EUROPEAN UNION RISK MANAGEMENT PLAN

Sotorasib ([redacted])

Marketing Authorization Applicant:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
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CONFIDENTIALITY STATEMENT

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Risk Management Plan (RMP) version to be assessed as part of this application

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Data lock point of this RMP:	01 September 2020
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Summary of significant changes in this RMP

Not applicable.

Other RMP versions under evaluation:	
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Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind, Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization applicant´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
2H	second half (of year)
ASIR	age-standardized incidence rate
ASMR	age-standardized mortality rate
ALK	anaplastic lymphoma kinase gene
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BRAF	B-raf gene
BUN	blood urea nitrogen
COPD	chronic obstructive pulmonary disease
CRC	colorectal cancer
CSR	clinical study report
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EEA	European Economic Area
EMA	European Medicines Agency
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European Public Assessment Report
EU	European Union
GLP	Good Laboratory Practice
INN	International Nonproprietary Name
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
$KRAS^{G12C}$	KRAS protein with a G12C amino acid substitution
KRAS p.G12C	*KRAS* gene with a mutation resulting in a G12C amino acid substitution at the protein level
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine kinase gene
ORR	objective response rate
OS	overall survival
PFS	progression-free survival

Term/Abbreviation	Explanation
PI	Product Information
PK	pharmacokinetic
PRO	patient reported outcomes
PSUR	Periodic Safety Update Report
RBC	red blood cell
RMP	Risk Management Plan
ROS1	proto-oncogene tyrosine-protein kinase ROS
RWE	Real World Evidence
QPPV	Qualified Person for Pharmacovigilance
SEER	Surveillance, Epidemiology, and End Results Program
SmPC	Summary of Product Characteristics
STD_{10}	toxic dose in 10% of animals
TBD	to be determined
UK	United Kingdom
US	United States
VEGF	vascular endothelial growth factor

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Sotorasib ([redacted])
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Antineoplastic agents, ATC code L01XX73
Marketing authorization applicant	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	To be determined (TBD)
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Antineoplastic agent
Summary of mode of action	Sotorasib is a potent and highly selective $KRAS^{G12C}$ (Kirsten rat sarcoma viral oncogene homolog) inhibitor, which covalently and irreversibly binds to the unique cysteine of $KRAS^{G12C}$. Inactivation of $KRAS^{G12C}$ by sotorasib blocks tumor cell signaling and survival, inhibits cell growth, and promotes apoptosis selectively in tumors harboring $KRAS^{G12C}$, an oncogenic driver of tumorigenesis across multiple cancer types. The potency and selectivity of sotorasib is enhanced through the unique binding to both the P2 pocket and the His95 surface groove, locking the protein in an inactive state that prevents downstream signaling, without affecting wild-type KRAS.
Important information about its composition	Not applicable.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current	Not applicable.
Proposed	Sotorasib is indicated as monotherapy for the treatment of adult patients with previously treated *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC).

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Abbreviations are defined on the next page of this table.

Table 1. Product(s) Overview

Dosage in the EEA	
Current	Not applicable.
Proposed	The recommended dose of sotorasib is 960 mg (eight 120 mg tablets) orally once daily.
Pharmaceutical form(s) and strength(s)	
Current	Not applicable.
Proposed	Yellow, immediate release, film-coated tablet, oblong-shaped (7 mm x 16 mm), debossed with "AMG" on one side and "120" on the reverse.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

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ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; EU = European Union; INN = International Nonproprietary Name; KRAS = Kirsten rat sarcoma viral oncogene homolog (protein); *KRAS* = KRAS protein with a G12C amino acid substitution; KRAS p.G12C = *KRAS* gene with a mutation resulting in a G12C amino acid substitution at the protein level; NSCLC = non-small cell lung cancer; PI = Product Information; RMP = Risk Management Plan

PART II. SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Previously Treated *KRAS p.G12C*-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Incidence	Lung cancer is the third most common cancer in Europe. In 2018, there were 470 039 new lung cancer cases diagnosed in Europe (EU-28) (Bray et al, 2018). The age-standardized incidence rate (ASIR) was 29.8 per 100 000 population and was higher among men (ASIR = 44.3) than women (ASIR = 8.3). Non-small cell lung cancer comprises 80% of lung cancer cases, representing approximately 376 000 new cases in Europe in 2018 (World Health Organization Statistics [WHO], 2018). *KRAS p.G12C* mutation is found in approximately 13% of NSCLC cases (AACR Project GENIE Consortium, 2017; Biernacka et al, 2016; Fernández-Medarde and Santos, 2011) and based on this, the annual incidence of patients with *KRAS p.G12C*-mutated NSCLC in Europe in 2018 was estimated to be 48 884.
Prevalence	The number of 5-year prevalent cases of lung cancer in Europe was estimated to be 497 283 in 2018 (Bray et al, 2018). With NSCLC comprising 80% of lung cancer cases, the 5-year prevalence of NSCLC is estimated to be 397 826 cases. Assuming 13% of all NSCLC cases are patients with *KRAS p.G12C* mutation, the 5-year prevalence of *KRAS p.G12C*-mutated NSCLC is 51 717 in Europe. According to Globocan, 2018, the 1-year prevalence of lung cancer in Europe was estimated to be 244 731; therefore, the prevalence of *KRAS p.G12C*-mutated NSCLC is estimated to be 25 452 cases.
Demographics of population in the proposed indication and risk factors for the disease	Lung cancer incidence and mortality rates are higher among men than women (Bray et al, 2018; Malhotra et al, 2016). In Europe, lung cancer is the leading cause of cancer death among men and the second leading cause of cancer death in women (Ferlay et al, 2018; Torre et al, 2016). Those younger than 40 have a low incidence, while incidence peaks among those aged 65 to 84 years old (Duma et al, 2019; Malhotra et al, 2016). Lung cancer incidence and mortality rates vary substantially across geography and demographics in Europe, largely reflecting variations in patterns of tobacco smoking (Duma et al, 2019; Malhotra et al, 2016; Torre et al, 2016; Brennan et al, 2011; Molina et al, 2008). Cigarette smoking is an important risk factor, accounting for 85% to 90% of lung cancers (Duma et al, 2019). For men in Europe, lung cancer incidence rates per 100 000 population are highest in Central and Eastern Europe (ASIR = 49.3), slightly lower in Western (ASIR = 43.3) and Southern Europe (ASIR = 43.1); and lowest in Northern Europe (ASIR = 34). Similar geographical variation is observed for mortality in men. For women in Europe, lung cancer incidence rates are highest in Northern (ASIR = 26.9) and Western (ASIR = 25.7) Europe; and lower rates are found in Southern (ASIR = 15.7) and Central and Eastern Europe (ASIR = 11.9). Similar geographical variation is observed for mortality in women (Ferlay et al, 2018).

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Abbreviations are defined on the last page of this table

Table 2. Summary of Epidemiology of Previously Treated KRAS p.G12C-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Demographics of population in the proposed indication and risk factors for the disease (continued)	Over the past 2 decades, lung cancer incidence and mortality among men have been declining in most European countries, whilst among women they have been increasing (Malhotra et al, 2016; Jemal et al, 2010). These trends reflect the difference in smoking patterns; the prevalence of smoking among men has been decreasing for a longer time than it has been for women (Torre et al, 2016). Risk factors for lung cancer include: • cigarette smoking (Duma et al, 2019; Molina et al, 2008) • passive or secondhand smoking (Molina et al, 2008) • family history of lung cancer including high-penetrance genes and genetic polymorphisms (Brennan et al, 2011; Biesalski et al, 1998) • exposure to non-tobacco procarcinogens, carcinogens, and tumor promoters (Biesalski et al, 1998) • occupational exposures, including asbestos, antifungal outdoor wood preservatives, insecticides, herbicides, beryllium and beryllium oxide (X-ray and radiation technology), inhaled chemicals including cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ester and diesel exhaust (Loomis et al, 2018) • exposure to high particulate matter (Raaschou-Nielsen et al, 2013; Brennan et al, 2011) • previous tobacco-related cancer (Biesalski et al, 1998) • previous chronic inflammatory lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, and tuberculosis (Houghton, 2013; Rosenberger et al, 2012; Liang et al, 2009) Results from Amgen Real World Evidence (RWE) Studies [redacted] and [redacted] n the US showed that patients with *KRAS p.G12C*-mutated advanced NSCLC had similar demographic and clinical characteristics compared with the overall group of patients with advanced NSCLC; however, higher proportions of women, past or present smokers, and non-squamous cell carcinoma histology were observed in patients with *KRAS p.G12C*-mutated advanced NSCLC.
Main existing treatment options	Treatment of advanced NSCLC has unequivocally improved since the discovery of immunotherapies (the checkpoint inhibitors) and targeted therapies for a variety of oncogenic driver mutations (Planchard et al, 2018; Ettinger et al, 2017). However, no anticancer therapies are currently approved that specifically target tumors that have the *KRAS p.G12C* mutation (Román et al, 2018; McCormick, 2016). Further, oncogenic *KRAS* mutations rarely occur concomitantly with other actionable oncogenic driver mutations (Amgen RWE Studies [redacted], and [redacted]; Scheffler et al, 2019; Martorell et al, 2017; Gainor et al, 2013). Thus, most patients with oncogenic *KRAS* mutations, including the *KRAS p.G12C* mutation are not candidates for currently approved targeted therapies and consequently are typically treated as patients without targetable mutations (ie, with chemotherapy, immunotherapy, or antiangiogenic agents) (Planchard et al, 2018; Van Cutsem et al, 2014).

Abbreviations are defined on the last page of this table

Table 2. Summary of Epidemiology of Previously Treated KRAS p.G12C-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Main existing treatment options (continued)	In first-line therapy, patients with NSCLC without actionable oncogenic driver mutations are typically treated with checkpoint inhibitors with or without chemotherapy (eg, checkpoint inhibitors with or without platinum-containing doublets such as cisplatin/pemetrexed). Patients requiring subsequent second-line or later therapy for the disease are commonly treated with taxane chemotherapy (eg, docetaxel) with or without a vascular endothelial growth factor (VEGF) inhibitor or checkpoint inhibitors/platinum-containing doublet chemotherapy (if not already given in first-line). Patients whose tumors have been screened and identified to have "actionable" mutations (eg, *EGFR*, *ALK*, *ROS1*, *BRAF*, *NTRK*) may also receive targeted therapies directed at these specific oncogenic driver mutations in first or later lines (Planchard et al, 2018).
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Lung cancer is the leading cause of cancer death in Europe, representing 20% of all cancer deaths (Ferlay et al, 2018). In 2018, the age-standardized mortality rate (ASMR) in Europe was 23.5 per 100 000 population. The ASMR was higher among men (ASMR = 36.8) than women (ASMR = 13.0). There was some geographical variation in mortality rates across Western (ASMR = 24.6), Central and Eastern (ASMR = 23.6), Southern (ASMR = 22.7) and Northern Europe (ASMR = 21.3). Results from the EUROCARE-5 study found that European patients with lung cancer diagnosed between 2000 to 2007 had a mean age-standardized 5-year survival of 13.0%, varying from 9.0% in the UK and Ireland, 10.6% in Eastern Europe, 12.2% in Northern Europe, 13.2% in Southern Europe to 14.8% in central Europe (De Angelis et al, 2014). Non-small cell lung cancer accounts for the majority of lung cancer cases and 5-year survival is approximately 15% (Molina et al, 2008). The Eindhoven Cancer Registry in the Netherlands found that between 1993 to 1997 the relative 5-year survival rate for those with NSCLC in Europe was 19% for those < 70 years old and 16% for those ≥ 70 years old (Janssen-Heijnen and Coebergh, 2003). Survival depends on stage at diagnosis with earlier stage at diagnosis showing better survival (Torre et al, 2016).

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Table 2. Summary of Epidemiology of Previously Treated KRAS p.G12C-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Natural history of the indicated condition in the untreated population, including mortality and morbidity (continued)

In Germany, the 5-year survival from diagnosis decreases significantly from Stage III (men: 17%, and female: 17%) and Stage IV (men: 3%, and female: 5%) (Robert Koch Institute, 2019). Similar 5-year net survival rates were observed in the UK, Stage III is 12.6% (men: 11.6%, and female: 13.7%) and decreases to 2.9% for Stage IV (men: 2.3%, and female: 3.4%) (Office for National Statistics, 2019). In comparison, in the US, the 5-year relative survival rate for advanced NSCLC is 5.2% (Surveillance, Epidemiology, and End Results Program [SEER], 2019). Data from the French National Cancer Institute indicate that patients with *KRAS*-mutated NSCLC show a lower proportion of responses to cytotoxic chemotherapy and decreased survival compared with the overall population of patients with NSCLC (Barlesi et al, 2016), and this finding has been supported by other data indicating that patients with *KRAS*-mutated NSCLC have a poor prognosis (Wiesweg et al, 2019; Park et al, 2017; Hames et al, 2016; Svaton et al, 2016; Johnson et al, 2013).

Overall, the results from the Amgen natural history studies (Amgen RWE Studies [redacted] and [redacted] and published literature show that patients with *KRAS p.G12C*-mutated advanced NSCLC had poor treatment outcomes with existing therapies in second line or later, and their prognosis was as poor as the overall advanced NSCLC population, highlighting the unmet medical need for this patient population.

Real-world outcomes for patients with advanced NSCLC and *KRAS p.G12C*-mutated advanced NSCLC by line of therapy:

	KRAS p.G12C-mutated NSCLC		All NSCLC
Line of Therapy	Study [redacted]	Study [redacted]	Study [redacted]
Median (95% CI) OS (months)			
First	14.9 (12.2, 24.3)	12.0 (9.6, 15.3)	12.9 (11.9, 14.2)
Second	10.1 (7.1, 16.9)	9.5 (8.1, 13.1)	10.2 (9.5, 11.3)
Third	6.5 (5.0, NE)	6.7 (5.9, 10.7)	7.9 (6.6, 8.8)
Fourth	3.0 (2.2, NE)	5.9 (4.3, 12.9)	7.4 (6.4, 8.6)
Median (95% CI) real-world PFS (months)			
First	6.1 (4.4, 9.3)	5.0 (4.4, 5.8)	5.6 (5.3, 5.8)
Second	3.2 (2.1, 5.3)	4.0 (2.8, 5.3)	4.0 (3.7, 4.4)
Third	2.3 (1.4, 4.1)	3.1 (2.4, 4.3)	3.5 (3.1, 3.9)
Fourth	1.8 (1.4, 15.0)	2.6 (2.1, 4.7)	3.0 (2.7, 3.4)

[a] Retrospective Study [redacted] was conducted using the American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange database in 416 patients with *KRAS p.G12C*-mutated advanced NSCLC. Retrospective Studies [redacted] and [redacted] were conducted using the United States Flatiron Health - Foundation Medicine Clinico-Genomic Database in 743 patients with *KRAS p.G12C*-mutated advanced NSCLC and 7069 patients with advanced NSCLC (ie, regardless of *KRAS p.G12C* mutation), respectively.

Abbreviations are defined on the last page of this table

Table 2. Summary of Epidemiology of Previously Treated KRAS p.G12C-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Important comorbidities	Lung cancer is most frequent in smokers, and these patients frequently have tobacco-related conditions, mainly cardiovascular and other respiratory diseases (eg, COPD) (Leduc et al, 2017; Al-Kindi and Oliviera, 2016; Kravchenko et al, 2015; van Herk-Sukel et al, 2013; Young et al, 2009). Other unrelated comorbidities that are frequent include diabetes and its complications (eg, renal insufficiency, cardiovascular disease). The prevalence of these comorbidities vary by country which likely reflects the differences in lifestyle behaviors (eg, smoking and diet) (Herrero Rivera et al, 2019; Linden et al, 2020; Lembicz et al, 2018; Leduc et al, 2017; Kocher et al, 2015).

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ALK = anaplastic lymphoma kinase gene; ASIR = age-standardized incidence rate; ASMR = age standardized mortality rate; *BRAF* = B-raf gene; COPD = chronic obstructive pulmonary disease; *EGFR* = epidermal growth factor receptor gene; EU = European Union; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic tyrosine kinase gene; *ROS1* = proto-oncogene tyrosine-protein kinase ROS; RWE = real word evidence; UK = United Kingdom; US = United States; VEGF = vascular endothelial growth factor.

Part II: Module SII – Nonclinical Part of the Safety Specification

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity		
Key issues identified from single or repeat-dose toxicity studies	Renal tubular degeneration/necrosis was observed in the rat repeat-dose toxicology studies. The incidence and severity of tubular degeneration/necrosis was dependent on dose/exposure levels and treatment duration. In the rat 28-day study, sotorasib was well tolerated at 0, 10, 30, and 200 mg/kg; the severely toxic dose in 10% of animals (STD_{10}) was > 200 mg/kg, based on minimal to mild renal tubular degeneration/necrosis at 200 mg/kg. In the 3 month study (60, 180, and 750 mg/kg), the STD_{10} was 180 mg/kg. Renal tubular degeneration/necrosis increased in both incidence and severity (minimal to marked) compared to the renal changes in the 28-day study. This was attributed to the longer study duration and higher systemic exposures to sotorasib. At the end of the recovery phase, there was partial recovery at all dose levels. The time-course assessment revealed that the renal tubular changes at 750 mg/kg were associated with changes in serum or urine biomarkers such as blood urea nitrogen (BUN), creatinine, Kim-1 and clusterin in early phase (days 2 and 4); therefore, the toxicologically significant renal toxicity was monitorable with these biomarkers in the rat. No renal toxicity was identified in the dog.	Clinical data from pivotal Study [redacted] did not suggest a risk of renal toxicity with sotorasib use. Renal function is assessed in clinical studies. Specific eligibility criteria and dose modification guidelines for sotorasib are provided in the clinical study protocols.

Abbreviations are defined on the last page of this table

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity (continued)		
Key issues identified from single or repeat-dose toxicity studies (continued)	In a GLP 3-month dog toxicology study (0, 200, and 1000 mg/kg/day administered as 100 and 500 mg/kg twice daily [BID]), there were abnormal content in the gall bladder, and microscopic changes in the liver (hepatocellular hypertrophy with increased liver weight), pituitary (hypertrophy of basophils with increased pituitary weight), or thyroid (decreased colloid and hypertrophy of follicular epithelium with decreased thyroid weight) that were considered to be non-severely toxic and attributed to an adaptive or secondary response to hepatocellular enzyme induction. The highest non-severely toxic dose was 1000 mg/kg/day.	Clinical data from pivotal Study [redacted] did not suggest a risk of hypothyroidism or thyroid dysfunction; however, clinical safety data for potential effects on thyroid function have not been accumulated sufficiently enough to conclude the clinical relevance for the findings observed in the dog. Sotorasib clinical study protocols include thyroid function testing at screening, predose on day 1 of each cycle, at the end of treatment, and at safety follow-up. Clinical signs or symptoms concerning for thyroid dysfunction are assessed in clinical studies.
	Decrease in red blood cell (RBC) mass (hemoglobin, RBC count, and hematocrit) was observed in both rat and dog toxicology studies. Due to the small magnitudes of change, the sotorasib-related effects on hematology parameters were considered non-adverse and were reversible after a 28-day recovery in rats. Reversibility was expected based on the normal regenerative capacity of the hematopoietic system and the absence of overt bone-marrow toxicity (eg, hypocellularity).	Clinical data from pivotal Study [redacted] did not suggest a risk of clinically significant changes to RBC parameters with sotorasib use. Monitoring of hemoglobin, hematocrit, and associated adverse events will be conducted in ongoing and planned sotorasib clinical studies. Specific eligibility criteria and dose modification guidelines pertaining to hematology parameters are provided in the sotorasib clinical study protocol.

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Abbreviations are defined on the last page of this table

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity (continued)		
Reproductive/developmental toxicity	There were no adverse effects on male or female reproductive organs in general toxicology studies conducted in dogs and rats. In the rat and rabbit embryo-fetal development toxicology studies, sotorasib was not teratogenic. In the rat, there were no effects on embryo-fetal development up to the high dose (540 mg/kg) tested. In the rabbit, lower fetal body weights and a reduction in the number of ossified metacarpals in fetuses were observed only at the dose level (100 mg/kg) associated with decreased body weight gain and food consumption in dams during dosing phase. Reduced ossification as an evidence of growth retardation associated with reduced fetal body weight was interpreted as a non-specific fetal effect in the presence of significant maternal toxicity (Nitzsche, 2017).	There are no data from the use of sotorasib in pregnant women, it is unknown if sotorasib or its metabolites are excreted in human milk, and there are no clinical studies to evaluate the effect of sotorasib on fertility. Patients must be informed of the potential hazards to the fetus if sotorasib is used during pregnancy, or if the patient becomes pregnant whilst taking sotorasib. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from sotorasib therapy whilst breastfeeding, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

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BID = twice daily; BUN = blood urea nitrogen; GLP = Good Laboratory Practice; RBC = red blood cell; STD_{10} = severely toxic dose in 10% of animals

Part II: Module SIII – Clinical Trial Exposure

Table 4. Total Subject Exposure to Sotorasib in Clinical Trials by Indication and Duration
Safety Analysis Set

	Exposure by Duration						
Indication/therapy	< 1 Month n (subj-yrs)	1 - < 3 Months n (subj-yrs)	3 - < 6 Months n (subj-yrs)	6 - < 9 Months n (subj-yrs)	9 - < 12 Months n (subj-yrs)	≥ 12 Months n (subj-yrs)	Total n (subj-yrs)
All monotherapy indications	32 (1.44)	142 (24.21)	141 (51.47)	57 (35.49)	43 (35.68)	15 (17.28)	430 (165.57)
NSCLC	18 (0.86)	72 (12.19)	71 (25.28)	40 (25.31)	40 (32.89)	9 (10.40)	250 (106.93)
CRC	5 (0.25)	43 (7.45)	47 (17.40)	12 (7.15)	3 (2.79)	4 (4.28)	114 (39.33)
Other tumor types	8 (0.32)	26 (4.45)	22 (8.50)	5 (3.03)	0 (0.00)	2 (2.60)	63 (18.90)
Missing[a]	1 (0.01)	1 (0.12)	1 (0.29)	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.41)
All combination therapy - Exposure to sotorasib	23 (1.18)	28 (4.16)	8 (2.75)	2 (1.18)	2 (1.68)	0 (0.00)	63 (10.95)
Pembrolizumab combination	2 (0.09)	4 (0.65)	3 (1.01)	0 (0.00)	2 (1.68)	0 (0.00)	11 (3.44)
Trametinib combination	12 (0.62)	16 (2.43)	5 (1.74)	2 (1.18)	0 (0.00)	0 (0.00)	35 (5.97)
SHP2 (RMC-4630) combination	0 (0.00)	3 (0.38)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.38)
EGFR (afatinib) combination	2 (0.14)	3 (0.42)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.56)
Atezo combination	5 (0.21)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.21)
Panitumumab combination	2 (0.12)	2 (0.27)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.39)
Healthy volunteers	118 (2.20)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	118 (2.20)
Total	173 (4.82)	170 (28.38)	149 (54.22)	59 (36.67)	45 (37.37)	15 (17.28)	611 (178.72)

CRC = colorectal cancer; *EGFR* = epidermal growth factor receptor; NSCLC = non-small cell lung cancer.
n = number of subjects exposed to treatment; subj-yrs = total subject-yrs of follow-up.
[a] At the time of snapshot, the indication was not known.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Monotherapy includes subjects in studies [redacted] (phase 1 cutoff 06 July 2020, phase 2 cutoff 01 September 2020), and [redacted] (snapshot 01 September 2020)
Pembrolizumab combination therapy includes subjects in Study [redacted]. Other combination therapies includes subjects in Study [redacted] subprotocols (snapshot 01 September 2020) A: Trametinib, C: SHP2 (RMC-4630), D: Afatinib, E: Atezo, H: Panitumumab.
Healthy volunteers include subjects in studies [redacted], and [redacted].
[redacted]

Table 5. Total Subject Exposure to Sotorasib in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Adults (18 to < 65 years) n (subj-yrs)	Elderly (65 to < 75 years) n (subj-yrs)	Geriatric (≥ 75 years) n (subj-yrs)
Male			
All monotherapy indications	105 (37.20)	74 (32.99)	24 (7.90)
NSCLC	41 (17.61)	54 (26.41)	14 (4.72)
CRC	38 (12.71)	9 (3.96)	6 (1.82)
Other tumor types	24 (6.58)	10 (2.51)	4 (1.36)
Missing	2 (0.30)	1 (0.12)	0 (0.00)
All combination therapy - Exposure to sotorasib	20 (3.32)	7 (0.50)	2 (0.14)
Pembrolizumab combination	2 (0.19)	0 (0.00)	0 (0.00)
Trametinib combination	12 (2.65)	3 (0.29)	2 (0.14)
SHP2 (RMC-4630) combination	2 (0.25)	0 (0.00)	0 (0.00)
EGFR (Afatinib) combination	1 (0.06)	1 (0.08)	0 (0.00)
Atezo combination	2 (0.08)	3 (0.13)	0 (0.00)
Panitumumab combination	1 (0.08)	0 (0.00)	0 (0.00)
Healthy volunteers	103 (1.96)	0 (0.00)	0 (0.00)
Total	228 (42.49)	81 (33.49)	26 (8.04)

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Footnotes and abbreviations are defined on the last page of this table.

Table 5. Total Subject Exposure to Sotorasib in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Adults (18 to < 65 years) n (subj-yrs)	Elderly (65 to < 75 years) n (subj-yrs)	Geriatric (≥ 75 years) n (subj-yrs)
Female			
All monotherapy indications	127 (50.93)	77 (27.23)	23 (9.32)
NSCLC	66 (28.70)	55 (20.75)	20 (8.74)
CRC	47 (17.13)	12 (3.18)	2 (0.53)
Other tumor types	14 (5.09)	10 (3.30)	1 (0.05)
Missing	0 (0.00)	0 (0.00)	0 (0.00)
All combination therapy - Exposure to sotorasib	21 (4.82)	9 (1.72)	4 (0.45)
Pembrolizumab combination	5 (2.25)	4 (1.00)	0 (0.00)
Trametinib combination	11 (1.99)	4 (0.60)	3 (0.30)
SHP2 (RMC-4630) combination	0 (0.00)	1 (0.12)	0 (0.00)
EGFR (Afatinib) combination	3 (0.42)	0 (0.00)	0 (0.00)
Atezo combination	0 (0.00)	0 (0.00)	0 (0.00)
Panitumumab combination	2 (0.16)	0 (0.00)	1 (0.16)
Healthy volunteers	15 (0.24)	0 (0.00)	0 (0.00)
Total	163 (55.99)	86 (28.95)	27 (9.77)

CRC = colorectal cancer; *EGFR* = epidermal growth factor receptor; NSCLC = non-small cell lung cancer.
n = number of subjects exposed to treatment; subj-yrs = total subject-yrs of follow-up.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Monotherapy includes subjects in studies [redacted] (phase 1 cutoff 06 July 2020, phase 2 cutoff 01 September 2020), and [redacted] (snapshot 01September 2020).
Pembrolizumab combination therapy includes subjects in Study [redacted] Other combination therapies includes subjects in Study [redacted] subprotocols (snapshot 01 September 2020) A: Trametinib, C: SHP2 (RMC-4630), D: Afatinib, E: Atezo, H: Panitumumab.
Healthy volunteers include subjects in studies [redacted], and [redacted].
[redacted]

Table 6. Total Subject Exposure to Sotorasib in Clinical Trials by Dose Level and Indication
Safety Analysis Set

	180mg QD n (mean exposure in days) (subj-yrs)	360mg QD n (mean exposure in days) (subj-yrs)	720mg QD n (mean exposure in days) (subj-yrs)	960mg QD n (mean exposure in days) (subj-yrs)	480mg BID n (mean exposure in days) (subj-yrs)
All monotherapy indications	6 (208.8) (3.43)	27 (140.4) (10.38)	11 (188.2) (5.67)	360 (143.0) (140.95)	26 (72.3) (5.14)
NSCLC	3 (284.3) (2.34)	16 (139.1) (6.09)	6 (199.7) (3.28)	204 (163.0) (91.06)	21 (72.3) (4.16)
CRC	3 (133.3) (1.10)	10 (100.2) (2.74)	4 (153.8) (1.68)	92 (130.3) (32.83)	5 (72.0) (0.99)
Other tumor types	0 (0.0) (0.00)	1 (565.0) (1.55)	1 (257.0) (0.70)	61 (99.7) (16.65)	0 (0.0) (0.00)
Missing	0 (0.0) (0.00)	0 (0.0) (0.00)	0 (0.0) (0.00)	3 (50.3) (0.41)	0 (0.0) (0.00)
All combination therapy - Exposure to sotorasib	0 (0.0) (0.00)	7 (39.1) (0.75)	2 (120.5) (0.66)	54 (64.5) (9.54)	0 (0.0) (0.00)
Pembrolizumab combination	0 (0.0) (0.00)	5 (48.6) (0.67)	2 (120.5) (0.66)	4 (193.0) (2.11)	0 (0.0) (0.00)
Trametinib combination	0 (0.0) (0.00)	0 (0.0) (0.00)	0 (0.0) (0.00)	35 (62.3) (5.97)	0 (0.0) (0.00)
SHP2 (RMC-4630) combination	0 (0.0) (0.00)	0 (0.0) (0.00)	0 (0.0) (0.00)	3 (45.7) (0.38)	0 (0.0) (0.00)
EGFR (Afatinib) combination	0 (0.0) (0.00)	0 (0.0) (0.00)	0 (0.0) (0.00)	5 (41.2) (0.56)	0 (0.0) (0.00)
Atezo combination	0 (0.0) (0.00)	2 (15.5) (0.08)	0 (0.0) (0.00)	3 (15.3) (0.13)	0 (0.0) (0.00)
Panitumumab combination	0 (0.0) (0.00)	0 (0.0) (0.00)	0 (0.0) (0.00)	4 (36.0) (0.39)	0 (0.0) (0.00)
Healthy volunteers	0 (0.0) (0.00)	28 (5.0) (0.38)	8 (1.0) (0.02)	82 (8.0) (1.80)	0 (0.0) (0.00)
Total	6 (208.8) (3.43)	62 (67.8) (11.52)	21 (110.4) (6.35)	496 (112.1) (152.28)	26 (72.3) (5.14)

BID = twice daily; CRC = colorectal cancer; *EGFR* = epidermal growth factor receptor; NSCLC = non-small cell lung cancer;
Mean exposure in days = average number of days per subject; n = number of subjects exposed to treatment; subj-yrs = total subject-yrs of follow-up.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Monotherapy includes subjects in studies [redacted] (phase 1 cutoff 06 July 2020, phase 2 cutoff 01 September 2020), and [redacted] (snapshot 01 September 2020)
Pembrolizumab combination therapy includes subjects in Study [redacted]. Other combination therapies includes subjects in Study [redacted] subprotocols (snapshot 01 September 2020) A: Trametinib, C: SHP2 (RMC-4630), D: Afatinib, E: Atezo, H: Panitumumab.
Healthy volunteers include subjects in studies [redacted], and [redacted].

Table 7. Total Subject Exposure to Sotorasib in Clinical Trials by Product and Race Group
Safety Analysis Set

	White n (subj-yrs)	Black or African American n (subj-yrs)	American Indian or Alaska Native n (subj-yrs)	Asian n (subj-yrs)	Other n (subj-yrs)	Total n (subj-yrs)
All monotherapy indications	332 (132.56)	12 (2.83)	0 (0.00)	70 (25.25)	16 (4.93)	430 (165.57)
NSCLC	204 (90.43)	8 (2.00)	0 (0.00)	31 (12.39)	7 (2.11)	250 (106.93)
CRC	82 (28.13)	2 (0.40)	0 (0.00)	24 (9.26)	6 (1.54)	114 (39.33)
Other tumor types	46 (14.00)	2 (0.42)	0 (0.00)	12 (3.19)	3 (1.28)	63 (18.90)
Missing	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.41)	0 (0.00)	3 (0.41)
All combination therapy - Exposure to sotorasib	51 (9.21)	7 (1.05)	2 (0.27)	1 (0.06)	2 (0.36)	63 (10.95)
Pembrolizumab combination	10 (3.31)	0 (0.00)	1 (0.13)	0 (0.00)	0 (0.00)	11 (3.44)
Trametinib combination	28 (4.72)	4 (0.84)	0 (0.00)	1 (0.06)	2 (0.36)	35 (5.97)
SHP2 (RMC-4630) combination	1 (0.12)	1 (0.12)	1 (0.14)	0 (0.00)	0 (0.00)	3 (0.38)
EGFR (Afatinib) combination	5 (0.56)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.56)
Atezo combination	4 (0.15)	1 (0.06)	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.21)
Panitumumab combination	3 (0.35)	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.39)
Healthy volunteers	63 (1.03)	50 (1.06)	0 (0.00)	3 (0.07)	2 (0.04)	118 (2.20)
Total	446 (142.81)	69 (4.94)	2 (0.27)	74 (25.38)	20 (5.33)	611 (178.72)

CRC = colorectal cancer; *EGFR* = epidermal growth factor receptor; NSCLC = non-small cell lung cancer.
n = number of subjects exposed to treatment; subj-yrs = total subject-yrs of follow-up.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Monotherapy includes subjects in studies [redacted] (phase 1 cutoff 06 July 2020, phase 2 cutoff 01 September 2020), and [redacted] (snapshot 01 September 2020).
Pembrolizumab combination therapy includes subjects in Study [redacted] Other combination therapies includes subjects in Study [redacted] subprotocols (snapshot 01 September 2020) A: Trametinib, C: SHP2 (RMC-4630), D: Afatinib, E: Atezo, H: Panitumumab.
Healthy volunteers include subjects in studies [redacted], and [redacted].

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subject is pregnant or breastfeeding, or planning to become pregnant.	Adequate and well-controlled studies with sotorasib have not been conducted in pregnant women due to the potential risk to the fetus. It is not known if sotorasib or its metabolites are excreted in human milk	No	Non-small cell lung cancer (NSCLC) is mostly a disease of the elderly and it is anticipated to have a low number of female patients of child-bearing potential. The Summary of Product Characteristics (SmPC) states that patients must be informed of the potential hazards to the fetus if sotorasib is used during pregnancy, or if the patient becomes pregnant while taking sotorasib. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sotorasib therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Hypersensitivity to the active substance or to any of the excipients	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing hypersensitivity to the product.	No	Sotorasib is contraindicated in patients with a known hypersensitivity to the active ingredient or to any of the excipients.
Active infection requiring intravenous (IV) antibiotics within 1 week of study enrollment (day 1)	To ensure that the evaluation for the safety profile in clinical studies was not affected by underlying infection.	No	Preliminary data do not suggest that sotorasib affects underlying infection.

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Abbreviations are defined on the last page of this table

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
History or presence of hematological malignancies unless curatively treated with no evidence of disease ≥ 2 years	Due to competing risks of death due to other active cancer the treatment effect of sotorasib in this setting would be confounded. This patient population was excluded from clinical studies to enable clearer interpretation of data.	No	The coexistence of another active malignancy is unlikely to predict adverse outcome with sotorasib. Limited clinical data are available in this population. The safety profile is not expected to differ in this population.
Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Association > class II), unstable angina, or cardiac arrhythmia requiring medication	To ensure that the evaluation of the safety profile in clinical studies was not affected by pre-existing cardiac conditions.	No	No effect of sotorasib on cardiac function is known or suspected. The safety and efficacy of sotorasib is not expected to differ between subjects with or without cardiac disease.
Active brain metastases from non-brain tumors	Due to the poor outcome and short survival of subjects with active (untreated) brain metastases, the efficacy and safety of sotorasib could not be accurately evaluated in the pivotal phase 2 portion of the single cohort study (Study [redacted]). Furthermore, the appropriate therapy for untreated brain metastases is brain-directed therapy. Once the brain is treated, subjects were eligible to be enrolled in this pivotal study.	No	No effect of sotorasib on brain tissue is known or suspected. The safety profile is not expected to differ in this population.

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Abbreviations are defined on the last page of this table.

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2	Due to the poor outcome and short survival of subjects with ECOG performance ≥ 2, the efficacy and safety of sotorasib may not be accurately evaluated in the pivotal phase 2 part of the single cohort study (Study [redacted]).	No	The mechanism of action of sotorasib does not suggest that subjects with ECOG performance of ≥ 2 would have any specific safety issues related to the drug. Subjects with an ECOG performance of 2 were excluded from the pivotal phase 2 part of Study [redacted], but are eligible in some other sotorasib clinical studies. The safety profile is not expected to differ in this population.
Moderate or severe renal impairment	Subjects with moderate or severe renal impairment were excluded to ensure that the interpretation of safety profile in clinical studies was not affected by pre-existing renal dysfunction.	No	Sotorasib is primarily metabolized by the liver, with minimal renal elimination; therefore, the safety profile is not expected to differ in this patient population. Preliminary data do not suggest a risk of renal toxicity with sotorasib use. There is no evidence to suggest that the pharmacokinetics (PK) of sotorasib are affected by renal function impairment.
Moderate or severe hepatic impairment	Subjects with moderate or severe hepatic impairment were excluded to ensure that the interpretation of safety profile in clinical studies was not affected by pre-existing hepatic dysfunction.	Yes	Not applicable.

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ECOG = Eastern Cooperative Oncology Group; IV = intravenous; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; SmPC = Summary of Product Characteristics.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 9. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the clinical development program
Patients with renal impairment	Not included in the clinical development program
Patients with cardiovascular impairment	Not included in the clinical development program
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Table 7 provides the race of subjects included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Part II: Module SV – Postauthorization Experience

SV.1 Postauthorization Exposure

Sotorasib has not been authorized for marketing in any country.

SV.1.1 Method Used to Calculate Exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI – Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 10. Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks
Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the Product Information are adhered to by prescribers (eg, actions being part of standard clinical practice in each European Union Member state where the product is authorized)	Increased liver enzymes

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are currently no risks considered important for inclusion in the list of safety concerns for sotorasib.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable, as this is an initial marketing authorization application.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2 Presentation of the Missing Information

Table 11. Missing Information: Use in Patients with Hepatic Impairment

Evidence source	No formal studies of sotorasib have been conducted in subjects with hepatic impairment.
Population in need of further characterization	Study [redacted], an open-label, non-randomized, absorption, metabolism, and excretion study of sotorasib in healthy subjects, was performed to characterize the primary route of elimination of sotorasib after oral administration. The results showed that sotorasib is primarily metabolized by the liver, with minimal renal elimination. Results from a population PK analysis from clinical studies, performed to characterize the PK of sotorasib in healthy subjects and subjects with advanced solid tumors, did not show significant effects of sotorasib apparent clearance in subjects with hepatic impairment (mild [n = 83], and moderate [n = 3]) evaluated by the National Cancer Institute (NCI) Organ Dysfunction Working Group. Sotorasib has not been administered to individuals with severe hepatic impairment; therefore, it is not known how the PK of sotorasib will be affected in this patient population and whether this will affect the safety and efficacy of sotorasib in these individuals. A clinical pharmacology, single-dose PK study (Study [redacted]) in healthy volunteers and subjects with moderate and severe hepatic impairment (non-oncology population) is planned.

NCI = National Cancer Institute; PK = pharmacokinetic

Part II: Module SVIII - Summary of the Safety Concerns

Table 12. Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in patients with hepatic impairment

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

There are no further routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

III.2 Additional Pharmacovigilance Activities

Table 13. Category 1 to 3 Postauthorization Safety Studies

Study Short Name, Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Study [redacted] An open label study to evaluate the pharmacokinetics of AMG 510 in healthy subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Category 3	Primary objectives: • To evaluate the PK of a single 960 mg oral dose of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Secondary objectives: • To evaluate the safety and tolerability of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Safety concerns addressed: • Use in patients with hepatic impairment	Single-dose, PK study	Healthy volunteers Subjects with moderate and severe hepatic impairment (non-oncology indication)	Protocol submission: [redacted] Final CSR: [redacted]

CSR = clinical study report; PK = pharmacokinetic; TBD = to be determined.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 14. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study [redacted] An open label study to evaluate the pharmacokinetics of AMG 510 in healthy subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Planned	Primary objectives: • To evaluate the PK of a single 960 mg oral dose of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Secondary objectives: • To evaluate the safety and tolerability of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment	Use in patients with hepatic impairment	Protocol submission Final CSR	[redacted] [redacted]

CSR = clinical study report; PK = pharmacokinetic; TBD = to be determined.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table 15. (Table Part IV.1) Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Study [redacted] A phase 3, multicenter, randomized, open-label, active-controlled study of AMG 510 versus docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic NSCLC subjects with mutated *KRAS p.G12C* Ongoing	Primary Objectives • To compare the efficacy of AMG 510 versus docetaxel as assessed by progression-free survival (PFS) in previously treated subjects with *KRAS p.G12C* mutated non-small cell lung cancer (NSCLC) Key Secondary Objectives • To compare the efficacy of AMG 510 versus docetaxel as assessed by: – Overall Survival (OS) – Objective response rate (ORR) • To compare patient reported outcomes (PRO) as assessed by: – European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 13 (EORTC QLQ-LC13) – European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30)	Preliminary efficacy	CSR for primary analysis (PFS)	[redacted]

2H = second half (of year); CSR = clinical study report; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 16. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
None	
Important Potential Risks	
None	
Missing Information	
Use in patients with hepatic impairment	Routine risk communication: • SmPC Section 4.2 • SmPC Section 5.2 Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other risk minimization measures beyond the PI: • Medicine's legal status: Medicinal product subject to restricted medical prescription

PI = Product Information; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

Not applicable.

V.3 Summary of Risk Minimization Measures

Table 17. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
None		
Important Potential Risks		
None		
Missing Information		
Use in patients with hepatic impairment	Routine risk minimization measures: • SmPC Sections 4.2 and 5.2 • Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study [redacted]

PK = pharmacokinetic; SmPC = Summary of Product Characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the Risk Management Plan for sotorasib is presented below.

Summary of Risk Management Plan for Lumakras™ (Sotorasib)

This is a summary of the risk management plan (RMP) for Lumakras™. The RMP details important risks of Lumakras, how these risks can be minimized, and how more information will be obtained about Lumakras's risks and uncertainties (missing information).

Lumakras's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lumakras should be used.

This summary of the RMP for Lumakras should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lumakras's RMP.

I. The medicine and what it is used for

Lumakras is authorized as monotherapy for the treatment of adult patients with previously treated Kirsten rat sarcoma viral oncogene homolog *(KRAS) G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC)] (see SmPC for the full indication). It contains sotorasib as the active substance and it is given orally.

Further information about the evaluation of Lumakras's benefits can be found in Lumakras's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Lumakras's, together with measures to minimize such risks and the proposed studies for learning more about Lumakras's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Lumakras is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Lumakras are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lumakras. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in patients with hepatic impairment

II.B. Summary of Important Risks

Important Missing information: Use in patients with hepatic impairment	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 5.2 Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other risk minimization measures beyond the Product Information (PI): • Medicine's legal status: Medicinal product subject to restricted medical prescription Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study [redacted] See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization.

Study Short Name	Purpose of the Study
Study [redacted] A phase 3, multicenter, randomized, open-label, active-controlled study of AMG 510 versus docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic NSCLC subjects with mutated *KRAS p.G12C*	Primary Objectives: • To compare the efficacy of AMG 510 versus docetaxel as assessed by progression-free survival (PFS) in previously treated subjects with *KRAS p.G12C* mutated non-small cell lung cancer (NSCLC) Key Secondary Objectives: • To compare the efficacy of AMG 510 versus docetaxel as assessed by: – Overall Survival (OS) – Objective response rate (ORR) • To compare patient reported outcomes (PRO) as assessed by: – European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 13 (EORTC QLQ-LC13) – European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30)

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study [redacted] An open label study to evaluate the pharmacokinetics of AMG 510 in healthy subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Category 3	Primary objectives: • To evaluate the PK of a single 960 mg oral dose of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Secondary objectives: • To evaluate the safety and tolerability of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Safety concerns addressed: • Use in patients with hepatic impairment

PART VII: ANNEXES

Annex 1. EudraVigilance Interface

Annex 2. Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Table 18. Annex II: Planned and Ongoing Studies From the Pharmacovigilance Plan

Study	Summary of Objectives	Safety Concerns Addressed	Protocol Link Milestone
Study [redacted] An open label study to evaluate the pharmacokinetics of AMG 510 in healthy subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Category 3	Primary objectives: • To evaluate the PK of a single 960 mg oral dose of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Secondary objectives: • To evaluate the safety and tolerability of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment	Use in patients with hepatic impairment	Protocol submission: [redacted] Final CSR: [redacted]

CSR = clinical study report; PK = pharmacokinetic; TBD = to be determined

Annex 3. Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Not applicable.

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

Table of Contents

Study Protocols

Study Number	Version Number	Date of Protocol
Study [redacted]	Superseding Amendment 2	29 June 2020

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Redacted according to Section 43, FOI Act

Redacted according to Section 40, FOI Act

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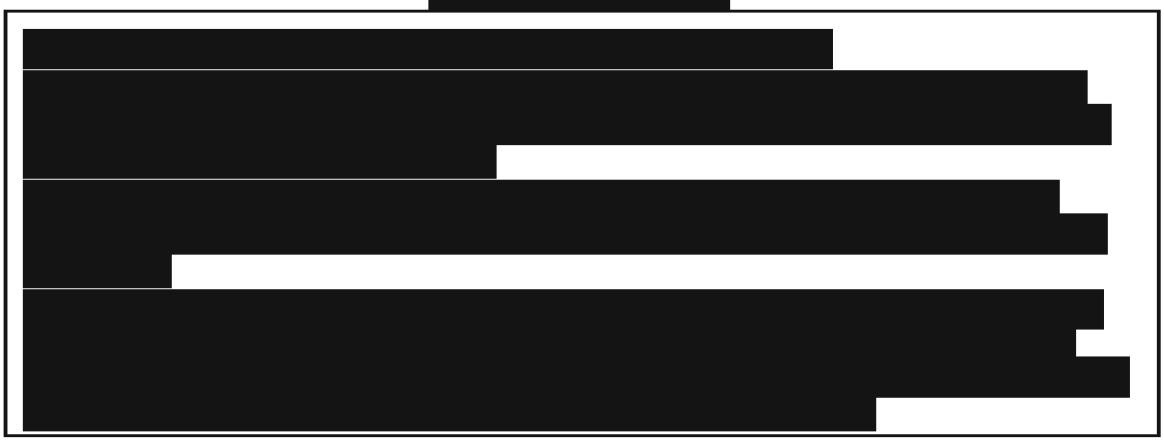

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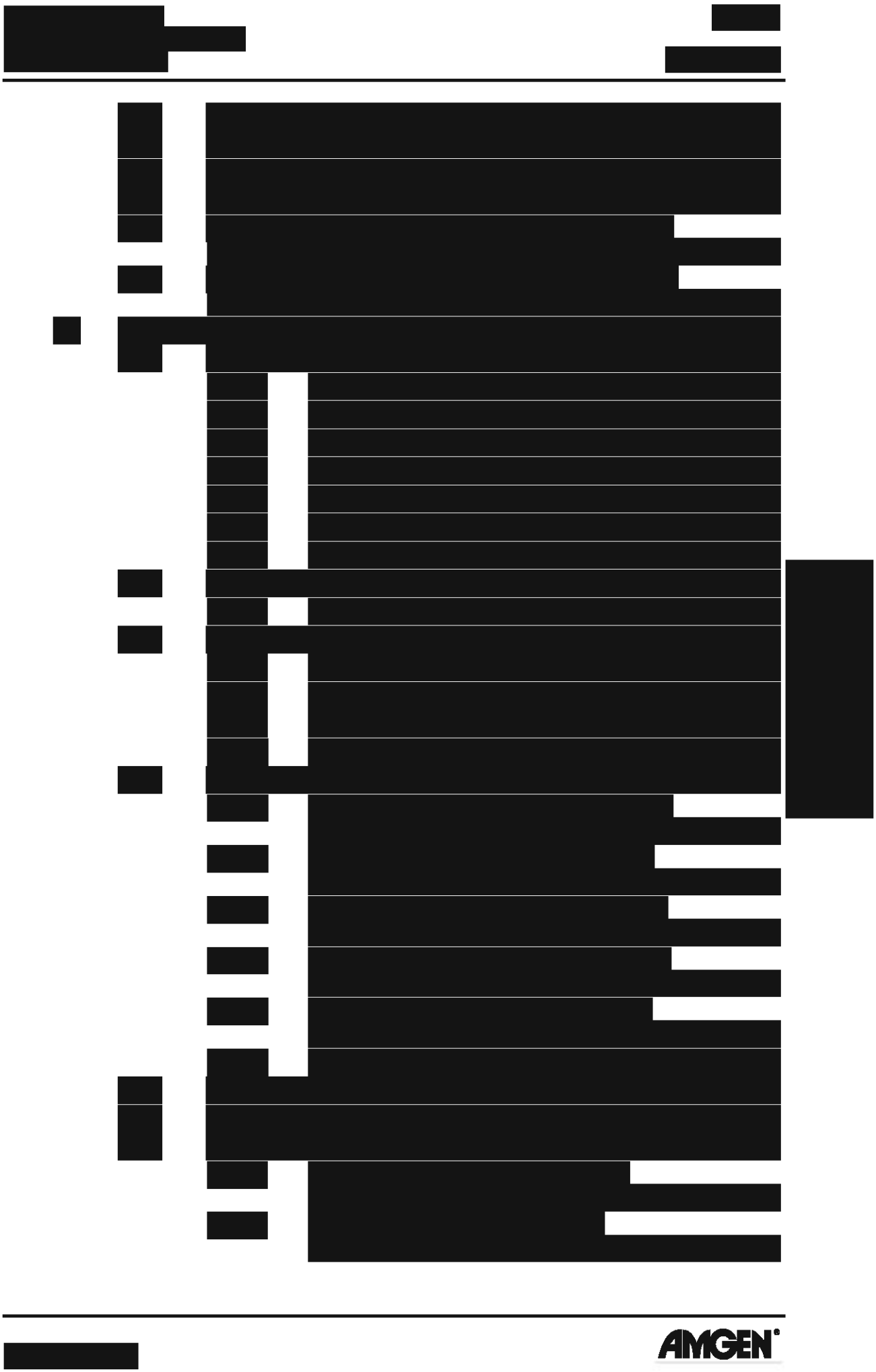

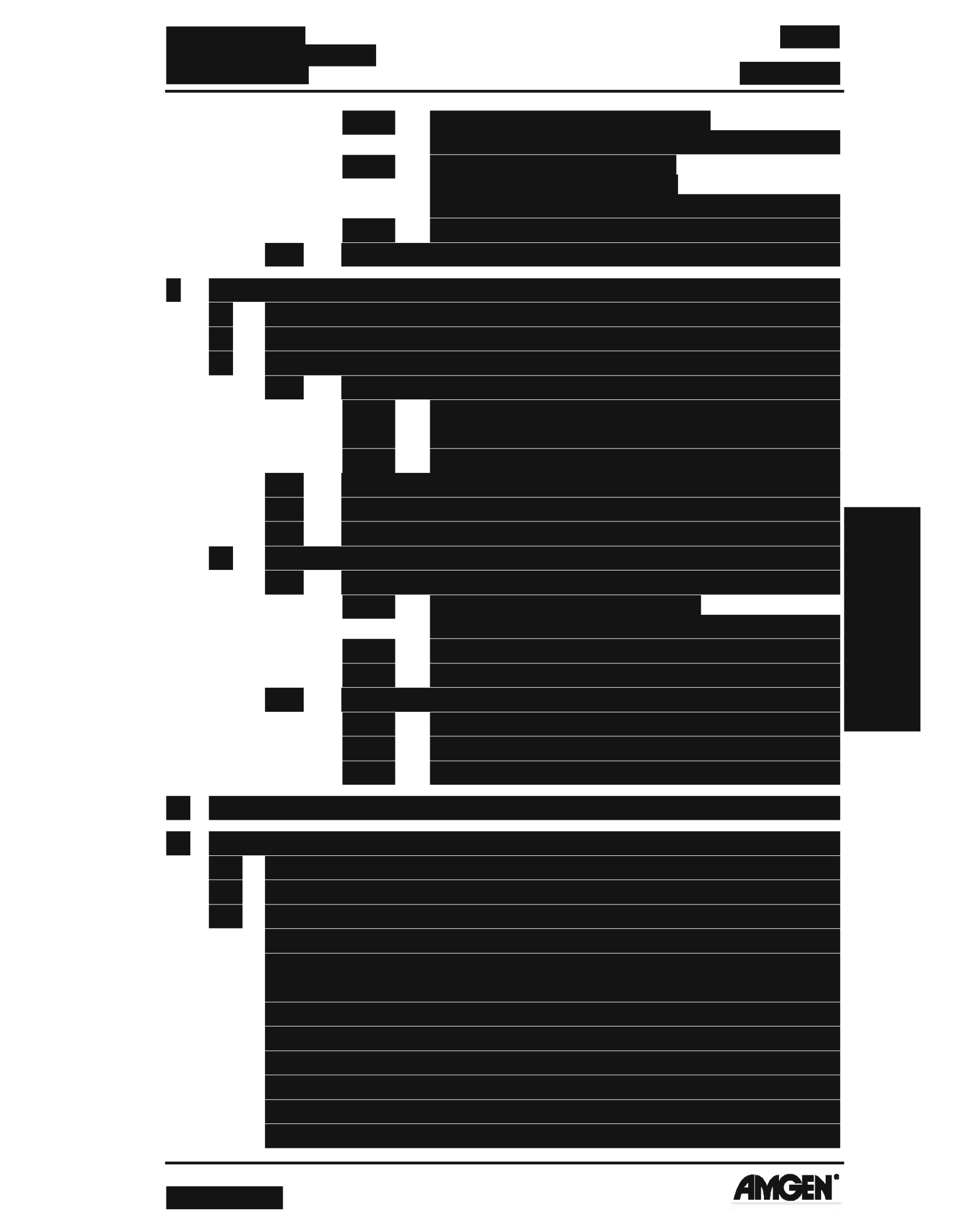

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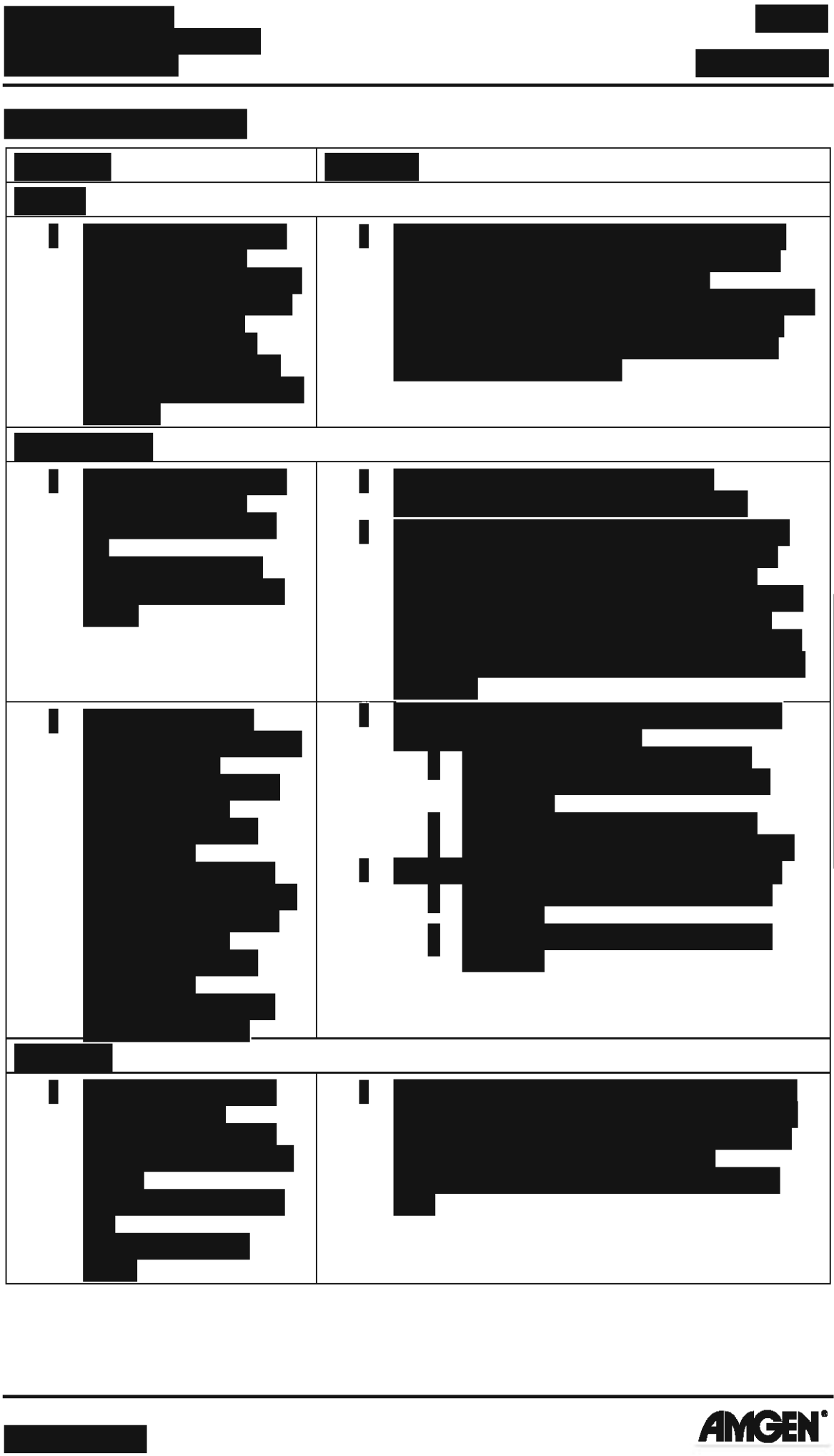

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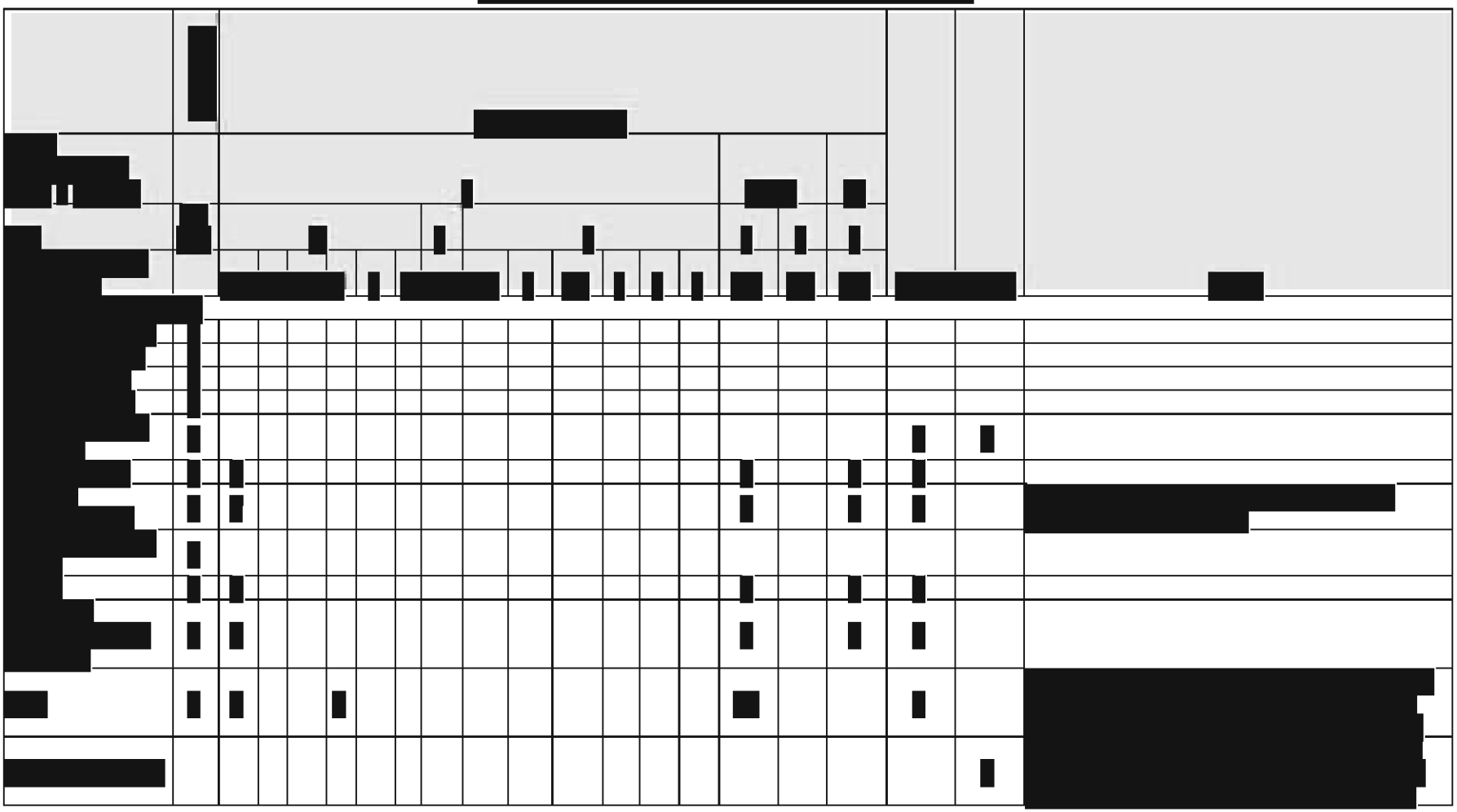

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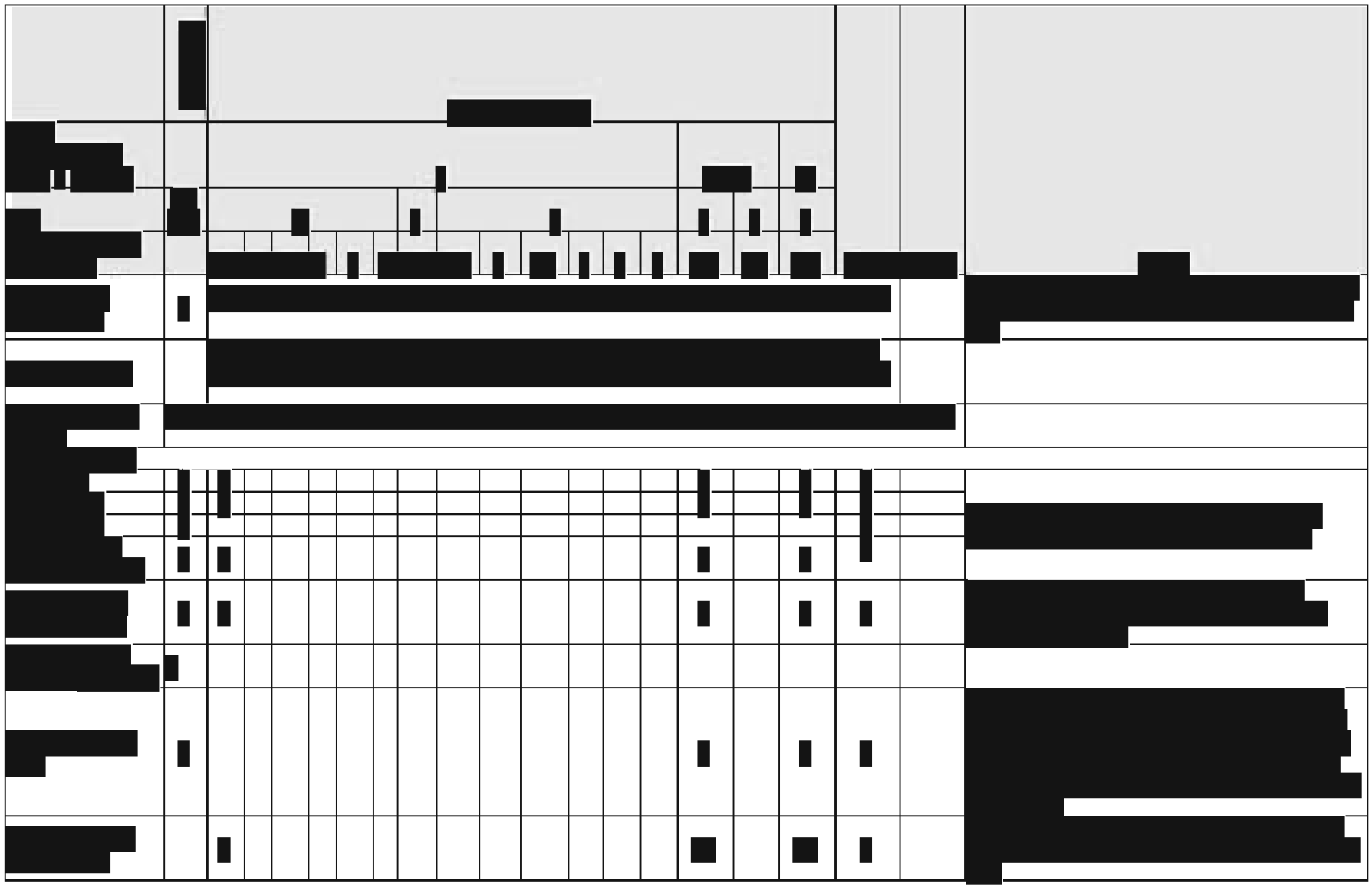

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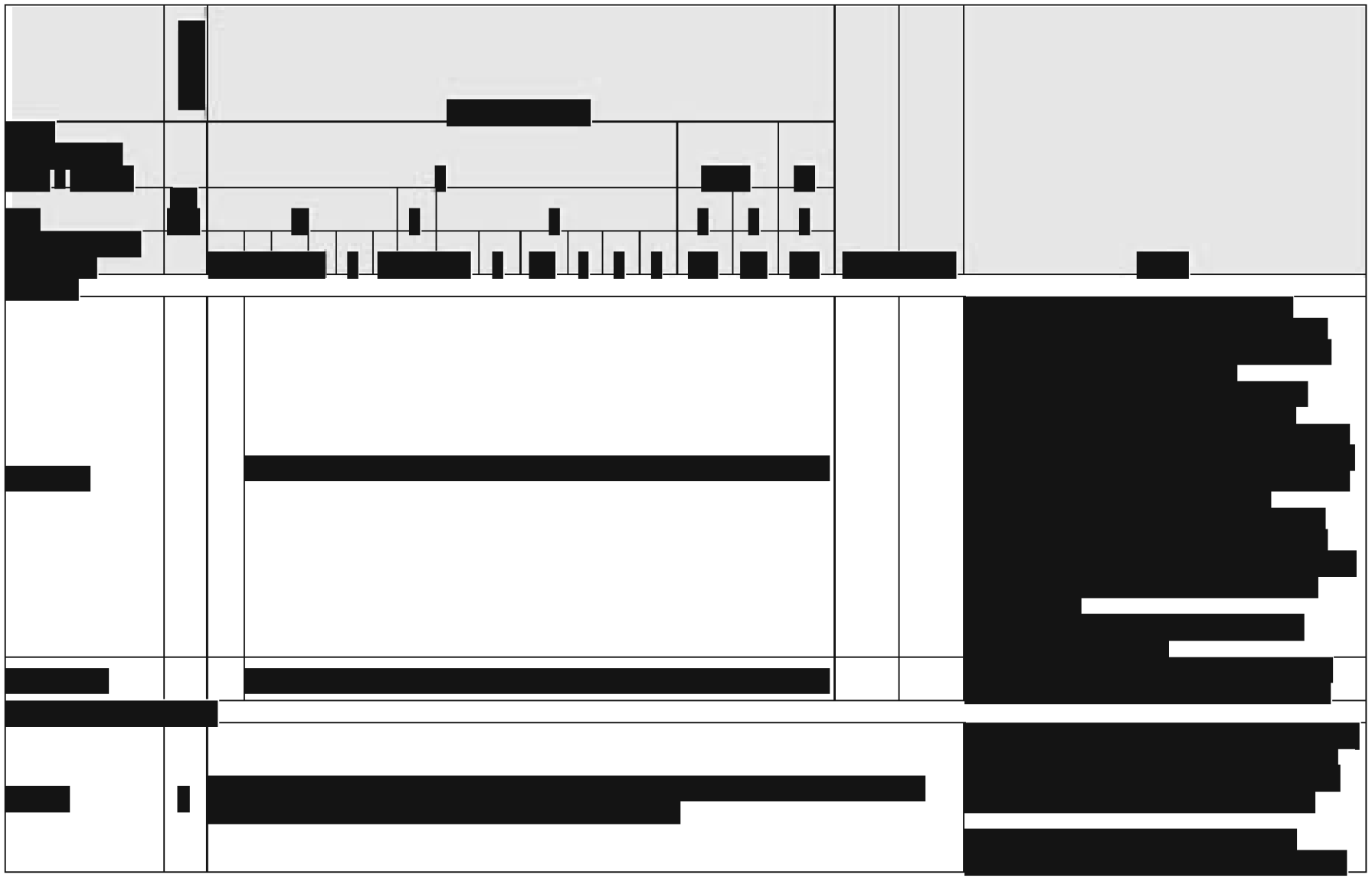

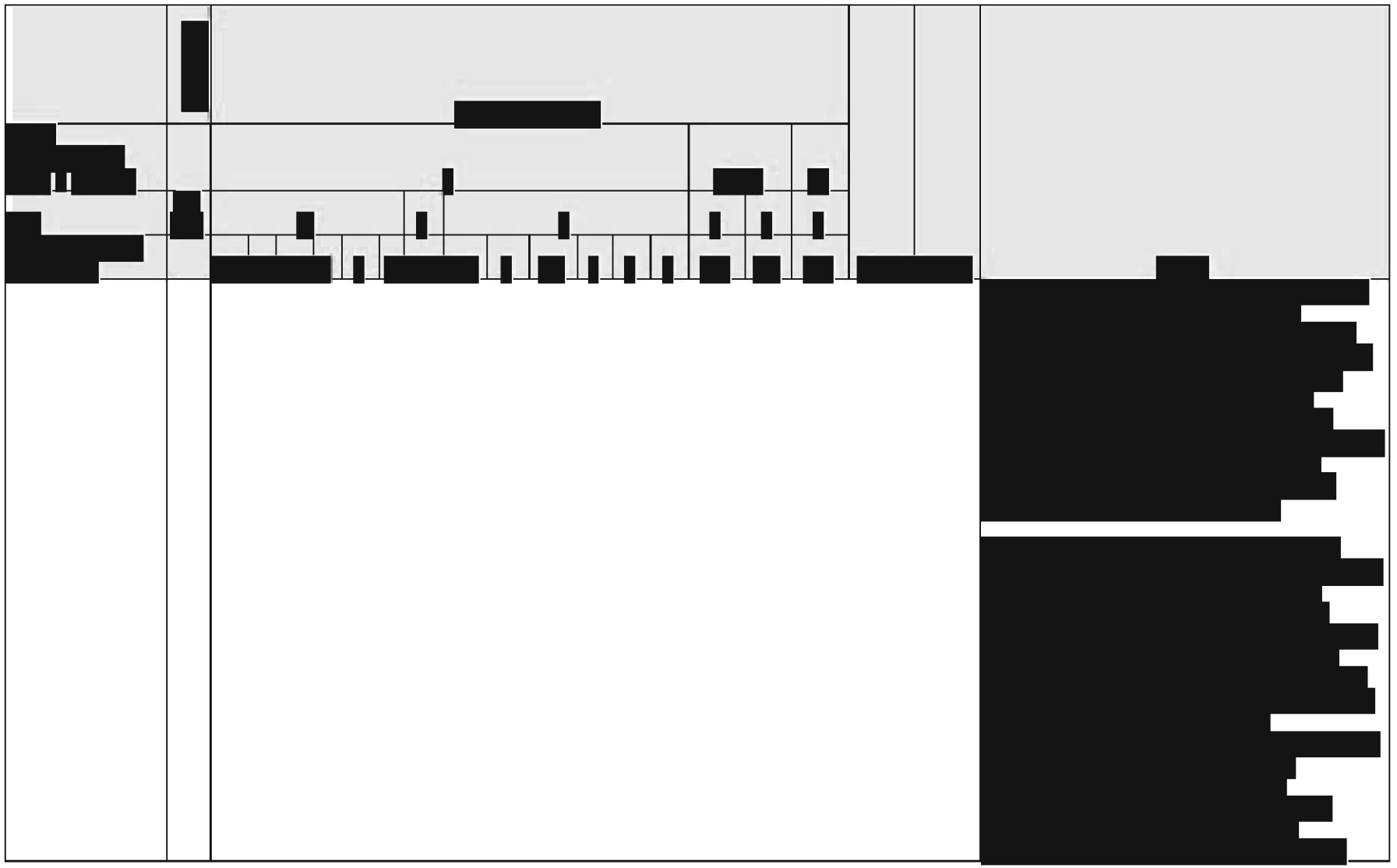

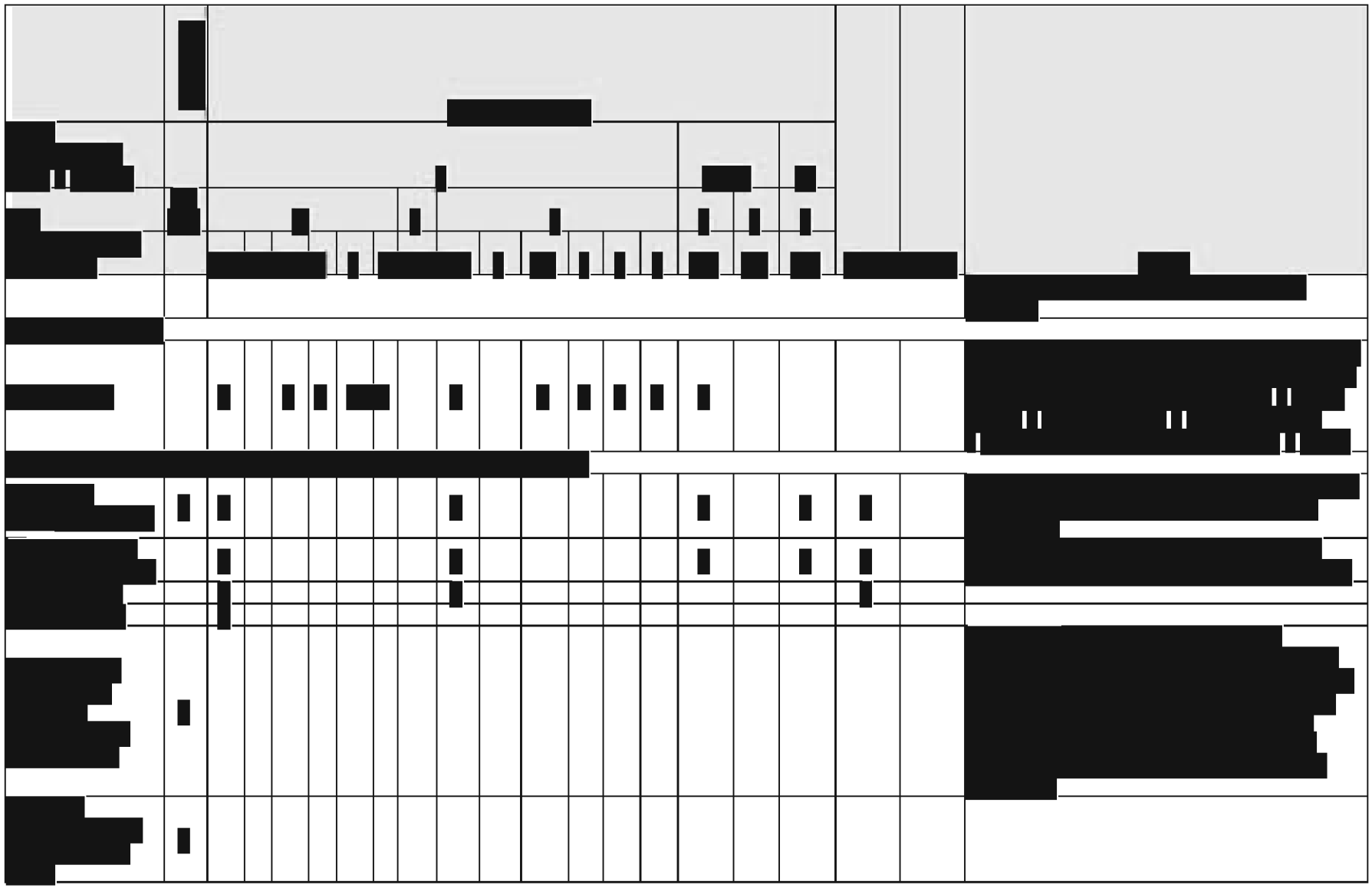

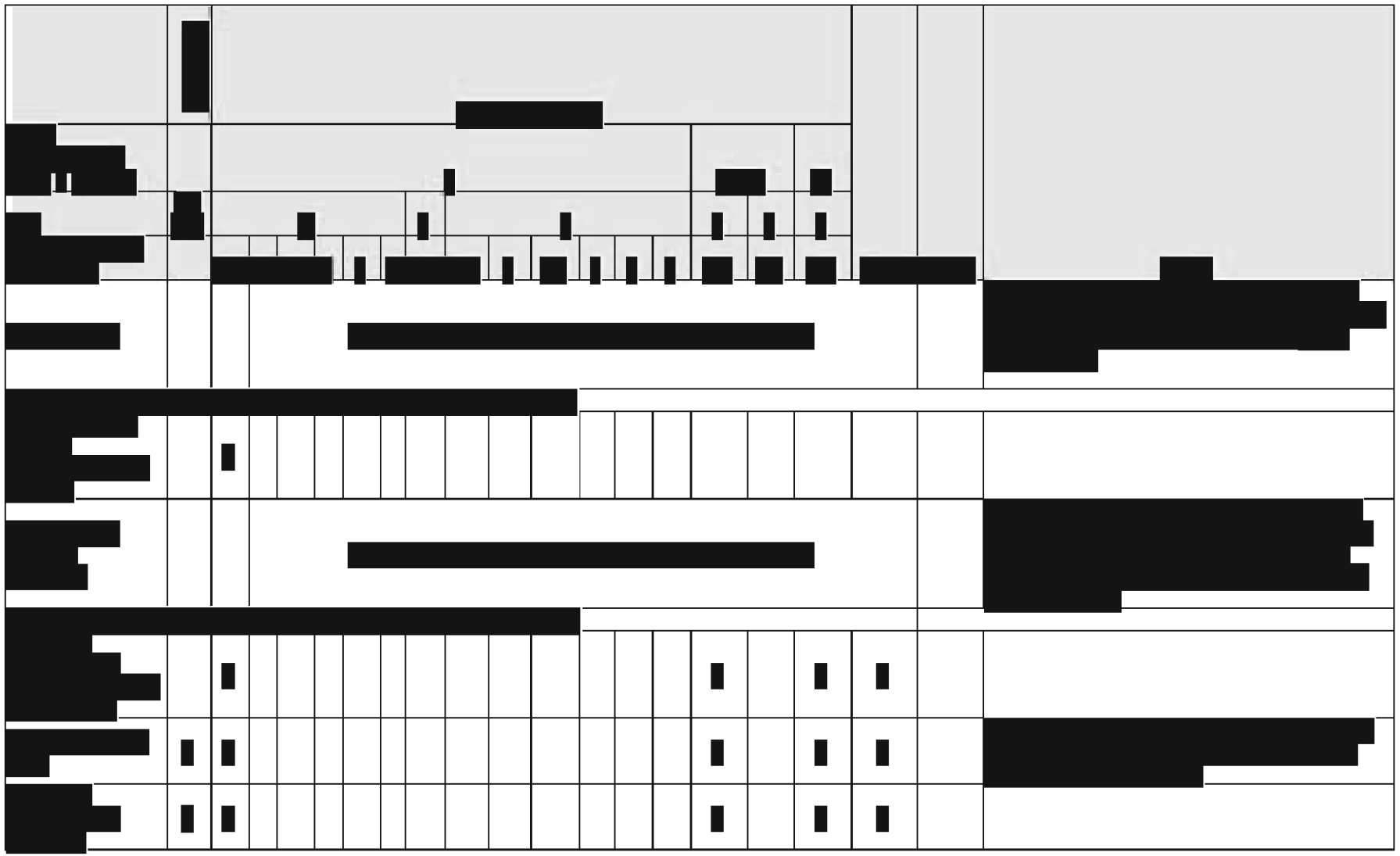

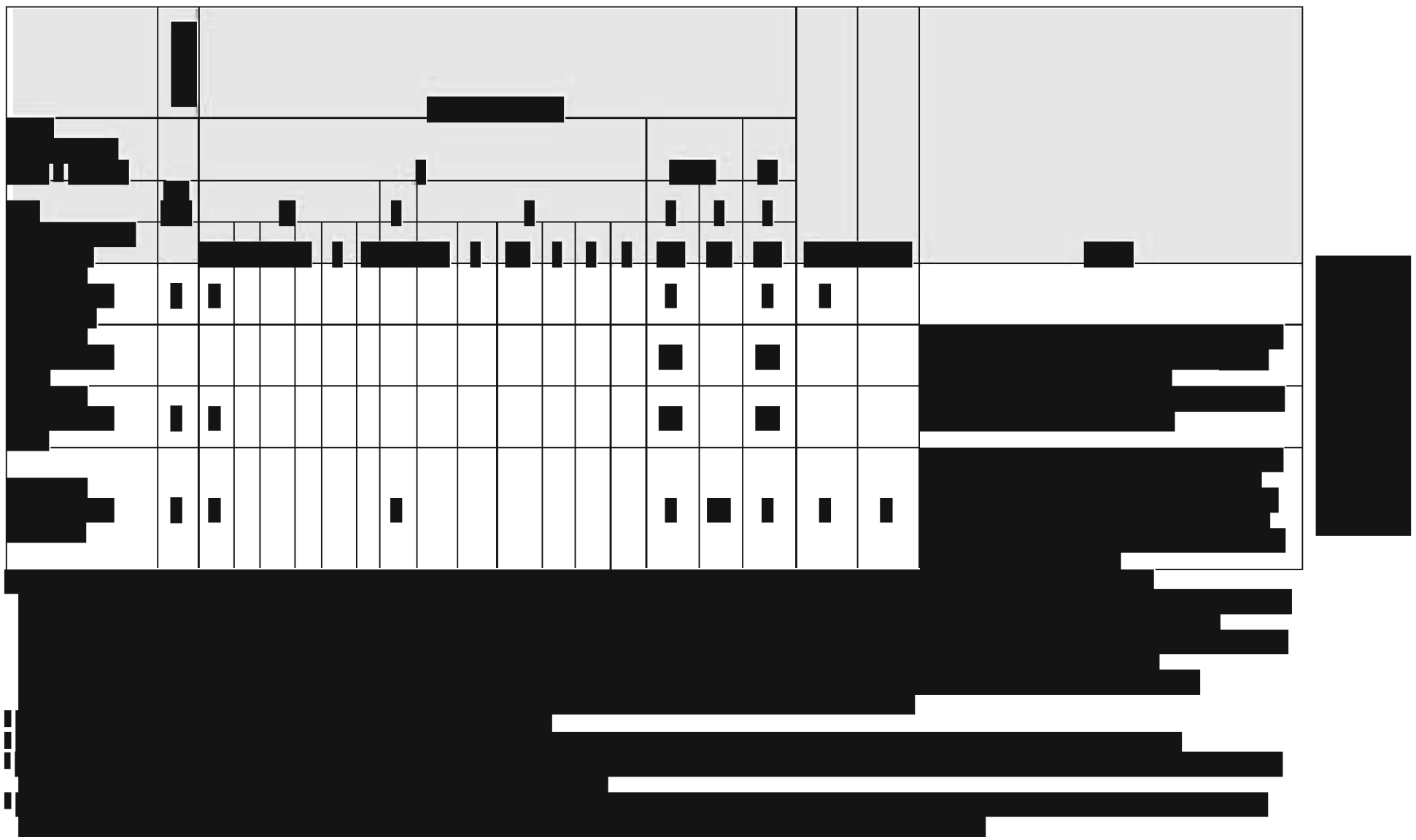

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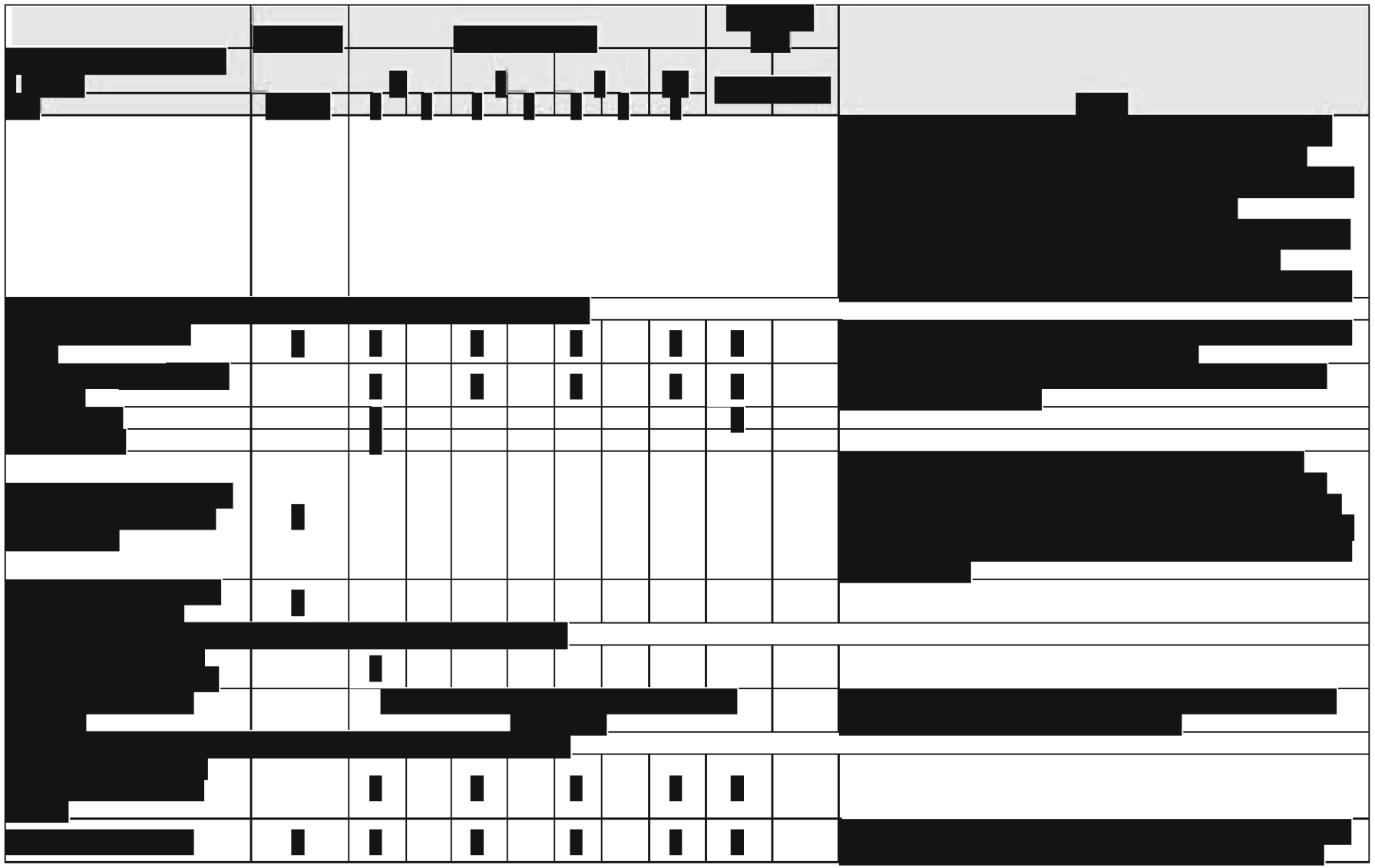

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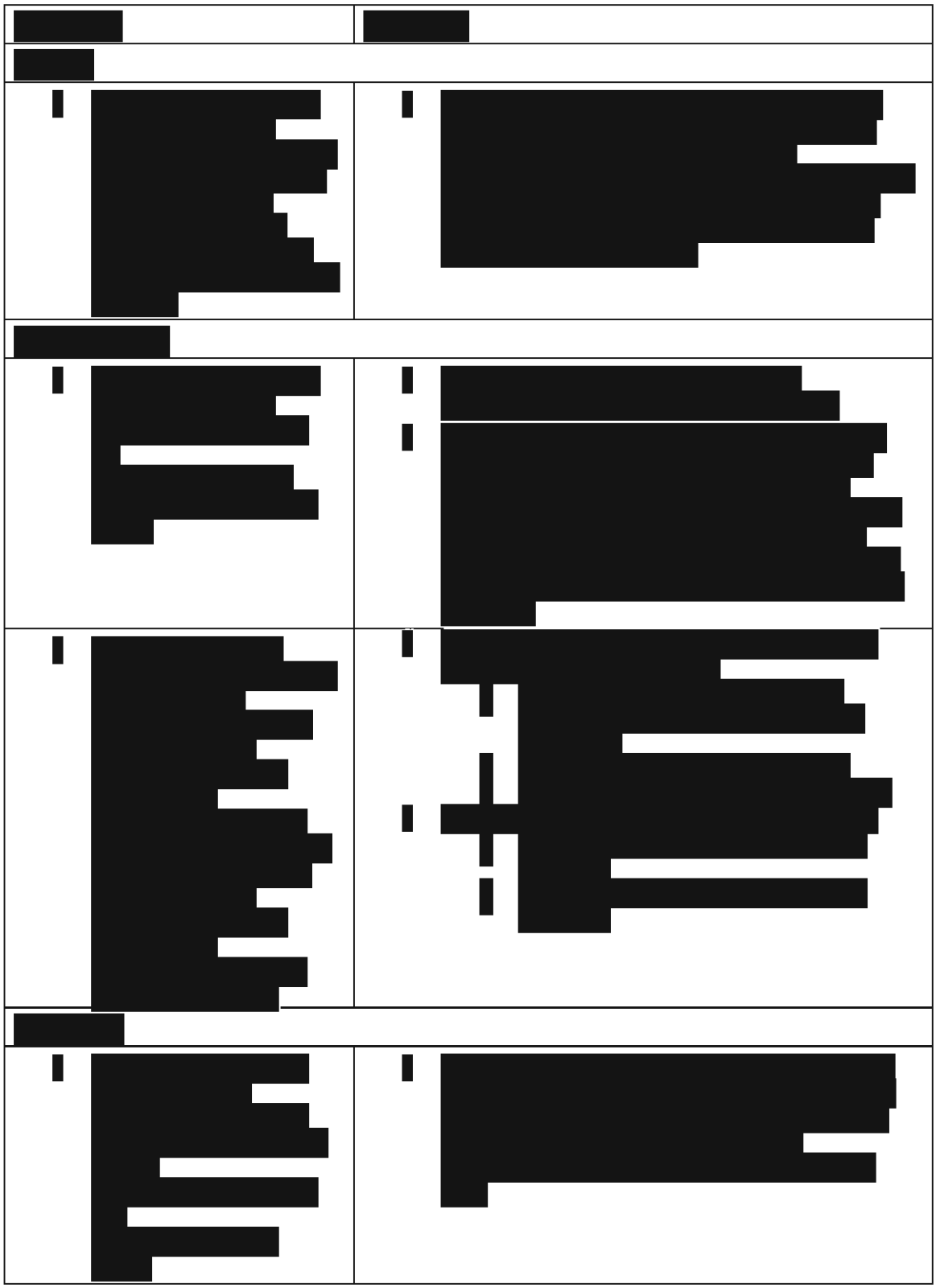

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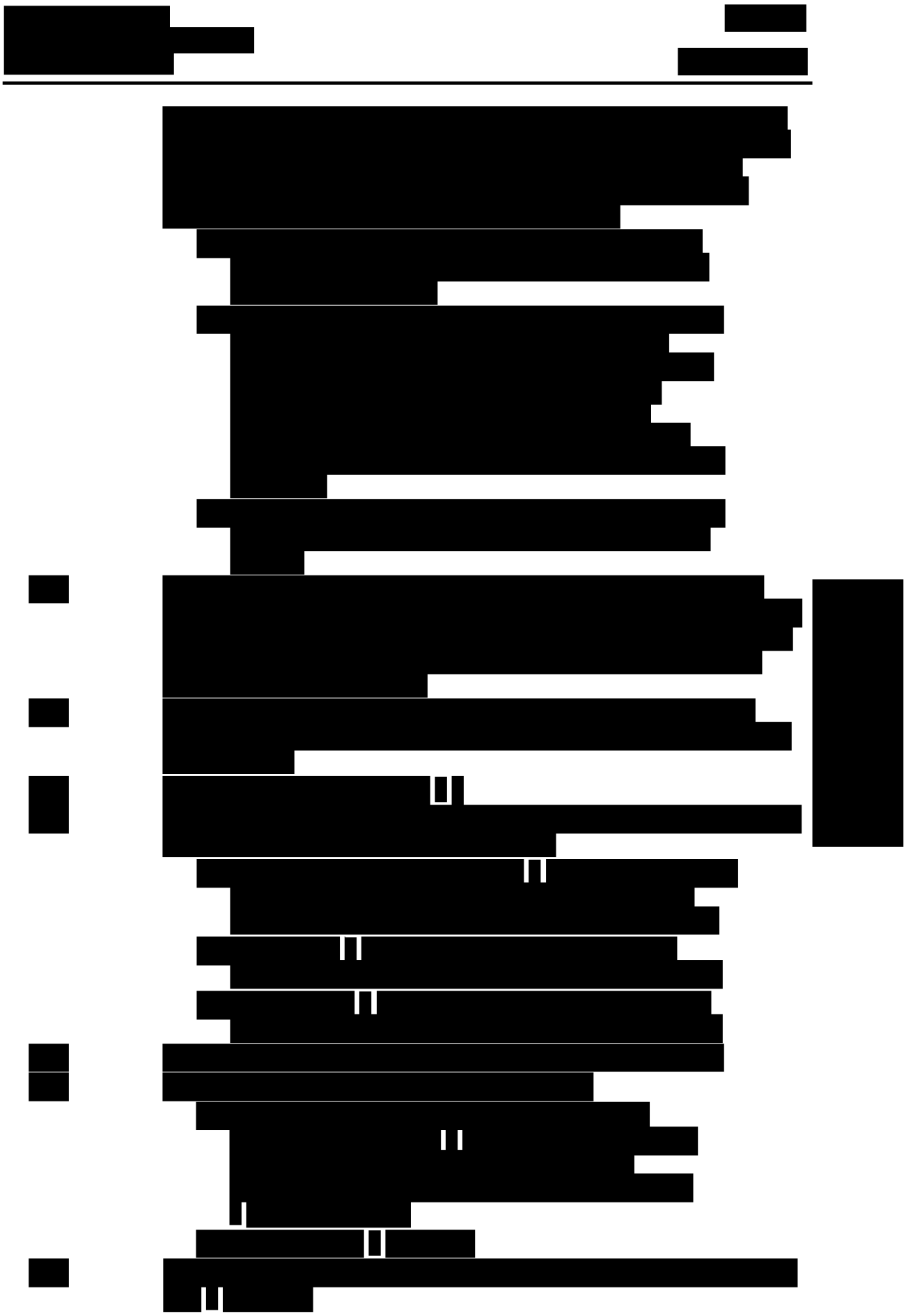

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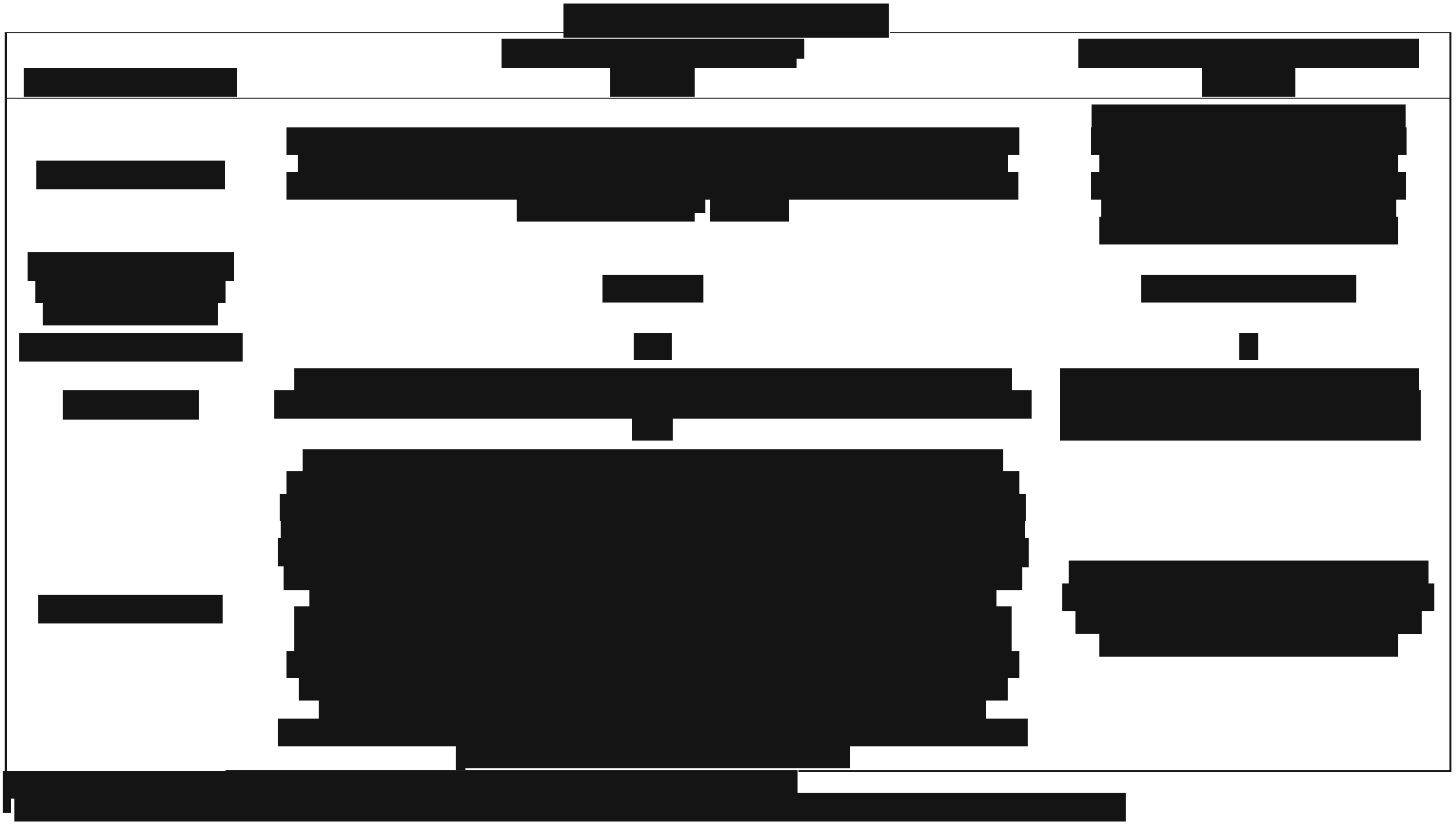

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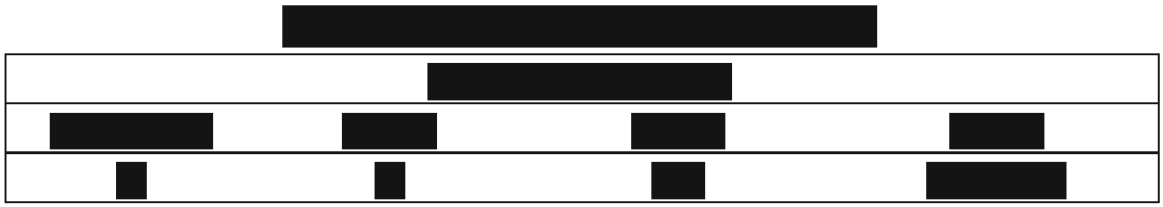

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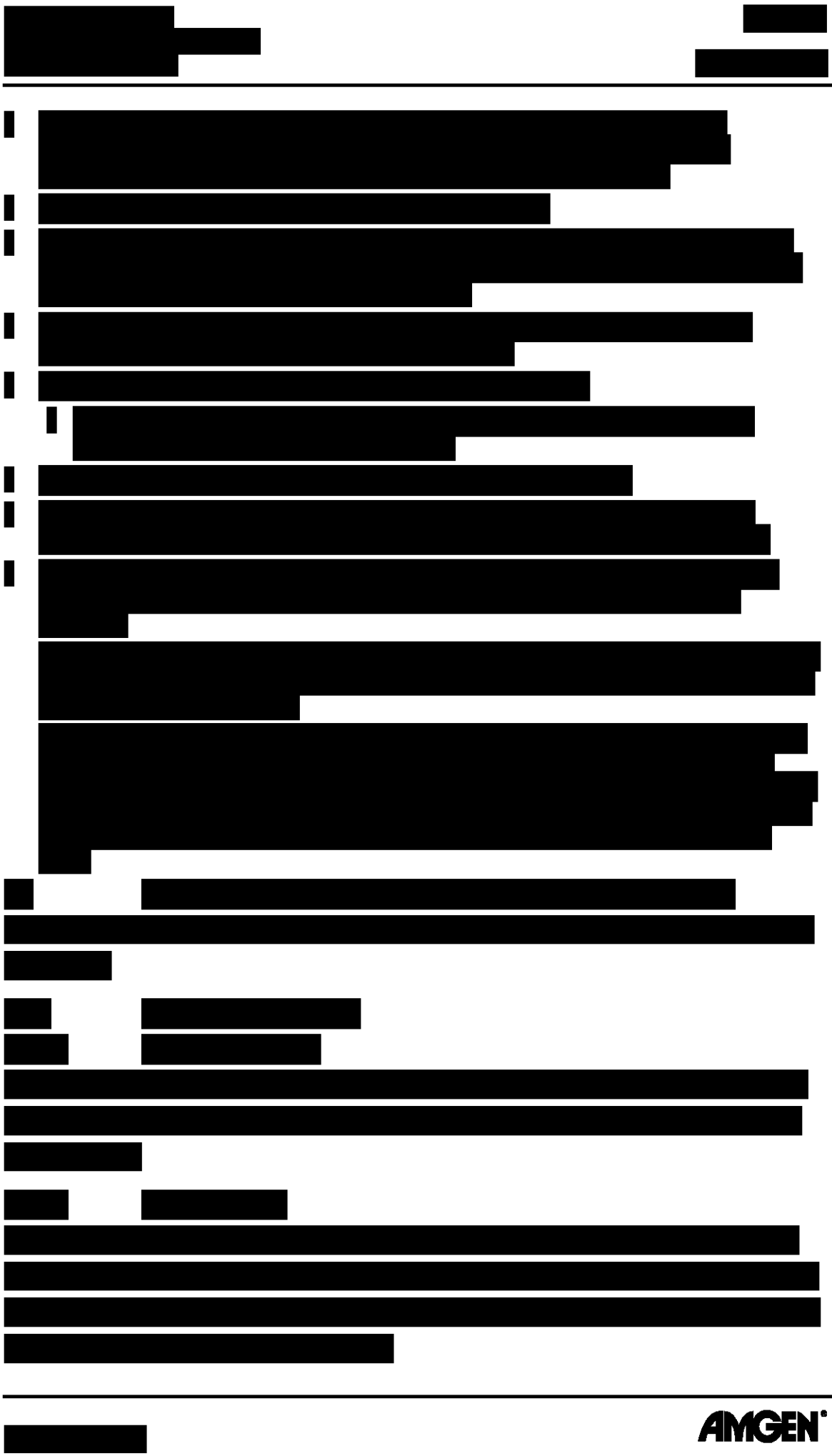

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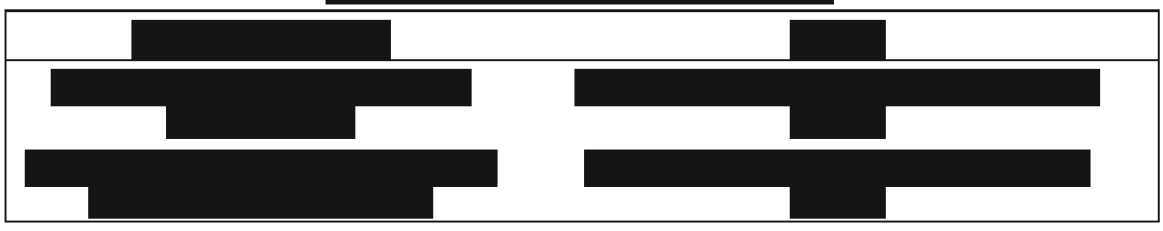

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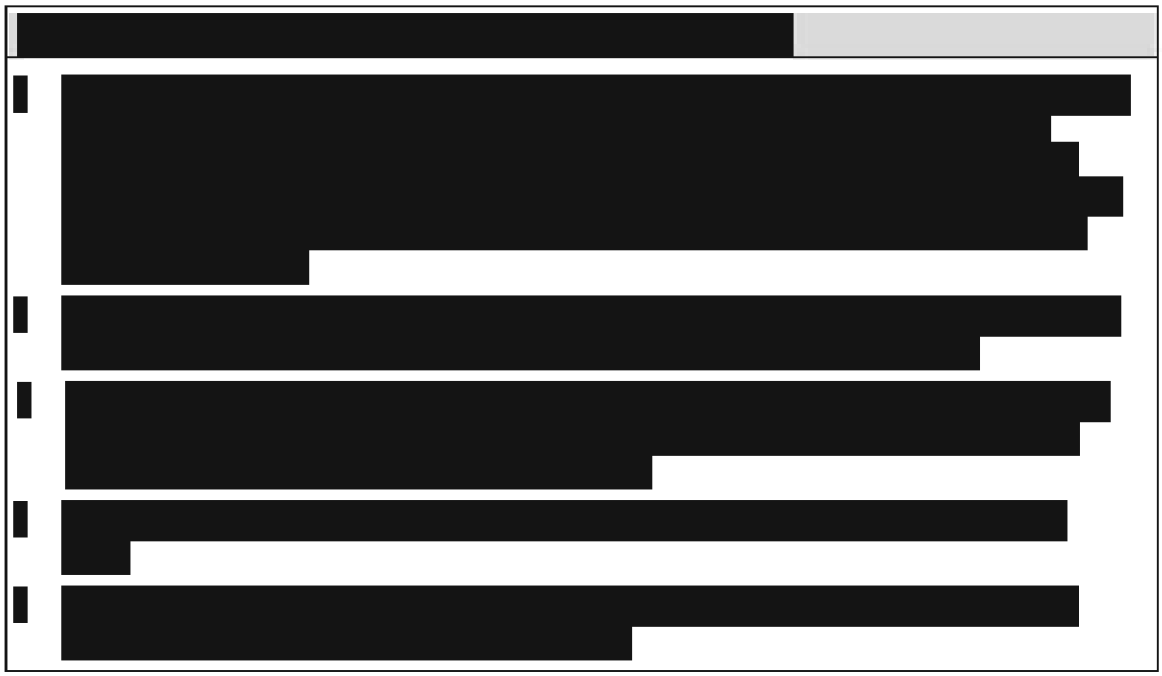

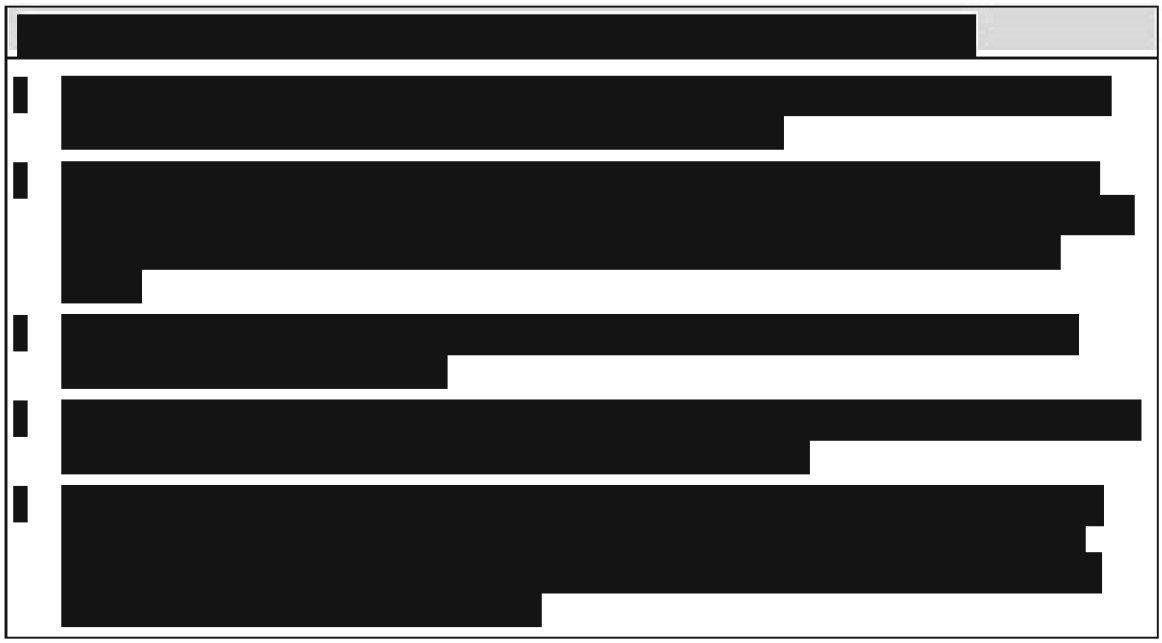

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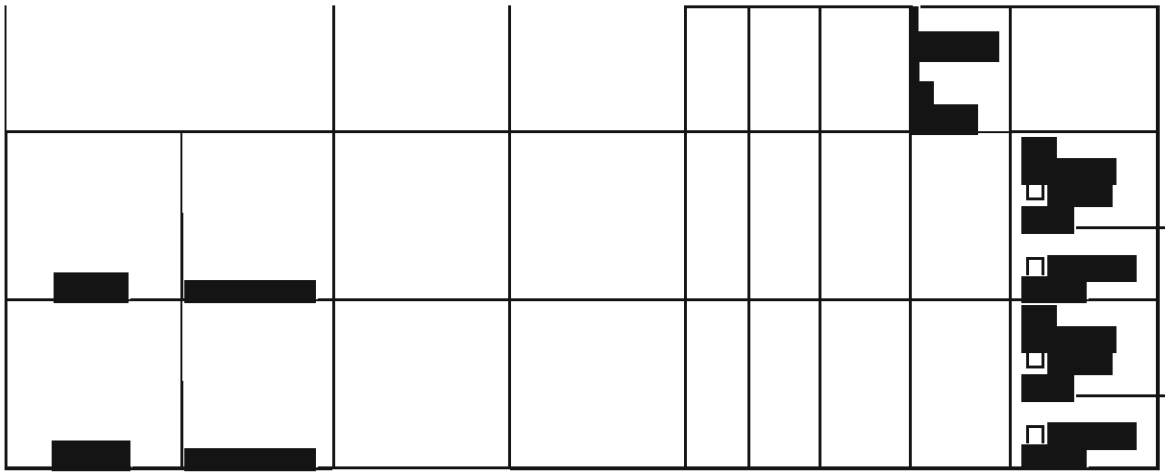

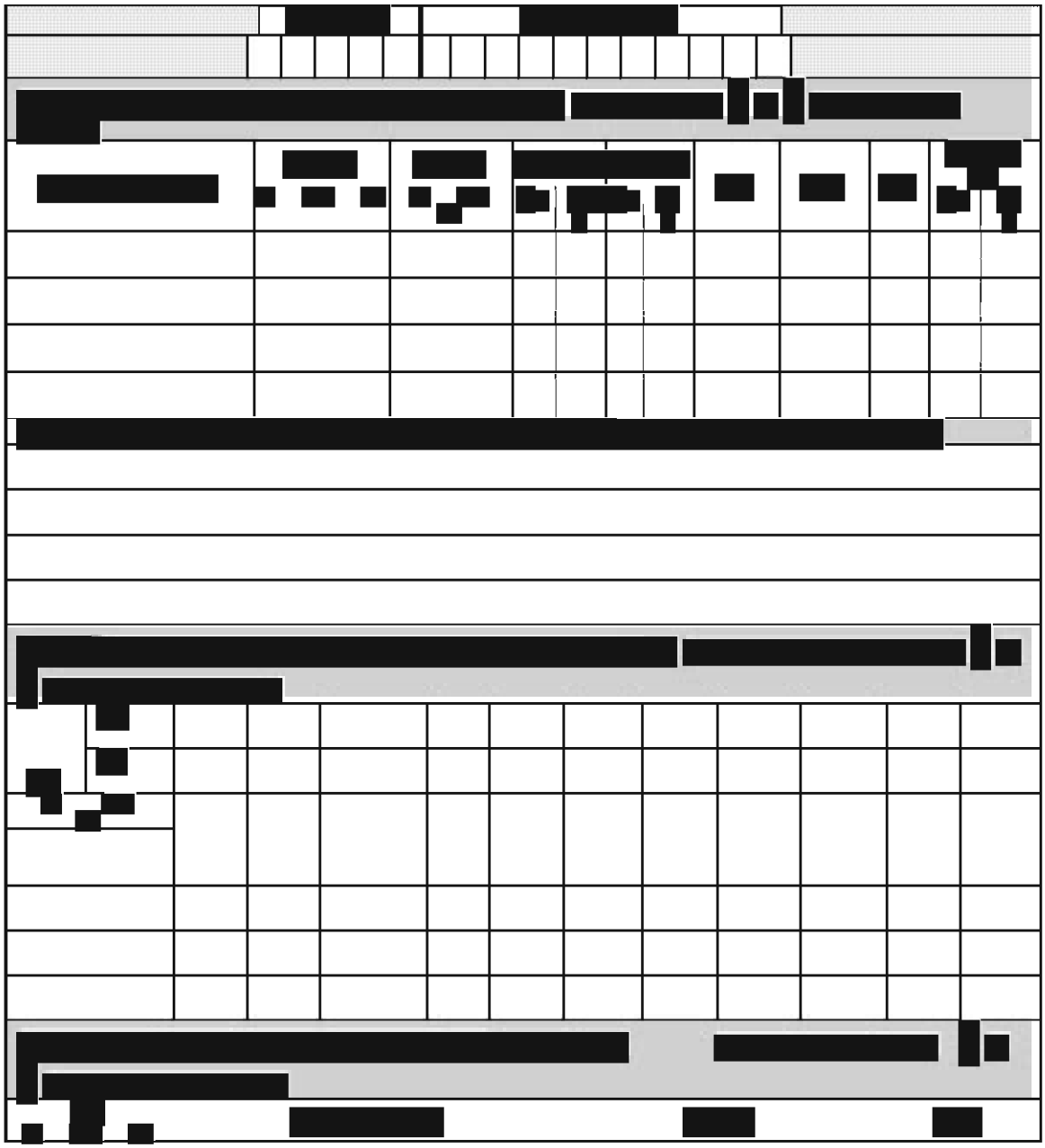

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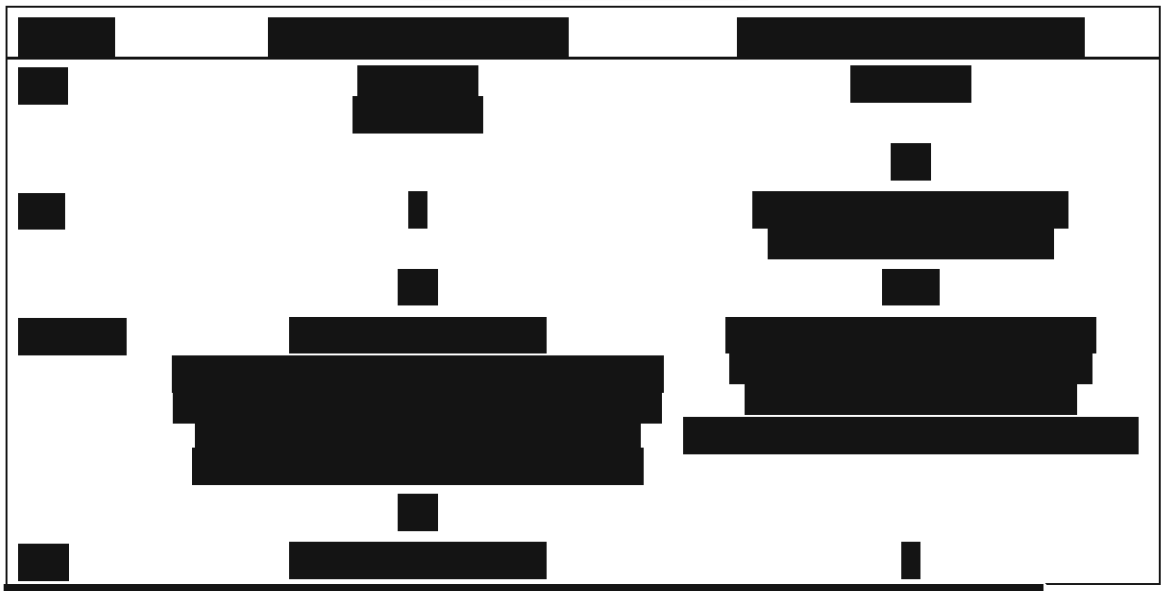

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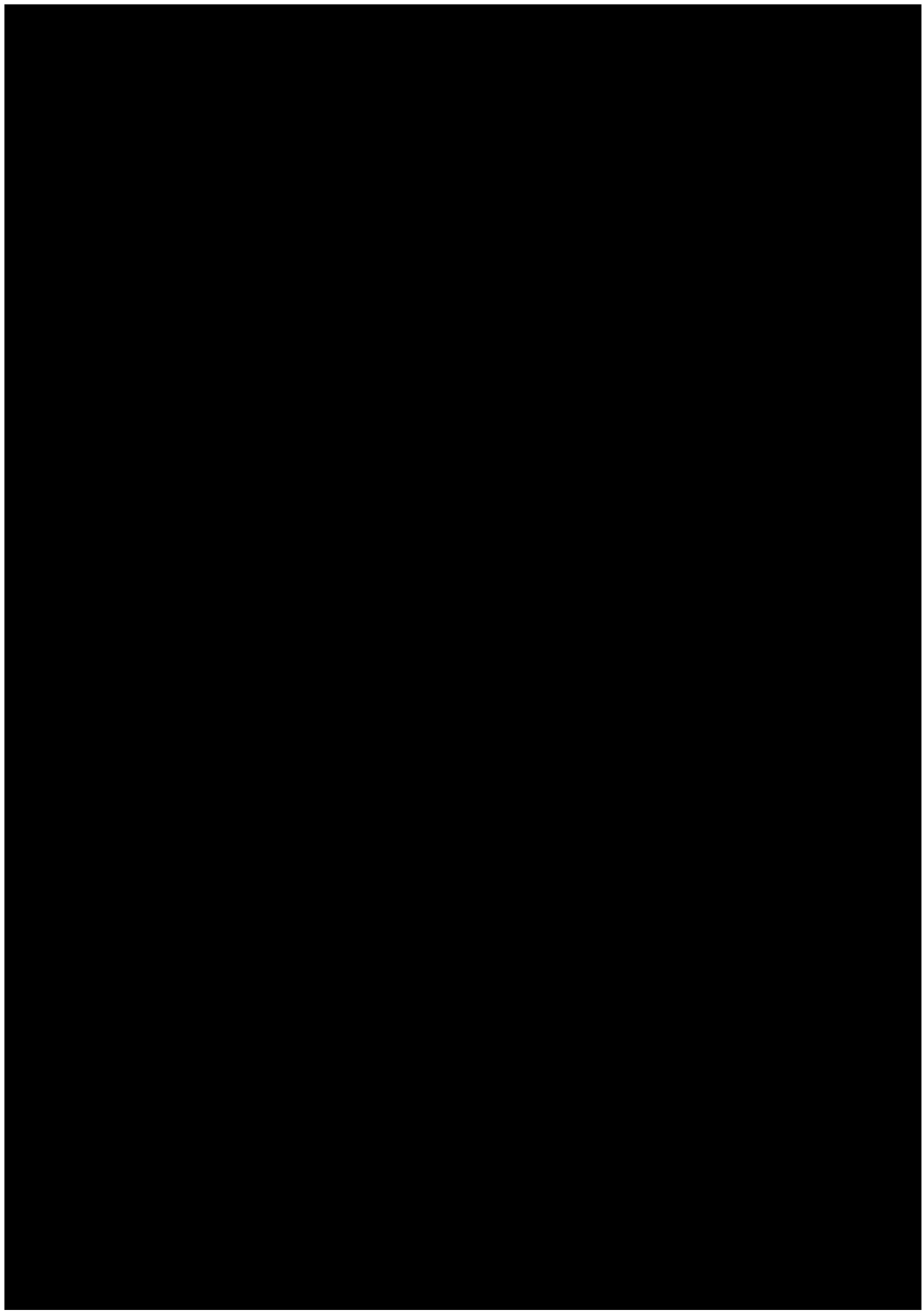

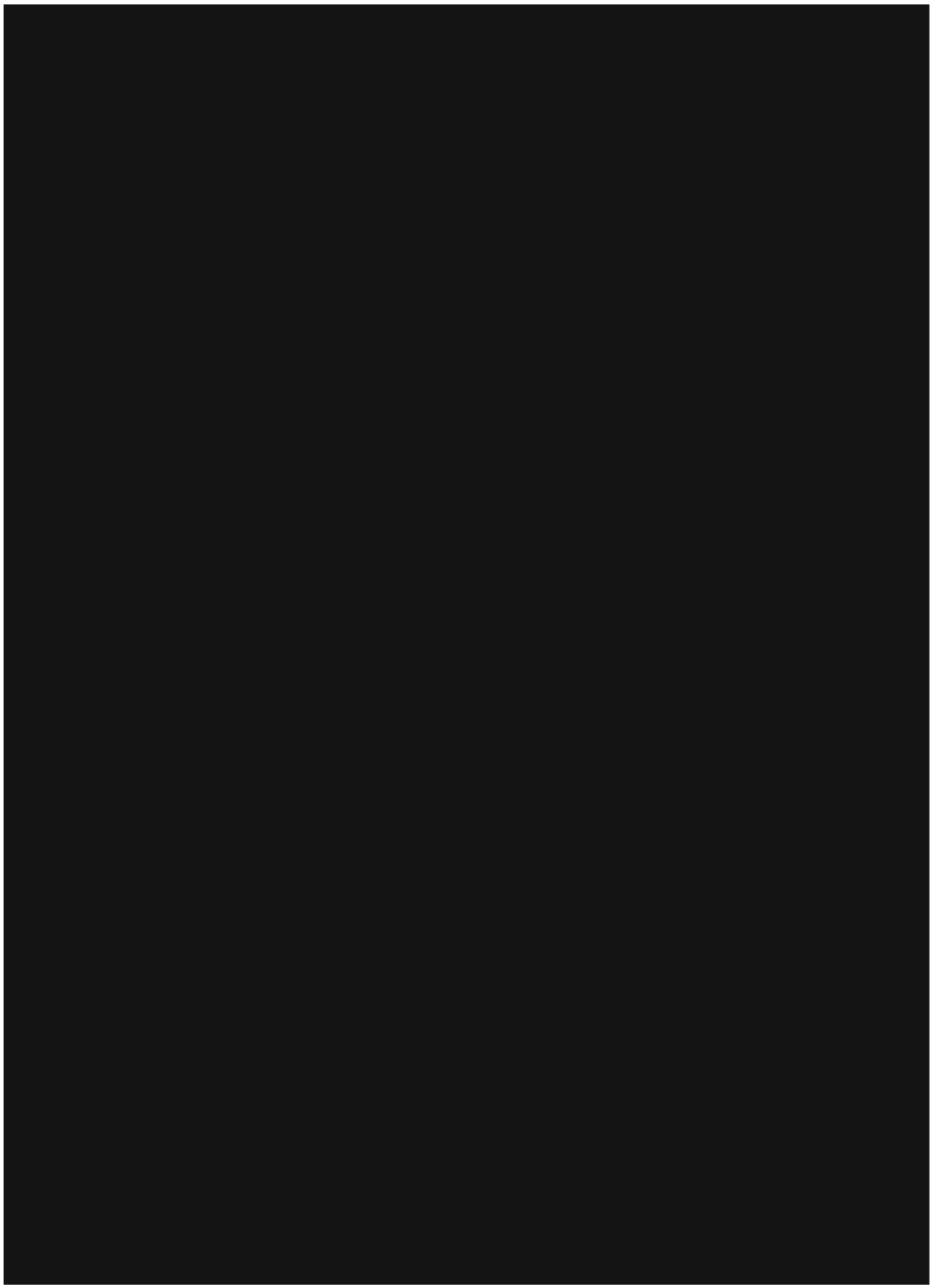

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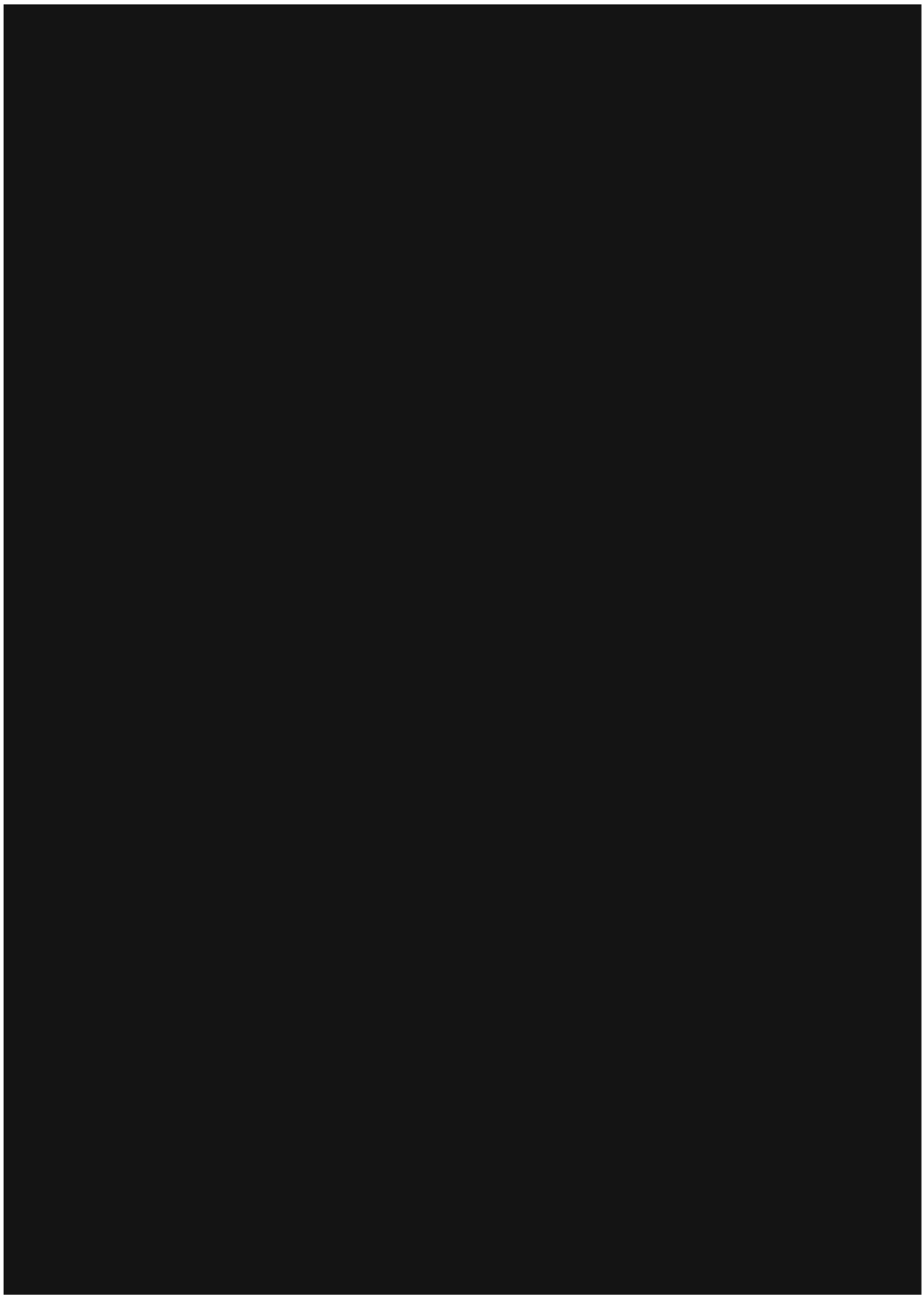

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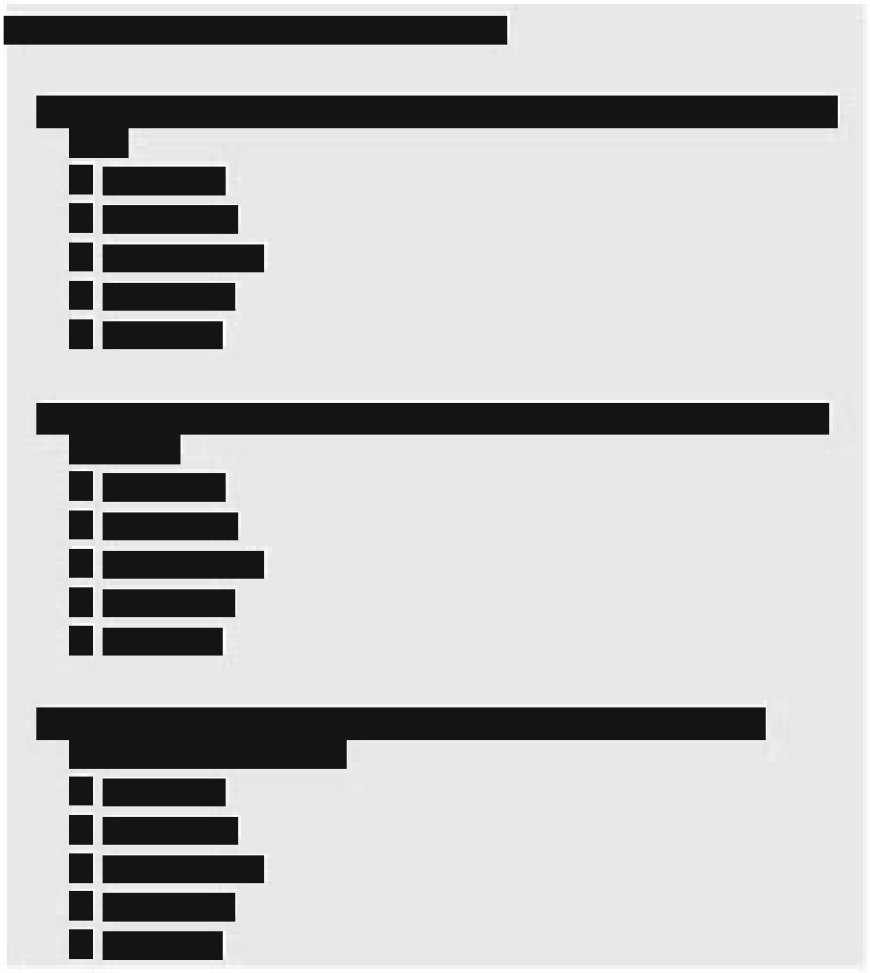

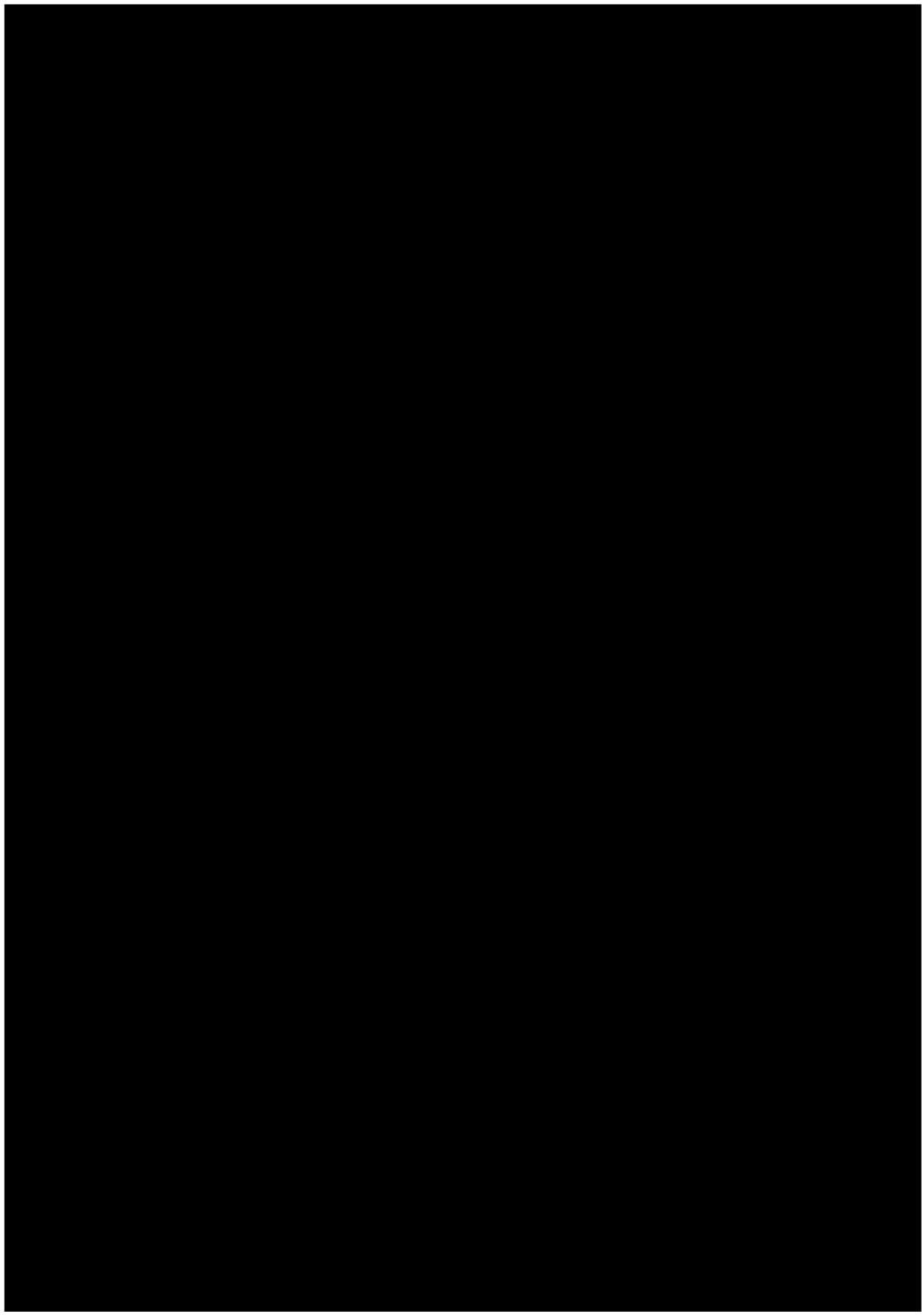

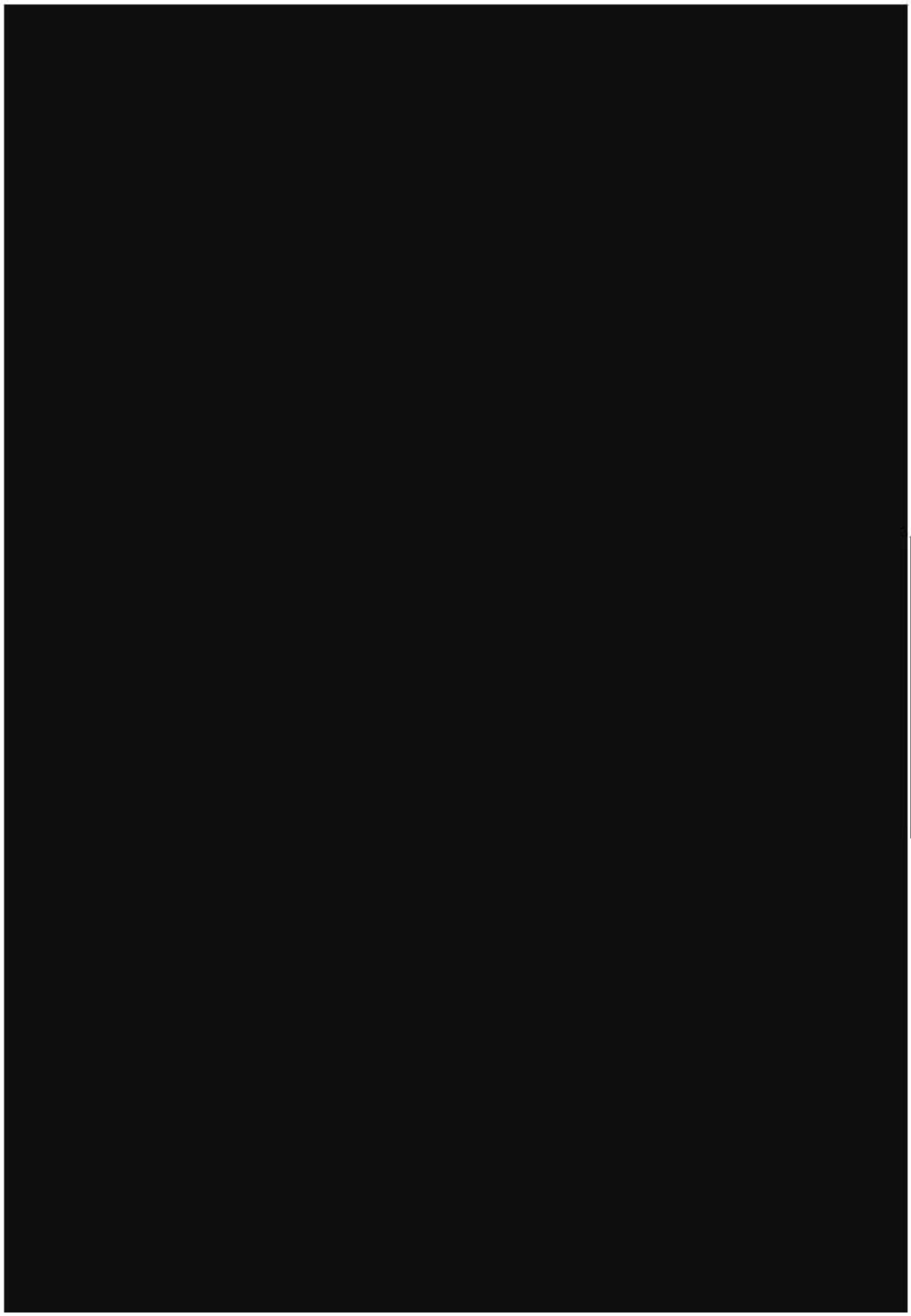

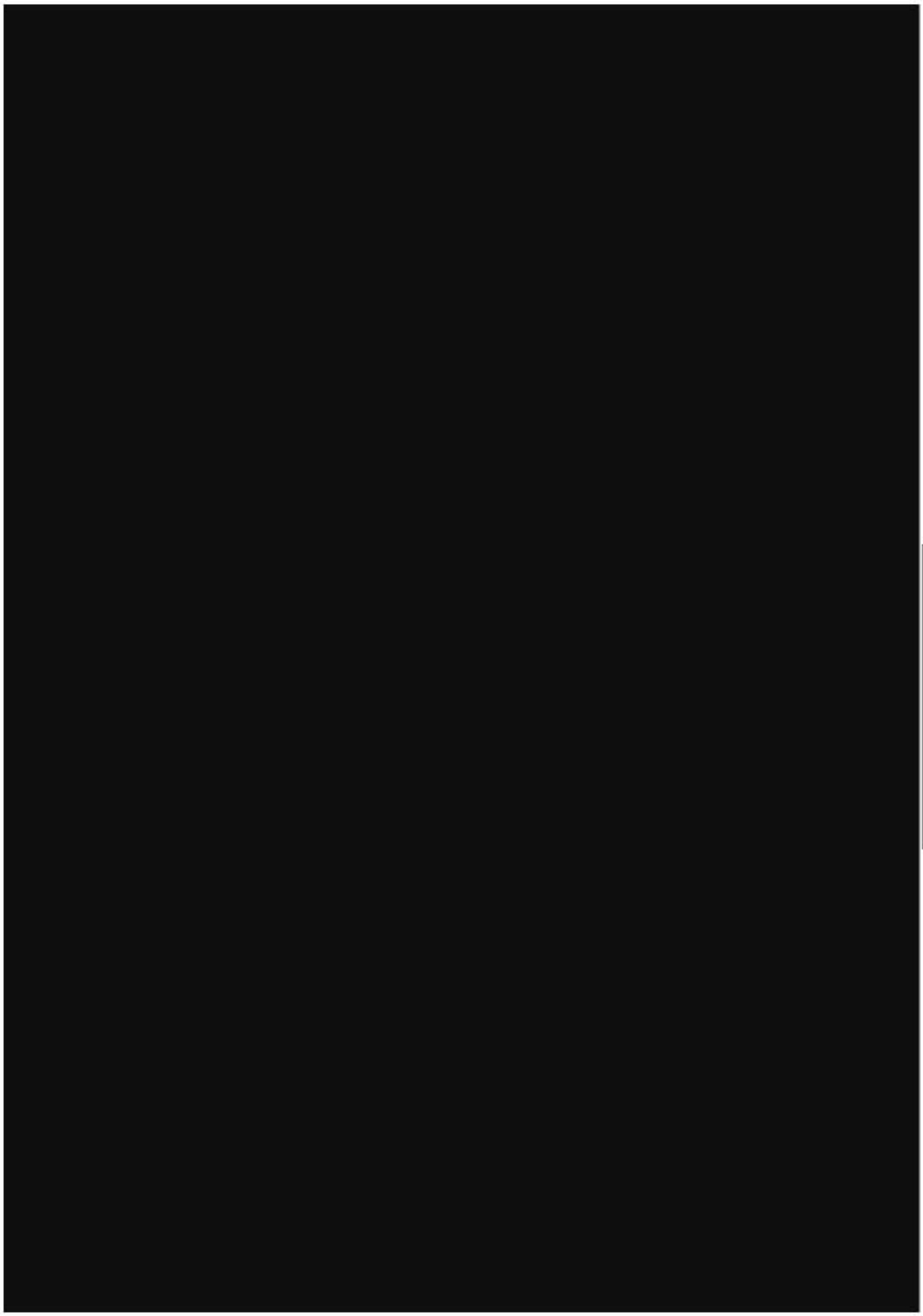

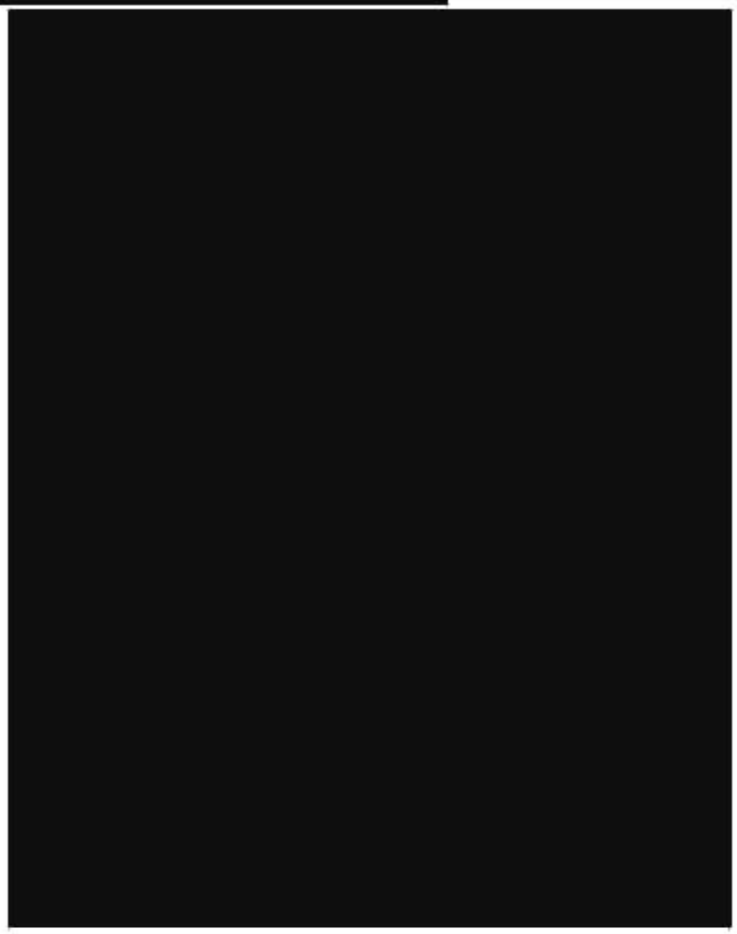

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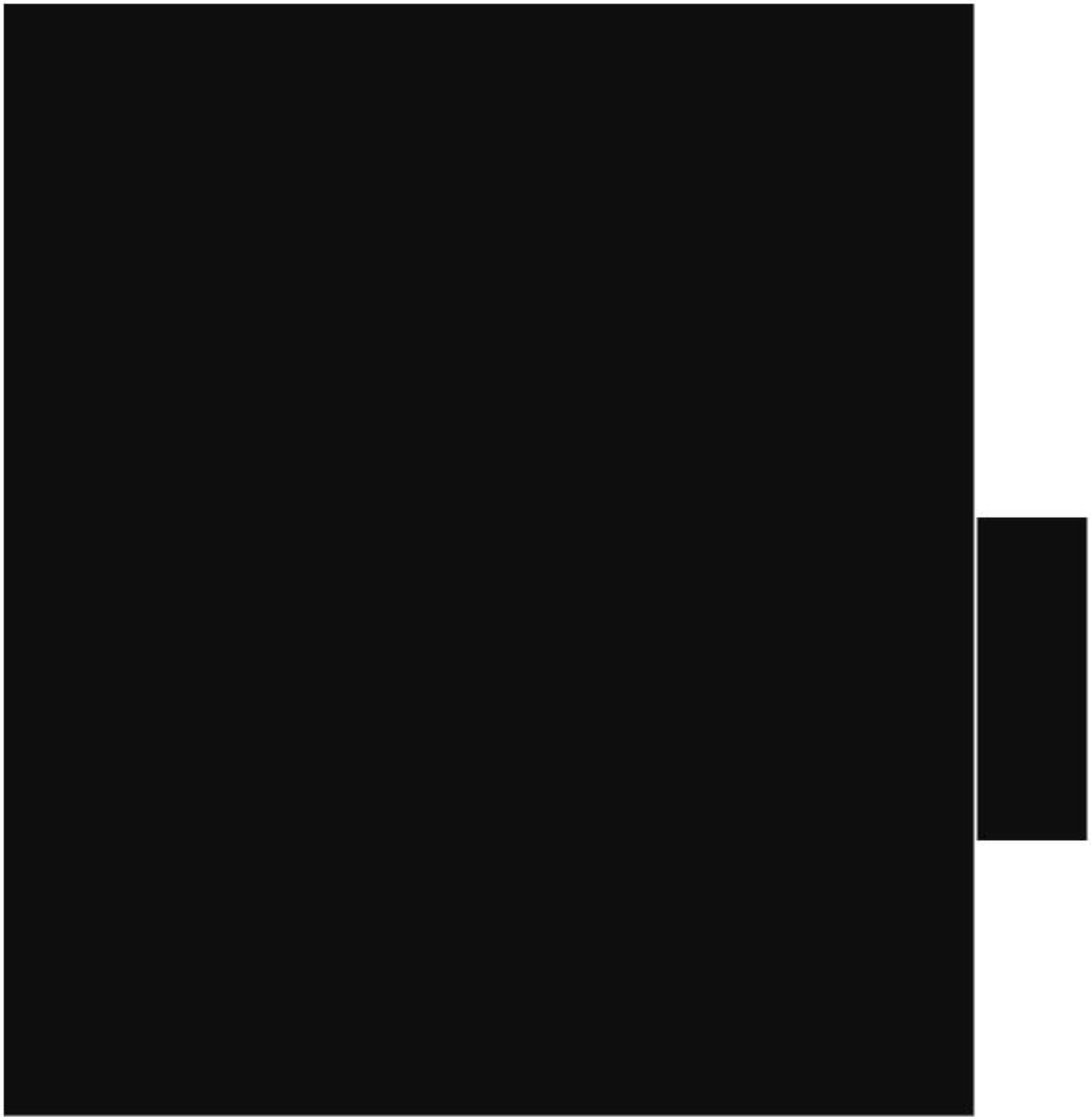

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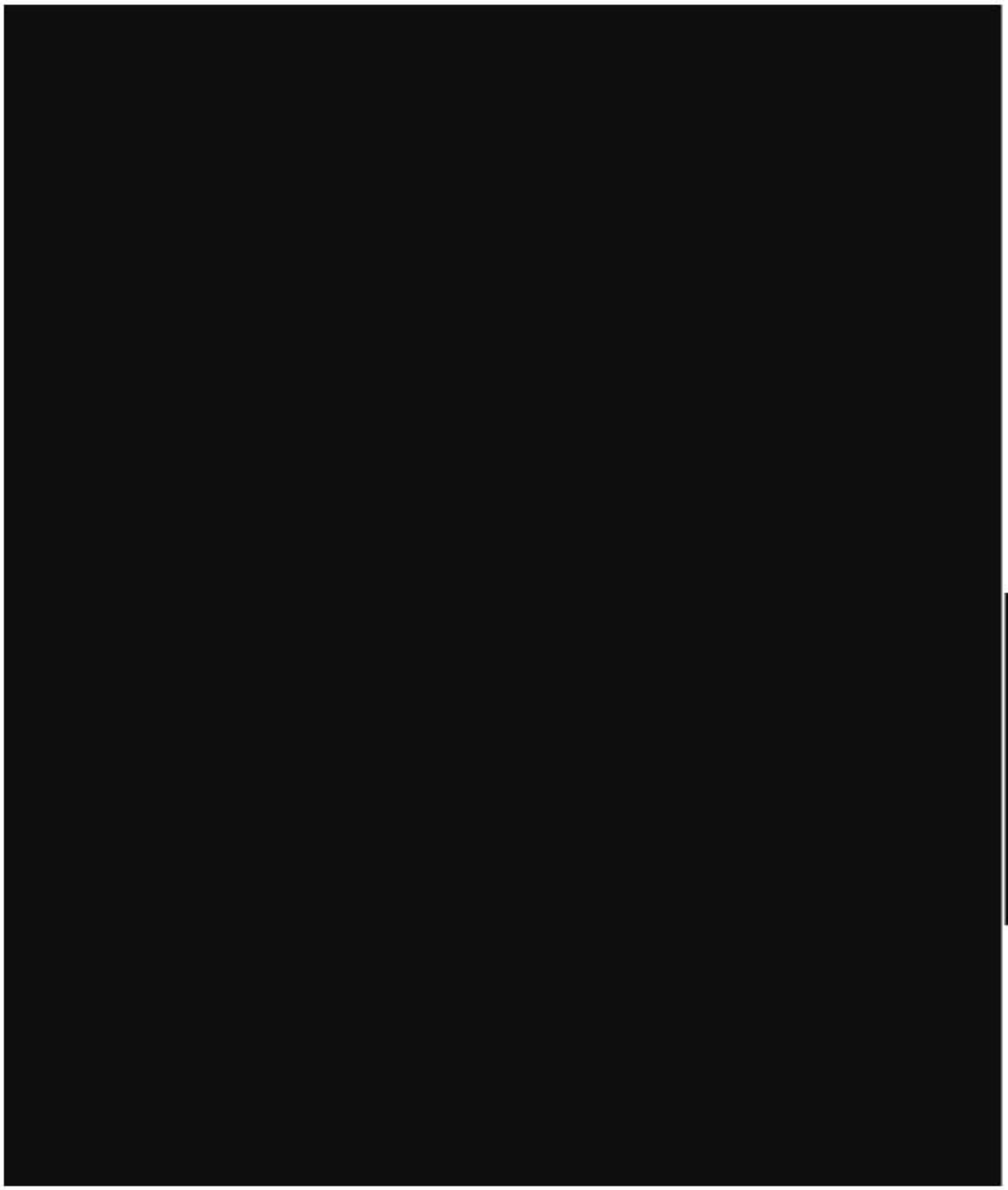

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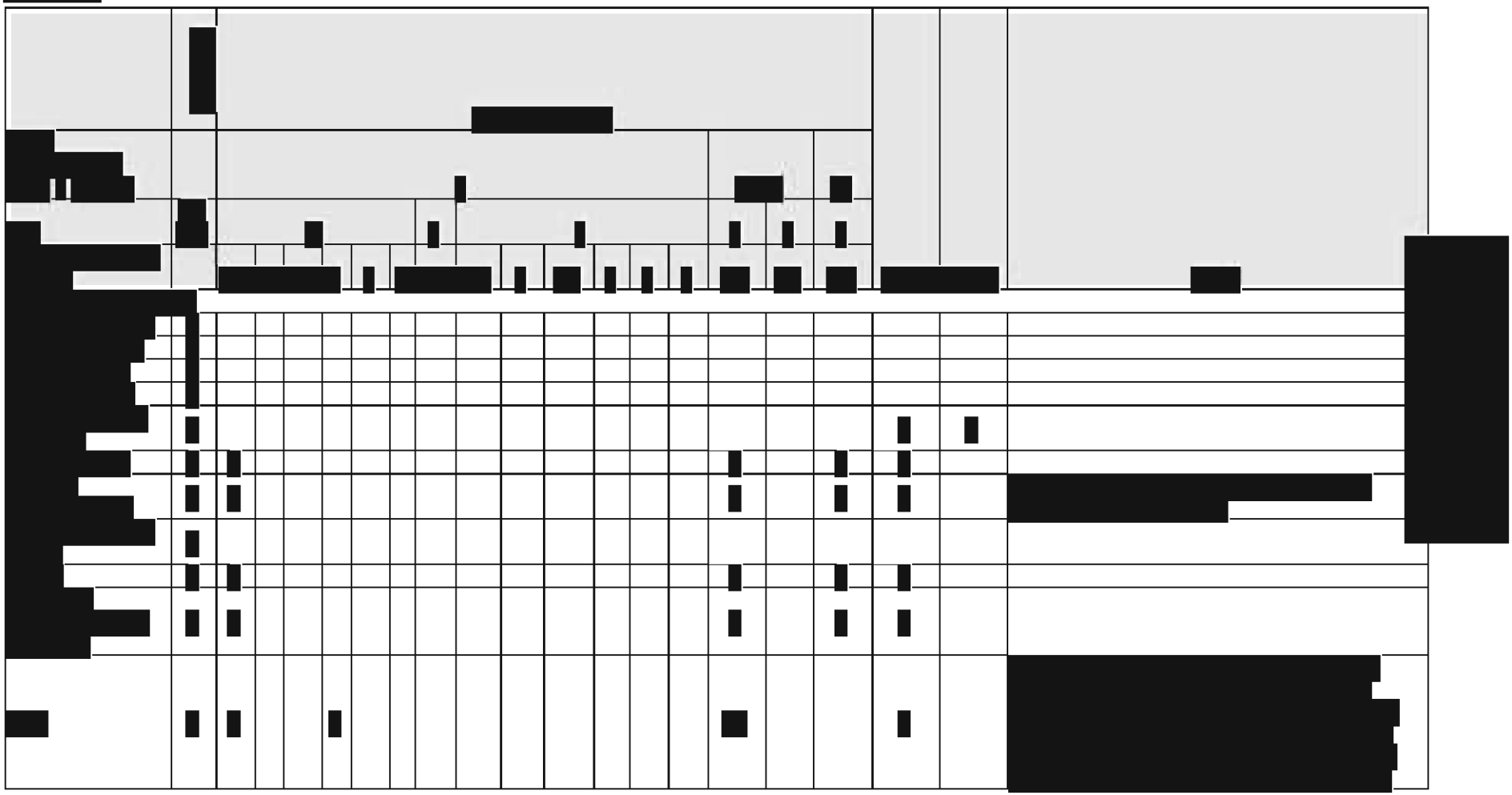

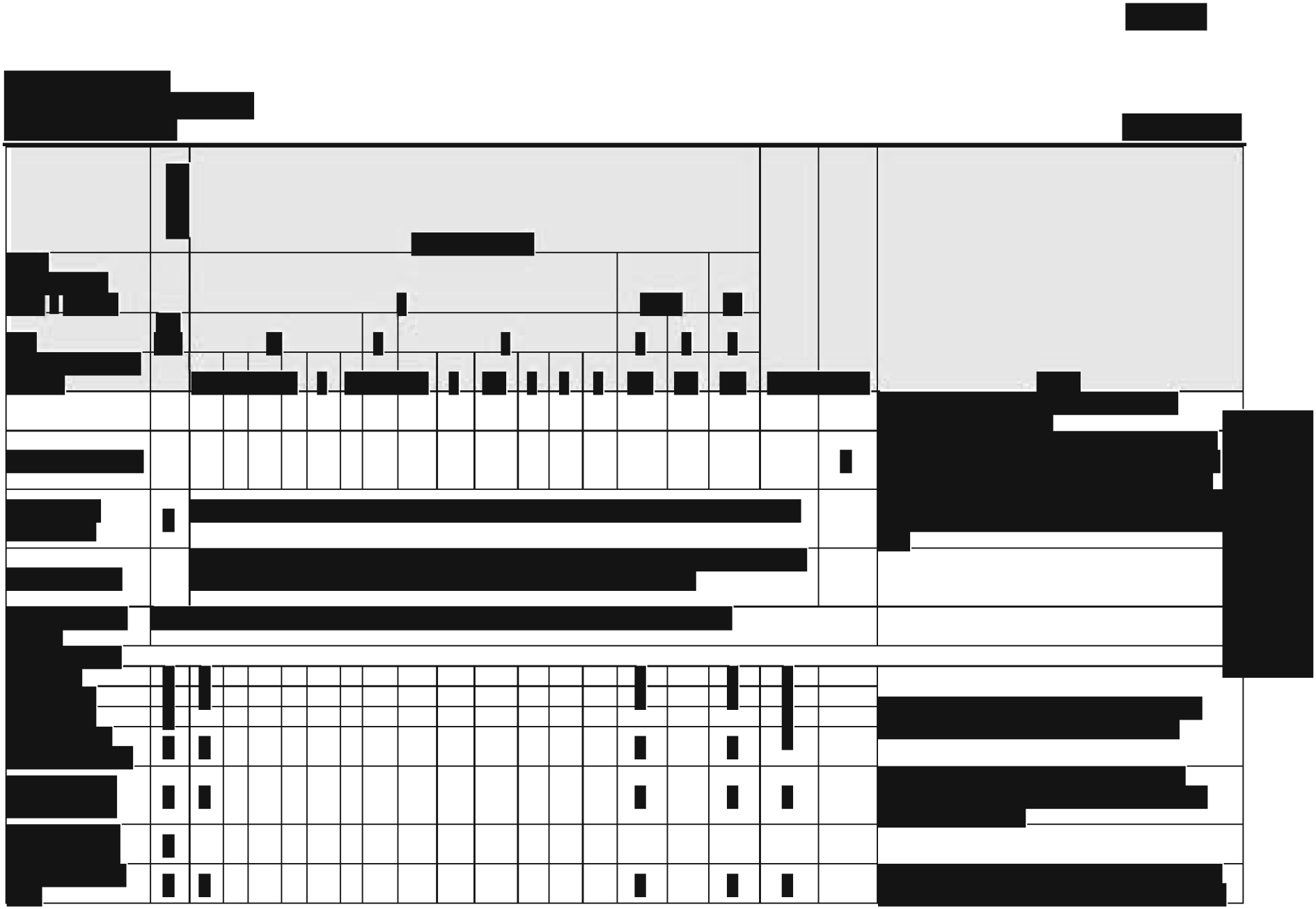

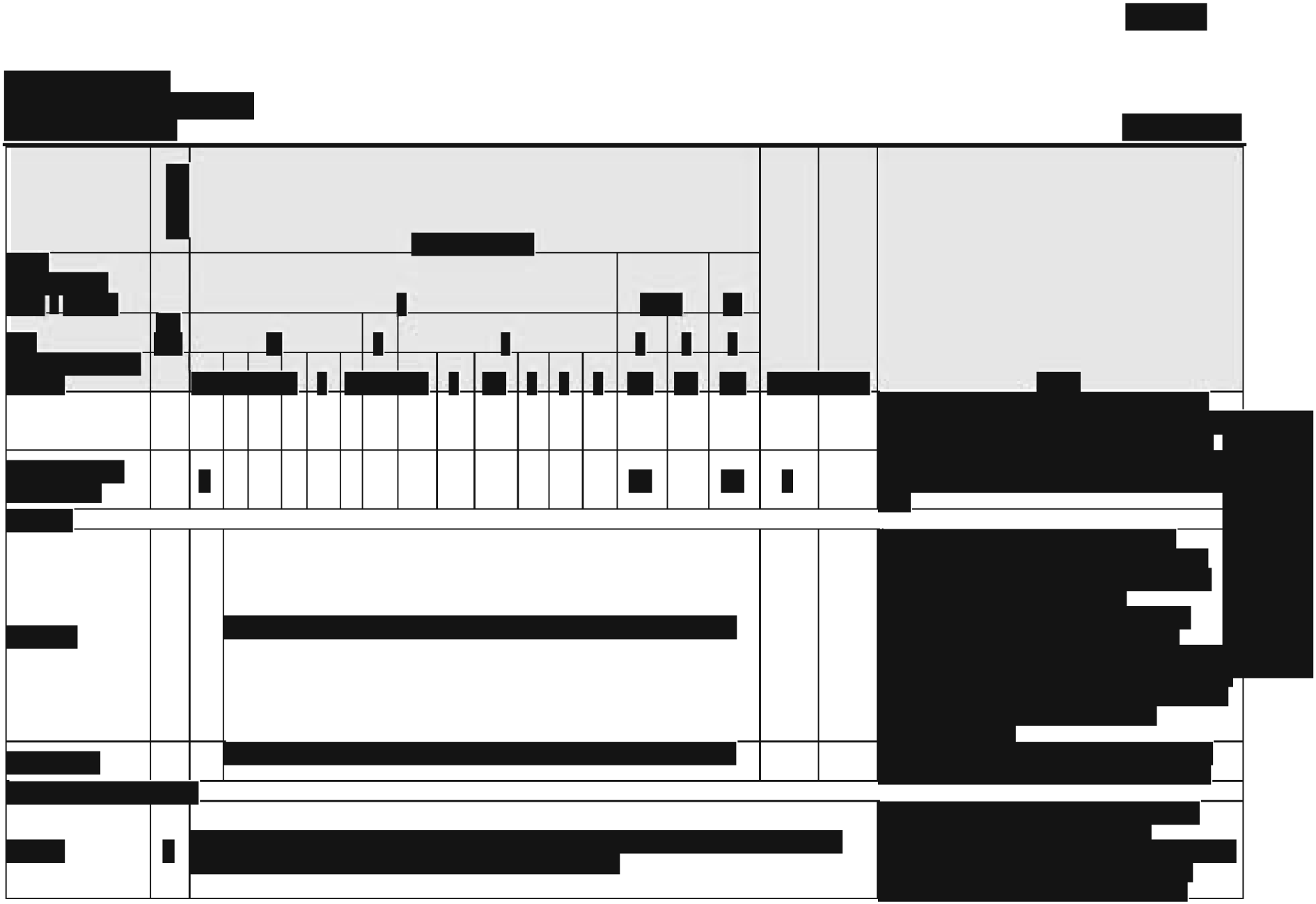

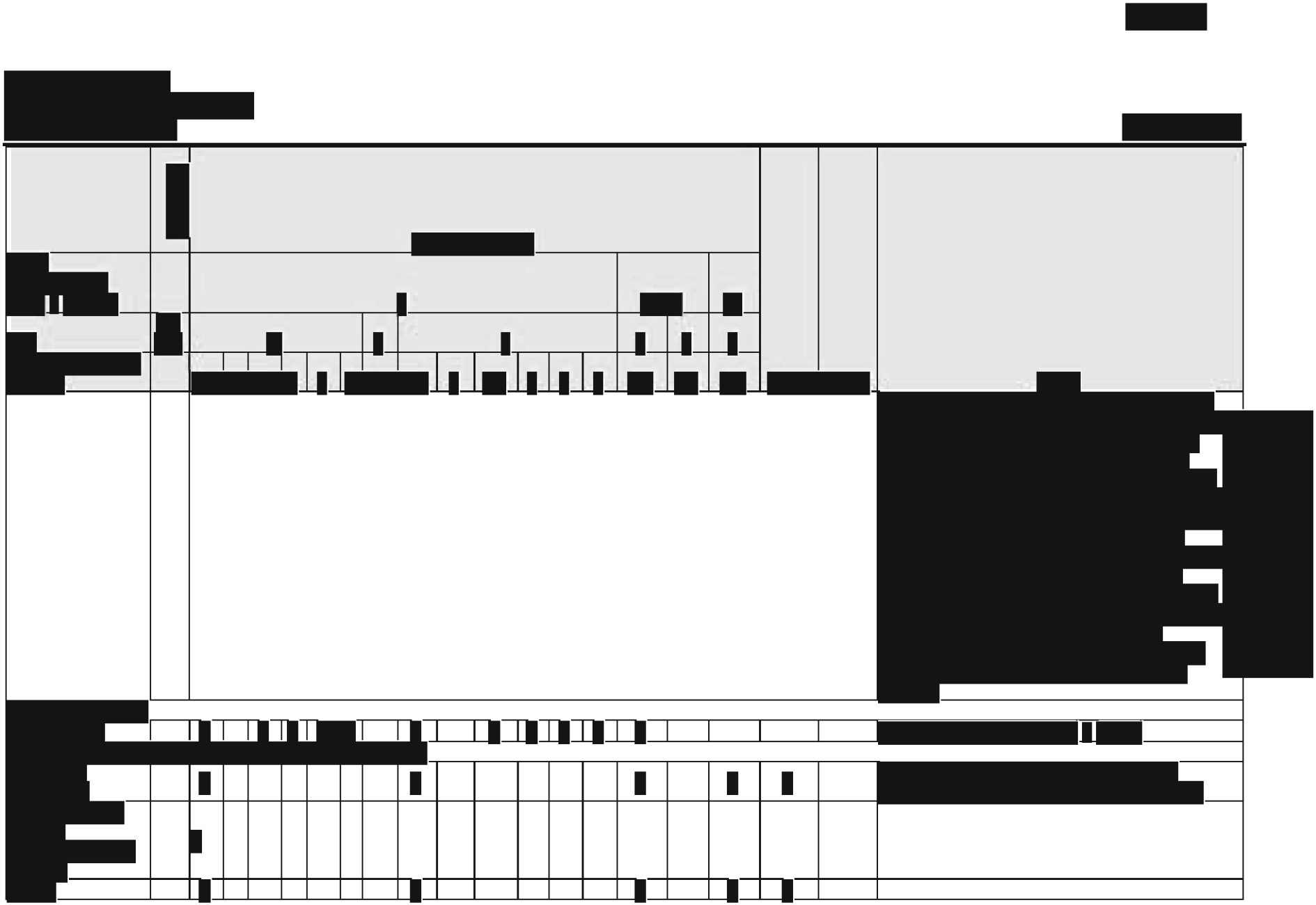

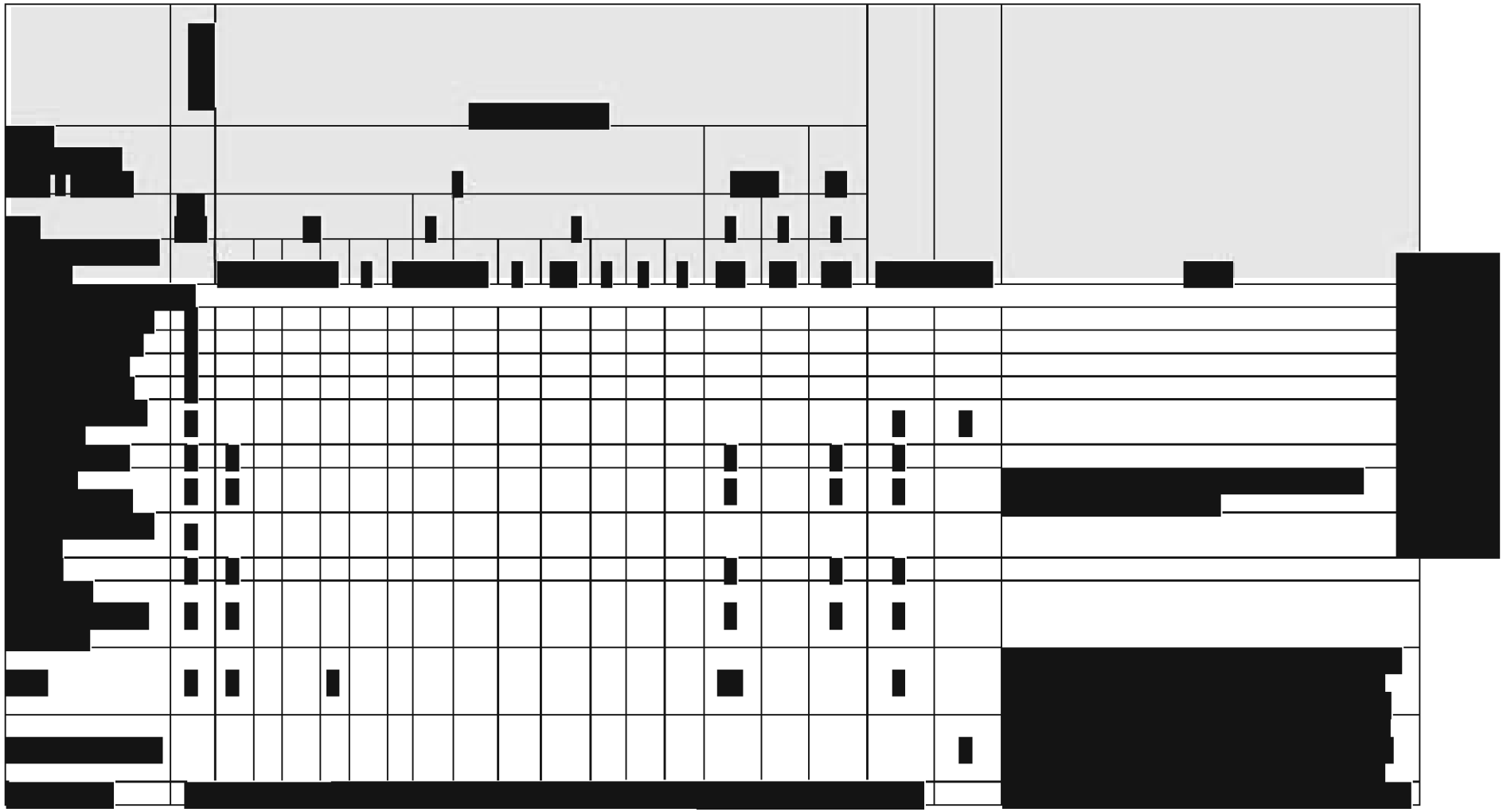

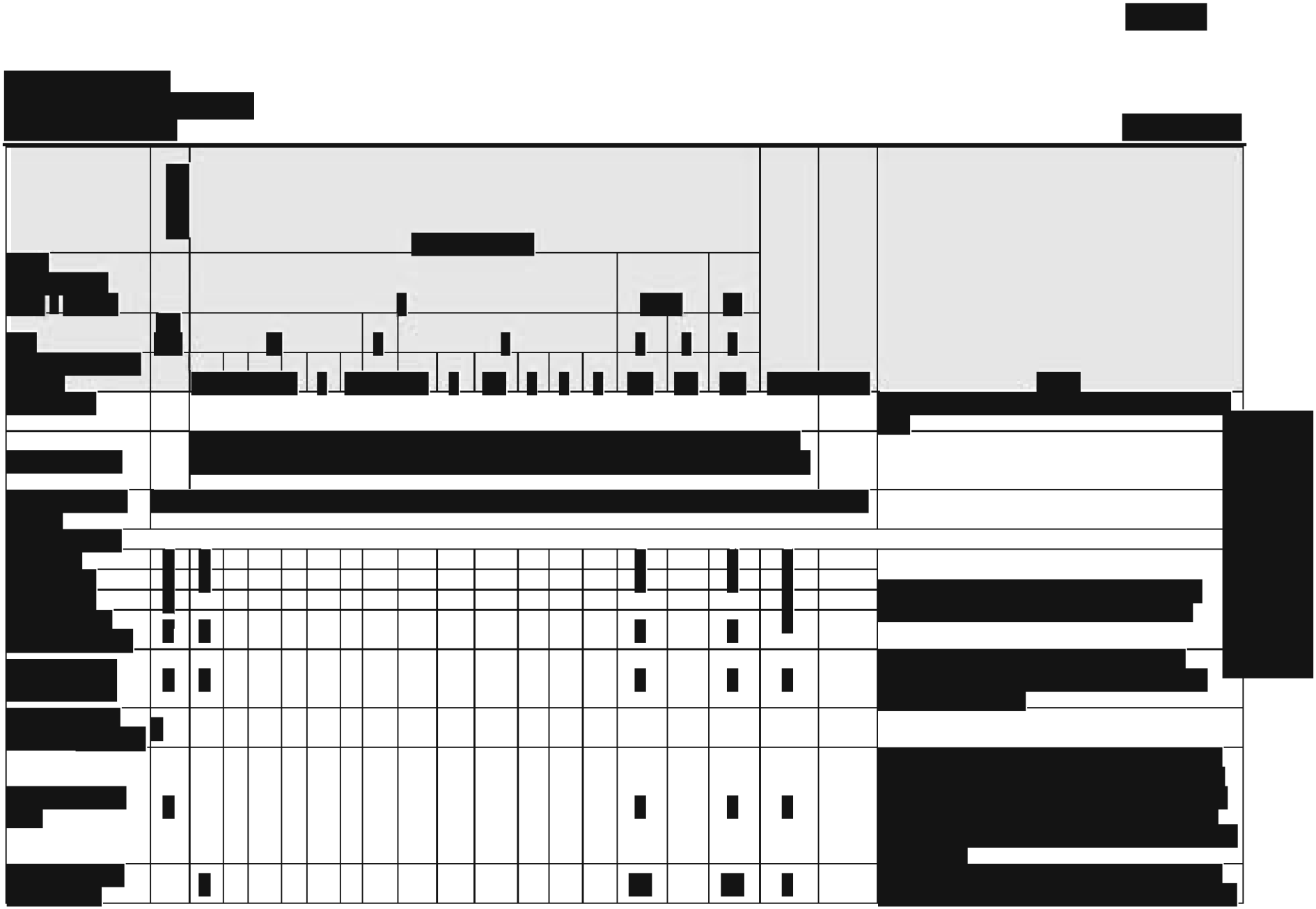

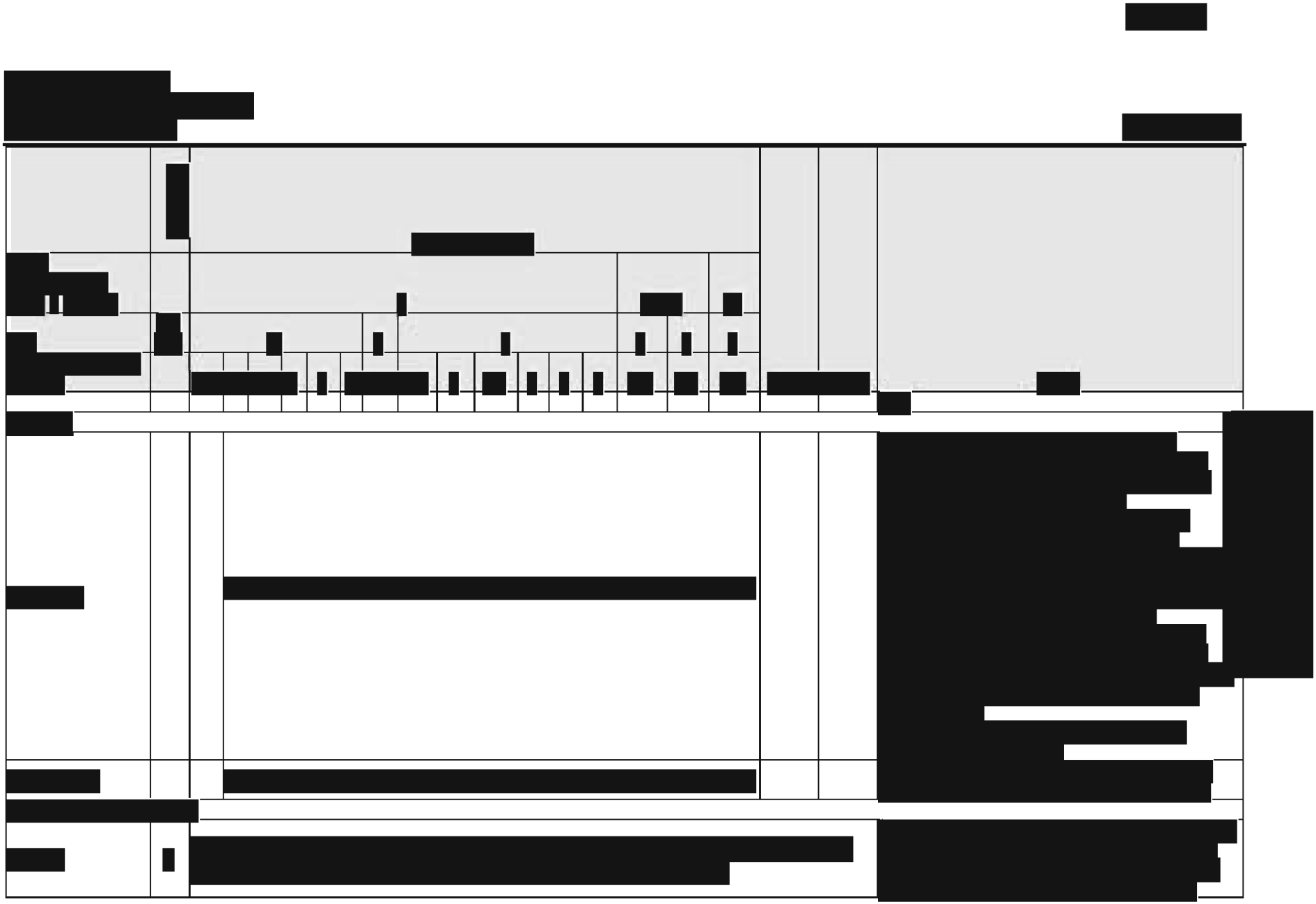

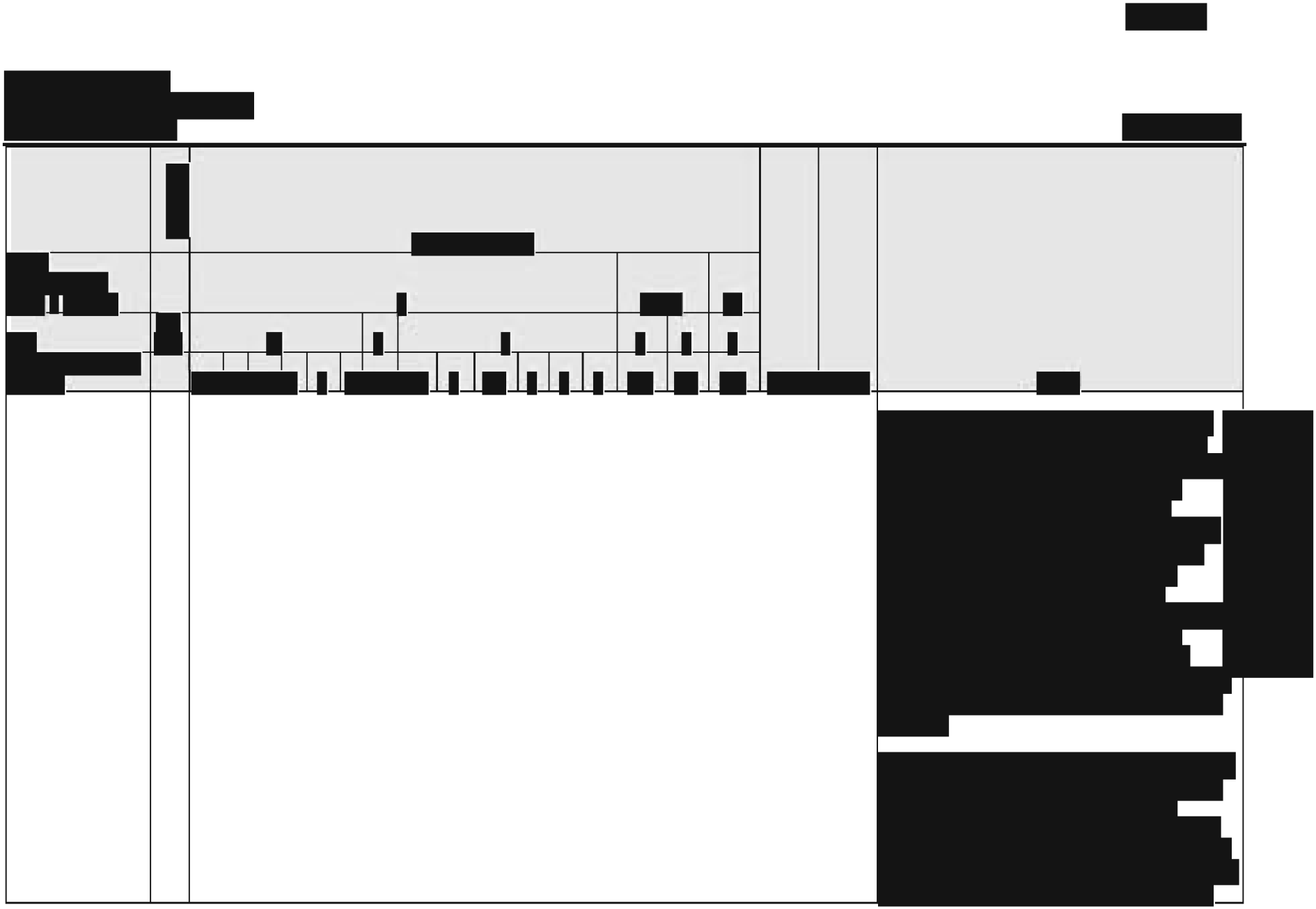

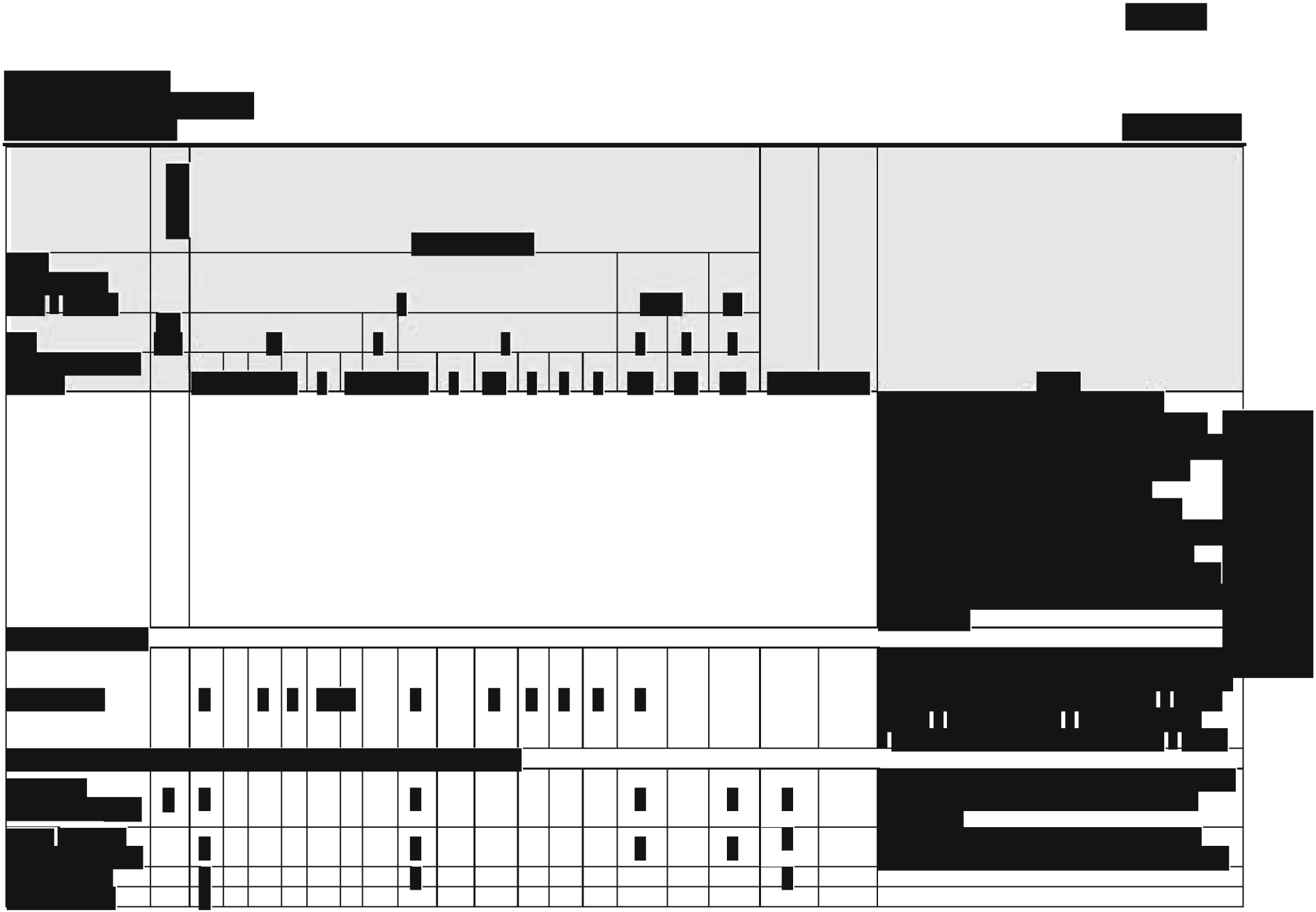

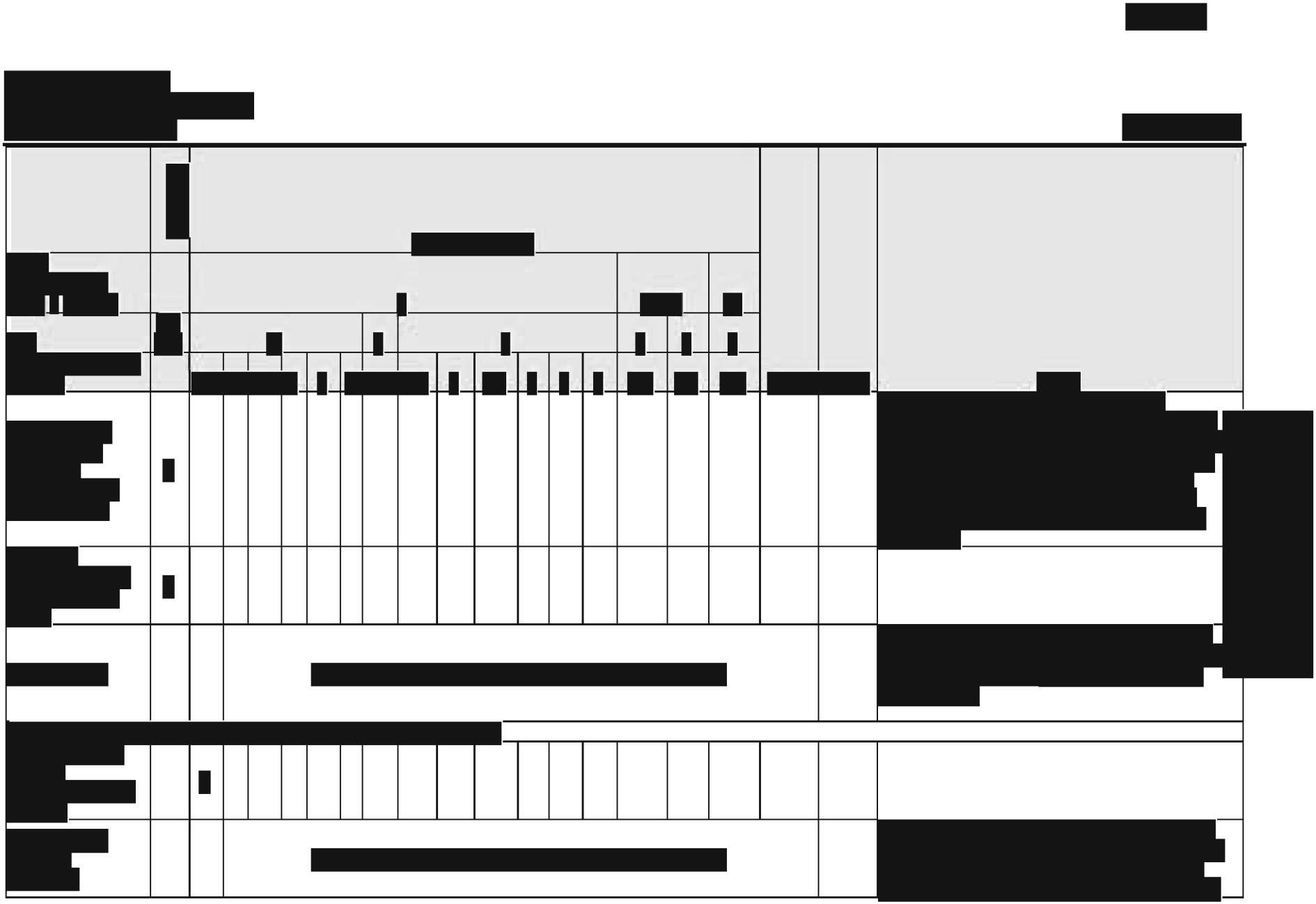

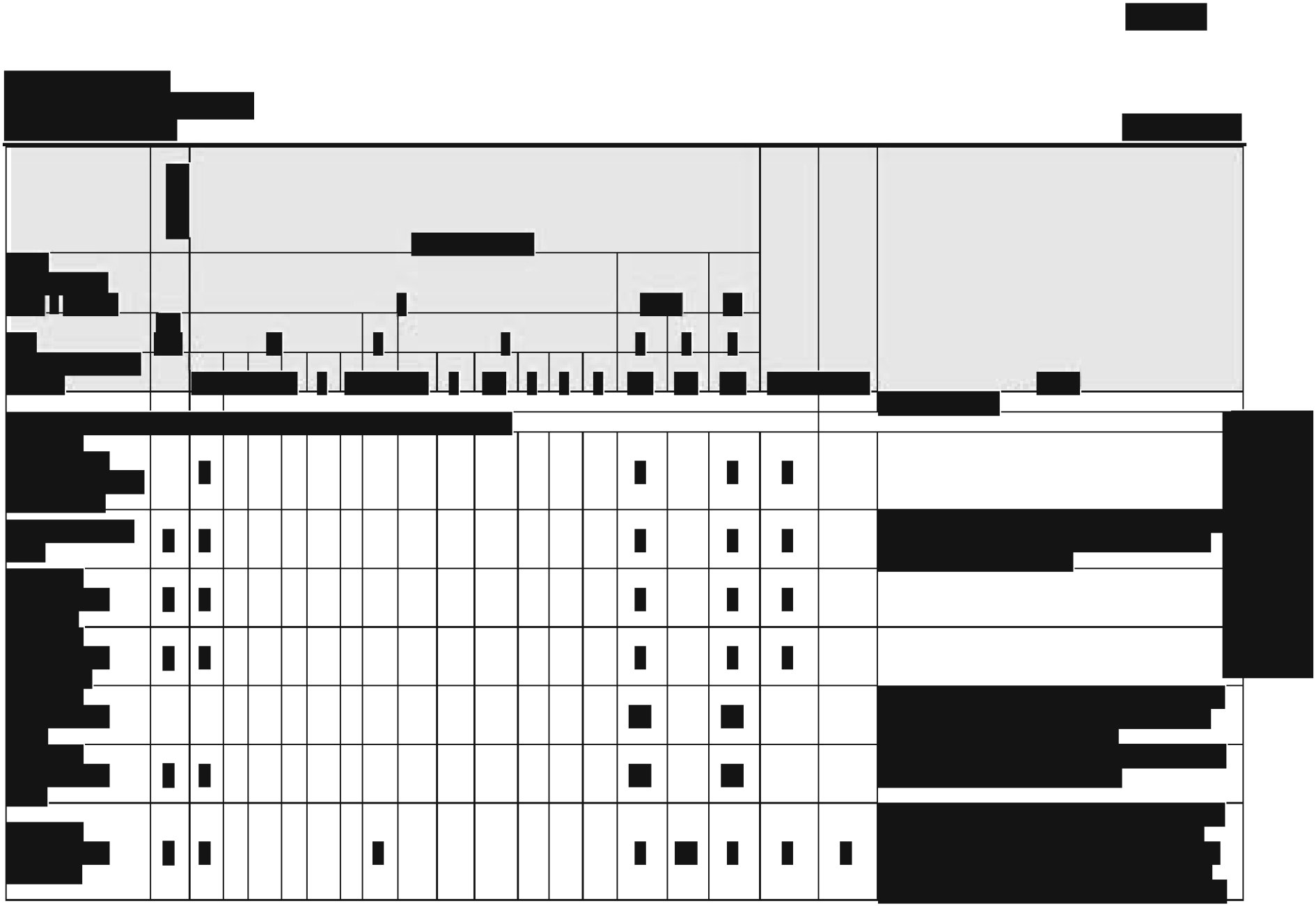

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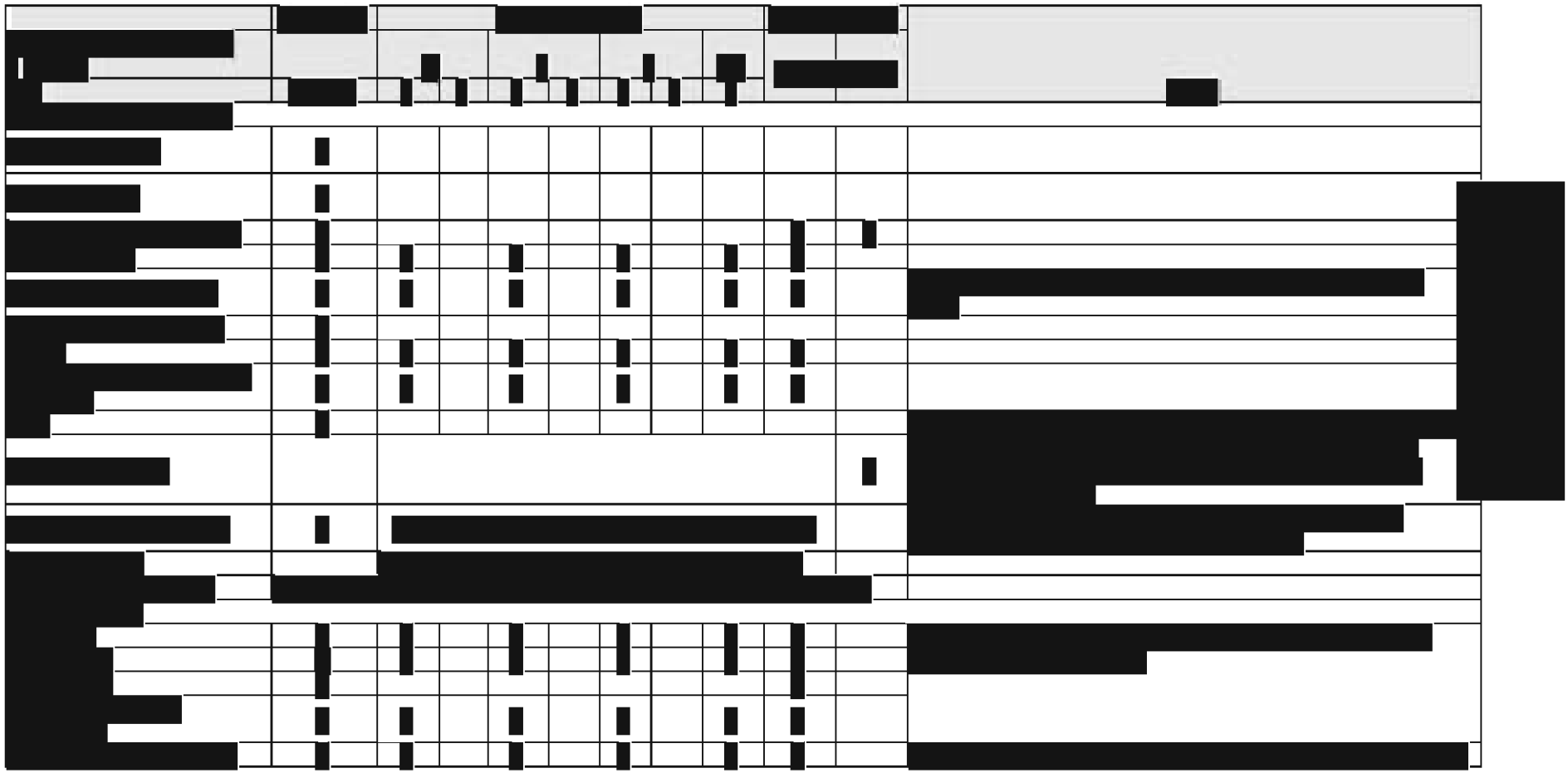

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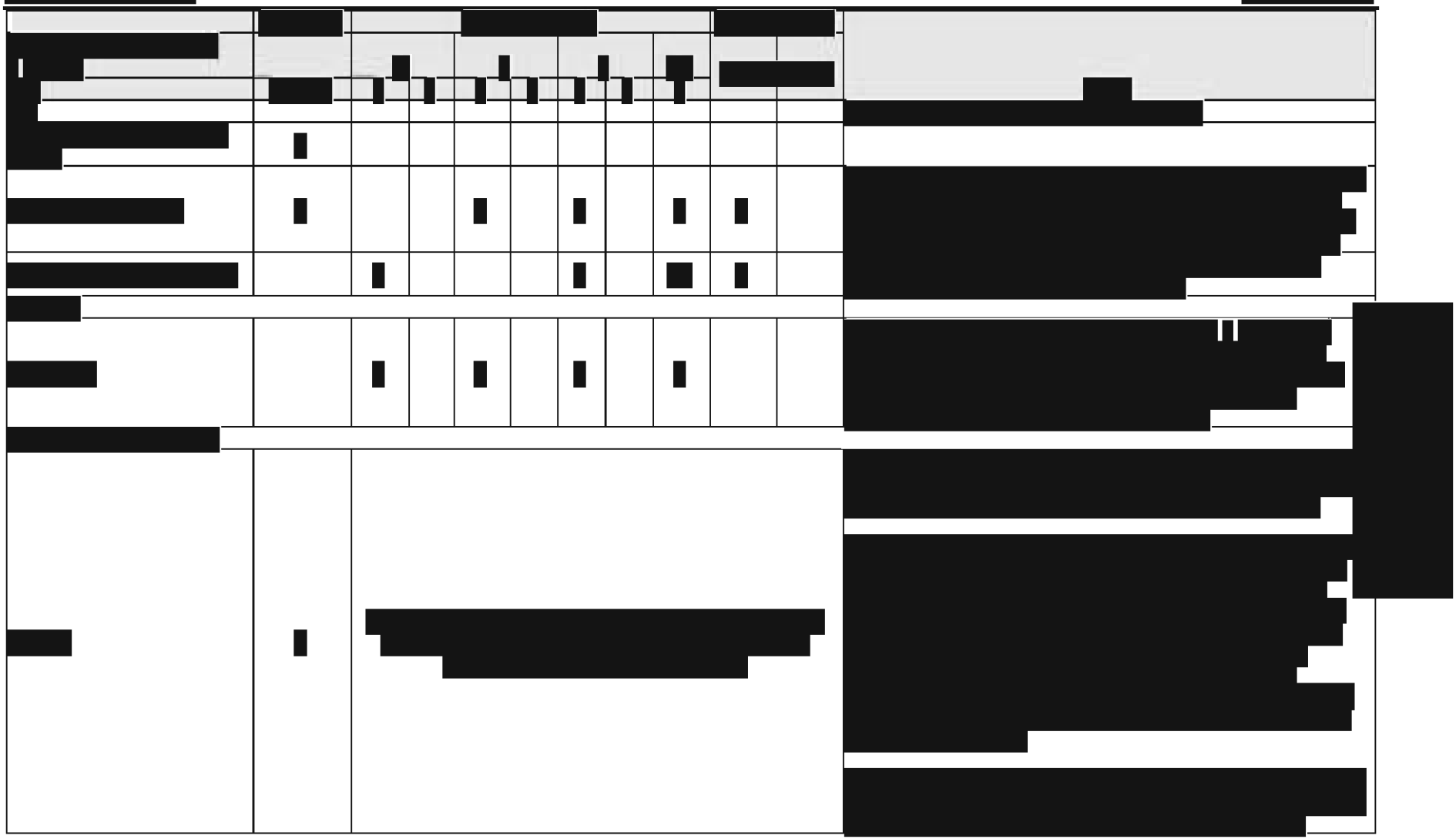

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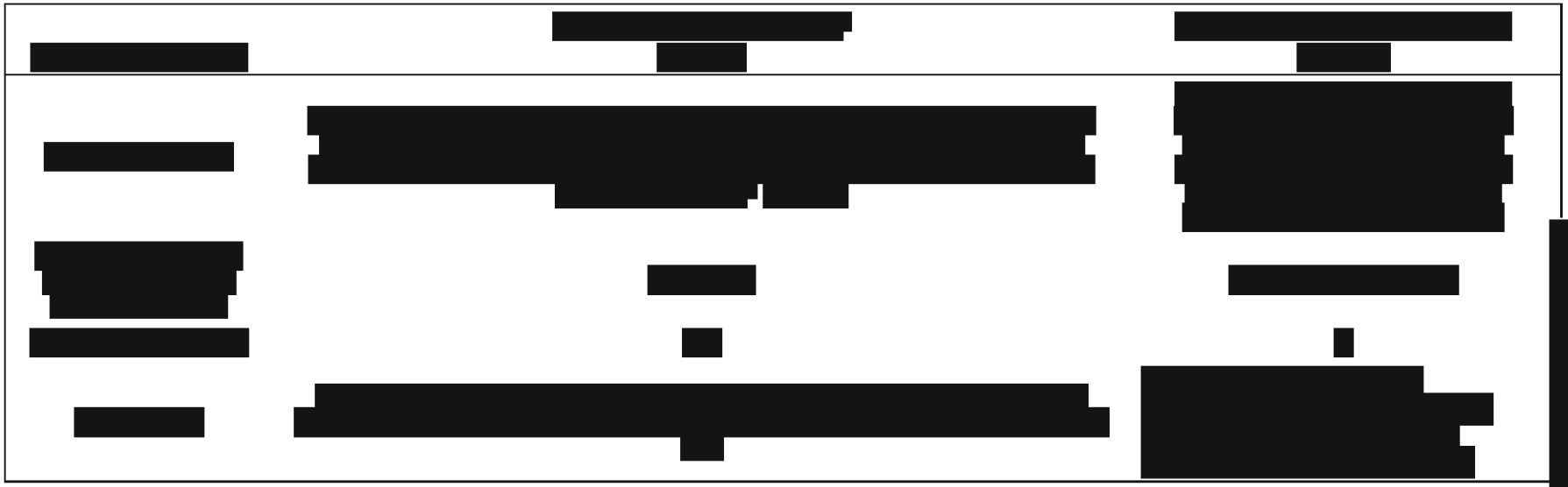

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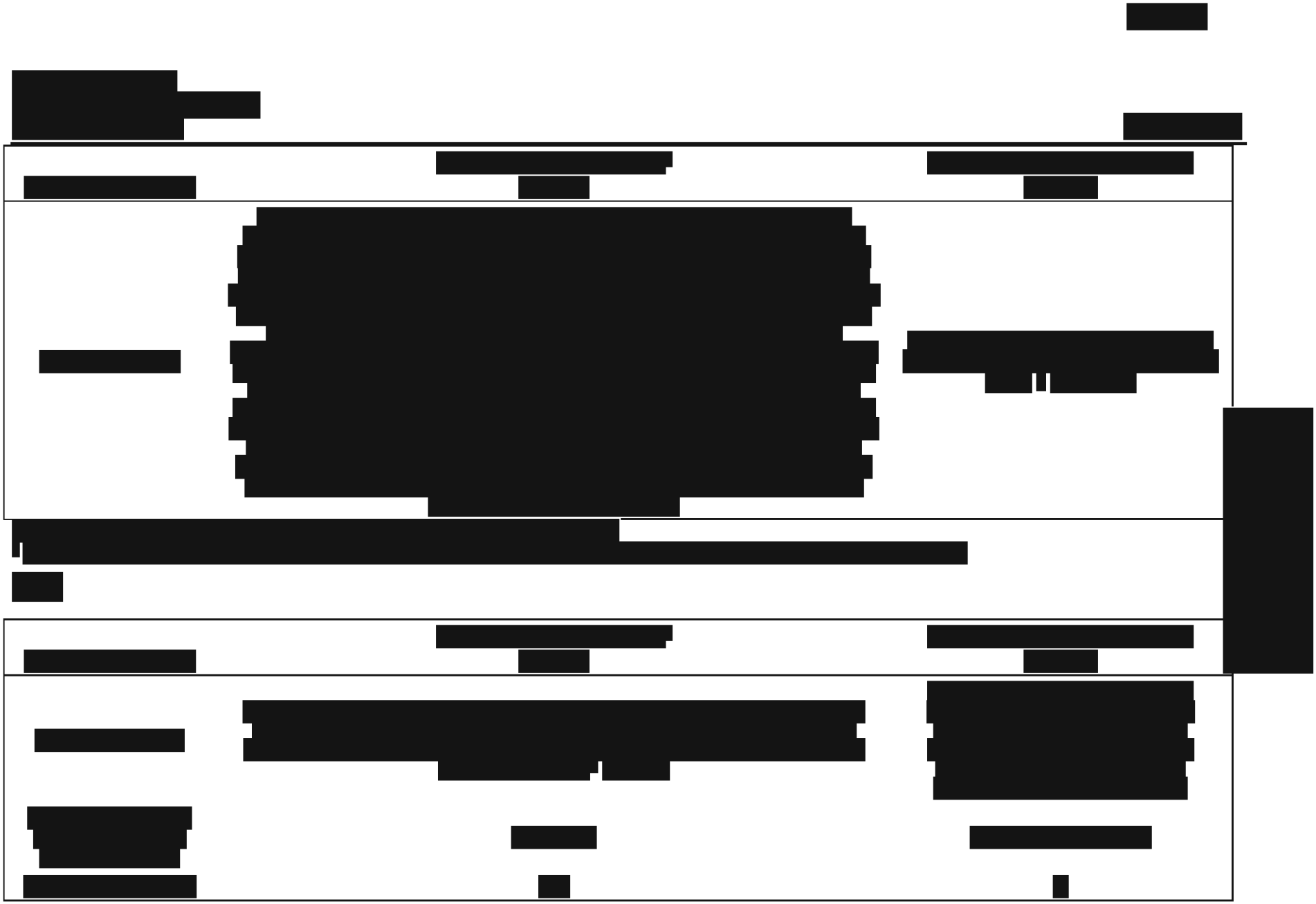

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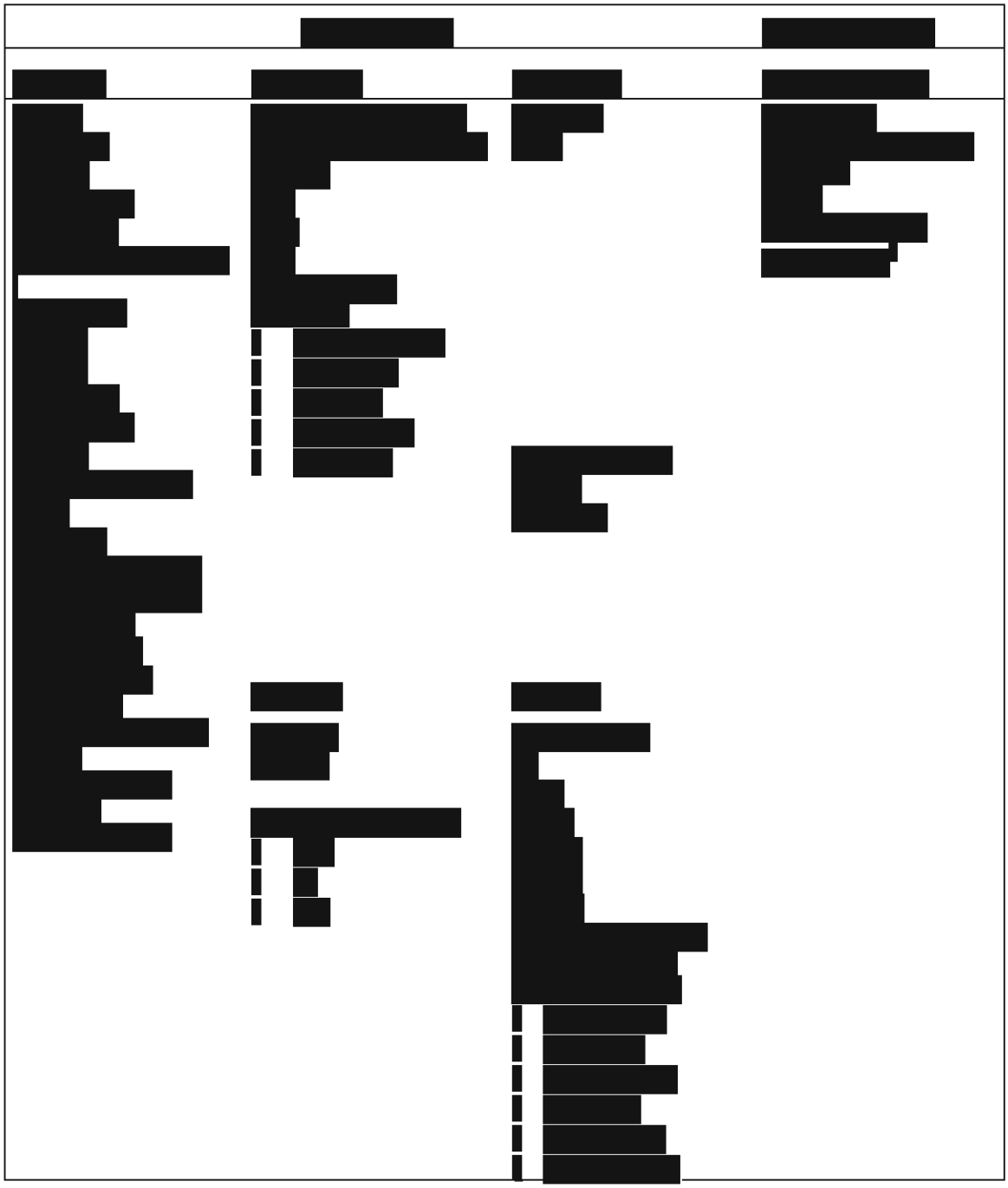

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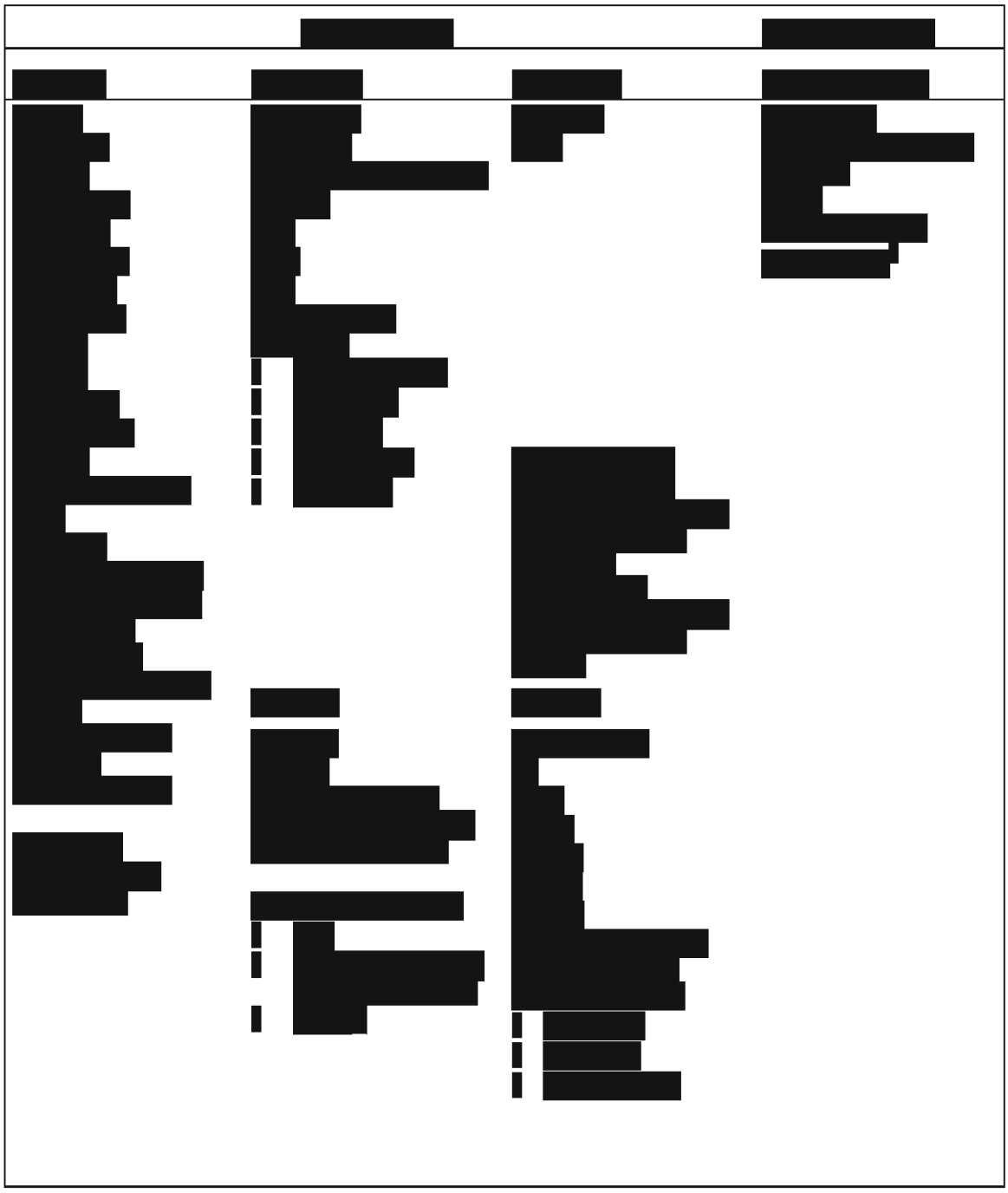

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Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable.

Annex 7. Other Supporting Data (Including Referenced Material)

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Annex 8. Summary of Changes to the Risk Management Plan Over Time

Table 19. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
0.1	Date of RMP: 04 December 2020 Approval Date: To be determined Procedure: To be determined	Not applicable