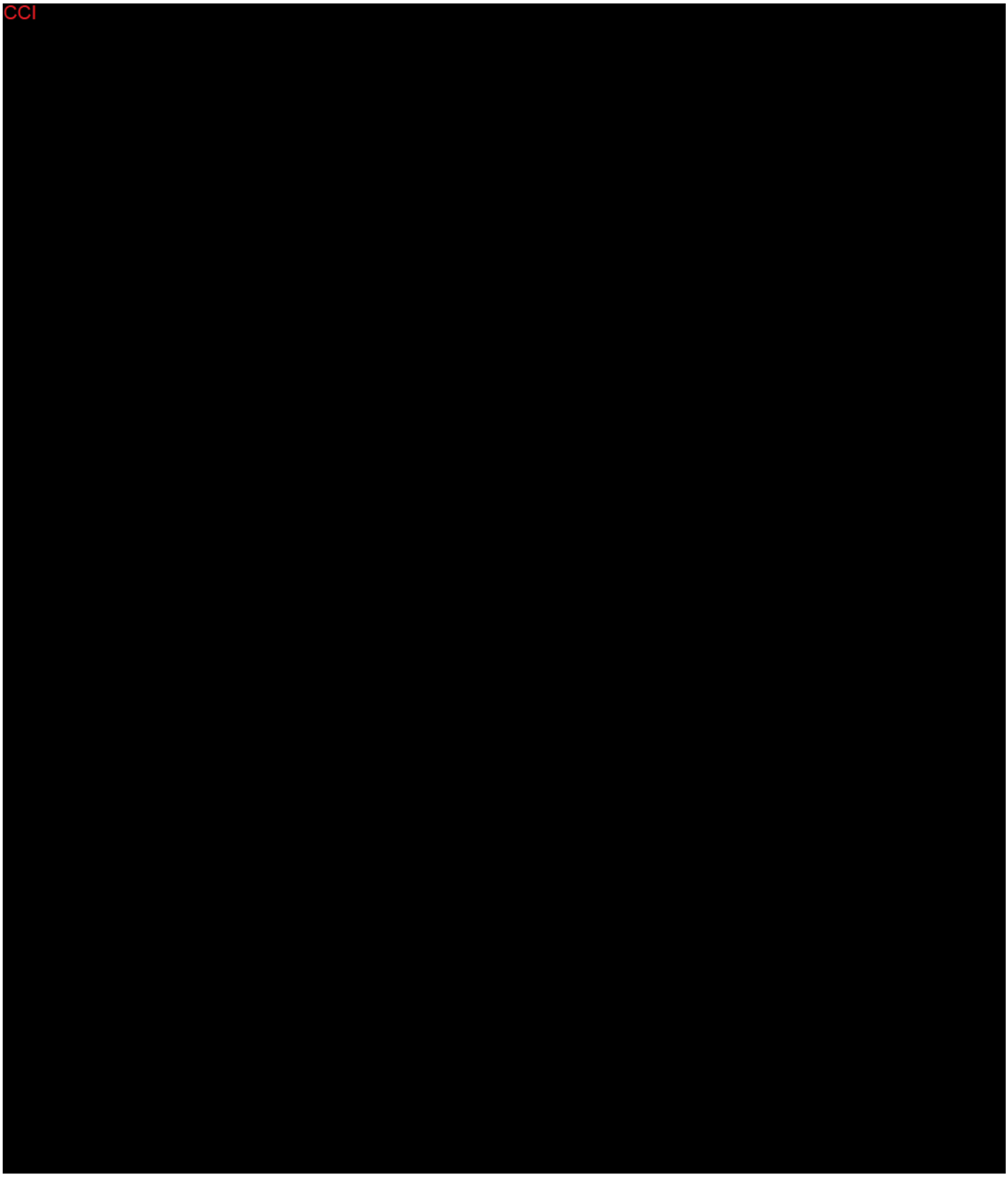

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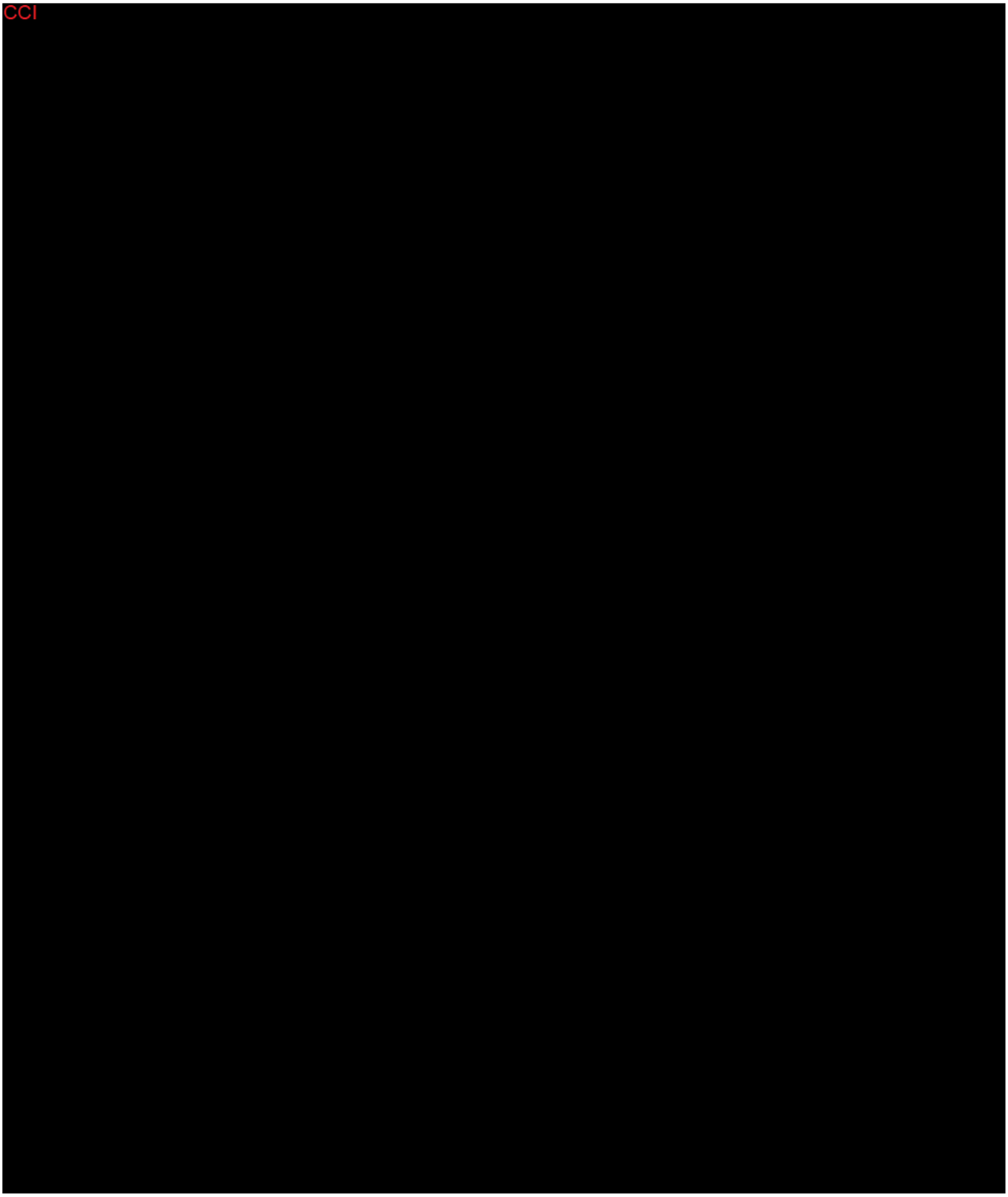

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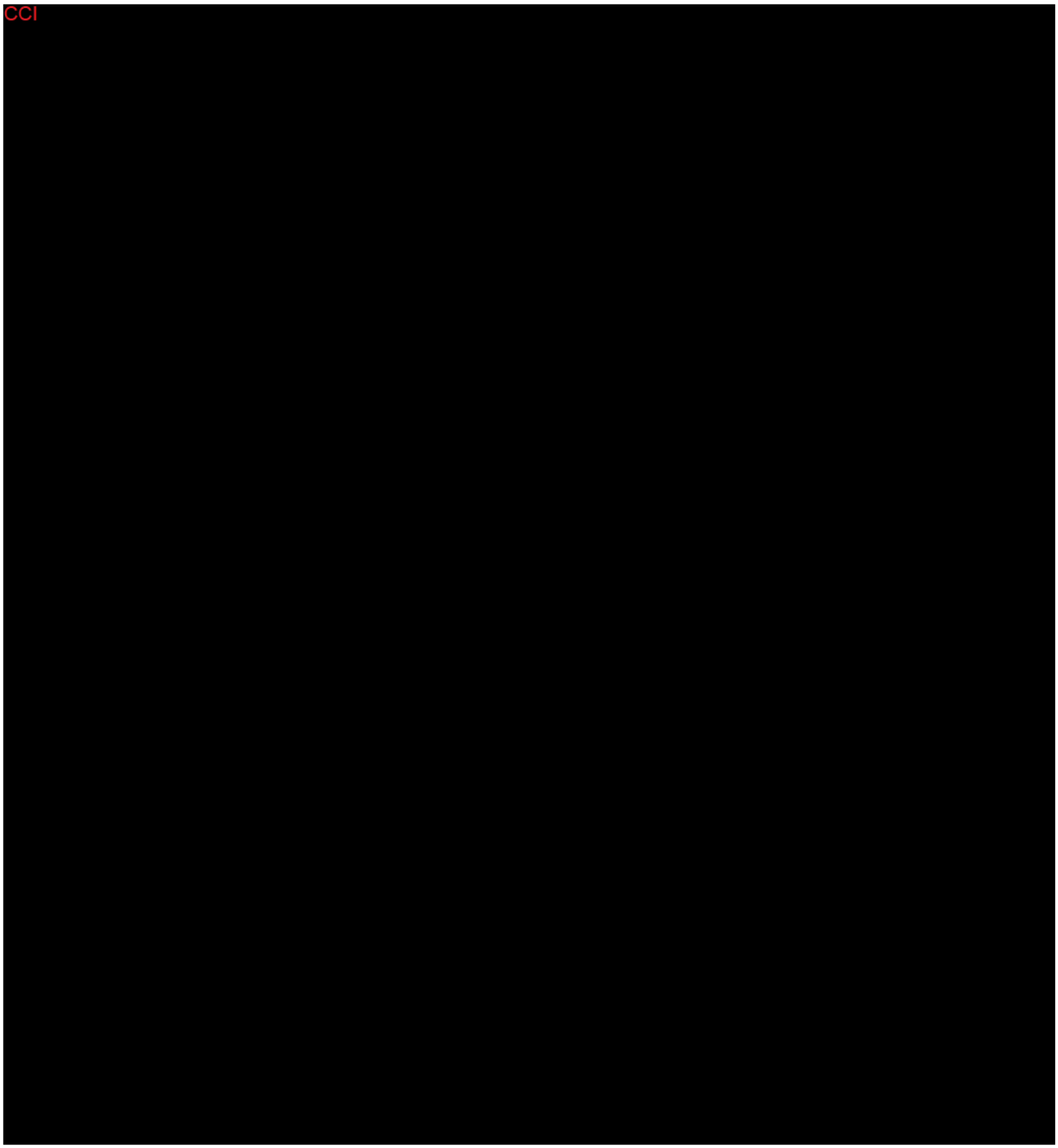

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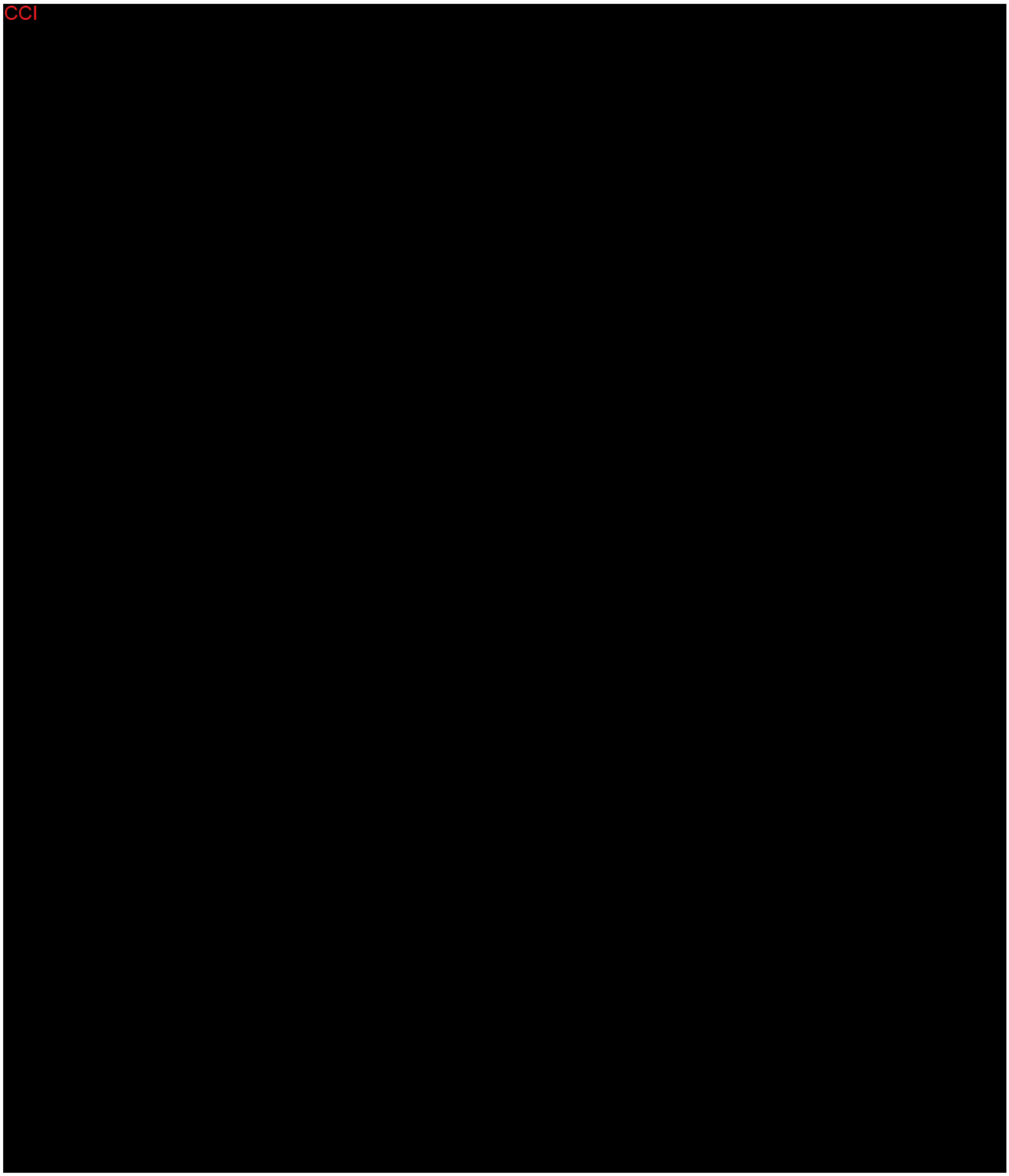

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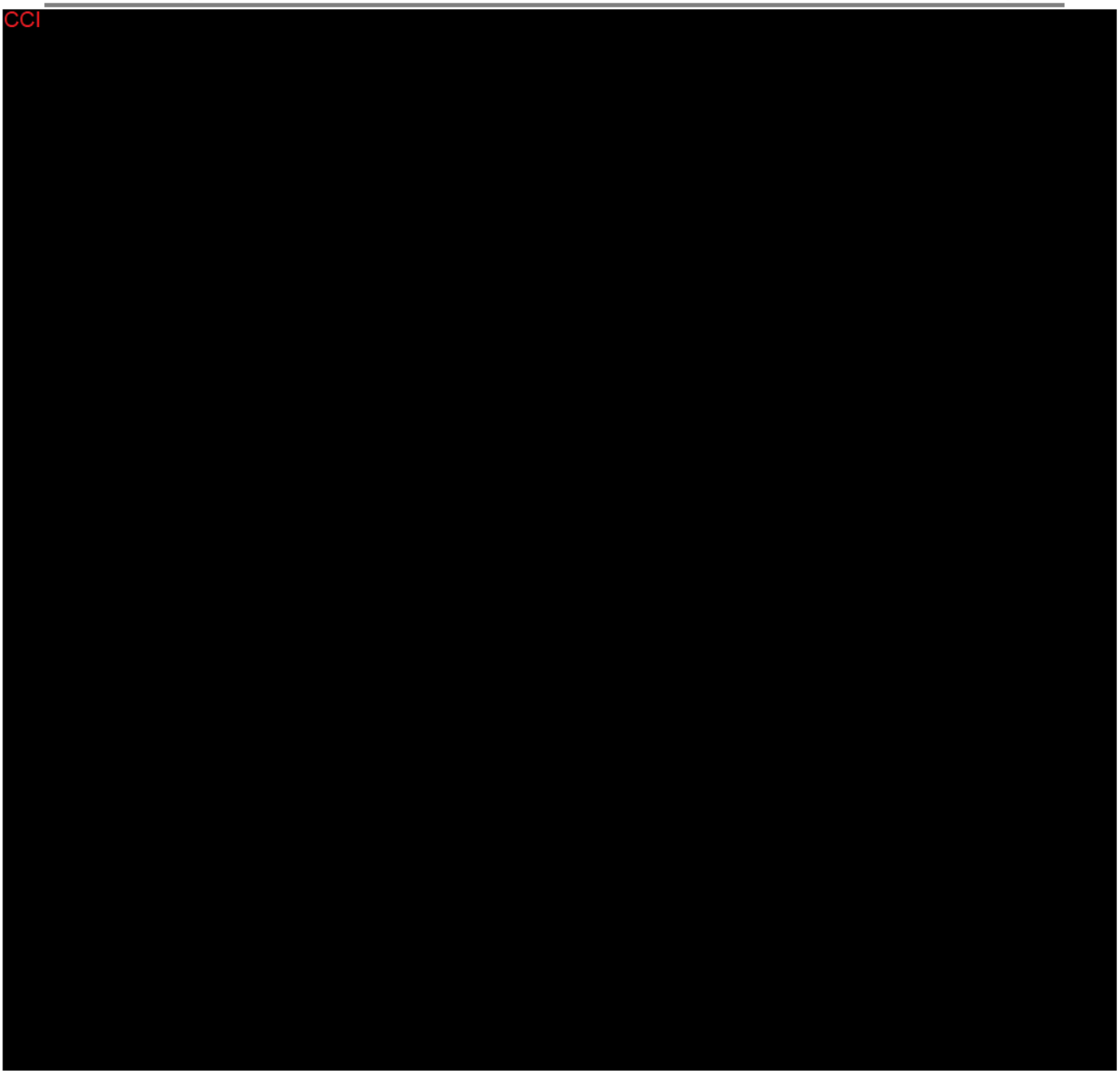

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10.2 Figure Shells

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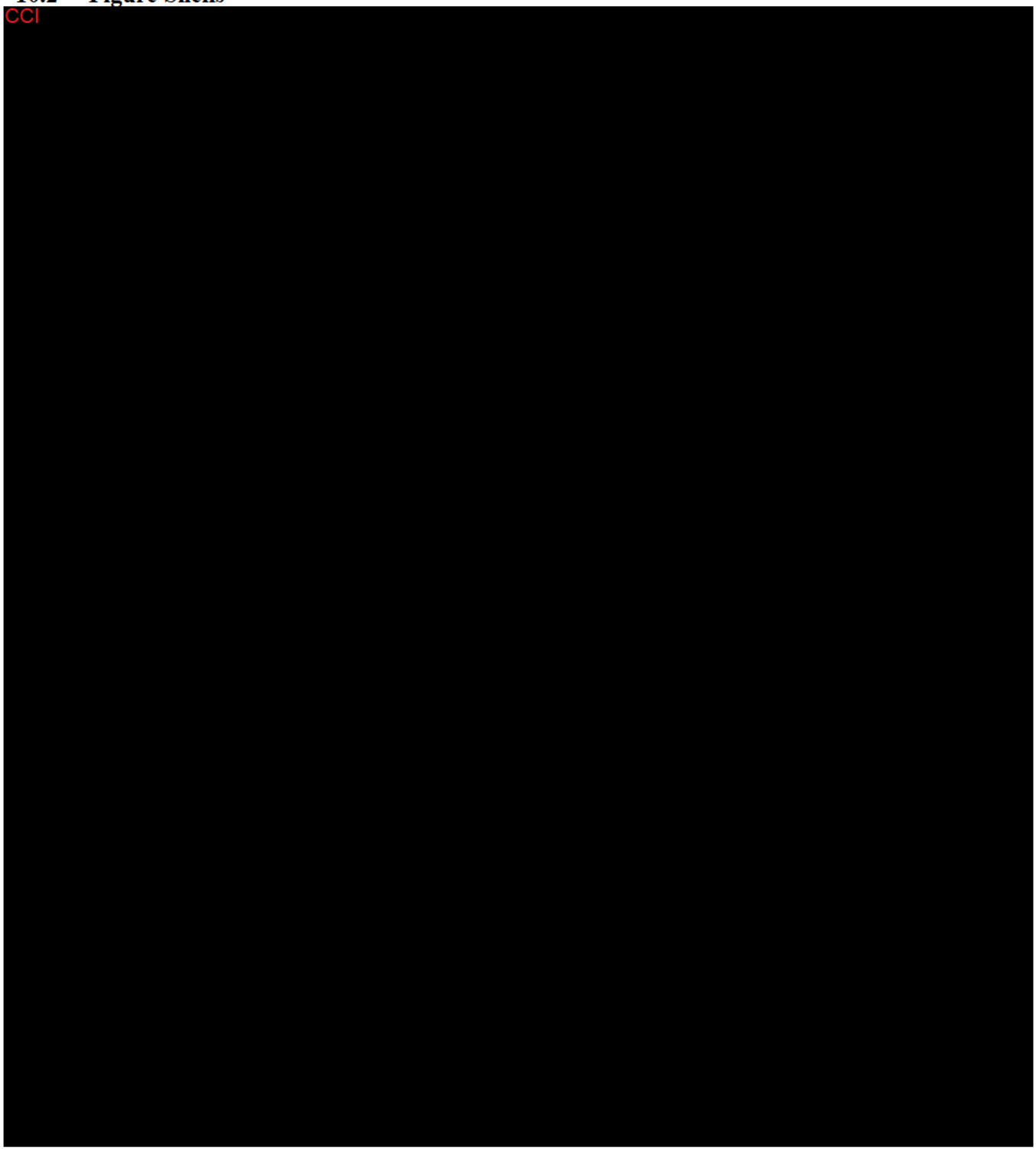

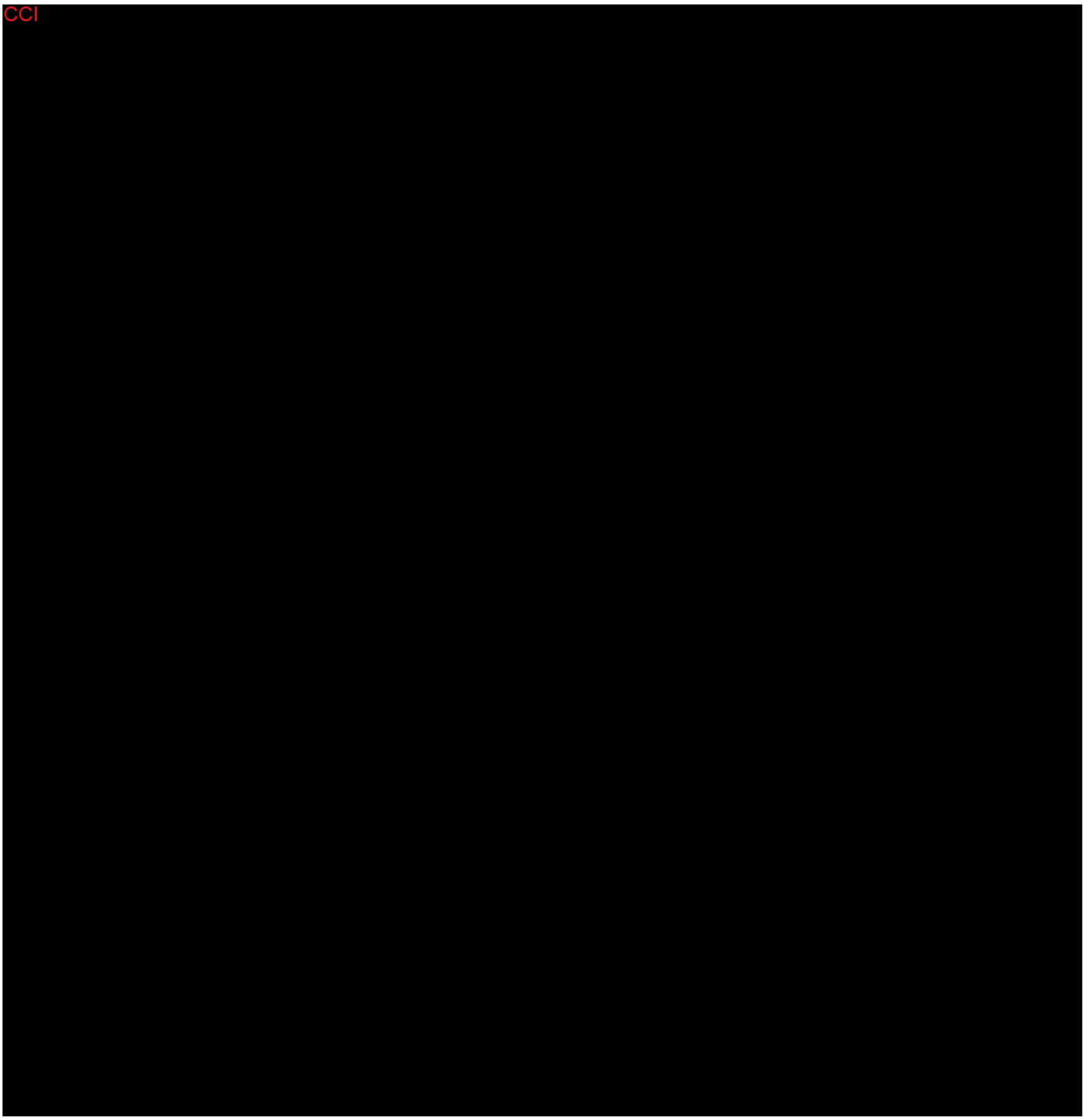
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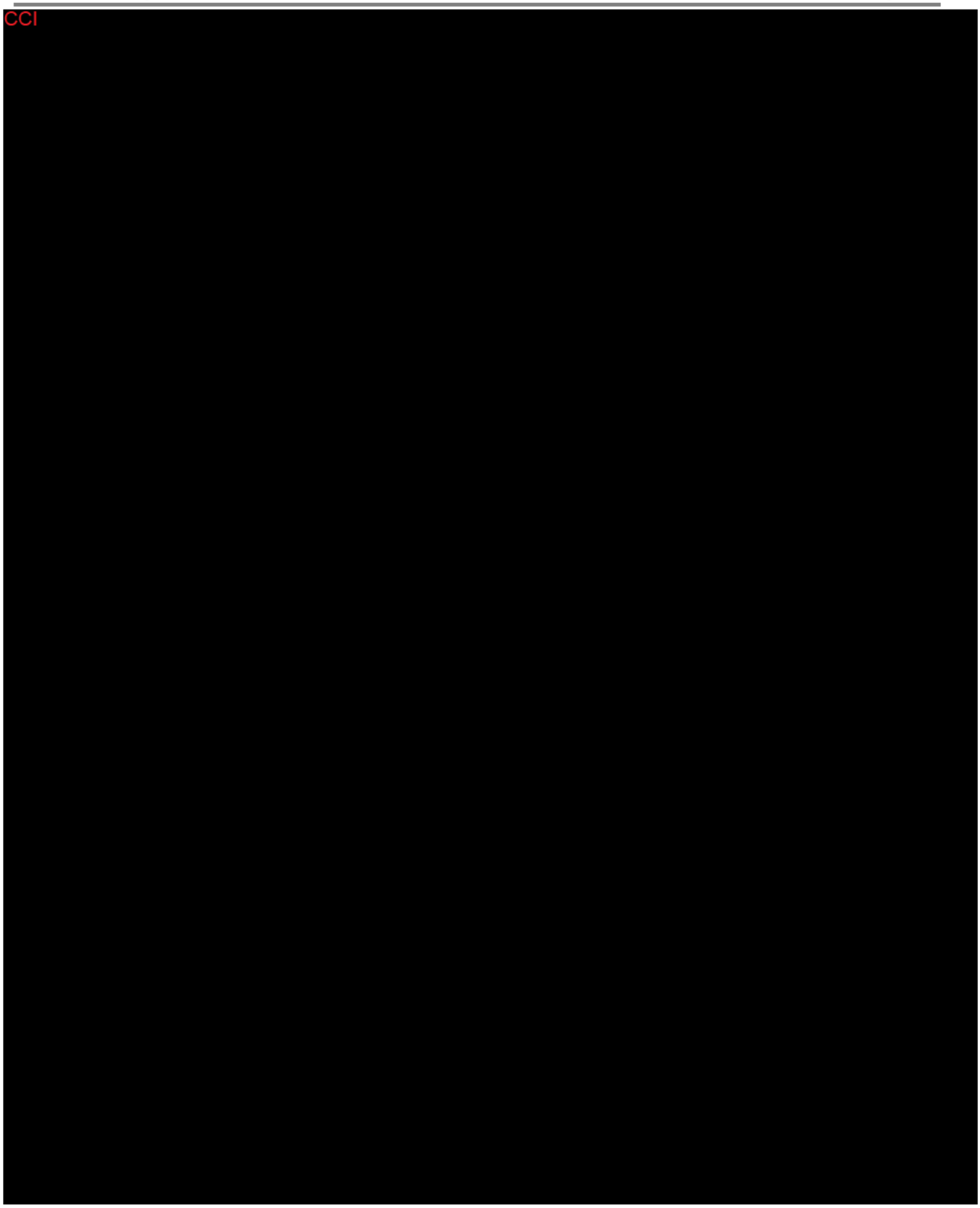

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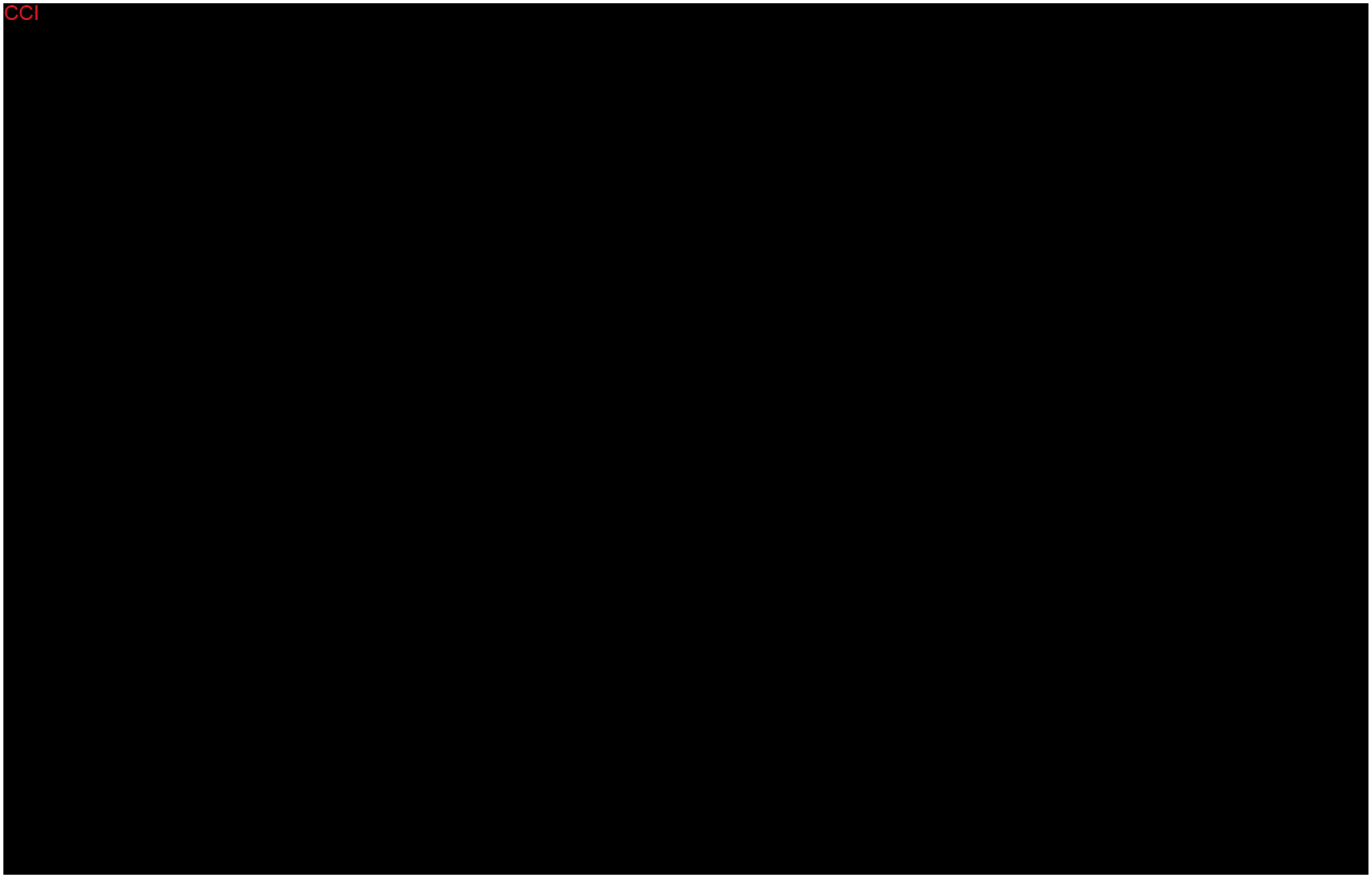

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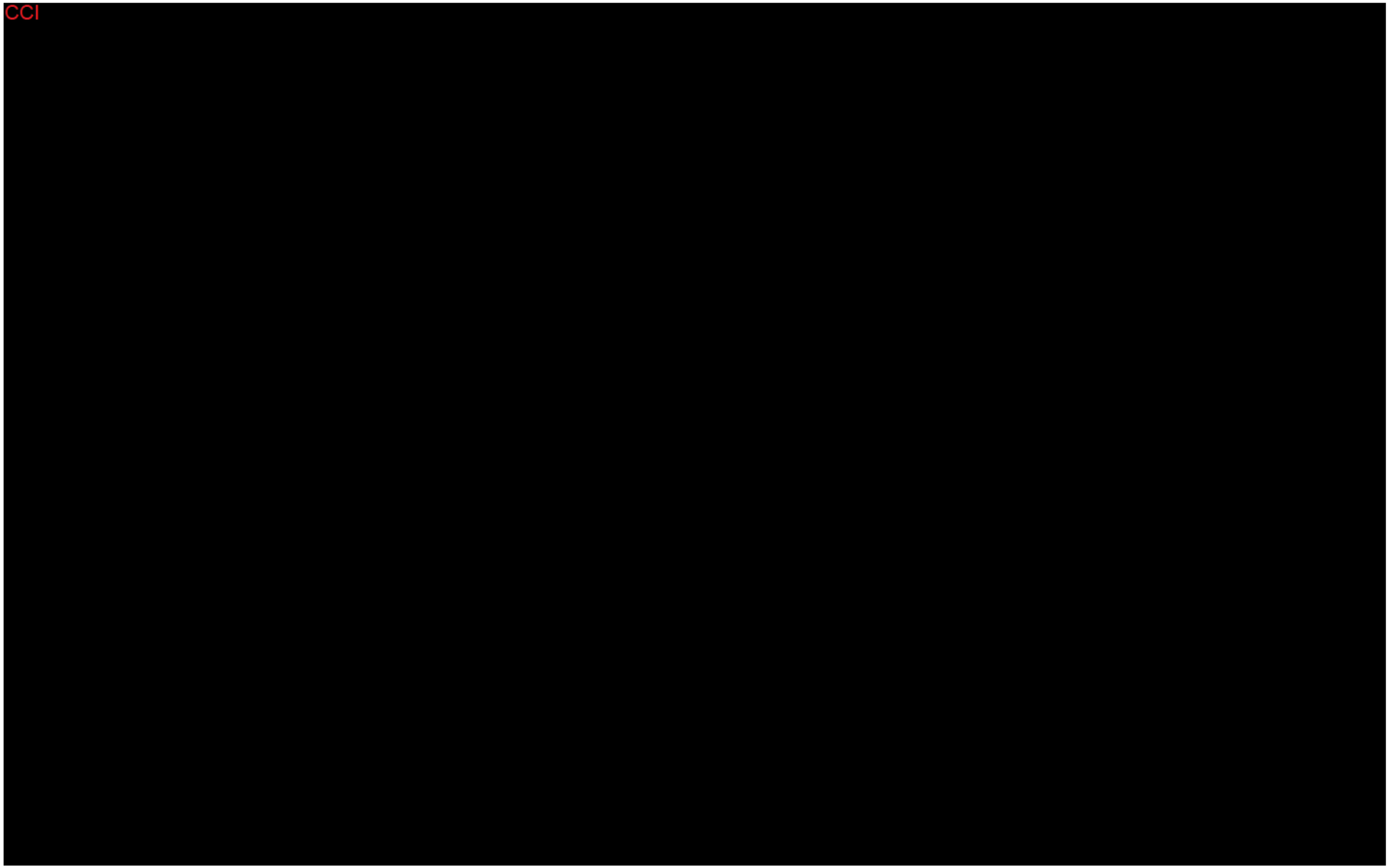

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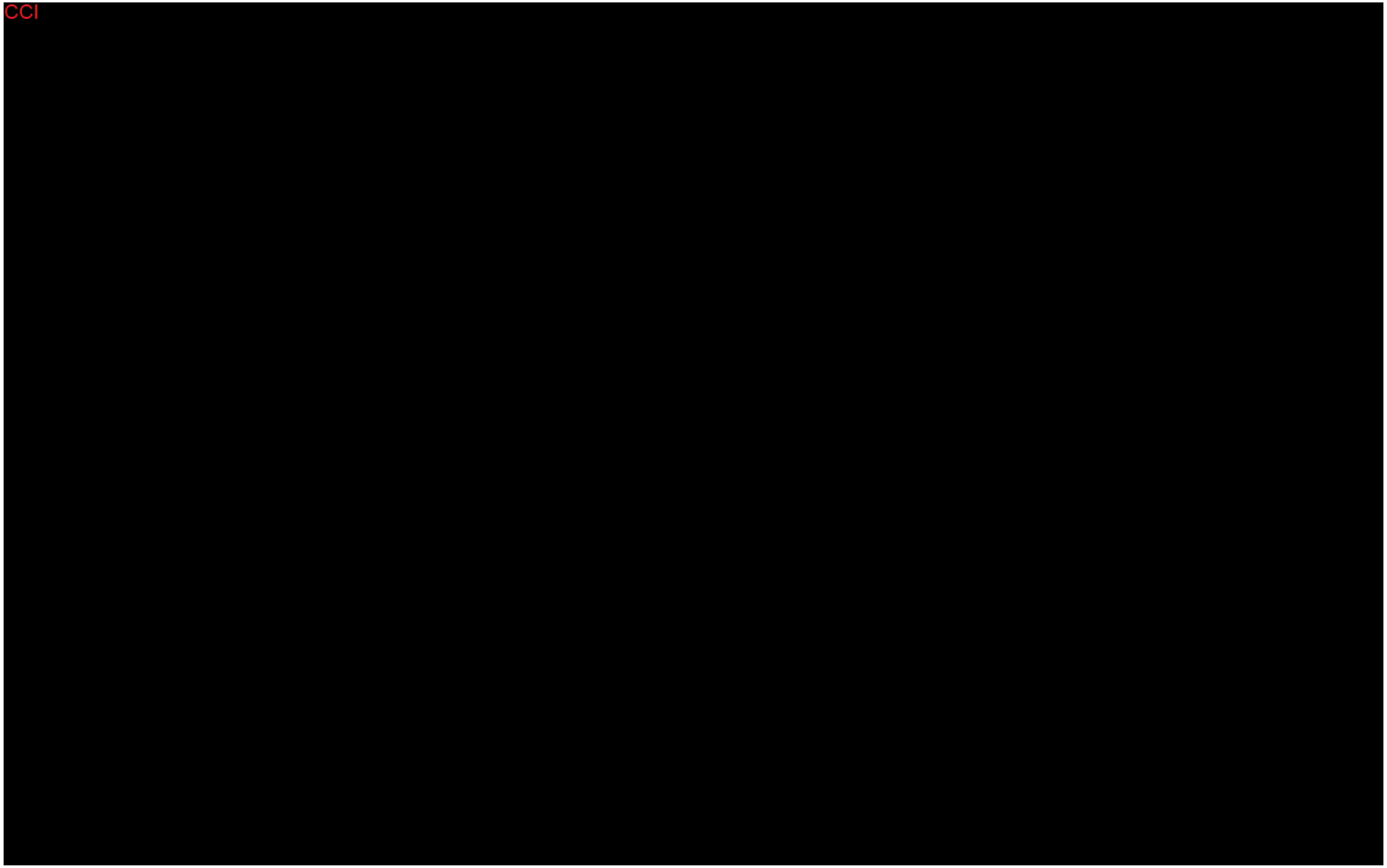

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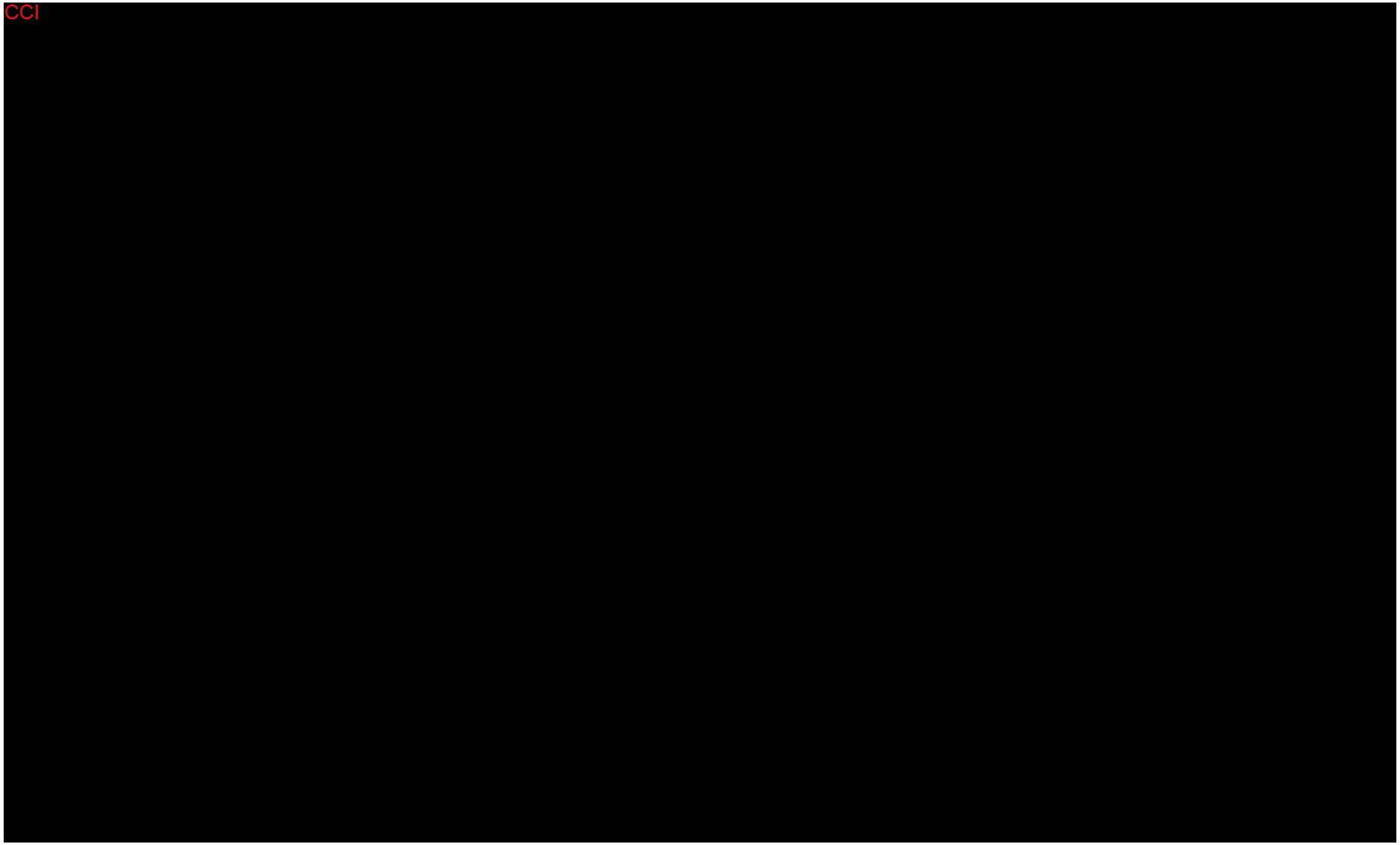

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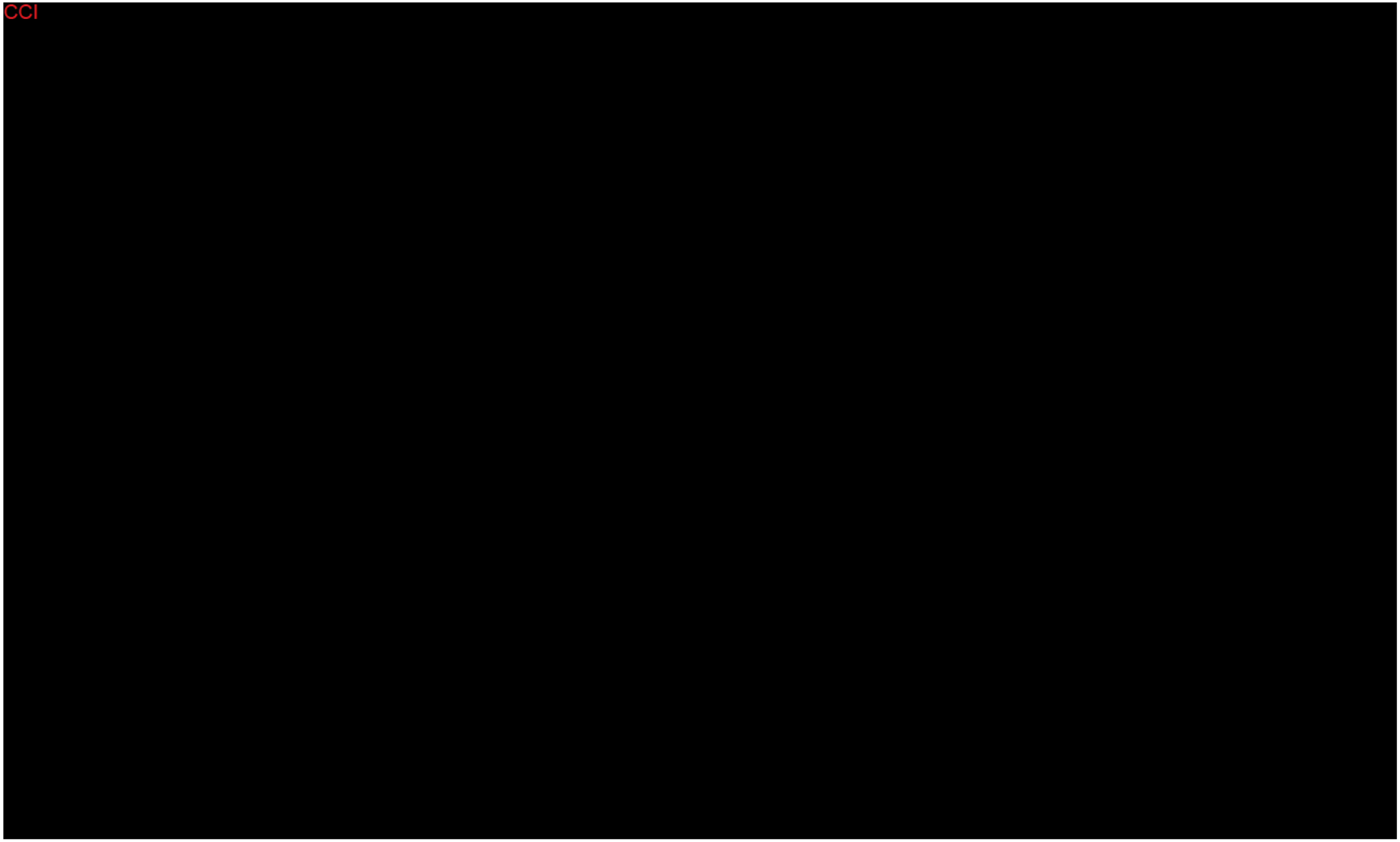

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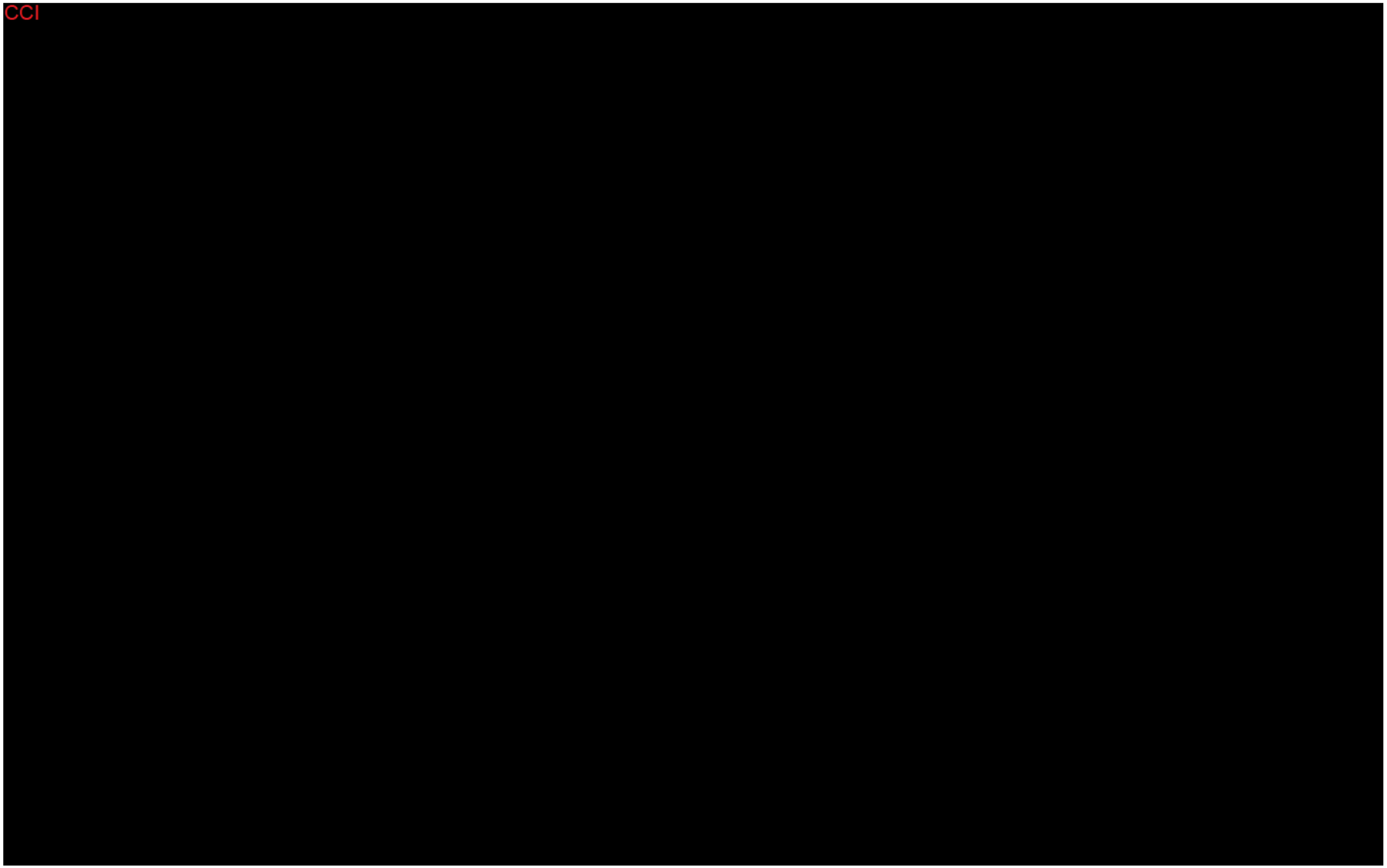

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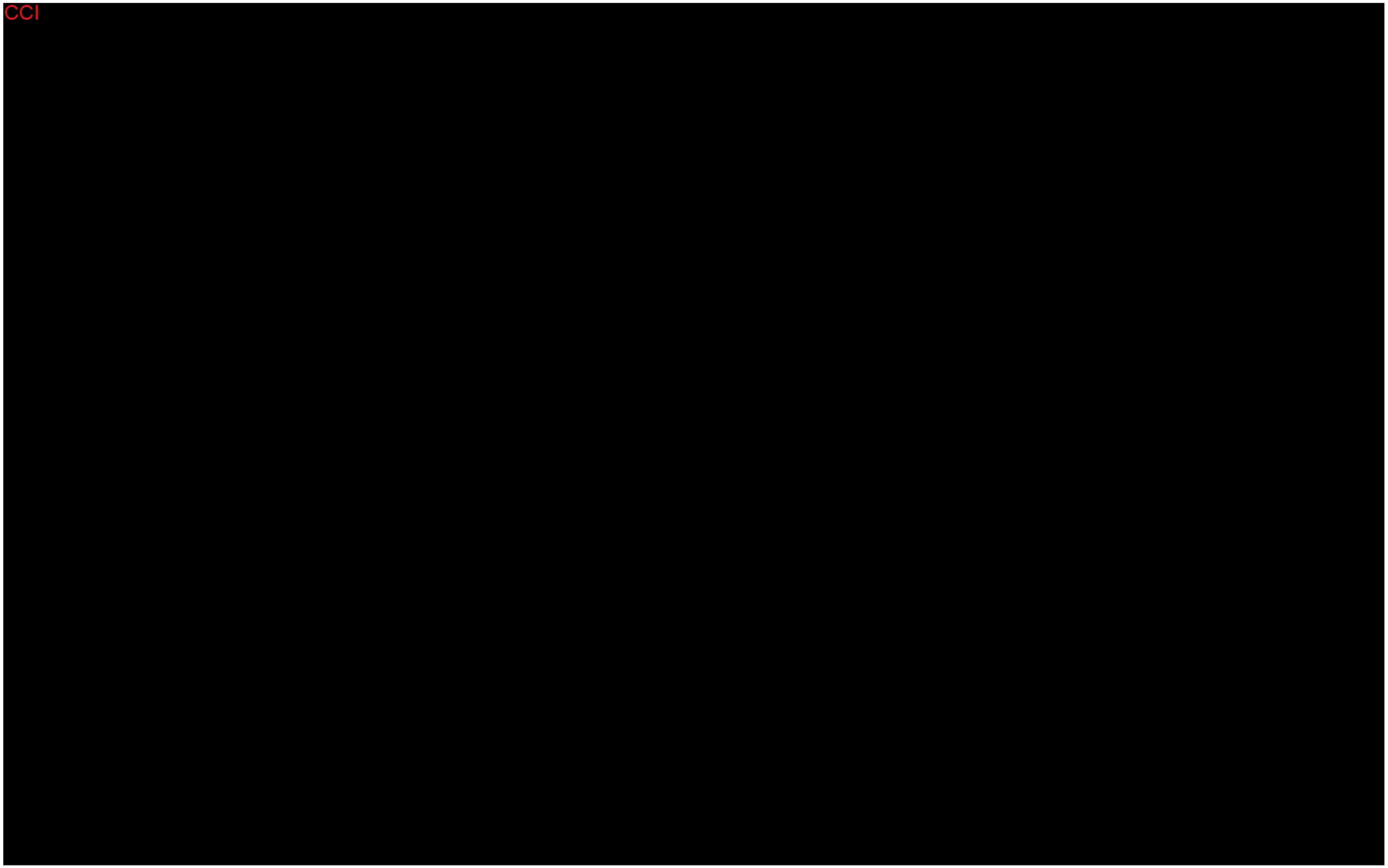

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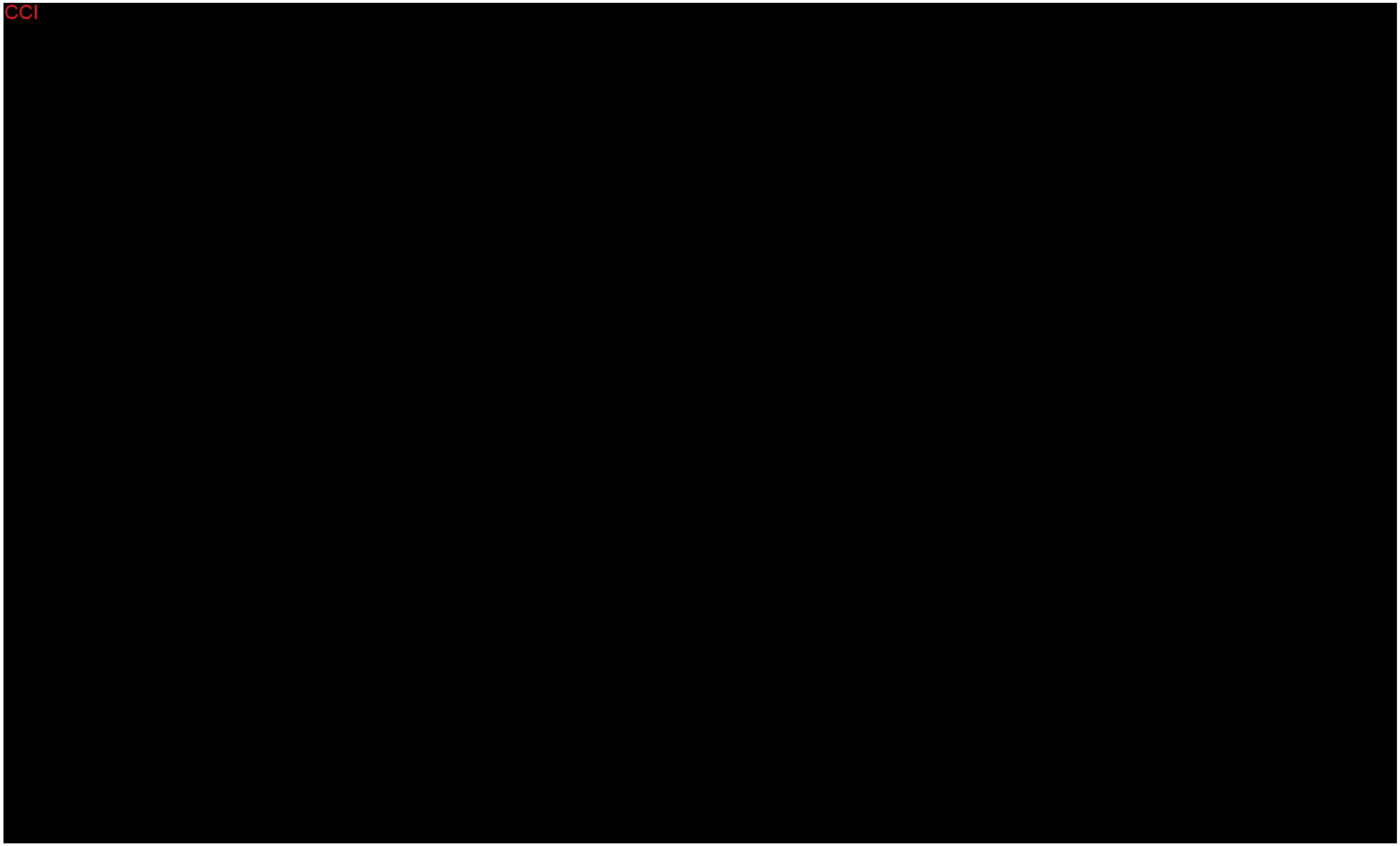

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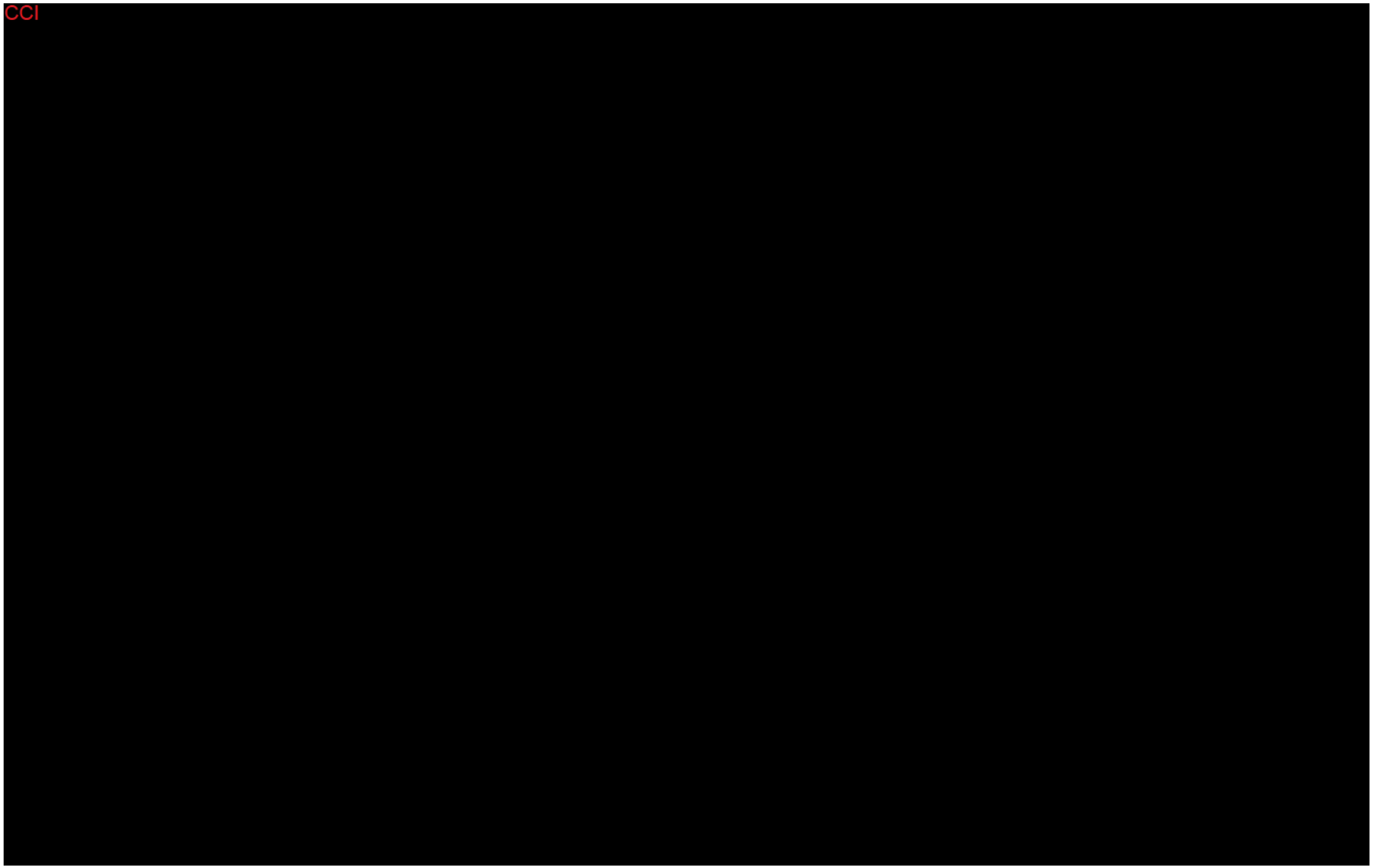

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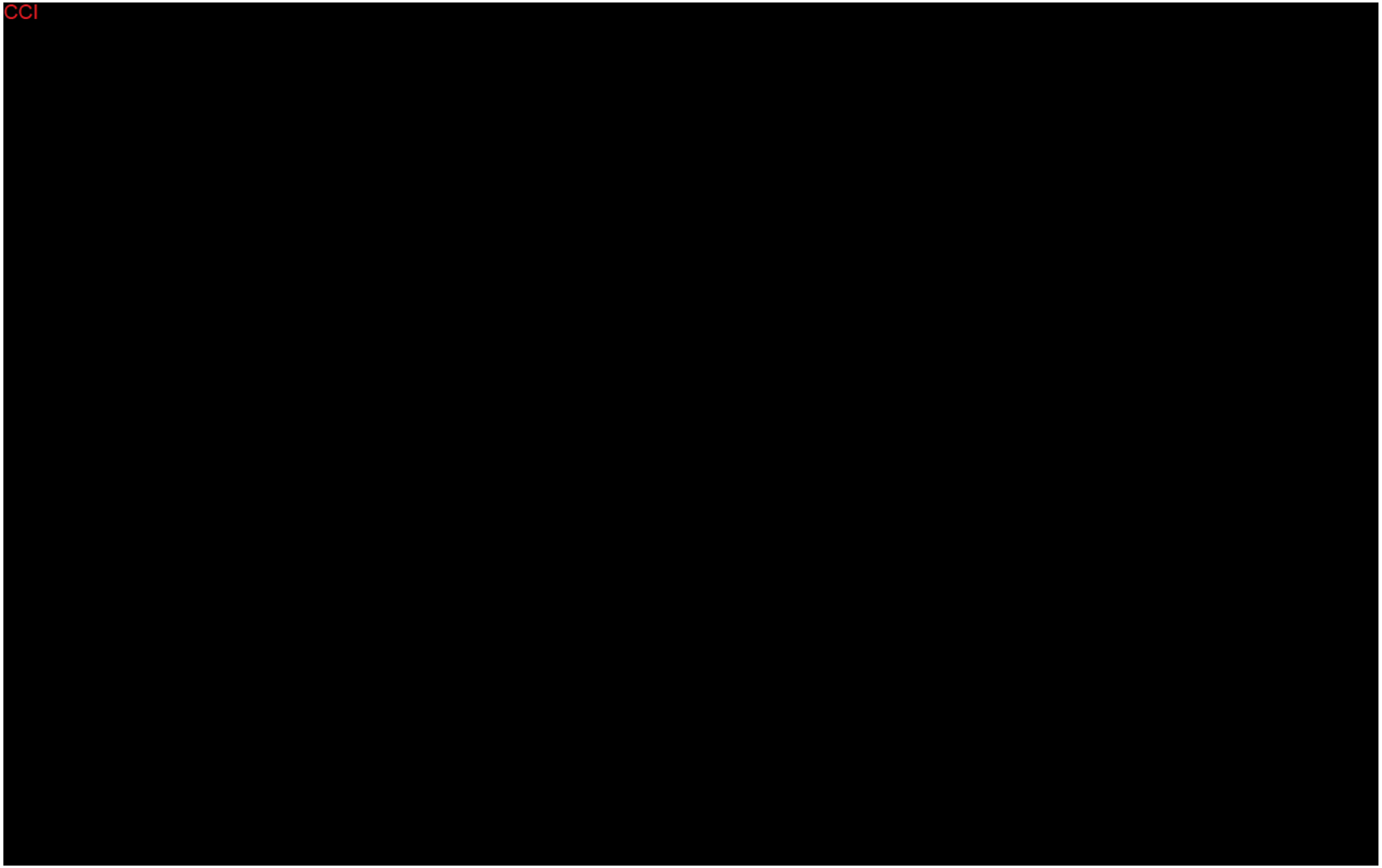

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11.0 LISTING SHELLS

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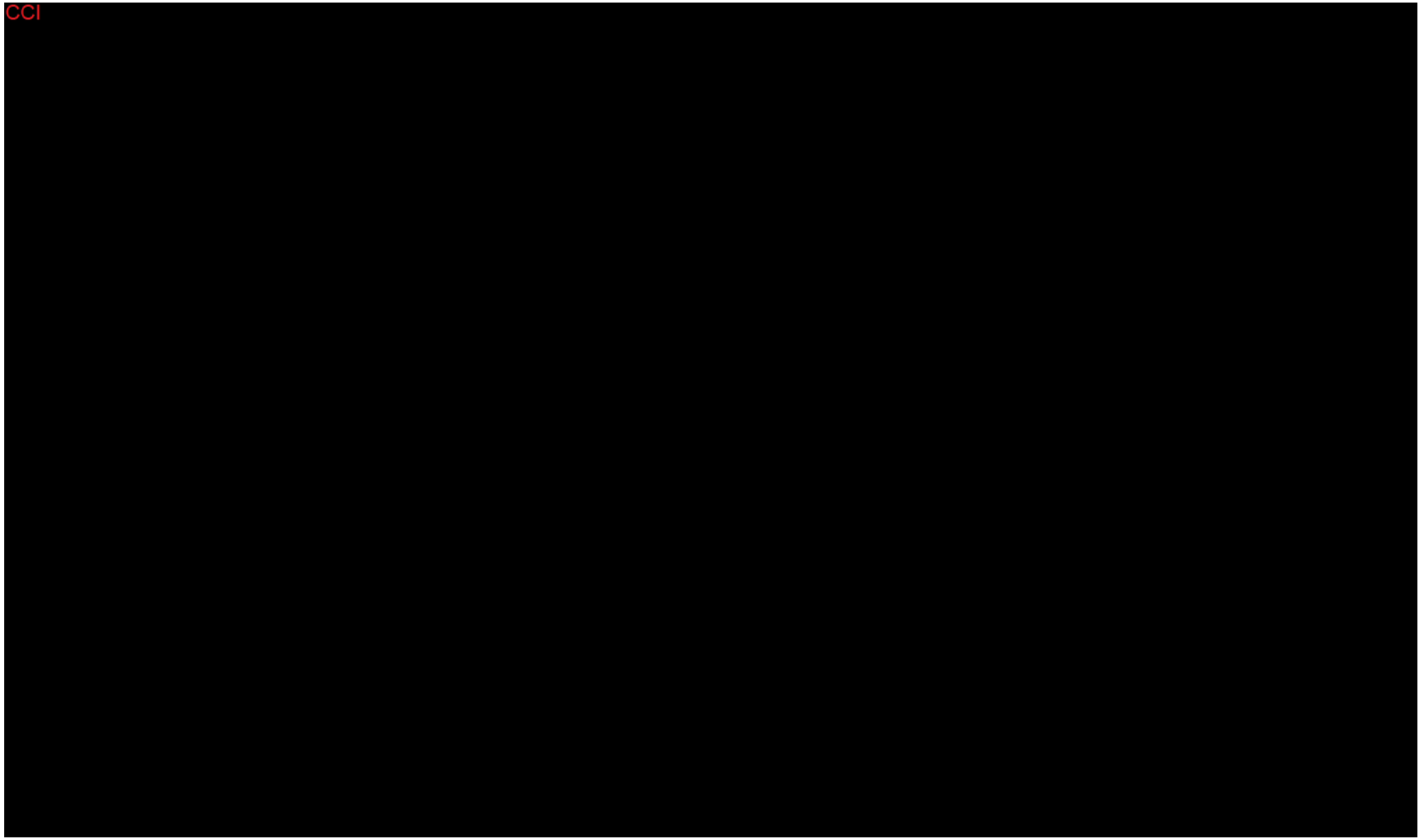

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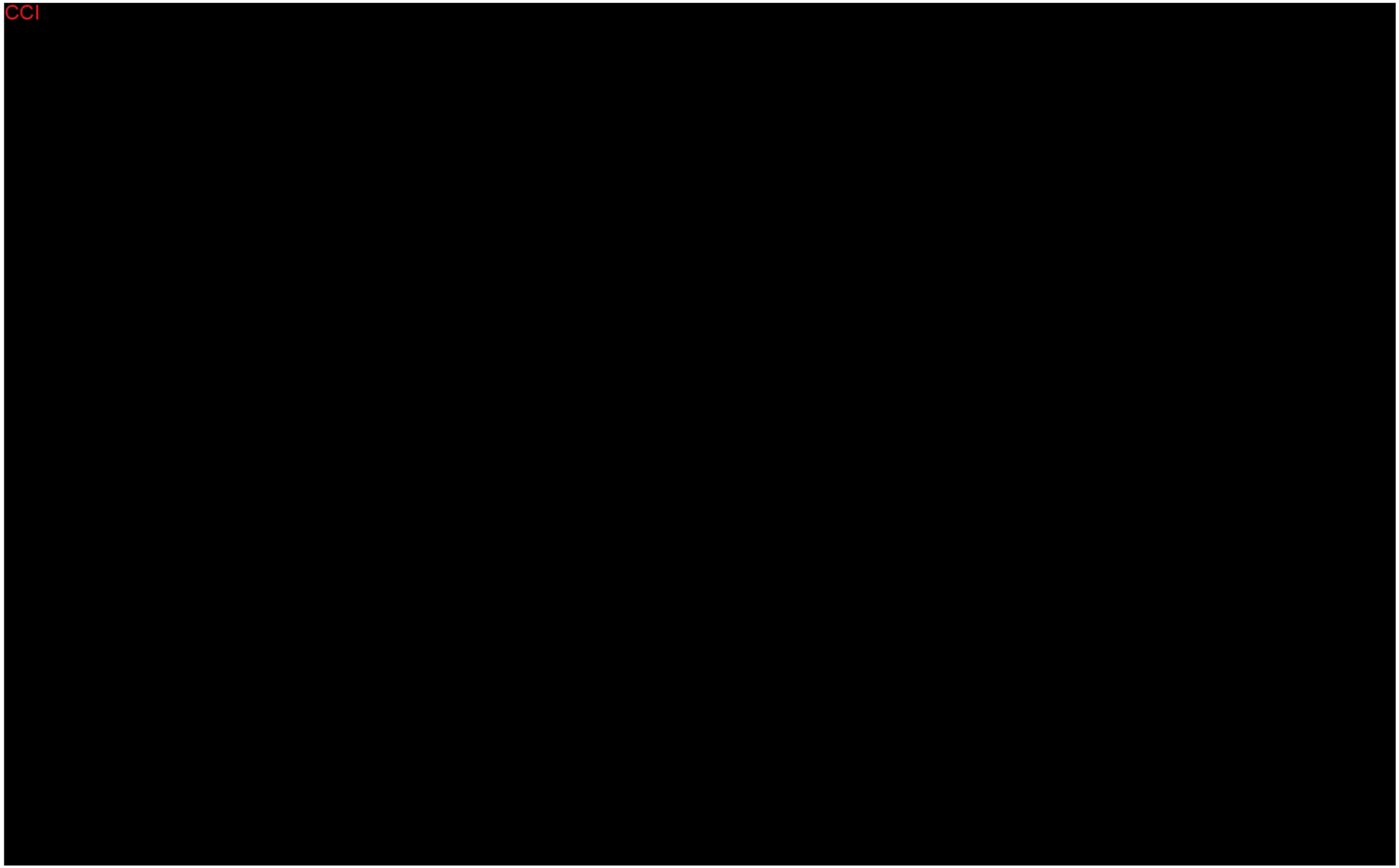

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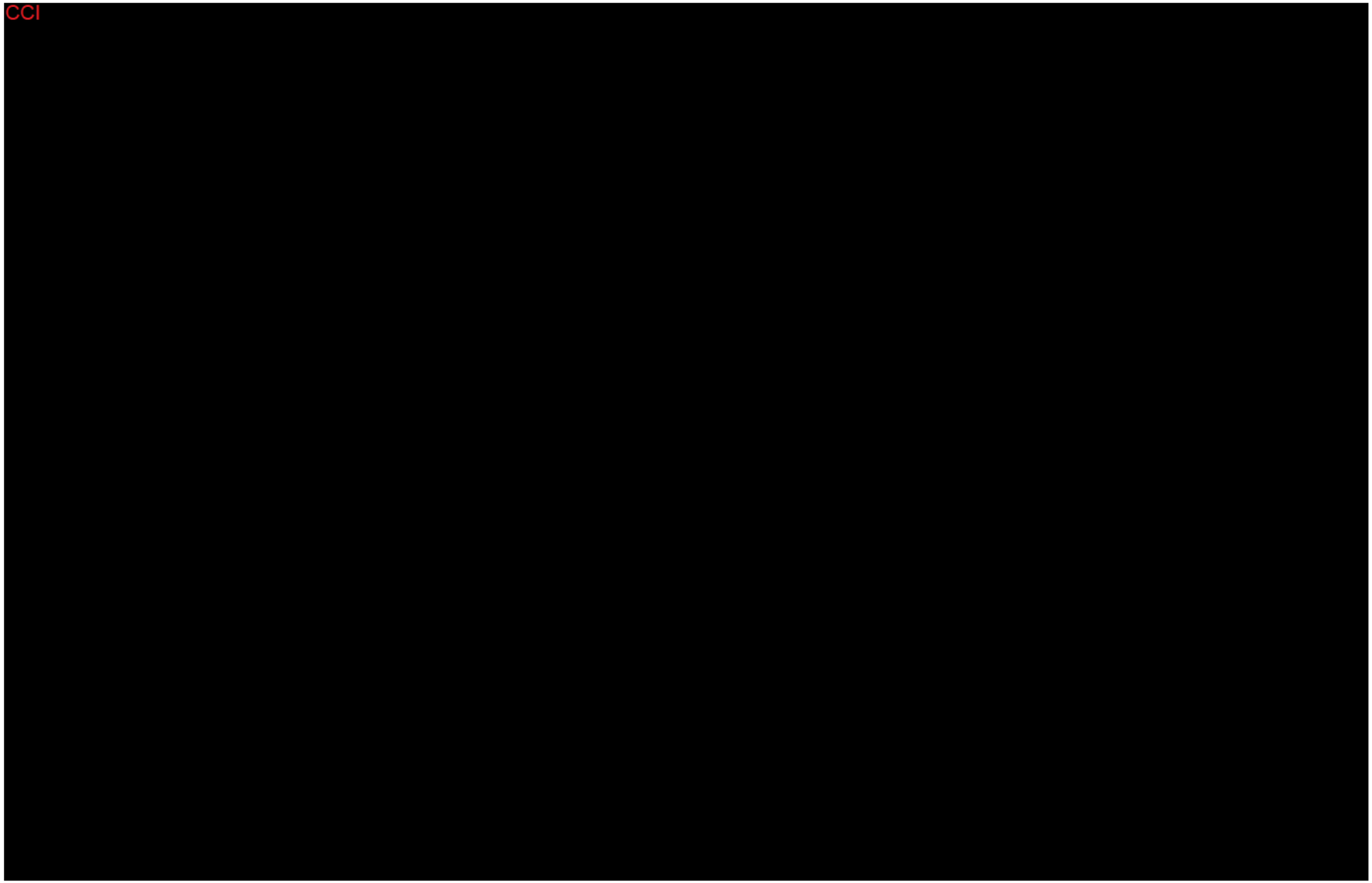

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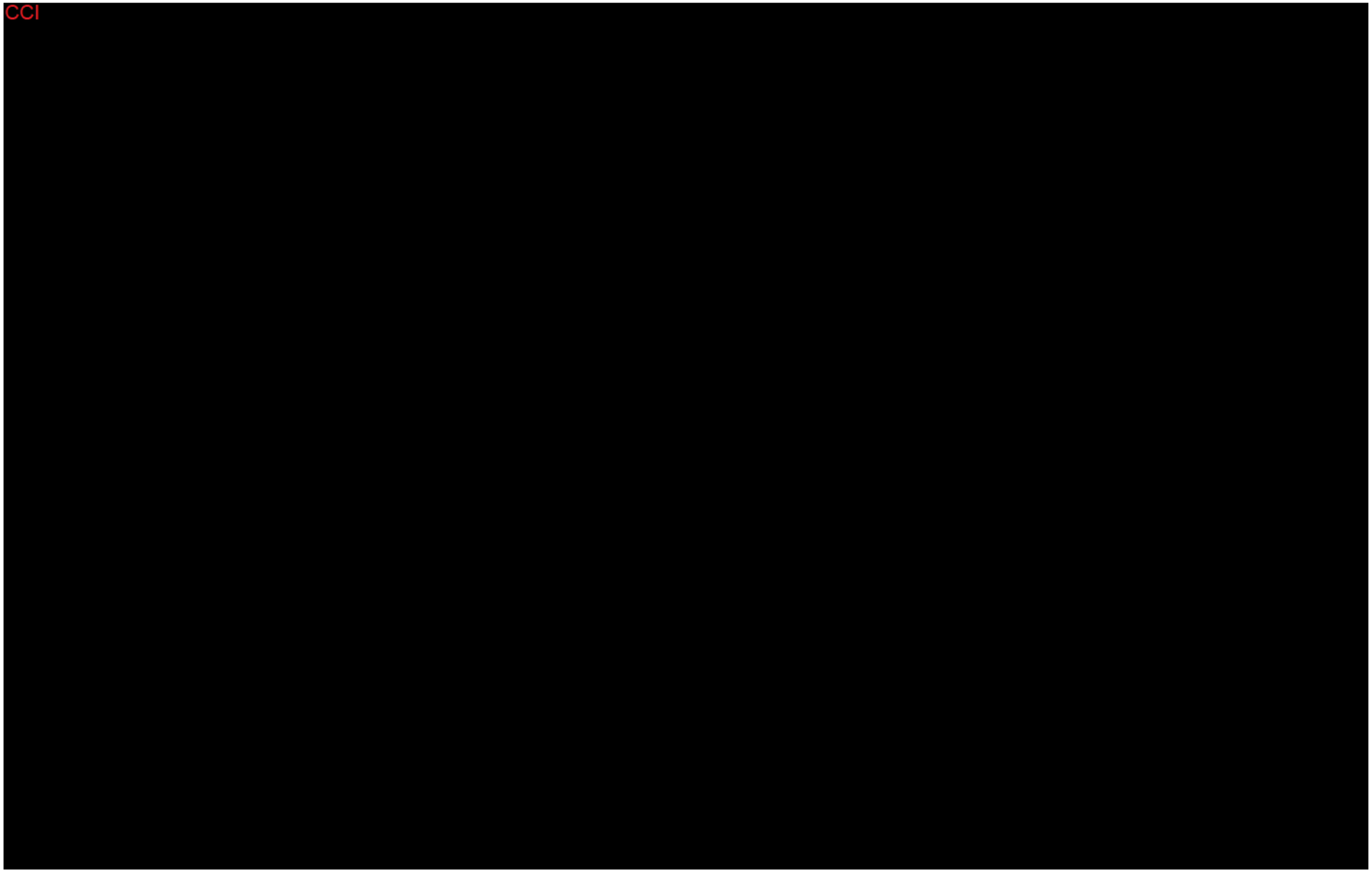

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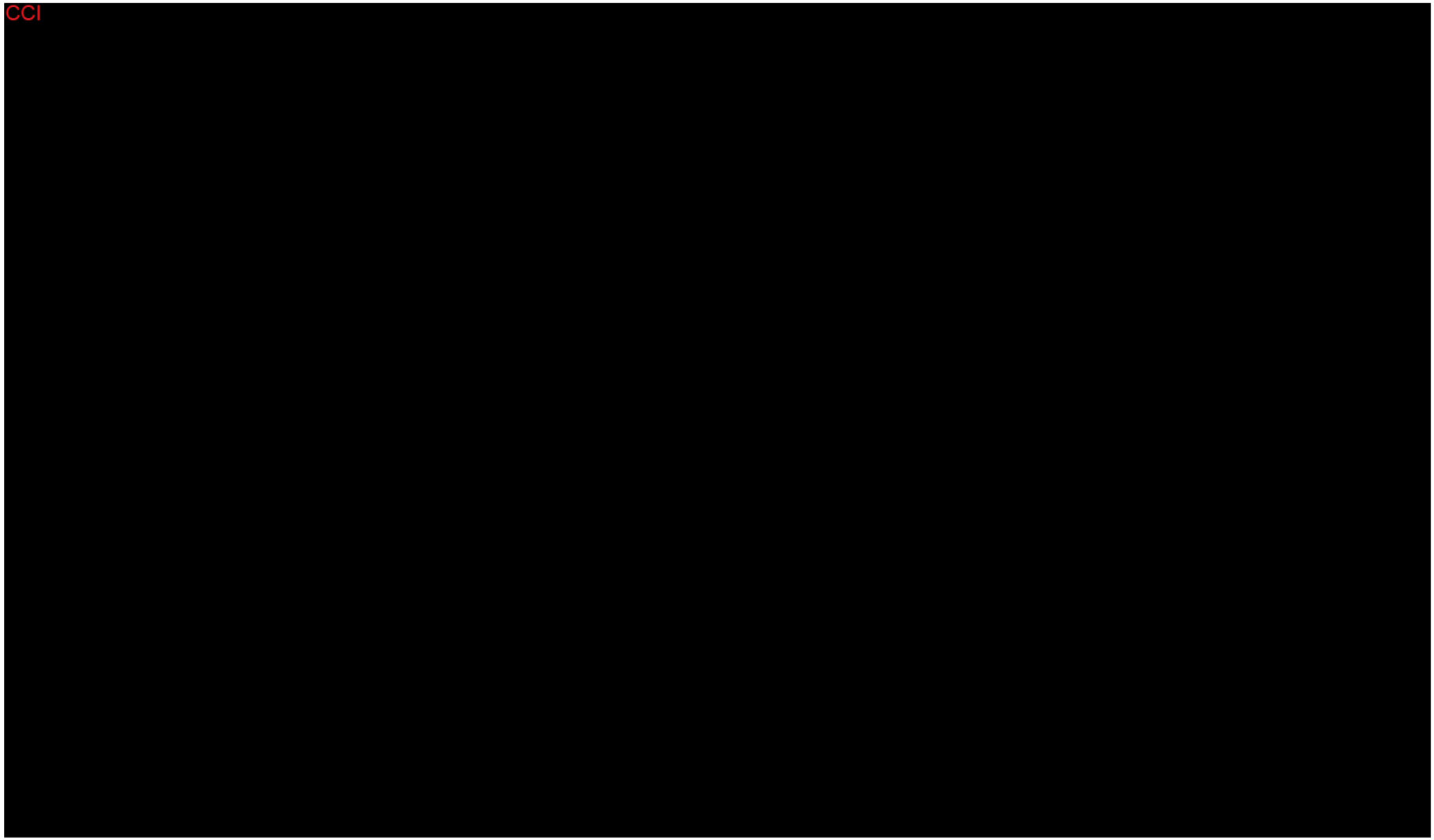

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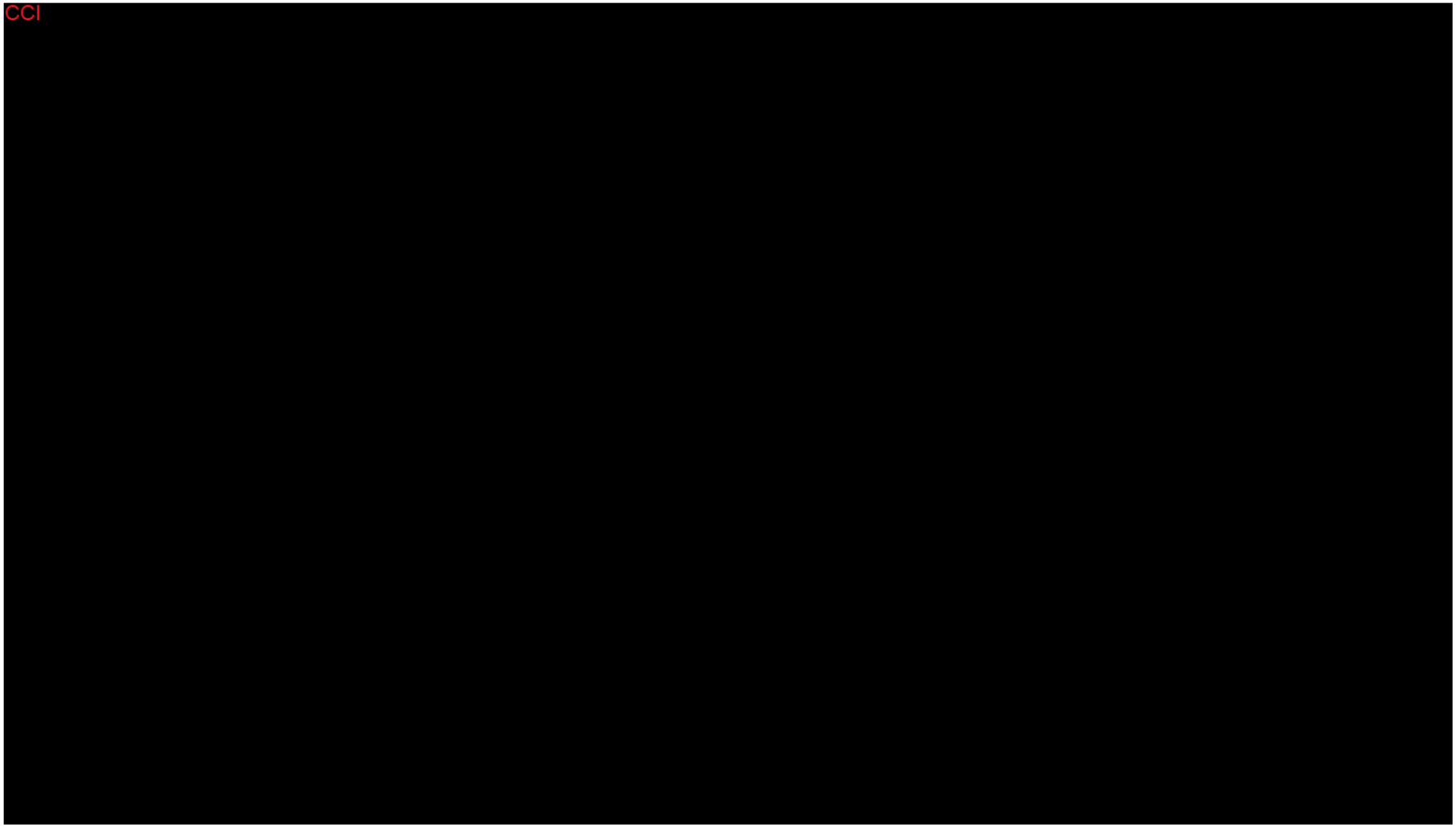

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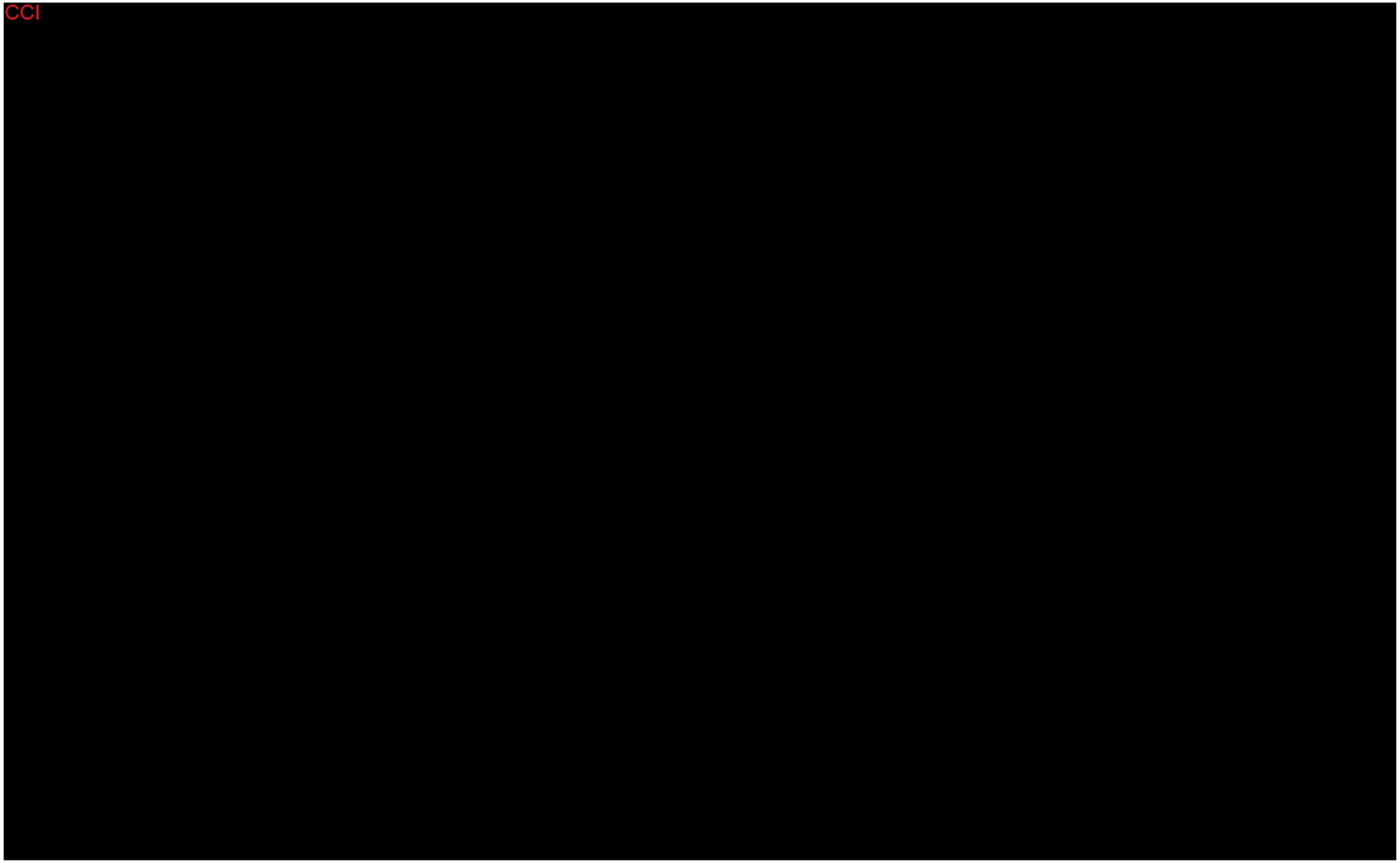

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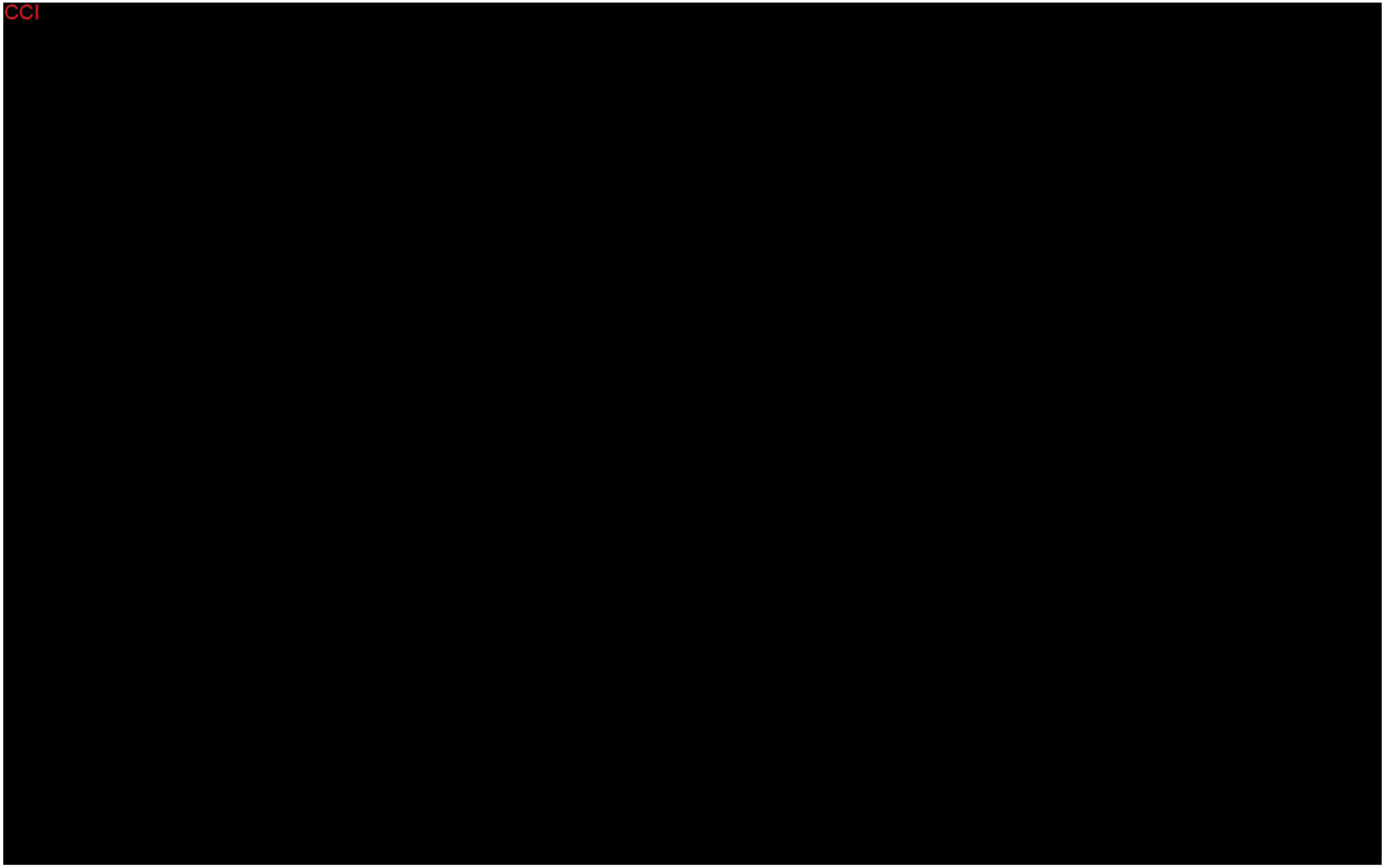

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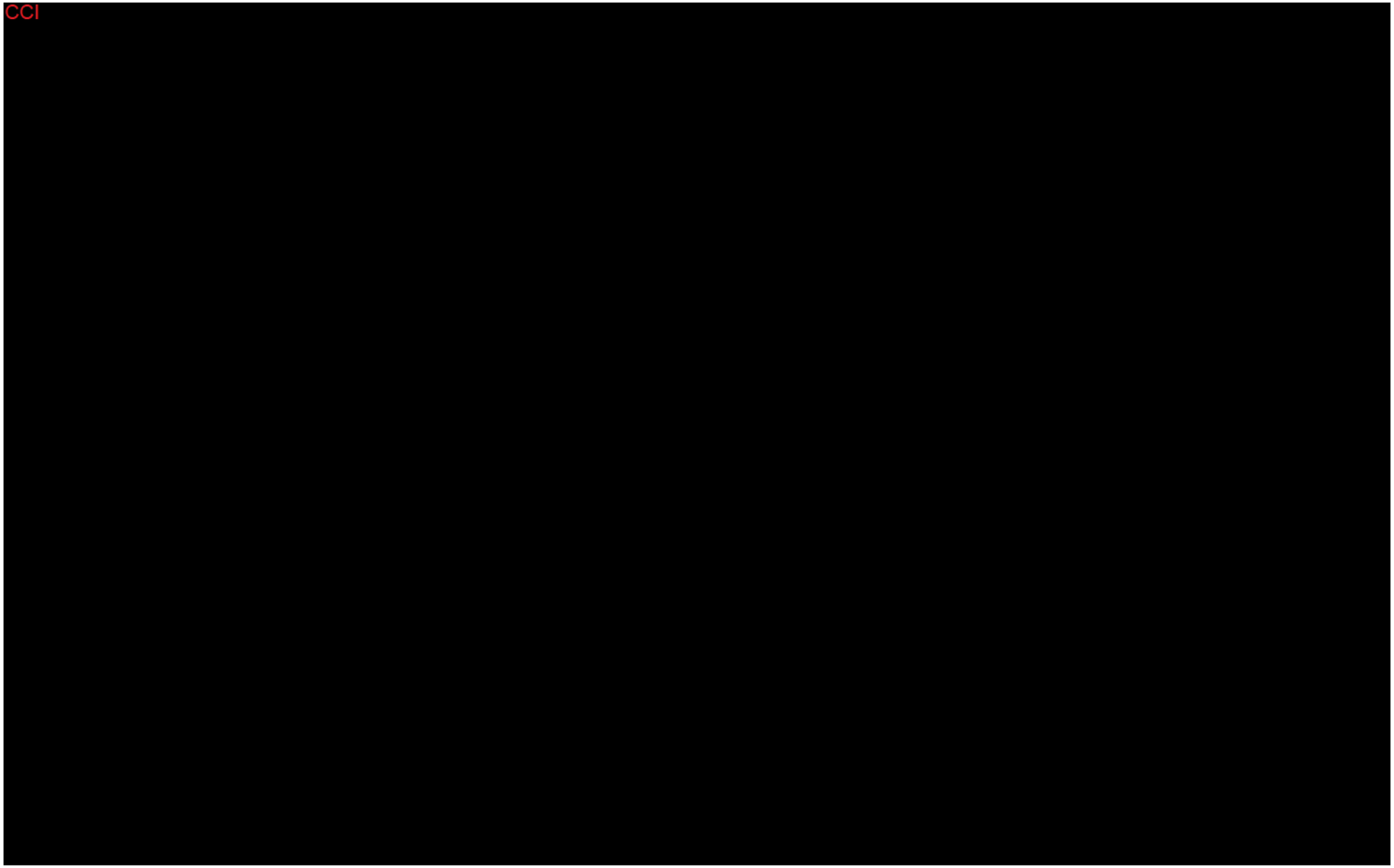

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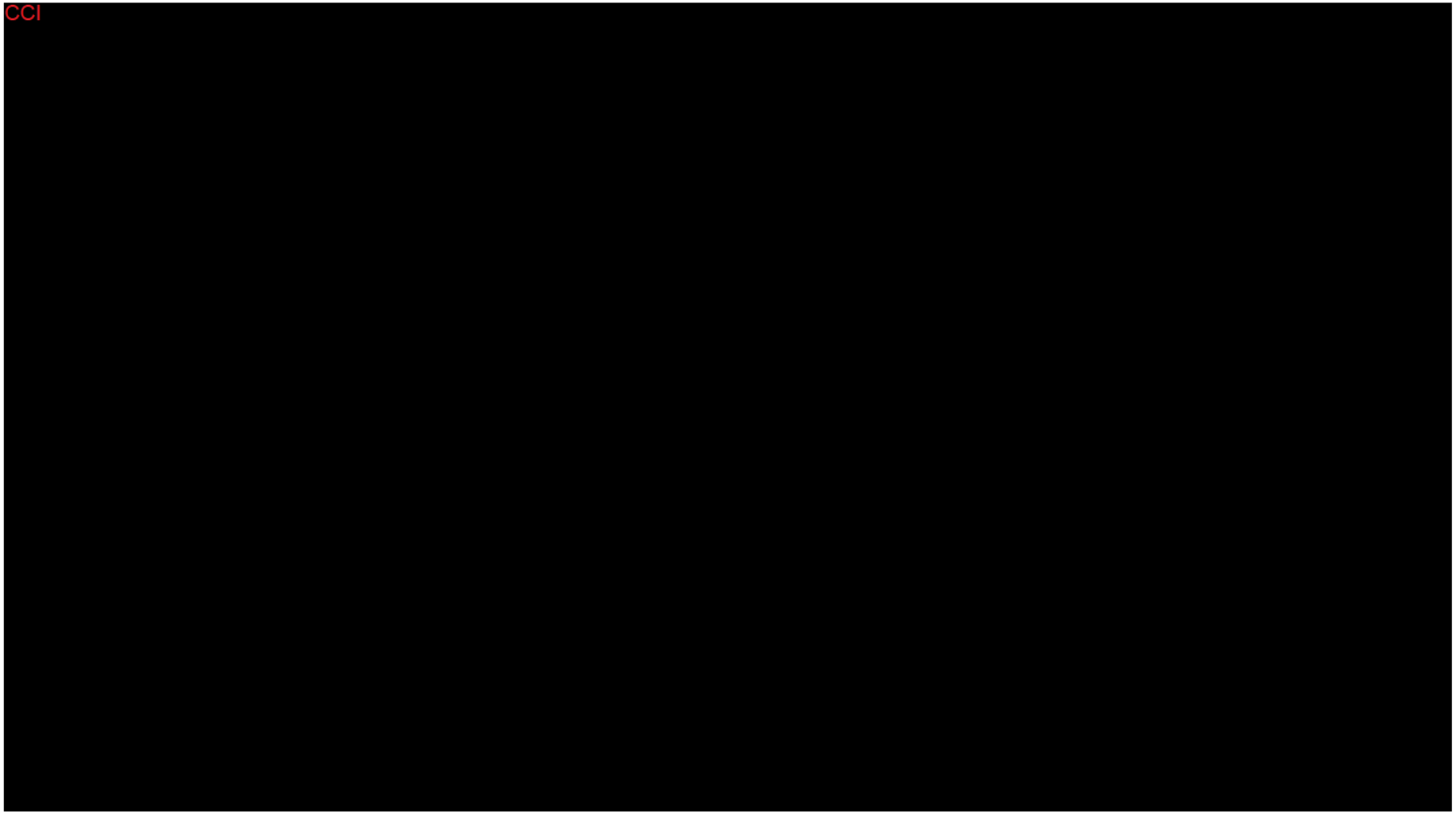

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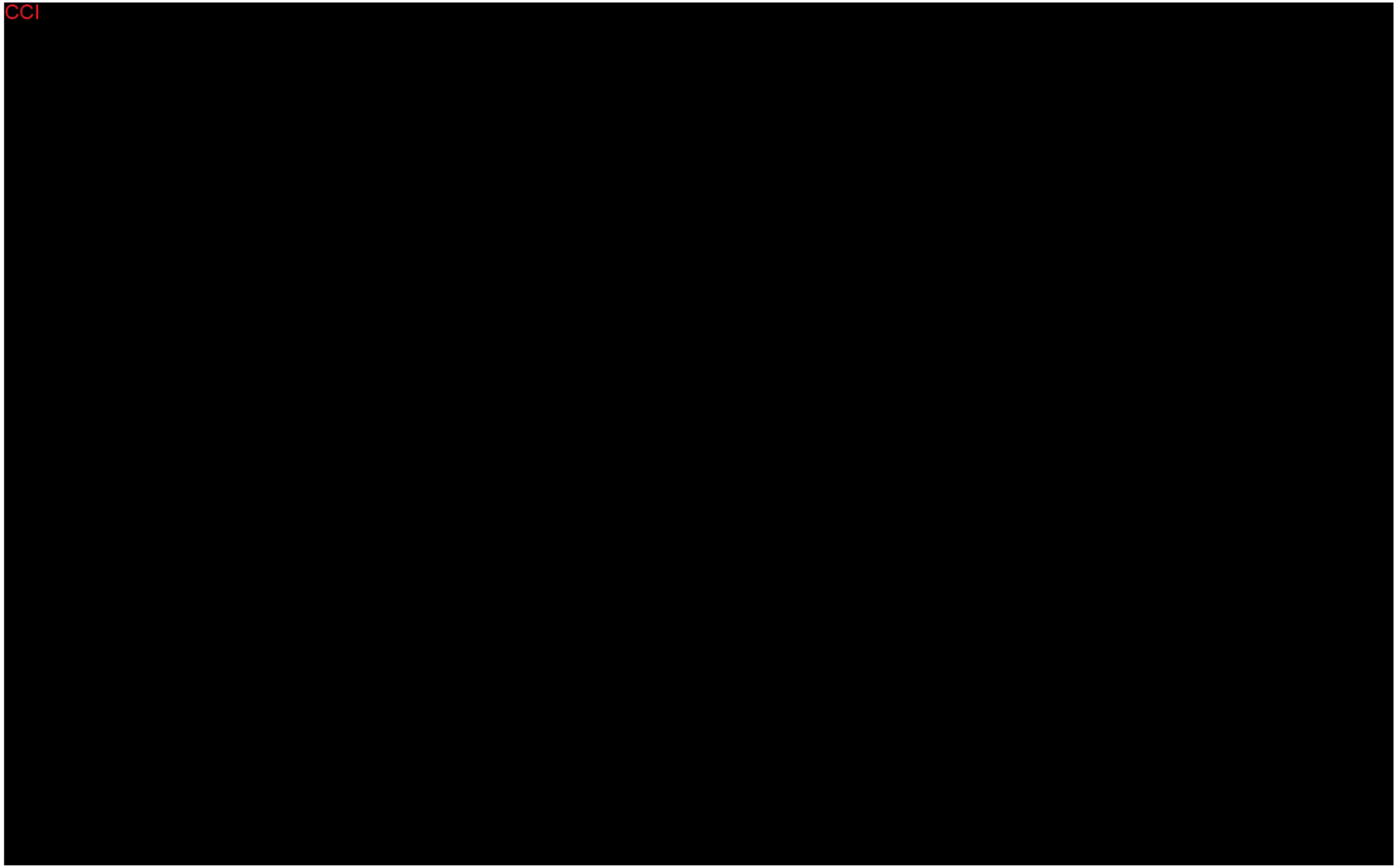

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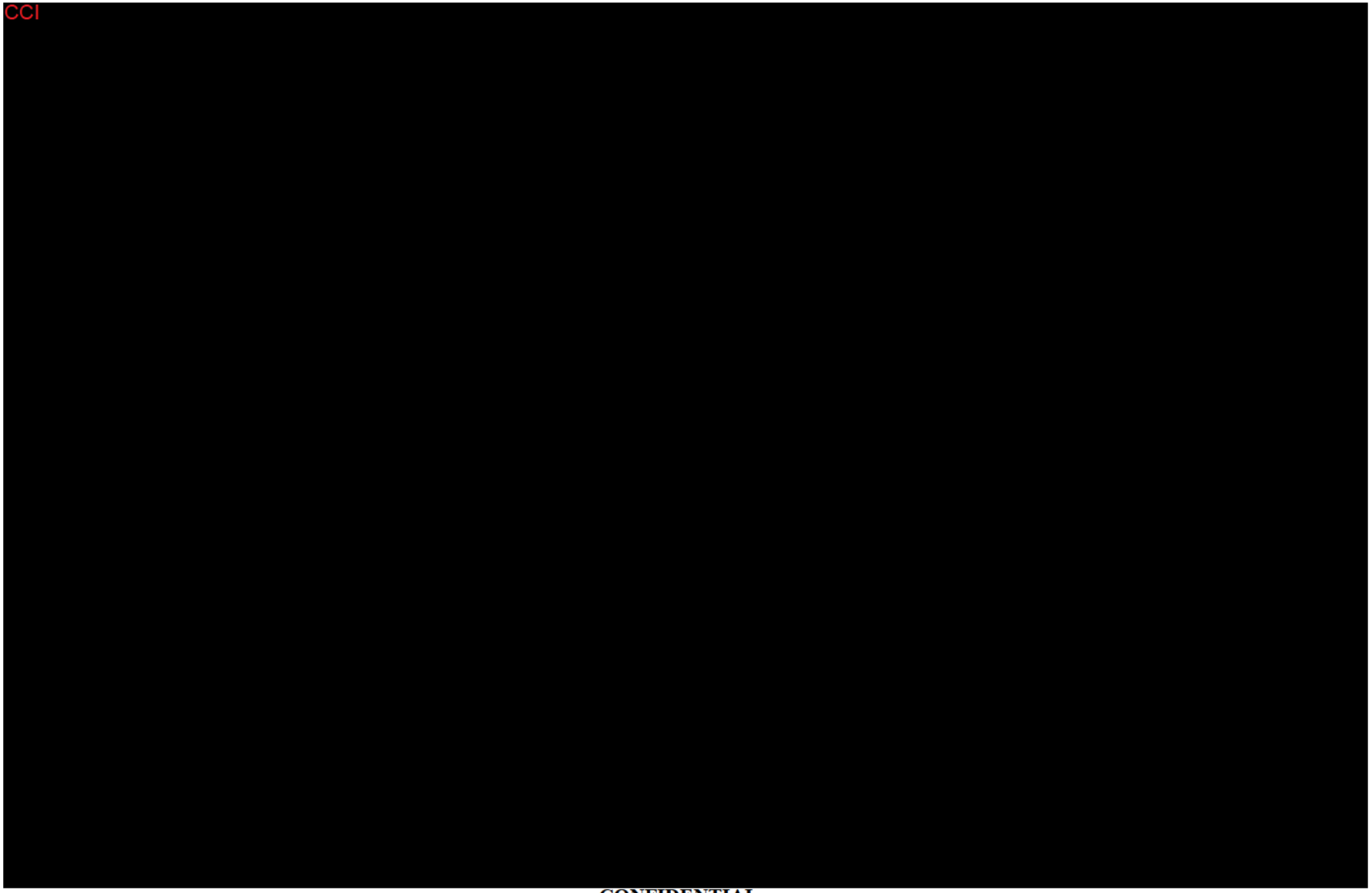

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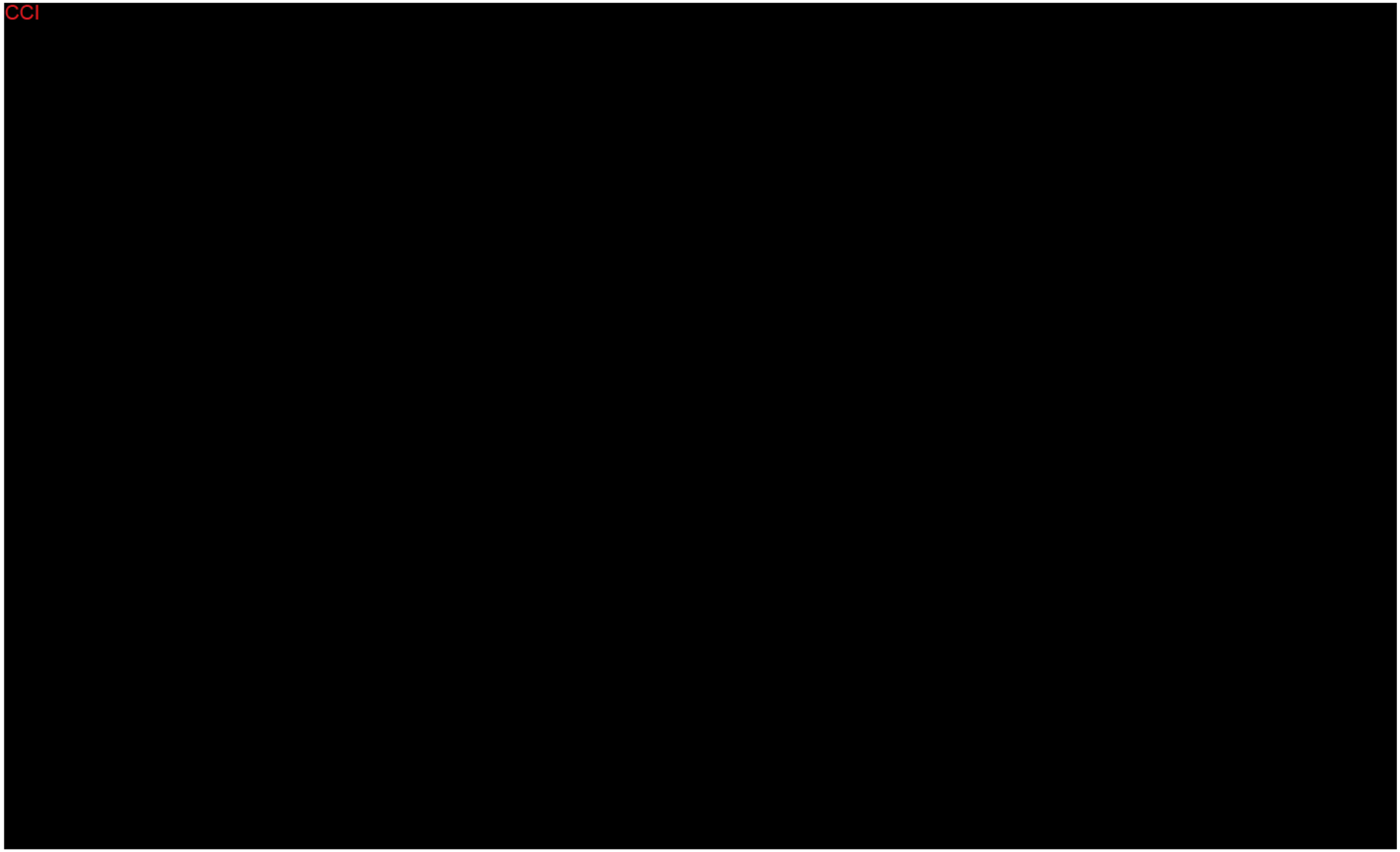

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
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	Clinical Pharmacology Approval	06-Jul-2018 15:41 UTC
	Biostatistics Approval	06-Jul-2018 15:52 UTC
	Clinical Approval	06-Jul-2018 17:40 UTC