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OptumRx

Response to 1a and 1c

OptumRx administers pharmacy benefits for its health plan customers, on whose behalf the Company negotiates prescription drug discounts. In that context, OptumRx contracts with the following insulin manufacturers: Sanofi-Aventis, U.S., LLC ("Sanofi"), Eli Lilly and Company ("Eli Lilly"), and Novo Nordisk, Inc. ("Novo Nordisk").

Drug manufacturers independently set the prices for the products they manufacture and market. OptumRx cannot and does not set these list prices. OptumRx does work to reduce the net price its customers pay for drugs through vigorous discount negotiations with manufacturers. OptumRx has negotiated discounts with Sanofi, Eli Lilly, and Novo Nordisk for insulin products and certain other prescription drugs that the companies manufacture.

Additionally, to discourage list price increases and keep net costs as low as possible for its customers, OptumRx negotiates price protection guarantees with drug manufacturers. These guarantees trigger additional discounts if the manufacturer increases the price of a drug above a negotiated threshold. OptumRx has negotiated price protection guarantees with each of the insulin manufacturers with whom it contracts.

OptumRx passes on approximately 98 percent of its negotiated discounts to its customers, which in turn decide how to pass that value onto individual consumers—either through direct point-of-sale discounts, lower premiums, or both. In those limited instances in which OptumRx retains a portion of a discount, it is because the Company's customers have chosen to compensate it that way. OptumRx passes on an even greater percentage of negotiated discounts to government plan customers.

OptumRx performs various services in connection with the administration of its negotiated discounts, in exchange for which it receives administrative fees from insulin manufacturers. OptumRx also passes on the value of these administrative fees to its customers in many circumstances, pursuant to the terms of its customer agreements. OptumRx does not perform consultative services for insulin manufacturers.

Response to 4a, 4b and 4d

OptumRx's formulary design and management is focused on providing access to high-quality, clinically appropriate, cost-effective products. As a general matter, the design of plan formularies follows a multi-step process.

First, OptumRx's Pharmacy & Therapeutics ("P&T") Committee, described in greater detail below, evaluates clinical evidence to assess a medication's role in therapy and overall clinical value. The P&T Committee provides evidence-based review and appraisal of new drugs, existing drugs, and their appropriate places in therapy. As necessary, the P&T Committee will review and evaluate medical criteria, standards, and educational intervention methods in the process of developing clinical recommendations for drugs and drug management.

Second, subject to the clinical designations and recommendations of the P&T Committee, OptumRx makes decisions regarding the placement of prescription drugs on OptumRx's standard formularies. Its primary goal in doing so is to design standard formularies that are attractive to current and potential customers, particularly by providing customers with the lowest possible net cost of drugs.

Additionally, formulary and utilization management decisions are ultimately the authority of OptumRx's customers, which retain complete and exclusive control over their own benefit plans—including formulary design. OptumRx designs standard national formularies based upon objective evaluation of the therapeutic merits, safety, and cost of available prescription drugs. OptumRx's customers may select one or more of these standard formularies as the basis for their pharmacy benefit plan, or may opt to establish their own tailored formularies. OptumRx may also assist customers with the administration of their custom formularies.

OptumRx's P&T Committee is an independent advisory body that evaluates existing and emerging drugs based on scientific evidence. It reviews and appraises those drugs in an evidenced-based manner. Membership on the P&T Committee currently consists of 11 members from a range of specialties, including ten physicians and a pharmacist. To ensure that P&T Committee recommendations are independent and unbiased, no Committee member is an employee or client of OptumRx, or a drug manufacturer representative, and each member must sign conflict of interest disclosures.

The P&T Committee meets several times per year, sometimes in person and sometimes by teleconference, to make, review, update, develop and approve clinical recommendations regarding placement of new drugs on OptumRx standard formularies, procedures for formulary management activities such as prior authorizations and step-therapies, drug utilization management strategies, and clinical educational programs.

The P&T Committee commences a drug review upon the release of a new drug, including a new FDA-approved indication for an existing drug, a new FDA-approved formulation for an existing chemical entity, or release of a new strength of an existing product. Where a new drug is part of an existing therapeutic drug class, a new drug review will often require review of other drugs within that class. The P&T Committee's reviews are based on scientific evidence and standards of practice; drug discounts are not considered during P&T Committee reviews and do not factor into the Committee's evaluation.

Each P&T Committee review results in one or more clinical drug recommendations to OptumRx. Recommendations can include, for example, designation of a drug or drug class as: "Essential Drug," "Essential Class," "Unique Risk," "Additional Data Required," "Optional Inclusion," "Non-Essential Non-FDA-Approved Drug," or "Vaccine."

Subject to the clinical designations and recommendations of the P&T Committee, OptumRx makes decisions regarding formulary placement of FDA-approved prescription drugs for its standard formularies. OptumRx recommendations regarding formulary placement are also shared with certain OptumRx clients that choose to create and follow custom formularies. Such OptumRx customers are the final decision-makers for any custom client-specific formularies.

OptumRx's primary goal is to promote the highest quality, cost-effective products and achieve the lowest possible net cost of drugs for OptumRx's customers, including the promotion of lower-cost generic drugs where they are available.

OPTUMRx

OptumRx Pharmacy and Therapeutics (P&T) Committee Quarterly Meeting Agenda Summary

August 2016

New Drug Reviews	Therapeutic Class Reviews	Re-classifications
• **Basaglar** (LY insulin glargine U-100) injection [redacted]	[redacted]	[redacted] • Long-acting Insulin Agents: **Lantus, Lantus Solostar** (insulin glargine U-100) injection; **Levemir, Levemir FlexTouch** (insulin detemir U-100) injection; **Toujeo SoloStar** (insulin glargine U-300) injection [redacted]

Note: Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text

NEW DRUG REVIEW – Basaglar
RECLASSIFICATION – Long-acting Insulin Agents

Medication	Previous P&T Recommendation	Previous Clinical Notes	Current P&T Recommendation	Current Clinical Notes	UM†
Basaglar (LY insulin glargine U-100) injection	**N/A**	**N/A**	**Essential Class** (long acting insulin analogs; long acting insulin analogs are the preferred basal insulin therapy due to lower hypoglycemic rates compared to intermediate-acting insulin NPH; in clinical trials and using indirect comparisons, long-acting insulin agents are similarly effective in achieving and maintaining glycemic control and have mostly similar rates	• Pharmacokinetic and pharmacodynamic (PK/PD) differences may result in: o A steadier PK/PD profile for Toujeo with a potentially smoother insulin effect o Potential for twice-daily dosing with Levemir	ST
Lantus, Lantus Solostar (insulin glargine U-100) injection	**Essential Class** (long acting insulin analogs; long acting insulin analogs are the preferred basal insulin therapy due to lower hypoglycemic rates compared to intermediate-acting insulin NPH) (5/2015)	• In clinical trials, Lantus and Levemir are similarly effective in achieving and maintaining glycemic control and they have similar rates of hypoglycemia; however, due to pharmacokinetic and pharmacodynamic differences, higher doses of total basal			--
Levemir, Levemir FlexTouch (insulin detemir U-100) injection					--
Toujeo SoloStar (insulin glargine U-300) injection					--

		insulin and twice-daily dosing are often required with Levemir compared to Lantus.	of hypoglycemia)		
Therapeutic Class: Antidiabetic agents, Insulin					

†An asterisk next to the UM type indicates UM programs that were reviewed and approved at the August 2016 P&T meeting; all others indicate existing UM

Indications

- Basaglar (LY insulin glargine) is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM).
- Limitations of use: Not recommended for the treatment of diabetic ketoacidosis.

Summary

Background

- Long-acting insulin analogs (Levemir [insulin detemir], Tresiba [insulin degludec], Lantus and Toujeo [insulin glargine]) are the mainstay of basal insulin therapy in patients with diabetes mellitus. In December 2015, long-acting insulin, Basaglar (LY insulin glargine), was Food and Drug Administration (FDA)-approved by standard review.
  - Based on pharmacokinetic data, Toujeo and Tresiba have a longer duration of action (greater than 24 hours) compared to the other long-acting insulin agents, which allows greater flexibility in administration times.
  - Levemir is the only long-acting insulin with a peak seen anywhere from 4 to 12 hours post-dose (*Prescribing information: Basaglar, 2016; Lantus, 2015; Levemir, 2015; Toujeo, 2015; Tresiba, 2015*).
- The New Drug Application (NDA) for Basaglar evaluated by standard review was tentatively approved by the FDA in 2014.
  - The final FDA-approval of Basaglar could not commence until the end of an automatic stay of 30 months due to patent infringement litigation filed by Sanofi. The final FDA-approval of Basaglar was granted on December 16, 2015. Under the settlement agreement, the United States (US) launch of Basaglar may occur on December 15, 2016 (*Drugs@FDA 2016; Eli Lilly press release 2015; FDA approval letter 2014*).
  - In October 2014, LY insulin glargine (Abasaglar) was the first biosimilar insulin approved for marketing authorization in Europe (*European Medicines Agency [EMA] summary, 2014*). LY insulin glargine is not considered a biosimilar in the US, but is considered a "follow-on biologic" to Lantus. A handful of biologics are evaluated by the FDA under the 505(b)(2) pathway under the Federal Food, Drug, and Cosmetic Act (FD&C Act). In March of 2016, the FDA released draft guidance interpreting the Biologics Price Competition and Innovation Act (BPCIA) to mean that all biologics approved under the 505(b)(2) path will be considered approved under the 351 path, known as the "biosimilar pathway," after March 23, 2020 (*FDA guidance for industry 2000; FDA guidance for industry 2016; FDA press release, 2016; Howard et al 2015; Shehan et al 2016*).

Clinical trial data

- The safety and efficacy of LY insulin glargine compared to insulin glargine were evaluated through 2 pivotal studies in approximately 1300 patients with T1DM through the ELEMENT 1 trial, or T2DM through the ELEMENT 2 trial. Both trials were multicenter (MC), parallel group (PG), randomized controlled trials (RCTs); ELEMENT 1 was open-label (OL) and ELEMENT 2 was double-blinded (DB). Both trials were conducted over 24 weeks; however, ELEMENT 1 also included a 28-week comparative safety extension period. The primary efficacy endpoint tested the non-inferiority of agents by the reduction in (hemoglobin A1c [HbA1c]) from baseline to 24 weeks, and key secondary endpoints included overall and severe hypoglycemic events and mean weight change (*Basaglar prescribing information 2016*; *Blevin et al 2015; Rosenstock et al 2015*).
  - Based on the primary analysis, a non-inferiority margin of 0.4% was tested. If this was met, a non-inferiority margin of 0.3% was also tested.
  - Dose adjustments were only made after week 12 in the case of safety concerns.
  - Mealtime insulin lispro was administered 3 times daily in both groups within the ELEMENT 1 trial. Oral antidiabetic medication was permitted in conjunction with insulin treatment within the ELEMENT 2 trial.

Table 1. Summary of results from the ELEMENT trials

Patient Group	T1DM		T2DM
Study name (Weeks)	**ELEMENT 1 (24)**	**ELEMENT 1 (52)**	**ELEMENT 2 (24)**

Comparators* (n)	LY IGlar (n = 268*)	IGlar (n = 267)	LY IGlar (n = 268*)	IGlar (n = 267)	LY IGlar (n = 376*)	IGlar (n = 380)
HbA1c						
Baseline, mean ± SD	7.75 ± 1.13	7.79 ± 1.03	7.75 ± 1.13	7.79 ± 1.03	8.34 ± 1.09	8.31 ± 1.06
Change from baseline, %†‡	-0.35	-0.46	-0.26	-0.28	-1.29	-1.34
LSMD†‡ (95% CI)	0.108 (-0.002 to 0.219)		0.020 (-0.099 to 0.140)		0.052 (-0.070 to 0.175)	
Hypoglycemia‖, events/patient/year ± SD						
Overall ± SD	86.5 ± 77.3	89.2 ± 80.1	77.0 ± 68.7	79.8 ± 74.5	21.3 ± 24.4	22.3 ± 28.2
Severe ± SD	0.06 ± 0.52	0.09 ± 0.50	0.07 ± 0.46	0.08 ± 0.46	0.04 ± 0.66	0.01 ± 0.16
Weight gain						
LS mean increase in weight, kg	0.36	0.12	0.71	0.36	1.8	2.0

Abbreviations: CI = confidence interval; HbA1c = hemoglobin A1c; IGlar = insulin glargine (Lantus); LS = least square; LSMD = least square mean difference; LY IGlar = insulin glargine (Basaglar); SD = standard deviation

*One patient randomized in the ELEMENT 1 trial and 3 patients randomized in the ELEMENT 2 trial in the LY IGlar group was not included in the full analysis set (FAS).

†ANCOVA model includes treatment, country, sulfonylurea use (for the ELEMENT 2 trial only), and time of baseline basal insulin injection (daytime or evening/bedtime) as fixed effects and baseline HbA1c as covariate.

‡The results were calculated based on the number of patients in the FAS using their last observed post-baseline value of HbA1c. Observed HbA1c data at 24 weeks were available from 256 (95.5%) and 258 (96.6%) subjects randomized to the ELEMENT 1 LY IGlar and comparator IGlar groups, respectively; and 331 (88%) and 329 (87%) subjects randomized to the ELEMENT 2 LY IGlar and comparator IGlar groups, respectively.

‖The overall rate at 24 or 52 weeks accounts for all events reported during the 24- or 52-week treatment period.

- LY insulin glargine was non-inferior to insulin glargine for the reduction in HbA1c. No statistically significant differences were observed between endpoints outlined in Table 1.

Safety

- LY insulin glargine has similar contraindications and warnings and precautions as other insulin glargine products.
- The most common adverse events (incidence ≥ 5%) with LY insulin glargine use are hypoglycemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, edema, and weight gain. Additional adverse reactions include infection, nasopharyngitis, and upper respiratory tract infection. As with all therapeutic proteins, there is potential for immunogenicity. In T1DM patients, a total of 65% had detectable antibodies to insulin at 52 weeks and in T2DM patients, 51% had detectable antibodies to insulin at 24 weeks. There is no evidence that the antibodies had any impact on efficacy and safety outcomes *(Basaglar prescribing information 2016)*.

Guidelines

- According to the American Diabetes Association (ADA) treatment guidelines for diabetes, most individuals with T1DM should be treated with multiple-dose insulin or continuous subcutaneous insulin infusion. In contrast, the ADA and the American Association of Clinical Endocrinologists (AACE) recommend a patient-centered approach to guide the choice of pharmacological agents for the treatment of T2DM. Considerations include efficacy, cost, potential side effects, comorbidities, hypoglycemia risk, and patient preferences (*Garber et al 2016; Handelsman et al 2015; ADA 2016*).
  - Treatment guidelines from the ADA and AACE have not been updated to include LY insulin glargine; however, it is anticipated that treatment will follow that of insulin glargine.

Dosing

- Patients may administer 1 to 80 units of LY insulin glargine subcutaneously per injection once daily at any time during the day but at the same time every day. Patients may inject. Individualized dosing is recommended based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, and prior insulin use of the patient (*Basaglar prescribing information 2016*).

Conclusion

- Basaglar (LY insulin glargine) is a follow-on biologic to similar to Lantus (insulin glargine). Based on 2 non-inferiority trials, LY insulin glargine and insulin glargine appear to be similarly effective in achieving and maintaining glycemic control in T1DM and T2DM patients. ELEMENT 1 and 2 did not reveal any significant differences in the incidence of antibodies, body weight changes, the rate of hypoglycemia, and the incidences of adverse events (overall, serious,

Response to 3

Drug manufacturers, including insulin manufacturers, independently set the prices for the products they manufacture and market. OptumRx does not set or affect these list prices. Instead, OptumRx works to reduce the net price its customers pay for drugs through vigorous discount negotiations with manufacturers. OptumRx's Industry Relations group negotiates contracts and discounts with drug manufacturers, including manufacturers of insulin. Industry Relations plays no role in the independent clinical evaluation by, or resulting recommendations from, OptumRx's Pharmacy and Therapeutics Committee.

OptumRx utilizes purchasing volume and other market forces to negotiate discounts with manufacturers and offer price predictability to its customers. The manner in which OptumRx negotiates these discounts varies case-to-case, but in general the discounts are predicated on an analysis of marketplace trends and predictions about what the market for insulin pricing will be when the contract at issue takes effect. OptumRx has negotiated discounts and price protection guarantees with each insulin manufacturer with whom it currently contracts.

OptumRx regularly communicates with manufacturers regarding discounts. For example, following the release of a new drug into the market, a revised P&T Committee classification, or a regular therapeutic class review, Industry Relations may initiate discussions with a manufacturer regarding the potential for improved discount terms. In other cases, a manufacturer may initiate contact with OptumRx to propose new or different discount structures.

OptumRx's customers may choose to manage insulin utilization through the use of evidence-based utilization management tools (for instance, step edits or exclusions), or they may have an open benefit design where all products are available at a similar co-payment for members. Price concessions offered by manufacturers may depend on the level of control that OptumRx's customers exercise over insulin utilization, with higher control yielding higher discounts and thus lower net costs. But the discount structures OptumRx negotiates with insulin manufacturers permit OptumRx's customers to place a full range of insulin products on Tier 1 of their formularies—the tier usually reserved for generics, and that usually results in the lowest co-payment for members. A majority of OptumRx's customers place insulin products on that tier.

Response to 1.d:

OptumRx currently contracts with the following insulin manufacturers: Sanofi-Aventis, U.S., LLC ("Sanofi"), Eli Lilly and Company ("Eli Lilly"), and Novo Nordisk, Inc. ("Novo Nordisk"). OptumRx's agreements with the manufacturers have not been terminated before their expiration dates.

Response to 4.b:

The members of the OptumRx Pharmacy and Therapeutics Committee ("P&T Committee") for the period from 2016 to the present are listed below:

P&T Committee Member	Degree
Alexander, Caleb	M.D.
Chan, Paul	M.D.
Gandhi, Darshan	M.D.
Karlamangla, Arun	M.D.
Koronowski, Michael	Pharm.D.
Kowaloff, Ed	M.D.
Lewis, Stuart	M.D.
McQuaid, Ken	M.D.
Polston, Gregory	M.D.
Potter, Jeffrey	M.D.
Shuster, John	M.D.
Stein, Regina	M.D.
Swarr, Peter	M.D.

OPTUMRx

Therapeutic Class Review
Rapid-Acting Insulins

MEDICATION*	MARKETER	AVAILABILITY
Admelog (insulin lispro) injection	Sanofi-Aventis	**Brand:** 100 units/mL (U100) in 10 mL multiple-dose vial and 3 mL SoloStar prefilled pen
Afrezza (insulin human) inhalation powder	Mannkind Corp.	**Brand:** 4, 8, 12 unit single-use cartridges
Apidra (insulin glulisine) injection	Sanofi-Aventis	**Brand:** U100 in 10 mL multiple-dose vial and 3 mL SoloStar prefilled pen
Fiasp (insulin aspart) injection	Novo Nordisk	**Brand:** U100 in 10 mL multiple-dose vial and 3 mL FlexTouch prefilled pen
Humalog (insulin lispro) injection	Eli Lilly	**Brand:** U100 in 3 mL, 10 mL multiple-dose vials, 3 mL KwikPen and Junior KwikPen prefilled pens, 3 mL cartridges; U200 in 3 mL KwikPen prefilled pens
Novolog (insulin aspart) injection	Novo Nordisk	**Brand:** U100 in 10 mL multiple-dose vial, 3 mL PenFill cartridges, 3 mL FlexPen prefilled pens
Purpose of Review: To evaluate the safety and efficacy of the rapid-acting insulins, including Admelog, a new follow-on insulin lispro formulation, for formulary consideration.		

*Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text

Note: Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

SUMMARY

Background

- In 2015, an estimated 30.3 million people, or 9.4% of the United States (US) population, had diabetes mellitus (DM); as many as 7.2 million were undiagnosed *(Centers for Disease Control and Prevention [CDC] 2017)*.
- Individuals with type 1 diabetes mellitus (T1DM) account for 5% of the overall DM population; T1DM is a result of autoimmune pancreatic β-cell destruction that leads to absolute insulin deficiency. Type 2 diabetes mellitus (T2DM) accounts for 90 to 95% of the DM population and is characterized by both insulin resistance and relative insulin deficiency; risk factors for the development of T2DM include aging, obesity, and physical inactivity *(American Diabetes Association [ADA] 2017, McCulloch 2016)*.
  - T1DM is treated with multiple daily injections of prandial and basal insulin or continuous subcutaneous insulin infusion (CSII) with a rapid-acting insulin analog.
  - Pharmacologic options for T2DM include first-line metformin and second- or third-line oral antidiabetic drugs (OADs) such as sulfonylureas (SFUs), thiazolidinediones (TZDs), meglitinides (GLNs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors and the injectable agents, glucagon-like peptide-1 (GLP-1) receptor agonists and insulin products .
- Rapid-acting insulin analogs have more rapid absorption, faster onset of action, and shorter duration of action than regular insulin due to modifications of the insulin molecule that prevent it from forming hexamers or polymers that slow absorption and delay action. These rapid-acting insulin analogs better mimic endogenous insulin production and allow more flexibility in administration around meals than regular insulin *(McCulloch 2016)*.

Available Products

- There are currently 6 rapid-acting insulins approved by the Food and Drug Administration (FDA) *(FDA Web site)*.
  - The first rapid-acting insulin analogs, Humalog (insulin lispro) and Novolog (insulin aspart) received FDA approval in 1996 and 2000, respectively. Apidra (insulin glulisine) was approved in 2004.
  - Afrezza (insulin human), FDA approved in 2014, is the only available inhaled insulin.
  - Fiasp (insulin aspart) was FDA approved in September 2017 and is comprised of insulin aspart with the addition of niacinamide; nonclinical data have demonstrated that the addition of niacinamide promotes the formation of insulin aspart monomers after subcutaneous (SC) injection, facilitating a more rapid rate of insulin aspart absorption across

the endothelium into the blood *(Russell-Jones et al 2017)*.
  - Admelog (insulin lispro) was FDA approved in December 2017 via the 505(b)(2) pathway and is the first follow-on rapid-acting insulin.
- Admelog, Apidra, Humalog, and Novolog are indicated to improve glycemic control in adults and children with DM. Fiasp and Afrezza are indicated to improve glycemic control in adults with DM.
  - Afrezza must be used with a long-acting insulin in patients with T1DM and is not recommended in patients who smoke or for treating diabetic ketoacidosis.

Clinical Efficacy

- The safety and efficacy of Humalog and Novolog have been well-established in the various DM populations *(Fullerton et al 2016, Plank et al 2005)*.
  - In a systematic review (SR) and meta-analysis (MA) evaluating randomized controlled trials (RCTs) (42 trials; N = 7933 patients) of Humalog or Novolog vs regular insulin, glycosylated hemoglobin (HbA1c) reduction was comparable across T1DM, T2DM, and gestational diabetes patients. In T1DM, a minor, statistically significant benefit was identified in HbA1c lowering (weighted mean difference: -0.12%; 95% confidence interval [CI], -0.17 to -0.07%). No significant differences were identified in rates of hypoglycemia *(Plank et al 2005)*
  - In a Cochrane Review evaluating RCTs (9 trials; N = 2693 patients) of Humalog and Novolog vs regular insulin in T1DM, the mean difference in HbA1c was -0.15% (95% CI, -0.2 to -0.1%; $p < 0.00001$; low quality evidence) in favor of rapid-acting insulins. There were no substantial differences in rates of overall hypoglycemia between the groups. The comparison of the risk of severe hypoglycemia between the 2 treatments showed an odds ratio (OR) of 0.89 (95% CI, 0.71 to 1.12; $p = 0.31$; 7 trials, very low quality evidence) *(Fullerton et al 2016)*.
- The safety and efficacy of Apidra were evaluated in several 26-week, open-label (OL), parallel-group (PG) RCTs vs regular insulin or Humalog. In a trial enrolling T2DM patients (N = 876) on insulin therapy *(Dailey et al 2004)*, a slightly greater HbA1c reduction from baseline to 26 weeks was seen with Apidra vs regular insulin (-0.46% vs -0.30%; $p = 0.0029$). In a similar trial *(Rayman et al 2007)* in the same patient population (N = 890), no differences in baseline to endpoint HbA1c reductions were seen (Apidra -0.32%; regular insulin -0.35%; $p = 0.5726$), but Apidra statistically significantly lowered post-prandial glucose (PPG) more at 2 hours. When Apidra was compared to Humalog in a basal/bolus regimen in T1DM patients (N = 683), no significant differences in HbA1c lowering or rates of hypoglycemia were identified *(Dreyer et al 2005)*.
- Afrezza was evaluated in both T1DM and T2DM patients. In a 24-week OL, active-comparator (AC), noninferiority trial, patients with T1DM on basal insulin were randomized to receive prandial Afrezza or Novolog. Afrezza met the prespecified noninferiority margin of 0.4% reduction of HbA1c from baseline, but reductions were significantly less with Afrezza compared to Novolog and fewer Afrezza patients achieved an HbA1c target of < 7% *(Bode et al 2015)*. T2DM patients inadequately controlled on OADs were randomized to receive Afrezza or placebo in a double-blind (DB) trial. At week 24, treatment with Afrezza provided a statistically significantly greater mean reduction in HbA1c than placebo *(Rosenstock et al 2015[a])*.
- Fiasp was evaluated in the Onset clinical trial program. Onset 1 *(Russell-Jones et al 2017)* was a 26-week, Phase 3, AC, RCT that compared Fiasp (mealtime and postmeal) to Novolog in patients with T1DM. Both mealtime and postmeal Fiasp were demonstrated to be noninferior to Novolog in change in HbA1c (estimated treatment difference [ETD], -0.15; $p < 0.0001$; ETD 0.04%; $p < 0.0001$, respectively). Onset 2 *(Bowering et al 2017)* was a 26-week, Phase 3, DB, AC, RCT in T2DM patients on insulin and OADs. Patients were randomized to receive mealtime Fiasp (n = 345) or Novolog (n = 344). Fiasp demonstrated noninferiority to Novolog in HbA1c lowering (ETD -0.02%; $p < 0.0001$). Onset 3 *(Rodbard et al 2017)* was an 18-week, Phase 3, OL, RCT in T2DM patients inadequately controlled on basal insulin and OADs. Patients were randomized to receive mealtime Fiasp + basal insulin (n = 116), or basal insulin alone (n = 120). The addition of Fiasp to basal insulin demonstrated superior HbA1c lowering from baseline (ETD -0.94%; $p < 0.0001$ for superiority) and significantly more patients achieved an HbA1c < 7.0% (60.3% vs 18.3%; OR, 9.31; $p < 0.0001$); however, with the addition of Fiasp, there was an increase in the frequency of severe or blood glucose (BG)-confirmed hypoglycemic episodes (rate ratio [RR], 8.24; $p < 0.0001$) and modest weight gain.
- The safety and efficacy of Admelog were evaluated in two 26-week, Phase 3, OL, PG, RCTs in both T1DM (N = 506) (SORELLA 1; *Garg et al 2017)* and T2DM (N = 505) patients (SORELLA 2; *Derwahl et al 2018)*. Patients were randomized to receive Admelog or its reference product, Humalog. Change in HbA1c in Admelog-treated patients was found to be noninferior in both trials (SORELLA 1: least squares [LS] mean difference, 0.06%; 95% CI, -0.084 to 0.197; SORELLA 2: LS mean difference, -0.07%; 95% CI, -0.215 to 0.067). Rates of hypoglycemia were similar between the treatment arms in both trials.

Place in Therapy

- Rapid-acting insulin analogs are an important part of T1DM insulin therapy and are often utilized in T2DM when escalation of therapy is required. Guidelines from the ADA and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend basal insulin plus prandial insulin, or CSII with rapid-acting insulin for patients with T1DM; rapid-acting insulin analogs are preferred over regular insulin in

T1DM as they carry less hypoglycemia risk. Patients with T2DM unable to maintain glycemic control on OADs should be considered for basal insulin therapy and subsequently intensified to combination injectable therapy with a GLP-1 receptor agonist or prandial insulin if additional glycemic control is needed. No injectable rapid-acting insulin analog is preferred over another; the guidelines have not been updated to address Admelog *(ADA 2018, Garber et al 2018)*.

Safety

- The rapid-acting insulins are contraindicated during episodes of hypoglycemia and have warnings for hypoglycemia, hypokalemia, hypersensitivity reactions, and fluid retention and heart failure with concomitant use of TZDs.
  - Afrezza is additionally contraindicated in chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD). Afrezza has a boxed warning for bronchospasm in patients with chronic lung disease. Additionally, Afrezza has a warning for lung cancer and should not be used in patients with active lung cancer. In patients with a history of lung cancer or at risk for lung cancer, the benefit of Afrezza use should outweigh this potential risk.
- The most common adverse effects (AEs) associated with the injectable rapid-acting insulins include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash. Common AEs for Afrezza include hypoglycemia, cough, and throat pain or irritation.

Dosing

- The dosage of rapid-acting insulins should be individualized based on the patient's metabolic needs, BG monitoring results, and glycemic control goal. Rapid-acting injectable insulins should be administered SC just prior to or immediately following a meal. Afrezza should be inhaled at each meal as directed. Additionally, Admelog, Apidra, Humalog (U100), and Novolog are indicated for use as CSII; product- and pump-specific instructions should be followed.
- The pharmacologic profiles of the rapid-acting insulin analogs are comparable (see Table 1).

Table 1. Pharmacologic characteristics of rapid-acting insulins *(Facts and Comparisons Web site 2018)*

Insulin	Onset (hrs)	Peak Glycemic Effect (hrs)	Duration (hrs)
Admelog (insulin lispro)	0.25 to 0.5	0.5 to 2.5	≤ 5
Afrezza (insulin human)	~0.25	~0.88	2.5 to 3
Apidra (insulin glulisine)	0.2 to 0.5	1.6 to 2.8	3 to 4
Fiasp (insulin aspart)	~0.2 to 0.3	~1.5 to 2.2	~5 to 7
Humalog (insulin lispro)	0.25 to 0.5	0.5 to 2.5	≤ 5
Novolog (insulin aspart)	0.2 to 0.3	1 to 3	3 to 5

Conclusion

- The rapid-acting insulins have established efficacy and safety in both the T1DM and T2DM populations. The injectable agents are guideline-recommended for T1DM due to less hypoglycemia risk vs regular insulin.
- The injectable rapid-acting insulins have demonstrated comparable HbA1c lowering in clinical trials. Newly-approved Admelog, the first follow-on rapid-acting insulin, demonstrated noninferiority to its reference drug Humalog in RCTs in both T1DM and T2DM patients. Afrezza, the only inhalation rapid-acting insulin, demonstrated noninferior HbA1c lowering vs Novolog, but reductions were significantly less with Afrezza and fewer Afrezza patients achieved an HbA1c target of < 7%.
- Safety profiles of the injectable rapid-acting insulins are comparable. Afrezza has a boxed warning for bronchospasm and is contraindicated in patients with chronic lung disease.

BACKGROUND

- In 2015, an estimated 30.3 million people, or 9.4% of the US population, had DM; as many as 7.2 million were undiagnosed *(CDC 2017)*.
- Individuals with T1DM account for 5% of the overall DM population. Insulin is the mainstay of therapy in these patients, as autoimmune pancreatic β-cell destruction typically leads to absolute insulin deficiency. Most patients with T1DM require treatment with multiple daily injections of prandial insulin and basal insulin or CSII. The use of rapid-acting insulin analogs in these patients reduces hypoglycemia risk vs regular insulin *(ADA 2017)*.
- T2DM accounts for 90 to 95% of the DM population and is characterized by both insulin resistance and relative insulin deficiency. Patients are typically started on non-pharmacologic interventions (eg, diet, exercise, weight loss) and OADs, such as metformin. Addition of insulin is indicated if goal glycemic control is not attained. Initiation of insulin therapy is often delayed due to clinician or patient reluctance; however, most patients with T2DM will eventually require insulin therapy due to the decline in endogenous insulin production. Basal insulin is typically initiated and optimized before prandial dosing with rapid-acting or regular insulin is considered *(McCulloch 2016)*.
  - Both basal and prandial insulin regimens have demonstrated similar efficacy in reduction of HbA1c concentrations when titrated to achieve glycemic goals in T2DM; however, basal insulin is associated with less frequent hypoglycemia and greater patient satisfaction *(McCulloch 2017)*.

- Rapid-acting insulin analogs have more rapid absorption, faster onset of action, and shorter duration of action than regular insulin due to modifications of the insulin molecule that prevent it from forming hexamers or polymers that slow absorption and delay action. These rapid-acting insulin analogs better mimic endogenous insulin production and allow more flexibility in administration around meals than regular insulin *(McCulloch 2016)*.
- The pharmacologic profiles of the injectable rapid-acting insulin analogs are comparable (see Table 3).
- The first rapid-acting insulin analogs, Humalog (insulin lispro) and Novolog (insulin aspart) received FDA approval in 1996 and 2000, respectively. Apidra (insulin glulisine) was approved in 2004 *(FDA Web site)*.
- Fiasp (insulin aspart) was FDA approved in September 2017 and consists of insulin aspart with the addition of niacinamide; nonclinical data have demonstrated that the addition of niacinamide promotes the formation of insulin aspart monomers after SC injection, facilitating a more rapid rate of insulin aspart absorption across the endothelium into the blood *(FDA Web site, Russell-Jones et al 2017)*.
- Admelog (insulin lispro) was FDA approved in December 2017 via the 505(b)(2) pathway and is the first follow-on rapid-acting insulin *(FDA Web site)*.
- Afrezza (insulin human), FDA approved in 2014, is the only available inhaled insulin and is approved for prandial dosing; noninferiority in HbA1c lowering was demonstrated in a head-to-head trial with Novolog, although the mean HbA1c reduction was greater with Novolog and more patients in the Novolog arm achieved HbA1c goals of ≤ 7% and ≤ 6.5% *(Bode et al 2015)*. Afrezza is contraindicated in patients with chronic lung disease such as asthma or COPD and has a boxed warning for bronchospasm in this patient population.

INDICATIONS

Table 2. FDA-approved indications for the rapid-acting insulins

Drug	Improve glycemic control in adults and children with diabetes mellitus	Improve glycemic control in adults with diabetes mellitus
Admelog (insulin lispro)	✓	
Afrezza (insulin human)		✓*
Apidra (insulin glulisine)	✓	
Fiasp (insulin aspart)		✓
Humalog (insulin lispro)	✓	
Novolog (insulin aspart)	✓	

*Limitations of use: Must use with a long-acting insulin in patients with T1DM. Not recommended for treating diabetic ketoacidosis. Not recommended in patients who smoke.

PHARMACOLOGY

Table 3. Pharmacologic characteristics of rapid-acting insulins *(Facts and Comparisons Web site 2018)*

Insulin	Onset (hrs)	Peak Glycemic Effect (hrs)	Duration (hrs)
Admelog (insulin lispro)	0.25 to 0.5	0.5 to 2.5	≤ 5
Afrezza (insulin human)	~0.25	~0.88	2.5 to 3
Apidra (insulin glulisine)	0.2 to 0.5	1.6 to 2.8	3 to 4
Fiasp (insulin aspart)	~0.2 to 0.3	~1.5 to 2.2	~5 to 7
Humalog (insulin lispro)	0.25 to 0.5	0.5 to 2.5	≤ 5
Novolog (insulin aspart)	0.2 to 0.3	1 to 3	3 to 5

CLINICAL EFFICACY

STUDY DESIGN ABBREVIATIONS: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover

***Search Strategy**: Studies supporting the FDA-approved indications were identified using search terms "insulin aspart, insulin lispro, insulin glulisine, rapid-acting insulins" and "diabetes" February 7, 2018. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

Admelog (insulin lispro)

Study 1. Garg et al, *Diabetes Technol Ther.* 2017;19(9):516-526. SORELLA 1

Study Objective: Evaluate the safety, efficacy, and immunogenicity of Admelog vs Humalog in adult patients with

T1DM.

Study Design, Follow-up	Treatment Groups
• 26-week, Phase 3, MC, OL, PG, RCT ○ The main study period was followed by a 26-week safety extension.	• Admelog SC before meals with basal insulin glargine U100 (n = 253) • Humalog SC before meals with basal insulin glargine U100 (n = 254) • The starting doses of Admelog and Humalog were based on a unit-to-unit conversion from the patients' previous rapid-acting insulin dose. • Admelog and Humalog doses were titrated based on a 2-hr PPG goal of 120 to 160 mg/dL. Patients were instructed to self-adjust doses according to local guidelines. • Insulin glargine U100 was maintained at the pre-study dose and given once daily at the same time as used before study initiation. • The basal insulin fasting prebreakfast goal was between 80 to 130 mg/dL. There was no formal titration algorithm for basal insulin.
Inclusion Criteria	**Exclusion Criteria**
• ≥ 18 years of age with T1DM diagnosed for at least 12 months • HbA1c ≥ 7 and ≤ 10% • Treated with insulin glargine as basal insulin and Humalog or Novolog as rapid-acting mealtime insulin for at least 6 months	• Body mass index (BMI) ≥ 35 kg/m^2 • Use of noninsulin antidiabetic treatments or the use of CSII • History of severe hypoglycemia requiring treatment by emergency room admission within 6 months • Poor metabolic control requiring hospitalization within 6 months
Primary Endpoint	**Secondary Endpoints**
• Change in HbA1c from baseline to week 26	• Change in HbA1c from baseline to week 52 • Hypoglycemic event rates

- **Results:**
  - Baseline demographics were balanced between the groups, although there were slightly more elderly (≥ 65 years) and overweight (BMI ≥ 25 to < 30 kg/m^2) patients in the Admelog group. The mean age of the study population was 43 years, 8.7% of patients were ≥ 65 years old, and mean BMI at baseline was 26.0 kg/m^2.
  - Overall, 94.7% of patients completed the 26-week treatment period, and 90.9% completed the 52-week treatment period. A similar number of patients in each treatment group discontinued the study prematurely; the most common reason reason for withdrawal was "other," which included patient decision or consent withdrawal.
  - Admelog and Humalog demonstrated similar reductions in mean HbA1c from baseline to week 26; noninferiority of Admelog to Humalog was confirmed at the prespecified 0.3% margin (see Table 4). Additionally, fasting plasma glucose (FPG), 7-point self-measured plasma glucose (SMPG) profiles, and body weight changes from baseline were similar between treatment groups.
  - Rates of treatment-emergent adverse events (TEAEs) were comparable between the Admelog and Humalog groups (54.4% vs 55.5%, respectively); incidence of treatment-emergent anti-insulin antibody (AIA) responses was similar (22.6% vs 24.2%, respectively). Rates of hypoglycemia and severe hypoglycemia were also similar (see Table 4).

Table 4. Efficacy outcomes SORELLA 1

Outcomes	Admelog (n = 253)*	Humalog (n = 254)*
Mean HbA1c at baseline	8.08%	8.00%
LS mean change in HbA1c at 26 weeks	-0.42%	-0.47%
LS mean difference (95% CI)	0.06% (-0.084 to 0.197)	
LS mean change in HbA1c at 52 weeks	-0.22%	-0.30%
LS mean difference (95% CI)	0.07% (-0.084 to 0.232)	
	Admelog (n = 252)**	**Humalog (n = 254)****
Any hypoglycemia during 52-week treatment period	250 (99.2%)	254 (100%)
Severe hypoglycemia during 52-week treatment period	34 (13.5%)	34 (13.4%)

Abbreviations: CI = confidence interval, LS = least squares
*intention-to-treat (ITT) population
** Safety population

- **Authors' conclusion:**
  - The results of this RCT in patients with T1DM also using insulin glargine U100 support similar efficacy and safety of Admelog to its reference drug Humalog.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Sanofi
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study used an appropriate comparator and had a safety extension.
  - **Study limitations:**
    - The study was OL.
    - No common insulin titration algorithm was used.

Study 2. Derwahl et al, *Diabetes Technol Ther.* 2018;20(2):160-170. SORELLA 2

Study Objective: Evaluate the safety, efficacy, and immunogenicity of Admelog vs Humalog in adult patients with T2DM treated with multiple daily injections, while using insulin glargine (Lantus) as basal insulin.

Study Design, Follow-up	Treatment Groups
• 26-week, Phase 3, MC, OL, PG, RCT	• Admelog SC before meals with basal insulin glargine U100 (n = 253) • Humalog SC before meals with basal insulin glargine U100 (n = 252) • The starting doses of Admelog and Humalog were based on a unit-to-unit conversion from the patients' previous rapid-acting insulin dose. • Admelog and Humalog doses were titrated based on a 2-hr PPG goal of 120 to 160 mg/dL. Patients were instructed to self-adjust doses according to local guidelines. • Insulin glargine U100 was maintained at the pre-study dose and given once daily at the same time as used before study initiation. • The basal insulin fasting prebreakfast goal was between 80 to 130 mg/dL. There was no formal titration algorithm for basal insulin
Inclusion Criteria	**Exclusion Criteria**
• Adults with T2DM diagnosed for at least 12 months • HbA1c ≥ 6.5% and ≤ 10% • Treated with insulin glargine as basal insulin and Humalog or Novolog as mealtime insulin for at least 6 months	• BMI ≥ 40 kg/m^2 • Use of GLP-1 receptor agonists or other peptides or the use of CSII • History of severe hypoglycemia requiring treatment by emergency room admission within 6 months • Poor metabolic control requiring hospitalization within 6 months • Unstable proliferative diabetic retinopathy
Primary Endpoint	**Key Secondary Endpoint**
• Change in HbA1c from baseline to week 26	• Hypoglycemic event rates

- **Results:**
  - Baseline demographics were well balanced between the groups. Mean age was 62.5 years and more than 40% of the population was ≥ 65 years. The mean BMI was 32.2 kg/m^2, with most of the patients (93%) being overweight or obese. The mean duration of T2DM was 17.1 years and 19.8% had moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 and < 60 mL/min/1.73m^2.
  - Overall, a similar number of patients in each group discontinued the study prematurely (9.9% in the Admelog group and 8.7% in the Humalog group); the most common reasons for discontinuation were "other reasons" and "adverse events".
  - Admelog and Humalog demonstrated similar reductions in mean HbA1c from baseline to week 26; noninferiority of

Admelog to Humalog was confirmed at the prespecified 0.3% margin (see Table 5). Additionally, FPG, 7-point SMPG profiles, and body weight changes from baseline were similar between treatment groups.
- Rates of hypoglycemia were similar between the groups (see Table 5). Severe hypoglycemia was rare, with 9 events reported in 6 patients in the Admelog group and 4 events reported in 4 patients in the Humalog group; the higher rate in the Admelog group was due to 1 patient who reported 4 events of severe hypoglycemia. Incidence of treatment-emergent AIA responses was similar between the Admelog and Humalog groups (24.5% vs 25.4%, respectively).

Table 5. Efficacy outcomes SORELLA 2

Outcomes	Admelog (n = 253)	Humalog (n = 252)
Mean HbA1c at baseline	7.99%	8.03%
LS mean change in HbA1c 26 weeks	-0.92%	-0.85%
LS mean difference (95% CI)	-0.07% (-0.215 to 0.067)	
Any hypoglycemia	68.4%	74.6%
Severe hypoglycemia	2.4%	1.6%

Abbreviations: CI = confidence interval, LS = least squares

- **Authors' conclusion:**
  - The results of this RCT in patients with T2DM also using insulin glargine U100 support similar efficacy and safety of Admelog to its reference drug Humalog.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Sanofi
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study used an appropriate comparator.
  - **Study limitations:**
    - The study was OL.
    - No common insulin titration algorithm was used.

Afrezza (insulin human)

Study 3a. Bode et al, *Diabetes Care*. 2015;38(12):2266-2273.
Study 3b. Rosenstock et al, *Diabetes Care*. 2015;38:2274-2281.

Study	Description
Study 3a: Afrezza vs Novolog in T1DM	• **Study Design:** ○ 24-week, Phase 3, MC, OL, PG, RCT (N = 351) ○ Adults with T1DM (HbA1c 7.5 to 10.0%) for at least 12 months ○ Patients were required to be nonsmokers for ≥ 6 months and have adequate baseline lung function tests • **Treatment Arms:** ○ Prandial Afrezza + basal insulin; prandial Novolog + basal insulin ○ Patients continued their pre-enrollment basal insulin • **Efficacy Results:** ○ Mean change in HbA1c in Afrezza patients (-0.21%) from baseline was noninferior to that in Novolog patients (-0.40%) from baseline. The between-group difference was 0.19%, satisfying the noninferiority margin of 0.4%. ○ More Novolog patients achieved HbA1c < 7.0% (30.7% vs 18.3%). ○ The mean daily dose of Afrezza increased throughout the randomized treatment phase (from 84.7 U at week 1 to 115.4 U at week 24). By contrast, in the Novolog group, the mean daily dose of Novolog showed only a slight increase (24.3 U at week 1 and 25.9 U at week 24). Additionally, doses of basal insulin used were higher in the Afrezza group than in the Novolog group. ○ The Afrezza arm experienced a slight weight loss (-0.4 kg) vs a gain (+0.9 kg) for Novolog patients (p = 0.0102). ○ Afrezza patients had a lower hypoglycemia event rate than Novolog patients (9.8 vs 14.0 events/patient-month; p < 0.0001). ○ Cough was the most frequent AE (31.6% with Afrezza vs 2.3% with Novolog), leading to discontinuation of 5.7% of patients. • **Authors' Conclusion:**

	○ In patients with T1DM receiving basal insulin, HbA1c reduction with Afrezza was noninferior to that of Novolog, with less hypoglycemia and less weight gain but increased incidence of cough.
Study 3b: Afrezza vs placebo in T2DM	• **Study Design:** ○ 24-week, Phase 3, MC, DB, PC, RCT (N = 353) ○ Adults with T2DM (HbA1c 7.5 to 10.0%) on metformin alone or 2 or more OADs ○ Patients were required to be nonsmokers for ≥ 6 months and have adequate baseline lung function tests • **Treatment Arms:** ○ Prandial Afrezza or placebo as add-on therapy to baseline OAD regimen • **Efficacy Results:** ○ From baseline to 24 weeks, Afrezza significantly reduced HbA1c by -0.8% vs -0.4% for placebo (treatment difference, -0.4%; 95% CI, -0.57 to -0.23; $p < 0.0001$). ○ Mean fasting BG was reduced more in the Afrezza arm, but the difference was not statistically significant (treatment difference, -7.42 mg/dL; 95% CI, -18.03 to 3.18; $p = 0.1698$). ○ Rates of hypoglycemia were higher in the Afrezza group vs placebo (67.8% vs 30.7%; $p < 0.0001$). Mild, transient dry cough was the most common AE and occurred similarly in both groups. • **Authors' Conclusion:** ○ Prandial Afrezza added to 1 or more OADs in inadequately controlled T2DM is an effective treatment option.

Apidra (insulin glulisine)

Study 4a. Daily et al, *Diabetes Care.* 2004;27:2363-2368.
Study 4b. Dreyer et al, *Horm Metab Res.* 2005;37:702-707.
Study 4c. Rayman et al, *Diabetes Res Clin Pract.* 2007;76(2):304-312.

Study	Description
Study 4a: Apidra/Neutral Protamine Hagedorn (NPH) insulin vs regular insulin/ NPH insulin in T2DM	• **Study Design:** ○ 26-week, Phase 3, MC, OL, PG, RCT (N = 876) ○ Adults with T2DM (HbA1c 6.0 to 11.0%) on insulin therapy for ≥ 6 months • **Treatment Arms:** ○ Apidra/NPH insulin SC twice daily; regular insulin/NPH insulin SC twice daily ○ Subjects were allowed to continue the same prestudy regimens of OADs • **Efficacy Results:** ○ A slightly greater HbA1c reduction from baseline to 26 weeks was seen with Apidra vs regular insulin (-0.46% vs -0.30%; $p = 0.0029$). ○ BG values were lower with Apidra vs regular insulin at all treatment points of the 7-point SMBP, with statistical significance reached at 2 hours post-breakfast and 2 hours post-dinner ($p < 0.05$). ○ Symptomatic hypoglycemia and weight gain were comparable between the treatment groups. • **Authors' Conclusion:** ○ Twice-daily Apidra with NPH insulin can provide small improvements in glycemic control compared with regular insulin in patients with T2DM who are already relatively well controlled on insulin ± OADs.
Study 4b: Apidra/insulin glargine vs Humalog/insulin glargine in T1DM	• **Study Design:** ○ 26-week, Phase 3, MC, OL, PG, RCT (N = 683) + 26-week safety extension ○ Adults with T1DM (HbA1c 6.0 to 11.0%) with BMI < 35 kg/m^2 • **Treatment Arms:** ○ Apidra SC before meals/insulin glargine SC daily; Humalog SC before meals/insulin glargine SC daily • **Efficacy Results:** ○ From baseline to 26 weeks, a similar reduction in mean HbA1c occurred in both groups (adjusted mean change from baseline -0.14% in both groups; $p = 0.9329$ for noninferiority). ○ SMBP were similar between the groups, with no between-group differences in terms of pre-prandial, bedtime, or nocturnal BG levels. ○ Basal insulin dose was relatively unchanged in the Apidra group (+ 0.12 U) but increased in the Humalog group (+1.82 U; $p < 0.001$ for between-group difference). The clinical relevance of this difference is unknown. ○ Rates of symptomatic hypoglycemia and TEAEs were similar between the groups.

	• **Authors' Conclusion:** ○ Apidra is as effective and well-tolerated as Humalog as part of basal-bolus therapy in combination with insulin glargine for the treatment of T1DM.
Study 4c: Apidra/NPH insulin vs regular insulin/NPH insulin in T2DM	• **Study Design:** ○ 26-week, Phase 3, MC, OL, PG, RCT (N = 890) ○ Adults with T2DM (HbA1c 6.0 to 11.0%) on insulin therapy for ≥ 6 months • **Treatment Arms:** ○ Apidra/NPH insulin SC twice daily; regular insulin/NPH insulin SC twice daily ○ Subjects were allowed to continue the same prestudy regimens of OADs (except for repaglinide, nateglinide, or glitazones) • **Efficacy Results:** ○ There were no differences in baseline to endpoint HbA1c reductions (Apidra -0.32% vs regular insulin -0.35%; 95% CI, -0.07 to 0.13; p = 0.5726). ○ Post-prandially, Apidra lowered BG more vs regular insulin at 2 hours (14.14 mmol/L vs 15.28 mmol/L; 95% CI, -1.87 to -0.40; p = 0.0025). ○ No between-group differences were seen in the frequency of symptomatic hypoglycemia; nocturnal hypoglycemia from Month 4 to treatment end was less frequent with Apidra vs regular insulin (9.1% vs 14.5%; p = 0.029). • **Authors' Conclusion:** ○ Apidra was noninferior to regular insulin in reducing HbA1c in T2DM. Apidra was superior in terms of post-prandial control and was associated with fewer nocturnal hypoglycemic episodes.

Fiasp (insulin aspart)

Study 5a. Russell-Jones et al, *Diabetes Care.* 2017;40:943-950. Onset 1
Study 5b. Mathieu C et al, *Diabetes Obes Metab.* 2018. [Epub ahead of print] Onset 1 safety extension

Study Objective: Evaluate the safety and efficacy of Fiasp vs Novolog in adults with T1DM.

Study Design, Follow-up	Treatment Groups
• 26-week, Phase 3, MC, AC, PG, RCT ○ After an 8-week run-in period, patients were randomized to DB mealtime Fiasp or Novolog or OL postmeal Fiasp. • Additional 26-week OL treatment period to document safety	• Fiasp SC 0 to 2 minutes before each main meal (n = 381) • Novolog SC 0 to 2 minutes before each main meal (n = 380) • Fiasp SC 20 minutes after the start of a meal (n = 382) • Patients were optimized on basal insulin detemir during the 8-week run-in period. All subjects commenced mealtime Novolog at the start of the 8-week run-in period; after run-in, patients were randomized to receive their respective trial treatments. • Randomization was stratified in part by the method used by the subject for adjusting bolus insulin (carbohydrate counting or dosing algorithm). • After run-in, basal adjustments were only performed when required as judged by the investigator; dose frequency could not be changed.
Inclusion Criteria	**Exclusion Criteria**
• Adults (≥ 18 years old) with T1DM • Treated with basal-bolus insulin for ≥ 12 months prior to screening and treated with any regimen of insulin detemir or glargine for ≥ 4 months prior to screening • HbA1c of 7.0 to 9.5% • Body mass index (BMI) ≤ 35.0 kg/m^2	• Use of an antidiabetes drug other than insulin within 3 months prior to screening • Cardiovascular (CV) disease within 6 months prior to screening • Recurrent, severe hypoglycemia (> 1 event during the past 12 months) • Hypoglycemic unawareness as judged by the investigator • Hospitalization for diabetic ketoacidosis within 6 months prior to screening
Primary Endpoint	**Confirmatory Secondary Endpoints**
• Change from baseline in HbA1c after 26 weeks (noninferiority of mealtime Fiasp vs Novolog)	• Change from baseline in HbA1c after 26 weeks (noninferiority of postmeal Fiasp vs Novolog) • Change from baseline after 26 weeks of treatment in 2-hr

	PPG increment • Number of treatment-emergent severe or BG-confirmed hypoglycemic episodes (as defined according to the ADA classification or by a BG < 56 mg/dL with or without hypoglycemic symptoms) • Change from baseline in bodyweight after 26 weeks

- **Results:**
  - Baseline characteristics were similar among the 3 treatment arms; across the trial, median age was 44.4 years, median BMI was 26.7 kg/m^2, and median duration of diabetes was 19.9 years. Overall, 92.9% of patients completed the 26-week trial.
  - In regard to the effect on HbA1c from baseline, noninferiority of Fiasp, both mealtime and postmeal dosing, to mealtime Novolog was confirmed (see Table 6). The reduction in HbA1c was statistically significantly greater for mealtime Fiasp than Novolog, but superiority could not be confirmed as this was not part of the hierarchical testing procedure.
  - Mealtime Fiasp demonstrated a statistically significant change from baseline in 2-hr PPG increment vs Novolog (see Table 6). There were no significant differences between the groups in change from baseline in 3-hr or 4-hr PPG increments.
  - The mean body weight increase from baseline in all 3 treatment groups was < 1 kg over the 26-week period; there were no statistically significant differences between the groups.
  - There were no statistically significant differences in the overall rate of treatment-emergent severe or BG-confirmed hypoglycemic episodes among the groups (see Table 6). The rate of severe or BG-confirmed hypoglycemic episodes during the first hour after the start of a main meal was statistically significantly higher for mealtime Fiasp than for Novolog (RR, 1.48; 95% CI, 1.11 to 1.96; p < 0.0073); however, the number of episodes reported during this time period was a small fraction of the overall hypoglycemic episodes (~1 of 40).
  - Rates of treatment-emergent AEs (TEAEs) and serious AEs (SAEs) were comparable among the groups. Injection-site reactions occurred in 7, 9, and 3 patients in the Fiasp mealtime, postmeal, and Novolog groups, respectively; all were of mild or moderate severity.

Table 6. Efficacy outcomes Onset 1

	Fiasp mealtime (n = 381)	Novolog mealtime (n = 380)	Fiasp postmeal (n = 382)
Mean HbA1c at baseline	7.6%	7.6%	7.6%
Mean HbA1c at 26 weeks	7.3%	7.4%	7.5%
ETD (95% CI; p-value)	-0.15% (-0.23 to 0.07; p < 0.0001 for noninferiority)		
ETD (95% CI; p-value)		0.04% (-0.04 to 0.12; p < 0.0001 for noninferiority)	
Change from baseline in 2-hr PPG increment	-5.2 mg/dL	6.8 mg/dL	--
ETD (95% CI; p-value)	-12.01 mg/dL (-23.33 to -0.70; p = 0.0375 for superiority)		
ETD (95% CI; p-value)		5.32 mg/dL (-6.05 to 16.68; p = 0.93)	
Severe or BG-confirmed hypoglycemic episodes, no.	358 (92.7%)	370 (97.4%)	358 (95.0%)
RR (95% CI; p-value)	1.01 (0.88 to 1.15; p = 0.9191)		
RR (95% CI; p-value)		0.92 (0.81 to 1.06; p = 0.2435)	

Abbreviations: BG = blood glucose, CI = confidence interval, ETD = estimated treatment difference, PPG = post-prandial glucose, RR = rate ratio

  - Patients from the mealtime Fiasp and Novolog arms continued treatment for an additional 26 weeks. After 52 weeks, estimated mean changes from baseline in HbA1c levels were -0.08% for Fiasp and +0.01% for Novolog (ETD -0.10%; 95% CI, -0.19 to -0.00; p = 0.0424). There was no difference in rate of overall severe or BG-confirmed hypoglycemic episodes between the groups *(Mathieu et al 2018)*.
- **Authors' conclusion:**
  - In patients with T1DM on a basal-bolus insulin regimen, both mealtime and postmeal Fiasp were noninferior to mealtime Novolog regarding HbA1c change from baseline. Fiasp offered superior control of PPG excursions vs Novolog without increased risk of overall hypoglycemia.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Novo Nordisk
  - **Study rating:**
    - Fair
  - **Study strengths:**

- All statistical analyses were based on the full analysis set (FAS).
- The study was DB (mealtime Fiasp and Novolog groups).

- **Study limitations:**
  - Confirmatory endpoints were tested using a hierarchical procedure. Because step 4 (number of treatment-emergent severe or BG-confirmed hypoglycemic episodes: superiority of mealtime Fiasp vs Novolog) was not confirmed, the stepwise testing procedure was stopped.
  - Baseline 1- to 4-hr PPG levels were assessed after a bolus dose of Novolog (0.1 units/kg) administered 0 to 2 minutes before a standardized mixed liquid meal test. The meal test was repeated at week 26, with patients administering the same bolus dose with their assigned treatment regimen. No adjustment was made for individual insulin-to-carbohydrate ratios and therefore the insulin dose was only an approximation of the patients' usual doses.

Study 6. Bowering et al, *Diabetes Care.* 2017;40:951-957. Onset 2

Study Objective: Evaluate the safety and efficacy of Fiasp vs Novolog in adults with T2DM receiving basal insulin and OADs.

Study Design, Follow-up	Treatment Groups
• 26-week, Phase 3, MC, DB, AC, RCT ○ After an 8-week run-in period, patients were randomized to DB mealtime Fiasp or Novolog	• Fiasp SC 0 to 2 minutes before each main meal (n = 345) • Novolog SC 0 to 2 minutes before each main meal (n = 344) • During the 8-week run-in period, patients were optimized on basal insulin glargine; OADs (except for metformin) were discontinued. After run-in, patients were randomized to receive their respective trial treatments in addition to basal insulin glargine and metformin. • After randomization, bolus insulin dose adjustments were performed daily by the subject based on a titration guideline. • After run-in, basal adjustments were only performed when required as judged by the investigator; dose frequency could not be changed.
Inclusion Criteria	**Exclusion Criteria**

• Adults with T2DM
• Treated with basal insulin for ≥ 6 months prior to screening
• Treated with metformin (stable dose ≥ 1000 mg) alone or with an SFU, GLN, DPP-4 inhibitor, and/or an alpha-glucosidase inhibitor for ≥ 3 months prior to screening
  ○ Patients receiving metformin monotherapy were required to have an HbA1c of 7.0 to 9.5% at screening
  ○ Patients receiving metformin + additional OADs were required to have an HbA1c of 7.0 to 9.0%
• BMI ≤ 40 kg/m^2
	• Previous bolus insulin use (except for short-term use due to intermittent illness)
	• GLP-1 agonist and/or TZD use within 3 months prior to screening
	• CV disease within 6 months prior to screening
	• Recurrent, severe hypoglycemia (> 1 event during the past 12 months)
	• Hypoglycemic unawareness as judged by the investigator
	• Hospitalization for diabetic ketoacidosis within 6 months prior to screening

Primary Endpoint	**Confirmatory Secondary Endpoints**
• Change from baseline in HbA1c after 26 weeks	• Change from baseline after 26 weeks of treatment in 2-hr PPG increment • Number of treatment-emergent severe or BG-confirmed hypoglycemic episodes (as defined according to the ADA classification or by a BG < 56 mg/dL with or without hypoglycemic symptoms) • Change from baseline in bodyweight after 26 weeks

- **Results:**
  - Baseline characteristics were similar between the treatment arms. Across the trial, median age was 59.5 years, median BMI was 31.2 kg/m^2, and median duration of diabetes was 12.7 years. At baseline, 53.8% of patients were on basal insulin + 1 OAD, 43.7% were on basal insulin + 2 OADs, and 2.5% were on basal insulin + > 2 OADs. Overall, 88% of patients completed the trial.
  - Noninferiority of Fiasp to Novolog was confirmed in regard to effect on HbA1c (see Table 7). Superiority of Fiasp vs

Novolog in 2-hr PPG increment lowering was not confirmed; however, the estimated change from baseline in 1-hr PPG increment was -38.5 mg/dL for Fiasp and -27.9 mg/dL for Novolog (ETD -10.63 mg/dL; 95% CI, -19.56 to -1.69; p < 0.0198). There was no statistical difference in ETD for change from baseline in 3-hr or 4-hr PPG increments.
- In both groups, body weight increased by ~2.7 kg over the trial period.
- The difference in overall rate of severe or BG-confirmed hypoglycemia was not statistically significant between treatment groups (see Table 7). For the interval 0 to 2 hours after meals, a statistically significantly higher rate of meal-related hypoglycemia was reported for Fiasp (RR, 1.60; 95% CI, 1.13 to 2.27; p = 0.0082).
- The rate of TEAEs was similar between groups; most were mild or moderate in severity.

Table 7. Efficacy outcomes Onset 2

	Fiasp (n = 345)	Novolog (n = 344)
Mean HbA1c at baseline	8.0%	7.9%
Mean HbA1c at 26 weeks	6.6%	6.6%
ETD (95% CI; p-value)	-0.02% (-0.15 to 0.10; p < 0.0001 for noninferiority)	
Change from baseline in 2-hr PPG increment	-58.3 mg/dL	-51.8 mg/dL
ETD (95% CI; p-value)	-6.57 mg/dL (-14.54 to 1.41; p = NS for superiority)	
Severe or BG-confirmed hypoglycemic episodes, no.	262 (76.8%)	250 (73.3%)
RR (95% CI; p-value)	1.09 (0.88 to 1.36; p = NS for superiority)	

Abbreviations: BG = blood glucose, CI = confidence interval, ETD = estimated treatment difference, NS = not significant, PPG = post-prandial glucose, RR = rate ratio

- **Authors' conclusion:**
  - In adults with T2DM inadequately controlled on basal insulin and OADs, insulin intensification with Fiasp or Novolog improved overall glycemic and PPG control. Overall hypoglycemia rates were similar between groups, with an increase in hypoglycemia rates during the 0 to 2-hr postmeal interval with Fiasp. Both Fiasp and Novolog are effective, well-tolerated treatment options for patients requiring mealtime insulin.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Novo Nordisk
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - All statistical analyses were based on the FAS.
    - The study was DB.
  - **Study limitations:**
    - Confirmatory endpoints were tested using a hierarchical procedure. Because step 2 (change from baseline in 2-hr PPG increment: superiority of Fiasp vs Novolog) was not confirmed, the stepwise testing procedure was stopped.
    - Baseline 1- to 4-hr PPG levels were assessed after a bolus dose of Novolog (0.1 units/kg) administered 0 to 2 minutes before a standardized mixed liquid meal test. The meal test was repeated at week 26, with patients administering the same bolus dose with their assigned treatment regimen. No adjustment was made for individual insulin-to-carbohydrate ratios and therefore the insulin dose was only an approximation of the patients' usual doses.
    - The initiation of 3 bolus insulin doses simultaneously in patients with T2DM is not representative of real world clinical practice.

Study 7. Rodbard et al, *Diabetes Obes Metab.* 2017;19:1389-1396. Onset 3

Study Objective: To evaluate the safety and efficacy of adding Fiasp to basal insulin therapy vs basal insulin alone, both in combination with metformin, in patients with inadequately controlled T2DM.

Study Design, Follow-up	Treatment Groups
• 18-week, Phase 3, MC, OL, PG, RCT	• Fiasp SC before each main meal + basal insulin (n = 116) • Basal insulin (n = 120) • Patients continued their basal insulin of choice from baseline (insulin glargine, insulin detemir, or NPH insulin). • During the 8-week run-in period, patients were optimized on basal insulin; OADs (except for metformin) were discontinued. After run-in, patients were randomized to continue with basal insulin + metformin, or mealtime Fiasp + basal insulin + metformin.

	• After randomization, bolus insulin dose adjustments were performed daily by the subject based on a titration guideline. • After run-in, the basal insulin dose was adjusted at the investigator's discretion.
Inclusion Criteria	**Exclusion Criteria**

• Adults with T2DM
• Treated with basal insulin and metformin ≥ 1000 mg with or without other OADs for ≥ 3 months prior to screening
  ○ Patients receiving metformin monotherapy were required to have an HbA1c of 7.5 to 9.5% at screening
  ○ Patients receiving metformin + additional OADs were required to have an HbA1c of 7.5 to 9.0%
• BMI ≤ 40 kg/m^2
	• Previous bolus insulin use (except for short-term use due to intermittent illness)
	• GLP-1 agonist and/or TZD use within 3 months prior to screening
	• CV disease within 6 months prior to screening
	• Recurrent, severe hypoglycemia or hypoglycemia unawareness

Primary Endpoint	**Key Secondary Endpoints**
• Change from baseline in HbA1c after 18 weeks	• Proportion of patients achieving HbA1c targets of < 7.0% • Change from baseline in overall 2-hr PPG increment (all meals) • Number of treatment-emergent severe or BG-confirmed hypoglycemic episodes (as defined according to the ADA classification or by a BG < 56 mg/dL with or without hypoglycemic symptoms)

- **Results:**
  - Baseline characteristics were well-matched between the groups. Mean age was 57.4 years, mean BMI was 30.8 kg/m^2, and duration of diabetes was 10.9 years for the Fiasp + basal group and 11.8 years for the basal group. An equivalent proportion of patients utilized insulin glargine, insulin detemir, and NPH insulin as their basal insulin in both groups. Overall, 94.1% of patients completed the trial.
  - Superiority of Fiasp + basal insulin over basal insulin alone was confirmed in regard to HbA1c reduction and the proportion of patients achieving an HbA1c < 7.0% (see Table 8).
  - Mean body weight increased by 1.8 kg in the Fiasp + basal insulin group and 0.2 kg in the basal only group (ETD, 1.66; 95% CI, 0.89 to 2.43; p < 0.0001).
  - Severe or BG-confirmed hypoglycemic episodes occurred at a significantly higher rate in the Fiasp + basal insulin group (see Table 8).
  - Overall, TEAEs were reported in 40.9% of patients in the Fiasp + basal insulin group and 51.7% of patients in the basal only group; most TEAEs were mild or moderate in severity.

Table 8. Efficacy outcomes Onset 3

	Fiasp + basal insulin (n = 116)	Basal insulin (n = 120)
HbA1c at baseline	7.9%	7.9%
HbA1c at 18 weeks	6.8%	7.7%
ETD (95% CI; p-value)	-0.94% (-1.17 to -0.72; p < 0.0001 for superiority)	
Patients achieving HbA1c < 7.0% at 18 weeks	60.3%	18.3%
OR (95% CI; p-value)	9.31 (4.72 to 18.33; p < 0.0001)	
Change from baseline in 2-hr PPG increment	-26 mg/dL	-9 mg/dL
ETD (95% CI; p-value)	-20.5 mg/dL (-27.1 to -13.8; p < 0.0001)	
Severe or BG-confirmed hypoglycemic episodes, no.	67 (58.3%)	30 (25.0%)
RR (95% CI; p-value)	8.24 (4.93 to 13.76; p < 0.0001)	

Abbreviations: BG = blood glucose, CI = confidence interval, ETD = estimated treatment difference, OR = odds ratio, PPG = post-prandial glucose, RR = rate ratio

- **Authors' conclusion:**
  - In patients with T2DM, Fiasp in a basal-bolus regimen provided superior glycemic control as compared with basal-only insulin, but with an increase in the frequency of hypoglycemia and modest weight gain.
- **Study Appraisal:**
  - **Study sponsorship:**

- Novo Nordisk
- **Study rating:**
  - Fair to Poor
- **Study strengths:**
  - All statistical analyses were based on the FAS.
- **Study limitations:**
  - The study was of short duration.
  - The study was OL with no active comparator; therefore, no conclusion can be drawn regarding the benefit of Fiasp vs other mealtime insulins.
  - The initiation of 3 bolus insulin doses simultaneously in patients with T2DM is not representative of real world clinical practice.

Comparative Efficacy and Meta-Analyses

Study 8a. van Bon et al, *Diabetes Technol Ther.* 2011;13(6):607-614.
Study 8b. Plank et al, *Arch Intern Med.* 2005;165:1337-1344.
Study 8c. Fullerton et al, *Cochrane Database Syst Rev.* 2016;(6):CD012161.

Study	Description
Study 8a: Apidra (GLU) vs Humalog (LIS) and Novolog (ASP) for CSII	• **Study Design:** ○ 39-week, MC, OL, 3-way XO, RCT (N = 256) ○ Adults with T1DM (HbA1c < 8.5%) treated with insulin for ≥ 2 years and CSII for ≥ 6 months ○ The study was designed to demonstrate superiority of GLU over ASP or LIS in rates of unexplained hyperglycemia and/or perceived infusion set occlusion. A prespecified p-value of 0.025 was considered significant to correct for multiple testing. • **Treatment Arms:** ○ Patients were randomized to 1 of 3 treatment orders: GLU-ASP-LIS, ASP-LIS-GLU, LIS-GLU-ASP ○ Each insulin was used for 13 weeks. • **Efficacy Results:** ○ The percentage of patients with unexplained hyperglycemia and/or perceived infusion set occlusion was not significantly different between GLU and ASP (68.4% vs 62.1%; p = 0.04) or GLU and LIS (68.4% vs 61.3%; p = 0.03). ○ No differences were seen in HbA1c, severe hypoglycemia, or symptomatic ketoacidosis. ○ The overall rate of hypoglycemia (BG < 70 mg/dL) per patient-year was significantly different between GLU and ASP (73.84 vs 65.01; p = 0.008) and GLU and LIS (73.84 vs 62.69; p < 0.001). • **Authors' Conclusion:** ○ GLU was not superior to ASP and LIS in CSII use with respect to unexplained hyperglycemia and/or perceived catheter set occlusion. GLU was associated with a higher frequency of symptomatic hypoglycemia, possibly because of slight overdosing, as previous trials have suggested lower insulin requirements when GLU is initiated in T1DM.
Study 8b: SR/MA of rapid-acting insulins (Humalog and Novolog) vs regular insulin	• **Study Design:** ○ 42 RCTs (N = 7933 patients) assessing the effects of rapid-acting insulins vs regular insulin in patients with T1DM (n = 5925), T2DM (n = 1901), or gestational diabetes (n = 107) • **Efficacy Results:** ○ *HbA1c* ▪ In T1DM, the weighted mean difference of HbA1c values was estimated to be -0.12% (95% CI, -0.17 to -0.07%) in favor of rapid-acting insulins vs regular insulin. Heterogeneity was non-significant (p = 0.06). ▪ In T2DM, the weighted mean difference of HbA1c values was estimated to be -0.02% (95% CI, -0.10 to 0.07) between rapid-acting insulins and regular insulin. Similar results were found in studies with children and adolescents with T1DM and in gestational diabetes. ○ *Hypoglycemia* ▪ In T1DM, the standardized mean difference of overall mean hypoglycemic episodes per patient per month was -0.05 (95% CI, -0.22 to 0.11) for rapid-acting insulins vs regular insulin. In the included studies, distinct heterogeneity was observed (p < 0.001). ▪ In T2DM, the standardized mean difference of overall mean hypoglycemic episodes per patient per month was -0.04 (95% CI, -0.12 to 0.04; heterogeneity: p = 0.74) for rapid-acting insulins vs regular insulin. • **Authors' Conclusion:**

	○ In patients with T1DM, a minor benefit to HbA1c values was seen with the rapid-acting insulins vs regular insulin. No benefit was identified in patients with T2DM or gestational diabetes.
Study 8c: Cochrane Review: rapid-acting insulins vs regular insulins in T1DM	• **Study Design:** ○ SR of 9 RCTs with an intervention duration of at least 24 weeks that compared rapid-acting insulins with regular insulins in the treatment of non-pregnant adults with T1DM (N = 2693) ○ Of the included trials, 6 were of insulin lispro (Humalog) vs regular insulin and 3 were of insulin aspart (Novolog) vs regular insulin. None of the included trials used insulin glulisine (Apidra). • **Efficacy Results:** ○ The mean difference in HbA1c was -0.15% (95% CI, -0.2 to -0.1%; p < 0.00001; 9 trials, low quality evidence) in favor of rapid-acting insulins. ○ There were no substantial differences in rates of overall hypoglycemia between the groups. The comparison of the risk of severe hypoglycemia between the 2 treatments showed an OR of 0.89 (95% CI, 0.71 to 1.12; p = 0.31; 7 trials, very low quality evidence). ○ In terms of nocturnal severe hypoglycemia, 2 trials reported statistically significant effects in favor of insulin aspart; however, due to inconsistent reporting, the validity of the results remains questionable. • **Authors' Conclusion:** ○ The analysis suggests only a minor benefit of rapid-acting insulins on BG control in patients with T1DM; however, long-term efficacy and safety data are needed to draw conclusions on long-term patient-relevant outcomes such as all-cause mortality or diabetic complications.

CLINICAL GUIDELINES

- **American Diabetes Association (ADA): Standards of Medical Care in Diabetes** *(2018)* (see Appendix for levels of evidence)
  - HbA1c goals
    - A reasonable HbA1c goal for many nonpregnant adults is < 7%. (A)
    - Providers might reasonably suggest more stringent HbA1c goals (such as 6.5%) for selected patients if this can be achieved without significant hypoglycemia or other AEs of treatment. Appropriate patients might include those with short duration of diabetes, T2DM treated with lifestyle changes or metformin only, long life expectancy, or no significant cardiovascular disease (CVD). (C)
    - Less stringent HbA1c goals (such as < 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin. (B)
  - Pharmacological therapy for T1DM:
    - Most people with T1DM should be treated with multiple-dose injections of basal and prandial insulin or CSII. (A)
    - Consideration should be given to educating patients on matching prandial insulin dose to carbohydrate intake, premeal BG, and anticipated physical activity. (E)
    - Most patients should use rapid-acting insulin analogs to reduce hypoglycemia risk. (A)
      - Rapid-acting inhaled insulin was shown to be noninferior to insulin aspart for HbA1c lowering, with less hypoglycemia observed; however the mean HbA1c reduction with insulin aspart was greater and more patients in the insulin aspart group achieved HbA1c goals of ≤ 7.0%. Because inhaled insulin cartridges are only available in 4-, 8-, and 12-unit doses, limited dosing increments to fine-tune prandial insulin doses in T1DM are a potential limitation.
    - Individuals who have been successfully using CSII should have continued access after they turn 65 years of age. (E)
  - Pharmacological therapy for T2DM:
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM. (A)
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated. (A)
    - Initiation of insulin therapy (with or without additional agents) should be considered in patients with newly diagnosed T2DM who are symptomatic and/or have elevated BG levels (≥ 300 mg/dL) and/or HbA1c (≥ 10%). (E)
    - Initiation of dual therapy should be considered in patients with newly diagnosed T2DM who have HbA1c ≥ 9%. (E)
    - For patients with T2DM who are not achieving glycemic goals, drug intensification, including consideration of insulin therapy, should not be delayed. (B)
    - In patients without atherosclerotic cardiovascular disease (ASCVD), if monotherapy or dual therapy does not achieve or maintain the HbA1c target over 3 months, an additional antihyperglycemic agent should be added based on drug-specific and patient factors. (A)
    - In patients with T2DM and established ASCVD, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events

(MACE) and cardiovascular (CV) mortality (currently empagliflozin and liraglutide), after consideration of drug-specific and patient factors. (A)
    - In patients with T2DM and established ASCVD, after lifestyle management and metformin, the antihyperglycemic agent canagliflozin may be considered to reduce MACE, based on drug-specific and patient factors. (C)
    - A patient-centered approach should be used to guide the choice of pharmacological agents. Considerations include efficacy, cost, potential AEs, impact on weight, hypoglycemia risk, history of ASCVD, renal effects, route of administration, and patient preferences. (E)
  - Treatment Algorithm:
    - At diagnosis, lifestyle management should be initiated; the HbA1c target should be set; and pharmacologic therapy based on HbA1c should be initiated:
      - HbA1c < 9%: Consider Monotherapy.
      - HbA1c ≥ 9%: Consider Dual Therapy.
      - HbA1c ≥ 10%, BG ≥ 300 mg/dL, or patient is markedly symptomatic: Consider Combination Injectable Therapy.
  - Monotherapy: Lifestyle Management + Metformin
    - Metformin should be initiated if there are no contraindications.
    - If the patient is at the target HbA1c after 3 months of monotherapy, the HbA1c should be monitored every 3 to 6 months. If the patient is not at target after 3 months, Dual Therapy should be considered.
  - Dual therapy: Lifestyle Management + Metformin + Additional Agent
    - If the patient has ASCVD, an agent proven to reduce MACE and/or CV mortality should be added. If the patient does not have ASCVD, a second agent should be added after consideration of drug-specific effects and patient factors.
    - If the patient is at the target HbA1c after 3 months of monotherapy, the HbA1c should be monitored every 3 to 6 months. If the patient is not at target after 3 months, medication-taking behavior should be assessed and Triple Therapy should be considered.
  - Triple therapy: Lifestyle Management + Metformin + 2 Additional Agents
    - A third agent should be added based on drug-specific effects and patient factors.
    - If the patient is at the target HbA1c after 3 months of monotherapy, the HbA1c should be monitored every 3 to 6 months. If the patient is not at target after 3 months, medication-taking behavior should be assessed and Combination Injectable Therapy should be considered.
  - Combination injectable therapy:
    - Insulin therapy may be initiated in patients with an HbA1c ≥ 10%, BG ≥ 300 mg/dL, or in patients who are markedly symptomatic. If the HbA1c is not controlled, the following combination injectable therapy escalations may be considered:
    - Adding 1 rapid-acting insulin injection before the largest meal; adding a GLP-1 receptor agonist; or changing to premixed insulin 2 times daily (before breakfast and dinner). If goals are not met, an alternative insulin regimen may be considered.
      - Rapid-acting insulin analogs are preferred due to their prompt onset of action after dosing.
    - If HbA1c is not controlled from adding 1 rapid-acting insulin injection, adding ≥ 2 rapid-acting insulin injections before meals (basal-bolus) may be considered. If HbA1c is not controlled by premixed insulin twice daily, changing to a premixed analog insulin 3 times daily (breakfast, lunch, and dinner) may be considered.

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (2018 Executive Summary)** (*Garber et al 2018*)
  - Lifestyle optimization is essential for all patients with diabetes.
  - The HbA1c target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence. An HbA1c level of ≤ 6.5% is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
  - Glycemic control targets include fasting and post-prandial glucose as determined by self-monitoring of BG.
  - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety in heart, kidney, or liver disease.
  - Minimizing risk of both severe and nonsevere hypoglycemia is a priority. Minimizing risk of weight gain is also a priority.
  - The treatment algorithm stratifies choice of therapies based on initial HbA1c level. It provides guidance as to what therapies to initiate and add but respects individual circumstances that could lead to different choices.
    - The algorithm includes every FDA-approved class of medications for T2DM (as of December 2016).

- Combination therapy is usually required and should involve agents with complementary mechanisms of action. Comprehensive management includes lipid and blood pressure therapies and treatment of related comorbidities.
- The therapeutic regimen should be as simple as possible to optimize adherence.
- Therapy must be evaluated frequently (eg, every 3 months) until the patient is stable, using multiple criteria (eg, HbA1c, self-monitoring of BG records, lipid and blood pressure levels, hypoglycemia events, AEs).
- Pharmacotherapy for T2DM:
  - In patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended. Acceptable alternatives to metformin include a GLP-1 receptor agonist, SGLT-2 inhibitor, DPP-4 inhibitor, and TZD. Alpha-glucosidase inhibitors and SFUs/GLNs may also be appropriate as monotherapy for select patients.
    - A TZD, SFU, or GLN should be used with caution due to their AE profiles.
    - The order of agents listed suggests a hierarchy of recommended usage.
  - If monotherapy fails to achieve the HbA1c goal in 3 months or the patient presents with an HbA1c ≥ 7.5%, then dual therapy should be started by adding 1 of the following agents to metformin (or other first-line agent): GLP-1 receptor agonist, SGLT-2 inhibitor, DPP-4 inhibitor, TZD, basal insulin, colesevelam, bromocriptine quick release (QR), alpha-glucosidase inhibitor, or SFU/GLN.
    - TZDs, basal insulin, SFUs, and GLNs should be used with caution due to their AE profiles.
    - The order of agents listed suggests a hierarchy of recommended usage.
  - If dual therapy does not achieve the HbA1c goal in 3 months, then triple therapy should be started by adding 1 of the following agents to metformin (or other first-line agent) plus a second-line agent: GLP-1 receptor agonist, SGLT-2 inhibitor, TZD, basal insulin, DPP-4 inhibitor, colesevelam, bromocriptine QR, alpha-glucosidase inhibitor, or SFU/GLN.
    - TZDs, basal insulin, SFUs, and GLNs should be used with caution due to their AE profiles.
    - The order of agents listed suggests a hierarchy of recommended usage.
    - Patients taking 2 oral antihyperglycemic agents who have an HbA1c > 8.0% and/or long-standing T2DM are unlikely to reach their target HbA1c with a third oral antihyperglycemic agent. A GLP-1 receptor agonist as the third agent may successfully lower glycemia, but eventually many patients will still require insulin. In such cases, a single daily dose of basal insulin should be added to the regimen.
  - If triple therapy fails to achieve the HbA1c goal in 3 months, then the patient should proceed to or intensify insulin therapy.
  - In patients with an HbA1c > 9.0%, dual therapy or triple therapy is recommended if the patient is asymptomatic. If the patient is symptomatic, insulin therapy alone or in combination with other agents is recommended.

SAFETY

- **Contraindications**

  Class Contraindications
  - During episodes of hypoglycemia
  - Hypersensitivity to the active ingredient or any of the excipients in the rapid-acting insulins

  Afrezza Contraindications
  - Chronic lung disease, such as asthma, or COPD
- **Warnings/precautions**
  - **Boxed warning: Afrezza: Risk of acute bronchospasm in patients with chronic lung disease**
    - Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza. Before initiating Afrezza, a detailed medical history, physical examination, and spirometry (forced expiratory volume in 1 second [FEV_1]) should be performed to identify potential lung disease in all patients.
  - Insulin pens should never be shared, even if the needle is changed, due to the risk for transmission of blood-borne pathogens.
  - Hyper- or hypoglycemia with changes in insulin regimen
    - Doses of insulin should be changed under close medical supervision and the frequency of BG monitoring increased to minimize the risk of hyper- or hypoglycemia.
  - Hypoglycemia
    - Monitoring should be increased with changes to insulin dosage, concomitant glucose lowering agents, meal patterns, physical activity, and in patients with hypoglycemia unawareness, renal, or hepatic impairment.
  - Hypoglycemia due to medication errors
    - Patients should be informed to check insulin labels before injecting as accidental mix-ups between insulin products can occur.
  - Hypokalemia
    - Hypokalemia may be life-threatening and potassium levels should be monitored and treated, if indicated, in patients at risk for hypokalemia.
  - Hypersensitivity reactions

- Severe, life-threatening, generalized allergy, including anaphylaxis can occur.
- Fluid retention and heart failure with concomitant use of TZDs
  - Patients should be monitored for signs and symptoms of heart failure, and a dose reduction or discontinuation should be considered if heart failure occurs.
- Acute bronchospasm/decline in pulmonary function (Afrezza)
  - Acute bronchospasm has been observed in patients with asthma and COPD. Pulmonary function should be assessed before initiating, after 6 months of therapy, and annually, even in the absence of pulmonary symptoms.
- Lung cancer (Afrezza)
  - Afrezza should not be used in patients with active lung cancer. In patients with a history of lung cancer or at risk for lung cancer, the benefit of Afrezza use should outweigh this potential risk.

- **Adverse effects**
  - Common AEs for the injectable rapid-acting insulins include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash.
  - Common AEs for Afrezza (≥ 2%) include hypoglycemia, cough, and throat pain or irritation.
- **Drug Interactions**

Table 9. Significant drug interactions for rapid-acting insulins

Precipitant Drug	Object Drug		Description of Effects
Antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blocking (ARB) agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (eg, octreotide), and sulfonamide antibiotics	rapid-acting insulins	↑	Concomitant use increases the risk of hypoglycemia. Dose reductions and increased glucose monitoring may be required
Atypical antipsychotics (eg, olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (eg, in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (eg, albuterol, epinephrine, terbutaline), and thyroid hormones	rapid-acting insulins	↓	Concomitant use decreases BG lowering effects of rapid-acting insulins. Dose increases and increased glucose monitoring may be required.
Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.	rapid-acting insulins	↔	Concomitant use may increase or decrease the BG lowering effects of rapid-acting insulins. Dose increases and increased glucose monitoring may be required.
Beta-blockers, clonidine, guanethidine, and reserpine	rapid-acting insulins	↔	Concomitant use may blunt the signs and symptoms of hypoglycemia. Increased glucose monitoring may be required.

↑ = Object drug increased. ↓ = Object drug decreased. ↔ = Undetermined clinical effect.

DOSAGE AND ADMINISTRATION

General Dosing Considerations

- The dosage of rapid-acting insulins should be individualized based on the patient's metabolic needs, BG monitoring results, and glycemic control goal.
- Dose adjustments may be needed when switching from another insulin, with changes in physical activity, changes in concomitant medications, changes in meal patterns, changes in renal or hepatic function, or during acute illness to minimize the risk of hypo- or hyperglycemia.
- Injection sites (abdominal wall, thigh, upper arm, or buttocks) should be rotated within the same region from one injection to the next to reduce the risk of lipodystrophy.
- Rapid-acting insulins given by SC injection should generally be used in regimens with intermediate or long-acting insulin.
- For rapid-acting insulins approved for CSII use, product- and pump-specific instructions should be followed.
- Rapid-acting insulins should be administered by IV infusion only under medical supervision with close monitoring of BG and potassium levels to avoid hypoglycemia and hypokalemia.

Table 10. Dosing of rapid-acting insulins

Drug	Approved Routes of Administration	Dosing
Admelog (insulin lispro)	SC, IV, CSII	SC: administer within 15 minutes before a meal or immediately after a meal

		IV: dilute to concentrations from 0.1 unit/mL to 1 unit/mL in 0.9% sodium chloride
Afrezza (insulin human)	Inhalation	Starting mealtime dose: *Insulin naïve:* 4 units at each meal *Using SC prandial insulin:* determine the appropriate Afrezza dose by using the conversion chart provided in the prescribing information. For Afrezza doses exceeding 12 units, inhalations from multiple cartridges are necessary
Apidra (insulin glulisine)	SC, IV, CSII	SC: administer within 15 minutes before a meal or within 20 minutes after starting a meal IV: dilute to concentrations from 0.05 unit/mL to 1 unit/mL in 0.9% sodium chloride
Fiasp (insulin aspart)	SC, IV	SC: administer at the start of a meal or within 20 minutes after starting a meal IV: dilute to concentrations from 0.5 unit/mL to 1 unit/mL in 0.9% sodium chloride or 5% dextrose
Humalog (insulin lispro)	SC (U100, U200), IV (U100), CSII (U100)	SC (U100, U200): administer within 15 minutes before a meal or immediately after a meal IV (U100): dilute to concentrations from 0.1 unit/mL to 1 unit/mL in 0.9% sodium chloride
Novolog (insulin aspart)	SC, IV, CSII	SC: administer within 5 to 10 minutes before a meal IV: dilute to concentrations from 0.05 unit/mL to 1 unit/mL in 0.9% sodium chloride

Abbreviations: CSII = continuous subcutaneous insulin infusion, IV = intravenous, SC = subcutaneous

SPECIFIC POPULATIONS

- **Geriatrics**
  - In elderly patients, caution should be taken with initial insulin dosing and subsequent dose changes to avoid hypoglycemic reactions.
- **Pediatrics**
  - Admelog, Humalog, Apidra, and Novolog are approved for use in pediatric patients.
    - Admelog and Humalog have not been studied in pediatric patients with T1DM < 3 years of age or in pediatric patients with T2DM.
    - Apidra has not been studied in pediatric patients with T1DM < 4 years of age or in pediatric patients with T2DM.
    - Novolog has not been studied in pediatric patients with T1DM < 2 years of age or in pediatric patients with T2DM.
- **Renal dysfunction**
  - Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent insulin dose adjustment and more frequent BG monitoring.
- **Hepatic dysfunction**
  - Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent insulin dose adjustment and more frequent BG monitoring.
- **Pregnancy and nursing**
  - Humalog and Novolog are Pregnancy Category B (no evidence of risk in studies); Apidra is Pregnancy Category C (risk cannot be ruled out; either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available).
  - Admelog, Afrezza, and Fiasp are uncategorized in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR). Limited data available in pregnant women are insufficient to determine a drug-associated risk of adverse developmental outcomes.

CONSULTANT: PC, M.D. (Endocrinology)

- **Consultant's Comments:**
  - The injectable rapid-acting insulin analogs are more similar than they are different. In practice, the consultant uses them interchangeably and has not noticed a difference in terms of efficacy or safety.
  - The consultant has limited experience with Fiasp. It may be useful for patients who need a faster onset of action, but the benefit remains unclear.
  - The SORELLA trials evaluating Admelog were relatively standard. The outcomes, populations, and duration were adequate to show nonnferiority of Admelog to Humalog. SORELLA 1 had an extended period to look for antibodies as

well.
- Admelog will likely become clinically interchangeable with Humalog.
- Afrezza has been available for several years, but utilization is low. Generally, patients do not mind daily injections with the available pen devices. One niche may be for truck drivers who have T2DM as they are not allowed to use injectables. Afrezza could get around this issue while still providing similar efficacy to insulin.
- In terms of efficacy, Afrezza is probably similar to the other rapid-acting insulins, but safety is very different. It cannot be used in patients with pulmonary issues, and pulmonary function needs to be monitored long-term.

- **Disclosure of financial relationships:**
  - No potential conflicts of interest identified

CONSULTANT: EK, M.D. (Endocrinology)

- **Consultant's Comments:**
  - Given the impact of PPG on HbA1c as well as concerns with mealtime glucose excursions on vascular health, there has been great interest over recent years in more closely approximating true insulin response physiology. Despite pharmacologic advances which have reduced onset and peak times, we still have not reproduced finely tuned mealtime insulin effects. In addition, application of rapid-acting insulin analogs has not shown dramatic benefits on long-term outcomes.
  - The injectable rapid-acting insulin analogs are basically identical in their safety, efficacy, and kinetics.
    - Fiasp has been shown to have faster onset and peak action by 5 to 10 minutes. Its effect on HbA1c, however, has demonstrated, at best, minimal improvement to noninferiority.
  - The SORELLA trials for Admelog in T1DM and T2DM were well-designed with appropriate primary and secondary endpoints. The study populations were quite representative of the real world situation, particularly around age, duration of disease, obesity, and renal disease. Non-Caucasians were underrepresented. In the T1DM study, the authors acknowledged they did not rely on C-peptide determinations to define the group.
  - Afrezza has clearly demonstrated quicker onset and a sharp early peak effect. It appears to have less weight gain and probable decreased hypoglycemia risk. Studies have not shown consistent or clinically significant HbA1c lowering over comparator rapid insulins. It serves people who have a need for flexibility and convenience, or patients who are needle-resistant/phobic. It may have a place in patients with T2DM who have been holding back from starting insulin by offering an injection-free option.
  - Afrezza may have a little less weight gain and hypoglycemia vs the injectable rapid-acting insulins, but there are other safety concerns. Candidate selection is difficult, as it cannot be used in smokers, asthma, or COPD. It requires a rigorous and expensive lung function screening, causes cough, and may cause lung function to decline. Additionally, there is imprecision in the dosing and some information that exercise alters its kinetics. These limitations have likely kept Afrezza from becoming a game changer.
- **Disclosure of financial relationships:**
  - No potential conflicts of interest identified

APPENDIX

- **ADA guideline levels of evidence** *(ADA 2018)*

Level of Evidence	Description
A	• Clear evidence from well-conducted, generalizable RCTs that are adequately powered, including: ◦ Evidence from a well-conducted MC trial ◦ Evidence from a meta-analysis that incorporated quality ratings in the analysis • Compelling nonexperimental evidence, ie, "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford • Supportive evidence from well-conducted RCTs that are adequately powered, including: ◦ Evidence from a well-conducted trial at 1 or more institutions ◦ Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	• Supportive evidence from well-conducted cohort studies ◦ Evidence from a well-conducted prospective cohort study or registry ◦ Evidence from a well-conducted meta-analysis of cohort studies • Supportive evidence from a well-conducted case-control study
C	• Supportive evidence from poorly controlled or uncontrolled studies ◦ Evidence from RCTs with 1 or more major or 3 or more minor methodological flaws that could invalidate the results ◦ Evidence from observational studies with high potential for bias (such as case series with

	comparison with historical controls) ○ Evidence from case series or case reports • Conflicting evidence with the weight of evidence supporting the recommendation
E	• Expert consensus or clinical experience

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Therapeutic Class Review created by: C.Ellsworth, Pharm.D., BCPS
Reviewed by: J. D'Aloia, Pharm.D.
Publication date: 5/3/2018

OPTUMRX

SUBJECT: FORMULARY MANAGEMENT COMMITTEE CHARTER AND POLICY

POLICY ADOPTED: January 2018

POLICY REVISED: APRIL 25, 2018

SCOPE

This Policy outlines the responsibilities and activities of the Formulary Management Committee ("FMC") of OptumRx.

INTRODUCTION AND PURPOSE

FMC provides pharmacy management decisions for the OptumRx Formularies (OptumRx National Formularies, Innoviant Formulary, Legacy Catamaran Formularies and other formularies as determined by the business. FMC makes final classification on the placement of a Food and Drug Administration ("FDA") approved prescription drug to an assigned tier, exclusion programs or other clinical coverage programs and whether utilization management tools ("UM"), such as, prior authorizations, quantity limits, and step therapies, should be applied based on P&T designations and recommendations. In addition, FMC provides tier and coverage recommendation to Clients for consideration on custom formularies upon request.

COMPOSITION

FMC shall have the following voting members:
Clinical

Senior Vice President, Chief Pharmacy Officer
Vice President, Clinical Services
Senior Director, Drug Intelligence
Senior Director, Clinical Formulary Strategy
Senior Director, Utilization Management

Industry Relations

Senior Vice President,
Vice President, Industry Relations - Part D
Vice President, Industry Relations - Commercial
Vice President, Industry Relations
Senior Director, Industry Relations - Commercial
Senior Director, Industry Relations - Part D

Clinical Consulting/Client Management/Specialty Client Management
Vice President, Clinical Consulting

Vice President(s), Client Management

Vice President, Specialty Pharmacy Client Management

Senior Clinical Consultant
Senior Director, Clinical Account Management – UHC Relations
UMR Clinical Program Consultant
UMR Clinical Consultant

The following individuals shall serve on FMC as nonvoting, advisory members:
Vice President, Formulary Operations
Director, Formulary Operations
Director, Industry Relations – Commercial
Project Manager, Formulary Operations

The Director, Formulary Operations shall serve as the FMC Chairperson. The FMC Chairperson shall appoint other voting and advisory Committee members, including a Vice Chairperson and Secretary, who is capable of carrying out the responsibilities of the Committee. Committee attendance and membership is limited to employees of UnitedHealth Group (UHG). Consultants, client representatives and representatives of pharmaceutical, biologic or device manufacturers are excluded from membership and may only attend Committee meetings as invited guests, at the discretion of the FMC Chairperson, for the purpose of providing presentations or other information. In the event of the absence of a voting member, the absent voting member may designate a non-voting member to take their place during the FMC Meeting.

MEETINGS

FMC meets on a monthly basis. The FMC Chairperson may convene additional meetings as necessary to conduct FMC business. FMC members are expected to attend all meetings.

A quorum is achieved at monthly meetings when at least fifty percent (50%) of FMC's voting members from each group are present.
A motion or decision is passed or approved by an affirmative vote of at least fifty percent (50%) of the voting members present at a duly held meeting. All voting FMC members have the authority to vote on official FMC motions and decisions. Guests in attendance at FMC meetings do not have the authority to vote.

The agenda and meeting materials shall be provided to FMC members sufficiently in advance of meetings to enable FMC members to review materials in advance and participate actively in the discussion and decision-making. OptumRx staff shall maintain results of the FMC meeting in meeting minutes. OptumRx shall retain the minutes in accordance with UHG's document retention policies and procedures. The FMC meeting minutes, unless otherwise provided in relevant law or regulation, are for internal use only.

RESPONSIBILITIES OF THE CHAIRPERSON

Responsibilities of the FMC Chairperson include:

- Coordinating and conducting FMC meetings;
- Finalizing the meeting agenda and ensuring that meeting materials are provided in advance of meetings;
- Facilitating the discussion;
- Managing FMC support activities performed by OptumRx staff members;
- Ensuring appropriate documentation and distribution of FMC meeting minutes; and
- Ensuring that decisions are promptly communicated.

RESPONSIBILITIES AND DUTIES OF THE COMMITTEE

Responsibilities of FMC include, but are not limited to, the following:

- Formulary Strategy: FMC is responsible for reviewing evidence provided by the OptumRx National P&T Committee ("P&T Committee") and OptumRx staff members in recommending the assignment of FDA approved new drugs, existing drugs with new indications or new dosage forms, or drugs that otherwise have new evidence, within the OptumRx National Formulary and/or FMC's final recommendations for other Client's formularies. FMC will receive from the P&T Committee Drug Classification Designations as identified in **Exhibit A**, which may be updated from time to time based on the P&T Committee's current practices. FMC will use the Drug Classification Designations to make decisions and/or recommendations about the Formulary structure as outlined in **Exhibit B**, which may be amended from time to time to reflect FMC's current practices. In addition to the Drug Classifications Designations, FMC will also consider economic, pharmacoeconomic, and business/benefit strategy analyses (as defined below) in making Formulary placement decisions.
  - Economic evidence may include, but is not limited to, the drug's acquisition cost, including rebate information, and market and utilization data.
  - Pharmacoeconomic evidence may include, but is not limited to, the drug's impact on medical cost and quality, and cost offset.

  Once FMC has decided on the structure for the OptumRx National Formularies, such decisions shall be reviewed by the P&T Committee for clinical concerns as required by law or as required or as determined by FMC.

- Clinical Program Strategy: FMC also provides economic guidance into the type of utilization management tools ("UM") for use with particular drugs or a particular Formulary, including, but not limited to, prior authorizations, quantity limits, step therapies, and provider education. FMC makes these decisions by considering clinical, economic and pharmacoeconomic evidence (as available) provided by the P&T Committee, OptumRx staff, and other supporting financial, business and benefit strategy analyses. FMC reviews and considers recommendations and other information, including, but not limited to:

- Recommendations either from the P&T Committee or other sources regarding the use of UM tools; UM tools recommended as a result of specific drug safety concerns must be included as part of the clinical strategy program
- Prior authorizations (including step therapy and quantity limits) reviewed and approved by the P&T Committee or a subcommittee of the P&T Committee to whom the P&T Committee has delegated its authority.

COMMUNICATION

FMC will deliver all approved decisions to SVP of Clinical, and SVP of Industry Relations, for their reference.

FMC will deliver final decisions to the Benefit Implementation Committee ("BIC") for implementation and communication to internal and external stakeholders. Refer to BIC Charter. Depending on the terms of the Client's contract, the Account Management Team will either provide the FMC final recommendations or the OptumRx National Formularies to the Client. When FMCs final recommendations are provided to Clients for review and approval, the Client makes the final decision regarding the Formulary structure and management, creating a Client-specific Formulary. When the Client chooses to implement the OptumRx National Formulary as recommended as the Formulary for that particular Client's pharmacy benefit plan, FMC makes the final decision regarding the structure of the OptumRx National Formulary, which is then provided to the Client for final approval. In either circumstance, OptumRx will provide supporting documentation regarding its Formulary recommendations if such information is requested by the Client and provided for under the terms of the Client's pharmacy benefit management contract. Following receipt of Client's approval of either the recommendations or the OptumRx National Formulary, OptumRx Account Management teams shall communicate Formulary positions or utilization management assignments, reassignments or other decisions to affected staff and business groups promptly following the final decision.

The description of the Formulary management and clinical program strategy process contained in this policy is intended to be shared with our constituencies, including customers, regulators, consumers and physicians; however the underlying analytics of specific decisions are confidential, proprietary information.

CONFIDENTIALITY

During the course of participation in FMC, voting members, advisory members, and other participants ("Participants") may become aware of, develop for OptumRx, or come into possession of confidential or proprietary information. In order to protect the confidentiality of this information, Participants will adhere to the guidelines in the UHG Confidentiality Policy for Participants in Business Implementation Committee.

CONFLICT OF INTEREST

Participants must review the Conflict of Interest Policy for Participants in the Formulary Management Committee upon their appointment to FMC and annually thereafter. Participants must update their Conflict of Interest Attestation any time their circumstances change in order to ensure their information is current.

Participants must disclose any existing or potential conflicts of interest to the FMC Chairperson and Legal Counsel upon becoming aware of such conflict of interest or potential conflict of interest. Participants shall not participate in any Committee meeting until such disclosure has been made. If a Participant has questions or doubts as to whether an interest or activity is or may constitute a conflict of interest, Participant should initially consider the activity or interest to be a conflict and should provide the FMC Chairperson and Legal Counsel with the appropriate disclosure.

The decision as to whether or not a Participant may participate in any portion of a Committee meeting where a conflict may arise and in what capacity, if any, such participation is permissible, shall be made by the Committee Chairperson in consultation with Legal Counsel. In any case, a Participant may choose to recuse him/herself at any time.

Approvals of the FMC Charter and Policy:

FMC Chairperson Date

OptumRx CEO Date

Exhibit A
OptumRx Pharmacy and Therapeutics Committee Designations

P&T Committee Designations	Characteristics
Essential Drug: *Modifier:* (specify the significant unmet need fulfilled and the affected population) *Examples*: Glucophage (metformin); Entresto (sacubitril-valsartan); Zetia (ezetimibe)	A drug which has a documented clinically significant, unique therapeutic benefit in efficacy and/or safety relative to other therapeutic alternatives (where available) used to treat, manage or prevent the same or similar medical condition(s), as supported by the preponderance of available peer reviewed published data (including product labeling and information available as part of FDA review), in the overall target
Essential Class*: *Modifier:* (Define the class; explain why the class is "essential") *Clinical Note:* (Specify any niche for which a drug is essential, if any exists) *Examples*: Angiotensin converting enzyme inhibitors, Glucagon-like Peptide-1 (GLP-1) Receptor Agonists; Opioid-Induced Constipation Agents	• Drugs which, as a group, demonstrate a clinically significant, unique therapeutic benefit and have comparable safety and efficacy to one another when used to treat, manage or prevent the same or similar medical condition(s) • Drugs as a group that are similar in their pharmacology, and/or indications for use which may include individual drugs that fulfill an unmet need for a specific patient population
Unique Risk Issues: (specify the risk(s) posed) *Examples*: Ketek (telithromycin), Demerol (meperidine)	Drug(s) which, as compared to other therapeutic alternatives to treat the same or similar medical condition, have a documented increased risk of harm that substantially outweighs potential benefits, as supported by the preponderance of available peer reviewed published data (including product labeling and information available as part of FDA review) and/or based on documented action taken by a US regulatory body
Additional Data Required *Examples*:	Insufficient evidence available for the P&T Committee to weigh the clinical risks & benefits of the drug or compare it to other therapeutic options but additional data is expected within next 12 months. Drugs designated as "additional data required" shall be re-evaluated at a subsequent P&T meeting when new or additional clinical studies or evidence are available.
Optional Inclusion*: *Modifier:* (specify the reason why inclusion does not fulfill an unmet need) *Examples*: Flagyl ER (metronidazole), Addyi (flibanserin), Oralair (multiple allergens extract); Avycaz (cetazidime-avibactam)	• Drug(s) that are safe and effective, but provide no unique therapeutic benefit relative to other alternatives to treat, manage, or prevent medical condition(s) • Drug(s) that have limited evidence demonstrating safety and/or efficacy • Drug(s) that have adequate data as supported by the preponderance of available peer reviewed published literature (including product labeling and information available as part of FDA review) demonstrating the drug provides a unique therapeutic benefit for a small sub-population where the majority of clinical need could be met by other therapies

Non-Essential Non-FDA-Approved Drug *Examples*: Benziq (benzoyl peroxide 5.25% gel), Levsin (hyoscyamine); : choline magnesium trisalicylate tablets; Disalcid (salsalate) tablets	Applicable to drugs that are not approved by the FDA
Vaccine *Examples*: Menveo (meningococcal [A, C, Y, AND W-135] conjugate vaccine, Gardasil 9 ((human papillomavirus 9-valent vaccine, recombinant); Quadracel (DTaP-IPV)	Includes agents for vaccine-preventable diseases

Exhibit B

Formulary Management Committee Guidelines

P&T Committee Designations	Implications to Formulary Management Committee
Essential Drug (Specify the reason why and/or the population.)	FMC shall adhere to the following guidelines with respect to the Formulary/PDL placement of essential drugs: • Essential drugs must be available to treat the indication which rendered the drug an essential drug on an unrestricted basis, except for such restrictions that are medically indicated and appropriate. • The Formulary/PDL placement of essential drugs must comply with all legal and regulatory requirements. • The Formulary/PDL tier placement must be at least equivalent to other single source products within the same therapeutic category or products to treat the same disease state. • ORx: preferred or non-preferred tier • An uptier requires alternative in lower tier. • Cannot be Excluded • Essential drugs may not be placed on a higher copayment or coinsurance tier than the drug would otherwise be placed given the applicable scientific evidence, pharmacoeconomic factors, benefit design and other criteria used to ensure appropriate, safe and cost effective drug therapy. • The FMC shall periodically review its Formulary/PDL to ensure that the Formulary/PDL design does not discriminate or substantially discourage enrollment by certain groups. • Contracts with pharmaceutical manufacturers and other third parties must be consistent with this policy. • The FMC shall conduct reviews, but not less than once a year, to ensure that essential drugs have been placed on Formulary/PDL in accordance with these policies.
Essential Class (Specify what constitutes the class.)	• FMC will determine which of the drugs (at least one) in the particular class will be included on the Formulary/PDL, subject to the applicable benefit. • The Formulary/PDL tier placement must be at least equivalent to other single source products within the same therapeutic category or products to treat the same disease state. • An uptier of a drug with this designation to T3 requires alternative in lower tier. • May exclude with the availability of an exception process if Clinical Note specifies that access must be maintained for a specific population or indication
Unique Risk Issues: (Specify the reason why and/or the population)	FMC will take actions to limit use of Unique Risk Issues drug designations. This may include any of the following: • Placing the drug in higher Formulary/PDL tier within open formularies • Excluding the drug from closed Formularies/PDLs • Requiring Utilization Management controls designed to limit inappropriate use as recommended by the P&T Committee • Enrollee, pharmacy, and prescriber education programs

	• Online messaging to dispensing pharmacists
Additional Data Required	Drugs designated Additional Data Required will remain excluded or non-preferred within open Formularies/PDLs and will not be added to closed Formularies/PDLs. *Drugs on the New Drugs to Market (NDTM) list that are still awaiting final P&T review of Additional Data by the 6 month decision date, may stay on the NDTM list as per policy, until final P&T designation.
Optional Inclusion with Notes	• FMC will determine Formulary/PDL status of Optional Inclusion drugs. • May exclude with the availability of an exception process if Clinical Note specifies that access must be maintained for a specific population or indication • Typically T3 but rebate may allow for lower tiering. • Tier cannot be lower than Essential Drug within the same therapeutic category or products to treat the same disease state.
Optional Inclusion without notes	• FMC will determine Formulary/PDL status of Optional Inclusion drugs. • May exclude. • Tier cannot be lower than Essential Drug within the same therapeutic category or products to treat the same disease state.
Non-Essential Non-FDA-Approved Drug	• FMC will determine Formulary/PDL status of Non-Essential Non-FDA-Approved Drugs. • Tier cannot be lower than Essential Drug within the same therapeutic category or products to treat the same disease state. • May exclude
Vaccine	• FMC will determine Formulary/PDL status as necessary subject to the applicable benefit.
Vigilant Drug List	• Refer to Vigilant Drug List policy and procedure • Policy and procedures will be reviewed yearly to ensure conformance with FMC policy and procedures

Supplemental Response to No. 3:

As described in OptumRx's previous responses, OptumRx's Industry Relations group negotiates contracts and discounts with drug manufacturers, including manufacturers of insulin. Kent Rogers is Senior Vice President, Industry Relations, and is responsible for supervising the teams that conduct discount and contract negotiations with pharmaceutical manufacturers, including for insulin products. Gina Guinasso is also Senior Vice President, Industry Relations, and is responsible for formulary contracting strategy. Other Industry Relations personnel with responsibility for discount and contract negotiations with the three insulin manufacturers with whom OptumRx currently contracts include Magally Smith, Senior Manager of Pharmaceutical Contracting; Kathy Chang, Vice President, Industry Relations; Robert Earnest, Vice President, Industry Relations; Stephen Crowe, Director, Industry Relations; Jack Daly, Director, Industry Relations; Sandi Malone, Contract Manager; and Sanaz Sadeghi, Contract Manager.

Supplemental Response to Nos. 4a and 4b:

As described in OptumRx's previous responses, the design of plan formularies generally follows a multi-step process that begins with OptumRx's independent Pharmacy & Therapeutics ("P&T") Committee, which evaluates clinical evidence to assess a medication's role in therapy and overall clinical value.

Subject to the clinical designations and recommendations of the P&T Committee, OptumRx's Formulary Management Committee ("FMC") has authority to make decisions regarding the placement of prescription drugs on OptumRx's standard formularies. The FMC provides pharmacy management decisions for OptumRx's standard formularies and makes final classification decisions concerning the placement of FDA-approved drugs on an assigned formulary tier. The FMC also provides economic guidance about appropriate utilization management ("UM") tools for use with particular drugs or a particular formulary, including prior authorizations, quantity limits, step therapies, and provider education. Additionally, the FMC makes recommendations regarding formulary placement for many OptumRx clients that choose to create and follow custom formularies.

The FMC reviews and votes on recommendations to make changes to formulary placement for the OptumRx standard formularies, including assignment of new drugs, existing drugs with new indications or new dosages, or drugs that otherwise have new evidence concerning safety or efficacy. Requests for the FMC to make decisions or recommendations regarding formulary placement of drugs may be initiated by a range of different groups within OptumRx, including, most commonly, the P&T Committee and Industry Relations. Lynn Starmann, Vice President, Formulary Operations, is responsible for the Formulary Operations group, which facilitates the work of the FMC.

Subject to compliance with the clinical determinations of the P&T Committee, the FMC may also evaluate economic, pharmacoeconomic, and business/benefit considerations when making formulary placement decisions. OptumRx's primary business strategy in designing its standard formularies is to design formularies that are attractive to current and potential clients, particularly by providing clients with the lowest possible net cost of drugs.

The FMC generally meets on a monthly basis. It consists of eighteen voting members, including representatives from OptumRx Clinical Affairs, OptumRx Industry Relations, and OptumRx Client Management. The FMC also includes four non-voting advisory members, including the

FMC Chairperson. The current FMC Chairperson is Lynn Starmann. The concurrently produced FMC Charter identifies the committee's other participants.

A description of how formulary placement decisions are communicated to external and internal stakeholders is contained in the concurrently produced FMC Charter. Depending on the terms of a particular client's contract, the client is provided with either OptumRx's standard formularies or the FMC's final recommendations regarding a custom formulary. When a client chooses to implement OptumRx's standard formulary as recommended as the formulary for that particular client's pharmacy benefit plan, the FMC makes the final decision regarding the structure of OptumRx's standard formulary, which is then provided to the client for final approval. When a client chooses to implement a custom formulary, the FMC's final recommendations are provided to the client for review and approval and the client makes the final decision regarding the formulary structure and management, creating a client-specific formulary. Following receipt of the client's approval of either the recommendations or OptumRx's standard formulary, OptumRx's Account Management teams then communicate formulary positions or utilization management assignments, reassignments or other decisions to relevant internal stakeholders.

Supplemental Response to Request Nos. 1a, 1c

OptumRx negotiates with insulin manufacturers to obtain discounts on behalf of its clients and consumers. The discounts are established by the terms of rebate agreements with these manufacturers. While the specific terms are the result of negotiation, all of the insulin manufacturers pay rebates under the agreements if, and to the extent that, a particular drug receives specified formulary placement. Rebates are generally calculated as discounts off of a manufacturer's wholesale acquisition costs ("WAC"). The agreements generally define WAC to be the distributor list price for a drug as published in Medi-Span or a mutually agreed upon third party publication as of the date that the drug is dispensed.

OptumRx's rebate agreements with insulin manufacturers do not obligate OptumRx or any of its clients to provide any insulin product or other drug with any specific, preferred, or minimum placement on the OptumRx standard formularies or any custom formulary adopted by any OptumRx client. Rather, under the agreements the manufacturers make certain rebate payments if, and to the extent that, a manufacturer's drug receives a specified formulary placement. For example, an insulin manufacturer will typically pay a larger rebate for drugs that receive preferential formulary placement, which may include, for example, placement on a preferred formulary tier or absence of utilization controls unless clinically appropriate. OptumRx's rebate agreements with insulin manufacturers make clear that neither OptumRx nor its clients are obligated to grant the manufacturers preferred formulary placement for insulin products or other drugs, or to conform to the placement that creates eligibility for the agreed upon rebates. OptumRx and its clients are generally free under the rebate contracts to change their formularies at any time and without penalty.

In other words, OptumRx negotiates with insulin manufacturers regarding the conditions under which insulin purchases by its clients may become eligible to earn rebates. By lowering the net cost of insulin products, these rebates may create an incentive, but not a binding obligation, to grant preferred formulary placement to a manufacturer's product.

Commercial rebate agreements with insulin manufacturers contain administrative fees for insulin products in consideration for OptumRx's administrative services, including, but not limited to, providing general maintenance, administration, and oversight of the manufacturer's rebate program as well as negotiating and contracting with payors participating in the rebate program. The administrative fee is not charged on Qualified Prescription Drug Coverage Plans ("QRPDP"), Managed Medicaid, and CHIP utilization, and any other utilization where such fees are prohibited by law. OptumRx also does not collect any administrative fees under its Medicare rebate agreements. Administrative fees are calculated as a percentage of WAC per unit of each insulin product.

A number of OptumRx's rebate contracts with insulin manufacturers include price protection provisions, which generally provide that a manufacturer that increases its prices by more than a certain percentage over a specified period must rebate the incremental revenues above that percentage to OptumRx. Price protection provisions for insulin products are a tool to discourage insulin manufacturers from imposing significant price increases because they eliminate the manufacturers' financial incentive to do so. OptumRx passes through these payments to its clients in accordance with the clients' contracts.

OptumRx's clients retain complete and exclusive discretionary authority over their plans, and are responsible for administering, managing, and operating such plans, including establishing

and amending a plan's formulary and utilization management programs, such as prior authorization and step therapies.

Formulary Management Committee (FMC) Meeting

Tina Chuong

April 25, 2018

OPTUMRx®

Essential Class - 2

FMC APPROVED

Recommendation: At least 1 agent within the class should be formulary; consider clinical notes

Class	Clinical Notes
[redacted]	
Long-acting insulin analogs	

[redacted]

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Formulary Ops – NDTM

FMC APPROVED

Rationale for Review

- NDTM products are set to term off list within next 60 days
- Decision needed for future management:
  1. Setup on an exclusion list (i.e. Premium Exclusion) OR
  2. Allow NDTM product to term at scheduled date and default to Select tier

Product	Therapeutic Class	Term Date (NDTM)	Future Premium Tier
[redacted]			
ADMELOG	INSULIN	7/4/2018	Exclude via PEL
ADMELOG SOLOSTAR	INSULIN	7/4/2018	Exclude via PEL
[redacted]			

Recommendation

- All products should remain on NDTM until scheduled term date, unless deemed as "Essential Drug" at P&T
- Essential drugs cannot be excluded and it will be termed from NDTM exclusion list per DI recommendations

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EHB FORMULARY CHANGES effective 1/1/2019

FMC APPROVED

CLASS	DRUG	GENERIC DESC	EHB Base	EHB Enhanced
[redacted]				
Insulins	APIDRA	INSULIN GLULISINE INJ 100 UNIT/ML	T3 → EX	T4 → EX
Insulins	LEVEMIR	INSULIN DETEMIR INJ 100 UNIT/ML	T3 → T2	T4 → T3
Insulins	APIDRA SOLOSTAR	INSULIN GLULISINE SOLN PEN-INJECTOR INJ	T3 → EX	T4 → EX
Insulins	LEVEMIR FLEXTOUCH	INSULIN DETEMIR SOLN PEN-INJECTOR	T3 → T2	T4 → T3
Insulins	TRESIBA FLEXTOUCH	INSULIN DEGLUDEC SOLN PEN-INJECTOR	EX → T2	EX → T3
[redacted]				

FMC APPROVED

Formulary Ops – EHB Updates Post FMC

Rationale for Exclusion

- Exclude for EHB 1/1/2019 (Premium PEL exclusions)

Drug	Therapeutic Class	Key Points
[redacted]		
APIDRA	Insulins	PEL
APIDRA SOLOSTAR	Insulins	PEL
[redacted]		

+ Me Too
* High Cost Generic
^ NEDEL
PEL = Premium Exclusion List

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Formulary Management Committee (FMC) Meeting

Tina Chuong

May 30, 2018

OPTUMRx®

Essential Class

FMC APPROVED

Recommendation: At least 1 agent within the class should be formulary; consider clinical notes

Class	Clinical Notes
[redacted]	
Rapid-acting insulins	
[redacted]	

NDTM

FMC APPROVED

Product	Therapeutic Class	Designation	Status	Recommendation
[redacted]				
ADMELOG and ADMELOG SOLO (INSULIN LISPRO)	INSULIN	Essential Class	NDTM (term 7/4/2018)	No change
[redacted]				

Formulary Management Committee (FMC) Meeting

Tina Chuong

June 27, 2018

OPTUM Rx®

Therapeutic Categories for Review - 2019

[redacted]

4) Diabetes (Basal Insulins) [redacted]

[redacted]

2019 Summary of Changes - 1

Therapeutic Class	Drug Name	Premium		Select	
		Current	Proposed	Current	Proposed
[redacted]					
Basal Insulin	Tresiba	Excluded	Excluded	T3	T2
[redacted]					

FMC approved pending P&T approval

Diabetes (Basal Insulins) – Tresiba

RATIONALE FOR REVIEW

- Tresiba is a basal insulin product that was approved by the FDA in Dec 2016. The basal insulin class was evaluated as part of 2019 recontracting effort to leverage competition and reduce the overall cost of the category.
- Tresiba is a long-acting, once-daily basal insulin analog indicated for patients 1 year of age or older with type 1 and or type 2 diabetes. It is available as a 100-unit/ml and 200-unit/ml prefilled pen

KEY POINTS

- **P&T Designation:** Essential Class
- A1C reduction and CV safety for Tresiba is similar to insulin glargine. Tresiba has less hypoglycemic episodes and nocturnal hypoglycemic episodes compared to insulin glargine
- Tresiba can be administered at any time during the day, allows for flexibility in dosing administration.
- Tresiba continues to gain market share despite Non-Preferred Brand status on Select Formulary
- Adding Tresiba to T2 will provide another alternative to patients in a class that is continuing to grow.
- Annual rebate impact: Redacted

RECOMMENDATION

	Current Tier / UM	Proposed Tier / UM
Premium Formulary	Excluded	Excluded
Select Formulary	Tier 3	Tier 2 [eff 1/1/19]

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Diabetes (Basal Insulins) – Drug Level Data

DRUG LEVEL DATA (4Q17)							TIER COMPARISON		
MFG	Drug	Dosage Form	Rx / Qtr	Pts / Qtr	IC / Rx	Net Cost/Rx	ORx Select	ORx Prem	UHC E&I
Lilly	Basaglar	SOPN	5,424	3,266	Redacted	Redacted	3^	EXCL	1*
Novo	Levemir	SOPN/SOLN	22,566	13,600	Redacted	Redacted	2	EXCL	2*
Sanofi	Lantus	SOPN/SOLN	114,494	70,485	Redacted	Redacted	2	2	EXCL
Sanofi	Toujeo	SOPN	28,209	16,106	Redacted	Redacted	2	2	EXCL
Novo	**Tresiba**	**SOPN**	**13,268**	**8,145**	Redacted	Redacted	**3**	**EXCL**	**NF***

† Subject to prior authorization * Subject to quantity limits ^ Step Therapy

- **Member Impact**
  - Positive impact – Tresiba downtier for Select Formulary. Member cost share reduction for an additional basal insulin product

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FMC approved

Essential Class - 3

Recommendation: At least 1 agent within the class should be formulary; consider clinical notes

Class	Clinical Notes
Rapid-acting insulins	

[redacted]

FMC approved

Formulary Ops – NDTM

Rationale for Review

- NDTM products are set to term off list within next 60 days
- Decision needed for future management:
  1. Setup on an exclusion list (i.e. Premium Exclusion) OR
  2. Allow NDTM product to term at scheduled date and default to Select tier

Product	Therapeutic Class	Term Date (NDTM)	Future Premium Tier
[redacted]			
ADMELOG (new NDC)	Insulin	7/4/2018	EXCLUDED

Recommendation

- All products should remain on NDTM until scheduled term date, unless deemed as "Essential Drug" at P&T
- Essential drugs cannot be excluded and it will be termed from NDTM exclusion list per DI recommendations

OPTUM Rx®

Formulary Management Committee (FMC) Meeting

Trang Tran

August 29, 2018

OPTUMRx®

FMC Approved

Diabetes

Rationale for Review:

- 2019 Contract Changes
- Revise current ST requirements: Add Tresiba to list of step 1 alternatives.
- Effective 1/1/19

Current UM:

Therapeutic Category	Current UM: ST	Recommended Changes
Basal Insulin	**Preferred Agents:** Lantus, Levemir, Toujeo **Non-preferred Agents:** Basaglar	**Preferred Agents:** Lantus, Levemir, Toujeo, Tresiba **Non-preferred Agents:** Basaglar

Formulary Management Committee (FMC) Meeting

Tina Chuong

January 23, 2019

OPTUMRx®

Essential Class - 3

FMC Approved

Recommendation: At least 1 agent within the class should be formulary; consider clinical notes

Class	Clinical Notes
Long-acting insulin analogs	
[redacted]	

Note: Refer to the P&T Decision Grid for all of the agents within each class. Refer to the Agenda Summary/FMC Grid for the clinical notes.

Formulary Management Committee (FMC) Meeting

Tina Chuong

May 29, 2019

OPTUMRx®

Approved Ad-hoc FMC Proposals

[redacted]

- Humalog (insulin lispro)

Humalog (insulin lispro) – Summary

RATIONALE FOR REVIEW

- Humalog ABA products are expected to launch in early May 2019
- Reevaluation of the Humalog brand and ABA products needed to address market dynamics
    - Additional rebate opportunities available for the various benefit designs

FINANCIAL EVALUATION

- For OptumRx Commercial LOB, Humalog PMPM = Redacted
- Premium: net costs of Humalog brands are lower than the ABAs
- Select Comprehensive: net costs of Humalog brands and ABAs are comparable
- All other plan types: net costs of Humalog ABAs are lower than brands

KEY POINTS

- For Premium, recommend to continue the exclusion of Humalog ABA products as the brands are the lowest net cost products
- For Select, recommend to downtier Humalog ABA products to T2 with ST, which will help drive to lower cost products
- The strategy is to balance client agreements while passing the savings to clients and members

FMC Approved via email vote

Humalog (insulin lispro) – Financial Analysis

Drug	Tier/UM					PRICING DATA	
Drug Name	Select		Premium		Eff Date	WAC/ Rx	Net WAC/ Rx
	Current	New	Current	New			
Humalog vial	2	2	2	2	n/a	$288.44	Redacted
Humalog Kwikpen	2	2	2	2	n/a	$404.52	Redacted
Insulin Lispro vial (ABA)	3^	2^	EXCL	EXCL	5/2/2019	$144.27	Redacted
Insulin Lispro Kwikpen (ABA)	3^	2^	EXCL	EXCL	5/2/2019	$202.26	Redacted

^ Step Therapy (step through both Humalog and Novolog brand products pending P&T approval)

Premium: Remove from NDTM early and add to PEL effective 5/2/19

OPTUMRx®

FIFTH (5TH) AMENDMENT TO THE
OPTUMRX, INC.
REBATE AGREEMENT

This FIFTH (5th) AMENDMENT TO THE OPTUMRX, INC. REBATE AGREEMENT ("Amendment"), dated as of July 1, 2015 ("Amendment Effective Date"), is made and entered into by and between, sanofi-aventis U.S. LLC, on behalf of itself and its affiliate Genzyme Corporation, ("Manufacturer"), and OptumRx, Inc. ("Administrator"), on behalf of itself and its Contracting Payors, with reference to the following facts:

RECITALS

WHEREAS, Manufacturer and Administrator entered into that certain Rebate Agreement (as previously amended, the "Agreement"), with an effective date of January 1, 2013, providing, among other things, for Manufacturer to pay rebates to Administrator on units of certain Manufacturer Drugs; and

WHEREAS, Manufacturer and Administrator mutually desire to amend the Agreement as stated below.

NOW THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Manufacturer and Administrator hereby agree to amend the Agreement as follows:

1. Exhibit A Rebate and Administrative Fee Schedule of the Agreement is hereby deleted its entirety and replaced with the following new Exhibit A Rebate and Administrative Fee Schedule attached hereto.

2. Exhibit D of the Agreement is hereby deleted in its entirety and replaced with the following new Exhibit D attached hereto.

3. Effect of this Amendment. Capitalized terms used but not defined in this Amendment shall have the meanings ascribed to them in the Agreement. Except as otherwise amended by this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect. In the event there is any inconsistency or conflict between the provisions in this Amendment and those in the Agreement, the provisions in this Amendment shall supersede and control.

SIGNATURE PAGE FOLLOWS

IN WITNESS WHEREOF, Manufacturer and Administrator have executed this Amendment as of the date first written above.

ADMINISTRATOR

By: Robert C. Lahman

Name: Robert C. Lahman

Title: S.V.P., Industry Relations

Date: 12-4-2015

MANUFACTURER

By: James Borneman

Name: James Borneman

Title: Vice President Strategic Pricing & Contracting

Date: 12/8/15

MANUFACTURER

By: Gregory Rubert

Name: Gregory Rubert

Title: Sr. Director Managment Reporting

Date: 12/8/15

IRC

EXHIBIT A
REBATE AND ADMINISTRATIVE FEE SCHEDULE

1. Definitions

1.1 Benefit Design

i. "Covered" means a Benefit design that does not qualify as a Managed or Highly Managed Benefit design.

ii. "Managed" means a Benefit design characterized by a Formulary under which the Contracting Payor directly or indirectly influences availability or gives preference in dispensing decisions of Drugs in the same Defined Drug Market through monetary restrictions; for example, differential dollar Consumer co-payments for generic, branded Preferred and branded non-Preferred status as defined and determined by the Contracting Payor, where branded non-Preferred Drugs and branded Preferred Drugs have no less than an average co-payment differential of ten dollars ($10.00), or an equivalent co-insurance percentage differential.

iii. "Highly Managed" means a Benefit design characterized by a Formulary under which a Contracting Payor also has the ability, and in fact exercises such ability, to directly or indirectly influence availability or give preference in dispensing decisions of Drugs in the same Defined Drug Market through hard edit prior authorizations, NDC locks for non-Preferred Drugs, step edits, or other similar mechanisms where certain Drugs are intended to be more restricted in availability than other Preferred Drugs in the same Defined Drug Market.

1.2 "Formulary Status" means the position a Manufacturer Drug has on Formulary. A Formulary Status that is designated as 1 of [X] means that the Manufacturer Drug is 1 of [X] single-source branded Drugs in the Defined Drug Market with the applicable Formulary Status; provided that for the purpose of determining if this condition for Rebate has been met, line extensions of Drugs within the Manufacturer Drug's Defined Drug Market manufactured by the same manufacturer shall be considered as one Drug (e.g. [redacted]

1.3 "Preferred" means (i) a Drug is covered by a Benefit and is adjudicated in the lowest copayment tier for branded Drugs for the applicable Defined Drug Market and where the copayment amount or coinsurance percentage for such Drug is lower than that of Drugs in the Defined Drug Market designated as "non-preferred", or (ii) a Drug is covered by a Benefit where the Drugs designated as "preferred" are covered by the Benefit and the Drugs excluded from Formulary or designated on Formulary as "non-preferred" or "excluded" are not covered by the Benefit or (iii) for Covered Benefit designs only, a Drug is covered by a Benefit where Drugs designated as "preferred" are covered by the Benefit and Manufacturer Drug is no more restricted in its availability than other branded Drugs in the same Defined Drug Market.

1.4 "Unrestricted Access" when referring to Lantus means a Manufacturer Drug is covered by a Benefit with no Utilization Controls. But when referring to all other Manufacturer Drugs, means a Manufacturer Drug covered by a Benefit with no Utilization Controls, except for the allowances set forth in 1.5 Utilization Controls.

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1.5 "Utilization Controls" mean, unless such Utilization Controls applied are clinically appropriate in accordance with FDA labeling or indications and/or applied to all Drugs in the applicable Defined Drug Market, i) counter-detailing or counter-promoting, ii) switching or therapeutic substitution, iii) hard edit prior authorization, iv) NDC lock, v) step edit, and vi) quantity limit based upon package insert. For purposes of this definition, "Utilization Controls" excludes communications or education programs designed to encourage the use of generic Drugs, and any aspects of Administrator's or Contracting Payor's communication, website, or other activity whereby Consumers have access to or are made aware of prices of Drugs and/or the availability of over-the-counter products for purposes of managing Consumer cost sharing amounts.

2. Rebate Calculation

Rebates for each Manufacturer Drug will be based upon the Formulary status of the Manufacturer Drug at the time such Manufacturer Drug is dispensed. Rebates will be calculated on a per Unit dispensed basis. For each month, the Rebates for each Manufacturer Drug shall be calculated as follows:

Rebate = (Unit(s) of Manufacturer Drug) x (WAC) x (Total Rebate Rate for the applicable Manufacturer Drug)

3. Administrative Fee. The Administrative Fee rate is 3% for each Rebate eligible Unit of Manufacturer Drug. The Administrative Fee shall not be charged on QRPDP, Managed Medicaid and CHIP utilization, and any other utilization where prohibited by Law. For each month, the Administrative Fee shall be calculated as follows:

Administrative Fee = (Unit(s) of Manufacturer Drug) x (WAC) x (Administrative Fee rate %)

4. Protection of Rebate Amount.

4.1 [redacted] and Lantus Price Protection

Rebate rates are subject to automatic adjustment in the event the "WAC per Unit" for Manufacturer Drug is increased to a price that is greater than the "Allowed WAC per Unit" during any corresponding month of the Agreement. The initial "Allowed WAC per Unit" for a Manufacturer Drug is calculated by multiplying the "WAC per Unit" as of the date set forth in the Rebate terms below ("Baseline WAC Date") for the applicable Manufacturer Drug by (100% plus the "Price Protection" factor). The "Net WAC per Unit" is calculated by multiplying the "WAC per Unit" by (100% minus the Base Rebate Rate %). The "Base Rebate Rate %" is the Rebate percentage for the Manufacturer Drug set forth in the applicable Rebate tables below. The "Allowed WAC per Unit" for subsequent Contract Years is calculated by multiplying the "Allowed WAC" for the previous Contract Year by (100% plus the "Price Protection" factor). The initial Allowed

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WAC per Unit for a Manufacturer Drug will apply during the 12-month period following the Manufacturer Drug's Contract Year Start Date (which date is set forth in the Rebate terms below). Such initial 12-month period and each subsequent 12- month period is referred to as the applicable Manufacturer Drug's "Contract Year". The "Net Allowed WAC per Unit" is calculated by multiplying the "Allowed WAC per Unit" by (100% minus the Base Rebate Rate %). The "Price Protection" factor is set forth in the Rebate terms below for the applicable Manufacturer Drug. Effective as of the date the "WAC per Unit" first exceeds the "Allowed WAC per Unit" and continuing for the remainder of that Contract Year, subject to further adjustments in accordance with this Section 4.1 of this Exhibit A Rebate and Administrative Fee Schedule, an "Additional Rebate Rate" will be provided. The "Additional Rebate Rate" is calculated by determining the amount, if any, that the Current Net WAC Per Unit for a given month exceeds the Net Allowed WAC per Unit for the same month, divided by the then-current WAC per Unit. The resulting percentage is the "Additional Rebate Rate" and is added to the "Base Rebate Rate %" to produce a "Total Rebate Rate" that applies during that month. The Additional Rebate Rate will be paid each month in which the "Current Net WAC per Unit" exceeds the "Net Allowed WAC per Unit". The Additional Rebate Rate is re-calculated each month. For avoidance of doubt, the Total Rebate Rate calculation for [redacted] is subject to the terms of Section 2.2.6 Best Price. [redacted]

*The terms "Current Net WAC" and "Net Allowed WAC" are solely used for purposes to explain the calculation of price protection in this Agreement. These terms are not used outside of this Agreement and, furthermore, are not meant to define or describe any pricing terms of a Manufacturer Drug.

[redacted] AND LANTUS EXAMPLE 1:

Price Protection factor	6%	Year 1 Price increase 10%						Year 2 Price increase 10%						Year 3 Price increase 10%				
	Assumed WAC as of 12/31/2013	Jan. 2014	Feb. 2014	Mar. 15 2014		Dec. 2014		Jan. 2015	Feb. 2015	Mar. 2015		Dec. 2015		Jan. 2016	Feb. 2016	Mar. 2016		Dec. 2016
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60	→	6.60		6.60	6.60	7.26	→	7.26		7.26	7.26	7.99	→	7.99
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36		6.36	→	6.74	6.74	6.74		6.74	→	7.15	7.15	7.15		7.15
Current WAC/ Unit (New NDC)									6.60	7.26	→	7.26		7.26	7.26	7.99	→	7.99
Allowed WAC/ Unit (New NDC)									6.74	6.74		6.74	→	7.15	7.15	7.15		7.15
Current Net WAC / Unit		5.40	5.40	5.94		5.94		5.94	5.94	6.53		6.53		6.53	6.53	7.19		7.19
Net Allowed WAC / Unit	5.40	5.72	5.72	5.72		5.72		6.07	6.07	6.07		6.07		6.43	6.43	6.43		6.43
Additional Rebate :		$0.00	$0.00	$0.22		$0.22		$0.00	$0.00	$0.47		$0.47		$0.10	$0.10	$0.76		$0.76
Additional Rebate Rate.		0.0%	0.0%	3.3%		3.3%		0.0%	0.0%	6.4%		6.4%		1.4%	1.4%	9.5%		9.5%
Base Rebate Rate %	10.0%	10.0%	10.0%	10.0%		10.0%		10.0%	10.0%	10.0%		10.0%		10.0%	10.0%	10.0%		10.0%
Total Rebate Rate	10.0%	10.0%	10.0%	13.3%	→	13.3%		10.0%	10.0%	16.4%	→	16.4%		11.4%	11.4%	19.5%	→	19.5%

If a new NDC ("New NDC") matching the labeler code and product code ("9-digit National Drug Code" or "NDC-9") of a Manufacturer Drug covered by this Agreement comes into existence after the date that such Manufacturer Drug becomes covered by this Agreement, the Additional Rebate Rate for such New NDC(s) will be calculated consistent with the preceding paragraph except that (i) the Net Allowed WAC per Unit for the Existing NDCs (defined below) will apply to the New NDC(s) during each billing period and (ii) the Net WAC per Unit of such New NDC(s) will be adjusted to account for differences, if any, in days of therapy, unit size, strength, or similar factors, between the New NDC(s) and their corresponding Existing NDCs, which adjustment(s) the parties will work in good faith to establish. As used herein, the term "Existing NDCs" refers to the Manufacturer Drug NDC(s) covered by the Agreement on the day prior to the date that the applicable New NDC comes into existence that has the highest Net Allowed WAC per Unit; provided, however, that either party may elect for the Existing NDC to be the NDC that most closely resembles the New NDC with respect to days of therapy, unit size, strength, or similar factors, which the parties will mutually determine working together in good faith. Example 2 below demonstrates the Additional Rebate Rate calculation for a New NDC.

[redacted] AND LANTUS EXAMPLE 2:

New NDC introduced Feb14, subject to same PP rate increase as current NDCs.
New NDC WAC normalized to Current NDC WAC, same Baseline WAC date
Price Protection factor: 6%

	Assumed WAC as of 12/31/2012	Year 1 Price increase 10%					Year 2 Price increase 10%					Year 3 Price increase 10%				
		Jan. 2013	Feb. 2013	Mar. 15 2013		Dec. 2013	Jan. 2014	Feb. 2014	Mar. 2014		Dec. 2014	Jan. 2015	Feb. 2015	Mar. 2015		Dec. 2015
Current WAC/ Unit (Current NDC)	6.00	6.00	6.00	6.60	→	6.60	6.60	6.60	7.26	→	7.26	7.26	7.26	7.99	→	7.99
Allowed WAC/ Unit (Current NDC)		6.36	6.36	6.36	→	6.36	→ 6.74	6.74	6.74	→	6.74	→ 7.15	7.15	7.15	→	7.15
Current WAC/ Unit (New NDC)								10.50	11.55	→	11.55	11.55	11.55	12.71	→	12.71
Current Normalized WAC/ Unit (New NDC)								9.90	10.89	→	10.89	10.89	10.89	11.98	→	11.98
Allowed WAC/ Unit (New NDC)								10.11	10.11		10.11	→ 10.72	10.72	10.72		10.72
Current Net WAC / Unit (Current NDC)		5.40	5.40	5.94		5.94	5.94	5.94	6.53		6.53	6.53	6.53	7.19		7.19
Net Allowed WAC / Unit (Current NDC)	5.40	5.72	5.72	5.72		5.72	6.07	6.07	6.07		6.07	6.43	6.43	6.43		6.43
Current Net WAC / Unit (New NDC)								9.45	10.40		10.40	10.40	10.40	11.43		11.43
Net Allowed WAC / Unit (New NDC)								9.10	9.10		9.10	9.65	9.65	9.65		9.65
Additional Rebate (Current NDC) :		$0.00	$0.00	$0.22		$0.22	$0.00	$0.00	$0.47		$0.47	$0.10	$0.10	$0.76		$0.76
Additional Rebate Rate (Current NDC)		0.0%	0.0%	3.3%		3.3%	0.0%	0.0%	6.4%		6.4%	1.4%	1.4%	9.5%		9.5%
Additional Rebate (New NDC)								$0.35	$1.29		$1.29	$0.75	$0.75	$1.79		$1.79
Additional Rebate Rate (New NDC)								3.3%	11.2%		11.2%	6.5%	6.5%	14.1%		14.1%
Base Rebate Rate %:	10.0%	10.0%	10.0%	10.0%		10.0%	10.0%	10.0%	10.0%		10.0%	10.0%	10.0%	10.0%		10.0%
Total Rebate Rate (Current NDC)	10.0%	10.0%	10.0%	13.3%	→	13.3%	10.0%	10.0%	16.4%	→	16.4%	11.4%	11.4%	19.5%	→	19.5%
Total Rebate Rate (New NDC)					→			13.3%	21.2%	→	21.2%	16.5%	16.5%	24.1%	→	24.1%

	Current WAC	DOT (can be changed to whatever the 'normalization' factor should be)	Normalized WAC / per DOT	WAC in effect for New NDC
Current NDC	6.60	60	0.11	
New NDC	10.50	90		9.90

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4.2 [redacted], Toujeo and [redacted] Price Protection

Rebate rates are subject to automatic adjustment in the event the "WAC per Unit" for Manufacturer Drug is increased to a price that is greater than the "Allowed WAC per Unit" during any corresponding month of the Agreement. The "Allowed WAC per Unit" for 2013 is calculated by multiplying the "WAC per Unit" as of the date set forth in the Rebate terms below ("Baseline WAC Date") for the applicable Manufacturer Drug by (100% plus the "Price Protection" factor). The "Net WAC per Unit" is calculated by multiplying the "WAC per Unit" by (100% minus the Base Rebate Rate %). The "Base Rebate Rate %" is the Rebate percentage for the Manufacturer Drug set forth in the Rebate tables below. The initial Allowed WAC per Unit for a Manufacturer Drug will apply during the 12-month period following the Agreement's Effective Date. Such initial 12-month period and each subsequent 12-month period is referred to as the applicable Manufacturer Drug's "Contract Year". The "Allowed WAC per Unit" for subsequent Contract Years is calculated by multiplying the "WAC per Unit" in effect for the applicable Manufacturer Drug on December 31 of the Contract Year immediately prior to the current Contract Year by (100% plus the "Price Protection" factor). The "Net Allowed WAC per Unit" is calculated by multiplying the "Allowed WAC per Unit" by (100% minus the Base Rebate Rate %). For avoidance of doubt: (a) the first pricing period shall be Contract Year 2013; (b) the second pricing period shall be Contract Year 2014; (c) the third pricing period shall be Contract Year 2015; (d) the fourth pricing period shall be Contract Year 2016; and (e) the fifth pricing period shall be Contract Year 2017. Price increases in one pricing period shall not be added to price increases in another pricing period for purposes of determining Additional Rebate Rates. The "Price Protection" factor is set forth in the Rebate terms below for the applicable Manufacturer Drug. Effective as of the date the "WAC per Unit" first exceeds the "Allowed WAC per Unit" and continuing for the remainder of that Contract Year, subject to further adjustments in accordance with this Section 4.2 of this Exhibit A Rebate and Administrative Fee Schedule, an "Additional Rebate Rate" will be provided. The "Additional Rebate Rate" is calculated by determining the amount, if any, that the Net WAC Per Unit for a given month exceeds the Net Allowed WAC per Unit for the same month, divided by the then-current WAC per Unit. The resulting percentage is the "Additional Rebate Rate" and is added to the "Base Rebate Rate %" to produce a "Total Rebate Rate" that applies during that month. The Additional Rebate Rate will be paid each month in which the "Current Net WAC Per Unit" exceeds the "Net Allowed WAC per Unit". The Additional Rebate Rate is re-calculated each month. For avoidance of doubt, the Total Rebate Rate calculation is subject to the terms of Section 2.2.6 Best Price. [redacted]

*The terms "Current Net WAC" and "Net Allowed WAC" are solely used for purposes to explain the calculation of price protection in this Agreement. These terms are not used outside of this Agreement and, furthermore, are not meant to define or describe any pricing terms of a Manufacturer Drug.

[redacted], TOUJEO, AND [redacted] EXAMPLE 1:

Price Protection factor:	6%	Year 1 Price increase 10%				Year 2 Price increase 10%					
	Assumed WAC as of 12/31/2012	Jan. 2013	Feb. 2013	Mar. 15 2013	Dec. 2013	Jan. 2014	Feb. 2014	Mar. 2014	Dec. 2014	Jan. 2015	Feb. 2015
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60	6.60	6.60	6.60	7.26	7.26	7.26	7.26
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36	6.36	7.00	7.00	7.00	7.00	7.70	7.70
Current WAC/ Unit (New NDC)							6.60	7.26	7.26	7.26	7.26
Allowed WAC/ Unit (New NDC)							7.00	7.00	7.00	7.70	7.70
Current Net WAC / Unit		5.40	5.40	5.94	5.94	5.94	5.94	6.53	6.53	6.53	6.53
Net Allowed WAC / Unit	5.40	5.72	5.72	5.72	5.72	6.30	6.30	6.30	6.30	6.93	6.93
Additional Rebate :		$0.00	$0.00	$0.22	$0.22	$0.00	$0.00	$0.24	$0.24	$0.00	$0.00
Additional Rebate Rate:		0.0%	0.0%	3.3%	3.3%	0.0%	0.0%	3.3%	3.3%	0.0%	0.0%
Base Rebate Rate %:	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
Total Rebate Rate	10.0%	10.0%	10.0%	13.3%	13.3%	10.0%	10.0%	13.3%	13.3%	10.0%	10.0%

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If a new NDC ("New NDC") matching the labeler code and product code ("9-digit National Drug Code" or "NDC-9") of a Manufacturer Drug covered by this Agreement comes into existence after the date that such Manufacturer Drug becomes covered by this Agreement, the Additional Rebate Rate for such New NDC(s) will be calculated consistent with the preceding paragraph except that (i) the Net Allowed WAC per Unit for the Existing NDCs (defined below) will apply to the New NDC(s) during each billing period and (ii) the Net WAC per Unit of such New NDC(s) will be adjusted to account for differences, if any, in days of therapy, unit size, strength, or similar factors, between the New NDC(s) and their corresponding Existing NDCs, which adjustment(s) the parties will work in good faith to establish. As used herein, the term "Existing NDCs" refers to the Manufacturer Drug NDC(s) covered by the Agreement on the day prior to the date that the applicable New NDC comes into existence that has the highest Net Allowed WAC per Unit; provided, however, that either party may elect for the Existing NDC to be the NDC that most closely resembles the New NDC with respect to days of therapy, unit size, strength, or similar factors, which the parties will mutually determine working together in good faith. Example 2 below demonstrates the Additional Rebate Rate calculation for a New NDC.

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[redacted] TOUJEO, AND [redacted] EXAMPLE 2:

New NDC introduced Feb14, subject to same PP rate increase as Existing NDCs.
Same WAC/unit, same Baseline WAC date.
Price Protection factor: 6%

Year 1 Price increase 10%

Allowed was 6.74

Year 2 Price increase 10%

	Assumed WAC as of 12/31/2012	Jan. 2013	Feb. 2013	Mar. 15 2013	Dec. 2013	Jan. 2014	Feb. 2014	Mar. 2014	Dec. 2014	Jan. 2015	Feb. 2015
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60 →	6.60	6.60	6.60	7.26 →	7.26	7.26	7.26
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36	6.36	7.00	7.00	7.00	7.00	7.70	7.70
Current WAC/ Unit (New NDC)							10.50	11.55 →	11.55	11.55	11.55
Current Normalized WAC/ Unit (New NDC)							9.90	10.89	10.89	10.89	10.89
Allowed WAC/ Unit (New NDC)							10.49	10.49	10.49	12.24	12.24
Current Net WAC / Unit (Existing NDC)		5.40	5.40	5.94	5.94	5.94	5.94	6.53	6.53	6.53	6.53
Net Allowed WAC / Unit (Existing NDC)	5.40	5.72	5.72	5.72	5.72	5.30	6.30	6.30	6.30	6.93	6.93
Current Net WAC / Unit (New NDC)							9.45	10.40	10.40	10.40	10.40
Net Allowed WAC / Unit (New NDC)							9.44	9.44	9.44	11.02	11.02
Additional Rebate (Existing NDC):		$0.00	$0.00	$0.22	$0.22	$0.00	$0.00	$0.24	$0.24	$0.00	$0.00
Additional Rebate Rate (Existing NDC):		0.0%	0.0%	3.3%	3.3%	0.0%	0.0%	3.3%	3.3%	0.0%	0.0%
Additional Rebate (New NDC) :							$0.01	$0.95	$0.95	$0.00	$0.00
Additional Rebate Rate (New NDC):							0.1%	8.2%	8.2%	0.0%	0.0%
Base Rebate Rate %:	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
Total Rebate Rate (Existing NDC)	10.0%	10.0%	10.0%	13.3% →	13.3%	10.0%	10.0%	13.3% →	13.3%	10.0%	10.0%
Total Rebate Rate (New NDC)							10.1%	18.2% →	18.2%	10.0%	10.0%

	Current WAC	DOT (can be changed to whatever the 'normalization' factor should be)	Normalized WAC / per DOT	WAC in effect for New NDC
Existing NDC	6.60	60	0.11	
New NDC	10.50	90		9.90

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5. Rebate Terms – non-QRPDP, non-Managed Medicaid and non-CHIP

5.1 PREFERRED

Option A: (Effective 7/1/2015 through 6/30/2017)

Manufacturer Drug Name: Lantus*			
Benefit Design:	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	42%*	n/a	n/a
Administrative Fee	3%	n/a	n/a
Price Protection factor	7%	n/a	n/a
Baseline WAC Date:	1/1/14	n/a	n/a
Contract Year Start Date	7/1/14	n/a	n/a

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

Conditions to Rebate:

1. All NDC's of Manufacturer Drug are on Formulary with Unrestricted Access in tier 1, 2 or 3 as of the date of dispensing. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and
2. A certain package form of Lantus may be disadvantaged to one (1) comparable package form of another Drug in Lantus' Defined Drug Market, provided all Lantus package forms are still listed and adjudicated with Unrestricted Access in accordance with Condition 1 above. In the event that a package form of Lantus is disadvantaged to more than one (1) comparable package form, all NDC's of Lantus, i.e. both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples are provided for clarification of rebate eligibility and not to be considered an exhaustive list:

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Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	3	Non-preferred	3	Non-preferred
Levemir	Vial	1	Preferred	1	Preferred
Comp #3	Vial	3	Non-preferred	3	Non-preferred
Lantus	Pen	3	Non-preferred	3	Non-preferred
Levemir	Pen	1	Preferred	3	Non-preferred
Comp #3	Pen	3	Non-preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	3	Non-preferred	3	Non-preferred
Levemir	Vial	1	Preferred	1	Preferred
Comp #3	Vial	2	Preferred	3	Non-preferred
Lantus	Pen	3	Non-preferred	3	Non-preferred
Levemir	Pen	1	Preferred	1	Preferred
Comp #3	Pen	2	Preferred	2	Preferred

Option B: (Effective /1/2015 through 6/30/2017)

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 2	n/a	12%*	7%*
Administrative Fee		n/a	3%	3%
Price Protection factor		n/a	7%	7%
Baseline WAC Date:		n/a	1/1/14	1/1/14
Contract Year Start Date		n/a	7/1/14	7/1/14

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

Conditions to Rebate:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; and
2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and
3. No package form of Lantus will be disadvantaged to a comparable package form of any other Drug in Lantus' Defined Drug Market. In the event that a package form of Lantus is disadvantaged to a comparable package form, all NDC's of Lantus, i.e. both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples

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are provided for clarification of Rebate eligibility and not to be considered an exhaustive list:

Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	1	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	1	Preferred	2	Preferred
Levemir	Pen	1	Preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	2	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	3	Non-preferred	2	Preferred
Levemir	Pen	3	Non-preferred	2	Preferred

5.2 PREFERRED

5.2(a) (Effective 7/1/2015 through 6/30/2017)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 2 or less	47%	47%	47%
Base Rebate Rate %	1 of 3	42%	42%	42%
Administrative Fee		3%	3%	3%
Price Protection factor		n/a	n/a	n/a
Baseline WAC Date:		n/a	n/a	n/a

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[redacted]

5.3 PREFERRED – EXCLUSION

5.3.1 Only for Benefit Contracts with less than two (2) million Consumers

5.3.1 (a) (Effective 7/1/2015 through 12/31/2015)

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	43%*	N/A	N/A
Administrative Fee		3%	N/A	N/A
Price Protection factor		7%	N/A	N/A

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Baseline WAC Date:		1/1/14	N/A	N/A
Contract Year Start Date		7/1/14	N/A	N/A

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

5.3.1 (b) (Effective 7/1/2015 through 12/31/2015)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	57%	N/A	N/A
Administrative Fee		3%	N/A	N/A
Price Protection factor		N/A	N/A	N/A
Baseline WAC Date:		N/A	N/A	N/A
Contract Year Start Date		N/A	N/A	N/A

Conditions to Rebate for Rebate Tables 5.3(a) Lantus and 5.3(b) Apidra:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; provided that Drugs manufactured, marketed or distributed by one manufacturer in the Defined Drug Market will be considered as one Drug. All other competitive Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and
2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus and Apidra shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus and Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus and Apidra pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to quantity limit consistent with their respective package inserts.

5.3.2 Only for Benefit Contracts with less than three and one-half (3.5) million Consumers

5.3.2 (a) (Effective 1/1/2016 through 12/31/2017)

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary**	**Highly**	**Managed**	**Covered**

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	Status	Managed		
Base Rebate Rate %	1 of 1	43%*	N/A	N/A
Administrative Fee		3%	N/A	N/A
Price Protection factor		7%	N/A	N/A
Baseline WAC Date:		1/1/14	N/A	N/A
Contract Year Start Date		7/1/14	N/A	N/A

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

5.3.2 (b) (Effective 1/1/2016 through 12/31/2017)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	57%	N/A	N/A
Administrative Fee		3%	N/A	N/A
Price Protection factor		N/A	N/A	N/A
Baseline WAC Date:		N/A	N/A	N/A
Contract Year Start Date		N/A	N/A	N/A

Conditions to Rebate for Rebate Tables 5.3(a) Lantus and 5.3(b) Apidra:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; provided that Drugs manufactured, marketed or distributed by one manufacturer in the Defined Drug Market will be considered as one Drug. All other competitive Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and
2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus and Apidra shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus and Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus and Apidra pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to quantity limit consistent with their respective package inserts.

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[redacted]

6. Rebate Terms – QRPDP and utilization ineligible for Administrative Fees per Section 3 of this Exhibit A (other than Managed Medicaid and CHIP).

6.1 PREFERRED

Option A (Effective 7/1/2015 through 6/30/2017):

Manufacturer Drug Name: Lantus*			
Benefit Design:	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	45%*	n/a	n/a
Administrative Fee	0%	n/a	n/a
Price Protection factor	7%	n/a	n/a
Baseline WAC Date:	1/1/14	n/a	n/a
Contract Year Start Date	7/1/14	n/a	n/a

*The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative

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Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6 ("Best Price").

Conditions to Rebate:

1. All NDC's of Manufacturer Drug are on Formulary with Unrestricted Access in tier 1, 2 or 3 as of the date of dispensing. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and
2. A certain package form of Lantus may be disadvantaged to one (1) comparable package form of another Drug in Lantus' Defined Drug Market, provided all Lantus package forms are still listed and adjudicated with Unrestricted Access in accordance with Condition 1 above. In the event that a package form of Lantus is disadvantaged to more than one (1) comparable package form, all NDC's of Lantus, i.e. both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples are provided for clarification of rebate eligibility and not to be considered an exhaustive list:

Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	3	Non-preferred	3	Non-preferred
Levemir	Vial	1	Preferred	1	Preferred
Comp #3	Vial	3	Non-preferred	3	Non-preferred
Lantus	Pen	3	Non-preferred	3	Non-preferred
Levemir	Pen	1	Preferred	3	Non-preferred
Comp #3	Pen	3	Non-preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	3	Non-preferred	3	Non-preferred
Levemir	Vial	1	Preferred	1	Preferred
Comp #3	Vial	2	Preferred	3	Non-preferred
Lantus	Pen	3	Non-preferred	3	Non-preferred
Levemir	Pen	1	Preferred	1	Preferred
Comp #3	Pen	2	Preferred	2	Preferred

Option B (Effective 7/1/2015 through 6/30/2017):

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 2	n/a	15%*	10%*
Administrative Fee		n/a	0%	0%
Price Protection factor		n/a	7%	7%
Baseline WAC Date:		n/a	1/1/14	1/1/14
Contract Year Start Date		n/a	7/1/14	7/1/14

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* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

Conditions to Rebate:

1. All NDC's of Manufacturer Drug were on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; and
2. A Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and
3. No package form of Lantus will be disadvantaged to a comparable package form of any other Drug in Lantus' Defined Drug Market. In the event that a package form of Lantus is disadvantaged to a comparable package form, all NDC's of Lantus, both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples are provided for clarification of Rebate eligibility and not to be considered an exhaustive list:

Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	1	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	1	Preferred	2	Preferred
Levemir	Pen	1	Preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	2	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	3	Non-preferred	2	Preferred
Levemir	Pen	3	Non-preferred	2	Preferred

6.2 PREFERRED

6.2(a) (Effective 7/1/2015 through 6/30/2017)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 2 or less	50%	50%	50%
Rebate %	1 of 3	45%	45%	45%
Administrative Fee		0%	0%	0%
Price Protection		n/a	n/a	n/a

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factor				
Baseline WAC Date:		n/a	n/a	n/a

[redacted]

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[redacted]

6.3 PREFERRED – EXCLUSION

6.3.1 Only for Benefit Contracts with less than three and one-half (3.5) million Consumers.

6.3.1 (a) (Effective 1/1/2016 through 6/30/2017)

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	46%*	N/A	N/A
Administrative Fee		0%	N/A	N/A
Price Protection factor		7%	N/A	N/A
Baseline WAC Date:		1/1/14	N/A	N/A
Contract Year Start Date		7/1/14	N/A	N/A

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

6.3.1 (b) (Effective 1/1/2016 through 6/30/2017)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	60%	N/A	N/A
Administrative Fee		0%	N/A	N/A
Price Protection factor		N/A	N/A	N/A
Baseline WAC Date:		N/A	N/A	N/A
Contract Year Start Date		N/A	N/A	N/A

Conditions to Rebate for Rebate Tables 6.3.1 (a) Lantus and 6.3.1 (b) Apidra:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; provided that Drugs manufactured, marketed or distributed by one manufacturer in the Defined

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Drug Market will be considered as one Drug. All other competitive Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and

2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus and Apidra shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus and Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus and Apidra pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to quantity limit consistent with their respective package inserts.

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Manufacturer Drug Name: Lantus*		
	Formulary Status	**Managed Medicaid**
Base Rebate Rate %	1 of 2	5%*
Administrative Fee		0%
Price Protection factor		n/a
Baseline WAC Date:		n/a

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

[redacted]

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[redacted]

Conditions to Rebate for Rebate Tables 7.1 Lantus, [redacted]

1. Manufacturer Drug was on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; and
2. A Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and
3. Notwithstanding the foregoing, the following Utilization Controls are permitted for the specifically identified Manufacturer Drug:

[redacted]

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[redacted]

7.6 (Effective 1/1/2016 through 12/31/16)

Manufacturer Drug Name: Toujeo		
Benefit Design:	**Formulary Status**	**Managed Medicaid**
Base Rebate Rate %	1 of 1	15%
Administrative Fee		0%
Price Protection factor		9.0%
Baseline WAC Date:		12/31/15

Conditions to Rebate for Rebate Tables 7.6 Toujeo:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; provided that Drugs manufactured, marketed or distributed by one manufacturer in the Defined Drug Market will be considered as one Drug. All other competitive Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and
2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting

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Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Toujeo shall not violate this condition: (i) a quantity limit of no more than 225mls per 3-month supply on Toujeo provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Toujeo's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Toujeo's Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and

3. Drugs within the Defined Drug Market must be subject to a step edit that requires the use of Toujeo for those Consumers who previously have never filled a prescription for Drugs within the Defined Drug Market.

7.7 (Effective 1/1/2017 through 12/31/17)

Manufacturer Drug Name: Toujeo		
Benefit Design:	**Formulary Status**	**Managed Medicaid**
Base Rebate Rate %	1 of 1	15%
Administrative Fee		0%
Price Predictability factor		9.0%
Baseline WAC Date:		12/31/16

Conditions to Rebate for Rebate Tables 7.7 Toujeo:

1. All NDC's of Toujeo are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing. All other brand name Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and
2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Toujeo shall not violate this condition: (i) a quantity limit of no more than 225mls per 3-month supply on Toujeo provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Toujeo's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Toujeo's Defined Drug Market are subject to quantity limit consistent with their respective package inserts.

8. Rebate Terms – CHIP a stand-alone Federal healthcare program that operates independent from the Medicaid program as set forth in Article 2 Payment and Billing, Section 2.2.4

8.1 (Effective 7/1/2015 through 6/30/2017)

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Manufacturer Drug Name: Lantus*		
Benefit Design:	**Formulary Status**	**CHIP**
Base Rebate Rate %	1 of 2	45%*
Administrative Fee		0%
Price Protection factor		7%
Baseline WAC Date:		1/1/14
Contract Year Start Date		7/1/14

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

8.2 (Effective 7/1/2015 through 6/30/2017)

Manufacturer Drug Name: Apidra		
Benefit Design:	**Formulary Status**	**CHIP**
Base Rebate Rate %	1 of 2 or less	50%
Base Rebate Rate %	1 of 3	45%
Administrative Fee		0%
Price Protection factor		n/a
Baseline WAC Date:		n/a

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[redacted]

1. Manufacturer Drug was on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; and
2. A Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus and Apidra shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus

and Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus and Apidra pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and

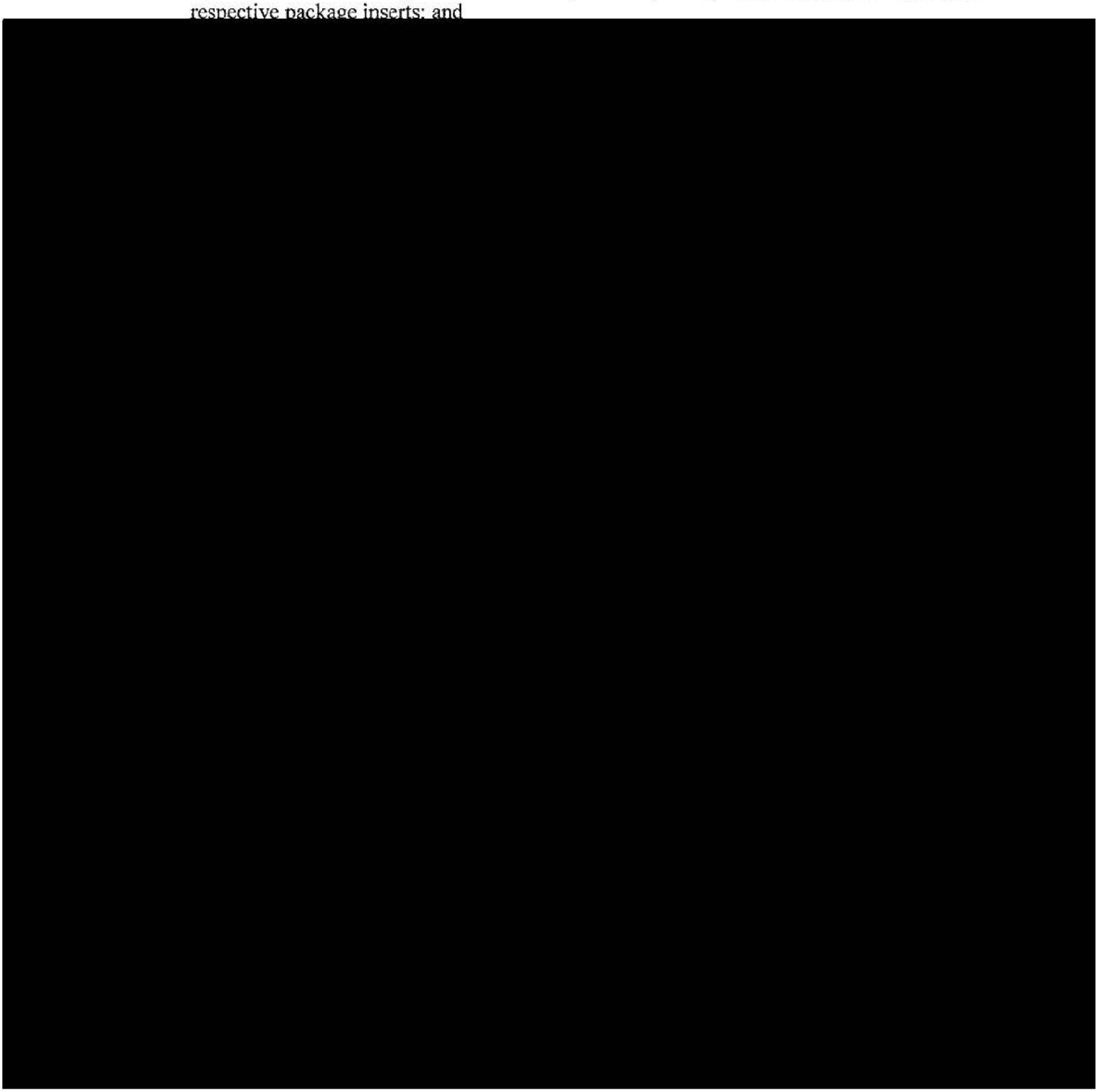

EXHIBIT D

DEFINED DRUG MARKET

MANUFACTURER DRUG	COMPETITIVE DRUG
Apidra® Apidra SoloStar®	Humalog Novolog Novolog FlexPen Humalog Kwik Pen
Toujeo SoloStar® Lantus® Lantus SoloStar®	Levemir Levemir FlexPen Levemir FlexTouch

[redacted]

SUPPLEMENTAL UTILIZATION DATA DRUG MARKET

MANUFACTURER DRUG	COMPETITIVE DRUG
Toujeo SoloStar® Lantus® Lantus SoloStar®	Insulin Humalog Mix 50/50 Humalog Mix 75/25 Humulin 50/50 Humulin 70/30 Humulin N Novolin Mix 70/30 Novolin N Novolog Mix 70/30 Relion Mix 70/30 Relion N [redacted]

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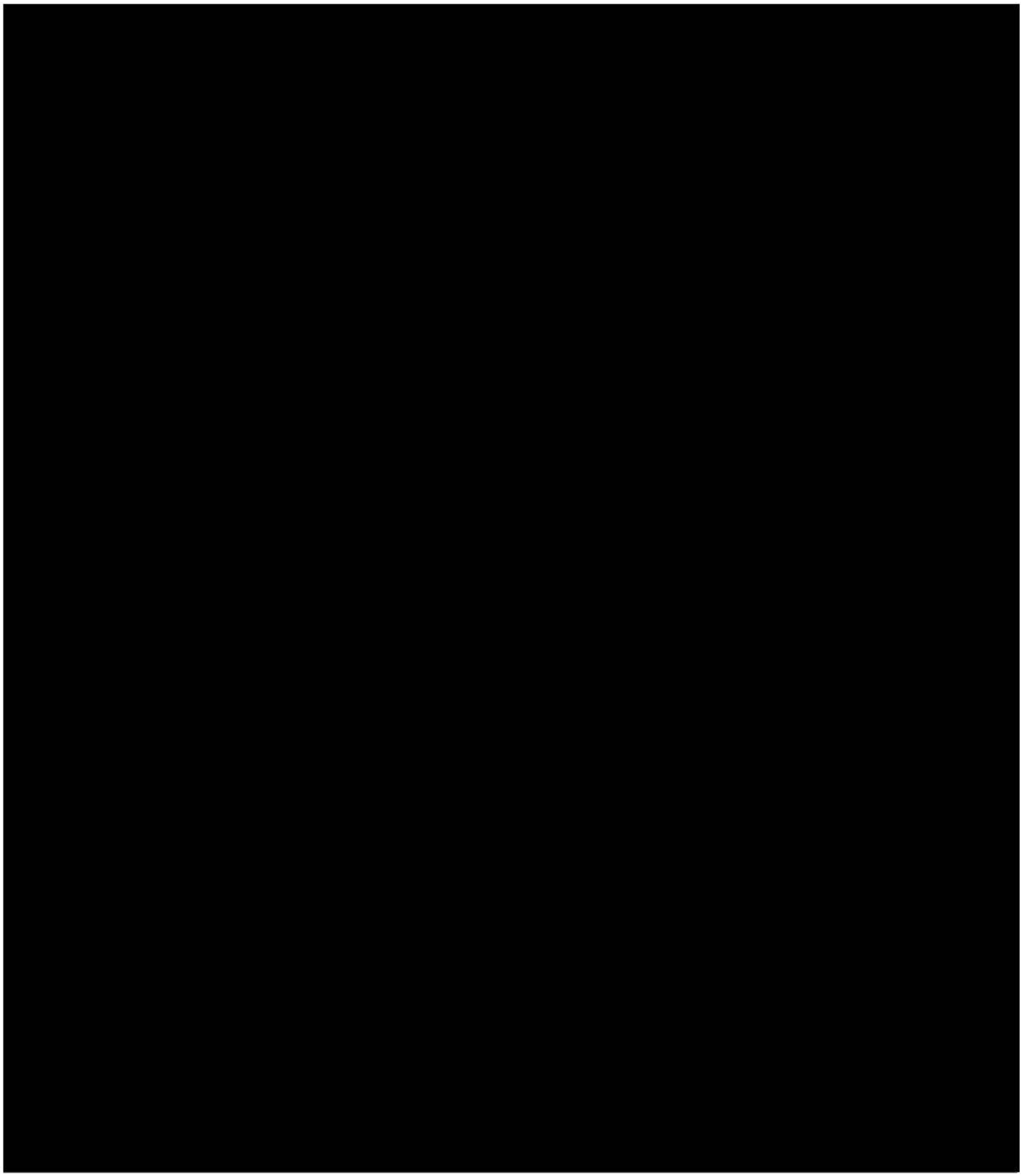

SIXTH (6TH) AMENDMENT TO THE
OPTUMRX, INC.
REBATE AGREEMENT

This SIXTH (6th) AMENDMENT TO THE OPTUMRX, INC. REBATE AGREEMENT ("Amendment"), dated as of December 15, 2015 ("Amendment Effective Date"), is made and entered into by and between, sanofi-aventis U.S. LLC, on behalf of itself and its affiliate Genzyme Corporation, ("Manufacturer"), and OptumRx, Inc. ("Administrator"), on behalf of itself and its Contracting Payors, with reference to the following facts:

RECITALS

WHEREAS, Manufacturer and Administrator entered into that certain Rebate Agreement (as previously amended, the "Agreement"), with an effective date of January 1, 2013, providing, among other things, for Manufacturer to pay rebates to Administrator on units of certain Manufacturer Drugs; and

WHEREAS, Manufacturer and Administrator mutually desire to amend the Agreement as stated below.

NOW THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Manufacturer and Administrator hereby agree to amend the Agreement as follows:

1. Section 3.1.1 of the Agreement is hereby deleted in its entirety and replaced with the following new Section 3.1.1:

   3.1.1 To be eligible for a Rebate under this Agreement, a Manufacturer Drug must have been listed in all applicable electronic and printed publications except as otherwise stated in Exhibit A with respect to this Section 3.1.1, and must have been dispensed by a Provider for use by a Consumer pursuant to a Benefit Contract and in accordance with the terms and conditions of this Agreement, unless otherwise specified on Exhibit A.

2. Section 5.1 of the Agreement is hereby deleted in its entirety and replaced with the following new Section 5.1:

   5.1 Term. This Agreement shall become effective as of the Effective Date and shall remain in effect through December 31, 2019. Unless otherwise terminated as provided for herein, this Agreement shall renew for successive terms of twelve (12) months on the applicable anniversary of the Effective Date, upon the mutual written agreement of the parties.

3. Exhibit A Rebate and Administrative Fee Schedule of the Agreement is hereby deleted in its entirety and replaced with the following new Exhibit A Rebate and Administrative Fee Schedule attached hereto.

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4. [redacted]

5. Effective January 1, 2016, Exhibit D Defined Drug Market of the Agreement is hereby deleted in its entirety and replaced with the following new Exhibit D Defined Drug Market attached hereto.

6. Effect of this Amendment. Capitalized terms used but not defined in this Amendment shall have the meanings ascribed to them in the Agreement. Except as otherwise amended by this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect. In the event there is any inconsistency or conflict between the provisions in this Amendment and those in the Agreement, the provisions in this Amendment shall supersede and control.

IN WITNESS WHEREOF, Manufacturer and Administrator have executed this Amendment as of the date first written above.

ADMINISTRATOR

By: Robert C. Lahman

Name: Robert C. Lahman

Title: S.V.P., Industry Relations

Date: 2-3-2016

MANUFACTURER

By: [signature]

Name: Joseph Geremia

Title: Senior Director Contract Development

Date: 2-8-16

MANUFACTURER

By: [signature]

Name: Gregory Rubert

Title: Sr. Director Managment Reporting

Date: 2/8/16

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EXHIBIT A
REBATE AND ADMINISTRATIVE FEE SCHEDULE

1. Definitions

1.1 Benefit Design

i. "Covered" means a Benefit design that does not qualify as a Managed or Highly Managed Benefit design.

ii. "Managed" means a Benefit design characterized by a Formulary under which the Contracting Payor directly or indirectly influences availability or gives preference in dispensing decisions of Drugs in the same Defined Drug Market through monetary restrictions; for example, differential dollar Consumer co-payments for generic, branded Preferred and branded non-Preferred status as defined and determined by the Contracting Payor, where branded non-Preferred Drugs and branded Preferred Drugs have no less than an average co-payment differential of ten dollars ($10.00), or an equivalent co-insurance percentage differential.

iii. "Highly Managed" means a Benefit design characterized by a Formulary under which a Contracting Payor also has the ability, and in fact exercises such ability, to directly or indirectly influence availability or give preference in dispensing decisions of Drugs in the same Defined Drug Market through hard edit prior authorizations, NDC locks for non-Preferred Drugs, step edits, or other similar mechanisms where certain Drugs are intended to be more restricted in availability than other Preferred Drugs in the same Defined Drug Market.

1.2 "Formulary Status" means the position a Manufacturer Drug has on Formulary. A Formulary Status that is designated as 1 of [X] means that the Manufacturer Drug is 1 of [X] single-source branded Drugs in the Defined Drug Market with the applicable Formulary Status; provided that for the purpose of determining if this condition for Rebate has been met, line extensions of Drugs within the Manufacturer Drug's Defined Drug Market manufactured by the same manufacturer shall be considered as one Drug [redacted]

1.3 "Preferred" means (i) a Drug is covered by a Benefit and is adjudicated in the lowest copayment tier for branded Drugs for the applicable Defined Drug Market and where the copayment amount or coinsurance percentage for such Drug is lower than that of Drugs in the Defined Drug Market designated as "non-preferred", or (ii) a Drug is covered by a Benefit where the Drugs designated as "preferred" are covered by the Benefit and the Drugs excluded from Formulary or designated on Formulary as "non-preferred" or "excluded" are not covered by the Benefit or (iii) for Covered Benefit designs only, a Drug is covered by a Benefit where Drugs designated as "preferred" are covered by the Benefit and Manufacturer Drug is no more restricted in its availability than other branded Drugs in the same Defined Drug Market.

1.4 "Specialty Tier" means a separate category or tier of the Formulary designated for very high cost or unique Drugs. This term only applies with respect to Sections 5.2(e), 6.2(e), 7.4, and 8.6 for [redacted] and Sections 5.5, 6.5, 7.8, and 8.8 for [redacted]

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1.5 "Unrestricted Access" when referring to Lantus means a Manufacturer Drug is covered by a Benefit with no Utilization Controls. But when referring to all other Manufacturer Drugs, means a Manufacturer Drug covered by a Benefit with no Utilization Controls, except for the allowances set forth in 1.5 Utilization Controls.

1.6 "Utilization Controls" mean, unless such Utilization Controls applied are clinically appropriate in accordance with FDA labeling or indications and/or applied to all Drugs in the applicable Defined Drug Market, i) counter-detailing or counter-promoting, ii) switching or therapeutic substitution, iii) hard edit prior authorization, iv) NDC lock, v) step edit, and vi) quantity limit based upon package insert. For purposes of this definition, "Utilization Controls" excludes communications or education programs designed to encourage the use of generic Drugs, and any aspects of Administrator's or Contracting Payor's communication, website, or other activity whereby Consumers have access to or are made aware of prices of Drugs and/or the availability of over-the-counter products for purposes of managing Consumer cost sharing amounts.

2. Rebate Calculation

Rebates for each Manufacturer Drug will be based upon the Formulary status of the Manufacturer Drug at the time such Manufacturer Drug is dispensed. Rebates will be calculated on a per Unit dispensed basis. For each month, the Rebates for each Manufacturer Drug shall be calculated as follows:

Rebate = (Unit(s) of Manufacturer Drug) x (WAC) x (Total Rebate Rate for the applicable Manufacturer Drug)

3. Administrative Fee. The Administrative Fee rate is 3% for each Rebate eligible Unit of Manufacturer Drug. The Administrative Fee shall not be charged on QRPDP, Managed Medicaid and CHIP utilization, and any other utilization where prohibited by Law. For each month, the Administrative Fee shall be calculated as follows:

Administrative Fee = (Unit(s) of Manufacturer Drug) x (WAC) x (Administrative Fee rate %)

4. Protection of Rebate Amount.

4.1 Price Protection.

This Section 4.1 is effective 12/15/15 through 12/31/15 for [redacted] (Sections 7.2) and Lantus (Section 5.3.1(a)).
This Section 4.1 is effective 12/15/15 through 6/30/17 for [redacted] (Sections 5.2(b), 6.2(b), and 8.3) and Lantus (Sections 5.1, 6.1, and 8.1).
This Section 4.1 is effective 1/1/16 through 6/30/17 for Lantus (Sections 5.3.2(a) 6.3.1(a)).

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This Section 4.1 is effective 12/15/15 through 12/31/18 for [redacted] (Sections 5.4(a), 6.4(a), 7.5 and 8.7) and [redacted] Sections 5.5, 6.5, 7.8(a), and 8.8(a)).
This Section 4.1 is effective 1/1/16 through 12/31/19 for [redacted] (Sections 5.2(d), 6.2(d), and 8.5).
This Section 4.1 is effective 1/1/16 through 12/31/17 for [redacted] (Sections 5.2(e) and 6.2(e)).

Rebate rates are subject to automatic adjustment in the event the "WAC per Unit" for Manufacturer Drug is increased to a price that is greater than the "Allowed WAC per Unit" during any corresponding month of the Agreement. The initial "Allowed WAC per Unit" for a Manufacturer Drug is calculated by multiplying the "WAC per Unit" as of the date set forth in the Rebate terms below ("Baseline WAC Date") for the applicable Manufacturer Drug by (100% plus the "Price Protection" factor). The "Net WAC per Unit" is calculated by multiplying the "WAC per Unit" by (100% minus the Base Rebate Rate %). The "Base Rebate Rate %" is the Rebate percentage for the Manufacturer Drug set forth in the applicable Rebate tables below. The "Allowed WAC per Unit" for subsequent Contract Years is calculated by multiplying the "Allowed WAC" for the previous Contract Year by (100% plus the "Price Protection" factor). The initial Allowed WAC per Unit for a Manufacturer Drug will apply during the 12-month period following the Manufacturer Drug's Contract Year Start Date (which date is set forth in the Rebate terms below). Such initial 12-month period and each subsequent 12- month period is referred to as the applicable Manufacturer Drug's "Contract Year". The "Net Allowed WAC per Unit" is calculated by multiplying the "Allowed WAC per Unit" by (100% minus the Base Rebate Rate %). The "Price Protection" factor is set forth in the Rebate terms below for the applicable Manufacturer Drug. Effective as of the date the "WAC per Unit" first exceeds the "Allowed WAC per Unit" and continuing for the remainder of that Contract Year, subject to further adjustments in accordance with this Section 4.1 of this Exhibit A Rebate and Administrative Fee Schedule, an "Additional Rebate Rate" will be provided. The "Additional Rebate Rate" is calculated by determining the amount, if any, that the Current Net WAC Per Unit for a given month exceeds the Net Allowed WAC per Unit for the same month, divided by the then-current WAC per Unit. The resulting percentage is the "Additional Rebate Rate" and is added to the "Base Rebate Rate %" to produce a "Total Rebate Rate" that applies during that month. The Additional Rebate Rate will be paid each month in which the "Current Net WAC per Unit" exceeds the "Net Allowed WAC per Unit". The Additional Rebate Rate is re-calculated each month. For avoidance of doubt, the Total Rebate Rate calculation for [redacted] is subject to the terms of Section 2.2.6 Best Price. [redacted]

*The terms "Current Net WAC" and "Net Allowed WAC" are solely used for purposes to explain the calculation of price protection in this Agreement. These terms are not used outside of this Agreement and, furthermore, are not meant to define or describe any pricing terms of a Manufacturer Drug.

EXAMPLE 1:

Price Protection factor:	6%	Year 1 Price increase 10%						Year 2 Price increase 10%						Year 3 Price increase 10%				
	Assumed WAC as of 12/31/2013	Jan. 2014	Feb. 2014	Mar. 15 2014		Dec. 2014		Jan. 2015	Feb. 2015	Mar. 2015		Dec. 2015		Jan. 2016	Feb. 2016	Mar. 2016		Dec. 2016
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60	→	6.60		6.60	6.60	7.26	→	7.26		7.26	7.26	7.99	→	7.99
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36		6.36	→	6.74	6.74	6.74		6.74	→	7.15	7.15	7.15		7.15
Current WAC/ Unit (New NDC)									6.60	7.26	→	7.26		7.26	7.26	7.99	→	7.99
Allowed WAC/ Unit (New NDC)									6.74	6.74		6.74	→	7.15	7.15	7.15		7.15
Current Net WAC / Unit		5.40	5.40	5.94		5.94		5.94	5.94	6.53		6.53		6.53	6.53	7.19		7.19
Net Allowed WAC / Unit	5.40	5.72	5.72	5.72		5.72		6.07	6.07	6.07		6.07		6.43	6.43	6.43		6.43
Additional Rebate :		$0.00	$0.00	$0.22		$0.22		$0.00	$0.00	$0.47		$0.47		$0.10	$0.10	$0.76		$0.76
Additional Rebate Rate:		0.0%	0.0%	3.3%		3.3%		0.0%	0.0%	6.4%		6.4%		1.4%	1.4%	9.5%		9.5%
Base Rebate Rate %:	10.0%	10.0%	10.0%	10.0%		10.0%		10.0%	10.0%	10.0%		10.0%		10.0%	10.0%	10.0%		10.0%
Total Rebate Rate	10.0%	10.0%	10.0%	13.3%	→	13.3%		10.0%	10.0%	16.4%	→	16.4%		11.4%	11.4%	19.5%	→	19.5%

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If a new NDC ("New NDC") matching the labeler code and product code ("9-digit National Drug Code" or "NDC-9") of a Manufacturer Drug covered by this Agreement comes into existence after the date that such Manufacturer Drug becomes covered by this Agreement, the Additional Rebate Rate for such New NDC(s) will be calculated consistent with the preceding paragraph except that (i) the Net Allowed WAC per Unit for the Existing NDCs (defined below) will apply to the New NDC(s) during each billing period and (ii) the Net WAC per Unit of such New NDC(s) will be adjusted to account for differences, if any, in days of therapy, unit size, strength, or similar factors, between the New NDC(s) and their corresponding Existing NDCs, which adjustment(s) the parties will work in good faith to establish. As used herein, the term "Existing NDCs" refers to the Manufacturer Drug NDC(s) covered by the Agreement on the day prior to the date that the applicable New NDC comes into existence that has the highest Net Allowed WAC per Unit; provided, however, that either party may elect for the Existing NDC to be the NDC that most closely resembles the New NDC with respect to days of therapy, unit size, strength, or similar factors, which the parties will mutually determine working together in good faith. Example 2 below demonstrates the Additional Rebate Rate calculation for a New NDC.

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EXAMPLE 2:

New NDC introduced Feb14, subject to same PP rate increase as current NDCs.
New NDC WAC normalized to Current NDC WAC, same Baseline WAC date.
Price Protection factor: 6%

	Assumed WAC as of 12/31/2012	Jan. 2013	Feb. 2013	Year 1 Price increase 10% Mar. 15 2013	Dec. 2013	Jan. 2014	Feb. 2014	Year 2 Price increase 10% Mar. 2014	Dec. 2014	Jan. 2015	Feb. 2015	Year 3 Price increase 10% Mar. 2015	Dec. 2015
Current WAC/ Unit (Current NDC)	6.00	6.00	6.00	6.60 →	6.60	6.60	6.60	7.26 →	7.26	7.26	7.26	7.99 →	7.99
Allowed WAC/ Unit (Current NDC)		6.36	6.36	6.36 →	6.36 →	6.74	6.74	6.74	6.74 →	7.15	7.15	7.15	7.15
Current WAC/ Unit (New NDC)							10.50	11.55 →	11.55	11.55	11.55	12.71 →	12.71
Current Normalized WAC/ Unit (New NDC)							9.90	10.89 →	10.89	10.89	10.89	11.98 →	11.98
Allowed WAC/ Unit (New NDC)							10.11	10.11	10.11 →	10.72	10.72	10.72	10.72
Current Net WAC / Unit (Current NDC)		5.40	5.40	5.94	5.94	5.94	5.94	6.53	6.53	6.53	6.53	7.19	7.19
Net Allowed WAC / Unit (Current NDC)	5.40	5.72	5.72	5.72	5.72	6.07	6.07	6.07	6.07	6.43	6.43	6.43	6.43
Current Net WAC / Unit (New NDC)							9.45	10.40	10.40	10.40	10.40	11.43	11.43
Net Allowed WAC / Unit (New NDC)							9.10	9.10	9.10	9.65	9.65	9.65	9.65
Additional Rebate (Current NDC) :		$0.00	$0.00	$0.22	$0.22	$0.00	$0.00	$0.47	$0.47	$0.10	$0.10	$0.76	$0.76
Additional Rebate Rate (Current NDC):		0.0%	0.0%	3.3%	3.3%	0.0%	0.0%	6.4%	6.4%	1.4%	1.4%	9.5%	9.5%
Additional Rebate (New NDC) :							$0.35	$1.29	$1.29	$0.75	$0.75	$1.79	$1.79
Additional Rebate Rate (New NDC):							3.3%	11.2%	11.2%	6.5%	6.5%	14.1%	14.1%
Base Rebate Rate %:	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
Total Rebate Rate (Current NDC)	10.0%	10.0%	10.0%	13.3% →	13.3%	10.0%	10.0%	16.4% →	16.4%	11.4%	11.4%	19.5% →	19.5%
Total Rebate Rate (New NDC)				→			13.3%	21.2% →	21.2%	16.5%	16.5%	24.1% →	24.1%

	Current WAC	DOT (can be changed to whatever the 'normalization' factor should be)	Normalized WAC / per DOT	WAC in effect for New NDC
Current NDC	6.60	60	0.11	
New NDC	10.50	90		9.90

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4.2 Price Protection

This section 4.2 is effective 12/15/15 through 12/31/15 for [redacted] (Sections 5.2(c), 6.2(c), 7.3 and 8.4).
This section 4.2 is effective 12/15/15 through 12/31/16 for [redacted] (Section 7.4)
This section 4.2 is effective 12/15/15 through 6/30/17 [redacted] (Section 8.6)
This section 4.2 is effective 1/1/16 through 12/31/16 for Toujeo (Section 7.6)
This section 4.2 is effective 1/1/17 through 12/31/17 for Toujeo (Section 7.7).

Rebate rates are subject to automatic adjustment in the event the "WAC per Unit" for Manufacturer Drug is increased to a price that is greater than the "Allowed WAC per Unit" during any corresponding month of the Agreement. The "Allowed WAC per Unit" for 2013 is calculated by multiplying the "WAC per Unit" as of the date set forth in the Rebate terms below ("Baseline WAC Date") for the applicable Manufacturer Drug by (100% plus the "Price Protection" factor). The "Net WAC per Unit" is calculated by multiplying the "WAC per Unit" by (100% minus the Base Rebate Rate %). The "Base Rebate Rate %" is the Rebate percentage for the Manufacturer Drug set forth in the Rebate tables below. The initial Allowed WAC per Unit for a Manufacturer Drug will apply during the 12-month period following the Agreement's Effective Date. Such initial 12-month period and each subsequent 12-month period is referred to as the applicable Manufacturer Drug's "Contract Year". The "Allowed WAC per Unit" for subsequent Contract Years is calculated by multiplying the "WAC per Unit" in effect for the applicable Manufacturer Drug on December 31 of the Contract Year immediately prior to the current Contract Year by (100% plus the "Price Protection" factor). The "Net Allowed WAC per Unit" is calculated by multiplying the "Allowed WAC per Unit" by (100% minus the Base Rebate Rate %). For avoidance of doubt: (a) the first pricing period shall be Contract Year 2013; (b) the second pricing period shall be Contract Year 2014; and (c) the third pricing period shall be Contract Year 2015. Price increases in one pricing period shall not be added to price increases in another pricing period for purposes of determining Additional Rebate Rates. The "Price Protection" factor is set forth in the Rebate terms below for the applicable Manufacturer Drug. Effective as of the date the "WAC per Unit" first exceeds the "Allowed WAC per Unit" and continuing for the remainder of that Contract Year, subject to further adjustments in accordance with this Section 4.2 of this Exhibit A Rebate and Administrative Fee Schedule, an "Additional Rebate Rate" will be provided. The "Additional Rebate Rate" is calculated by determining the amount, if any, that the Net WAC Per Unit for a given month exceeds the Net Allowed WAC per Unit for the same month, divided by the then-current WAC per Unit. The resulting percentage is the "Additional Rebate Rate" and is added to the "Base Rebate Rate %" to produce a "Total Rebate Rate" that applies during that month. The Additional Rebate Rate will be paid each month in which the "Current Net WAC Per Unit" exceeds the "Net Allowed WAC per Unit". The Additional Rebate Rate is re-calculated each month. For avoidance of doubt, the Total Rebate Rate calculation is subject to the terms of Section 2.2.6 Best Price. [redacted]

*The terms "Current Net WAC" and "Net Allowed WAC" are solely used for purposes to explain the calculation of price protection in this Agreement. These terms are not used outside of this Agreement and, furthermore, are not meant to define or describe any pricing terms of a Manufacturer Drug.

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EXAMPLE 1:

Price Protection factor:	6%			Year 1 Price increase 10%				Year 2 Price increase 10%			
	Assumed WAC as of 12/31/2012	Jan. 2013	Feb. 2013	Mar. 15 2013	Dec. 2013	Jan. 2014	Feb. 2014	Mar. 2014	Dec. 2014	Jan. 2015	Feb. 2015
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60	6.60	6.60	6.60	7.26	7.26	7.26	7.26
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36	6.36	7.00	7.00	7.00	7.00	7.70	7.70
Current WAC/ Unit (New NDC)							6.60	7.26	7.26	7.26	7.26
Allowed WAC/ Unit (New NDC)							7.00	7.00	7.00	7.70	7.70
Current Net WAC / Unit		5.40	5.40	5.94	5.94	5.94	5.94	6.53	6.53	6.53	6.53
Net Allowed WAC / Unit	5.40	5.72	5.72	5.72	5.72	6.30	6.30	6.30	6.30	6.93	6.93
Additional Rebate :		$0.00	$0.00	$0.22	$0.22	$0.00	$0.00	$0.24	$0.24	$0.00	$0.00
Additional Rebate Rate:		0.0%	0.0%	3.3%	3.3%	0.0%	0.0%	3.3%	3.3%	0.0%	0.0%
Base Rebate Rate %:	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
Total Rebate Rate	10.0%	10.0%	10.0%	13.3%	13.3%	10.0%	10.0%	13.3%	13.3%	10.0%	10.0%

If a new NDC ("New NDC") matching the labeler code and product code ("9-digit National Drug Code" or "NDC-9") of a Manufacturer Drug covered by this Agreement comes into existence after the date that such Manufacturer Drug becomes covered by this Agreement, the Additional Rebate Rate for such New NDC(s) will be calculated consistent with the preceding paragraph except that (i) the Net Allowed WAC per Unit for the Existing NDCs (defined below) will apply to the New NDC(s) during each billing period and (ii) the Net WAC per Unit of such New NDC(s) will be adjusted to account for differences, if any, in days of therapy, unit size, strength, or similar factors, between the New NDC(s) and their corresponding Existing NDCs, which adjustment(s) the parties will work in good faith to establish. As used herein, the term "Existing NDCs" refers to the Manufacturer Drug NDC(s) covered by the Agreement on the day prior to the date that the applicable New NDC comes into existence that has the highest Net Allowed WAC per Unit; provided, however, that either party may elect for the Existing NDC to be the NDC that most closely resembles the New NDC with respect to days of therapy, unit size, strength, or similar factors, which the parties will mutually determine working together in good faith. Example 2 below demonstrates the Additional Rebate Rate calculation for a New NDC.

EXAMPLE 2:

New NDC introduced Feb14, subject to same PP rate increase as Existing NDCs.
Same WAC/unit, same Baseline WAC date.
Price Protection factor: 6%

Year 1 Price increase 10%

Allowed was 6.74

Year 2 Price increase 10%

	Assumed WAC as of 12/31/2012	Jan. 2013	Feb. 2013	Mar. 15 2013	Dec. 2013	Jan. 2014	Feb. 2014	Mar. 2014	Dec. 2014	Jan. 2015	Feb. 2015
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60	6.60	6.60	6.60	7.26	7.26	7.26	7.26
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36	6.36	7.00	7.00	7.00	7.00	7.70	7.70
Current WAC/ Unit (New NDC)							10.50	11.55	11.55	11.55	11.55
Current Normalized WAC/ Unit (New NDC)							9.90	10.89	10.89	10.89	10.89
Allowed WAC/ Unit (New NDC)							10.49	10.49	10.49	12.24	12.24
Current Net WAC / Unit (Existing NDC)		5.40	5.40	5.94	5.94	5.94	5.94	6.53	6.53	6.53	6.53
Net Allowed WAC / Unit (Existing NDC)	5.40	5.72	5.72	5.72	5.72	6.30	6.30	6.30	6.30	6.93	6.93
Current Net WAC / Unit (New NDC)							9.45	10.40	10.40	10.40	10.40
Net Allowed WAC / Unit (New NDC)							9.44	9.44	9.44	11.02	11.02
Additional Rebate (Existing NDC):		$0.00	$0.00	$0.22	$0.22	$0.00	$0.00	$0.24	$0.24	$0.00	$0.00
Additional Rebate Rate (Existing NDC):		0.0%	0.0%	3.3%	3.3%	0.0%	0.0%	3.3%	3.3%	0.0%	0.0%
Additional Rebate (New NDC) :							$0.01	$0.95	$0.95	$0.00	$0.00
Additional Rebate Rate (New NDC):							0.1%	8.2%	8.2%	0.0%	0.0%
Base Rebate Rate %:	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
Total Rebate Rate (Existing NDC)	10.0%	10.0%	10.0%	13.3%	13.3%	10.0%	10.0%	13.3%	13.3%	10.0%	10.0%
Total Rebate Rate (New NDC)							10.1%	18.2%	18.2%	10.0%	10.0%

	Current WAC	DOT (can be changed to whatever the 'normalization' factor should be)	Normalized WAC / per DOT	WAC in effect for New NDC
Existing NDC	6.60	60	0.11	
New NDC	10.50	90		9.90

5. Rebate Terms – non-QRPDP, non-Managed Medicaid and non-CHIP

5.1 PREFERRED

Option A: (Effective 12/15/2015 through 6/30/2017)

Manufacturer Drug Name: Lantus*			
Benefit Design:	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	42%*	n/a	n/a
Administrative Fee	3%	n/a	n/a
Price Protection factor	7%	n/a	n/a
Baseline WAC Date:	1/1/14	n/a	n/a
Contract Year Start Date	7/1/14	n/a	n/a

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

Conditions to Rebate:

1. All NDC's of Manufacturer Drug are on Formulary with Unrestricted Access in tier 1, 2 or 3 as of the date of dispensing. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and

2. A certain package form of Lantus may be disadvantaged to one (1) comparable package form of another Drug in Lantus' Defined Drug Market, provided all Lantus package forms are still listed and adjudicated with Unrestricted Access in accordance with Condition 1 above. In the event that a package form of Lantus is disadvantaged to more than one (1) comparable package form, all NDC's of Lantus, i.e. both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples are provided for clarification of rebate eligibility and not to be considered an exhaustive list:

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Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	3	Non-preferred	3	Non-preferred
Levemir	Vial	1	Preferred	1	Preferred
Comp #3	Vial	3	Non-preferred	3	Non-preferred
Lantus	Pen	3	Non-preferred	3	Non-preferred
Levemir	Pen	1	Preferred	3	Non-preferred
Comp #3	Pen	3	Non-preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	3	Non-preferred	3	Non-preferred
Levemir	Vial	1	Preferred	1	Preferred
Comp #3	Vial	2	Preferred	3	Non-preferred
Lantus	Pen	3	Non-preferred	3	Non-preferred
Levemir	Pen	1	Preferred	1	Preferred
Comp #3	Pen	2	Preferred	2	Preferred

Option B: (Effective 12/15/2015 through 6/30/2017)

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 2	n/a	12%*	7%*
Administrative Fee		n/a	3%	3%
Price Protection factor		n/a	7%	7%
Bascline WAC Date:		n/a	1/1/14	1/1/14
Contract Year Start Date		n/a	7/1/14	7/1/14

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6,Best Price.

Conditions to Rebate:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; and

2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and

3. No package form of Lantus will be disadvantaged to a comparable package form of any other Drug in Lantus' Defined Drug Market. In the event that a package form of Lantus is disadvantaged to a comparable package form, all NDC's of Lantus, i.e. both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples

are provided for clarification of Rebate eligibility and not to be considered an exhaustive list:

Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	1	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	1	Preferred	2	Preferred
Levemir	Pen	1	Preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	2	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	3	Non-preferred	2	Preferred
Levemir	Pen	3	Non-preferred	2	Preferred

5.2 PREFERRED

5.2(a) Effective 12/15/2015 through 6/30/2017)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 2 or less	47%	47%	47%
Base Rebate Rate %	1 of 3	42%	42%	42%
Administrative Fee		3%	3%	3%
Price Protection factor		n/a	n/a	n/a
Baseline WAC Date:		n/a	n/a	n/a

[redacted]

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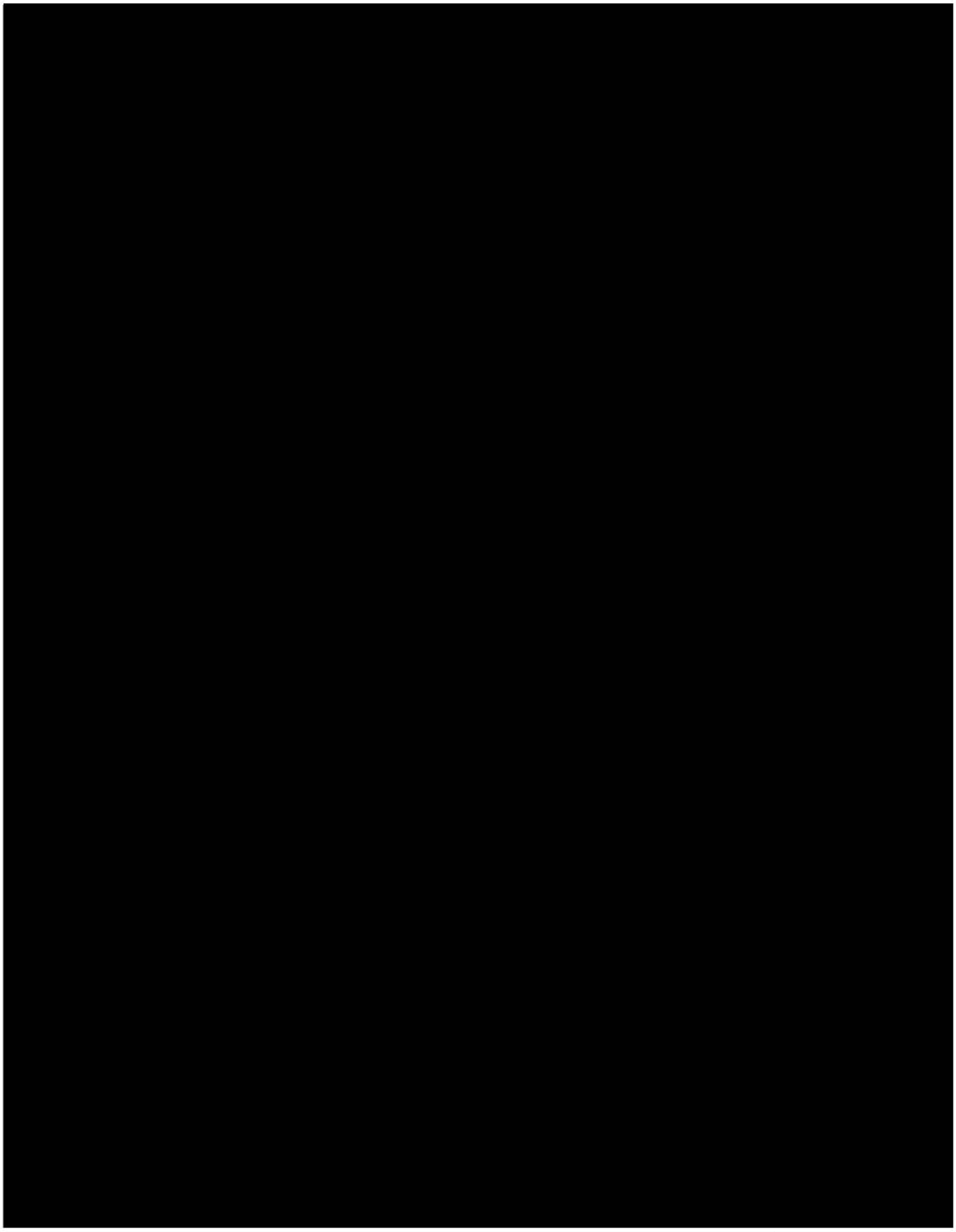

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5.3 PREFERRED – EXCLUSION

5.3.1 Only for Benefit Contracts with less than two (2) million Consumers

5.3.1 (a) (Effective 12/15/2015 through 12/31/2015)

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**

Base Rebate Rate %	1 of 1	43%*	N/A	N/A
Administrative Fee		3%	N/A	N/A
Price Protection factor		7%	N/A	N/A
Baseline WAC Date:		1/1/14	N/A	N/A
Contract Year Start Date		7/1/14	N/A	N/A

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

5.3.1 (b) (Effective 12/15/2015 through 12/31/2015)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	57%	N/A	N/A
Administrative Fee		3%	N/A	N/A
Price Protection factor		N/A	N/A	N/A
Baseline WAC Date:		N/A	N/A	N/A
Contract Year Start Date		N/A	N/A	N/A

Conditions to Rebate for Rebate Tables 5.3(a) Lantus and 5.3(b) Apidra:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; provided that Drugs manufactured, marketed or distributed by one manufacturer in the Defined Drug Market will be considered as one Drug. All other competitive Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and

2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus and Apidra shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus and Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus and Apidra pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to quantity limit consistent with their respective package inserts.

5.3.2 Only for Benefit Contracts with less than three and one-half (3.5) million Consumers

5.3.2 (a) (Effective 1/1/2016 through 6/30/2017)

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	43%*	N/A	N/A
Administrative Fee		3%	N/A	N/A
Price Protection factor		7%	N/A	N/A
Baseline WAC Date:		1/1/14	N/A	N/A
Contract Year Start Date		7/1/14	N/A	N/A

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

5.3.2 (b) (Effective 1/1/2016 through 12/31/2017)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	57%	N/A	N/A
Administrative Fee		3%	N/A	N/A
Price Protection factor		N/A	N/A	N/A
Baseline WAC Date:		N/A	N/A	N/A
Contract Year Start Date		N/A	N/A	N/A

Conditions to Rebate for Rebate Tables 5.3(a) Lantus and 5.3(b) Apidra:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; provided that Drugs manufactured, marketed or distributed by one manufacturer in the Defined Drug Market will be considered as one Drug. All other competitive Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and

2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus and Apidra shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus and Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus and Apidra pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided

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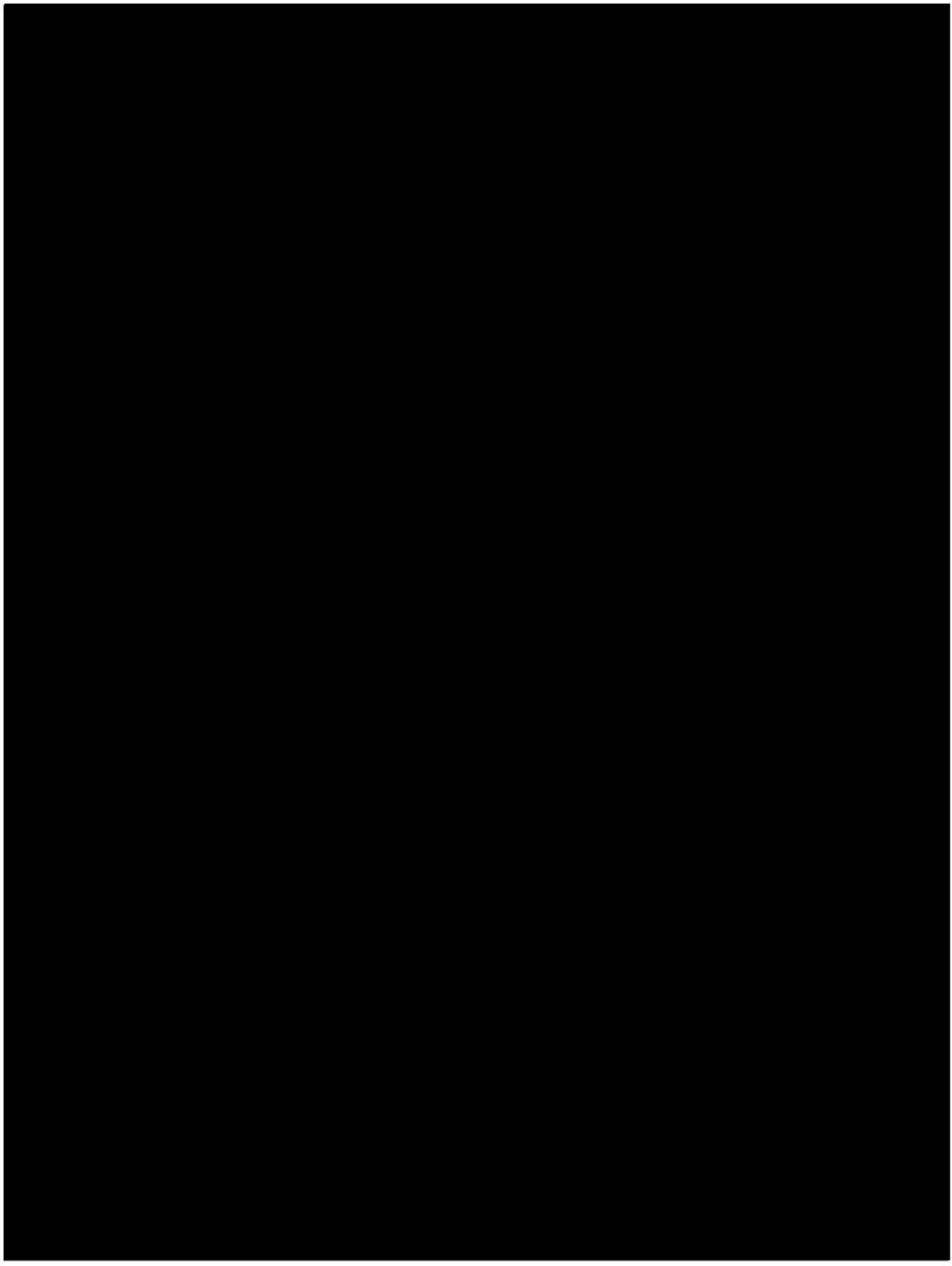
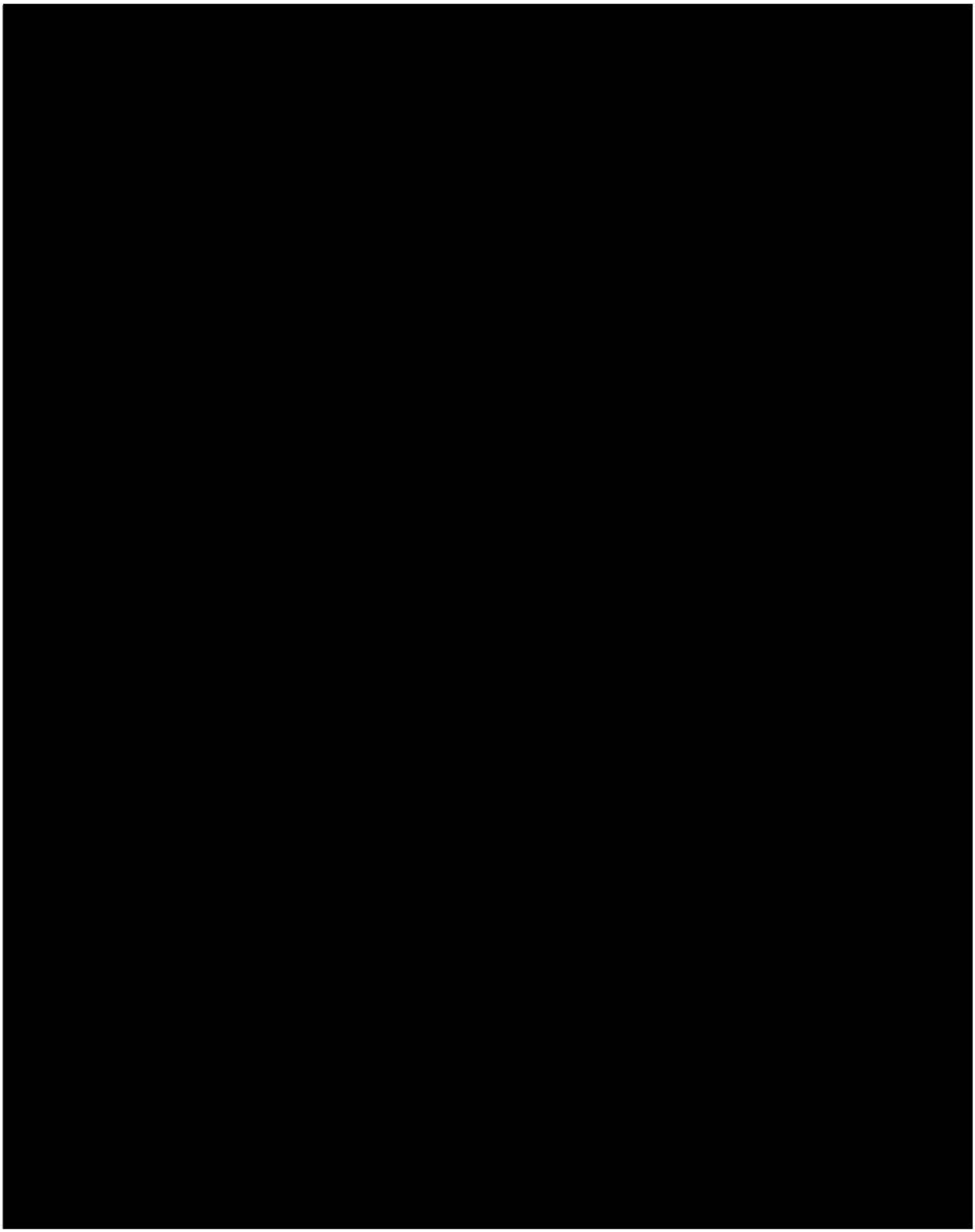
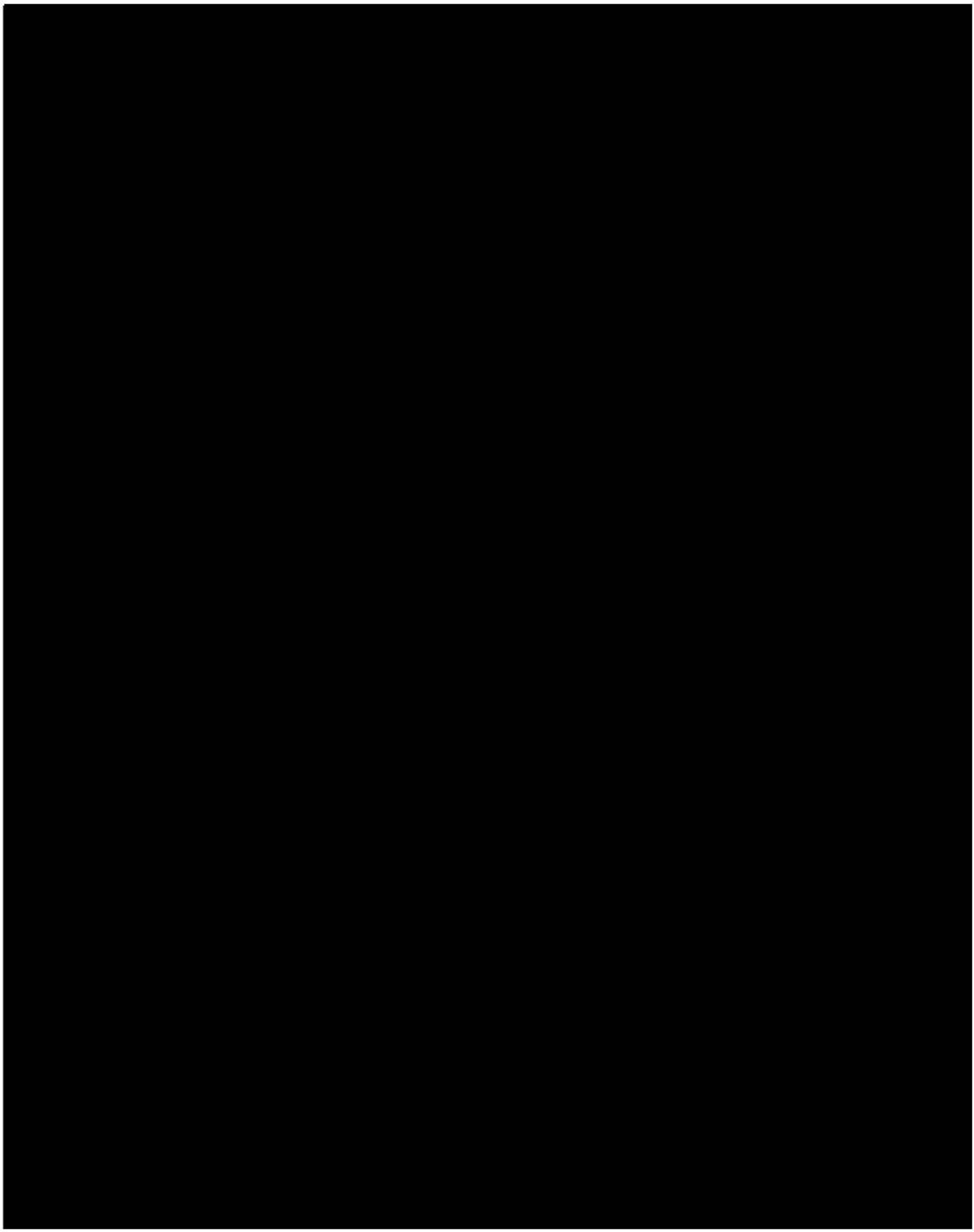
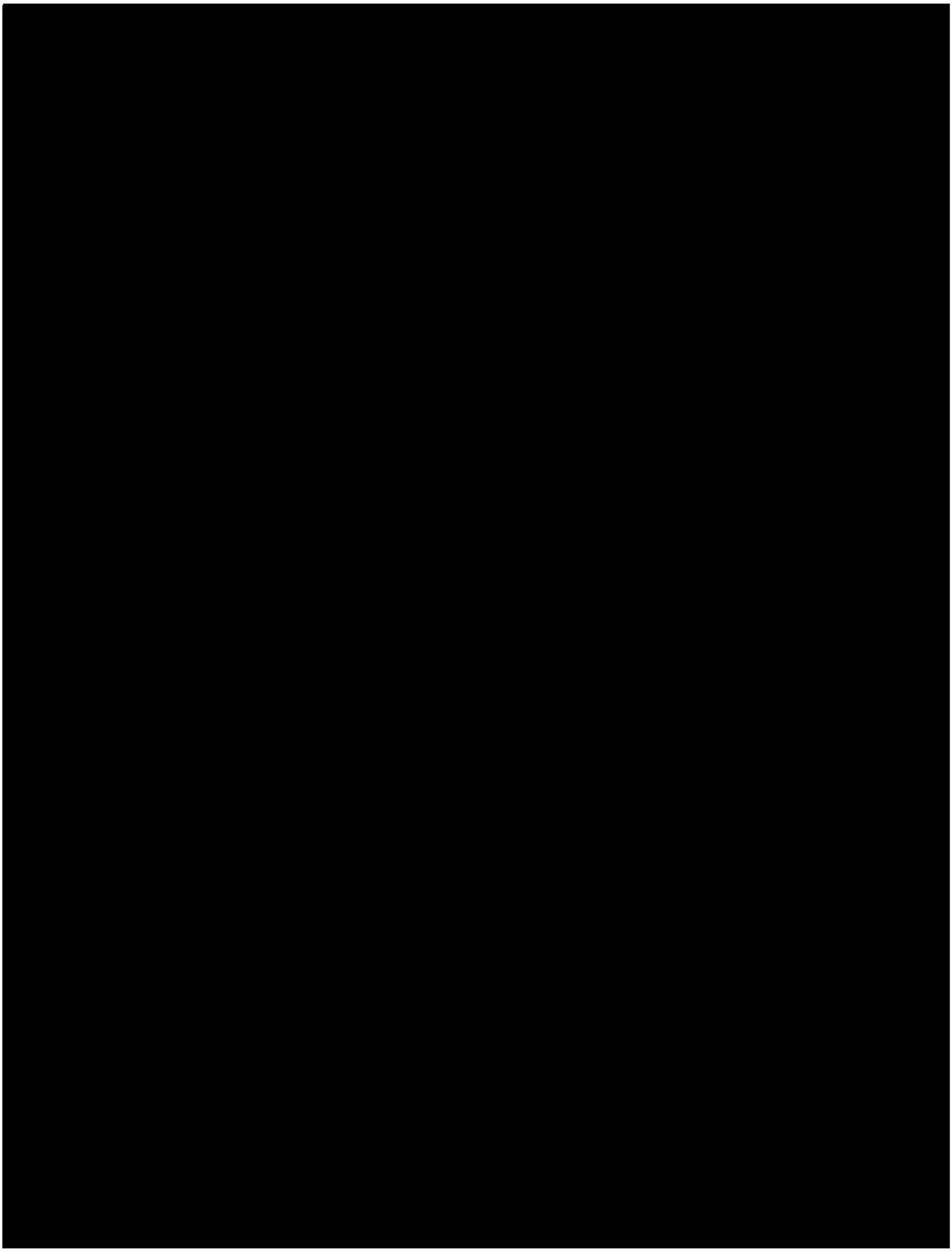
all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to quantity limit consistent with their respective package inserts.

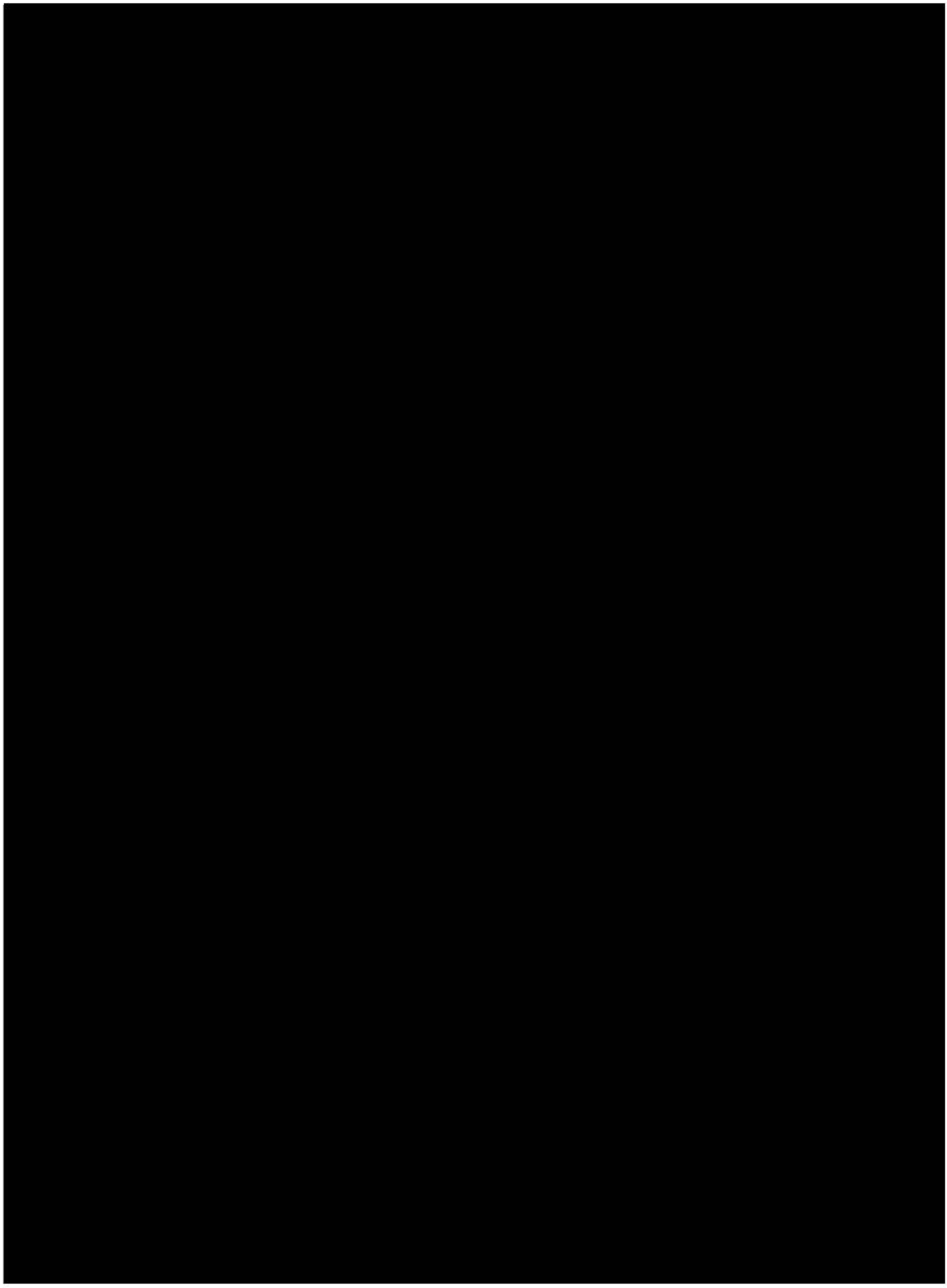
[redacted]

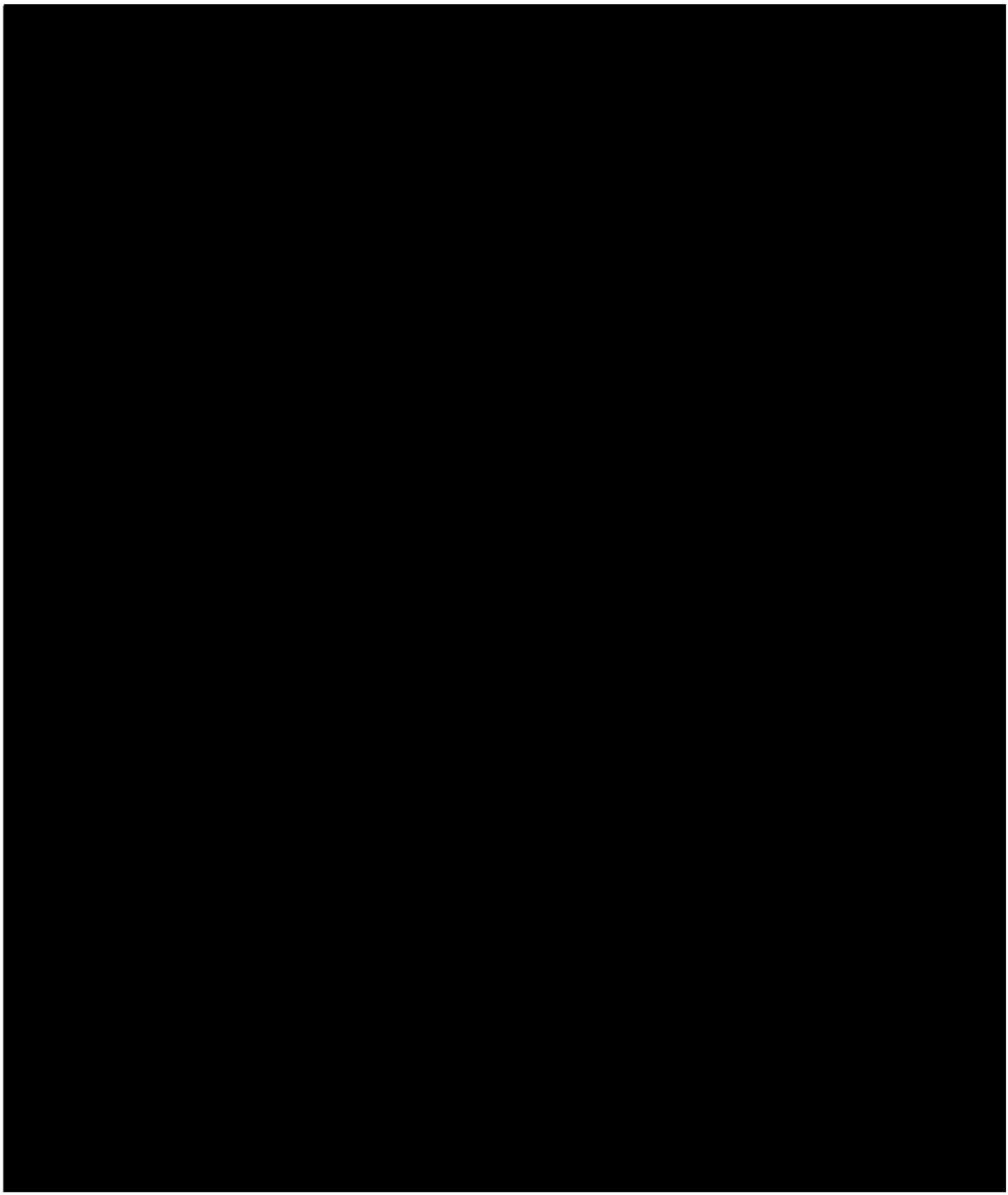












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6. Rebate Terms – QRPDP and utilization ineligible for Administrative Fees per Section 3 of this Exhibit A (other than Managed Medicaid and CHIP).

6.1 PREFERRED

Option A (Effective 12/15/2015 through 6/30/2017):

Manufacturer Drug Name: Lantus*			
Benefit Design:	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	45%*	n/a	n/a
Administrative Fee	0%	n/a	n/a
Price Protection factor	7%	n/a	n/a
Baseline WAC Date:	1/1/14	n/a	n/a
Contract Year Start Date	7/1/14	n/a	n/a

*The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6 ("Best Price").

Conditions to Rebate:

1. All NDC's of Manufacturer Drug are on Formulary with Unrestricted Access in tier 1, 2 or 3 as of the date of dispensing. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided

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all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and

2. A certain package form of Lantus may be disadvantaged to one (1) comparable package form of another Drug in Lantus' Defined Drug Market, provided all Lantus package forms are still listed and adjudicated with Unrestricted Access in accordance with Condition 1 above. In the event that a package form of Lantus is disadvantaged to more than one (1) comparable package form, all NDC's of Lantus, i.e. both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples are provided for clarification of rebate eligibility and not to be considered an exhaustive list:

Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	3	Non-preferred	3	Non-preferred
Levemir	Vial	1	Preferred	1	Preferred
Comp #3	Vial	3	Non-preferred	3	Non-preferred
Lantus	Pen	3	Non-preferred	3	Non-preferred
Levemir	Pen	1	Preferred	3	Non-preferred
Comp #3	Pen	3	Non-preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	3	Non-preferred	3	Non-preferred
Levemir	Vial	1	Preferred	1	Preferred
Comp #3	Vial	2	Preferred	3	Non-preferred
Lantus	Pen	3	Non-preferred	3	Non-preferred
Levemir	Pen	1	Preferred	1	Preferred
Comp #3	Pen	2	Preferred	2	Preferred

Option B (Effective 12/15/2015 through 6/30/2017):

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 2	n/a	15%*	10%*
Administrative Fee		n/a	0%	0%
Price Protection factor		n/a	7%	7%
Baseline WAC Date:		n/a	1/1/14	1/1/14
Contract Year Start Date		n/a	7/1/14	7/1/14

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

Conditions to Rebate:

1. All NDC's of Manufacturer Drug were on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; and

2. A Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is

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an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and

3. No package form of Lantus will be disadvantaged to a comparable package form of any other Drug in Lantus' Defined Drug Market. In the event that a package form of Lantus is disadvantaged to a comparable package form, all NDC's of Lantus, both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples are provided for clarification of Rebate eligibility and not to be considered an exhaustive list:

Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	1	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	1	Preferred	2	Preferred
Levemir	Pen	1	Preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	2	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	3	Non-preferred	2	Preferred
Levemir	Pen	3	Non-preferred	2	Preferred

6.2 PREFERRED

6.2(a) (Effective 12/15/2015 through 6/30/2017)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 2 or less	50%	50%	50%
Rebate %	1 of 3	45%	45%	45%
Administrative Fee		0%	0%	0%
Price Protection factor		n/a	n/a	n/a
Baseline WAC Date:		n/a	n/a	n/a

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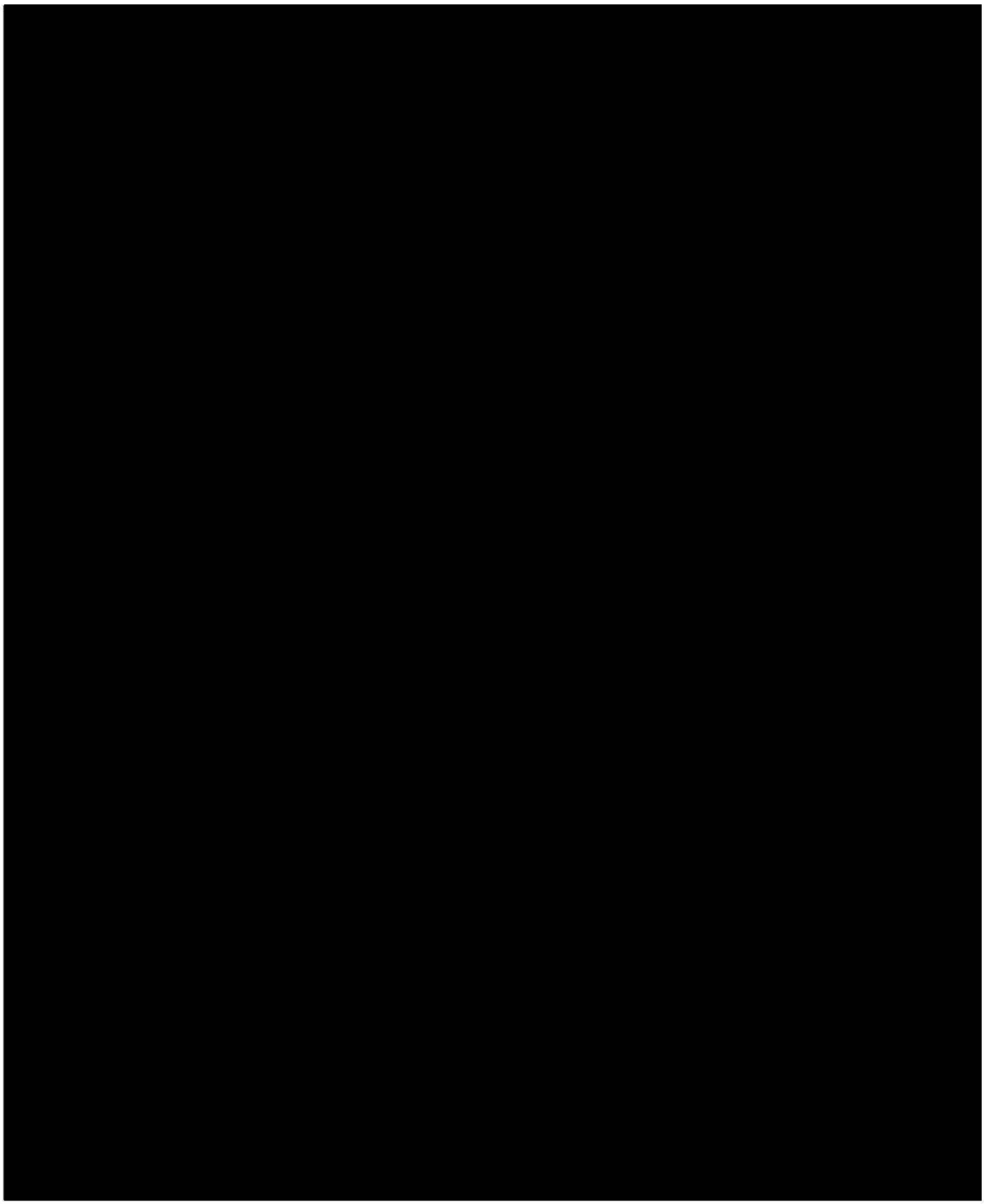

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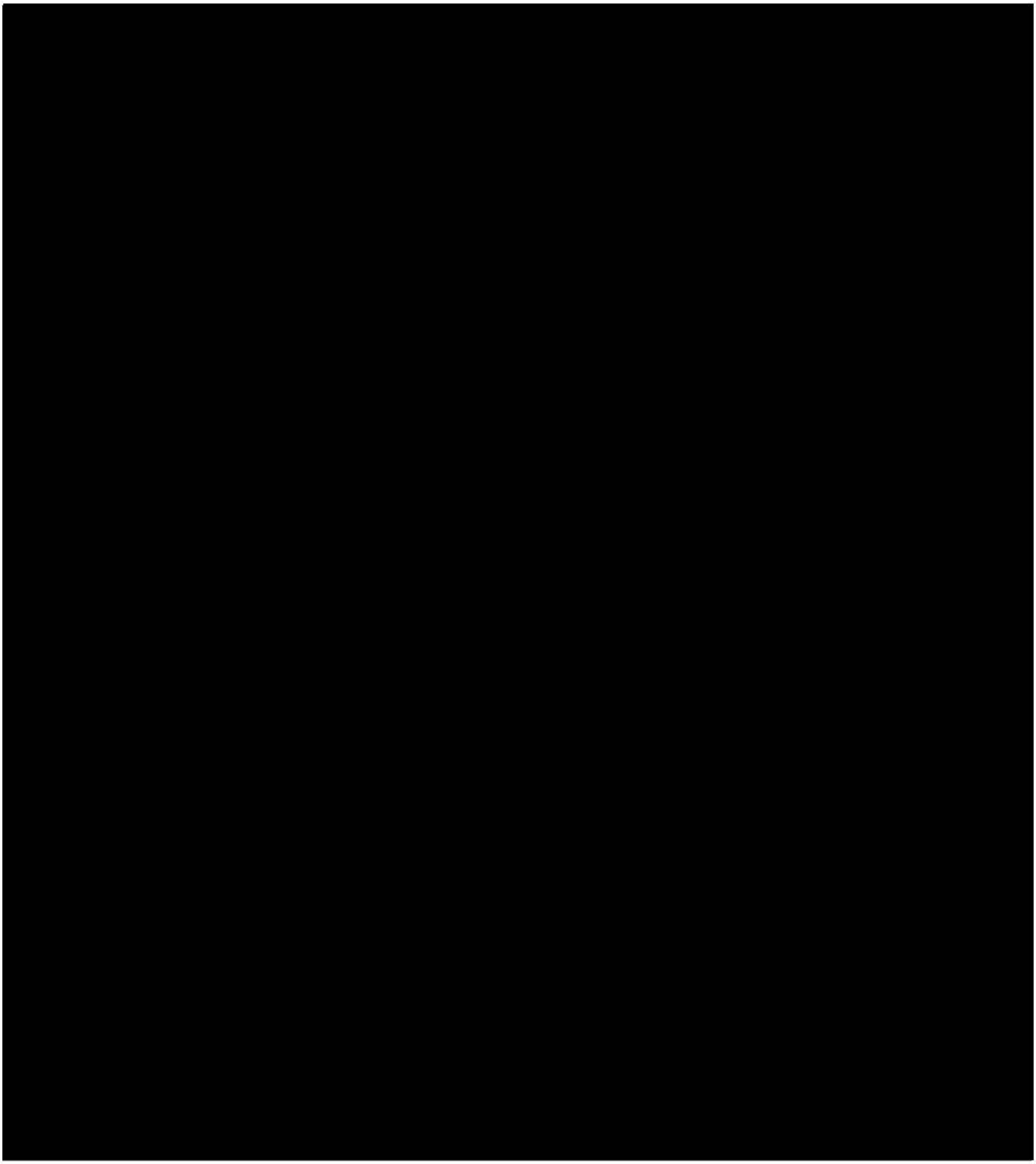

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6.3 PREFERRED – EXCLUSION

6.3.1 Only for Benefit Contracts with less than three and one-half (3.5) million Consumers.

6.3.1 (a) (Effective 1/1/2016 through 6/30/2017)

Manufacturer Drug Name: Lantus*				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	46%*	N/A	N/A
Administrative Fee		0%	N/A	N/A
Price Protection factor		7%	N/A	N/A
Baseline WAC Date:		1/1/14	N/A	N/A
Contract Year Start Date		7/1/14	N/A	N/A

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

6.3.1 (b) (Effective 1/1/2016 through 6/30/2017)

Manufacturer Drug Name: Apidra				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	60%	N/A	N/A
Administrative Fee		0%	N/A	N/A
Price Protection factor		N/A	N/A	N/A
Baseline WAC Date:		N/A	N/A	N/A
Contract Year Start Date		N/A	N/A	N/A

Conditions to Rebate for Rebate Tables 6.3.1 (a) Lantus and 6.3.1 (b) Apidra:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; provided that Drugs manufactured, marketed or distributed by one manufacturer in the Defined Drug Market will be considered as one Drug. All other competitive Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and

2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Lantus and Apidra shall not violate this condition: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus and Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus and Apidra pen provided there is an exception

process for such quantity limit when an exception is medically necessary and all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Lantus' and Apidra's Defined Drug Market are subject to quantity limit consistent with their respective package inserts.

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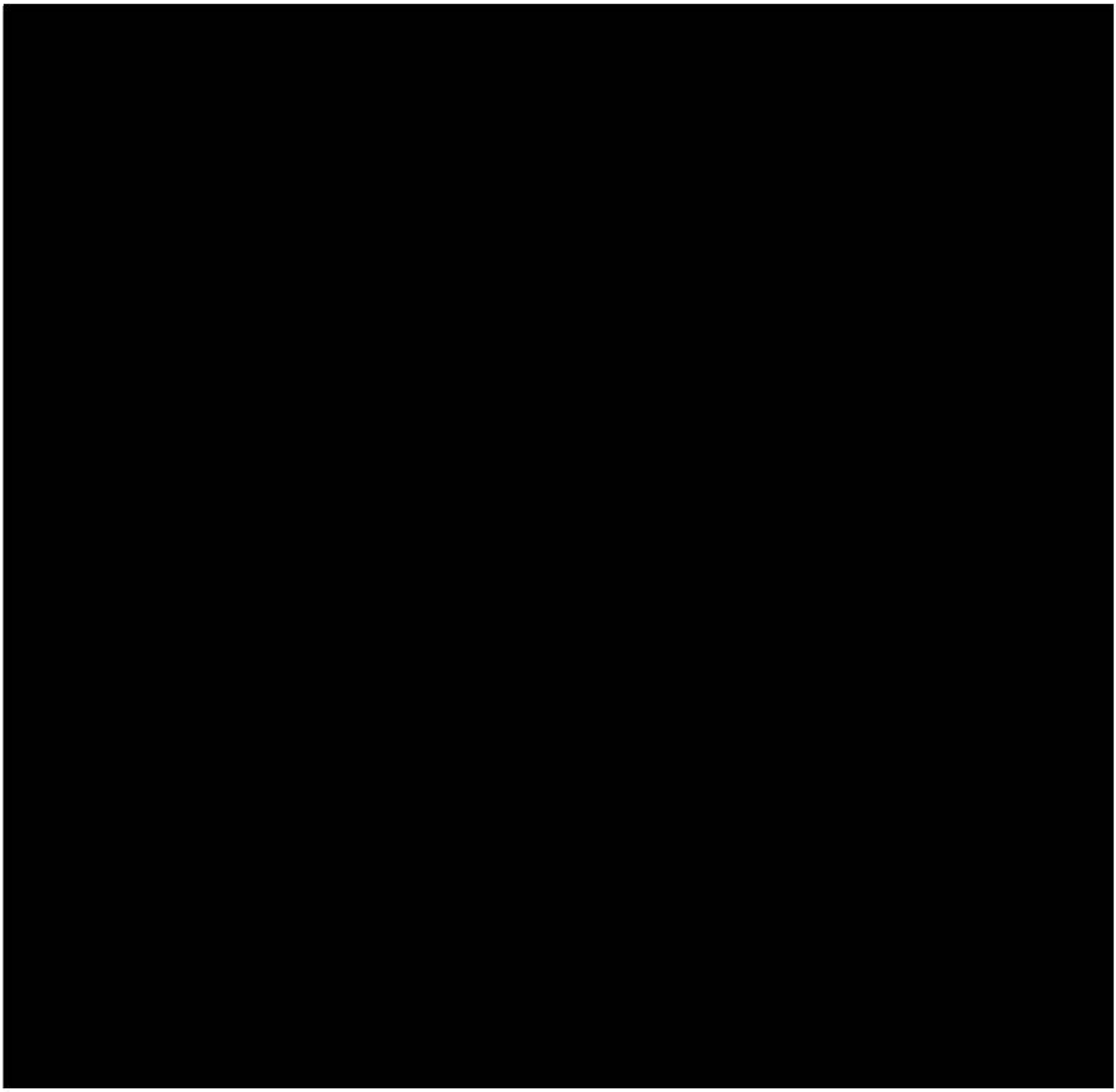

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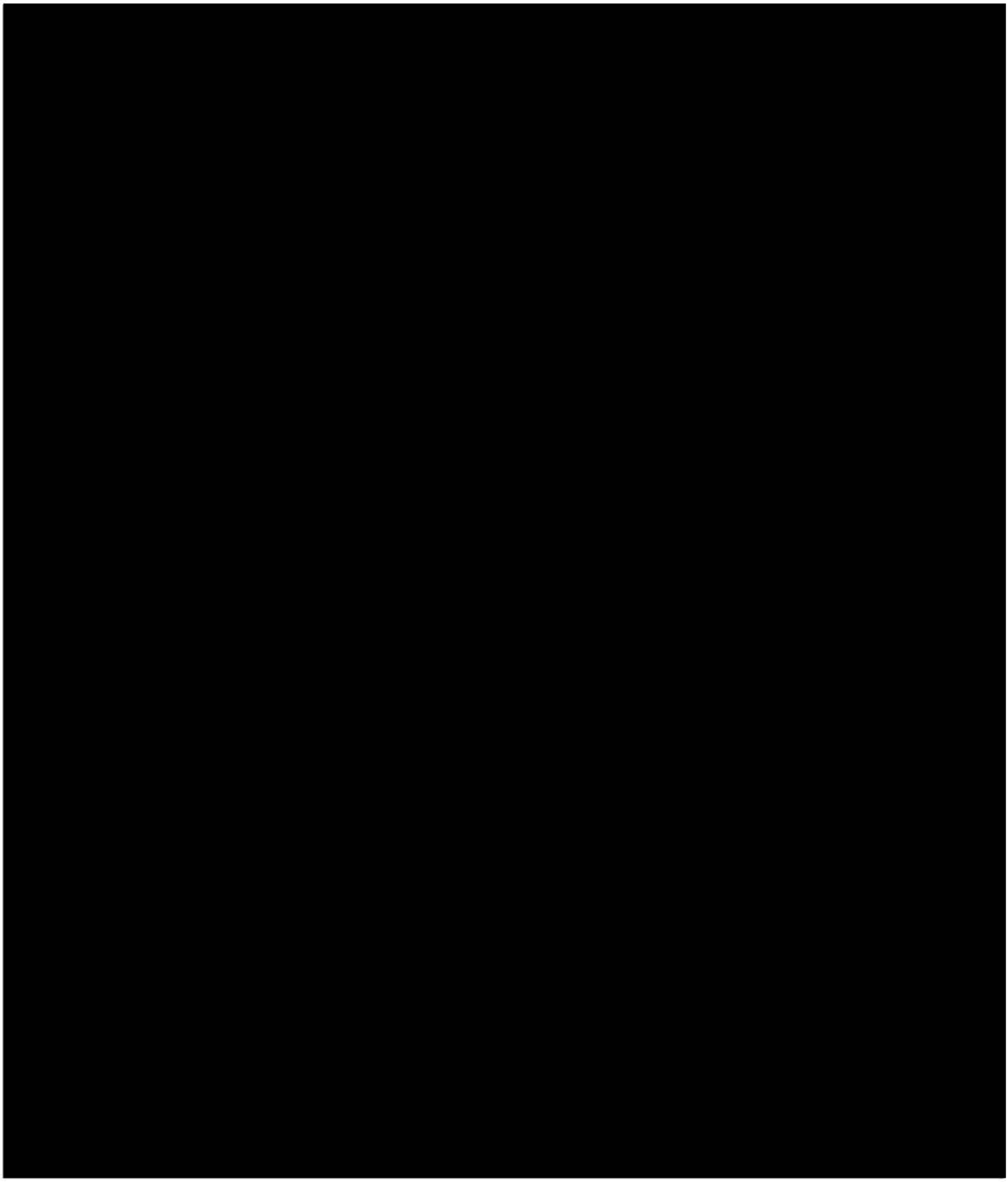

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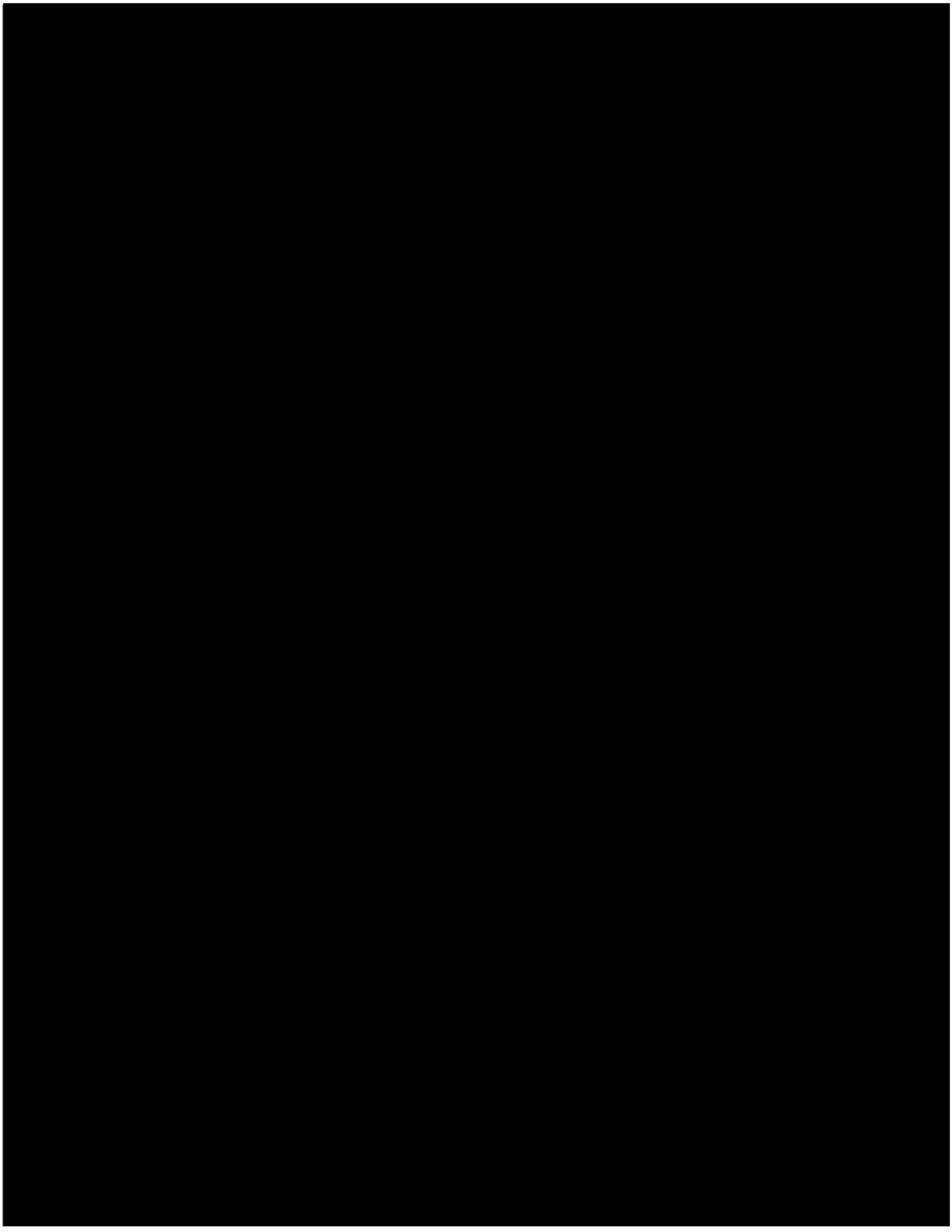

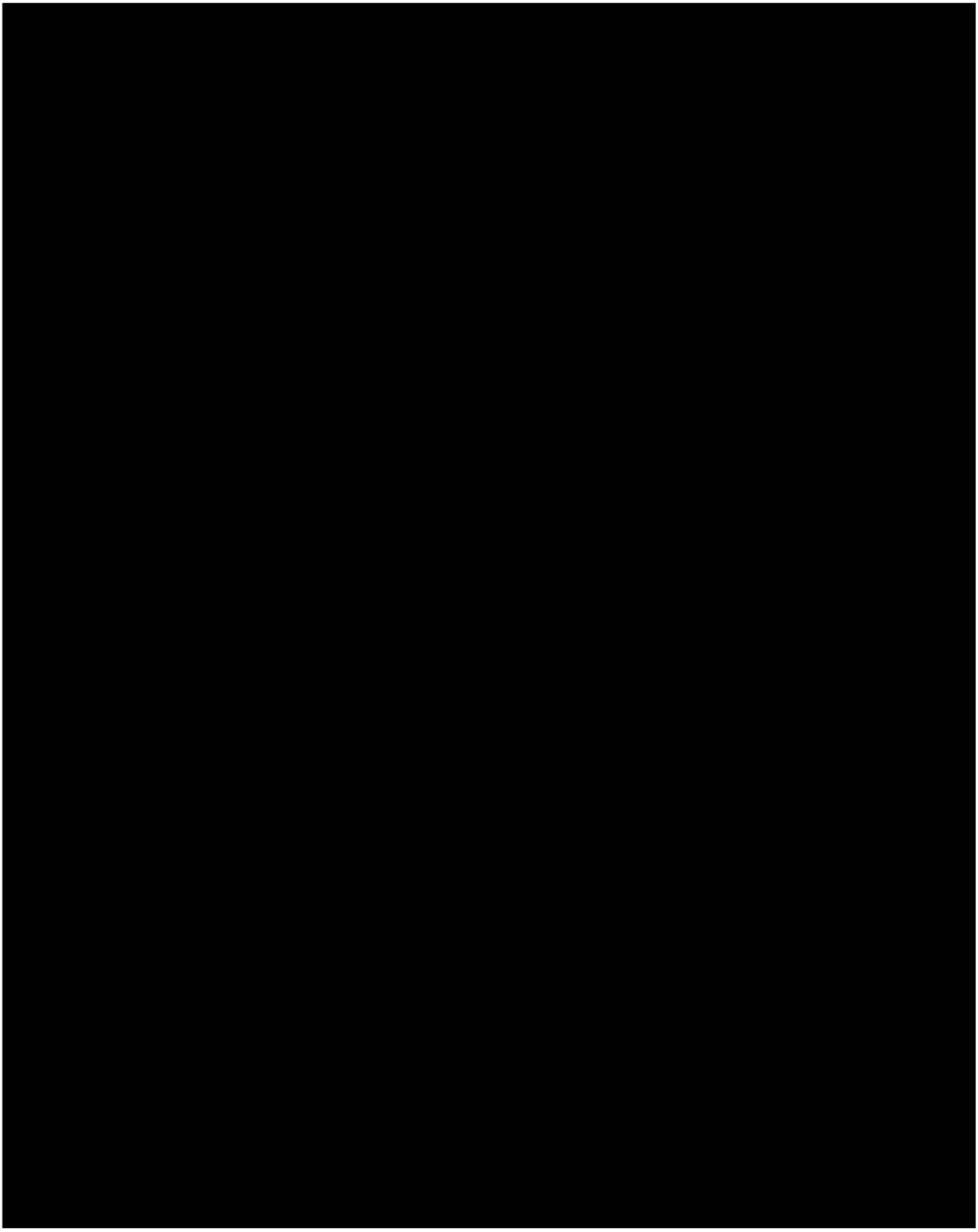

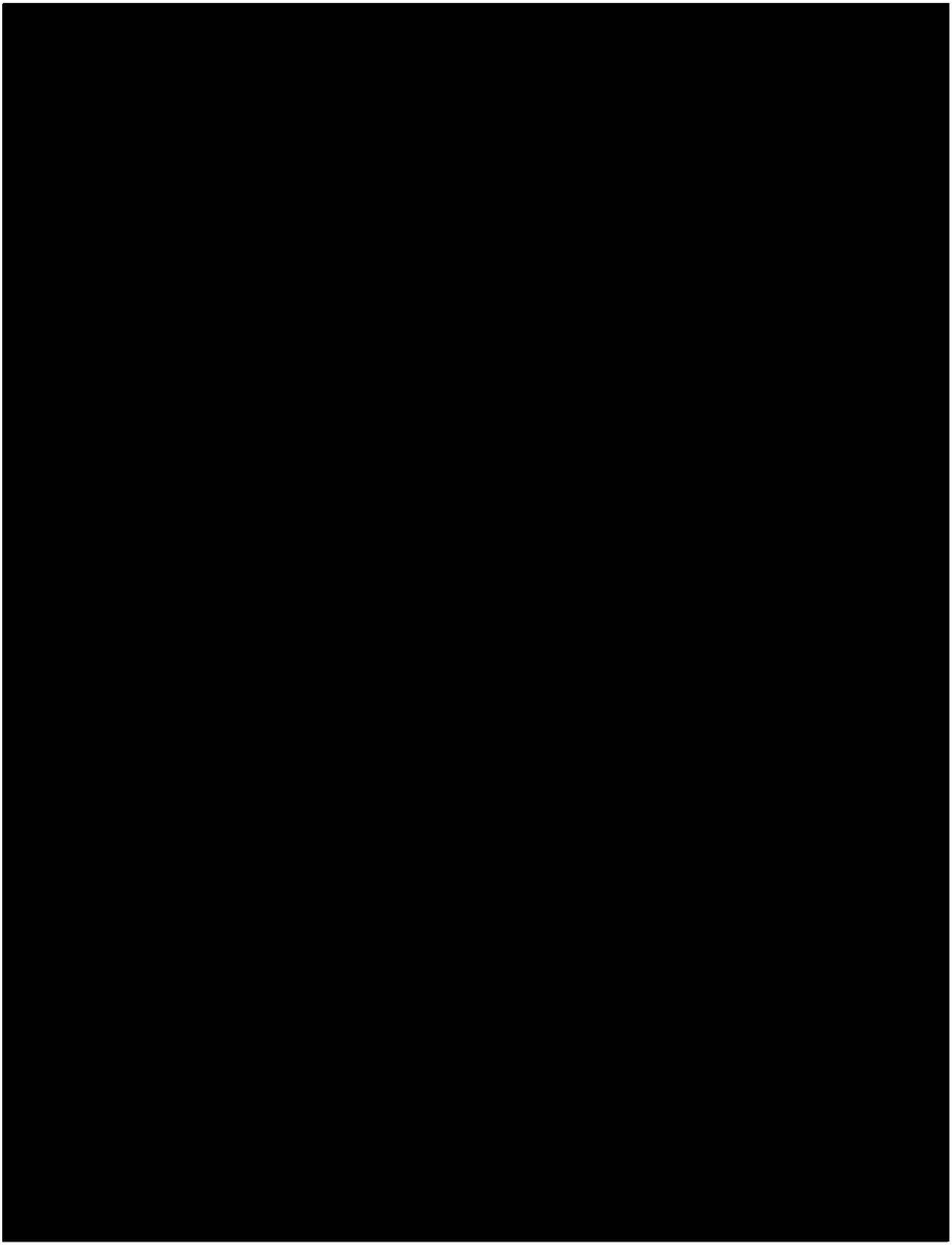

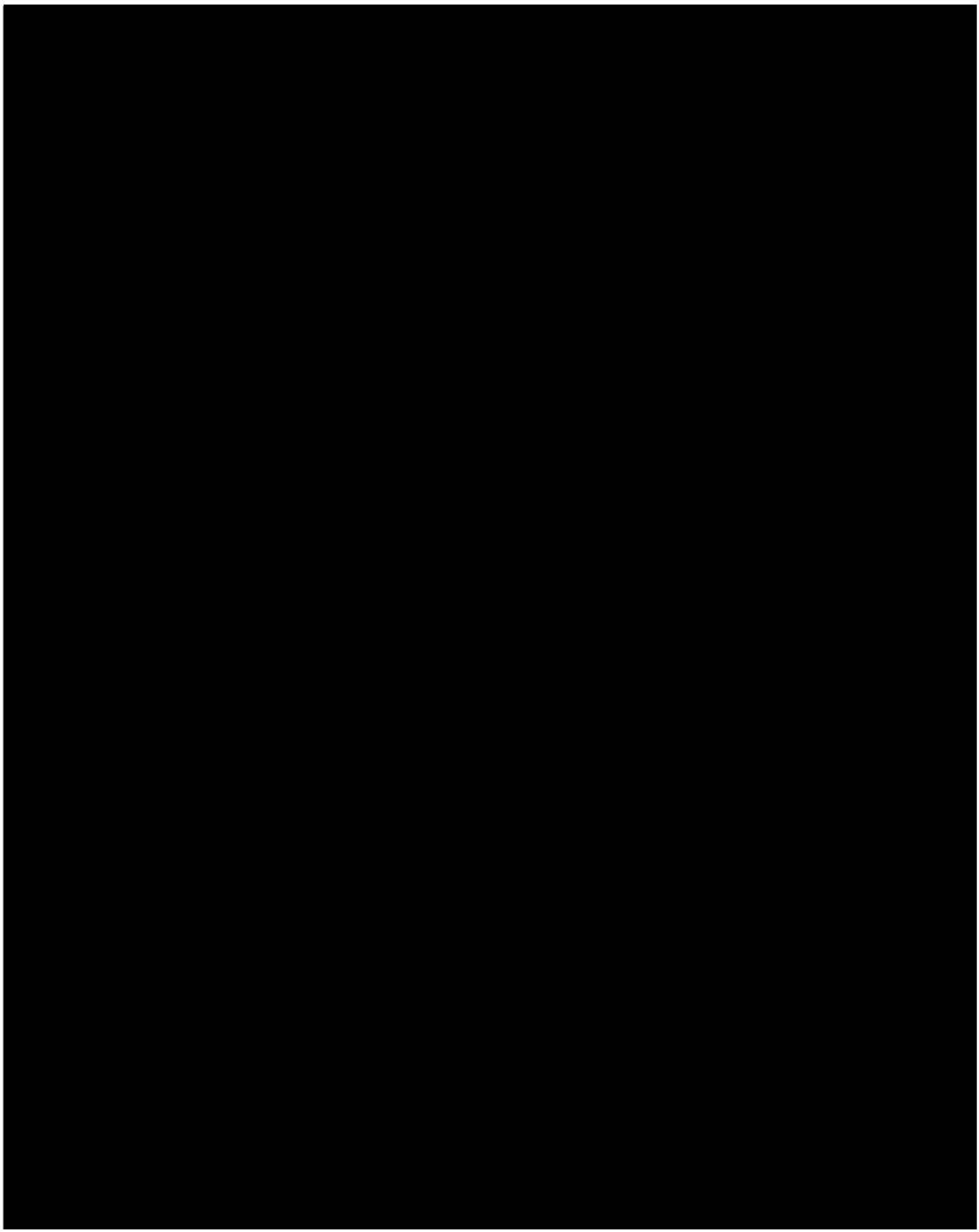

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7. **Rebate Terms - Managed Medicaid.**

7.1 **Lantus (Effective 12/15/2015 through 12/31/2015)**

Manufacturer Drug Name: Lantus*		
	Formulary Status	**Managed Medicaid**
Base Rebate Rate %	1 of 2	5%*
Administrative Fee		0%
Price Protection factor		n/a
Baseline WAC Date:		n/a

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

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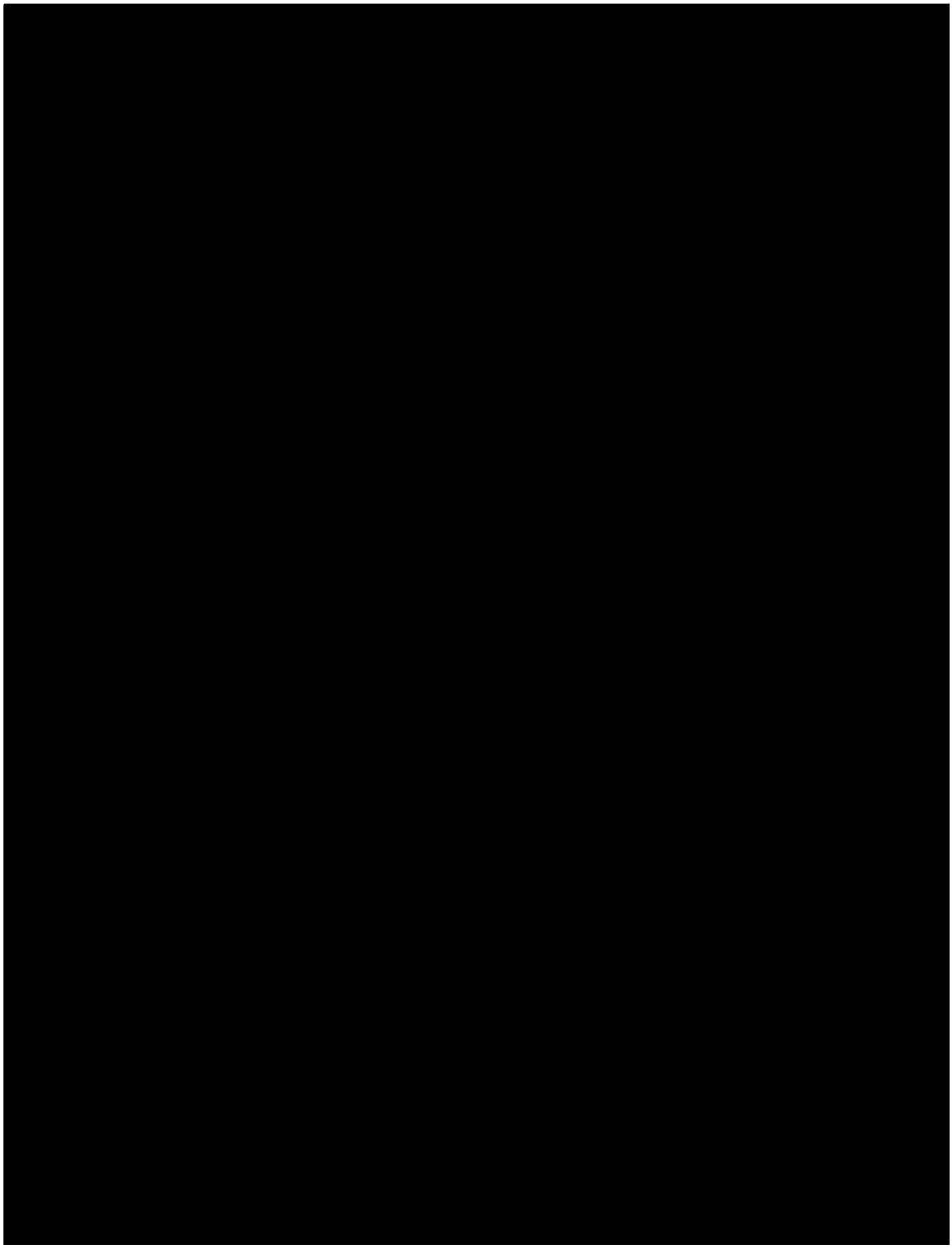

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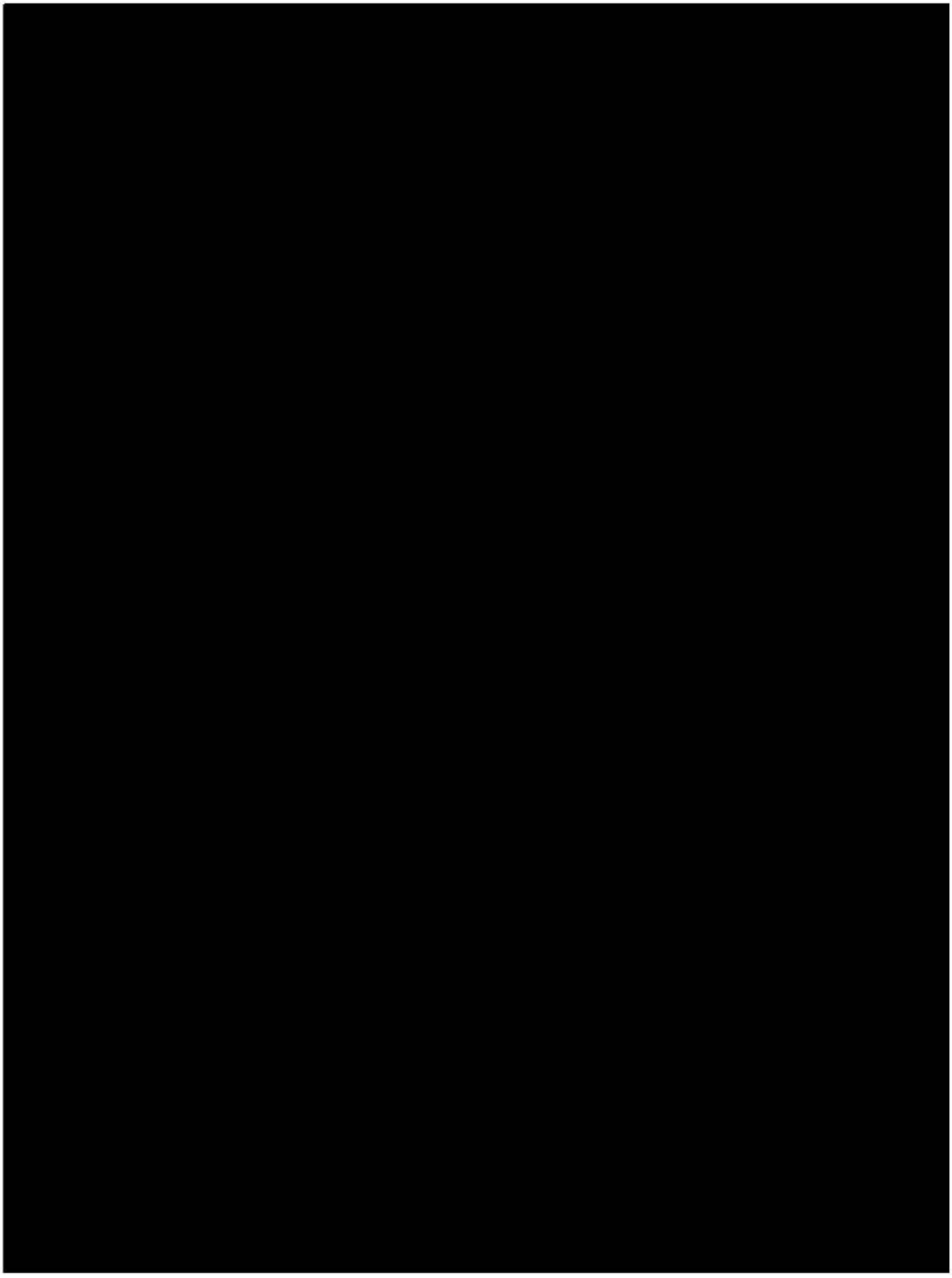

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7.6 (Effective 1/1/2016 through 12/31/16)

Manufacturer Drug Name: Toujeo		
Benefit Design:	**Formulary Status**	**Managed Medicaid**
Base Rebate Rate %	1 of 1	15%
Administrative Fee		0%
Price Protection factor		9.0%
Baseline WAC Date:		12/31/15

Conditions to Rebate for Rebate Tables 7.6 Toujeo:

1. All NDC's of Manufacturer Drug are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing; provided that Drugs manufactured, marketed or distributed by one manufacturer in the Defined Drug Market will be considered as one Drug. All other competitive Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and
2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Toujeo shall not violate this condition: (i) a quantity limit of no more than 225mls per 3-month supply on Toujeo provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Toujeo's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Toujeo's Defined Drug Market are subject to quantity limit consistent with their respective package inserts; and
3. Drugs within the Defined Drug Market must be subject to a step edit that requires the use of Toujeo for those Consumers who previously have never filled a prescription for Drugs within the Defined Drug Market.

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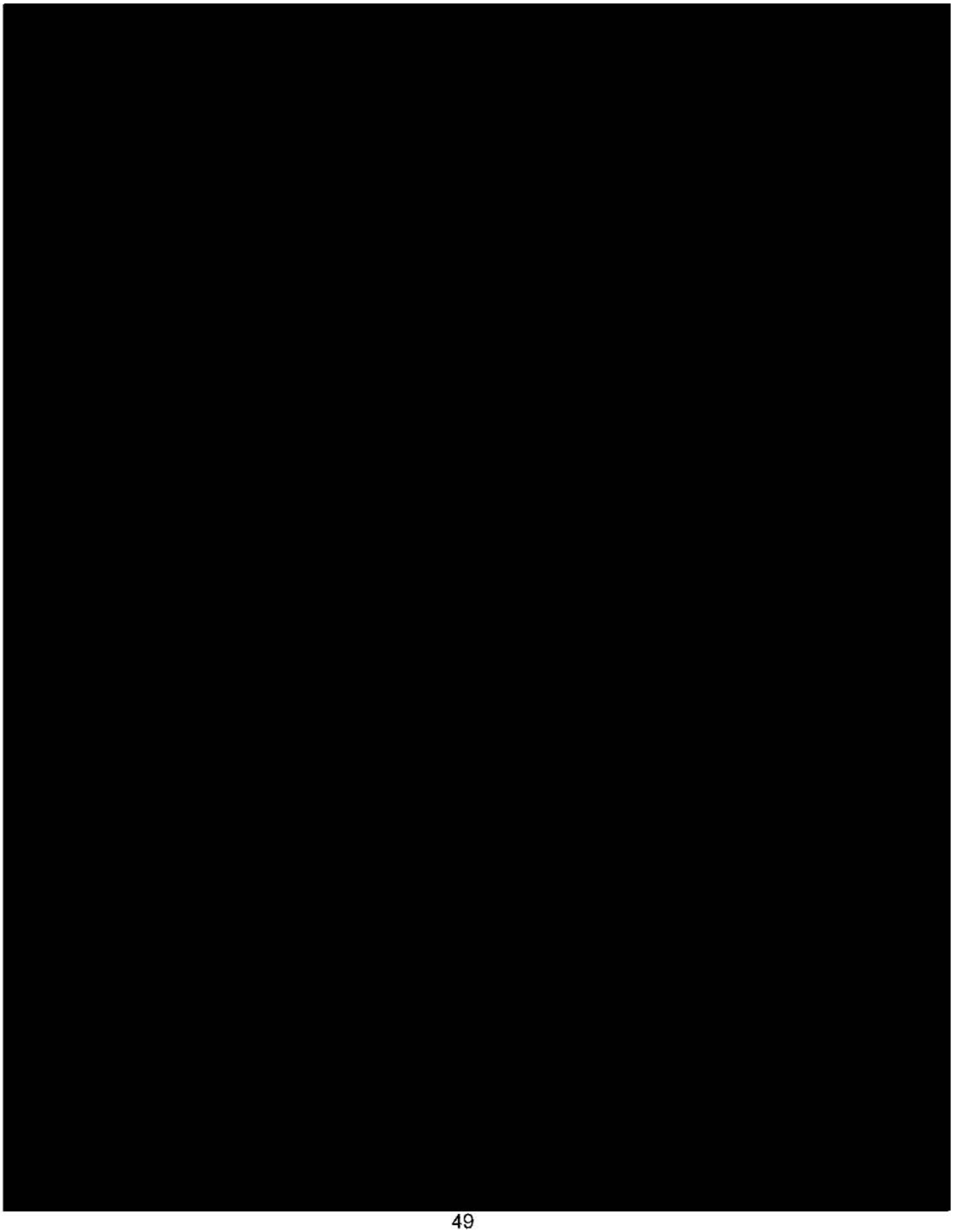
7.7 (Effective 1/1/2017 through 12/31/17)

Manufacturer Drug Name: Toujeo		
Benefit Design:	**Formulary Status**	**Managed Medicaid**
Base Rebate Rate %	1 of 1	15%
Administrative Fee		0%
Price Predictability factor		9.0%
Baseline WAC Date:		12/31/16

Conditions to Rebate for Rebate Tables 7.7 Toujeo:

1. All NDC's of Toujeo are on Formulary with Preferred status and the applicable Formulary Status in the table above as of the date of dispensing. All other brand name Drugs within the Defined Drug Market are not listed on Formulary and are not covered; and
2. Manufacturer Drug was not disadvantaged as compared to other brand name Drugs within the Defined Drug Market with regard to Administrator's or Contracting Payor's Utilization Controls. Notwithstanding the foregoing, imposition of any of the following quantity limit requirements on Toujeo shall not violate this condition: (i) a quantity limit of no more than 225mls per 3-month supply on Toujeo provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in Toujeo's Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in Toujeo's Defined Drug Market are subject to quantity limit consistent with their respective package inserts.

[redacted]



8. Rebate Terms – CHIP a stand-alone Federal healthcare program that operates independent from the Medicaid program as set forth in Article 2 Payment and Billing, Section 2.2.4

8.1 (Effective 12/15/2015 through 6/30/2017)

Manufacturer Drug Name: Lantus*		
Benefit Design:	**Formulary Status**	**CHIP**
Base Rebate Rate %	1 of 2	45%*
Administrative Fee		0%
Price Protection factor		7%
Baseline WAC Date:		1/1/14
Contract Year Start Date		7/1/14

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price.

8.2 (Effective 12/15/2015 through 6/30/2017)

Manufacturer Drug Name: Apidra		
Benefit Design:	**Formulary Status**	**CHIP**
Base Rebate Rate %	1 of 2 or less	50%
Base Rebate Rate %	1 of 3	45%
Administrative Fee		0%
Price Protection factor		n/a
Baseline WAC Date:		n/a

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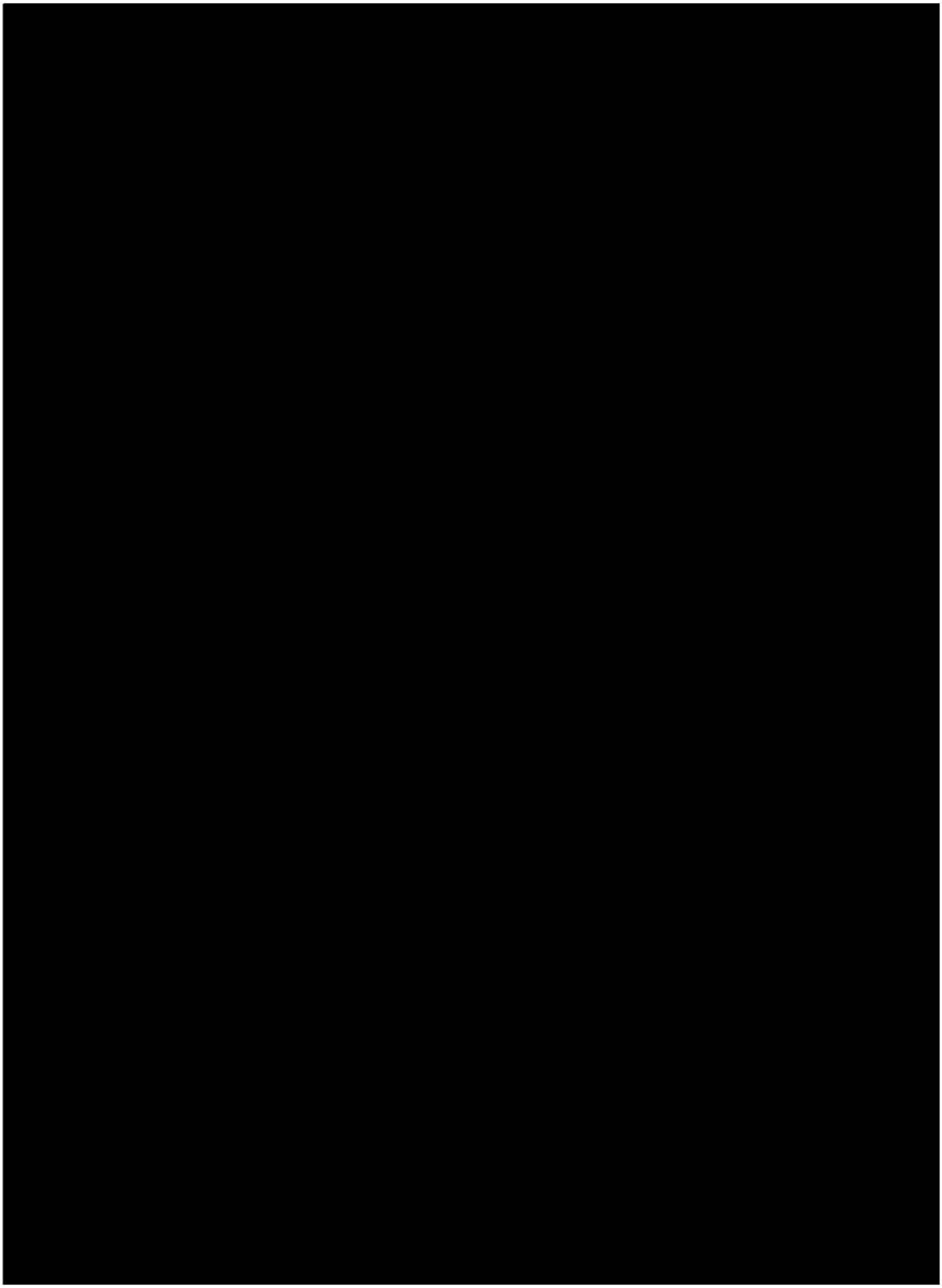

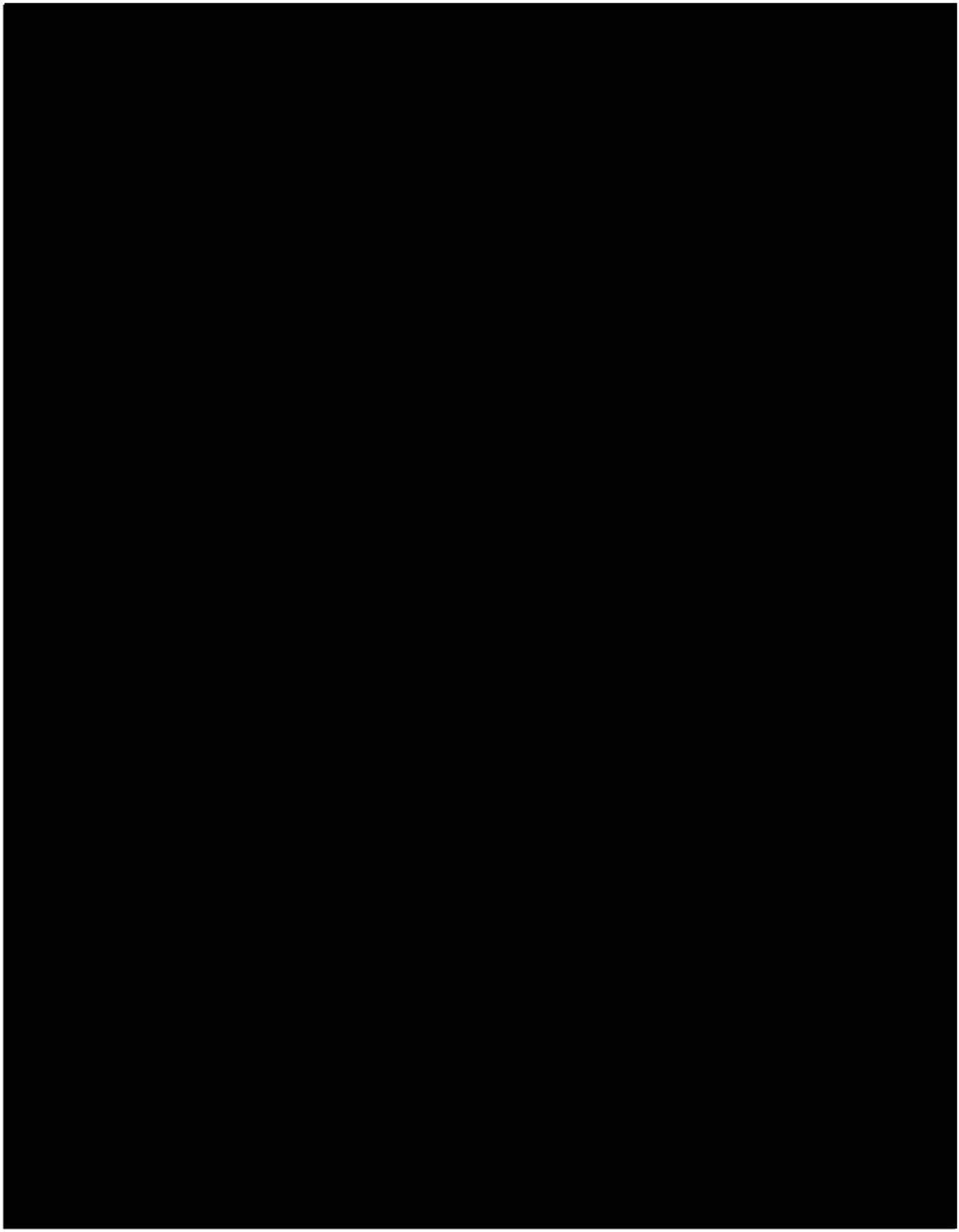

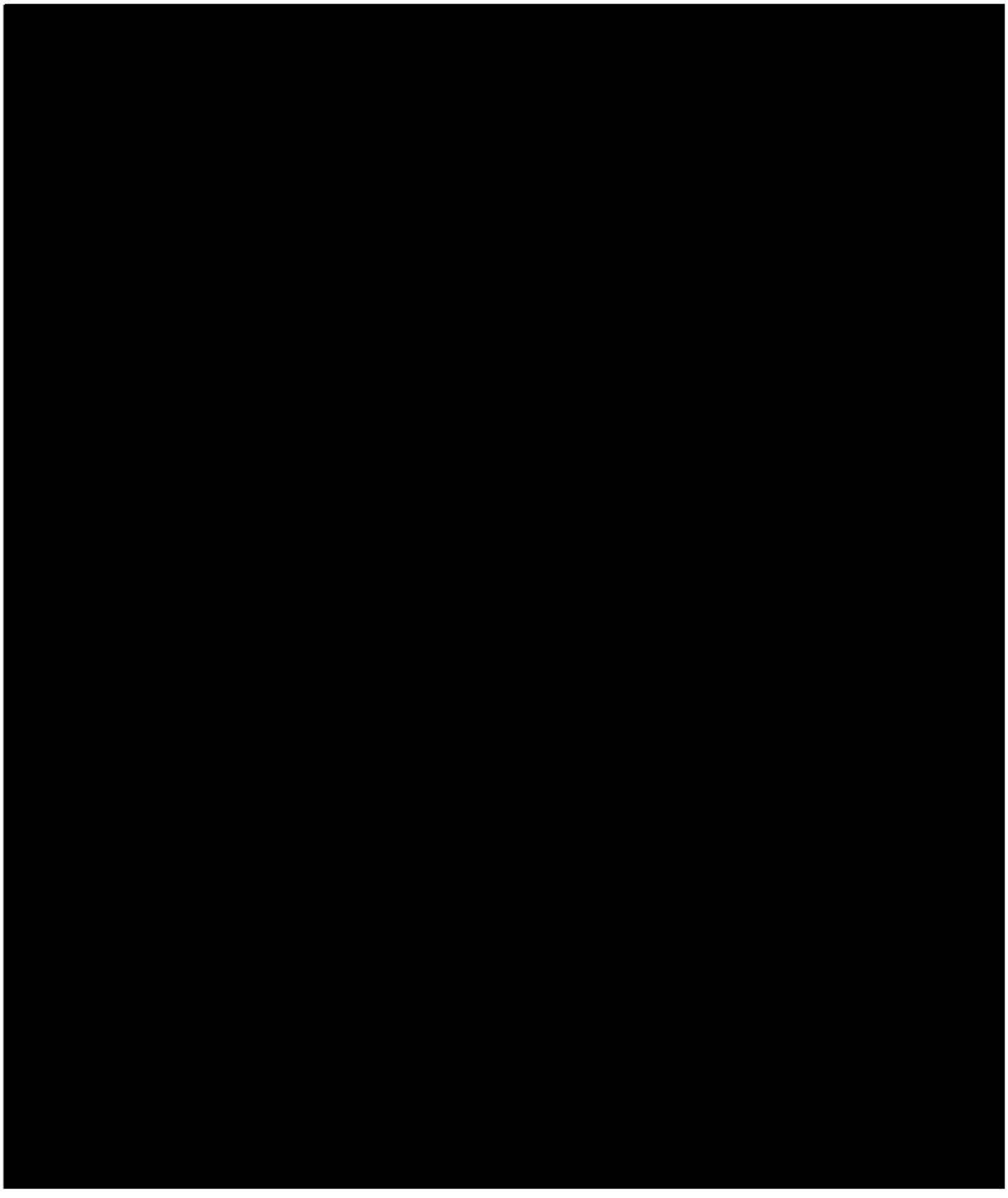

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General Rebate Criteria

This Section 8.8 is applicable to all Options in Section 8.8 of this Exhibit A. Manufacturer Drug may be subject to a prior authorization and such prior authorization shall not render the applicable utilization ineligible for Rebates or Administrative Fees so long as such prior authorization (or a modified version of such prior authorization that reflects clinically appropriate differences in FDA labeling or published clinical guidelines) is applied to all Drugs in Manufacturer Drug's Defined Drug Market.

Notwithstanding the foregoing, if a Benefit Contract subjects [redacted] utilization to a prior authorization program that contains or is more restrictive than the following criteria, such utilization is not eligible for Rebates:

ii. For patients with Atherosclerotic cardiovascular disease (ASCVD) (with or without heterozygous familial hypercholesterolemia (HeFH)) on a maximally tolerated lipid-lowering regimen, the requirement of an LDL-C threshold of more than 100 mg/dl.

ii. For patients with HeFH without ASCVD, on a maximally tolerated lipid-lowering regimen, the requirement of an LDL-C threshold of more than 130 mg/dl.

iii. As it relates to trial of other lipid lowering products, requirement of more than the following:

a. 12 week trial of maximally tolerated statin intensity (may require more than one statin trial to determine maximally tolerated intensity); and
b. 12 week trial of [redacted] or bile acid sequestrant.

Nothing in this section is intended to contradict FDA labeling or published clinical guidelines. If FDA labeling or clinical guidelines are updated to support criteria more restrictive than outlined above for the Defined Drug Market, prior authorization programs that include such criteria would be eligible for the Rebates and Administrative Fees outlined in this Amendment notwithstanding the inclusion of such criteria, provided such criteria is applied to all Drugs in Manufacturer Drug's Defined Drug Market.

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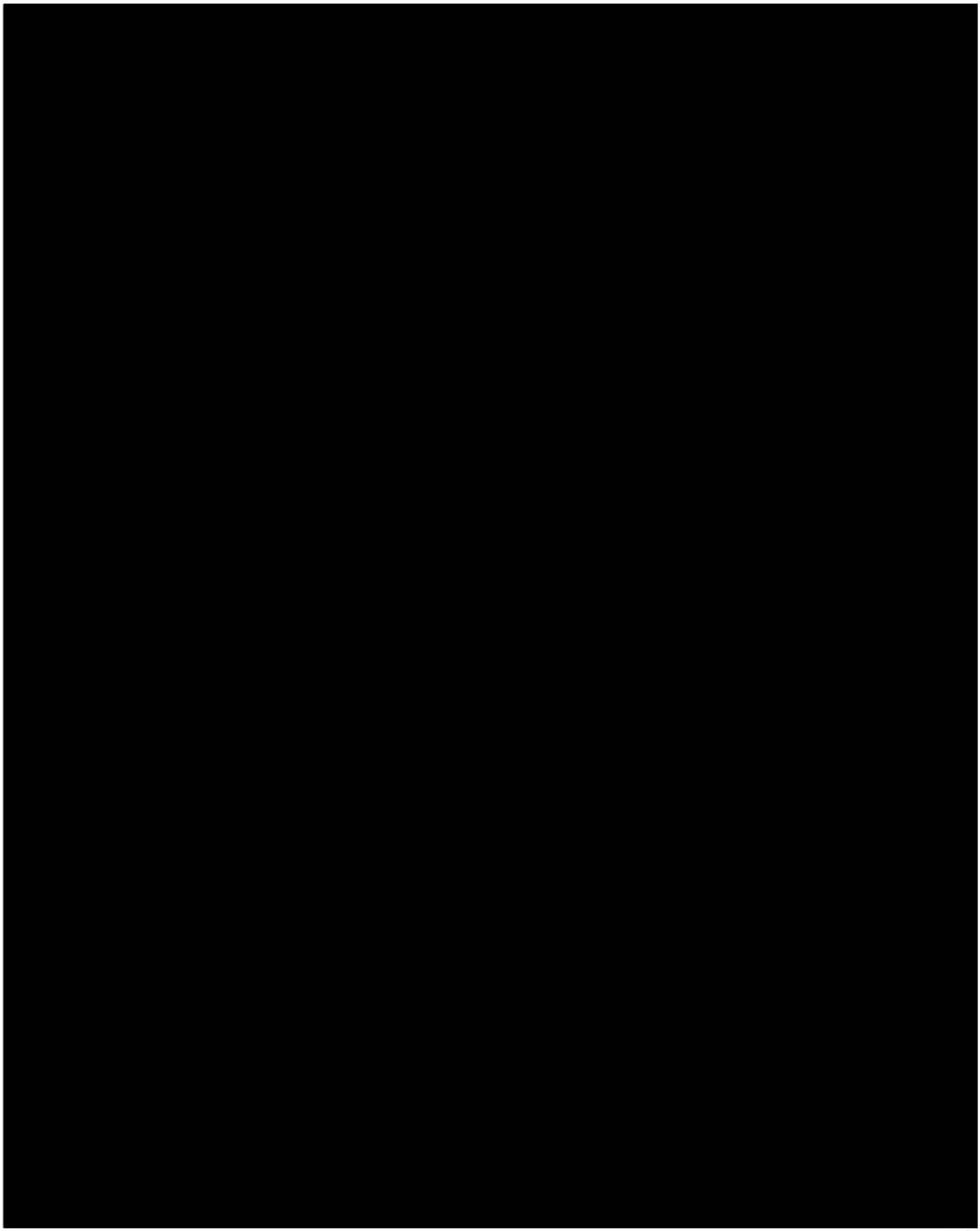

EXHIBIT D
DEFINED DRUG MARKET

MANUFACTURER DRUG	COMPETITIVE DRUG
Apidra® Apidra SoloStar®	Humalog Novolog Novolog FlexPen Humalog Kwik Pen
Toujeo SoloStar® Lantus® Lantus SoloStar®	Levemir Levemir FlexPen Levemir FlexTouch

[redacted]

SUPPLEMENTAL UTILIZATION DATA DRUG MARKET

MANUFACTURER DRUG	COMPETITIVE DRUG
Toujeo SoloStar®	Insulin
Lantus®	Humalog Mix 50/50
Lantus SoloStar®	Humalog Mix 75/25
	Humulin 50/50
	Humulin 70/30
	Humulin N
	Novolin Mix 70/30
	Novolin N
	Novolog Mix 70/30
	Relion Mix 70/30
	Relion N
	Ryzodeg 70/30
	Tresiba++
	Levemir
	Levemir FlexPen
	Levemir FlexTouch

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FOURTEENTH AMENDMENT TO THE REBATE AGREEMENT

This FOURTEENTH AMENDMENT TO THE REBATE AGREEMENT ("Amendment"), dated as of January 1, 2019 ("Amendment Effective Date"), is made and entered into by and between sanofi-aventis U.S. LLC, on behalf of itself and its affiliate Genzyme Corporation, ("Manufacturer") and OptumRx, Inc. ("Administrator"), on behalf of itself and its Contracting Payors, with reference to the following facts:

RECITALS

WHEREAS, Manufacturer and Administrator entered into that certain Rebate Agreement (as previously amended, the "Agreement"), with an effective date of January 1, 2013, providing, among other things, for Manufacturer to pay Rebates to Administrator on units of certain Manufacturer Drugs; and

WHEREAS, Manufacturer and Administrator mutually desire to amend the Agreement as stated below.

NOW THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Manufacturer and Administrator hereby agree to amend the Agreement as follows:

1. Effect of this Amendment. Capitalized terms used but not defined in this Amendment shall have the meanings ascribed to them in the Agreement. Except as otherwise amended by this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect. In the event there is any inconsistency or conflict between the provisions in this Amendment and those in the Agreement, the provisions in this Amendment shall supersede and control.

2. Section 1.17 is hereby deleted in its entirety and replaced as follows:

   1.17 "Provider" means any licensed prescriber or, licensed pharmacy, that is eligible to dispense Drugs to Consumers in accordance with the applicable Benefit Contract requirements and that has a valid National Provider Identifier (NPI) or National Council for Prescription Drug Programs (NCPDP) number. The term Provider does not include any pharmacy located outside of the United States, institutional pharmacy or government-owned pharmacy.

3. Sections 1.25 and 1.26 are hereby added to the Agreement as follows:

   1.25 "Rebate Sharing Program" means a program administered by Administrator on behalf of Contracting Payors pursuant to which a portion of Rebates are shared with Consumers to reduce the Consumer's share of a Drug's cost.

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1.26 "Utilization Controls" mean, unless such Utilization Controls applied are clinically appropriate in accordance with FDA labeling or indications and/or applied to all Drugs in the applicable Defined Drug Market, i) counter-detailing or counter-promoting, ii) switching or therapeutic substitution, iii) hard edit prior authorization, iv) NDC lock, v) step edit, and (vi) a quantity limit more restrictive than a Drug's package insert. For purposes of this definition, "Utilization Controls" excludes communications or education programs designed to encourage the use of generic Drugs, and any aspects of Administrator's or Contracting Payor's communication, website, or other activity whereby Consumers have access to or are made aware of prices of Drugs and/or the availability of over-the-counter products for purposes of managing Consumer cost sharing amounts.

4. Romanettes (vi) and (vii) are hereby added to Section 2.5 of the Agreement as follows:

(vi) if there is a material shortage or public health and/or other material safety concern impacting the availability of a Manufacturer Drug ("Shortage"), then beginning on the date provided in such notice that Administrator is required to provide to Manufacturer (as set forth below) and continuing through the first date following the end of such impacted availability on which the applicable Benefit Contract is reasonably capable of reversing the Formulary and Utilization Control changes made in response to such impacted availability, a Benefit Contract may place additional Drugs on the co-payment amount or co-insurance percentage tier on which such Manufacturer Drug is positioned, or remove Utilization Controls from Drugs in Manufacturer Drug's Defined Drug Market, without losing eligibility for the Rebate rate that such Benefit Contract would have been entitled to in the absence of such Formulary and/or Utilization Control changes, provided that (a) if any Contracting Payor elects to modify its Formulary or utilization management protocols in response to such Shortage, Administrator shall notify Manufacturer of such Shortage and specify the date that Contracting Payor(s) will be making Formulary and/or Utilization Control changes and (b) if Manufacturer reasonably disputes the existence of the Shortage on which such Formulary and/or Utilization Control changes were based, Manufacturer retains its right to dispute applicable portions of Rebate invoices in accordance with Section 2.2.3; and (vii) any impact to a Consumer's cost sharing obligation (e.g., co-payment amount, co-insurance percentage, or other patient cost responsibility) resulting from the implementation of a Rebate Sharing Program will not be taken into account when determining whether a Benefit Contract has satisfied applicable Rebate conditions set forth in Exhibit A and the implementation of a Rebate Sharing Program involving a Manufacturer Drug may cause Consumers to be aware that a Rebate relationship exists between Administrator and Manufacturer.

5. Section 5.1 of the Agreement is hereby deleted in its entirety and replaced by the following new Section 5.1:

5.1 Term. This Agreement shall become effective as of the Effective Date and shall remain in effect through **December 31, 2022**. Unless otherwise terminated as provided for herein, this Agreement shall renew for successive terms of twelve (12) months on the

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applicable anniversary of the Effective Date, upon the mutual written agreement of the parties.

6. Section 4.6 of the Agreement is hereby deleted in its entirety and replaced by the following new Section 4.6:

4.6 Regulatory Compliance.

4.6.1 The Rebates received under this Agreement may represent discounts within the meaning of Section 1128B(b) of the Social Security Act and its implementing regulations (42 C.F.R. § 1001.952) which shall be fully and accurately disclosed and reported by Administrator and/or Contracting Payor to the extent required under applicable Law; and (b) Administrator and/or Contracting Payor will disclose to each Qualified Health Plan, Exchange, or CMS the amount of Rebates received under this Agreement in the form and manner and to the extent required under applicable Law.

4.6.2 The parties intend that: (i) the Rebates qualify for safe harbor protection pursuant to the "Discount Safe Harbor," 42 C.F.R. 1001.952(h)(the "Discount Safe Harbor"); and (ii) the Administrative Fees qualify for safe harbor protection pursuant to the "GPO Safe Harbor," 42 C.F.R. 1001.952(j).

4.6.2.1 Manufacturer understands that Administrator's agreements with Contracting Payors may require Administrator to share some or all of the Administrative Fees with Contracting Payors.

7. Section 7.6 of the Agreement, "Notices," is hereby deleted in its entirety and replaced by the following new Section 7.6:

7.6 Notices. Except as set forth in Sections 2.1, 2.2, 3.2, 3.3 or as otherwise specified elsewhere in this Agreement, any notice required to be given under this Agreement shall be in writing and shall be deemed to have been duly given: (i) when delivered, if sent by United States registered or certified mail (return receipt requested); (ii) when delivered, if delivered personally by commercial courier; or (iii) on the second following business day, if sent by United States Express Mail, Federal Express or other commercial overnight courier, in each case to the following address (or at such other address as shall be specified by like notice) with applicable postage or delivery charges prepaid:

If to Administrator:
OptumRx, Inc.
17900 Von Karman Avenue, M/S CA016-0202
Irvine, CA 92614
Attn: S.V.P., Industry Relations

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With a copy to:
OptumRx, Inc.
2300 Main Street
M/S CA134-0507
Irvine, CA 92614
Attn: Industry Relations Legal Support

If to Manufacturer:
sanofi-aventis
Attention: Director, Contract Development
55 Corporate Drive
Mail Code 55B-300 US Market Access
Bridgewater, NJ 08807

With a copy to:
sanofi-aventis
Attention: Vice President and General Counsel
55 Corporate Drive
Mail Code 55A-525
Bridgewater, NJ 08807.

8. Exhibit A of the Agreement is hereby deleted in its entirety and replaced with the following new Exhibit A attached hereto.

9. Exhibit D of the Agreement is hereby deleted in its entirety and replaced with the following new Exhibit D attached hereto.

IN WITNESS WHEREOF the parties have caused this Amendment to be executed by their duly authorized officers or representatives as of the date first set forth above.

OptumRx, Inc.

By: _____

Print Name: Kent Rogers

Print Title: SVP, Industry Relations

Date: 9.21.18

sanofi-aventis U.S. LLC

By: _____

Print Name: [illegible]

Print Title: [illegible]

Date: 10/03/2018

EXHIBIT A
REBATE AND ADMINISTRATIVE FEE SCHEDULE

The terms and conditions in this Exhibit A are in addition to those Rebate terms and conditions otherwise set forth in Section 3.1.1 of the Agreement.

1. Definitions

1.1 Benefit Design

i. "Covered" means a Benefit design that does not qualify as a Managed or Highly Managed Benefit design.

ii. "Managed" means a Benefit design characterized by a Formulary under which the Contracting Payor directly or indirectly influences availability, or gives preference in dispensing decisions, of Drugs in one or more of the pharmaceutical categories serviced by such Formulary through (a) monetary restrictions (e.g., differential dollar Consumer co-payments for generic, branded Preferred and branded non-Preferred status as defined and determined by the Contracting Payor, where branded non-Preferred Drugs and branded Preferred Drugs have no less than an average co-payment differential of ten dollars ($10.00), or a co-insurance percentage differential), or (b) prior authorizations, NDC locks, step edits, or other similar mechanisms where certain Drugs are intended to be more restricted in availability than other Drugs.

iii. "Highly Managed" means a Benefit design characterized by a Formulary under which a Contracting Payor directly or indirectly influences availability, or gives preference in dispensing decisions, of Drugs in a significant portion of the pharmaceutical categories serviced by such Formulary through prior authorizations, NDC locks, step edits, or other similar mechanisms where certain Drugs are intended to be more restricted in availability than other Drugs.

1.2 "Formulary Status" means the position a Manufacturer Drug has on Formulary. A Formulary Status that is designated as 1 of [X] means that the Manufacturer Drug is 1 of [X] single-source brand name Drugs in the Defined Drug Market with the applicable Formulary Status; provided that for the purpose of determining if this condition for Rebate has been met, line extensions of Drugs within the Manufacturer Drug's Defined Drug Market manufactured by the same manufacturer shall be considered as one Drug [redacted]

1.3 "Preferred" means (i) a Drug is covered by a Benefit and is adjudicated on the Formulary tier that has the lowest co-payment amount or co-insurance percentage for brand name Drugs for the applicable Defined Drug Market and where the co-payment amount or co-insurance percentage for such Drug is lower than that of Drugs in the Defined Drug Market designated as "non-preferred", or (ii) a Drug is covered by a Benefit where the Drugs designated as "preferred" are covered by the Benefit and the Drugs excluded from Formulary or designated on Formulary as "non-preferred" or "excluded" are not covered by the Benefit or (iii) for Covered Benefit designs only, a Drug is covered by a Benefit

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where Drugs designated as "preferred" are covered by the Benefit and Manufacturer Drug is no more restricted in its availability than other brand name Drugs in the same Defined Drug Market.

1.4 "Specialty Tier" means a separate category or tier of the Formulary designated for very high cost or unique Drugs.

1.5 "Unrestricted Access" when referring to Lantus means a Manufacturer Drug is covered by a Benefit with no Utilization Controls, except for the allowances under the conditions to Rebates in Exhibit A. But when referring to all other Manufacturer Drugs, means a Manufacturer Drug covered by a Benefit with no Utilization Controls, except for the allowances set forth in 1.26 Utilization Controls in Article 1.

2. Rebate Calculation

Rebates for each Manufacturer Drug will be based upon the Formulary status of the Manufacturer Drug as of the date the Manufacturer Drug is dispensed. Rebates will be calculated on a per Unit dispensed basis. For each month, the Rebates for each Manufacturer Drug shall be calculated as follows:

Rebate = (Unit(s) of Manufacturer Drug) x (WAC) x (Total Rebate Rate for the applicable Manufacturer Drug)

3. Administrative Fee

The Administrative Fee rate is 4.75% for each Rebate eligible Unit of Manufacturer Drug. The Administrative Fee shall not be charged on QRPDP, Managed Medicaid and CHIP utilization, and any other utilization where prohibited by Law. With respect to any Administrative Fees paid by Manufacturer to Administrator, Administrator has informed Manufacturer that it will not agree not to pass through the Administrative Fee. Accordingly, Manufacturer will comply with the Discount Safe Harbor and recognize these as discounts in its federal price reporting. For each month, the Administrative Fee shall be calculated as follows:

Administrative Fee = (Unit(s) of Manufacturer Drug) x (WAC) x (Administrative Fee rate %)

4. Protection of Rebate Amount.

4.1 Price Protection

This Section 4.1 pertains to all Manufacturer Drugs except (a) where the "Price Protection factor" is denoted by "n/a" in the applicable Rebate tables in Sections 5, 6, 7, and 8 of Exhibit A of the Agreement or (b) those Manufacturer Drugs covered in Section 4.2 of Exhibit A of the Agreement.

i. Rebate rates are subject to automatic adjustment in the event the WAC per Unit for Manufacturer Drug exceeds the "Allowed WAC per Unit".

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ii. The initial "Allowed WAC per Unit" for a Manufacturer Drug is calculated by multiplying the WAC per Unit as of the date set forth in the Rebate terms below ("Baseline WAC Date") for the applicable Manufacturer Drug by (100% plus the "Price Protection" factor). The "Price Protection" factor is set forth in the Rebate terms below for the applicable Manufacturer Drug.

iii. The initial Allowed WAC per Unit for a Manufacturer Drug will apply during the "Initial Price Protection Period". The "Initial Price Protection Period" is defined as the 12-month period, or such other initial time period when indicated in the Rebate terms below, following such Manufacturer Drug's Price Protection Year Start Date, which date is set forth in the Rebate terms below. The applicable Manufacturer Drug's "Price Protection Year" is defined individually as the "Initial Price Protection Period" and each subsequent 12-month period.

iv. The "Base Rebate Rate %" is the then-current Rebate percentage for the Manufacturer Drug set forth in the Rebate tables below.

v. The "Allowed WAC per Unit" for subsequent Price Protection Years is calculated by multiplying the "Allowed WAC per Unit" for the previous Price Protection Year by (100% plus the "Price Protection" factor).

vi. The "Net WAC per Unit" is calculated by multiplying the WAC per Unit by (100% minus the Base Rebate Rate %).

vii. The "Net Allowed WAC per Unit" is calculated by multiplying the "Allowed WAC per Unit" by (100% minus the Base Rebate Rate %).

viii. Effective as of the date the WAC per Unit first exceeds the "Allowed WAC per Unit" and continuing for the remainder of that "Price Protection Year", subject to further adjustments in accordance with this Section 4.1 of this Exhibit A Rebate and Administrative Fee Schedule, an "Additional Rebate Rate" will be paid.

ix. The "Additional Rebate Rate" is calculated by determining the amount, if any, that the "Net WAC per Unit", in effect at the time the applicable Manufacturer Drug is dispensed, exceeds the "Net Allowed WAC per Unit" in effect at the time the applicable Manufacturer Drug is dispensed, divided by the then-current WAC per Unit.

x. The resulting percentage is the "Additional Rebate Rate" and is added to the "Base Rebate Rate %" to produce a "Total Rebate Rate" that applies to such utilization. For avoidance of doubt, the "Total Rebate Rate" calculation is subject to the terms of Section 2.2.6 Best Price in Article 2 except where otherwise indicated in this Exhibit A.

*The term "Net Allowed WAC" is used herein solely to explain the calculation of price protection in this Agreement. This term is not used outside of this Agreement and, furthermore, is not meant to define or describe any pricing terms of a Manufacturer Drug.

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EXAMPLE 1:

Price Protection factor	6%	Year 1 Price increase 10%					Year 2 Price increase 10%					Year 3 Price increase 10%				
	Assumed WAC as of 12/31/2013	Jan. 2014	Feb. 2014	Mar. 15 2014		Dec. 2014	Jan. 2015	Feb. 2015	Mar. 2015		Dec. 2015	Jan. 2016	Feb. 2016	Mar. 2016		Dec. 2016
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60	→	6.60	6.60	6.60	7.26	→	7.26	7.26	7.26	7.99	→	7.99
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36		6.36	→ 6.74	6.74	6.74		6.74	→ 7.15	7.15	7.15		7.15
Current WAC/ Unit (New NDC)								6.60	7.26	→	7.26	7.26	7.26	7.99	→	7.99
Allowed WAC/ Unit (New NDC)								6.74	6.74		6.74	→ 7.15	7.15	7.15		7.15
Current Net WAC / Unit		5.40	5.40	5.94		5.94	5.94	5.94	6.53		6.53	6.53	6.53	7.19		7.19
Net Allowed WAC / Unit	5.40	5.72	5.72	5.72		5.72	6.07	6.07	6.07		6.07	6.43	6.43	6.43		6.43
Additional Rebate		$0.00	$0.00	$0.22		$0.22	$0.00	$0.00	$0.47		$0.47	$0.10	$0.10	$0.76		$0.76
Additional Rebate Rate		0.0%	0.0%	3.3%		3.3%	0.0%	0.0%	6.4%		6.4%	1.4%	1.4%	9.5%		9.5%
Base Rebate Rate %	10.0%	10.0%	10.0%	10.0%		10.0%	10.0%	10.0%	10.0%		10.0%	10.0%	10.0%	10.0%		10.0%
Total Rebate Rate	10.0%	10.0%	10.0%	13.3%	→	13.3%	10.0%	10.0%	16.4%	→	16.4%	11.4%	11.4%	19.5%	→	19.5%

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If a New NDC is introduced in the market after the date that such Manufacturer Drug becomes covered by this Agreement, the Additional Rebate Rate for such New NDC(s) will be calculated consistent with the preceding paragraph except that (i) the Net Allowed WAC per Unit for the Existing NDCs (defined below) will apply to the New NDC(s) during each billing period and (ii) the Net WAC per Unit of such New NDC(s) will be adjusted to account for differences, if any, in days of therapy, unit size, strength, or similar factors, between the New NDC(s) and their corresponding Existing NDCs, which adjustment(s) the parties will work in good faith to establish. As used herein, the term "Existing NDCs" refers to the Manufacturer Drug NDC(s) covered by the Agreement on the day prior to the date that the applicable New NDC comes into existence that has the highest Net Allowed WAC per Unit; provided, however, that either party may elect for the Existing NDC to be the NDC that most closely resembles the New NDC with respect to days of therapy, unit size, strength, or similar factors, which the parties will mutually determine working together in good faith. Example 2 below demonstrates the Additional Rebate Rate calculation for a New NDC.

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EXAMPLE 2:

New NDC introduced Feb14, subject to same PP rate increase as current NDCs.
New NDC WAC normalized to Current NDC WAC, same Baseline WAC date.
Price Protection factor: 6%

	Assumed WAC as of 12/31/2012	Jan. 2013	Feb. 2013	Mar. 15 2013	Year 1 Price increase 10%	Dec. 2013	Jan. 2014	Feb. 2014	Mar. 2014	Year 2 Price increase 10%	Dec. 2014	Jan. 2015	Feb. 2015	Mar. 2015	Year 3 Price increase 10%	Dec. 2015
Current WAC/ Unit (Current NDC)	6.00	6.00	6.00	6.60	→	6.60	6.60	6.60	7.26	→	7.26	7.26	7.26	7.99	→	7.99
Allowed WAC/ Unit (Current NDC)		6.36	6.36	6.36		6.36	→ 6.74	6.74	6.74		6.74	→ 7.15	7.15	7.15		7.15
Current WAC/ Unit (New NDC)								10.50	11.55	→	11.55	11.55	11.55	12.71	→	12.71
Current Normalized WAC/ Unit (New NDC)								9.90	10.89	→	10.89	10.89	10.89	11.98	→	11.98
Allowed WAC/ Unit (New NDC)								10.11	10.11		10.11	→ 10.72	10.72	10.72		10.72
Current Net WAC / Unit (Current NDC)		5.40	5.40	5.94		5.94	5.94	5.94	6.53		6.53	6.53	6.53	7.19		7.19
Net Allowed WAC / Unit (Current NDC)	5.40	5.72	5.72	5.72		5.72	6.07	6.07	6.07		6.07	6.43	6.43	6.43		6.43
Current Net WAC / Unit (New NDC)								9.45	10.40		10.40	10.40	10.40	11.43		11.43
Net Allowed WAC / Unit (New NDC)								9.10	9.10		9.10	9.65	9.65	9.65		9.65
Additional Rebate (Current NDC)		$0.00	$0.00	$0.22		$0.22	$0.00	$0.00	$0.47		$0.47	$0.10	$0.10	$0.76		$0.76
Additional Rebate Rate (Current NDC)		0.0%	0.0%	3.3%		3.3%	0.0%	0.0%	6.4%		6.4%	1.4%	1.4%	9.5%		9.5%
Additional Rebate (New NDC)								$0.35	$1.29		$1.29	$0.75	$0.75	$1.79		$1.79
Additional Rebate Rate (New NDC)								3.3%	11.2%		11.2%	6.5%	6.5%	14.1%		14.1%
Base Rebate Rate %	10.0%	10.0%	10.0%	10.0%		10.0%	10.0%	10.0%	10.0%		10.0%	10.0%	10.0%	10.0%		10.0%
Total Rebate Rate (Current NDC)	10.0%	10.0%	10.0%	13.3%	→	13.3%	10.0%	10.0%	16.4%	→	16.4%	11.4%	11.4%	19.5%	→	19.5%
Total Rebate Rate (New NDC)					→			13.3%	21.2%	→	21.2%	16.5%	16.5%	24.1%	→	24.1%

	Current WAC	DOT (can be changed to whatever the 'normalization' factor should be)	Normalized WAC / per DOT	WAC in effect for New NDC
Current NDC	6.60	60	0.11	
New NDC	10.50	90		9.90

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4.2 Price Protection

This Section 4.2 pertains to the following Manufacturer Drugs with respect to the applicable Sections noted below in this Exhibit A:

[redacted]

Soliqua under Section 7.6

i. Rebate rates are subject to automatic adjustment in the event the WAC per Unit for a Manufacturer Drug exceeds the "Allowed WAC per Unit".

ii. The initial Allowed WAC per Unit" for a Manufacturer Drug is calculated by multiplying the WAC per Unit as of the date set forth in the Rebate terms below ("Baseline WAC Date") for the applicable Manufacturer Drug by (100% plus the "Price Protection" factor). The "Price Protection" factor is set forth in the Rebate terms below for the applicable Manufacturer Drug.

iii. The initial "Allowed WAC per Unit" for a Manufacturer Drug will apply during the "Initial Price Protection Period". The "Initial Price Protection Period" is defined as the 12-month period, or such other initial time period when indicated in the Rebate terms below, following such Manufacturer Drug's Price Protection Year Start Date, which date is set forth in the Rebate terms below. The applicable Manufacturer Drug's "Price Protection Year" is defined individually as the "Initial Price Protection Period" and each subsequent 12-month period.

iv. The "Base Rebate Rate %" is the then-current Rebate percentage for the Manufacturer Drug set forth in the Rebate tables below.

v. The "Allowed WAC per Unit" for Price Protection Years after the Initial Price Protection Period is calculated by multiplying the WAC per Unit as of December 31 of the immediately preceding calendar year by (100% plus the "Price Protection" factor).

vi. The "Net WAC per Unit" is calculated by multiplying the WAC per Unit by (100% minus the Base Rebate Rate %).

vii. The "Net Allowed WAC per Unit" is calculated by multiplying the "Allowed WAC per Unit" by (100% minus the Base Rebate Rate %).

viii. Effective as of the date the WAC per Unit first exceeds the "Allowed WAC per Unit" and continuing for the remainder of that "Price Protection Year", subject to further adjustments in accordance with this Section 4.2 of this Exhibit A Rebate and Administrative Fee Schedule, an "Additional Rebate Rate" will be paid. The "Additional Rebate Rate" is calculated by determining the amount, if any, that the "Net WAC per Unit", in effect at the time the applicable Manufacturer Drug is dispensed, exceeds the "Net Allowed WAC per Unit" in effect at the time the applicable Manufacturer Drug is dispensed, divided by the then-current WAC per Unit.

ix. The resulting percentage is the "Additional Rebate Rate" and is added to the "Base Rebate Rate %" to produce a "Total Rebate Rate" that applies to such utilization. For avoidance of doubt, the "Total Rebate Rate" calculation is subject to the terms of Section 2.2.6 Best Price in Article 2. Notwithstanding the above,

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the aggregate payment (Total Rebate Rate plus Administrative Fee) for [redacted] shall not exceed twenty-three percent (23%).

*The term "Net Allowed WAC" is solely used for purposes to explain the calculation of price protection in this Agreement. This term is not used outside of this Agreement and, furthermore, is not meant to define or describe any pricing terms of a Manufacturer Drug.

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EXAMPLE 1:

Price Protection factor:	6%			Year 1 Price increase 10%				Year 2 Price increase 10%			
	Assumed WAC as of 12/31/2012	Jan. 2013	Feb. 2013	Mar. 15 2013	Dec. 2013	Jan. 2014	Feb. 2014	Mar. 2014	Dec. 2014	Jan. 2015	Feb. 2015
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60	6.60	6.60	6.60	7.26	7.26	7.26	7.26
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36	6.36	7.00	7.00	7.00	7.00	7.70	7.70
Current WAC/ Unit (New NDC)							6.60	7.26	7.26	7.26	7.26
Allowed WAC/ Unit (New NDC)							7.00	7.00	7.00	7.70	7.70
Current Net WAC / Unit		5.40	5.40	5.94	5.94	5.94	5.94	6.53	6.53	6.53	6.53
Net Allowed WAC / Unit	5.40	5.72	5.72	5.72	5.72	6.30	6.30	6.30	6.30	6.93	6.93
Additional Rebate :		$0.00	$0.00	$0.22	$0.22	$0.00	$0.00	$0.24	$0.24	$0.00	$0.00
Additional Rebate Rate:		0.0%	0.0%	3.3%	3.3%	0.0%	0.0%	3.3%	3.3%	0.0%	0.0%
Base Rebate Rate %:	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
Total Rebate Rate	10.0%	10.0%	10.0%	13.3%	13.3%	10.0%	10.0%	13.3%	13.3%	10.0%	10.0%

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If a New NDC is introduced in the market after the date that such Manufacturer Drug becomes covered by this Agreement, the Additional Rebate Rate for such New NDC(s) will be calculated consistent with the preceding paragraph except that (i) the Net Allowed WAC per Unit for the Existing NDCs (defined below) will apply to the New NDC(s) during each billing period and (ii) the Net WAC per Unit of such New NDC(s) will be adjusted to account for differences, if any, in days of therapy, unit size, strength, or similar factors, between the New NDC(s) and their corresponding Existing NDCs, which adjustment(s) the parties will work in good faith to establish. As used herein, the term "Existing NDCs" refers to the Manufacturer Drug NDC(s) covered by the Agreement on the day prior to the date that the applicable New NDC comes into existence that has the highest Net Allowed WAC per Unit; provided, however, that either party may elect for the Existing NDC to be the NDC that most closely resembles the New NDC with respect to days of therapy, unit size, strength, or similar factors, which the parties will mutually determine working together in good faith. Example 2 below demonstrates the Additional Rebate Rate calculation for a New NDC.

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EXAMPLE 2:

New NDC introduced Feb14, subject to same PP rate increase as Existing NDCs
Same WAC/unit, same Baseline WAC date
Price Protection factor: 6%

Year 1 Price increase 10%

Allowed was 6.74

Year 2 Price increase 10%

	Assumed WAC as of 12/31/2012	Jan. 2013	Feb. 2013	Mar. 15 2013		Dec. 2013	Jan. 2014	Feb. 2014	Mar. 2014		Dec. 2014	Jan. 2015	Feb. 2015
Current WAC/ Unit (Existing NDC)	6.00	6.00	6.00	6.60	→	6.60	6.60	6.60	7.26	→	7.26	7.26	7.26
Allowed WAC/ Unit (Existing NDC)		6.36	6.36	6.36		6.36	↘ 7.00	7.00	7.00		7.00	↘ 7.70	7.70
Current WAC/ Unit (New NDC)								10.50	11.55	→	11.55	11.55	11.55
Current Normalized WAC/ Unit (New NDC)								9.90	10.89		10.89	10.89	10.89
Allowed WAC/ Unit (New NDC)								10.49	10.49		10.49	↘ 12.24	12.24
Current Net WAC / Unit (Existing NDC)		5.40	5.40	5.94		5.94	5.94	5.94	6.53		6.53	6.53	6.53
Net Allowed WAC / Unit (Existing NDC)	5.40	5.72	5.72	5.72		5.72	6.30	6.30	6.30		6.30	6.93	6.93
Current Net WAC / Unit (New NDC)								9.45	10.40		10.40	10.40	10.40
Net Allowed WAC / Unit (New NDC)								9.44	9.44		9.44	11.02	11.02
Additional Rebate (Existing NDC)		$0.00	$0.00	$0.22		$0.22	$0.00	$0.00	$0.24		$0.24	$0.00	$0.00
Additional Rebate Rate (Existing NDC)		0.0%	0.0%	3.3%		3.3%	0.0%	0.0%	3.3%		3.3%	0.0%	0.0%
Additional Rebate (New NDC)								$0.01	$0.95		$0.95	$0.00	$0.00
Additional Rebate Rate (New NDC)								0.1%	8.2%		8.2%	0.0%	0.0%
Base Rebate Rate %	10.0%	10.0%	10.0%	10.0%		10.0%	10.0%	10.0%	10.0%		10.0%	10.0%	10.0%
Total Rebate Rate (Existing NDC)	10.0%	10.0%	10.0%	13.3%	→	13.3%	10.0%	10.0%	13.3%	→	13.3%	10.0%	10.0%
Total Rebate Rate (New NDC)								10.1%	18.2%	→	18.2%	10.0%	10.0%

	Current WAC	DOT (can be changed to whatever the 'normalization' factor should be)	Normalized WAC / per DOT	WAC in effect for New NDC
Existing NDC	6.60	60	0.11	
New NDC	10.50	90		9.90

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5. **Rebate Terms – non-QRPDP, non-Managed Medicaid and non-CHIP.**

5.1 PREFERRED

5.1.1 Lantus: (Effective 1/1/2019 through 12/31/2022)

Manufacturer Drug Name: Lantus*				
Benefit Design	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1 manufacturer with Preferred Drugs	75%	65%	50%
Base Rebate Rate %	1 of 2 manufacturers with Preferred Drugs	65%	50%	40%
Base Rebate Rate %	1 of 3 manufacturers with Preferred Drugs	n/a	n/a	26%
Administrative Fee		4.75%	4.75%	4.75%
Price Protection factor		4%	4%	4%
Baseline WAC Date		4/1/18	4/1/18	4/1/18
Price Protection Year Start Date		1/1/19	1/1/19	1/1/19

*The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, in Article 2 of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price in Article 2.

Conditions to Rebate For Rebate Table 5.1.1 Lantus:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table above; and
2. The following requirements apply to the corresponding Benefit designs noted below:

   (a) **For the Highly Managed Rebate**, Manufacturer is 1 of 1 or 1 of 2 manufacturer(s), as applicable, with Drug(s) in the Lantus Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Lantus Defined Drug Market that are non-Preferred satisfy one of the following: (i) they are not listed on Formulary and not covered, (ii) they are listed on Formulary but indicated as not covered, or (iii) if the Benefit design does not allow for a Drug to be excluded from Formulary as set forth in (i) and (ii), then they are listed and adjudicated on

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a Formulary tier with a higher co-payment amount or co-insurance percentage and are subject to a prior authorization or step edit through a Preferred Drug.

(b) **For the Managed Rebate**, Manufacturer is 1 of 1 or 1 of 2 manufacturer(s), as applicable, with Drug(s) in the Lantus Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Lantus Defined Drug Market that are non-Preferred satisfy one of the following: (i) they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage, (ii) they are not listed on Formulary and not covered, or (iii) they are listed on Formulary but indicated as not covered.

(c) **For the Covered Rebate**, Manufacturer is 1 of 1, 1 of 2 or 1 of 3 manufacturer(s), as applicable, with Drug(s) in the Lantus Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Lantus Defined Drug Market that are non-Preferred are either (i) listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage tier or (ii) not listed on Formulary.

3. Imposition of any of the following quantity limit requirements on Lantus will not render the applicable utilization ineligible for Rebates: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in the Lantus Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in the Lantus Defined Drug Market are subject to a quantity limit consistent with their respective package inserts; and
4. No package form of Lantus is disadvantaged to a comparable package form of any other Drug in the Lantus Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls. In the event that a package form of Lantus is disadvantaged to a comparable package form, all package forms of Lantus, i.e. both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples are provided for clarification of Rebate eligibility and not to be considered an exhaustive list:

Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	1	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	1	Preferred	2	Preferred
Levemir	Pen	1	Preferred	2	Preferred

Would **NOT** Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	2	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	3	Non-preferred	2	Preferred
Levemir	Pen	3	Non-preferred	2	Preferred

5.1.2 Apidra - (Effective 1/1/2019 through 12/31/2022)

Manufacturer Drug Name: Apidra				
Benefit Design	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	57%	57%	57%
Base Rebate Rate %	1 of 2	47%	47%	47%
Base Rebate Rate %	1 of 3	42%	42%	42%

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Administrative Fee		4.75%	4.75%	4.75%
Price Protection factor		n/a	n/a	n/a
Baseline WAC Date		n/a	n/a	n/a
Price Protection Year Start Date		n/a	n/a	n/a

Conditions to Rebate For Rebate Table 5.1.2 Apidra:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table above; and
2. The following requirements apply to the corresponding Formulary Status referenced in Rebate Table 5.1.2:
   - **(a)** **For the 1 of 1 Formulary Status,** all other manufacturers' Drugs in the Apidra Defined Drug Market satisfy one of the following: (i) they are not listed on Formulary and not covered, (ii) they are listed on Formulary but indicated as not covered, or (iii) for Highly Managed Rebates only, if the Benefit design does not allow for a Drug to be excluded from Formulary as set forth in (i) and (ii), then they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage and are subject to a prior authorization or step edit through a Preferred Drug.
   - **(b)** **For the 1 of 2 and 1 of 3 Formulary Status,** Manufacturer Drug is not disadvantaged as compared to other brand name Drugs in the Apidra Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls.
3. Imposition of any of the following quantity limit requirements on Apidra will not render the applicable utilization ineligible for Rebates: a quantity limit on Apidra that is: (i) no more than 70mls per month or 210mls per 3-month supply on Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Apidra pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in the Apidra Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with Apidra's package insert provided all brand name Drugs in the Apidra Defined Drug Market are subject to a quantity limit consistent with their respective package inserts.

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5.1.5 Toujeo - (Effective 1/1/2019 through 12/31/2022)

Manufacturer Drug Name: Toujeo				
Benefit Design	Formulary Status	Highly Managed	Managed	Covered

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Base Rebate Rate %	1 of 1 manufacturers with Preferred Drugs	75%	65%	50%
Base Rebate Rate %	1 of 2 manufacturers with Preferred Drugs	65%	50%	40%
Base Rebate Rate %	1 of 3 manufacturers with Preferred Drugs	n/a	n/a	26%
Administrative Fee		4.75%	4.75%	4.75%
Price Protection factor		4.0%	4.0%	4.0%
Baseline WAC Date		4/1/18	4/1/18	4/1/18
Price Protection Year Start Date		1/1/19	1/1/19	1/1/19

Conditions to Rebate for Rebate Table 5.1.5 Toujeo:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table above; and
2. The following requirements apply to the corresponding Benefit designs noted below:
   - **(a)** **For the Highly Managed Rebate**, Manufacturer is 1 of 1 or 1 of 2 manufacturer(s), as applicable, with Drug(s) in the Toujeo Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Toujeo Defined Drug Market that are non-Preferred satisfy one of the following: (i) they are not listed on Formulary and not covered, (ii) they are listed on Formulary but indicated as not covered, or (iii) if the Benefit design does not allow for a Drug to be excluded from Formulary as set forth in (i) and (ii), then they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage and are subject to a step edit through a Preferred Drug.
   - **(b)** **For Managed Rebate**, Manufacturer is 1 of 1 or 1 of 2 manufacturer(s), as applicable, with Drug(s) in the Toujeo Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Toujeo Defined Drug Market that are non-Preferred satisfy one of the following: (i) they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage, (ii) they are not listed on Formulary and not covered, or (iii) they are listed on Formulary but indicated as not covered.
   - **(c)** **For Covered Rebate**, Manufacturer is 1 of 1, 1 of 2 or 1 of 3 manufacturers, as applicable, with Drug(s) in the Toujeo Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Toujeo Defined Drug Market that are non-Preferred are either (i) listed and adjudicated on a Formulary tier with

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a higher co-payment amount or co-insurance percentage tier or (ii) not listed on Formulary; and

3. A Manufacturer Drug is not disadvantaged as compared to other brand name Drugs in the Toujeo Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls.
4. Imposition of any of the following quantity limit requirements on Toujeo will not render the applicable utilization ineligible for Rebates: (i) a quantity limit of no more than 225mls per 3-month supply on Toujeo provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in the Toujeo Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in the Toujeo Defined Drug Market are subject to a quantity limit consistent with their respective package inserts.

5.1.6 Soliqua 100/33 - (Effective 1/1/2019 through 12/31/2021)

Manufacturer Drug Name: Soliqua 100/33				
Benefit Design	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of many	42%	18%	10%
Administrative Fee		4.75%	4.75%	4.75%
Price Protection factor		0%	0%	0%
Baseline WAC Date		12/15/16	12/15/16	12/15/16
Price Protection Year Start Date		4/1/17	4/1/17	4/1/17

Conditions to Rebate for Rebate Table 5.1.6 Soliqua 100/33:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table; and
2. Manufacturer Drug is not disadvantaged as compared to other brand name Drugs in the Soliqua 100/33 Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls.
3. The parties acknowledge that the following step edit requirement on Soliqua 100/33 will not be deemed a disadvantage and will not render the applicable utilization ineligible for Rebates so long as such step edit requirement is applied to all other brand name Drugs in the Soliqua 100/33 Defined Drug Market where it is clinically appropriate to do so: Consumer has a history of trial of (i) at least one basal insulin Drug, or (ii) at least one GLP-1 Drug prior to Administrator or Contracting Payor providing coverage for Soliqua 100/33.

   Administrator and Contracting Payor acknowledge that (i) Manufacturer only endorses use of Soliqua 100/33 in accordance with its FDA approved prescribing information, a copy of which is available at the following internet address: http://products.sanofi.us/Soliqua 100/33/Soliqua_100-33.pdf, and (ii) to the extent required by applicable Law, Administrator's applicable internal advisory committees will review and approve step-edit criteria.

   Administrator or Contracting Payor, as applicable, will consider any Consumer who has filled any of the basal insulin or GLP-1 Drugs listed in the table below as having met the

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step edit requirement listed in this section. A step edit that requires prior use of a specific basal insulin or GLP-1 Drug (as opposed to accepting any one of the Drugs in the table below) will render the applicable utilization ineligible for a Soliqua 100/33 Rebate.

Soliqua 100/33 Step Edit Requirement Table:

Basal Insulin*	GLP-1*
Lantus®	Adlyxin®
Levemir®	Bydureon®
Tresiba®	Byetta®
Basaglar®	Ozempic
Toujeo® SoloSTAR®	Tanzeum®
Toujeo® Max SoloSTAR®	Trulicity®
	Victoza®

*Other than Manufacturer Drugs that will be subject to section 2.4.1 in Article 2 of this Agreement, any new strengths, formulations and NDC numbers of the listed Drugs or addition of any new brand Drug will be added upon mutual written agreement of the parties, which agreement shall not be unreasonably withheld.

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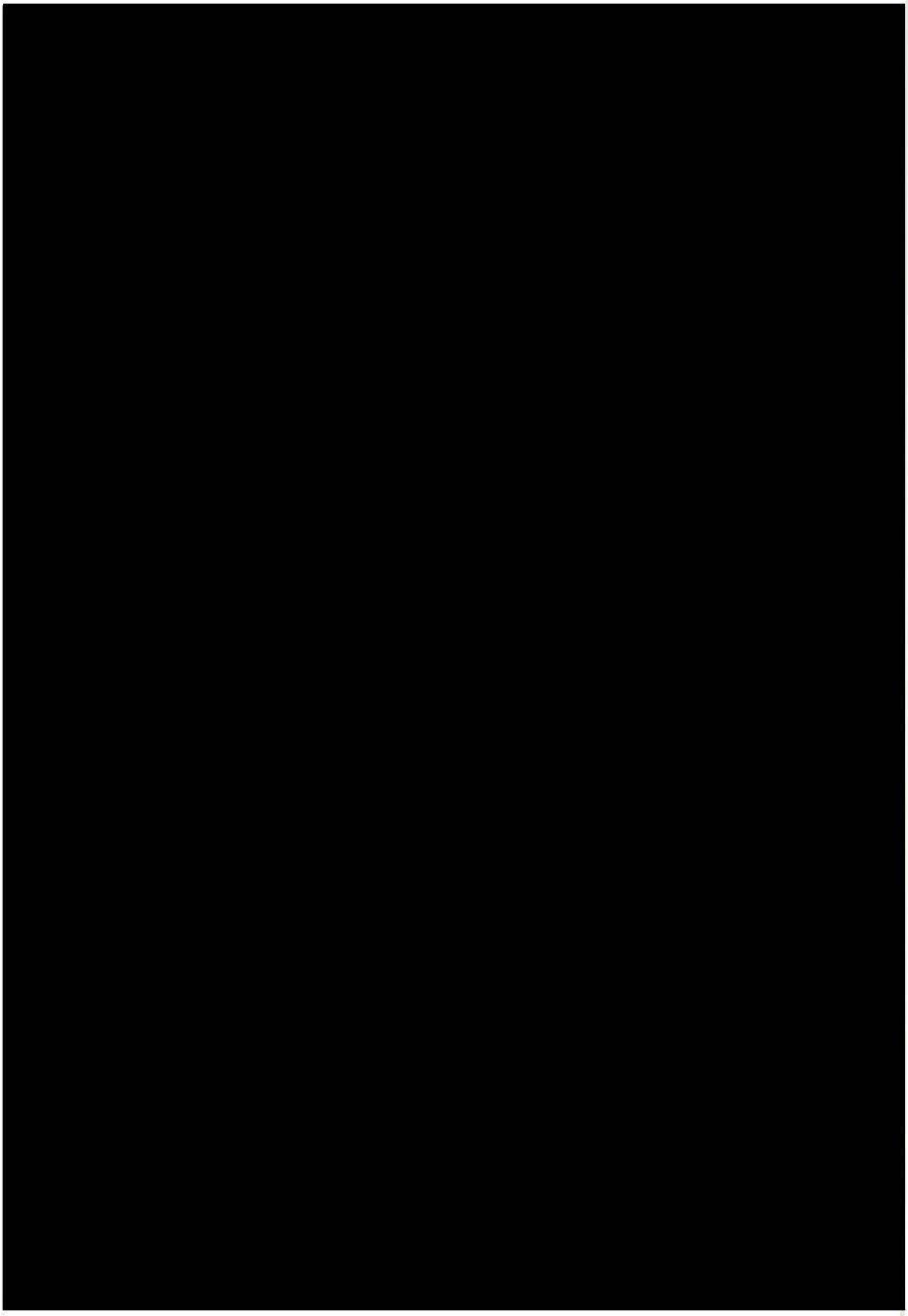

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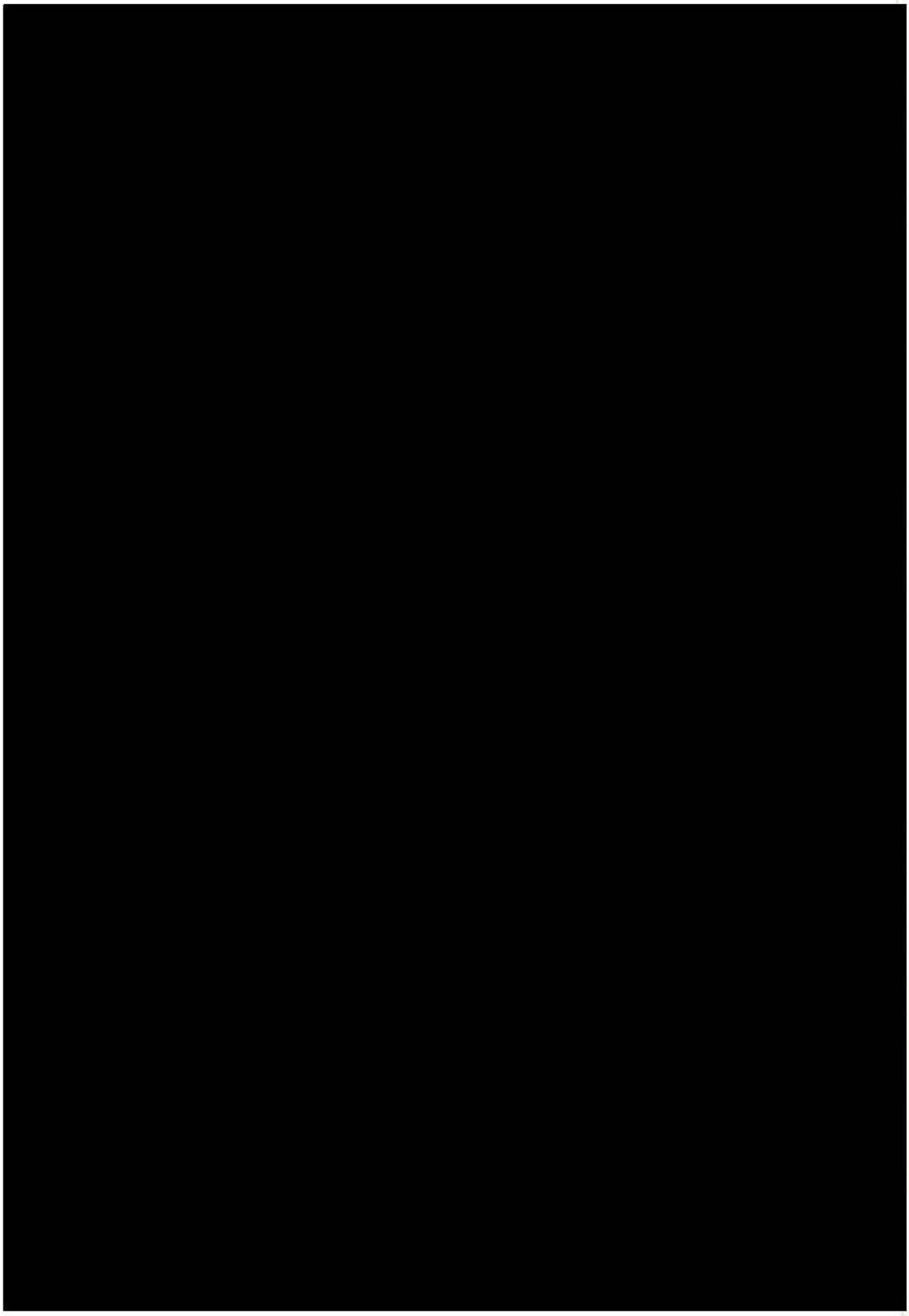

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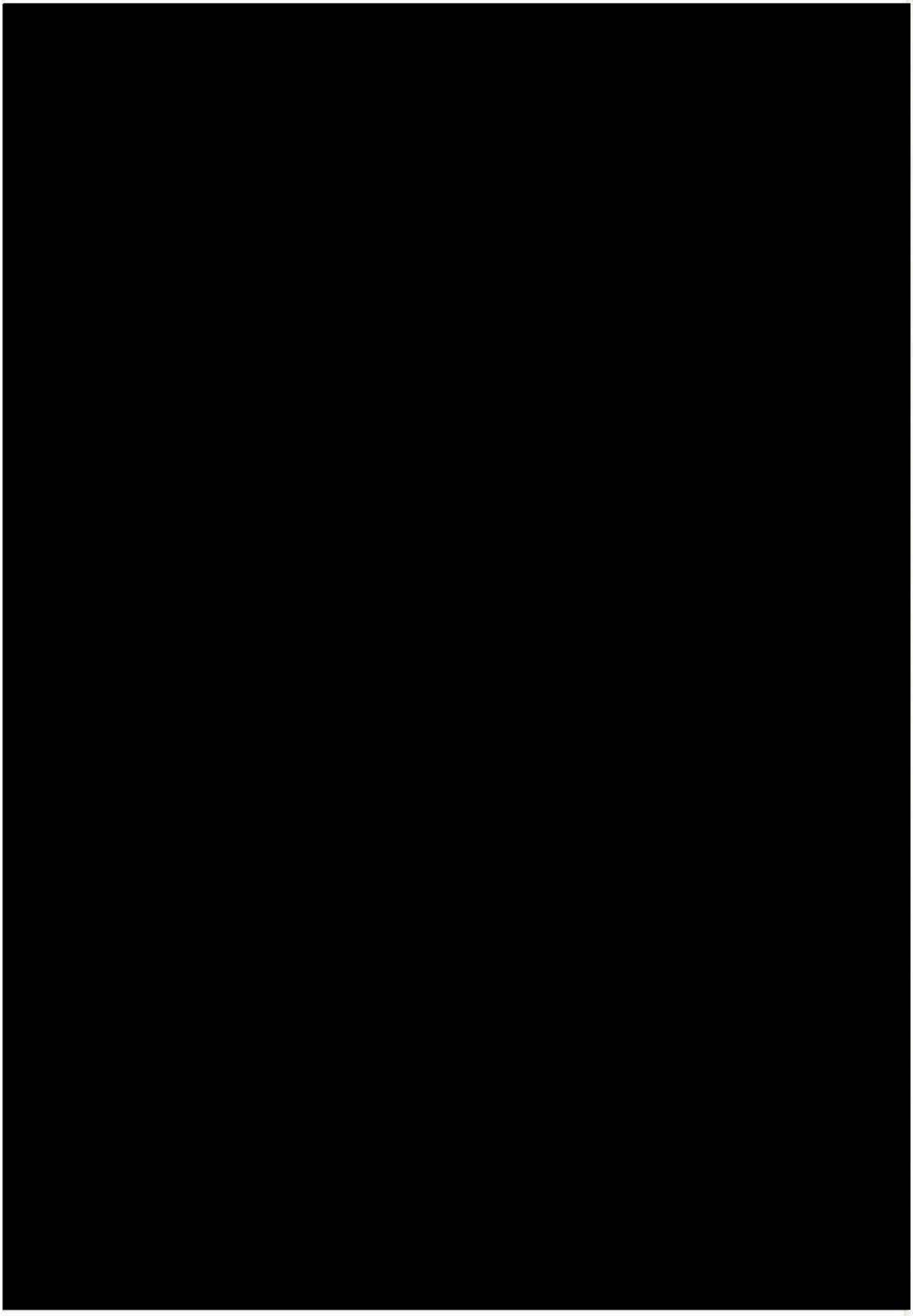

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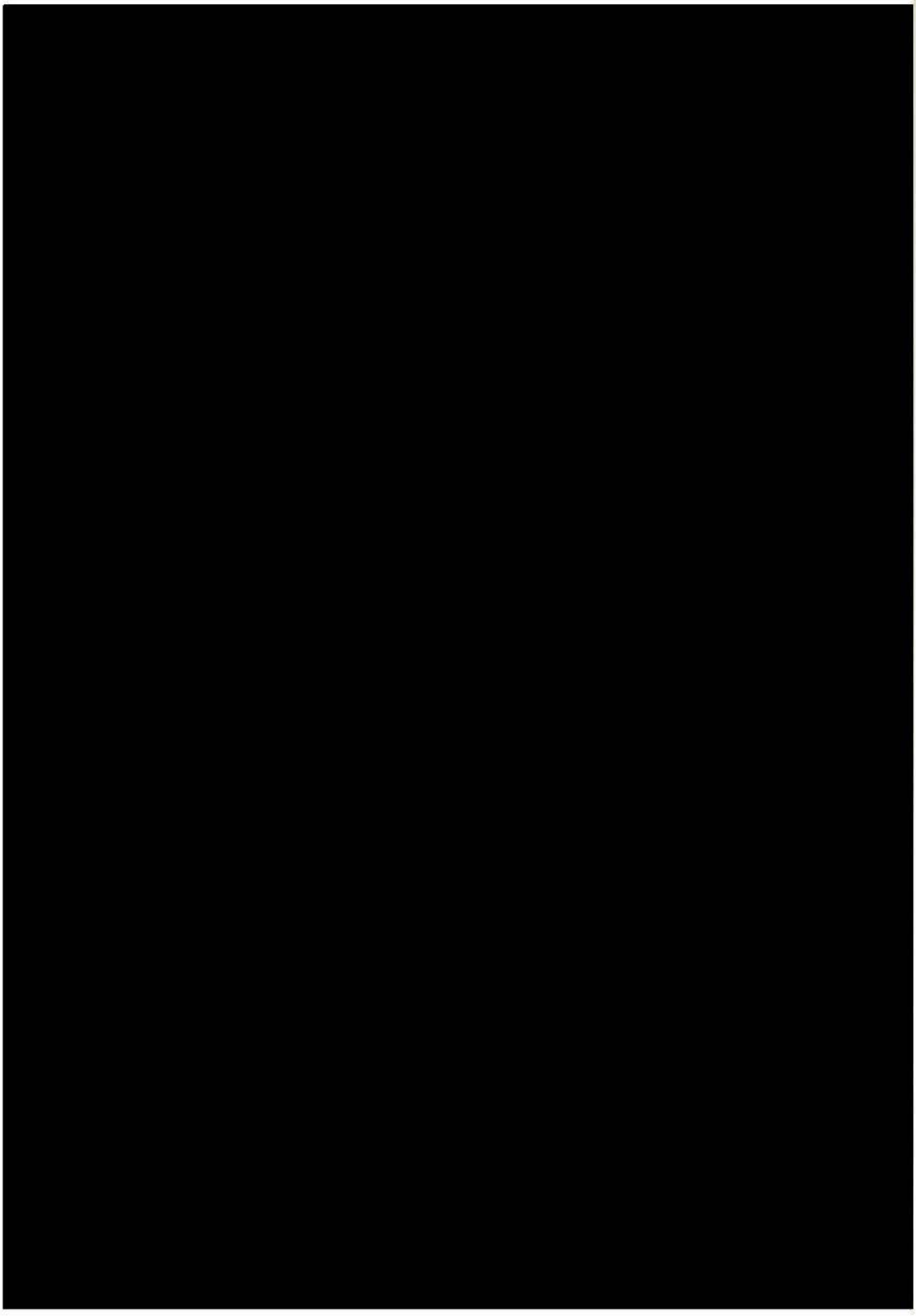

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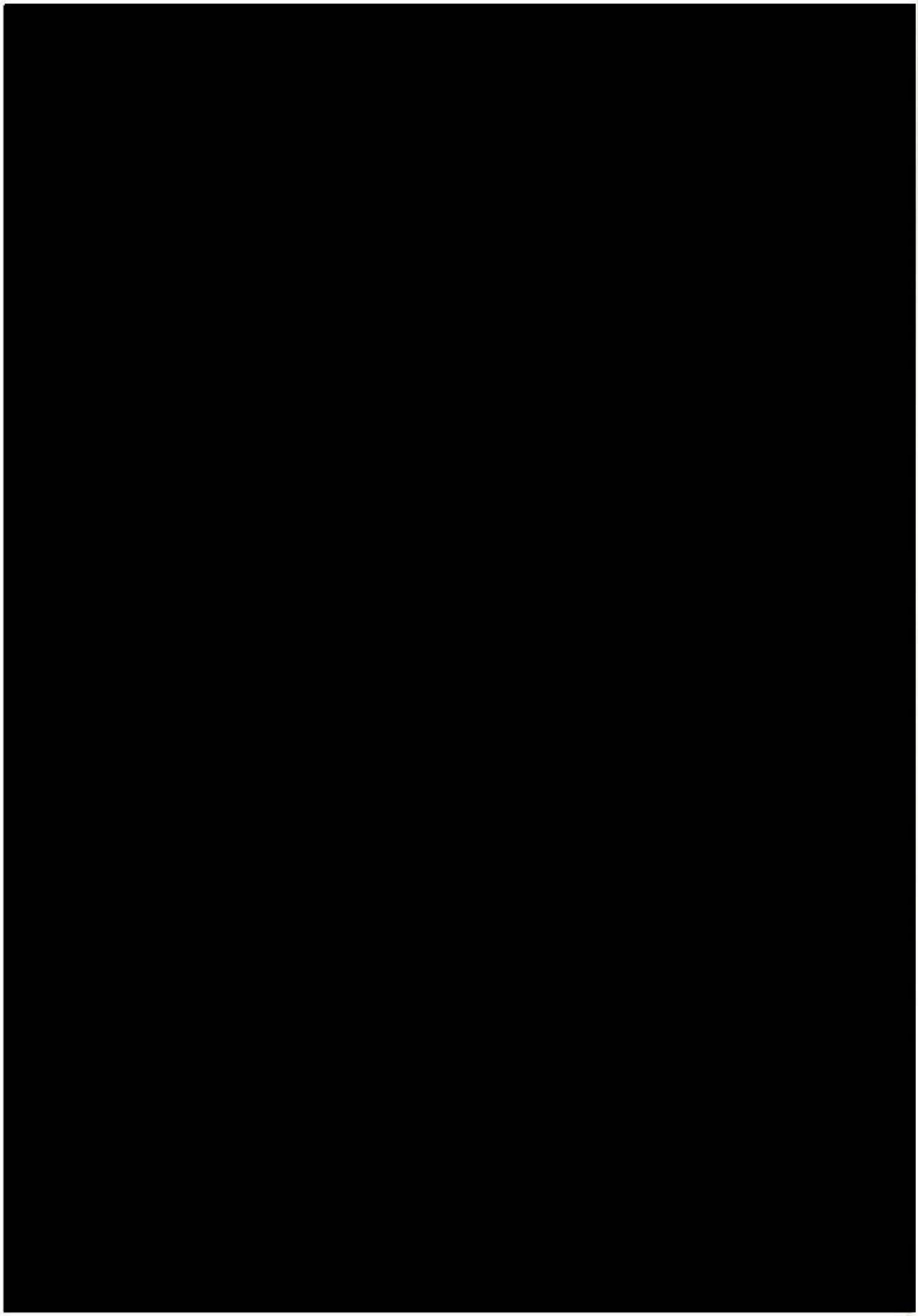

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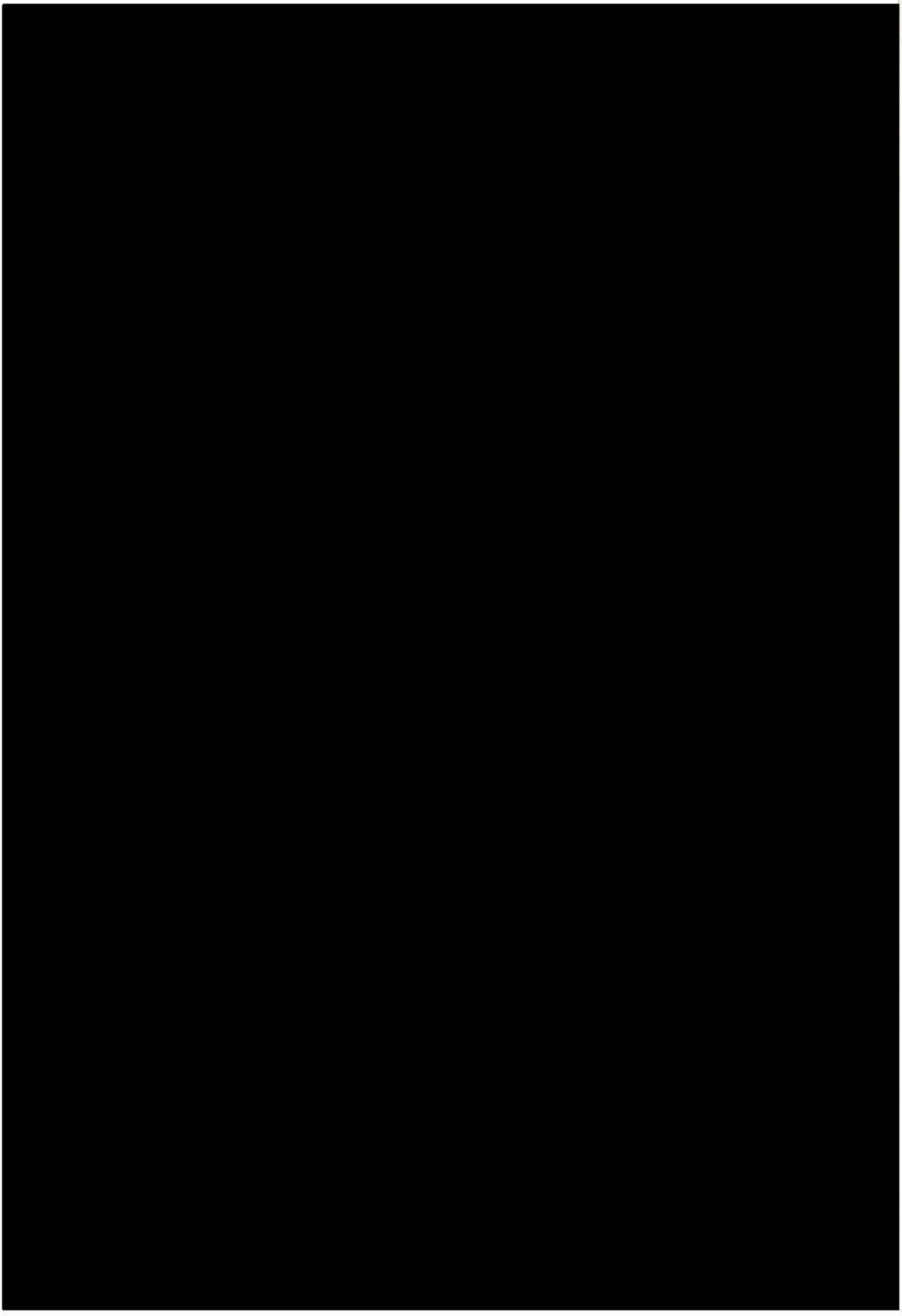

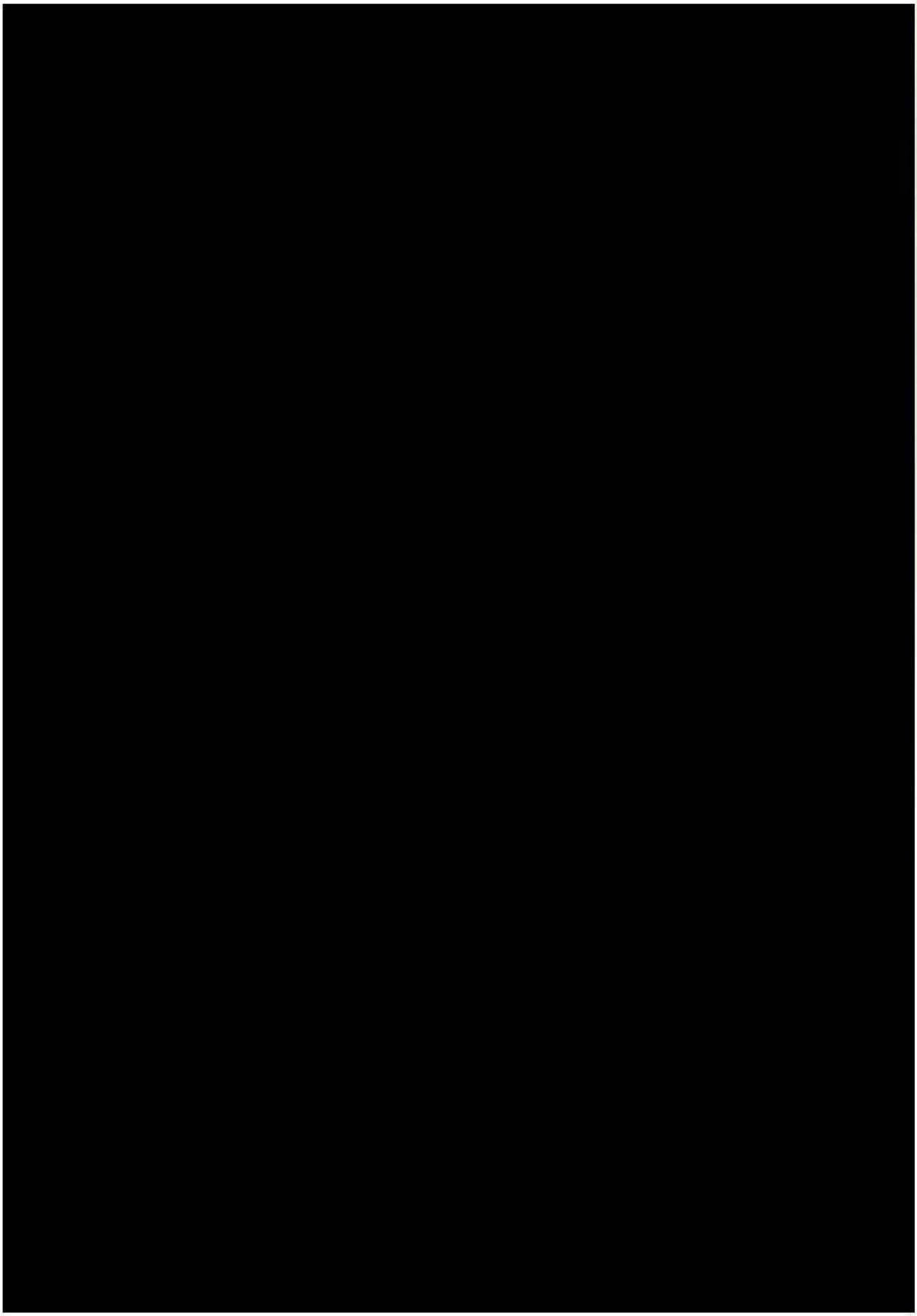

6.1 PREFERRED

6.1.1 Lantus - (Effective 1/1/2019 through 12/31/2022):

Manufacturer Drug Name: Lantus*				
Benefit Design	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1 manufacturers with Preferred Drugs	79.75%	69.75%	54.75%
Base Rebate Rate %	1 of 2 manufacturers with Preferred Drugs	69.75%	54.75%	44.75%
Base Rebate Rate %	1 of 3 manufacturers with Preferred Drugs	n/a	n/a	30.75%
Administrative Fee		n/a	n/a	n/a
Price Protection factor		4%	4%	4%
Baseline WAC Date		4/1/18	4/1/18	4/1/18
Price Protection Year Start Date		1/1/19	1/1/19	1/1/19

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, in Article 2 of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price in Article 2.

Conditions to Rebate For Rebate Table 6.1.1 Lantus:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table above; and
2. The following requirements apply to the corresponding Benefit designs listed below:
   - **(a)** **For the Highly Managed Rebate,** Manufacturer is 1 of 1 or 1 of 2 manufacturer(s), as applicable, with Drug(s) in the Lantus Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Lantus Defined Drug Market that are non-Preferred satisfy one of the following: (i) they are not listed on Formulary and not covered, (ii) they are listed on Formulary but indicated as not covered, or (iii) if the Benefit design does not allow for a Drug to be excluded from Formulary as set forth in (i) and (ii), then they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage and are subject to a prior authorization or step edit through a Preferred Drug.

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(b) **For the Managed Rebate**, Manufacturer is 1 of 1 or 1 of 2 manufacturer(s), as applicable, with Drug(s) in the Lantus Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Lantus Defined Drug Market that are non-Preferred satisfy one of the following: (i) they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage, (ii) they are not listed on Formulary and not covered, or (iii) they are listed on Formulary but indicated as not covered.

(c) **For the Covered Rebate**, Manufacturer is 1 of 1, 1 of 2 or 1of 3 manufacturer(s), as applicable, with Drug(s) in the Lantus Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Lantus Defined Drug Market that are non-Preferred are either (i) listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage or (ii) not listed on Formulary.

3. Imposition of any of the following quantity limit requirements on Lantus will not render the applicable utilization ineligible for Rebates: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in the Lantus Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in the Lantus Defined Drug Market are subject to a quantity limit consistent with their respective package inserts; and
4. No package form of Lantus will be disadvantaged to a comparable package form of any other Drug in the Lantus Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls. In the event that a package form of Lantus is disadvantaged to a comparable package form, all package forms of Lantus, both vial and pen, shall be ineligible for Rebates as of such date of dispensing. The following examples are provided for clarification of Rebate eligibility and not to be considered an exhaustive list:

Would Pay Vial and Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	1	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	1	Preferred	2	Preferred
Levemir	Pen	1	Preferred	2	Preferred

Would NOT Pay Vial or Pen

Product	Pkg Form	Tier	Status	Tier	Status
Lantus	Vial	1	Preferred	2	Preferred
Levemir	Vial	1	Preferred	1	Preferred
Lantus	Pen	3	Non-preferred	2	Preferred
Levemir	Pen	3	Non-preferred	2	Preferred

6.1.2 Apidra - (Effective 1/1/2019 through 12/31/2022)

Manufacturer Drug Name: Apidra				
Benefit Design	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of 1	61.75%	61.75%	61.75%
Base Rebate Rate %	1 of 2	51.75%	51.75%	51.75%
Base Rebate Rebate %	1 of 3	46.75%	46.75%	46.75%

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Administrative Fee		n/a	n/a	n/a
Price Protection factor		n/a	n/a	n/a
Baseline WAC Date		n/a	n/a	n/a
Price Protection Year Start Date		n/a	n/a	n/a

Conditions to Rebate For Rebate Table 6.1.2 Apidra:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table above; and
2. The following requirements apply to the corresponding Formulary Status referenced in Rebate Table 6.1.2:
   - **(a) For the 1 of 1 Formulary Status**, all other manufacturers' Drugs in the Apidra Defined Drug Market satisfy one of the following: (i) they are not listed on Formulary and not covered, (ii) they are listed on Formulary but indicated as not covered, or (iii) for Highly Managed Rebates only, if the Benefit design does not allow for a Drug to be excluded from Formulary as set forth in (i) and (ii), then they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage and are subject to a prior authorization or step edit through a Preferred Drug.
   - **(b) For the 1 of 2 and 1 of 3 Formulary Status**, Manufacturer Drug is not disadvantaged as compared to other brand name Drugs in the Apidra Defined Drug Market with regard to applicable Benefit Contract's Utilization Controls.
3. Imposition of the following quantity limit requirements on Apidra will not render the applicable utilization ineligible for Rebates: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Apidra vials and/or no more than 75mls per month or 225mls per 3-month supply on Apidra pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in the Apidra Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in the Apidra Defined Drug Market are subject to a quantity limit consistent with their respective package inserts.

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6.1.5 Toujeo - (Effective 1/1/2019 through 12/31/2022)

Manufacturer Drug Name: Toujeo				
Benefit Design	Formulary Status	Highly Managed	Managed	Covered

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Base Rebate Rate %	1 of 1 manufacturers with Preferred Drugs	79.75%	69.75%	54.75%
Base Rebate Rate %	1 of 2 manufacturers with Preferred Drugs	69.75%	54.75%	44.75%
Base Rebate Rate %	1 of 3 manufacturer with Preferred Drugs	n/a	n/a	30.75%
Administrative Fee		n/a	n/a	n/a
Price Protection factor		4.0%	4.0%	4.0%
Baseline WAC Date		4/1/18	4/1/18	4/1/18
Price Protection Year Start Date		1/1/19	1/1/19	1/1/19

Conditions to Rebate for Rebate Tables 6.1.5 Toujeo:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table above; and
2. The following requirements apply to the corresponding Benefit designs listed below:
   - **(a)** **For Highly Managed Rebate**, Manufacturer is 1 of 1 or 1 of 2 manufacturer(s), as applicable, with Drug(s) in the Toujeo Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Toujeo Defined Drug Market that are non-Preferred satisfy one of the following: (i) they are not listed on Formulary and not covered, (ii) they are listed on Formulary but indicated as not covered, or (iii) if Benefit design does not allow for a Drug to be excluded from Formulary as set forth in (i) and (ii), then they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage and are subject to a step edit through a Preferred Drug.
   - **(b)** **For Managed Rebate**, Manufacturer is 1 of 1 or 1 of 2 manufacturer(s), as applicable, with Drug(s) in the Toujeo Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Toujeo Defined Drug Market that are non-Preferred satisfy one of the following: (i) they are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage, (ii) they are not listed on Formulary and not covered, or (iii) they are listed on Formulary but indicated as not covered.
   - **(c)** **For Covered Rebate**, Manufacturer is 1 of 1, 1 of 2 or 1 of 3 manufacturer(s), as applicable, with Drug(s) in the Toujeo Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs in the Toujeo Defined Drug Market that are non-Preferred are either (i) listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage tier, or (ii) are not listed on Formulary; and

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3. Manufacturer Drug is not disadvantaged as compared to other brand name Drugs in the Toujeo Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls.
4. Imposition of any of the following quantity limit requirements on Toujeo will not render the applicable utilization ineligible for Rebates: (i) a quantity limit of no more than 225mls per 3-month supply on Toujeo provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in the Toujeo Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in the Toujeo Defined Drug Market are subject to a quantity limit consistent with their respective package inserts.

6.1.6 Soliqua 100/33 - (Effective 1/1/2019 through 12/31/2021)

Manufacturer Drug Name: Soliqua 100/33				
Benefit Design:	**Formulary Status**	**Highly Managed**	**Managed**	**Covered**
Base Rebate Rate %	1 of many	46.75%	22.75%	14.75%
Administrative Fee		n/a	n/a	n/a
Price Protection factor		0%	0%	0%
Baseline WAC Date:		12/15/16	12/15/16	12/15/16
Price Protection Year Start Date		4/1/17	4/1/17	4/1/17

Conditions to Rebate for Rebate Table 6.1.6 Soliqua 100/33:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table above; and
2. Manufacturer Drug is not disadvantaged as compared to other brand name Drugs in the Soliqua 100/33 Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls.
3. The parties acknowledge that the following step edit requirement on Soliqua 100/33 will not be deemed a disadvantage and will not render the applicable utilization ineligible for Rebates so long as such step edit requirement is applied to all other brand name Drugs in the Soliqua 100/33 Defined Drug Market where it is clinically appropriate to do so: Consumer has a history of trial of (i) at least one basal insulin Drug, or (ii) at least one GLP-1 Drug prior to Administrator or Contracting Payor providing coverage for Soliqua 100/33.

   Administrator and Contracting Payor acknowledge that (i) Manufacturer only endorses use of Soliqua 100/33 in accordance with its FDA approved prescribing information, a copy of which is available at the following internet address: http://products.sanofi.us/Soliqua 100/33/Soliqua 100-33.pdf, and (ii) to the extent required by applicable Law, Administrator's applicable internal advisory committees will review and approve step-edit criteria.

   Administrator or Contracting Payor, as applicable, will consider any Consumer who has filled any of the basal insulin or GLP-1 Drugs listed in the table below as having met the step edit requirement listed in this section. A step edit that requires prior use of a specific

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basal insulin or GLP-1 Drug (as opposed to accepting any one of the Drugs in the table below) will render the applicable utilization ineligible for a Soliqua 100/33 Rebate.

Soliqua 100/33 Step Edit Requirement Table:

Basal Insulin*	GLP-1*
Lantus®	Adlyxin®
Levemir®	Bydureon®
Tresiba®	Byetta®
Basaglar®	Tanzeum®
Toujeo® SoloSTAR®	Trulicity®
Toujeo® Max SoloSTAR®	Victoza®

*Other than Manufacturer Drugs that will be subject to section 2.4.1 in Article 2 of this Agreement, any new strengths, formulations and NDC numbers of the listed Drugs or addition of any new brand Drug will be added upon mutual written agreement of the parties, which agreement shall not be unreasonably withheld.

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7.6 Soliqua 100/33- (Effective 1/1/2019 through 12/31/2021)

Manufacturer Drug Name: Soliqua 100/33		
Benefit Design	**Formulary Status**	**Managed Medicaid**
Base Rebate Rate %	1 of 1	10%
Administrative Fee		n/a
Price Protection factor		9%
Baseline WAC Date		12/31/18
Price Protection Year Start Date		1/1/19

Conditions to Rebate for Rebate Table 7.6 Soliqua 100/33:

1. Manufacturer Drug is Preferred and in the applicable Formulary Status in the table above; and
2. All other Drugs in the Soliqua 100/33 Defined Drug Market are (a) in a non-Preferred Formulary tier or are non-Formulary and (b) subject to a step edit requiring trial and failure of all Preferred Drugs within the Soliqua 100/33 Defined Drug Market where it is clinically appropriate to so; and
3. Manufacturer Drug is not disadvantaged as compared to other brand name Drugs in the Soliqua 100/33 Defined Drug Market with regards to the applicable Benefit Contract's Utilization Controls; and
4. The parties acknowledge that the following step edit requirement on Soliqua 100/33 will not be deemed a disadvantage and shall not render the applicable utilization ineligible for Rebates so long as such step edit requirement is applied to all other brand name Drugs in the Soliqua 100/33 Defined Drug Market where it is clinically appropriate to do so: (i) Consumer has a history of trial of (i) at least one basal insulin Drug, or (ii) at least one GLP-1 Drug prior to Administrator or Contracting Payor providing coverage for Soliqua 100/33.

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Administrator and Contracting Payor acknowledge that (i) Manufacturer only endorses use of Soliqua 100/33 in accordance with its FDA approved prescribing information, a copy of which is available at the following internet address: http://products.sanofi.us/Soliqua 100/33/Soliqua_100-33.pdf, and (ii) to the extent required by applicable Law, Administrator's applicable internal advisory committees will review and approve step-edit criteria.

Administrator will or Contracting Payor, as applicable will consider any Consumer who has filled any of the basal insulin or GLP-1 Drugs listed in the table below as having met the step edit requirement listed in this section. A step edit that requires prior use of a specific basal insulin or GLP-1 Drug (as opposed to accepting any one of the Drugs in the table below) will render the applicable utilization ineligible for a Soliqua 100/33 Rebate.

Soliqua 100/33 Step Edit Requirement Table:

Basal Insulin*	**GLP-1***
Lantus®	Adlyxin®
Levemir®	Bydureon®
Tresiba®	Byetta®
Basaglar®	Tanzeum®
Toujeo® SoloSTAR®	Trulicity®
Toujeo® Max SoloSTAR®	Victoza®

*Other than Manufacturer Drugs that will be subject to section 2.4.1 of this Agreement, any new strengths, formulations and NDC numbers of the listed Drugs or addition of any new brand Drug will be added upon mutual written agreement of the parties, which agreement shall not be unreasonably withheld.

[redacted]

[redacted]

7.8 (Effective 1/1/2019 through 12/31/2020)

Manufacturer Drug Name: Admelog®		
Benefit Design	**Managed Medicaid**	**Managed Medicaid**
Formulary Status	1 of 1 manufacturer	1 of 2 manufacturer
Base Rebate Rate % Admelog® Vials	15%	3%
Base Rebate Rate % Admelog® SoloSTAR®	15%	4%
Administrative Fee	n/a	n/a
Price Protection factor	8%	8%
Baseline WAC Date	3/12/18	3/12/18
Price Protection Year Start Date	4/1/18	4/1/18

Conditions to Rebates for Rebate Table 7.8 Admelog:

1. Manufacturer Drug is Preferred with Unrestricted Access and in the applicable Formulary Status in the table above; and
2. All other single source brand name Drugs in the Admelog Defined Drug Market are (a) in a non-Preferred Formulary tier or are non-Formulary and (b) where the Benefit design allows, subject to a step edit requiring trial of all Preferred Drugs within the Admelog Defined Drug Market, where it is clinically appropriate to do so; and
3. No package form of Admelog is disadvantaged to a comparable package form of any other single-source brand name Drug in the Admelog Defined Drug Market with regard to the applicable Benefit Contract's [redacted]tilization Controls. In the event a package form of Admelog is disadvantaged to a comparable package form, all package forms of Admelog, i.e. both vial and pen, shall be ineligible for Rebates as of the date of dispensing. Notwithstanding the foregoing, Admelog SoloSTAR may be subject to a step edit, requiring the trial of Admelog vials before the utilization of Admelog SoloSTAR. If Administrator, or Contracting Payor, as applicable, implement a medical exception to such

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[redacted]

8. **Rebate Terms – CHIP a stand-alone Federal healthcare program that operates independent from the Medicaid program as set forth in Article 2 Payment and Billing, Section 2.2.4.**

8.1 Lantus - (Effective 1/1/2019 through 12/31/2022)

Manufacturer Drug Name: Lantus*		
Benefit Design	**Formulary Status**	**CHIP**
Base Rebate Rate %	1 of 2 or fewer manufacturers with Preferred Drugs	69.75%
Administrative Fee		n/a
Price Protection factor		4%
Baseline WAC Date		4/1/18
Price Protection Year Start Date		1/1/19

* The Rebate and Administrative Fee terms set forth in the above table are not subject to Section 2.2.6, Best Price, in Article 2of this Agreement; under no circumstances will the Rebate and Administrative Fee obligations set forth in the above table be reduced or otherwise affected by the application of Section 2.2.6, Best Price in Article 2.

Conditions to Rebate for Rebate Table 8.1 Lantus:

1. Manufacturer is one (1) of two (2) or fewer manufacturers with Drug(s) in the Lantus Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs are listed and adjudicated on a higher tier and are subject to a step edit through a Preferred Drug; and
2. Imposition of any of the following quantity limit requirements on Lantus will not rend the applicable utilization ineligible for Rebates: (i) a quantity limit of no more than 70mls per month or 210mls per 3-month supply on Lantus vials and/or no more than 75mls per month or 225mls per 3-month supply on Lantus pen provided there is an exception process for such quantity limit when an exception is medically necessary and all brand

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name Drugs in the Lantus Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in the Lantus Defined Drug Market are subject to a quantity limit consistent with their respective package inserts; and

3. No package form of Lantus will be disadvantaged to a comparable package form of any other Drug in the Lantus Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls. In the event that a package form of Lantus is disadvantaged to a comparable package form, all package forms of Lantus, i.e. both vial and pen, shall be ineligible for Rebates as of such date of dispensing.

[redacted]

[redacted]

8.5 Toujeo - (Effective 1/1/2019 through 12/31/2022)

Manufacturer Drug Name: Toujeo		
Benefit Design	**Formulary Status**	**CHIP**
Base Rebate Rate %	1 of 2 or fewer manufacturers	69.75%

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	with Preferred Drugs	
Administrative Fee		n/a
Price Protection factor		4%
Baseline WAC Date		4/1/18
Price Protection Year Start Date		1/1/19

Conditions to Rebate for Rebate Table 8.5 Toujeo:

1. Manufacturer is one (1) of two (2) or fewer manufacturers with Drug(s) in the Toujeo Defined Drug Market that is(are) Preferred. All other manufacturers' Drugs are listed and adjudicated on a Formulary tier with a higher co-payment amount or co-insurance percentage and are subject to a step edit through a Preferred Drug; and
2. Manufacturer Drug is not disadvantaged as compared to other brand name Drugs in the Toujeo Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls; and
3. Imposition of any of the following quantity limit requirements on Toujeo will not render the applicable utilization ineligible for Rebates: (i) a quantity limit of no more than 225mls per 3-month supply on Toujeo provided there is an exception process for such quantity limit when an exception is medically necessary and all brand name Drugs in the Toujeo Defined Drug Market are subject to the same quantity limit, or (ii) a quantity limit consistent with its package insert provided all brand name Drugs in the Toujeo Defined Drug Market are subject to a quantity limit consistent with their respective package inserts.

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8.13 (Effective 1/1/2019 through 12/31/2020)

Manufacturer Drug Name: Admelog®		
Benefit Design	**CHIP**	**CHIP**
Formulary Status	1 of 1 manufacturer	1 of 2 manufacturer
Base Rebate Rate % Admelog® Vials	15%	3%
Base Rebate Rate % Admelog® SoloSTAR®	15%	4%
Administrative Fee	n/a	n/a
Price Protection factor	8%	8%
Baseline WAC Date	3/12/18	3/12/18
Price Protection Year Start Date	4/1/18	4/1/18

Conditions to Rebates for Rebate Table 8.13 Admelog:

1. Manufacturer Drug is Preferred with Unrestricted Access and in the applicable Formulary Status in the table above; and
2. All other single-source brand name Drugs in the Admelog Defined Drug Market are (a) in a non-Preferred Formulary tier or are non-Formulary and (b) where the Benefit design allows, subject to a step edit requiring trial of all Preferred Drugs within the Admelog Defined Drug Market, where it is clinically appropriate to do so; and
3. No package form of Admelog is disadvantaged to a comparable package form of any other Drug in the Admelog Defined Drug Market with regard to the applicable Benefit Contract's Utilization Controls. In the event a package form of Admelog is disadvantaged to a comparable package form, all package forms of Admelog, i.e. both vial and pen, shall be ineligible for Rebates as of the date of dispensing. Notwithstanding the foregoing, Admelog SoloSTAR may be subject to a step edit, requiring the trial of Admelog vials before the utilization of Admelog SoloSTAR. If Administrator, or Contracting Payor, as applicable, implement a medical exception to such step edit that uses a prior authorization process to determine whether the step edit is medically appropriate, such prior authorization process will not be deemed disadvantaging for purposes of this Section 8.13(3).

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EXHIBIT D

DEFINED DRUG MARKET

[redacted]

Apidra® Apidra® SoloSTAR® Admelog® Vials Admelog® SoloSTAR®	Fiasp Fiasp FlexTouch Humalog Humalog Kwik Pen / Junior KwikPen Novolog Novolog FlexPen Novolog FlexTouch

[redacted]

Lantus® Lantus® SoloSTAR® Toujeo® SoloSTAR®	Basaglar KwikPen Levemir Levemir FlexTouch

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MANUFACTURER DRUG	COMPETITIVE DRUG
Toujeo® Max SoloSTAR®	Tresiba FlexTouch
[redacted]	
Apidra® Apidra® SoloSTAR® Admelog® Vials Admelog® SoloSTAR®	Fiasp Fiasp FlexTouch Humalog Humalog Kwik Pen / Junior KwikPen Novolog Novolog FlexPen Novolog FlexTouch
[redacted]	

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[redacted]

Lantus® Lantus® SoloSTAR® Toujeo® SoloSTAR® Toujeo® Max SoloSTAR®	Insulin Basaglar KwikPen Humalog Mix 50/50 Humalog Mix 50/50 KwikPen Humalog Mix 75/25 Humalog Mix 75/25 KwikPen Humulin 70/30 Humulin 70/30 KwikPen Humulin N Humulin N KwikPen Levemir Levemir FlexTouch Novolin 70/30 Novolin N Novolin Mix 70/30 Novolin Mix 70/30 FlexPen Relion Mix 70/30 Relion N Ryzodeg 70/30 Tresiba FlexTouch

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Response to Request No. 9.a:

OptumRx reimburses its network pharmacies for insulin that they dispense to members based on the terms of the specific agreements that OptumRx enters with each pharmacy. Generally, under OptumRx's agreements with network pharmacies, the reimbursement rates to pharmacies are calculated as the lesser of: (i) a specified percentage discount to the average wholesale price ("AWP"), as defined in each agreement, (ii) the pharmacy's usual and customer ("U&C") charge for the drug, or (iii) the Maximum Allowable Cost ("MAC") for certain generic drugs and brand drugs with generic alternatives managed on a MAC list. These reimbursement rates are not separately defined or negotiated for dispensing insulin as compared to other pharmaceuticals.

OptumRx reimburses its network pharmacies at competitive rates that balance compensating pharmacies fairly with providing an affordable benefit for clients and members. While OptumRx is not privy to the rates at which any given pharmacy purchases drugs, OptumRx consults a variety of independent data sources in an effort to reimburse pharmacies at competitive rates that exceed network pharmacies' overall acquisition costs.

Response to Request No. 9.b:

Maximum Allowable Cost ("MAC") pricing applies to certain generic drugs or brand name drugs with generic versions. OptumRx typically does not use a MAC list in connection with insulin products, which do not currently have generic versions.

Response to Request No. 9.c:

OptumRx works with highly sophisticated clients who choose how they prefer to compensate OptumRx for the pharmacy care services that OptumRx provides. OptumRx supports client choice and offers clients the option of contracting under a traditional, or "spread," pricing structure. Clients that choose a traditional pricing structure accounted for slightly less than 20 percent of OptumRx's total claims volume from 2016 through 2018. However, in the commercial sector, OptumRx continues to see many of its clients choose this type of arrangement. For example, in 2019 roughly 60% of OptumRx's largest commercial clients elected a traditional pricing arrangement. Under a traditional pricing structure, the client negotiates a contracted rate with OptumRx for drugs, irrespective of what OptumRx has contracted to pay the pharmacy. For a client that chooses a traditional model, OptumRx bears the risk that it can negotiate a rate with the pharmacy that is below the cost it has contracted with the client. Some clients do not want to assume the financial risks and potential financial uncertainty of a pass-through pricing structure and instead prefer risk-based contracting approaches, like a traditional pricing structure, which provide financial certainty and incentivizes performance and value.

As discussed in previous responses, OptumRx does not, in the ordinary course of business, calculate the annual gross profit per claim for insulin products or other drugs, because its costs and revenues are not typically allocated to particular drugs, classes of drugs, or claims. As a provider of pharmacy care services, OptumRx provides a wide range of interrelated services to its clients, including clinical services, formulary design, rebate negotiation, claims administration, claims adjudication, pharmacy network management, and home delivery pharmacy operations, among others. Many of these services result in revenues and costs that are not readily allocated on the basis of a particular transaction, drug, class of drugs, or prescription claim.

Response to Request No. 9.d:

OptumRx supports client choice and offers clients the option of contracting under a pass-through pricing structure. Clients that choose pass-through pricing structures accounted for more than 80 percent of OptumRx's total claims volume from 2016 through 2018. Under a pass-through pricing structure, the client pays OptumRx what OptumRx pays the pharmacy for every dispensed prescription.

As discussed in response to Request No. 9.c, OptumRx does not, in the ordinary course of business, calculate the annual gross profit per claim for insulin products or other drugs.

Supplemental Response to Request No. 3:

As described in OptumRx's previous responses, OptumRx's Industry Relations group negotiates contracts and discounts with drug manufacturers, including manufacturers of insulin. Numerous individuals are involved in these negotiations, but Lisa Erickson and Kent Rogers have primary leadership responsibility. OptumRx representatives have periodic discussions with insulin manufacturers concerning overall pricing issues. In the course of those discussions, OptumRx continually seeks to obtain the lowest possible net cost for its customers and consumers, regardless of the list prices set by the manufacturers.

OptumRx's Formulary Management Committee ("FMC") has the authority to make decisions regarding the placement of prescription drugs on OptumRx's standard formularies. Subject to the clinical designations and recommendations of the Pharmacy & Therapeutics ("P&T") Committee, the FMC considers the availability of rebates in making formulary placement decisions.

Standard formularies are available online and are viewable by members, clients, and partners in the supply chain. In addition, all formulary placement changes are communicated in advance of their effective dates to clients and members whose claims may be affected. OptumRx provides supporting documentation regarding its formulary recommendations if such information is requested and provided under the terms of the client's contract. Manufacturers are notified of formulary placement changes by an OptumRx Industry Relations business lead.