Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

ASTRAZENECA UK LIMITED

SILK ROAD BUSINESS PARK

MACCLESFIELD

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UNITED KINGDOM

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: **Targeted inspection relating to qualification and validation of new facility for the manufacture of Zoladex sterile depots.**

Licence or Reference Number: MIA 17901, MIA(IMP) 17901, MS 17901, WDA(H) 17901

Licence Holder/Applicant: ASTRAZENECA UK LIMITED

Details of Product(s)/ Clinical trials/Studies: The site manufactures and packages a range of dosage forms including: non-sterile solid dose, and sterile injectables.

This inspection was in addition to the routine rolling inspection cycle and was specific to the new 'SPP5' facility for the manufacture of [redacted]

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Activities carried out by company:	Y/N
Manufacture of Active Ingredients	Y
Manufacture of Finished Medicinal Products – Non sterile	Y
Manufacture of Finished Medicinal Products - Sterile	Y
Manufacture of Finished Medicinal Products - Biologicals	N
Manufacture of Intermediate or Bulk	Y
Packaging – Primary	Y
Packaging - Secondary	Y
Importing	Y
Laboratory Testing	Y
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	Y
Broker	N
Other: Specials and IMPs	Y

Name and Address of site(s) inspected (if different to cover): As cover page

Site Contact: [redacted]

Date(s) of Inspection: 26-27 Sep 2018

Lead Inspector: [redacted]

Accompanying Inspector(s): Not applicable

Case Folder References: Insp GMP/GDP/IMP 17901/10117-0038

Section B General Introduction

B1 Background information

The AstraZeneca, Macclesfield site covers approximately 100 acres. This is a large and complex operation and is inspected on a rotational program. The site and the associated inspection programme can be split into subparts.

1. Tablet manufacturing and the warehouse
2. Packaging operation.
3. Sterile product manufacturing areas.
4. General site systems not covered in detail during the three main manufacturing activities.

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This visit was in addition to the routine rolling inspection programme and focussed specifically on the qualification and validation of the facility, equipment and processes related to the new Sterile Products Processing 5 ('SPP5') facility for the manufacture of [redacted] The SPP5 facility was constructed in 2014/2015 and the site has kept the MHRA inspector updated with progress, including regular visits during the project for familiarisation.

It was the site's intent to market validation batches of [redacted] from the SPP5 facility following approval of the scaled-up batch size from markets where variations were required and following successful completion of this inspection.

The aseptic process for [redacted] is split into several stages and future inspectors should request the company to provide overview presentations and discussions prior to inspecting the facilities due to the unique nature of the process. The general stages are:

1. Solution preparation and filtration. This is a non-aqueous process where the copolymer and active are dissolved in acetic acid prior to filtration into a pre-sterilised vessel.
2. Drum freezing. The product is dripped onto a rotating drum at -50ºC and the resulting flakes are collected in trays in a [redacted] environment.
3. Freeze drying. The trays are subject to an approximate 24-hour cycle to remove solvent.
4. Equilibration. The trays are removed from the freeze dryer and allowed to equilibrate in a grade A cabinet to aid in further processing stages.
5. Compaction. The flakes are scraped into sterile cylinders and compacted using a piston.
6. Extrusion. The compacted material is extruded vertically to generate spaghetti-like stands which are collected in a cylinder.
7. Cutting. The strands are visually inspected and cut into depots of the required length using semi-automated equipment.
8. Checkweighing. The depots are subject to 100% checkweighing.
9. Syringe assembly / primary packaging. The depots are inserted into the pre-sterilised syringes which are labelled and placed into pre-sterilised foil pouches with a desiccant.

Previous Inspection Date(s): 11-15 Jun 2018

Previous Inspectors: [redacted]

B2 Inspected Areas

Targeted inspection for the new SPP5 facility.

Limitations / exclusions to inspected areas

Refer to Annex 1 and 2 – rolling inspection cycle for supersite.

B3 Key Personnel met/contacted during the inspection

Refer to Annex 3.

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	August 2018	Yes
Compliance Report	Dated 19 Sep 2018	Yes
Comments: Not applicable.		

Section C Inspector's Findings

C1 Summary of significant changes

Detailed changes are recorded in the pre-inspection compliance reports held in the case folder.

Changes since previous inspection which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

None – this inspection was specific to the new SPP5 facility.

Future planned changes which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

None.

C2 Action taken since the last inspection

Actions from the previous inspection had generally been addressed.

C3 Starting Materials

General

Materials were received centrally to the site before transfer to the SPP5 building. The receiving process was not included in the scope of this inspection.

Compliance with TSE Guidelines

Not included in scope of this inspection.

API Compliance

Not included in scope of this inspection.

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C4 Pharmaceutical Quality System

Aspects of the PQS were not specifically included in the scope of this inspection as it focussed on the qualification and validation of the new SPP5 facility.

The overall validation hierarchy of the SPP5 project was described in [redacted] which was originally approved in July 2014, with [redacted] issued in March 2016.

Process validation (PV) for the [redacted] presentations had been performed and equivalence to the existing processes in the SPP3 and SPP4 facilities had been demonstrated. The [redacted] presentation had not been qualified in SPP5 at the time of inspection as this was specific to one market only with low volumes produced. The batch size of the mother lot had been scaled up for the new facility and resulted in eight sub-parts as opposed to the six sub-parts produced per batch in the existing facilities. A total of 24 sub-parts for each of the [redacted] presentations had been produced for PV following the manufacture of tech-transfer and establishment batches during commissioning and qualification of the facility. These considered both inter and intra sub-part variation and covered the process from material dispensing to check-weighed depots as the primary packaging activities remained in the existing SPP3 and SPP4 facilities. Enhanced sampling and analysis were performed for critical quality attributes [redacted] predicted to have the lowest potential [redacted] scores based on six months' data from the SPP3 and SPP4 facilities. Deviations associated with the PV were well documented with appropriate levels of investigation and conclusion. These included:

- [redacted] (one particle contamination deviation during the [redacted]
- [redacted] (two sample sets not tested by QC in error)

During the process validation work it was determined that the water content of the product flakes prior to extrusion does not have an impact on the dissolution profile of the product as was thought to be the case during initial product development. A change control had been raised to remove this as a [redacted] from the [redacted] presentation and this had been highlighted in the revised submissions for the [redacted] presentation.

Process simulations for the [redacted] process involved placing actual product depots into growth medium and incubating. Studies had been previously performed to demonstrate effective recovery from this process and this is the routine process employed for the existing facilities. Simulations had been conducted prior to process validation batches, with three consecutive full-scale batches of both [redacted] presentations (all sub-parts) incubated, resulting in a total of 32,354 depots incubated. Two further routine simulations had been conducted since the initial qualification. All depots from the initial process simulations had been primary packaged within the [redacted] facility and the two subsequent routine trials were packaged within the [redacted] facility. Maximum room occupancy had been challenged for worst case and higher risk activities for example during [redacted] open door setup activities.

C5 Personnel

Personnel met during the inspection were very knowledgeable of the process and facility and were able to clearly and confidently discuss their areas of responsibility.

C6 Premises and Equipment

The SPP5 facility was finished to a good standard, with appropriate space provided for all activities. The overall process and personnel flows were appropriate and logical. Localised UDAF areas were installed to provide added protection to the interface areas between the grade B rooms and the grade A [redacted] Gauntlets used for the [redacted] were gamma-irradiated and replaced weekly. These were washed and re-sterilised for a second use before being discarded. The site was exploring other options at the time of inspection to minimise wastage however no alternative had been identified at that time.

Access to the SPP5 facility was controlled by the use of key-cards and all staff and visitors were required to log into the building. Adequate space was provided in the general change area where personnel were required to change into facility-dedicated pyjamas and shoes.

Access to the grade B aseptic area was via one of three changing rooms and all staff exited through one shared de-gowning room. The gowning process was observed and generally acceptable however it was noted that goggles were sanitised rather than sterilised. The site indicated that a project was ongoing to identify appropriate sterilisable face coverings in anticipation of the revision to EU GMP Annex 1. It was also noted that the site permitted 'plain' wedding bands to be worn into the facility.

One processing room was available for preparation of the bulk product, freeze-drying in one of two chambers and transfer of the flakes into extrusion canisters. These were then wrapped and transferred to one of three extrusion rooms. There were three rooms originally intended for automated cut and check-weighing however the site had encountered problems with the fully automated equipment designed for this part of the process therefore the site had reverted to the semi-automated cut and check-weighing process employed in the SPP3 and SPP4 facilities. One of the cut/check-weighing rooms had been set up for cutting and another for check-weighing at the time of inspection and this was the process and equipment that had been utilised during PV. A new design of cut and check weigh equipment had been designed and this was intended to be implemented later with appropriate qualification.

Smoke studies had been conducted for all activities and rooms. Several of these were selected for review and it was demonstrated that a good level of control of airflows and maintenance of first pass air during critical operations was maintained. Studies were reviewed for the following parts of the process:

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- Setup of drum freezer
- Transfer of items into the [redacted] or filtration
- Transfer of trays from drum freezer to the lyophiliser and from the lyophiliser to compaction
- Changing rooms (although adequate air clearance was demonstrated, it was discussed that these studies may benefit from filming perpendicular to the stepover to view the overall airflow direction within the room).

Product contact parts were subject to manual cleaning to remove visible contamination followed by automated washing in machines using specially designed trays to ensure parts were consistently positioned for the cycles. It was noted that cleaned / dried parts were stored unprotected within the grade C area until required for use, at which time they were wrapped for sterilisation.

Two autoclaves and one oven were used for sterilisation of contact parts. The autoclaves utilised both 121ºC/20-minute and 134ºC/4-minute cycles with setpoints of 122ºC and 135ºC respectively. The oven sterilisation cycle included an exposure phase of 170ºC for two hours (with an acceptance criterion for validation of >161ºC for two hours).

Routine autoclave control and use included daily air removal testing utilising commercially available test packs for the 134ºC cycle. It was recommended that a test cycle for the 121ºC cycle was also included in the programme however both cycles included use of appropriately implemented air detectors which were tested on a weekly basis. In addition to this, an annual [redacted] test was performed to demonstrate appropriate temperature / time conditions for the daily test. Some issues were encountered during the initial setup and qualification of the autoclaves. Appropriate investigation and modification to the load patterns were applied prior to final qualification activities.

A controlled copy of the validation report for the autoclave and oven cycles was available in the grade C preparation area to ensure correct loading patterns were used. Load patterns were

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generally well designed however it was noted that the bleed valve on the outlet of the product solution filter was not protected during transfer and setup within the [redacted] cabinet. Example raw data from autoclave validation were reviewed and found to demonstrate good control.

Two lyophilisers were in place within the processing area. These were subject to SIP sterilisation prior to each use and appropriate chamber leak tests. The shelves were temperature mapped during qualification and were monitored during use. The design of the shelf cooling system was such that any issues during routine use would be observed through the monitoring system.

C7 Documentation

The SPP5 facility utilised an electronic batch record system which had been appropriately qualified. Technical report [redacted] described the site's approach to maintenance of data integrity for the control systems utilised in the SPP5 facility.

Some paper-based systems and logbooks were also in use and appeared to be appropriately controlled.

C8 Production

The first commercial batch of [redacted] was manufactured in [redacted]

Primary packaging of the [redacted] depots (insertion to the applicator syringes and sealing into sterile foil pouches) was still conducted in the SPP3 and SPP4 facilities. A process of triple-wrapping the sterile conical flasks for transfer between the facilities was in place and had been included in the media fill qualification process.

C9 Quality Control

The environmental monitoring programme for the facility was derived from a detailed study base don the [redacted] monograph and ar [redacted] scoring system. This included review of the number of aseptic manipulations and interventions during routine processing within the grade A zones and 'heat-map' studies on activity in the supporting cleanrooms. The locations determined from the theory-based study were also 'sanity-checked' and additional locations added where appropriate.

It was discussed that applying the statement 'no contact parts exposed' when aseptic manipulations were performed via glove-ports may not be fully appropriate and also that defining which gauntlets were routinely monitored may not be fully representative of all activities, however the overall outcome of the study resulted in a comprehensive monitoring programme.

Active air monitoring was conducted using samplers designed specifically for AstraZeneca during the project which were then subsequently marketed by the manufacturer.

A study had been performed in February 2017 to demonstrate adequate removal of traces of agar when performing contact plate surface samples [redacted] gauntlets [redacted]

Environmental monitoring trend data were reviewed and these demonstrated the areas to be in good control, with improvements noted since initial commissioning of the facility.

C10 Outsourced Activities

Not included in scope of this inspection.

C11 Complaints and Product Recall

Not included in scope of this inspection.

C12 Self Inspection

Not included in scope of this inspection.

C13 Distribution and shipment (including WDA activities if relevant)

Not included in scope of this inspection.

C14 Questions raised by the Assessors in relation to the assessment of a marketing authorisation

None.

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

1 CRITICAL

None

2 MAJOR

None

3 OTHERS

3.1 **Contamination risks were not minimised at all stages of the process as evidenced by:**

3.1.1 Equipment was not handled after the final cleaning process in such a way to minimise the risk of recontamination in that items were not protected immediately after cleaning and drying and were only wrapped prior to sterilisation after an indeterminate storage period.

3.1.2 It was not required for all jewellery to be removed before entry to clean areas in that 'plain' wedding bands were permitted.

3.1.3 The bleed valve downstream of the sterilised product solution filter was not fully protected until the associated valve was closed and aseptically connected to the receiving vessel.

Reference: EU GMP Annex 1 (40, 64, 77)

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4 COMMENTS

4.1 It was discussed that the site was working to introduce sterilised eye coverings in place of the currently used sanitised goggles in preparation for the introduction of the updated EU GMP Annex 1.

4.2 It was discussed that it may be appropriate to review the environmental monitoring process where only specific gauntlets within the [redacted] were monitored as all were routinely used.

Section E Site Oversight Mechanism

Site referred or to be monitored by:	Tick (✓)	Referral date	Summary of basis for action
Risk Based Inspection Programme	✓	[redacted]	[redacted]
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The closing meeting was held with individuals listed in B3 and the deficiencies were verbally accepted in a positive manner. The company committed to addressing the issues.

F2 Assessment of response(s) to inspection report

A response was received on 25 Oct 2018 which was generally satisfactory.

F3 Documents or Samples taken

Copies of all presentations provided during the inspection and the environmental monitoring risk assessments were provided and saved to the inspection case folder.

F4 Final Conclusion/Recommendation, Comments and Evaluation of Compliance with GMP and GDP

The site operates in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
Directive 2001/83/EC, Directive(s) 2003/94/EC and 2011/62/EU	✓
GMP as required by HMR 2012 (as amended)	✓
Directive 2001/20/EC	✓
Directive 2001/82/EC	N/A
Article 84 and Article 85b(3) of Directive 2001/83/EC (GDP) and 2011/62/EU	✓

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector: [redacted] **Date: 01 Nov 2018**

Accompanying Inspector: Not applicable **Date: Not applicable**

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0*	Last inspection:	0
Major deficiencies this inspection:	0*	Last inspection:	0
Other deficiencies this inspection:	1*	Last Inspection:	3

* **Note: This was not part of the routine rolling inspection schedule.**

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(b). Provisional Rating based on Inspection Output (✔ applicable box)

Risk rating level	**Input from current Inspection Findings** (last inspection findings applicable to rating V only)	**Provisional rating – this assessment**	**Final rating last assessment**
0	Serious triggers outside the inspection cycle	[redacted]	[redacted]
I	Critical finding		
II	>/= 6 Major findings		
III	<6 Major findings		
IV	No critical or Major findings		
V	No critical or Major findings from current or previous inspection and <6 other findings on each.		

(c). Risk Assessment Inputs – discriminatory factors (✔applicable box)

[redacted]	None relevant (default)
	Significant concern over robustness of quality system to retain adequate control
	Significant failures to complete actions to close previous deficiencies raised at the last inspection
	Complex site
	Significant changes reported in Compliance Report
	Significant mitigating factors applied by the site
	Higher risk rating identified by other GxP and considered relevant to the GMP site
	Relevant site cause recalls, notifications to DMRC or rapid alerts since last inspection
	Nature of batch specific variations submitted since the last inspection give concern over the level of control
	Regulatory action related to the site
	Failure to submit interim update and/or failure to notify MHRA of significant change or slippage in commitments from post inspection action plan
	First Inspection by MHRA (does not require counter-signature for RR II)
	Other discriminatory factor (record details and justify below)

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(d). Inspectors Comments Related to Discriminatory Factors

[redacted]

(e). Risk Rating Result Incorporating Discriminatory factors (✔ applicable box)

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✔)
0	Immediate (as soon as practicable)	[redacted]
I	6 monthly	
II	12 months	
III	24 months	
IV	30 months	
V	30 months with 50% reduction in duration of the next inspection	

(f). Basis for risk-based acceptance of specific matters arising during the inspection

Not applicable

(g). GMP or GDP certificate conditioning remarks required as a result of risk-based decisions noted in section (f) above

[redacted]

(h). Conclusions

[redacted]

(i). Expert/ Operations Manager / Compliance Management Team (CMT) Comments (Risk rating level 0, I, II):

Expert / Operations Manager / CMT (delete as appropriate)
Risk Rating:
Comments:

[redacted]

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(j). Confirm Agreed Risk rating following this inspection:

Risk Rating:	Next Inspection target date:
[redacted]	

Notes regarding re-inspection and GMP certificate validity

1. The inspection schedule is based upon risk and resource. This date may change at any time due to factors not pertaining to your site.
2. The GMP certificate does not 'expire' it is provisionally assigned 3 year validity date. For external questions regarding your validity thereafter; please advise that this can be confirmed by contacting the inspectorate at gmpinspectorate@mhra.gov.uk

Annex 2

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[redacted]

Annex 3

List of personnel met during inspection

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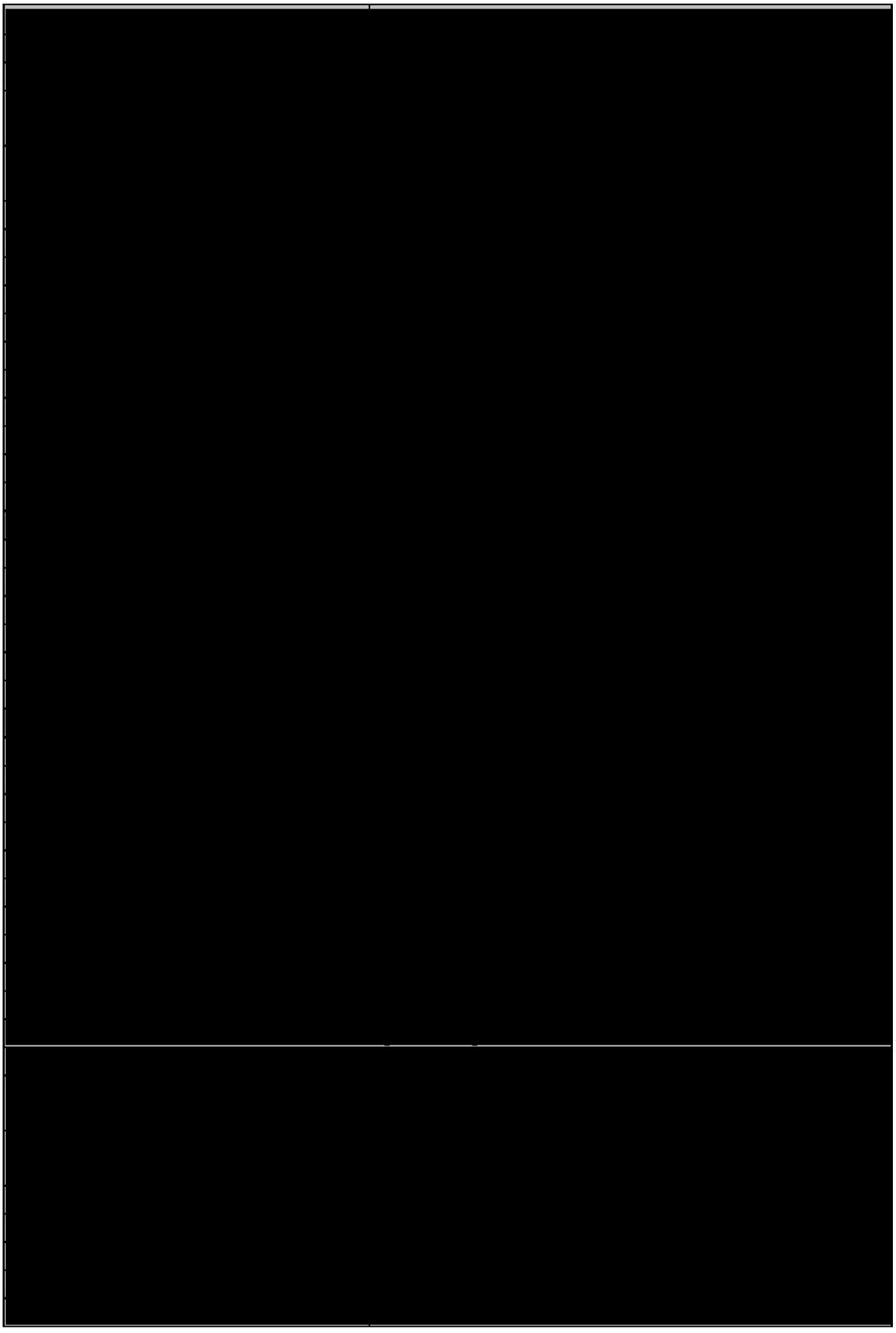

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[redacted]