بسم الله الرحمن الرحيم

MEGBI Antibiotics Production Pilot Plant (MEGBI-APP) - 5th Project Report (Jan 2017- Mar 2018)

- Feasibility Study for production of penicillin and semi-synthetic penicillins
- Completing integration of MEGBI-APP test rig (valves, automation)
- Chemical Process Simulation of MEGBI-APP

Authors:

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مركـز أبحـاث الشـرق الأوسـط للجينـات والتقنيـة البيولوجية

رأسنحاش – قضاء البترون- لبنان

Middle East Genetics and Biotechnology Institute (MEGBI)

A Member Institute of AECENAR

Main Road, Ras-Nhache, Batroun, Lebanon

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TEMO Biotechnology

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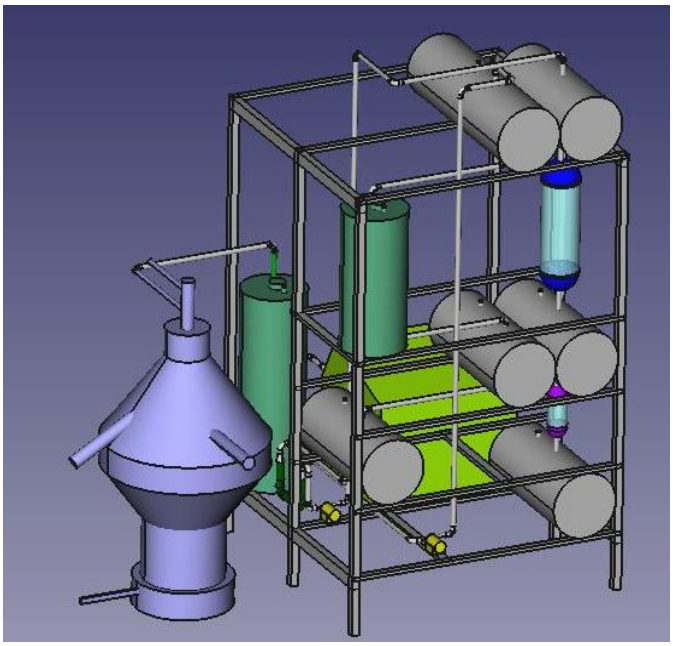
الشركة اللبنانية الالمانية للبيوتكنولوجيا

Lebanese-German Biotech

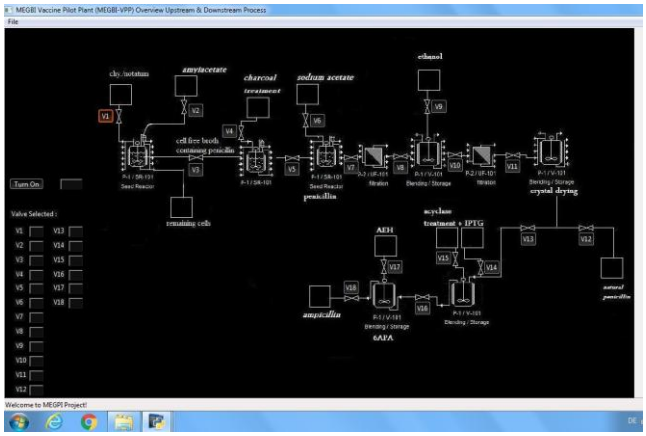
المضمون

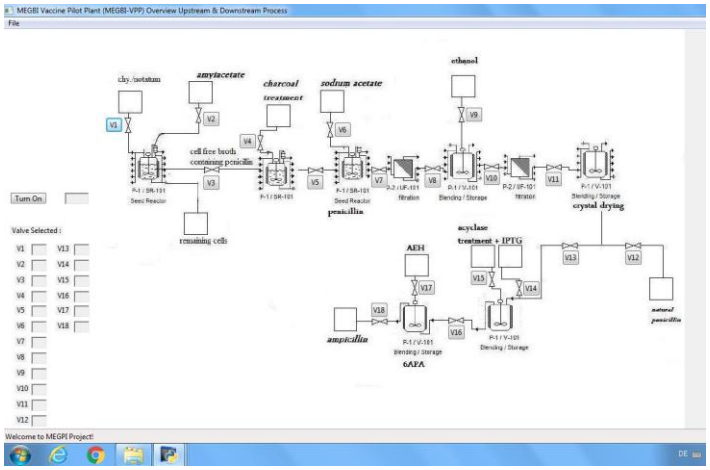
Project Status at beginning of this project phase



060116MEGBI-VPP_Assembly_simplified_manufactured.FCStd

- Mechanical parts of minimal USP-DSP manufactored





Process Control System

05121621uhr_MEGBI
-APP_automation.py

- Automation system, Graphical User Interface

1 إدارة المشروع (Project Management)

1.1 هدف العمل (Project phase goal)

The goal is to install a pilot plant for producing semi-synthetic penicillin.

1.2 Budget Planning

From 3rd project report, Ch. 1.4: Azm Association (Hani Maulawi, Dr Dani Saaduddin, Dr Kifah Tout) visited AECENAR Center at Ras Nhache on 6th March 2015 and Business Plan 2 was discussed. Result (Status 17th March 2015): Azm wants a more **detailed business plan with detailed market strategy. This is to be done in 2018.**

1.3 Time Schedule / الجدول الزمني

Originally planned: Nov/Dec 14: Financement and Concept Phase;

Jan – June 15: Finishing of Development of MEGBI Vaccine Production Pilot Plant (MEGBI-VPP)

Actually: March-May 2016: Migration of specification to semi-synthetic penicillin plant, 2017: Completing of MEGBI-APP prototype, 2018: Commercialization

1.3.1 Timeplan Sep-Dec 2017

Timeplan MEGBI-APP Sep-Dec 2017

Task	Due Date	Responsible
.pcd files of every compound (about 20)	Sun, 10.9.17	Razan
Moving lab (chemicals, some devices) to Hamra Facility	Sun, 10.9.17	Samir
Documentation	Sun, 10.9.17	Razan
Beginning of lab work	Sa, 16.9.17	Razan, Mariam, Rayyan
Integration MEGBI-APP plant	October 17	CNC Lab, Samir

1.3.2 Timeplan Jan-March 2018

Task	**Remarks**	**Due Date**	**Responsible**
Integration MEGBI-APP plant - Mixer, Pump, Connecting Cables to Arduino Interface - Connecting User Interface		Jan	Fatima, Mohamed(CNC Lab)
Operating &Testing MEGBI-APP with water		Jan	
Feasibility study for Amp, ...		Jan/Feb	Fatima
Lab work: Optimizing penicillin production, operation of MEGBI-APP		Feb-Mar	Fatima, ...
Bachelor Thesis: Design & cost calculation of optimized large scale semi-synthetic penicillin production plant		Apr-June	

1.4 Costs for completing protoype for Ampicillin production

1.4.1 Alternative 1: Stepper Motor for automatic valves

Automatic valves					
	piece cost	#pieces	total pieces		
سكر	$4	18	$72		
stepper motor	$40	18	$720		
acessories motor	$10	18	$180		
		Total cost	**$972**		

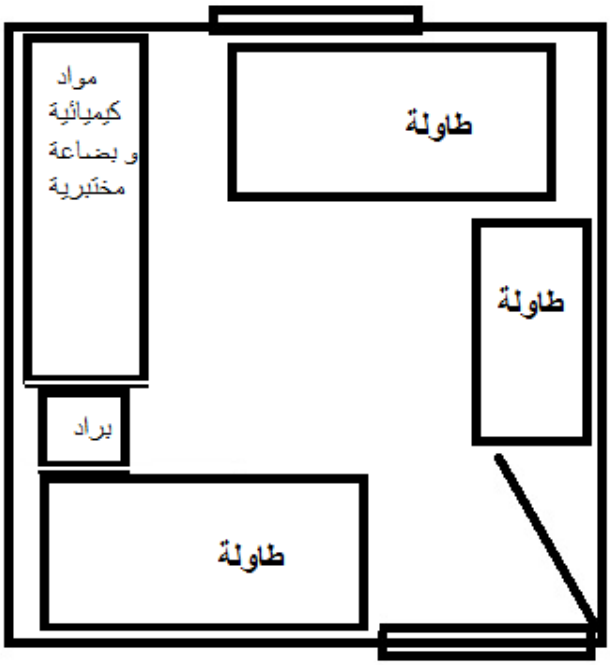
1.4.2 Alternative 2: DC Motor for automatic valves

Metal DC Geared Motor - 12V 50RPM 9kg.cm rated torque, Price : 15.95$, Serial number : ACT0022.

Automatic valves					
	piece cost	#pieces	total pieces		
سكر	$4	18	$72		
DC motor	$15	18	$270		
acessories motor	$10	18	$180		
		Total cost	**$522**		

1.4.3 Alternative 3: Low cost servo (see chapter 6)

Automatic valves					
	piece cost	#pieces	total pieces		
سكر	$4	18	$72		
low cost servo 9kg.cm	$8	18	$144		
acessories motor	$10	18	$180		
			$0		
		Total cost	**$396**		



Concept for Laboratory in Ras Nhache

1.5 Brochure for LG Biotech

بسم الله الرحمن الرحيم

الشركة اللبنانية الالمانية للبيوتكنولوجيا
Lebanese-German Biotech

لإنتاج ادوية عن طريق البيوتكنولوجيا

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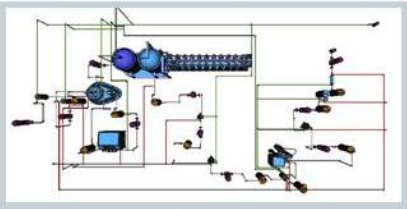
Website:
www.aecenar.com/companies/lgbiotech

إدارة الشركة – مستندات

تقوم على ادارة الشركة حاليا

الشركة اللبنانية الالمانية للبيوتكنولوجيا

رقم ٣٩٩ في سجل التجاري بيروت مسجل في تاريخ ٢٠٠٩/٥/٢٨



Eng. Samir Mourad , *Director/CEO*
Mobile: +96176341526
Email: samir.mourad@aecenar.com

Dr. Ahmad Trad , *Head of Antibodies Production*
Email: ahmad.trad@aecenar.com

@LG Biotech, August 2017

تاريخ الشركة

2006-2007

دراسات وابحاث حول انفلوينزا الطيور H5N1

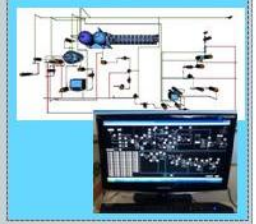
2008 - 2011

انشاء مختبر للهندسة الوراثية في راسنحاش

2012 - 2017

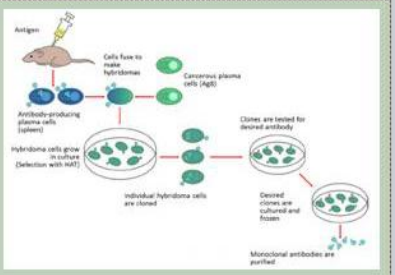
تصميم وانشاء مصنع تجريبي ل semi-synthetic antibiotics

تصميم مصنع لانتاج تلقيح ل Hepatitis B



منتجات الشركة

Production of Antibiotics Raw Material



Monoclonal Antibodies (Hybrodoma) Production

قيمة الشركة وسعر الاسهم

LG Biotech Sharika - Costs 2006-2022	
دراسات وابحاث حول انفلوينزا الطيور H5N1	$10.000
انشاء مختبر للهندسة الوراثية في راسنحاش	$300.000
تصميم مصنع لانتاج تلقيح ل Hepatitis B	$272.000
تصميم وانشاء مصنع تجريبي ل semi-synthetic antibiotics	$200.000
مكتب في طرابلس لمدة 5 سنوات	$30.000
محامي و محاسب لمدة 5 سنوات	$35.000
bureau assistent for 5 years	$60.000
3 laboratory workers	$234.000
maintanance of pilot plant about 3000$ per year (for 5 years)	$15.900
hybrodoma antibodies facility	$200.000
Total	$1.356.900
Total with overhead 15%	**$1.560.435**
Project is about 1,560,000 USD	
= 12 000 x 130 USD	
سعر السهم :	
$130	

2 Feasibility study

2.1 احتياجات السوق في الدول العربية وتركي

2.1.1 Situation in Egypt

1 أسماء أمين

2017-12-18 11:15:17

طباعة

البنسلين – أرشيفية

قال محمود فؤاد رئيس المركز المصرى للحق فى الدواء إن أزمة البنسلين انتهت بنسبة 95% منذ حوالى 48 ساعة.

وأوضح محمود فؤاد خلال مداخلة هاتفية ببرنامج "8 الصبح"، المذاع على فضائيةdmc ، أن هذه الأزمة لها أسباب محددة بأن مصر تستهلك من 6 إلى 8 ملايين عبوة بنسلين سنويا، مضيفا أن هناك شركة عامة مسؤولة عن استيراد حوالى 80% من الاستهلاك السنوى، وبدورها تورده للحكومة.

وأضاف فؤاد أن رئيس مجلس إدارة أحد الشركات قبل أن يترك عمله بالشركة أنشأ جمعية عمومية مصغرة للشركة ومجلس إدارة مقررين الاستغناء عن حوالى 45 منتجا من بينها البنسلين، ووافق مجلس الإدارة، على أن تتولى شركة خاصة جديدة هذه المهمة، إلا أنهم اكتشفوا فى النهاية أن رئيس مجلس الإدارة تنازل لنفسه من الباطن.

قالت الدكتورة رشا زيادة، رئيس الإدارة المركزية لشئون الصيادلة بوزارة الصحة والسكان، إن وزارة الصحة والسكان لديها مخزون استراتيجي من المواد الخام المصنعة لعقار «البنسلين» يكفي لإنتاج 2 مليون عبوة من البنسلين.

وأوضحت لـ«الدستور»، أن الاستهلاك الطبيعي للبنسلين يبلغ 300 ألف حقنة شهريًا على مستوى المحافظات.

وأكدت أن وزارة الصحة والسكان، وفرت 3 ملايين و800 ألف عبوة بنسلين طويل المفعول، ما بين مستورد ومحلي منذ ديسمبر الماضي، حيث قامت بتوفير 800 ألف عبوة بنسلين مستورد، وتم توزيع 400 ألف منها على شركات التوزيع، والاحتفاظ بـ400 ألف كمخزون استراتيجي بالوزارة، مشيرة إلى أن وزارة الصحة سوف تستورد مليون عبوة أخرى من المستورد خلال شهر فبراير المقبل.

وأضافت أنه تم توزيع الإنتاج المحلي الذي بلغ مليونا و200 ألف عبوة، وتم تخزين مثلها كمخزون استراتيجي، لافتةً إلى أنه تم توزيع البنسلين على الصيدليات دون كوتة محددة، مما ساعد على توافره في أى صيدلية.

وحذرت «زيادة» من تلاعب بعض الصيدليات في سعر العقار، أو إيهام المرضى بعدم وجوده، مناشدة المواطنين سرعة الاتصال بإدارة التفتيش الصيدلي في هذه الحالة؛ لاتخاذ الإجراءات اللازمة ضد هذه الصيدليات.

كانت وزارة الصحة والسكان قد شهدت نقصا حادا في حقن «البنسلين» طويل المفعول، خلال العام الماضي

هذة الحقن تشتهر بأسم البنسلين طويل (ممتد) المفعول. Long Acting Penicillin

توجد فى تركيز واحد فقط و هو مليون و 200 ألف وحدة دولية (1,200,000. (U

أشهر أستعمالاتها هى للوقاية من مرض الحمى الروماتيزمية.

الجرعة المعتادة هى مرة واحدة فقط فى الشهر .

كتبت ـ أسماء سرور وهدير الحضرى

نشر فى : الأربعاء 13 ديسمبر 2017 - 8:51 م | آخر تحديث : الأربعاء 13 ديسمبر 2017 - 8:51 م

–الصيادلة: احتياجات السوق 200 إلى 400 ألف عبوة شهريًا.. وقانون الهيئة العامة للدواء يمهد لحل الأزمة

قال المتحدث الرسمى لوزارة الصحة خالد مجاهد، إن 4 شركات محلية ستكون مسئولة عن إنتاج البنسلين خلال الفترة المقبلة، لتقليل الاعتماد على الاستيراد، وضمان عدم تكرار أزمة نقص الحقن، التى حدثت خلال الفترة الماضية، مشيرا إلى توفر رصيد استراتيجى يكفى لمدة 5 أشهر بنهاية ديسمبر الحالى.

https://www.shorouknews.com/news/view.aspx?cdate=13122017&id=5d982b45-ef04-42df-a526-b122c49eaeb1

11يناير 2018 4:52 م

تصاعدت أزمة نقص البنسلين والأنسولين المستورد بدمياط، وسط صرخات الأهالى بتوفير البنسلين والأنسولين لإنقاذ أبنائهم وإنقاذ المرضي خاصة من هم بحاجة إلى البنسلين وسرعة حل الأزمة وتنفيذ وعوده بتوفير الأدوية، عقب زيادة سعرها. وبيعها بالسوق السوداء بأضعاف ثمنها الأصلي.

وتأتى أزمة نقص البنسلين لتصدر المشهد فبعد إن كان متوافرا بالأسواق بسعر 9 جنيهات للزجاجة وصل سعره إلى 150 جنيها بدعوى أنه ناقص بالسوق وأنه مستورد.

تقول أمانى السيد إنها تعانى في الحصول على الأنسولين المستورد من مستشفيات التأمين الصحى وترفض الحصول على الأنسولين المصري لأنه غير فعال ويسبب اضطرابات في نسبة السكر في الدم ولهذا تلجأ إلى شرائه من الصيدليات بسعر 45 جنيها للعبوة الواحدة.

وتابع أحمد العزب موظف: ابنى الوحيد بيضيع منى، كل ده عشان مش عارف أجيب علاجه بحس أن قلبى بيتقطع، ومش عارف أعمل له حاجة، لفيت على جميع صيدليات المحافظة من أجل الحصول على علبة بنسلين وفي الآخر لقيت علبة واحدة ب150

جنيها وحجة الصيدلى أنها ناقصة بالسوق وأنها مستوردة ومش موجودة فاضطريت اشتريها وكمان 15 يوما هحتاج واحدة تانية وهدور تانى.

يقول الدكتور إيهاب قطارية وكيل نقابة الصيادلة بدمياط ورئيس لجنة الصيدليات، إن أزمة نقص البنسلين على مستوى الجمهورية ومتفاقمة رغم تصريحات وزير الصحة بأنه لا توجد أزمة وتم ضخ كميات كبيرة من البنسلين في الأسواق، فالبنسلين غير موجود بالمرة بالصيدليات باستثناء بعض الصيدليات التى توجد لديها علبة أو أكثر ويتم بيعها بالسوق السوداء بفارق سعر أزيد وبالنسبة للمستشفيات الحكومية فهناك شروط وتعقيدات للمرضي للحصول على البنسلين منها يجب إحضار صورة ميلاد الطفل أو الرقم القومى للمريض إضافة إلى الوقوف في طوابير للحصول على البنسلين ومن الممكن أنه بعد تلك المشقة لا يحصل عليه وداخل الأزمة ظهر مافيا السوق السوداء، ومحتكر الأدوية من أصحاب الصيدليات ممن خزنوا كميات من البنسلين، ليطرحوه فى السوق السوداء، وهو أمر اعتاد عليه معدومى الضمير من أصحاب الصيدليات في أزمات نقص الأدوية.

الصحة: «نوفارتس» توقفت عن إنتاج البنسلين وتوريده لمصر

"وهو خبر بتاريخ اليوم الموافق الخميس 18 يناير 2018 01:22 مساءً.

الصحة: «نوفارتس» توقفت عن إنتاج البنسلين وتوريده لمصر العرب نيوز ينشر لكم جديد الاخبار – ونبدء مع اهم الاخبار الصحة: «نوفارتس» توقفت عن إنتاج البنسلين وتوريده لمصر – العرب نيوز – الصحة: «نوفارتس» توقفت عن إنتاج البنسلين وتوريده لمصر .حيث ننشر لكم متابعينا في كل بقاع الوطن العربي جديد الاخبار اليوم عبر موقعنا العرب نيوز ونبدء مع الخبر الابرز، (العرب نيوز _ طريقك لمعرفة الحقيقة) – اخبر الدكتور مصطفى السيد مدير إدارة التفتيش الصيدلى بوزارة الصحة والسكان، إن هناك نوعين من البنسلين في السوق المصري.

وأوضح في تصريح خاص للدستور أن النوع الأول من إنتاج شركة نوفارتس العالمية، ولكنها أوقفت إنتاجه وتوزيعه لأنهم لا يحتاجون له لعدم وجود مرضي بالحمى الرماتزميه في دول أوروبا، موضحا أن مرضي الحمى الروماتزمية يتواجدون بأعداد كبيرة في دول العالم الثالث والهند، أما النوع الثاني وهو المنتج الصيني ويوزع لمنطقة الشرق الأوسط وفي مصر وهذا النوع هو المتواجد الآن في مصر.

والمح إلى أن أسباب تخبط شركات قطاع الأعمال التي كانت تنتج فيما مضي وحدوث الأزمة هى أن المرضي المصرين لديهم "عقدة الخواجة"، ويميلون لشراء الدواء المستورد عن الدواء المحلي، فأصبحت الشركات المحلية التي كانت تنتج بكميات كبيرة تواجه خسارة كبيرة وخفضت الإنتاج لعدم الإقبال عليه في السوق المصري.

واضاف إن المرضى يسألون الآن عن الدواء المستورد الذين كانوا يأخذونه، مؤكدا أنه خلال أسبوع سوف تنتهي الأزمة نهائيًا.

وأوضح أن لا توجد أزمة الآن فى البنسلين حيث أنه متوفر فى كافة الصيدليات الخاصة والحكومية.

Situation in Sudan 2.1.2

وقف استيراد الأدوية يهدد السودان بأزمة جديدة

الخرطوم . عاصم إسماعيل

31أغسطس 2017

أخبار مرتبطة

105%ارتفاع أسعار الأدوية بالسودان... وشكاوى المواطنين تتزايد

أزمة الدولار تهدّد صناعة الأدوية في السودان

اختفاء البنسلين من صيدليات مصر وبيعه في الأسواق بـ 25 ضعف سعره

أدوية مفقودة في تونس

وحذرت السلطات السودانية قبل أيام من التحايل على القرار الرئاسي الذي حظر استيراد الأدوية التي تُنتج محليا، فيما بدأت وزارة المالية والبنك المركزي في تنفيذ القرار، مع الالتزام باستيراد الأدوية المزمنة وفق سعر الدولار الرسمي.

وبدد وزير الصحة، بحر إدريس، في تصريحات صحافية قبل أيام، مخاوف المهنيين من شح الأدوية، قائلا إن الدولة تدعم الدواء بنحو 120 مليون دولار سنويا، فضلا عن توفير الدولار اللازم لاستيراد الأدوية بالسعر الرسمي.

وافتتح الرئيس السوداني عمر البشير، في إبريل/نيسان الماضي، أكبر مخزن دواء في العاصمة الخرطوم، بسعة تخزين 46 ألف متر مكعب، وبمواصفات ومعايير تستجيب لأسس التخزين الجيد، والتخلص من العمل اليدوي عبر استخدام التكنولوجيا والرافعات الحديثة لنقل الأدوية.

2.1.3 مقالات:واقع صناعة الدواء في العالم العربي - الخليج نموذجًا

19 فبراير 2017

صناعة الدواء في الخليج العربي

تولي دول مجلس التعاون الخليجي الرعاية الصحية اهتمامًا بالغًا لتطوير الخدمات الصحية لسكانها ويظهر ذلك من خلال حجم ما تقدمه الميزانية للقطاع الصحي حيث بلغت نحو 21.5 مليار دولار في العام 2011 وبلغت فاتورة قطاع التأمين الصحي في دول المجلس في العام 2010 أكثر من 13 مليار دولار.

كما حفزت الحكومات القطاع الخاص على الاستثمار في الصناعات الدوائية من خلال تقديم القروض والإعفاءات والحوافز وبادرت بإقامة شركات بالمشاركة مع القطاع الخاص للصناعات الدوائية والمستلزمات الطبية، إذ لا تزال دول الخليج تستورد احتياجاتها من الأدوية بنسبة كبيرة تقارب الـ95% مقارنة مع ما تنتجه محليًا، لذا تتوفر فرص كبيرة للمستثمرين لتغطية هذا النقص الهائل في الطلب.

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وارتفعت عدد مصانع الأدوية في دول مجلس التعاون من 18 مصنعًا في العام 1995 باستثمارات قدرها 174.4 مليون دولار إلى 55 مصنعًا في عام 2004 باستثمارات بلغت 793.1 مليون دولار، وحافظت السعودية على صدارة دول المجلس في عدد المصانع، بواقع 27 مصنعًا، وعدد المصانع في الإمارات وصل لـ16 مصنعًا، حيث ارتفع من 14 مصنعًا عام 2014 إلى 16 في 2015 يعمل لإنتاج أكثر من 1000 صنف دوائي مبتكر ومثيل .

ولا تزال السعودية تمثل الوزن الأكبر بين دول المجلس في صناعات الدواء، ففي دارسة أشارت أن الصناعات الدوائية السعودية تمثل 80% من إجمالي السوق الخليجية وتتخطى حاجز الـ13 مليار ﷼ سنويًا كما أنها تحقق نموًا سنويًا بلغ 12%، وتظهر الدارسة أن المصانع السعودية تغطي 20% فقط من حاجة السوق المحلية الدوائية ويذهب الباقي للتصدير.

وبلغت قيمة سوق الأدوية في دول مجلس التعاون الخليجي 10.1 مليار دولار في عام 2014، وتأتي السعودية على رأس دول المجلس بحجم سوق أدوية يبلغ 6.3 مليارات دولار، وتحتل الإمارات المرتبة الثانية حيث قدرت قيمة السوق الدوائية بـ2.4 مليار دولار ومن المتوقع أن تصل إلى 3.7 مليار دولار بحلول عام 2020، وجاءت الكويت في المرتبة الثالثة، كما تصل قيمة الأدوية المستوردة في دول الخليج العربية إلى نحو 9.5 مليارات دولار سنويًا، بنسبة تصل إلى 90% من حجم الاستهلاك المحلي.

ورغم حجم هذه الأرقام يؤكد خبراء أن صناعة الدواء في السعودية خصوصًا والخليج عمومًا بحاجة إلى مزيد من الاستثمارات في هذه الصناعة الواعدة، فالسعودية مثلاً استوردت في العام 2014 نحو 96.28 ألف طن من الأدوية بلغت قيمتها نحو 20.6 مليار ﷼ في حين أنها صدرت 54.2 ألف طن من الأدوية المصنعة محليًا بلغت قيمتها 2.21 مليار ﷼ في نفس العام.

2.1.4 الصومال

طائرة إغاثية ثالثة تحمل مساعدات طبية تصل للصومال ونؤكد لكم باننا نسعى دائما لامدادكم بكل ماهو جديد وحصري والان ندخل في التفاصيل

الرياض – عبدالله السعيد – إنفاذاً لتوجيهات خادم الحرمين الشريفين الملك سلمان بن عبدالعزيز آل سعود وسمو ولي عهده الأمين –حفظهما الله– حيال تقديم المساعدات الطبيه للحكومة الصومالية، وصلت الاثنين إلى مقديشو طائرة القوات الجوية الملكية السعودية تحمل على متنها مساعدات طبية يرافقها فريق من مركز الملك سلمان للإغاثة والأعمال الإنسانية.

وكان في استقبال الطائرة في العاصمه مقديشو عدد من المسؤولين الصوماليين، وسيستكمل فريق المركز خطته لتسليم المساعدات وتوزيعها بالتنسيق مع الجهات ذات العلاقه، ويأتي هذا الدعم استمراراً لما تقدمة المملكة من مساعدات للأشقاء في جمهورية الصومال، بما يخدم المواطن الصومالي في كافة الاحتياجات وبما يتوافق مع المعايير الدولية.

الجدير بالذكر أن مركز الملك سلمان للإغاثة قدم العديد من المشاريع الإغاثية والإنسانية للأشقاء في الصومال.

2.1.5 الاحتلال يحارب صناعة الدواء في غزة

غزة . يوسف أبو وطفة

23أغسطس 2015

أخبار مرتبطة

مصانع غزة تترقب المواد الخام وحرية التصدير

أزمة الدولار تهدّد صناعة الأدوية في السودان

النظام الصحي بغزة مهدّد بالانهيار التام.. رواتب مقطوعة وقمامة ومخلفات أدوية

105%ارتفاع أسعار الأدوية بالسودان... وشكاوى المواطنين تتزايد

عام تفاقم الأزمات ... 2017 الأسوأ اقتصاديا على غزة

غزة تحتاج إلى أطباء

لم يعد مصنع "الشرق الأوسط" للأدوية في غزة المحاصرة، قادراً على العمل بكامل طاقته الإنتاجية، نتيجة المنع الإسرائيلي المتكرر لدخول المواد الكيمائية، التي تدخل في صناعة الأدوية والمستحضرات الطبية، والتي تقوم الشركة بإنتاجها منذ تأسيسها أواخر العام 1999، بسبب الذرائع الأمنية الإسرائيلية.

وتعاني الشركات والمؤسسات العاملة في مجال الصناعات الدوائية وتوريد المستلزمات الطبية في القطاع، من الممارسات الإسرائيلية، المتمثلة في منع دخول المواد الأولية المكونة للأدوية، وإرجاع المعدات وعدم السماح لها بالمرور عبر معبر كرم أبو سالم التجاري الذي يربط القطاع بالأراضي المحتلة عام 1948، وهو ما يكبد هذه المؤسسات خسائره مالية باهظة.

ويقول المدير العام لمصنع "الشرق الأوسط" للأدوية، الطبيب مروان الأسطل، لـ "العربي الجديد"، إنّ الناتج المحلي للمصنع يغطي ما نسبته 15% من حاجة السوق المحلي في غزة، بين مضادات حيوية وكبسولات وكريمات علاجية خاصة، حيث بلغ عدد الأصناف الإجمالية التي ينتجها نحو 90 صنفاً.

2.1.6 مصانع غزة تترقب المواد الخام وحرية التصدير

غزة ـ يوسف أبو وطفة

20أكتوبر 2017

ينتظر أصحاب المصانع والمنشآت الإنتاجية في قطاع غزة، المحاصر إسرائيلياً للعام الحادي عشر على التوالي، انعكاسا إيجابيا لتسلّم حكومة الوفاق الوطني مهامها، عبر رفع الحصار والتخفيف من الإجراءات المفروضة على حركة البضائع ودخول المواد الخام.

ويبدو انتظار أصحاب هذه المنشآت مشروعًا، في ظل الخسائر المالية الكبيرة التي تكبدوها، طيلة السنوات الماضية، بفعل الحصار وتلاحق الحروب التي شنها الاحتلال على القطاع وطاولت العديد من هذه المنشآت التي كانت مصدر رزق لآلاف العاملين.

وتعتبر المصانع العاملة في القطاع مصدرا من مصادر تشغيل الأيدي العاملة، في ظل ارتفاع معدلات البطالة لأكثر من 44%، بينهم نحو 60% من فئة الشباب، في الوقت الذي وصل فيه اعتماد الأسر الغزية على المعونات الإغاثية لأكثر من 80.%

وبحسب تقديرات اللجنة الشعبية لكسر الحصار (منظمة غير حكومية)، فإن متوسط دخل الفرد اليومي في القطاع الذي يقطنه أكثر من مليوني مواطن غزي، وصل إلى نحو دولار أميركي فقط، في حين ارتفع عدد العاطلين عن العمل إلى نحو ربع مليون لا يجدون فرص عمل.

ويقول رئيس اللجنة الحكومية لكسر الحصار عن غزة، علاء البطة، لـ "العربي الجديد"، إن إنجاز المصالحة الفلسطينية يشكل بداية حقيقية لإنهاء الحصار، والعمل على تخفيف الإجراءات المفروضة على القطاع، طيلة السنوات الماضية، وسينعكس إيجابًا على حياة الفلسطينيين وعلى الاقتصاد الغزي.

ويوضح أن نحو 4 آلاف منشأة ومصنع تعمل في القطاع، يعمل فيها عشرات الآلاف من العمال، تنتظر وقف هذه الإجراءات التي اتخذت بفعل الحصار، طيلة السنوات الماضية، وأدت إلى توقف بعض المصانع وتعطل أخرى بشكل شبه كلي، وخفض إنتاجية العدد الأكبر من تلك المصانع التي ظلت تعمل.

ويلفت البطة إلى أنه، ووفقًا لآخر إحصائية موجودة، فإن نحو 90% من المصانع توقفت بشكل كلي وشكل شبه كلي، خلال الفترة الماضية، بفعل نقص المواد الخام ومنع إدخال الاحتلال لها عبر وضعها على قوائم السلع ذات الاستخدام المزدوج، ما تسبب في تسريح أعداد كبيرة من العاملين بها.

2.1.7 مختصون: 22 نوعاً من الأدوية قاتلة في السعودية

مختصون: 22 نوعاً من الأدوية قاتلة في السعودية في حال لم تصرف بوصفة طبية معتمدة وهذه الأدوية تقود إلى مضاعفات خطيرة بنسبة 30 بالمئة إضافة إلى التسمم والإصابة بالأمراض كالسرطانات وأمراض الكبد وتشوه الأجنة

...وأكد أن حقنة البنسلين الواحدة أو أي مضاد حيوي آخر، يمكن أن يتسبب في الوفاة، إذا تم حقنه وريدياً أو في العضلة، وإذا كان لدى المريض حساسية، يتم عمل اختبار الحساسية قبل القيام بحقن المضادات الحيوية، كون الأقراص، والكبسولات، والأشربة تؤدي إلى أعراض خطرة في حال وجود حساسية لدى المريض.

الشرقية خالية من حقن البنسلين

عصام أبو الفتوح: الشرقية خالية من حقن البنسلين

عصام أبو الفتوح: شرق خالية من البنسلين حقن المملكة أخبار حقن البنسلين، عصام أبو الفتوح: الشرقية خالية من حقن البنسلين ننشر لكم زوارنا الجدد أخبار اليوم من خلال موقعنا الإخباري والبدء مع أهم الأخبار عصام أبو الفتوح: الشرقية خالية من حقن البنسلين.

أخبار المملكة الدكتور عصام أبو الفتوح، الشرقية، على اختفاء حقن البنسلين طويل المفعول، والذي يسبب أزمة حقيقية؛ بسبب الأمراض المزمنة، والمخدرات، وأنه يحتاج إلى عدد كبير من المواطنين.

وفي مكالمة هاتفية مع البرنامج، "ما بعد ذلك"، طالبت علا شوشة، وهي هيئة الإذاعة الساتلية لتس، بزيادة سعر البنسلين حتى تتمكن شركات الإنتاج من توفير الكميات المطلوبة في السوق. وأوضح أن الشركات لم تعد قادرة على إنتاج البنسلين، وبسبب تحرير سعر الصرف، هناك نقص في الإنتاج، وتوقفت المصانع عن إنتاج كميات كافية لتغطية احتياجات السوق.

شكرا لكم على متابعتنا ونحن نعدكم دائما لتقديم كل ما هو أفضل .. ونقل الأخبار من جميع مصادر الأخبار وتسهيل قراءتها. لا ننسى عمل إك لصفحتنا في الفيسبوك ومتابعة آخر الأخبار على تويتر. مع تحيات موقع عائلة المملكة.

المصدر: الصباح العربي

لأربعاء 17 يناير 2018 | اسطنبول 12° C

تركيا بوست المصدر:الأناضول

تستعد السعودية لاستخدام ''نظام تتبع الأدوية'' الذي طورته وزارة الصحة التركية، ويعد الأول من نوعه في العالم.

وقال مسؤولون في الوزارة، لمراسلنا، إن النظام الذي نفذته مؤسسة الأدوية والأجهزة الطبية التركية، التابعة لوزارة الصحة، تمكن من تخطي منافسيه من أوروبا وأمريكا، في تقييمات فنية صعبة، ضمن المشروع الذي أطلقته السعودية.

ووقع الجانبان التركي والسعودي اتفاقية بهذا الخصوص، في 21 أغسطس/آب الحالي؛ حيث سيتم العمل على مدار عام لتطوير نظام تتبع الأدوية السعودي، SAUDI DTTSومع دخوله حيز الخدمة، سيكون بوسع النظام رصد سوق الأدوية بالمملكة بنسبة 100.%

وزار مسؤولو أكثر من 20 دولة بينها السعودية وكوريا الجنوبية وكازخستان وقرغيزيا، مؤسسة الأدوية والأجهزة الطبية التركية، للاطلاع عن كثب على نظام تتبع الأدوية المطبق في تركيا، والذي يتيح مراقبة الأدوية التي تدخل السوق في عموم البلاد، سواء المنتجة محليا أو المستوردة.

وبهذه الطريقة يتم الحيلولة دون بيع الأدوية المزورة أو المهربة، والمنتهية صلاحيتها.

وبفضل أكواد رموز الاستجابة السريعة، الموجودة على علب الأدوية، يمكن تعقبها منذ دخولها السوق وحتى وصولها إلى المستهلك.

ومع إضافة آخر تحديث للنظام ''أين دوائي؟'' الذي يمكن تحميله على الهواتف الذكية، الموجه لمرضى سرطان الثدي بالمرحلة الأولى، بات بوسع المرضى رؤية أين يتواجد الدواء المطلوب، في أي أقرب صيدلية .

2.1.8 الدليل الوطني للأدوية المسجّلة في لبنان

Penicilline

سعر المبيع من العموم	الشكل الصيدلاني	العيار	التركيبة العلمية	أساسي / جنيسي	الاسم	لتصنيف العلاجي
33,606 L.L	Injectable powder for solution	1,000,000IU	Benzylpenicillin (sodium) - 1,000,000IU	G	PENICILLINE G PANPHARMA	J01CE01

لتصنيف العلاجي	الاسم	أساسي / جنيسي	التركيبة العلمية	العيار	الشكل الصيدلاني	سعر المبيع من العموم
J01CE01	PENICILLINE G PANPHARMA	G	Benzylpenicillin (sodium) - 5.000.000IU	5MUI	Injectable powder for solution	72,396 L.L
J01CE01	PENICILLINE G SOD. INJ.	G	Benzylpenicillin (sodium) - 1,000,000IU	1,000,000IU	Injectable powder for solution	64,045 L.L
J01CE01	PENICILLINE G SODIQUE	G	Benzylpenicillin (sodium) - 5.000.000IU	5MIO	Injectable powder for solution	129,703

Ampicilline

صنيف العلاجي	الاسم	أساسي / جنيسي	التركيبة العلمية	العيار	الشكل الصيدلاني	سعر المبيع من العموم
J01CA01	AMPICILLINE INJ.	G	Ampicillin (sodium) - 500mg	500mg	Injectable powder for solution	49,050 L.L
J01CA01	AMPICILLINE INJ.	G	Ampicillin (sodium) - 1g	1g	Injectable powder for solution	98,100 L.L

Amoxicilline

لتصنيف العلاجي	الاسم	أساسي / جنيسي	التركيبة العلمية	العيار	الشكل الصيدلاني	سعر المبيع من العموم
J01CA04	AMOXICILLIN	G	Amoxicillin (trihydrate) - 500mg	500mg	Capsule	85,726 L.L
J01CR02	AMOXICILLINA/ ACIDO CLAVULANICO	G	Amoxicillin (sodium) - 1g, Clavulanic Acid (potassium) - 200mg	1.2g	Injectable powder for solution	395,532 L.L
J01CA04	AMOXICILLINE INJ.	G	Amoxicillin (sodium) - 500mg	500mg	Injectable powder for solution	65,867 L.L

التصنيف العلاجي	الاسم	أساسي / جنيسي	التركيبة العلمية	العيار	الشكل الصيدلاني	سعر المبيع من العموم
J01CA04	AMOXICILLINE INJ.	G	Amoxicillin (sodium) - 1g	1g	Injectable powder for solution	100,902 L.L
J01CA04	AMOXICILLINE INJ.	G	Amoxicillin (sodium) - 1g	1g	Injectable powder for solution	21,338 L.L
J01CR02	AMOXICILLINE/ACIDE CLAVULANIQUE PANPHARMA	G	Amoxicillin (sodium) - 1g, Clavulanic Acid (potassium) - 200mg	1.2g	Injectable dry powder	34,923 L.L
J01CR02	AMOXICILLINE/ACIDE CLAVULANIQUE PANPHARMA	G	Amoxicillin (sodium) - 1g, Clavulanic Acid (potassium) - 200mg	1.2g	Injectable dry powder	82,937 L.L

نوال الأشقر – لبنان 24

تشهد أسعار سوق الأدوية في لبنان انخفاضاً ملحوظاً تخطى في بعض الأنواع نسبة الخمسين في المئة. فما سبب هذا الإنخفاض، وهل هو مرحلي؟

نقابة الصيادلة: الأسعار إلى مزيد من الإنخفاض

نقابة الصيادلة أكدت لـ''لبنان 24" أن أكثرية الأدوية انخفضت أسعارها بنسبة 25 %، وبعضها انخفض أكثر من 50 %. المستشار الإعلامي لنقيب الصيادلة جو سلّوم أعاد سبب تدني الأسعار إلى عاملين: ''أولاً أعادت وزارة الصحة جدولة أسعار الأدوية وعمدت إلى مقارنة أسعارها في بلد المنشأ، وخفضت السعر على هذا الأساس. ثانياً تقلب أسعار العملات الأجنبية وانخفاض أسعارها في بلد المنشأ نتيجة انخفاض صرف سعر اليورو.''

هذا التدني في أسعار الأدوية خلق ارتياحاً لدى المواطنين، إلتقينا عينة منهم في صيدلية ''محيو''، سارع أفرادها إلى إجراء مقارنة بين المبلغ الذي كانوا يتكبدونه شهرياً لشراء أدويتهم وما أصبح عليه اليوم. أحدهم رد معلقاً: ''اتساءل عن سبب هذا الإنخفاض اليوم، هل مافيا الدواء إلى تقهقر، أمّا أنه انخفاض مرحلي؟''

إلاّ أنّ هذا الإرتياح الشعبي يقابله امتعاض من قبل الصيادلة، كما أوضحوا لنا في صيدلية محيو أن ‘‘التخفيض كانت مفاعيله سلبية علينا كصيادلة، ونتج عنه تقلص في مداخيلنا بسبب تدني الأسعار وبقاء الجعالة على حالها، ولاسيما أن وزارة الصحة ومنذ ثلاث سنوات خفّضت الجعالة، وجعلتها مقطوعة بنسبة 46 $ فقط لكل دواء سعره فوق 300 $ حتى لو وصل سعره إلى مليون أو أكثر، كل دواء سعره فوق 100 $ انخفضت الجعالة من 22 % الى 20,7 % ، وفوق الـ 300 دولار لا تتعدى نسبة الربح 18 %. وكان يجب أن يلزموا الوكيل بنسب معينة من الربح.’’

وهذا نموذج مقارنة عن أسعار بعض الأدوية التي انخفضت بشكل كبير، كما كانت عليه وكما هي اليوم:

Cipralex –من 64000 إلى 25000.

Augmentin 1 g –من 26526 إلى 12080.

Plavix –من 129707 إلى 71052.

Diamicron –من 24813 إلى 9183.

Seroquel xr 300-من 359841 إلى 151305.

على أي حال سوق الدواء ليس سوى حلقة من منظومة صحية متكاملة يشوبها الكثير من الثغرات، ومحاربة الفساد الصحي فيها يحتاج إلى عشرات الوصفات السياسية قبل الطبية، تكون فيها ‘‘الوصفة الموحدة’’ أو الإرداة السياسية الجامعة برفع الغطاء عن ‘‘مافيا القطاع الصحي’’ بداية طريق الإصلاح.

2.2 Antibiotics technologies and global markets

بلغت قيمة سوق المضادات الحيوية النظامية العالمية 39.6 مليار دولار في عام 2013، ومن المتوقع أن تصل إلى 41.2 مليار دولار بحلول عام 2018 بمعدل نمو سنوي مركب يبلغ 0.8٪.

–تتوقع أبحاث بنك البحرين والكويت أن يزداد سوق الولايات المتحدة من 15.8 مليار دولار في عام 2013 إلى 16.4 مليار دولار في 2018، بمعدل نمو سنوي مركب قدره 0.7٪ في الفترة من 2013 إلى 2018.

– سيزداد السوق الأوروبي للمضادات الحيوية بمعدل نمو سنوي مركب قدره 0.5٪ من 9.8 مليار دولار في عام 2013 إلى 10.1 مليار دولار بحلول عام 2018.

https://www.prnewswire.com/news-releases/antibiotics-technologies-and-global-markets-262708941.html

2.2.1 Annual Output of 10,000 Tons of Penicillin Industrial Salt Project of Songyuan City (China)

2013/04/07 Source: Jilin Daily

Market Prospects

Anti-microbial infection drugs sales in today's global pharmaceutical market possesses the second place in a large class of drugs. Production and sales of penicillin is the largest in the world. After sixty years of development in the course of penicillin, especially in the 80s, and 90s, due to its efficacy, small side effects, low price, it is highly clinical welcomed. And it has become one of the first clinical drug choices of antibiotics. Globally, the world's antibiotic market experienced a middle term growth period in the 70s, the rapid growth period in the 80s, and maturity in the 90s, it has entered a new century of transition. The 1998 statistics show that annual world sale of anti-infective market is 40 billion U.S. dollars, accounting for about 10% of therapeutic drug market; the antibiotic is 25-26 billion U.S. dollars, 62-65% of the anti-infective drug, the largest share in the anti-infective market of the world.

Meanwhile, according to the relevant information over the years, annual growth rate of antibiotics is 8% on average. Also in this class of antibiotic drugs, sale of penicillin is 3.317 billion U.S. dollars, accounting for 13% of total sales of antibiotics.

With the different levels of development of global semi-synthetic penicillin and increase of market sales at the same time, it also brings about increase of 6-APA, 7-ADCA and other intermediates with penicillin as the raw material. In 1985, global production of 6-APA was 4200 tons, in 1990, 7000 tons, and from 1997 to the present, global production of 6-APA has been over 12000 tons. Annual growth rate is 15%. And the cephalosporins antibiotics with 7-ADCA and 7ACA as intermediates has dominated 31% antibiotics share of the world; from the future development trend of this kind of drug, the sales turnover of ceftriaxone, thienamycin sub-methylamine, ceftizoxime, cefuroxime axetil, cephalosporins, imatinib could reach 300 million U.S. dollars. Therefore, it will bring about increase of demand for 7-ADCA etc. intermediates during a given period. However, 7-ADCA is major derivative of penicillin G industrial salt, which shows the large development space of penicillin.

In addition, from dynamics of large penicillin companies, DSM Company, which accounts for 30% raw material market share of penicillin in the world, plans to establish a new joint venture company with Chemferm to further expand the scale of production of penicillin and its derivatives. This new plant to be built in the Netherlands plans to process 6-APA into 7-ADCA by enzymatic processing in order to reduce the production costs of 7-ADCA, improve efficiency and eliminate pollution. Bivchemie is another penicillin producer in the world, and the penicillin produced by this company occupies 10% of market share in the world. Aimed at the condition that the profitability of pharmaceutical raw material is low, the company said, it will not give up penicillin production, and look forward to the start of penicillin market and prices rise. Penicillin production in China in this year is expected to reach 34,000 tons, of which 20% are directly used as injection, 50% as the cephalosporin in producing intermediates products, and 30% as export to earn foreign currency.

China is a superpower in penicillin industrial salt export, and in 2003, exports accounted for 60% of global market share.

Penicillin of China is mainly focused in Huayao, Huaxing, Harbin Pharmaceutical, Shiyao and Lukang Pharmaceutical five enterprises, accounting for 90% of total output of penicillin.

http://english.jl.gov.cn/Investment/Opportunities/Industry/MedicineandBiotechnology/201304/t20130407_1439841.html

Scale of Project Construction

Construction scale is 10,000 tons of penicillin industrial salt.

Table 1 Product Plan

Name	Standard	Packaging	Reference discount kg / billion
Penicillin sodium (days powder)	CP2000 BP98	4 kg / Tin 5 billion / Tin	0.624
Penicillin potassium (sterile powder)	CP2000 CP2000 CP2000 BP98	4 kg / Tin 5 billion / Tin 3.15 kg / Tin 5 billion / Tin	0.652
Pharmaceutical intermediate penicillin potassium (penicillin industrial powder)	Industry standards VSP25	40 billion / barrel	0.652
Penicillin V potassium (oral powder)	CP2000 BP2000	40 billion / barrel	
Oxytetracycline (base)	BP2002/VSP26 Ministry of Health standards	25 kg / barrel 25 kg / bag	

2.3 Penicillin products on market (China, ..)[1]

2.3.1 Penicillin streptomycin injection For veterinary use only

US $2-2.4 / Box **5000 Boxes** (Min. Order) Dosage Form: **Injection,oral liquid** Animal Type: **Cattle,Fowl,Pets,Cattle, Fowl** Function: **Antibacterial Drugs** Appearance: **Colourless, Transparent** Place of Origin: **Hebei,China (Mainland)** Brand Name: **Depond**	 Hebei Depond Animal Health Care Science And Technology Co., Ltd., China (Mainland)

2.3.2 Penicillin

US $0.1-10 / Milliliter **32 Milliliters** (Min. Order) Dosage Form: **Powder** Animal Type: **Cattle,Fowl,Horse,Pets,Pig,Sheep** Function: **Antibacterial Drugs** Appearance: **White Powder** Place of Origin: **Tianjin,China (Mainland)** Brand Name: **Zoohance**	 Tianjin Glory Technology Co., Ltd., China (Mainland)

2.3.3 Animal antibodies & penicillin powder/ penicillin price

US $16-20 / Kilogram **1 Kilogram** (Min. Order) Dosage Form: **Powder** Animal Type: **Aquatic Animals,Cattle,Fowl,Horse,Pets,Pig,Sheep** Function: **Antibacterial Drugs** Type: **Animal Health Products** Appearance: **White crystalline powder**	

[1] from www.alibaba.com

Place of Origin: **Henan,China (Mainland)**	Zhengzhou Zhenhua Pharmaceutical Technology Service Co., Ltd., China (Mainland) Trade Assurance

2.3.4 Antibacterial Veterinary Prouducts Penicillin 30% Injection for cattle

US $0.1-1 / Piece **1 Piece** (Min. Order) Dosage Form: **Injection** Animal Type: **Cattle,Horse,Sheep,Dog** Function: **Antibacterial Drugs** Appearance: **an oil solution of fine particles suspended.** Place of Origin: **Hebei,China (Mainland)** Brand Name: **TIANYUAN**	 Hebei Tianyuan Pharmaceutical Co., Ltd., China (Mainland)

2.3.5 Penicillin G injection300.000iu

US $0.5-3 / Unit **50 Cartons** (Min. Order) Dosage Form: **Injection** Animal Type: **Cattle,Horse,Sheep** Function: **Antibacterial Drugs** Place of Origin: **Jiangxi,China (Mainland)** Brand Name: **Bolai** Model Number: **100ml**	 Jiangxi Bolai Pharmacy Co., Ltd., China (Mainland)

2.3.6 Veterinary products Procaine penicillin

US $0.39-1.09 / Box **1 Box** (Min. Order) Dosage Form: **Injection** Animal Type: **Cattle,Horse,Other Special Breeding Animals,Pets,Pig,Sheep** Function: **Antiviral** Appearance: **liquid** Place of Origin: **Hebei,China (Mainland)** Brand Name: **Jiuding**	 Shijiazhuang Jiuding Animal Pharmaceutical Co., Ltd., China (Mainland)

2.3.7 Cefalexin Medicine Grade/alternative to penicillin in patients with penicillin hypersensitivity

US $20-50 / Ton **1 Ton** (Min. Order) Dosage Form: **Aerosol** Animal Type: **Aquatic Animals** Function: **Antibacterial Drugs** Place of Origin: **Shandong,China (Mainland)** Brand Name: **WNN** Model Number: **WNN**	 Weifang Union Biochemistry Co., Ltd., China (Mainland)

2.3.8 Benzyl Penicillin+Penicillin powder for injection

US $0.1-1.5 / Box **2000 Boxes** (Min. Order) Dosage Form: **Injection,Powder** Animal Type: **Cattle,Fowl,Horse,Pig,Sheep** Function: **Antibacterial Drugs** Place of Origin: **Hebei,China (Mainland)** Brand Name: **GRDR** Model Number: **Vet - Medicine**	 Hebei Guangren Pharmaceutical Technology Co., Ltd., China (Mainland) Trade Assurance, Transaction Level: **7** Transactions(6 months), 1,000+

2.3.9 Procaine penicillin G & Dihydrostreptomycin sulphate 20:20 injectable suspension

US $2.4-2.8 / Box **10000 Boxes** (Min. Order) Dosage Form: **Injection** Animal Type: **Aquatic Animals,Cattle,Fowl,Horse,Pets,Pig,Sheep,camel dog** Function: **Antibacterial Drugs** Place of Origin: **Hebei,China (Mainland)** Brand Name: **ZDHF** Model Number: **20:20,20:25**	 Shijiazhuang ZDHF Stock-Raising Co., Ltd. China (Mainland) Trade Assurance Transaction Level: **1** Transaction(6 months), 100+

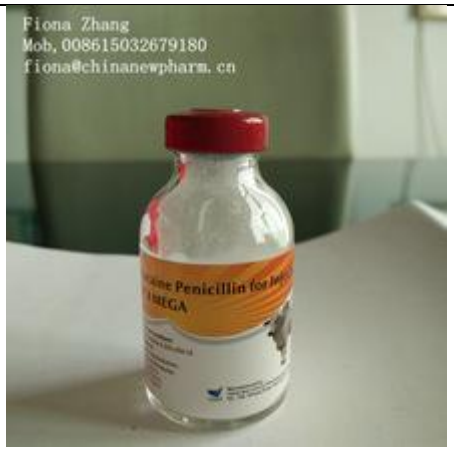
2.3.10 High Quality Veterinary USP Penicillin G 54-35-3

US $30-60 / Kilogram **1 Kilogram** (Min. Order) Dosage Form: **Powder** Animal Type: **Aquatic Animals,Cattle,Fowl,Horse,Other Special Breeding Animals,Pets,Pig,Sheep** Function: **Antibacterial Drugs** Appearance: **White or almost white crystalline powder** Place of Origin: **Hubei,China (Mainland)** Model Number: **Top grade**	 , Wuhan Vanz Pharm Inc. , China (Mainland) Trade Assurance Transaction Level: **39** Transactions(6 months), 10,000+

2.3.11 PENICILLIN G PROCAINE NON-STERILE(ORAL GRADE)

Function: **Antibacterial Drugs** Place of Origin: **Shanghai,China (Mainland)** Model Number: **USP**	 HUA YUN INTERNATIONAL (SINGAPORE)PTE LTD , Singapore

2.3.12 veterinary products streptomycin sulfate+procaine penicillin+benzyl penicillin powder for livestock

US $0.01-1 / Box **20000 Boxes** (Min. Order) Dosage Form: **Injection,Powder** Animal Type: **Cattle** Function: **Antibacterial Drugs** Place of Origin: **Hebei,China (Mainland)** Brand Name: **getion or your brand** Hebei New Century Pharmaceutical Co., Ltd., China (Mainland)	

2.3.13 Penicillin ,Penicillin industrial salt

200 Kilograms (Min. Order) Dosage Form: **Powder** Animal Type: **Cattle,Fowl,Horse,Pig,Sheep** Function: **Antibiotic** Place of Origin: **CN** Brand Name: **puertai** Model Number: **6008**	 Zhengzhou MCT International Co., Ltd., China (Mainland)

2.3.14 Procaine Penicillin 20%+Dihydrostreptomycin Sulfate 25% Injection for animal use

5000 Pieces (Min. Order) Dosage Form: **Injection** Animal Type: **Cattle,Horse,Sheep** Function: **Antibacterial Drugs** Place of Origin: **Hebei,China (Mainland)** Brand Name: **VEYONG** Model Number: **20%+25% 20%+20%**	 Hebei Veyong Animal Pharmaceutical Co., Ltd., China (Mainland)

2.3.15 APA Penstrep 20 S | High quality Veterinary Medicine| Dog Medicine with Penicillin (Vietnam)

US $0.5-1.5 / Unit **200 Units** (Min. Order) Dosage Form: **Suspension** Animal Type: **Pets** Function: **Antibacterial Drugs** Type: **Antibiotic** Place of Origin: **Ho Chi Minh City,Vietnam** Brand Name: **APA**	 APA UNITED NANO TECHNOLOGY CO., LTD , Vietnam

2.3.16 GMP, Dihydrostreptomycin sulphate + Procaine penicillin G suspension injection for veterinary medicine/cattle/poultry < ASIFAC> (Vietnam)

US $0.01-0.05 / Unit **2000 Units** (Min. Order) Dosage Form: **Injection,Suspension** Animal Type: **Cattle,Horse,Pig,Sheep** Function: **Antibacterial Drugs** Type: **Antibiotic** Appearance: **White suspension** Place of Origin: **Dong Nai,Vietnam** BRANCH OF THINH A VETERINARY MEDICINE TRADING AND MANUFACTURING JOINT STOCK COMPANY , Vietnam	

2.3.17 Benzyl Penicillin for Injection

US $0.1-0.2 / Box **10000 Boxes** (Min. Order) Place of Origin: **CN** Brand Name: **ZMC** Zhejiang Medicines & Health Products I/E Co., Ltd. China (Mainland)	

2.3.18 Benzyl penicillin potassium Injection for Veterinary

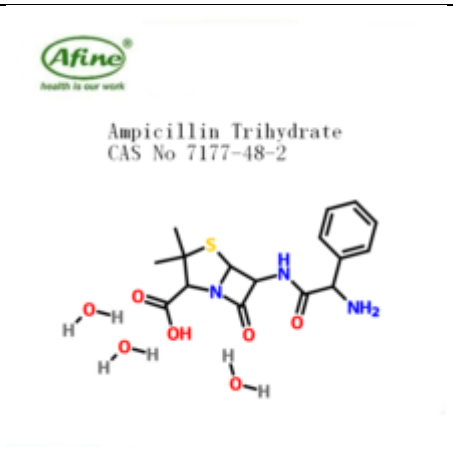
10 Kilograms (Min. Order) Dosage Form: **Injection** Animal Type: **Cattle,Pig** Function: **Antibacterial Drugs** Place of Origin: **Zhejiang,China (Mainland)** Model Number: **veterinary** white crystal powder: **off-white crystal powder** Hangzhou Union Biotechnology Co., Ltd. China (Mainland) Trade Assurance Transaction Level: **2** Transactions(6 months), 20,000+	

2.3.19 Top quality acid-resisting penicillin antibiotics Oxacillin Sodium Sterile

US $10-300 / Kilogram **1 Kilogram** (Min. Order) Dosage Form: **Injection,Powder,Tablet** Animal Type: **Cattle,Fowl,Horse,Pets,Pig,Sheep** Function: **Antibacterial Drugs** Appearance: **White or almost white powder.** Place of Origin: **CN** Brand Name: **TOP-PHARMCHEM** Shaanxi TOP Pharm Chemical Co., Ltd. China (Mainland)	

2.4 Ampicillin products on market (China, ..)

2.4.1 Ampicillin Trihydrate CAS 7177-48-2

US $30-50 / Kilogram **25 Kilograms** (Min. Order) MF: **C16H19N3O4S.3(H2O)** Other Names: **Ampicillin Trihydrate** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents** Grade Standard: **Medicine Grade** Usage: **Animal Pharmaceuticals**	

Afine Chemicals Limited China (Mainland) Trade Assurance	

2.4.2 Pharmaceutical raw materials ampicillin trihydrate from GMP manufacturer, CAS7177-48-2

US $1-50 / Kilogram **25 Kilograms** (Min. Order) MF: **C17H20N4O6** Purity: **96-102.0%** Type: **Antibiotic and Antimicrobial Agents** Grade Standard: **Medicine Grade,Tech Grade** Usage: **Animal Pharmaceuticals** Appearance: **White or almost white, crystalline powder**	 Beijing Infoark Co., Ltd. , China (Mainland)

2.4.3 high purity and free sample ampicillin

US $3-10 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3O4S3H2O** Other Names: **amfipen** Other name: **amfipen** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents,Antipyretic Analgesics and NSAIDs,Auxiliaries and Other Medicinal Chemicals,ampicillin** Grade Standard: **Food Grade,Medicine Grade,ampicillin**	 Daily Hi Industry (Shanghai) Co., Ltd. China (Mainland)

2.4.4 Ampicillin trihydrate CAS /NO:7177-48-2

US $1-1000 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3NaO4S** Other Names: **Ampicillin** Purity: **99%min** Type: **Urinary System Agents** Grade Standard: **Medicine Grade** Usage: **Animal Pharmaceuticals**	 Xi'an Sgonek Biological Technology Co., Ltd., China (Mainland) Trade Assurance , Transaction Level: **33** Transactions(6 months), 10,000+

2.4.5 GMP APPROVED HIGH PURITY LOW PRICE AMPICILLIN TRIHYDRATE

US $23.0-24.0 / Kilograms **200 Kilograms** (Min. Order) MF: **C16H19N3O4S.3H2O** Other Names: **AMPICILLINE** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents,Antibiotic and Antimicrobial Ag** Grade Standard: **Medicine Grade, Medicine Grade** Usage: **Animal Pharmaceuticals**	 Landy Enterprise Limited , China (Mainland) Trade Assurance

2.4.6 Veterinary hormones antibiotic compacted powder Ampicillin trihydrate

US $15-105 / Kilogram

1 Kilogram (Min. Order)

MF: **C16H19N3NaO4S**

Other name: **Ampicillin trihydrate compacted**

Other Names: **Ampicillin trihydrate**

Purity: **99%**

Type: Anesthetic Agents,Anti-Allergic Agents,Antibiotic and Antimicrobial Agents,Antidote,Antineoplastic Agents,Antiparasitic Agents,Antipyretic Analgesics and NSAIDs,Auxiliaries and Other Medicinal Chemicals, Blood System Agents, Cardiovascular Agents,Central Nervous System Agents,Disinfectant and Preservatives,Electrolyte Balance and Dialysis Agents,Endocrine System Agents,Gastrointestinal Agents,Immune Function Agents,Respiratory System Agents,Urinary System Agents,Vitamins, Amino Acids and Coenzymes

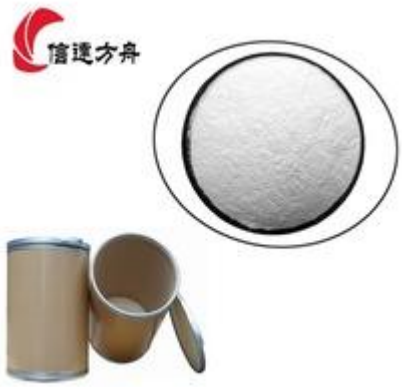
Grade Standard: **Cosmetic Grade,Feed Grade,Food Grade,Medicine Grade,Tech Grade**

2.4.7 Pharmaceutical raw material Ampicillin/cas no 69-53-4

US $2-10 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3O4S3H2O** Other Names: **amfipen** Purity: **99%-101%** Type: **Antibiotic and Antimicrobial Agents,Antipyretic Analgesics and NSAIDs,Auxiliaries and Other Medicinal Chemicals,Ampicillin** Grade Standard: **Cosmetic Grade,Food Grade,Medicine Grade,Ampicillin**	Daily Hi Industry (Shanghai) Co., Ltd. China (Mainland)

Usage: **Animal Pharmaceuticals**	

2.4.8 Pharmaceutical raw material Ampicillin Trihydrate powder,Ampicillin compacted

US $20-50 / Kilogram **25 Kilograms** (Min. Order) MF: **C16H19N3O4S** Purity: **99%** Type: **Antibiotic and Antimicrobial Agents** Grade Standard: **Feed Grade,Medicine Grade** Usage: **Animal Pharmaceuticals,Antibacterial Drugs** Appearance:: **white or a kind of white crystal powder**	 Beijing Infoark Co., Ltd. , China (Mainland)

2.4.9 High quality competitive price 69-53-4 Ampicillin in bulk supply

US $1-1000 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3NaO4S** Other Names: **Ampicillin** Purity: **99%min** Type: **Urinary System Agents** Grade Standard: **Medicine Grade** Usage: **Animal Pharmaceuticals**	 Xi'an Sgonek Biological Technology Co., Ltd. China (Mainland) Trade Assurance Transaction Level: **33** Transactions(6 months), 10,000+

2.4.10 PHARMACEUTICAL GRADE 99% AMPICILLIN MANUFACTURER

US $23.0-24.0 / Kilograms **200 Kilograms** (Min. Order) MF: **C16H19N3O4S.3H2O** Other Names: **AMPICILLINE** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents** Grade Standard: **Medicine Grade, Medicine Grade** Usage: **Animal Pharmaceuticals** Landy Enterprise Limited , China (Mainland) Trade Assurance	

2.4.11 High Quality Ampicillin CAS:7177-48-2 Ampicillin Trihydrate Powder

US $20-40 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3O4S.3H2O, C16H19N** Other Names: **AMPICILLINE** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents,API ampicillin trihydrate veterinary antibiotic ampicillin powder** Grade Standard: **Feed Grade,Medicine Grade,Tech Grade** Usage: **Animal Pharmaceuticals**	 Zhengzhou Panpan Chemical Co., Ltd. China (Mainland) Trade Assurance

2.4.12 factory supply High quality pharmaceutical Grade Ampicillin//69-53-4

US $1-1000 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3NaO4S** Other Names: **Ampicillin** Purity: **99%min** Type: **Urinary System Agents** Grade Standard: **Medicine Grade** Usage: **Animal Pharmaceuticals**	 Xi'an Sgonek Biological Technology Co., Ltd. China (Mainland) Trade Assurance Transaction Level: **33** Transactions(6 months), 10,000+

2.4.13 Pharmaceutical Material 99% Ampicillin Compacted

US $23.0-24.0 / Kilograms

200 Kilograms (Min. Order)

MF: **C16H19N3O4S.3H2O**

Other Names: **AMPICILLINE**

Purity: **99%min**

Type: **Antibiotic and Antimicrobial Agents,Antibiotic and Antimicrobial Ag**

Grade Standard: **Medicine Grade, Medicine Grade**

Usage: **Animal Pharmaceuticals**

Landy Enterprise Limited, China (Mainland) Trade Assurance

2.4.14 China API Medicine grade ampicillin animals compacted powder

US $20-40 / Kilogram

1 Kilogram (Min. Order)

MF: **C16H19N3O4S.3H2O, C16H19N**

Other Names: **AMPICILLINE**

Purity: **99%min**

Type: **Antibiotic and Antimicrobial Agents,China API Medicine grade ampicillin animals compacted powder**

Grade Standard: **Feed Grade,Medicine Grade,Tech Grade**

Usage: **Animal Pharmaceuticals**

Zhengzhou Panpan Chemical Co., Ltd., China (Mainland) Trade Assurance

2.4.15 Pharmaceutical raw material Ampicillin

US $2-10 / Kilogram

1 Kilogram (Min. Order)

MF: **C16H19N3O4S3H2O**

Other Names: **amfipen**

Other name: **amfipen**

Purity: **99%min**

Type: **Antibiotic and Antimicrobial Agents,Auxiliaries and Other Medicinal Chemicals,ampicillin**

Grade Standard: **Food Grade,Medicine**

Daily Hi Industry (Shanghai) Co., Ltd.

China (Mainland)

Grade,ampicillin	

2.4.16 SG supply Ampicillin powder CAS:69-53-4

US $20-500 / Kilogram **5 Kilograms** (Min. Order) MF: **C16H19N3O4S** Other Names: **Ampicillin** Purity: **99%min** Type: **Ampicillin** Grade Standard: **Medicine Grade** Color: **White**	 Xi'an Sgonek Biological Technology Co., Ltd., China (Mainland) Trade Assurance, Transaction Level: **33** Transactions(6 months), 10,000+

2.4.17 HIGH QUALITY PHARMACEUTICAL MATERIAL AMPICILLIN POWDER

US $23.0-24.0 / Kilograms **200 Kilograms** (Min. Order) MF: **C16H19N3O4S.3H2O** Other Names: **AMPICILLINE** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents** Grade Standard: **Medicine Grade** Usage: **Animal Pharmaceuticals**	 Landy Enterprise Limited , China (Mainland) Trade Assurance

2.4.18 China API ampicillin trihydrate veterinary antibiotic ampicillin powder

US $20-40 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3O4S.3H2O, C16H19N** Other Names: **AMPICILLINE** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents,API ampicillin trihydrate veterinary antibiotic ampicillin powder** Grade Standard: **Feed Grade,Medicine Grade,Tech Grade** Usage: **Animal Pharmaceuticals**	 Zhengzhou Panpan Chemical Co., Ltd., China (Mainland) Trade Assurance

2.4.19 FACTORY SUPPLY LOW PRICE COMPACTED AMPICILLIN GRANULES

US $23.0-24.0 / Kilograms **200 Kilograms** (Min. Order) MF: **C16H19N3O4S.3H2O** Other Names: **AMPICILLINE** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents** Grade Standard: **Medicine Grade, Medicine Grade** Usage: **Animal Pharmaceuticals**	 Landy Enterprise Limited, China (Mainland) Trade Assurance

2.4.20 High quality ampicillin trihydrate drug ampicillin compacted powder

US $20-40 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3O4S.3H2O, C16H19N** Other Names: **AMPICILLINE** Purity: **99%min** Type: **Antibiotic and Antimicrobial Agents,High quality ampicillin trihydrate drug ampicillin compacted powder** Grade Standard: **Feed Grade,Medicine Grade,Tech Grade** Usage: **Animal Pharmaceuticals**	 Zhengzhou Panpan Chemical Co., Ltd., China (Mainland) Trade Assurance

2.4.21 Wholesale 99% Purity CAS No 69-52-3 Ampicillin sodium (Georgia)

0.1 Kilograms (Min. Order) MF: **C16H18N3NaO4S** Other Names: **Reasonable** Purity: **99%min** Type: **Auxiliaries and Other Medicinal Chemicals, fitness** Grade Standard: **Food Grade,Medicine Grade** Appearance: **White Powder** Synprotech LLC , Georgia	

2.4.22 Ampicillin 5%, Colistin 20MUI/100g WSP, antibiotics (Vietnam)

US $0.01 / Pieces **1000 Pieces** (Min. Order) Dosage Form: **Powder** Animal Type: **Cattle,Fowl,Pig** Function: **Antibacterial Drugs** Place of Origin: **Hanoi,Vietnam** Model Number: **FIVEVET** Brand Name: **Five-Ampicon** CENTRAL VETERINARY MEDICINE JOINT STOCK COMPANY NO.5 , Vietnam	

2.4.23 Hydroxyl ampicillin/penicillin CAS:61336-70-7

US $1-100 / Kilogram **0.01 Kilograms** (Min. Order) MF: **C16H19N3O5S** Other Names: **Hydroxyl ampicillin penicillin** Purity: **99%** Type: **Anesthetic Agents,Anti-Allergic Agents,Antibiotic and Antimicrobial Agents,Antidote,Antineoplastic Agents,Antiparasitic Agents,Antipyretic Analgesics and NSAIDs,Auxiliaries and Other Medicinal Chemicals,Blood System Agents,Cardiovascular Agents,Central Nervous System Agents,Disinfectant and Preservatives,Electrolyte Balance and Dialysis Agents,Endocrine System Agents,Gastrointestinal Agents,Immune Function Agents,Respiratory System Agents,Urinary System Agents,Vitamins, Amino Acids and Coenzymes**	Grade Standard: **Cosmetic Grade,Feed Grade,Food Grade,Medicine Grade** Usage: **Animal Pharmaceuticals**  Hefei Joye Import & Export Co., Ltd. China (Mainland) Trade Assurance

2.5 Amoxicillin products on market (Products of China, ..)

2.5.1 Pet Medicine Antibiotics Amoxicilin Powder 10% for Cat chicken poultry amoxycillin poultry

US $1-20 / Kilogram **10 Kilograms** (Min. Order) Dosage Form: **Powder** Animal Type: **Aquatic Animals,Cattle,Fowl,Horse,Other Special Breeding Animals,Pets,Pig,Sheep** Function: **Antibacterial Drugs** Place of Origin: **CN;HUB,Hubei, China (Mainland)**	 Hubei Longxiang Pharmaceutical Tech

Brand Name: **Longxiang**	Co., Ltd. , China (Mainland)

2.5.2 Farming medicine Antibiotics Amoxicilin Powder 10% antibiotics for chickens

US $1-20 / Kilogram **10 Kilograms** (Min. Order) Dosage Form: **Powder** Animal Type: **Aquatic Animals,Cattle,Fowl,Horse,Other Special Breeding Animals,Pets,Pig,Sheep** Function: **Antibacterial Drugs** Place of Origin: **CN;HUB,Hubei, China (Mainland)** Brand Name: **Longxiang** Model Number: **10%**	 Hubei Longxiang Pharmaceutical Tech Co., Ltd. China (Mainland)

2.5.3 USP BP EP CP Amoxicilin,amoxicilina powder

US $10-100 / Kilogram **25 Kilograms** (Min. Order) MF: **C16H19N3O5S.3H2O** Other Names: **Almodan** Purity: **more than 99%** Type: **Antibiotic and Antimicrobial Agents** Grade Standard: **Medicine Grade** Usage: **Animal Pharmaceuticals** Shanghai Ruizheng Chemical Technology Co., Ltd., China (Mainland) Transaction Level: **25** Transactions(6 months), 130,000+	

2.5.4 Pharmaceutical grade medicine Amoxicilin,amoxicilina powder

US $10-100 / Kilogram **1 Kilogram** (Min. Order) MF: **C16H19N3O5S.3H2O** Other Names: **Almodan** Purity: **99%** Type: **Antibiotic and Antimicrobial Agents** Grade Standard: **Medicine Grade,Tech Grade** Usage: **Animal Pharmaceuticals** Xi'an Geekee Biotech Co., Ltd. , China (Mainland) Trade Assurance	

Transaction Level: **42** Transactions(6 months), 10,000+	

2.5.5 Amoxicillin raw material Amoxicilin

US $20-26 / Kilogram **10 Kilograms** (Min. Order) MF: **C16H25N3O8S** Other Names: **Amoxicillin trihydrate** Purity: **99%** Type: **Antibiotic and Antimicrobial Agents,Respiratory System Agents** Grade Standard: **Feed Grade,Medicine Grade,Tech Grade** Usage: **Animal Pharmaceuticals**	 Hebei Weierli Animal Pharmaceutical Group Co., Ltd. China (Mainland) Trade Assurance

2.5.6 jiangying,wuxi factory supply amoxicilin capsules/amoxicilina powder/amoxiciline

200000 Pieces (Min. Order) MF: **C16H19N3O5S.3H2O** Purity: **99%** Type: **Antibiotic and Antimicrobial Agents** color: **white** Place of Origin: **CN** CAS No.: **26787-78-0** SJ (Jiangsu) Pharmaceutical Co., Ltd. China (Mainland) Trade Assurance Transaction Level: **4** Transactions(6 months), 2,000+	

2.5.7 Amoxicilin Trihydrate Compact CAS 26787-78-0

US $60-100 / Kilogram **100 Grams** (Min. Order) MF: **C16H19N3O5S** Other Names: **amoxicillintrhydrate** Purity: **95%up** Type: **Anti infection** Grade Standard: **Medicine Grade** Sulphated ash: **0.1%**	

Sinoway Industrial Co., Ltd. China (Mainland) Trade Assurance	

2.6 صناعة الأردن (Jordan)

اسم المشروع	**مصنع البنسلين**
الموقع	عمان – الاردن
صاحب العمل	شركة الحكمة
المساحة المبنية	8000م^2
نطاق المشروع	تصميم خطوط الإنتاج وتشمل تصميم جميع التخصصات والخدمات لجميع منطقة التصنيع داخل مصنع الإنتاج

P. O. BOX 142 882 Amman - Um uthina - Saed Bin Abi waqas st

info@ucs-jo.com

00962 (6) 5529476

00962 (6) 5522476

http://ucs-jo.com/ar/index.php/project/item/53-apm-sterile-production-lines

Les précurseurs de β-lactame de toutes les pénicillines et céphalosporines sont produits par fermentation dans des fermenteurs jusqu'à 1000 m3. La concentration des produits dans le milieu à la fin de la

fermentation qui prend entre cinq et sept jours, est jusqu'à 100 g / L de pénicilline et 20 g / L de céphalosporine C.

2.6.1 ادوية المضاد الحيوي تبا تحقيق يفجر مفاجأة : الصيدليات تجني أرباح بمئات الملايين و شركات عملاقة تسيطر على الدواء بزيادة الاسعار 600%

تحقيق يفجر مفاجأة : الصيدليات تجني أرباح بمئات الملايين و شركات عملاقة تسيطر على الدواء بزيادة الاسعار 600%

27-12-2017 03:49 ع للحكومة بنفس الاسم التجاري بـ 282.18 دينار تباع في احدى سلسلات الصيدليات بـ 506.33 اي بفارق 224 دينارا اي بنسبة 100% فيما تباع احد انواع الادوية المخصصة لعلاج العيون ب4.4 قروش للحكومة بينما تباع في الصيدليات بـ 245 قرشا اي بنسبة 55 ضعف ما يباع للحكومة.

و تبين ان هناك ادوية مضادات حيوية تباع الحبة الواحدة ب 2.6 قرش بينما تباع في الصيدليات بـ 28.6 قرش اي اكثر من عشرة اضعاف ونوع اخر تباع الحبة الواحدة بـ 1.6 قرش بينما تباع في الصيدليات الخاصة بـ52 قرشا اي 32 ضعف السعر الحقيقي.

أسعار دواء أوجمنتين أقراص تركيز 1 جرام و 625 مجم

سعر دواء اوجمنتين اقراص مضاد حيوي 1 جم 2018

سعر دواء اوجمنتين اقراص مضاد حيوي 1 جم 2018

سعر دواء أوجمنتين أقراص مضاد حيوي 1 جم في مصر 2018:

89.75 جنيه مصري

سعر دواء أوجمنتين أقراص 1 جم في السعودية 2018 :

97.9ريال سعودي

سعر أقراص أوجمنتين تركيز 625 مجم في مصر 2018:

52.5 جنيه مصري

سعر اقراص دواء دواء اوجمنتين 625 مجم مضاد حيوي 2018

سعر اقراص دواء دواء اوجمنتين 625 مجم مضاد حيوي 2018

سعر أقراص أوجمنتين 625 مجم في المملكة العربية السعودية 2018:

79.75 ريال سعودي

سعر دواء اوجمنتين 375 أقراص مضاد حيوي في مصر 2017

36جنيه مصري

سعر اقراص اوجمنتين مضاد حيوي 375 مجم في السعودية

45.95ريال سعودي

موضوع كامل عن سعر دواء اوجمنتين شرب 156 و 312 و 457 و 600 مجم بكل التركيزات و البدائل بسعر أرخص اضغط هنا

بدائل أوجمنتين أقراص مثيل أقراص أوجمنتين سعر أقل سعر أرخص بنفس التركيبة و المادة الفعالة و الاستخدام :

كيورام أقراص 1 جم : سعر دواء كيورام أقراص في مصر 76 جنيه مصري.

ايموكسكلاف 1 جم أقراص : سعر ايموكسكلاف 1 جم في مصر 50.25 جنيه مصري.

هاي بيوتيك أقراص 1 جم : سعر هاي بيوتيك 1 جم في مصر 75 جنيه مصري.

ميجاموكس 1 جم أقراص : سعر ميجاموكس 1 جم في مصر 75 جنيه مصري.

أموكلاوين 1 جم أقراص سعر اموكلاوين 1 جم في مصر 34.5 جنيه مصري.

سعر ومواصفات ميجاموكس – مضاد حيوى واسع المجال – 1 جم 14 قرص

أفضل سعر لـ ميجاموكس – مضاد حيوى واسع المجال – 1 جم 14 قرص من دوايا فى مصر هو 50 ج.م.

طرق الدفع المتاحة هدفع عند الاستلام

تكلفة التوصيل هى 5 ج.م.

تباع المنتجات المماثلة لـ ميجاموكس – مضاد حيوى واسع المجال – 1 جم 14 قرص فى دوايا, سيف مع اسعار تبدأ من 40 ج.م.

أول ظهور لهذا المنتج كان فى إبريل 17, 2014

من بين المنتجات المماثلة لـ ميجاموكس – مضاد حيوى واسع المجال – 1 جم 14 قرص أرخص سعر هو 40 ج.م. من دوايا

2.7.1 AMOXICILLINE BIOGARAN 500 mg, gélule

- **AMOXICILLINE BIOGARAN 500 mg, 12 gélules** *P,* **Prix :** 2,55€ **Taux de remboursement :** 65%
- **Médicament princeps :** CLAMOXYL 500 mg, 12 gélules, **Prix** : 2,55€

2.7.2 Evolution des consommations d'antibiotiques en France entre 2000 et 2015

L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) analyse chaque année les données relatives à la consommation des antibiotiques en France. Les résultats présentés dans la nouvelle édition de son rapport montrent notamment que la consommation des antibiotiques repart à la hausse depuis 2010, et que la France reste parmi les pays européens où celle-ci est la plus élevée. Ce niveau élevé est très préoccupant car une utilisation non maîtrisée des antibiotiques est responsable du développement des résistances bactériennes. De surcroît, l'éventail des solutions de recours que constituent les antibiotiques dits « de réserve » s'appauvrit en raison de la diminution du nombre de substances antibiotiques disponibles et d'une innovation thérapeutique trop modeste.

La consommation d'antibiotiques a globalement diminué de 11,4 % entre 2000 et 2015, mais elle est en hausse de 5,4 % depuis 2010.

Plusieurs points doivent être soulignés :

La consommation d'antibiotiques en ville représente 93 % de la consommation totale.

Elle se caractérise par :

Un usage important des pénicillines et notamment de l'association amoxicilline-acide clavulanique, qui est particulièrement génératrice de résistances ;

Une diminution de l'usage des quinolones, ce qui constitue un point positif ;

Des durées de prescription très variables, avec une moyenne se situant à 9,2 jours ;

Des disparités de consommation importantes entre plusieurs régions françaises.

À l'hôpital, la consommation d'antibiotiques représente 7 % de la consommation totale. Elle a peu évolué au cours de ces dernières années et se caractérise par :

Une stabilisation de la consommation des céphalosporines de 3ème et 4ème générations ;

Une diminution de la consommation de la colistine injectable, substance active qui exige un suivi spécifique en raison du développement de souches bactériennes multi-résistantes.

En revanche, d'autres évolutions demeurent défavorables, comme la progression de l'usage des carbapénèmes.

En Europe, aucun changement majeur n'a été observé depuis 2000 dans la cartographie des consommations.

En ville, la France se situe en 2015 au 4ème rang et son niveau de consommation reste très supérieur à la moyenne européenne. A l'hôpital, cependant, la consommation française se rapproche de la moyenne européenne

Le travail d'analyse effectué par l'ANSM a pour but de contribuer au meilleur usage des antibiotiques.

L'objectif poursuivi ne doit pas seulement être quantitatif et aboutir à ce que la consommation française rejoigne la moyenne européenne. Une évolution qualitative de la consommation doit également être recherchée. Les prescriptions inadaptées, inutiles ou trop longues doivent être évitées. Le bon usage demeure ainsi plus que jamais une priorité.

2.7.3 AMOXICILLINE ACIDE CLAVULANIQUE 500 mg/62,5 mg

Médicament	Notice	Prix	Remboursement
AMOXICILLINE/ACIDE CLAVULANIQUE SANDOZ 500 mg/62,5 mg ADULTES, 24 comprimés pelliculés *P*	Notice	7,48€	65%
AMOXICILLINE/ACIDE CLAVULANIQUE SANDOZ 500 mg/62,5 mg ADULTES, 16 comprimés pelliculés *P*	Notice	6,15€	65%

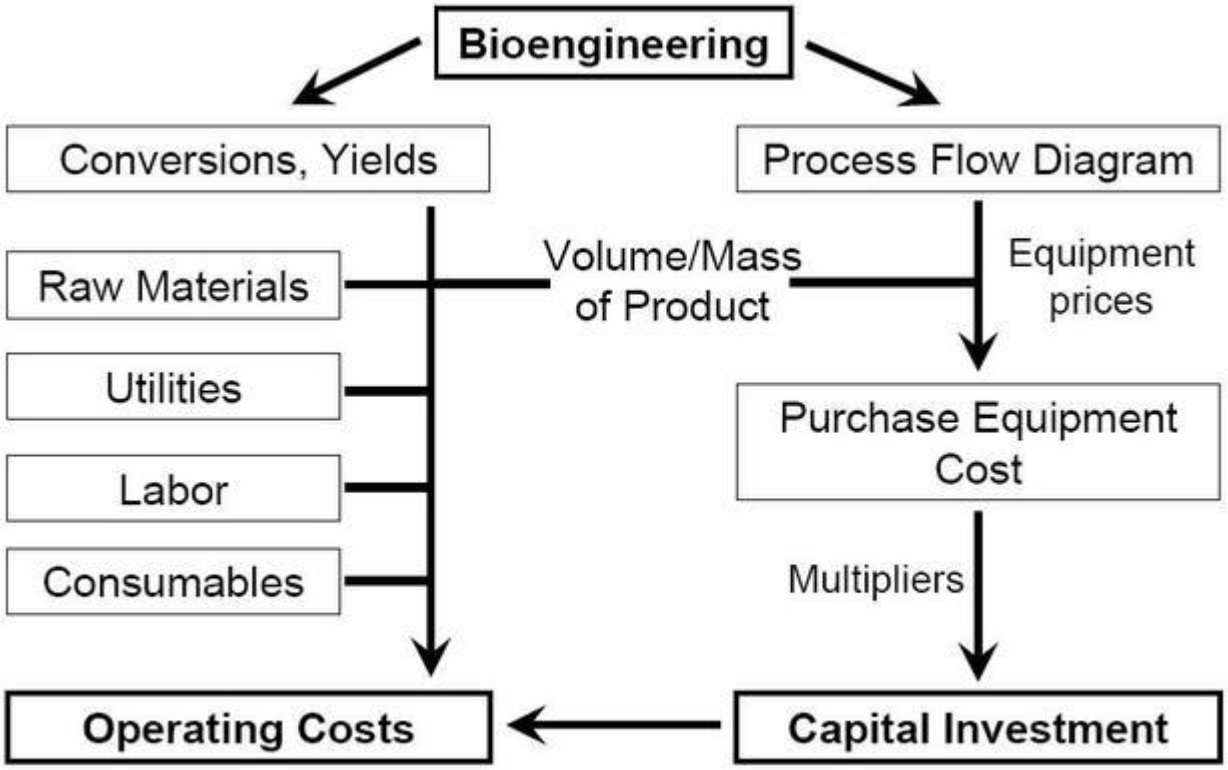
2.8

2.9 تكلفة الإنتاج (Production costs)

The cost of production of penicillin

وتبلغ التكلفة المقدرة لإنشاء مصنع للبنسلين 625 طنا في السنة ما بين 50 و 52 مليون دولار أمريكي تقريبا

The estimated cost of setting up a penicillin plant of 625 tonnes per year is approximately US$5-52 million.



وكما هو مبين في الرسم البياني أعلاه، فإن التكلفة المقدرة تأتي من عنصرين رئيسيين .وتشمل هذه :

1. تكاليف االستثمارات الرأسمالية

2. تكاليف الإنتاج

1. تكاليف االستثمارات الرأسمالية

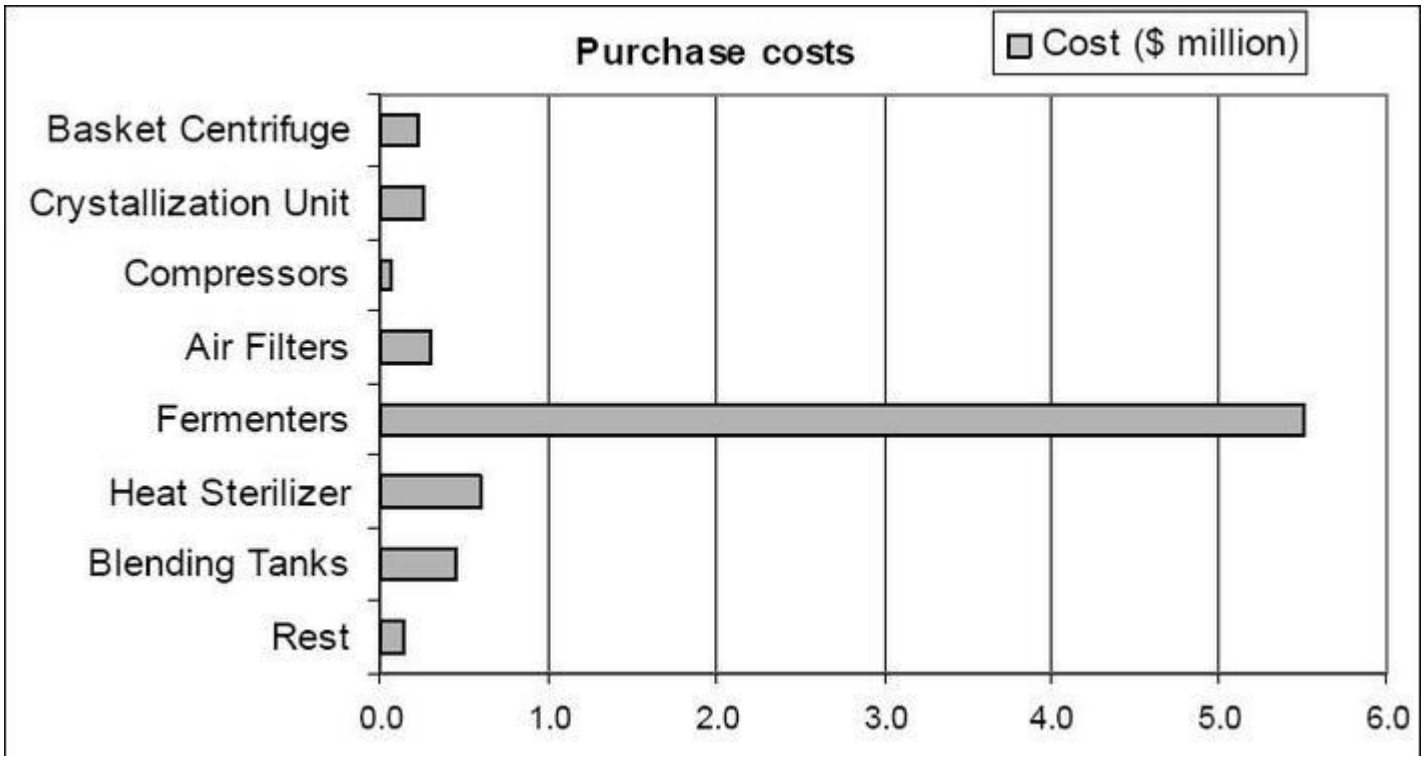
ويشمل ذلك تكاليف البناء والتشييد وتكاليف المعدات .الجدول أدناه هو تقدير تقريبي لتكاليف استثمار رأس المال، حيث تم فصل المكونات إلى تكاليف مباشرة وغير مباشرة .

Description	Range %	Ave	Used	of	Costs	
I. Direct Costs (DC)				FCI		
A. Equipment plus				FCI		
1. Purchased equipment (**PEC**)				FCI	$300,000	
2. Installation, insulation, painting	20-150	50	50%	PEC	$150,000	
3. Instrumentation & control, installed	20-60	35	35%	PEC	$105,000	
4. Piping, installed	30-60	40	40%	PEC	$120,000	
5. Electrical, installed	10-20	15	15%	PEC	$45,000	
B. Buildings including services	10-200	45	45%	PEC	$135,000	
C. Service facilities	20-100	50	50%	PEC	$150,000	
D. Yard Improvement	5-20	15		PEC		
Total Direct Costs (TDC)					**$1,005,000**	
II. Indirect costs (IDC)						
A. Engineering & supervision	20-30	25	25%	TDC	$0	
B. Legal expenses	1-3	2	2%	FCI	$0	H19*F15
C. Construction & contractor's fee	35-50	40	40%	FCI	$402,000	H19*F16
D. Contingency	7-15	10	10%	FCI	$0	H19*F17
Total Indirect Costs					**$402,000**	
III. Fixed Capital Investment (**FCI**)=DC+IDC	0.4-1				**$2,093,751**	(H12+H14)/(1-sum(f15:f17))
IV. Working Capital (WC)	10-20	15	15%	TCI	$369,485	
V. Total Capital Investment (**TCI**)=**FCI+WC**					**$2,463,236**	H19/(1-F20)

Source: Peters, et al., Plant Design and Economics for Chemical Engineers (2003)
Harrison, et al., Bioseparations Science and Engineering (2003)

تكاليف المعدات

ويتوقف ذلك على حجم النبات المستمد من حجم وعدد المخمرات والمبلغ السنوي للمنتجات التي يتم إنتاجها .ويوضح الرسم البياني التالي تكلفة شراء المعدات المقدرة لإنشاء مصنع للبنسلين .



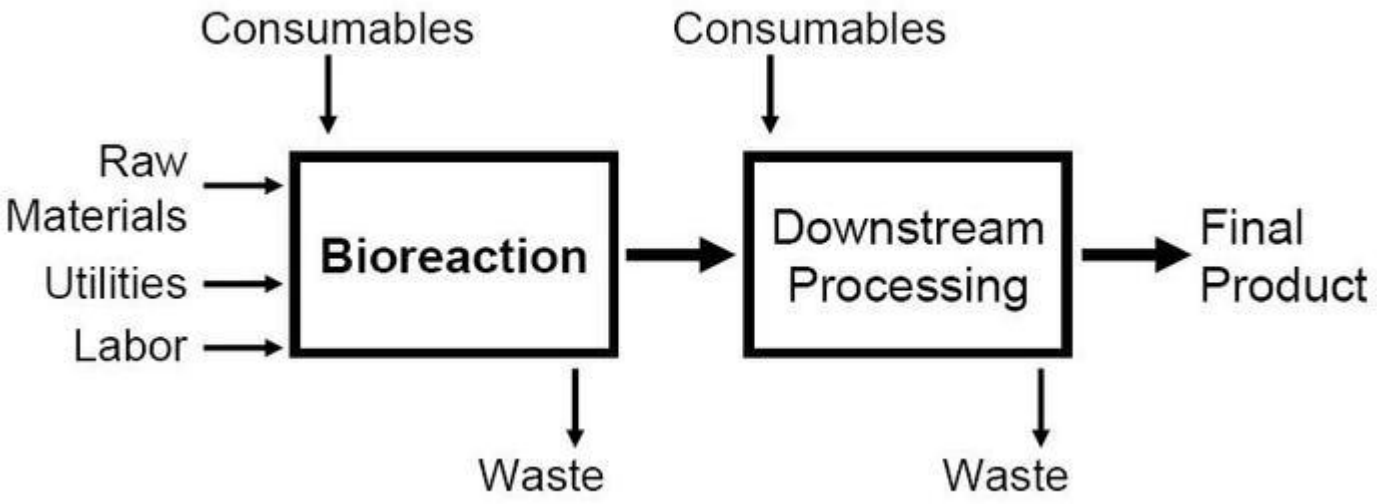
.2تكاليف الإنتاج

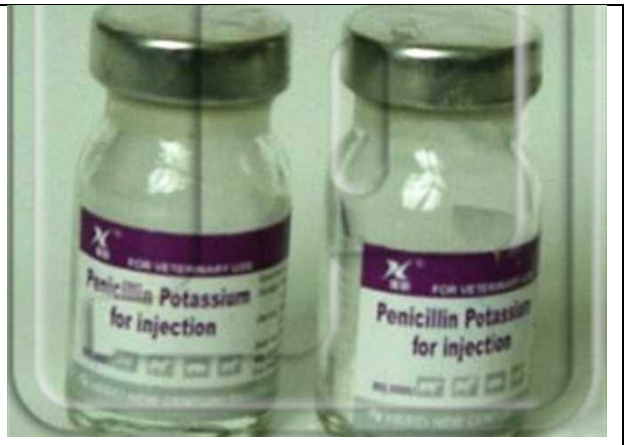
تكلفة الإنتاج الإجمالية المقدرة تشمل أيضا تكلفة التشغيل .

Description	Range %	Used	of	
Fixed Capital Inv (FCI)				2,500,000
Total Capital Inv (TCI)	110-120	115%	FCI	2,875,000
I. Manufacturing cost				
A. Direct Production Costs	66		TPC	
1. Raw materials	10-80		TPC	500,000
2. Operating labor	20-50		TPC	1,000,000
3. Direct supervisory labor	10-20	15%	Op Labor	150,000
4. Utilities	1-30	15%	TPC	701,937
5. Maintenance and Repair	2-10	6%	FCI	150,000
6. Operating supplies	10-20	15%	Mainten.	22,500
7. Lab/QCont/QAssurance	10-20	15%	Op Labor	22,500
8. Patents and royalty	0-6	3%	TPC	140,387
9. Waste Disposal	1-20	1%	TPC	46,796
B. Fixed Charges	10-20		FCI	
1. Depreciation	Depends	10%	FCI	250,000
2. Local taxes	1-4	2.5%	FCI	62,500
3. Insurance	0.4-1	0.7%	FCI	17,500
4. Rent	8-12		Value	
5. Financing	0-10	6%	TCI	172,500
C. Plant overhead	50-70	60%	Labor+Maint	780,000
Total Manufacturing Cost				**4,016,620**
II. General Expense				
A. Administrative costs	20	15%	Labor+Maint	195,000
B. Distribution & selling	2-20	5%	TPC	233,979
C. R&D	2-5	5%	TPC	233,979
III. Total Product Cost (TPC) =TMC+Gen Exp				**4,679,577** G29/(1-E2
Factor depending on TPC		29%		
Term not depending on TPC				3,322,500
Source: Peters, et al., Plant Design and Economics for Chemical Engineers (2003)				
Harrison, et al., Bioseparations Science and Engineering (2003)				

تكاليف التشغيل

تتضمن تكلفة التشغيل التكلفة الازمة للمواد الخام والمواد االستهالكية والنفايات واستهالك الطاقة وتكلفة العمالة واالستهالك .





1 تكاليف المواد الخام

•مقدار تكلفة التكلفة x

•التسعير يعتمد اعتمادا كبيرا على المصدر والحجم

4 استهلاك الطاقة

•استهالك الطاقة النموذجية :

)ط) عملية التدفئة والتبريد

'2التبخر / التقطير

'3تهوية المفاعل الحيوي، والتحريض

'4الطرد المركزي، وتعطيل الخلايا، وما إلى ذلك .

•تكاليف المرافق

(1)الكهرباء: 4.5 سنت / كيلوواط ساعة

'2البخار: 4.40 دولار للطن

'3مياه التبريد: 8 سنتات / م 3

2 المواد الاستهلاكية

العوامل :

)ط) المبلغ لكل دفعة

'2استبدال التردد / ساعات التشغيل

'3السعر

•المواد الاستهلاكية الرئيسية

(1)راتنجات الامتزاز / اللوني

5 تكلفة العمالة

•مقدار العمل :

)ط) محسوبة من الطلب على كل خطوة من خطوات العملية

'2يحدد عدد الأشخاص لكل نوبة / عدد التحولات

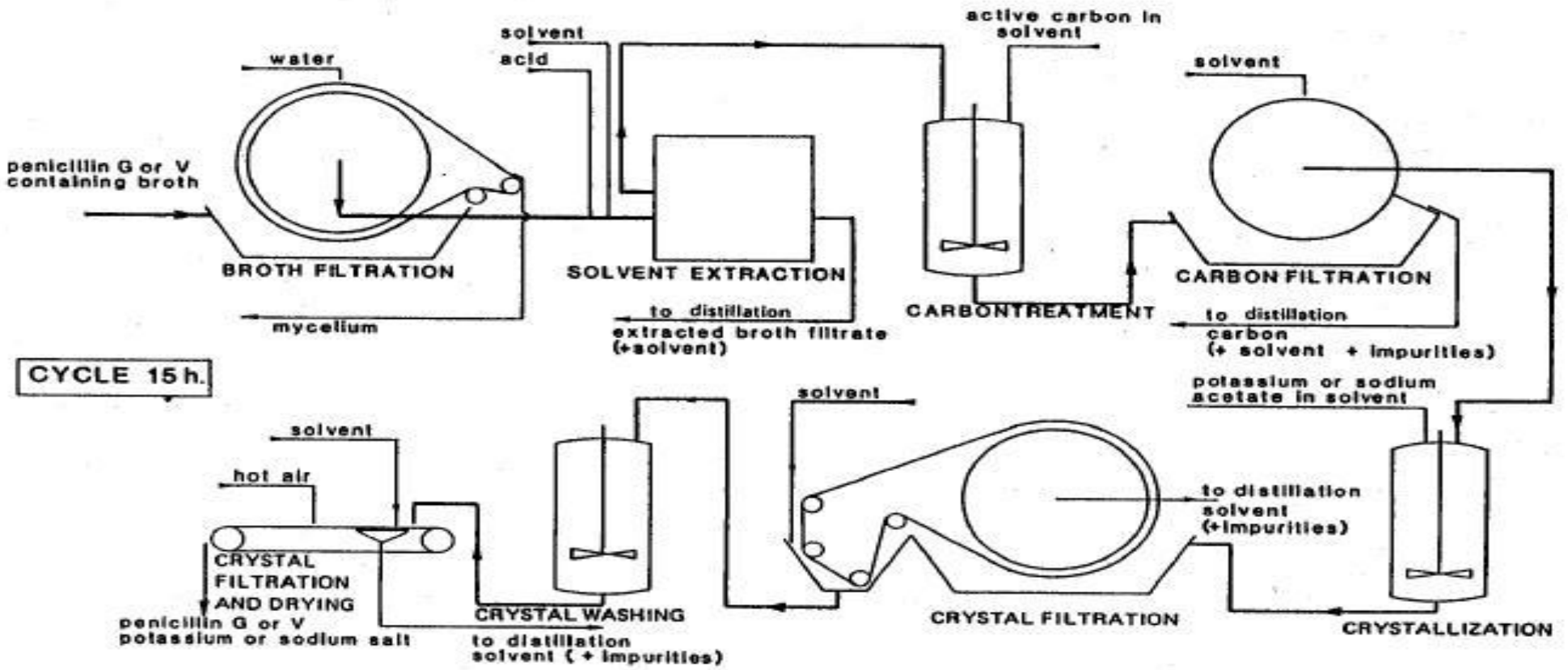
•التكلفة كل ساعة

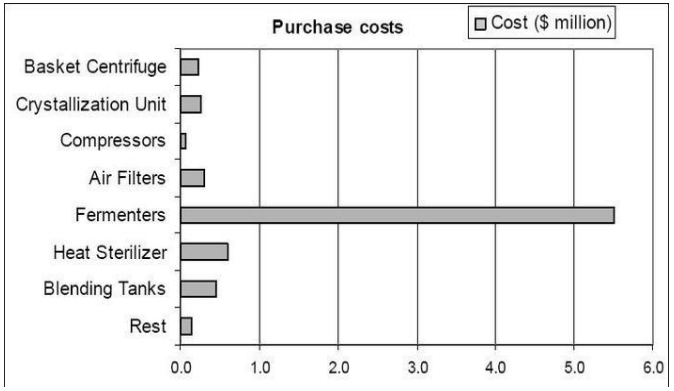
)ط) القيمة المتوسطة للشركة الداخلية

'2الأدب، مثل العمالة الماهرة: 34 دولارا في الساعة

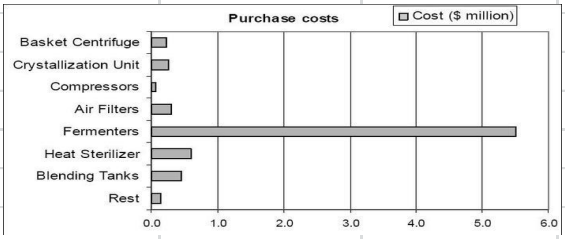
)إي) الأغشية (فيلتيراتيونس، غسيل الكلى، ديافيلتراتيون، هـ (	
3 النفايات	**6 الاستهلاك**
أنواع النفايات وتكاليفها *	•تكلفة االستهالك = "رد" التكلفة االستثمارية
)ط) النفايات الصلبة	•فترة الاستهلاك Life≈ وقت المشروع: 3–10 سنوات
•غير خطرة: 35 دولار للطن	•طريقة االستهالك :
•الخطرة: $ 145 / طن	)ط) خط مستقيم (نفس دولار سنويا (
'2النفايات السائلة / مياه الصرف: 0.5 دولار / م 3	'2انخفاض الرصيد
'3الانبعاثات: تعتمد التكلفة على التركيب	

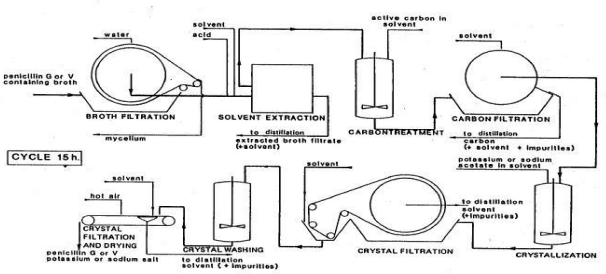
https://penicillin.wikispaces.com/Estimated++cost


water
solvent
acid
active carbon in solvent
solvent
penicillin G or V containing broth
BROTH FILTRATION
SOLVENT EXTRACTION
CARBONTREATMENT
CARBON FILTRATION
mycelium
to distillation
extracted broth filtrate (+solvent)
to distillation
carbon (+ solvent + impurities)
CYCLE 15 h.
potassium or sodium acetate in solvent
solvent
solvent
hot air
to distillation solvent (+impurities)
CRYSTAL FILTRATION AND DRYING
penicillin G or V potassium or sodium salt
CRYSTAL WASHING
to distillation solvent (+ impurities)
CRYSTAL FILTRATION
CRYSTALLIZATION


Purchase costs
Cost ($ million)
Basket Centrifuge
Crystallization Unit
Compressors
Air Filters
Fermenters
Heat Sterilizer
Blending Tanks
Rest
0.0
1.0
2.0
3.0
4.0
5.0
6.0

MEGBI-APP010218

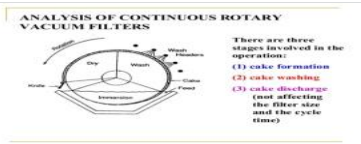


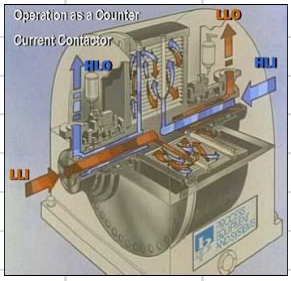


Penicillin Recovery

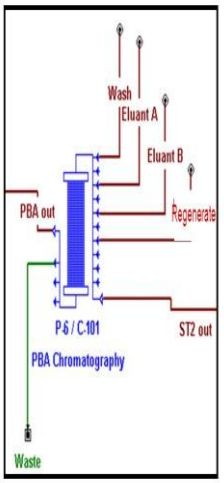
Material Costs

SYSTEM	#	Piece Priece	Total
valve	18	$60	$1.08
CNC LAB			
Rotary Vacuum Filter	5	$15,000	$75,000
$2,300-23,000/ Piece			
Corn_steep_liquor	1 ton		
	US $ 499-599 / Ton		
	Min. Order: **20**	**$570**	**$570**
solvent amyl acetate	Kg	$6	
heat_sterilization	1	**$3,400**	**$3,400**





Fermenters 1000 L		40	**$5,000**	**$200,000**	
					
Crystallization Unit		1	**$3,000**	**$3,000**	
					
Mixer+ blending tank		**1**	**$2,268**	**$2,268**	
US $2,268-12,368 / Piece					https://www.made-in-china.com
Air Filter		2	**$8,000**	$16,000	
$7					
Total			**$37,304**	$300,239.08	

PH metre **$ 159.5-200**	1	**$170**	**$170**	
control system	1	**$350**	**$350**	
temperature sensor **$5-300**	1	**$100**	**$100**	
	1	**$272.09**	**$272.09**	
PO2 metre **Lutron PO2-250 Oxygen Meter** i-zone.in/index.php?route=common/home				
Homogenizer ali baba.com	1	**$1,000.00**	**$1,000.00**	
PBA chromatography colunm colunm volume=344.10L	3	**$302.00**	**$906.00**	GENERAL DESCRIPTION : PBA CHROMATOGRAPHY
PBA chromatography colunm colunm volume=358.19L.	2	**$310.00**	**$620.00**	4 different PBA Chromatography Column; 1)Column Loading (Load) 2)Column Washing (Wash) 3)Column Elution (Elute) 4)Column Regeneration (Regenerate) 
PBA chromatography colunm colunm volume=276.87L	1	**$268.00**	**$268.00**	
PBA chromatography colunm colunm volume=271.76L	1	**$265.00**	**$265.00**	

blinding tank		1	**$250.00**	**$250.00**	
vessel volume=20349.40L					
Stirred reactor		1	**$365.00**	**$365.00**	
vessel volume=198.34L					
$520-3000					
Stirred reactor		1	**$570.00**	**$570.00**	
vessel volume=5107.53L					
Diafilter		1	**$62.00**	**$62.00**	
membrane Area=24.11 m2					
Diafilter		1	**$45.00**	**$45.00**	
membrane Area=13.99 m2					
stirred reactor		1	**$624.00**	**$624.00**	
vessel volume=9841.19L					
total			**$5,158**	**$6,072**	

Description	Range %	Ave	Used	of	Costs	
I. Direct Costs (DC)				FCI		
A. Equipment plus				FCI		
1. Purchased equipment (**PEC**)				FCI	$300,000	
2. Installation, insulation, painting	20-150	50	50%	PEC	$150,000	
3. Instrumentation & control, installed	20-60	35	35%	PEC	$105,000	
4. Piping, installed	30-60	40	40%	PEC	$120,000	
5. Electrical, installed	10-20	15	15%	PEC	$45,000	
B. Buildings including services	10-200	45	45%	PEC	$135,000	
C. Service facilities	20-100	50	50%	PEC	$150,000	
D. Yard Improvement	5-20	15		PEC		
Total Direct Costs (TDC)					$1,005,000	
II. Indirect costs (IDC)						
A. Engineering & supervision	20-30	25	25%	TDC	$0	
B. Legal expenses	1-3	2	2%	FCI	$0	H19*F15
C. Construction & contractor's fee	35-50	40	40%	FCI	$402,000	H19*F16
D. Contingency	7-15	10	10%	FCI	$0	H19*F17
Total Indirect Costs					$402,000	
III. Fixed Capital Investment (**FCI**)=DC+IDC	0.4-1				$2,093,751	(H12+H14)/(1-sum(f15:f17))
IV. Working Capital (WC)	10-20	15	15%	TCI	$369,485	
V. Total Capital Investment (**TCI**)=**FCI**+**WC**					$2,463,236	H19/(1-F20)

Source: Peters, et al., Plant Design and Economics for Chemical Engineers (2003)
Harrison, et al., Bioseparations Science and Engineering (2003)

total plan Direct cost				
direct costs				
Equipment purchase cost		$30,480,444		
installation		$150,000		
process piping		$120,000		
Instrumentation		$105,000		
Electrical		$45,000		
Buildings		$135,000		
Auxiliary facilities		$150,000		
yard improvement				
toyal		$31,035,444		
		indirect costs		
		Engineering	$20,554,000	
		construction	$402,000	
		legal expenses		
		contingency		
Cost of workers				
labor type	$/h	Annual Amoun	Annual cost($)	
operator	69	117,606	8,114,800	

Materials Cost

Glucose	$5-60	1 kg	$60
salts			$1
water			$0
H3PO4			$1
NaOH			0,500
WF1			$0
Ammonia			0,700
Air			0,000
EDTA			$19
Tris base			$6
triton-x-100			$2
Mr ETOH			$3
Urea			$2
CNBr			$11
Formic acid			$2
guanidine HCl			$2
Na2O6S4			0,600
Sodium sulfite			0,400
sodium chloride			$1
Enzymes			$500,000
Acetonitrile			$3
Ammonium Acetat			$15
Zinc chloride			$12
total			$500,139

Description	Range %	Used	of	
Fixed Capital Inv (FCI)				2,500,000
Total Capital Inv (TCI)	110-120	115%	FCI	2,875,000
I. Manufacturing cost				
A. Direct Production Costs	66		TPC	
1. Raw materials	10-80		TPC	500,000
2. Operating labor	20-50		TPC	1,000,000
3. Direct supervisory labor	10-20	15%	Op Labor	150,000
4. Utilities	1-30	15%	TPC	701,937
5. Maintenance and Repair	2-10	6%	FCI	150,000
6. Operating supplies	10-20	15%	Mainten.	22,500
7. Lab/QCont/QAssurance	10-20	15%	Op Labor	22,500
8. Patents and royalty	0-6	3%	TPC	140,387
9. Waste Disposal	1-20	1%	TPC	46,796
B. Fixed Charges	10-20		FCI	
1. Depreciation	Depends	10%	FCI	250,000
2. Local taxes	1-4	2.5%	FCI	62,500
3. Insurance	0.4-1	0.7%	FCI	17,500
4. Rent	8-12		Value	
5. Financing	0-10	6%	TCI	172,500
C. Plant overhead	50-70	60%	Labor+Maint	780,000
Total Manufacturing Cost				**4,016,620**
II. General Expense				
A. Administrative costs	20	15%	Labor+Maint	195,000
B. Distribution & selling	2-20	5%	TPC	233,979
C. R&D	2-5	5%	TPC	233,979
III. Total Product Cost (TPC) =TMC+Gen Exp				4,679,577 G29/(1-E2
Factor depending on TPC		29%		
Term not depending on TPC				3,322,500

Source: Peters, et al., Plant Design and Economics for Chemical Engineers (2003)
Harrison, et al., Bioseparations Science and Engineering (2003)

$30,174,133

Laborers	#		
	9	150000$	
	1	16500$	

تصليحات
150000$
البيع كلفة
1000000$

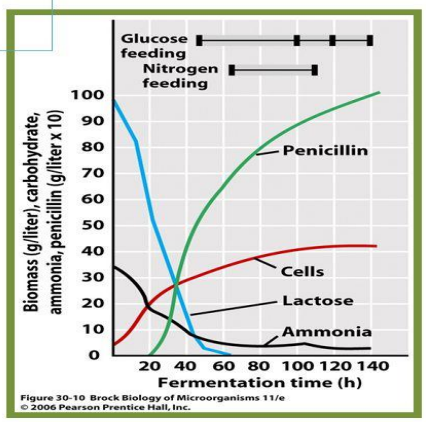
المصنع انشاء كلفة	سنويا الربح	
المكان+المعدات+تركيبا		
$641,211	$1,000,000	المدخول =
	$655,000	

سنويا التشغيل كلفة	Amortisation	years
كهرباء+ عمال+تصليحات	$655,000	1
$345,000	$1,310,000	2
	$1,965,000	3
الانتاج كلفة مجموع		
$986,211		

MEGBI-APP010218

Penicillin Recovery

The graph shows the kinetics of the penicillin fermentation with *Penicillium chrysogenum*.



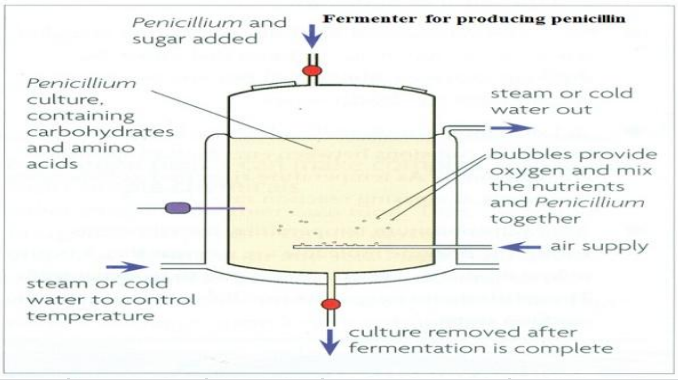
Enzyme processes in the production of β-Lactam antibiotics

Penicillins and cephalosporins belong to the class of β-lactam antibiotics that are formed from the common precursor tripeptide isopenicillin N. The β-lactam structure is formed by ring-closure reactions between Cys and Val, where (S)-Val is isomerized to (R)-Val. The β-lactam precursors of all penicillins and cephalosporins are produced by fermentation in fermentors of up 1000 m3.

The concentration of the products in the medium on completion of fe Les précurseurs de β-lactame de toutes les pénicillines et céphalosporines sont produits par fermentation dans des fermenteurs jusqu'à 1000 m3.

La concentration des produits dans le milieu à la fin de la fermentation qui prend entre cinq et sept jours, est jusqu'à 100 g / L de pénicilline et 20 g / L de céphalosporine C.

http://slideplayer.com/slide/4214453/ Methods of industrial production



1m3=1000L

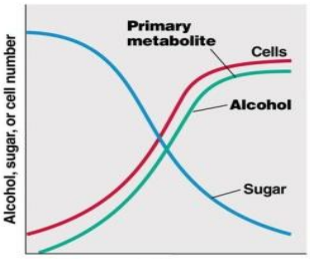
g/1000=Kg

1ton=1000Kg

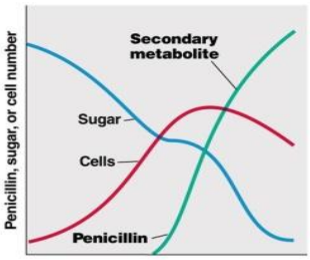
lb الباوند الواحد = 0,4536 كيلوغرام

fermenteur m3	penicillin g/l	
1000	100	
1,000,000 L	100,000,000 g	
1,000L	100,000 g	100Kg

Primary and Secondary Metabolites



(a) Yeast Fermentation



(b) Antibiotic Production: *P. chrysogenum*

Clicker Question:

rendement maximum de production de penicilline disponible lorsque la concentration de lactosse et cell de liqueure de cornsteep dans le milieu de base ont été ajustée à 60 Kg / m3
et 30kg/ m3 respectivement

https://translate.googleusercontent.com/translate_c?depth=1&hl=fr&prev=search&rurl=translate.google.com&sl=en&sp=nmt4&u=https://healtheappointments.com/cdn-cgi/l/email-protection&xid=17259,15700021,15700105,15700124,15700149,15700168,15700173,15700201&usg=ALkJrhgdgWS-zdzncshWKpiJLN8lQ8wQ6Q#0a63646c654a626f6b667e626f6b7a7a6563647e676f647e7924696567

		Kg /m3	
lactose		60	
liqueure de cornsteep		30	
	#	Volume	$
	1	1000L	1250
	40	40000L	50000
200 tons /ans			
		penicilline	cost$
		1Kg	5
		1000Kg	5000
		200 tons	1000000

Fermentation medium In addition to physical parameters like pH, agitation and aeration rate, air saturation, temperature, dissolved CO2 and foaming, medium composition is a very important factor strongly influencing fermentation processes, often being object of extensive process development and optimization studies. Common fermentation media for L-lysine production contain various carbon and nitrogen sources, inorganic ions and trace elements (Fe^{++}, Mn^{++}), amino acids, vitamins (biotin, thiamine-HCl, Nicothinamide) and numerous complex organic compounds. An overexpression of genes is also achieved by optimizing the composition of the media and the culture technique in addition to physiological and genetic parameters .

CARBON SOURCE Mutants of Corynebacterium and related microorganisms enable the inexpensive production of amino acids from cheap renewable carbon sources by direct fermentation. Various carbohydrates are utilized individually or as a mixture for the production of L-lysine such as glucose, fructose, sucrose, molasses (sucrose, glucose, fructose etc.), maltose, blackstrap molasses, starch hydrolyzate (glucose, oligosaccharides), lactose, maltose, starch and starch hydrolysates, cellulose, cellulose hydrolysate, organic acids such as acetic acid, propionic acid, benzoic acid, formic acid, malic acid, citric acid and fumaric acid, alcohols such as ethanol, propanol, inositol and glycerol and certainly hydrocarbons, oils and fats such as soy bean oil, sunflower oil, groundnut oil and coconut oil as well as fatty acids such as e.g. palmitic acid, stearic acid and linoleic acid.

42 NITROGEN SOURCE Various sources of nitrogen are utilized individually or as mixtures for the commercial and pilot scale production of L-lysine, including inorganic compounds such as gaseous and aqueous ammonia, ammonium salts of inorganic or organic acids such as ammonium sulfate, ammonium nitrate, ammonium phosphate, ammonium chloride, ammonium acetate and ammonium carbonate. Alternatively, natural nitrogen containing organic materials like soybean-hydrolyzate, soyprotein HCl-hydrolyzate (total nitrogen of about 7%), soybean meal, soybean cake hydrolysate, corn steep liquor, casein hydrolysate, yeast extract, meat extract, malt extract, urea, peptones and amino acids may also be utilized.

43 INFLUENCE OF OXYGEN L-lysine fermentation is an aerobic process demanding large amounts of oxygen and strongly influenced by the air saturation in bioreactor. Lactic acid is formed as a byproduct under anaerobic conditions, which is reconsumed after the establishment of aerobic conditions.

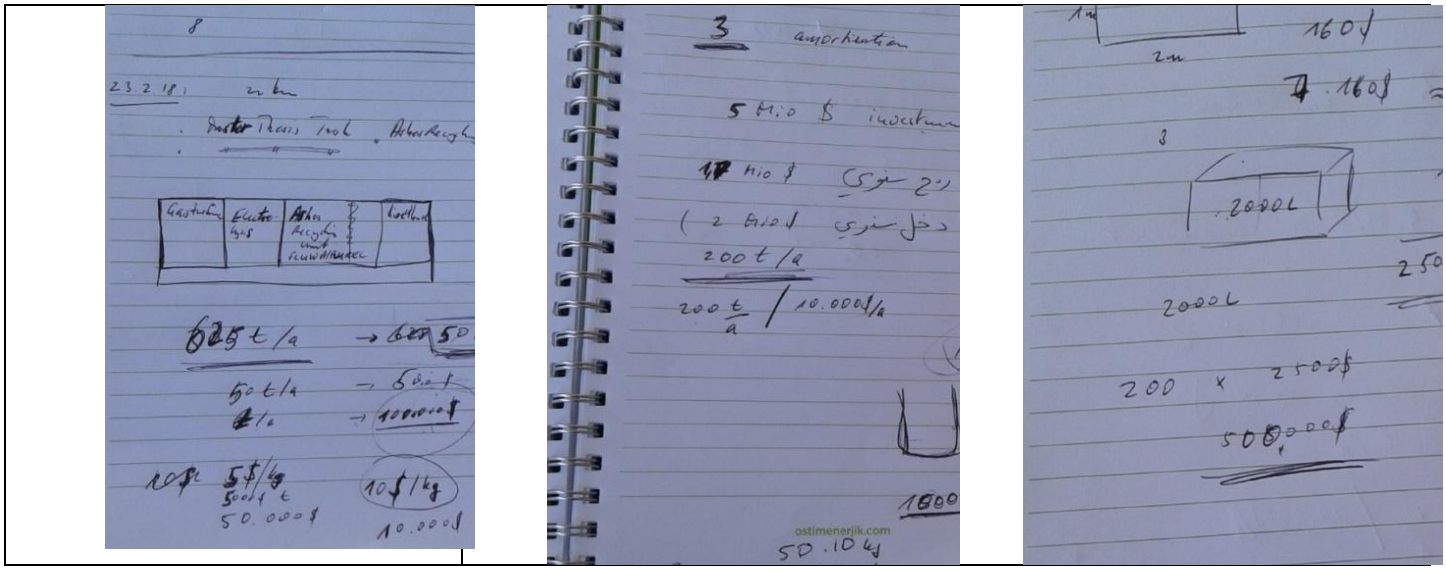
44 pH The pH is a very important factor strongly influencing microbial fermentations. Basic compounds such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium carbonate, urea, ammonia and gaseous ammonia, or inorganic acid compounds such as phosphoric or sulfuric acid and organic acids are utilized

Rotary Vacuum Filter

www.911metallurgist.com/blog/rotary-drum-filter

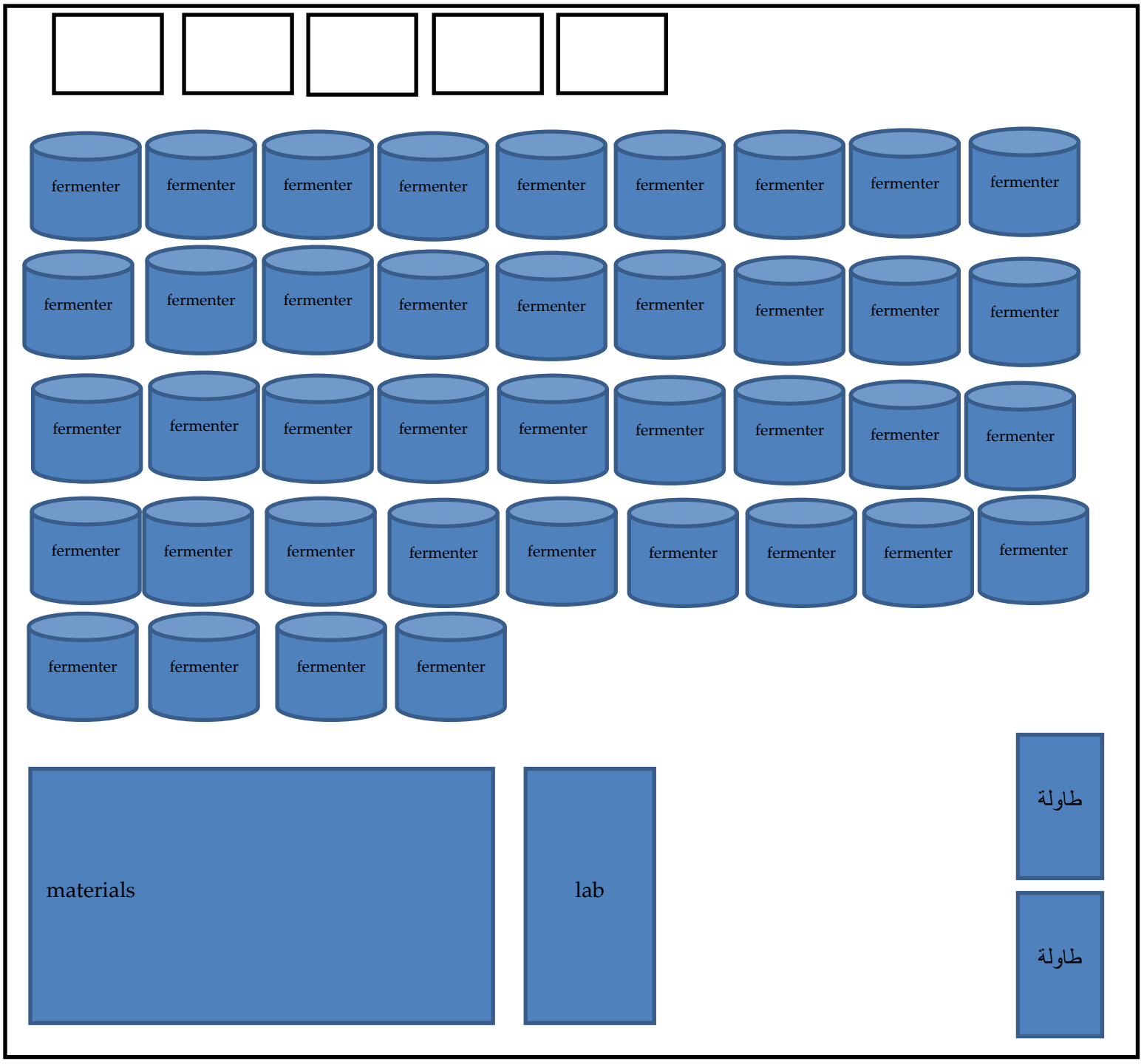
the capacity of a vacuum rotory drum filter varies from about 200 to 2,000 Lb.of dry concentrate per square foot of filtering surface per 24 hours according to the nature of the materiel and the amount of water that it contains.For the puproses of rough calculation it is usual to assume a capacity of 1000lb .Per square foot, although this figure is generally exceeded under conditions the moisture cake normally ranges from 8 to 12%.

	kg	lb (ponde)
	0.4536	1
	90.72	200
907.2 L	~~907~~.2	2000
5	Rotory vacuum	



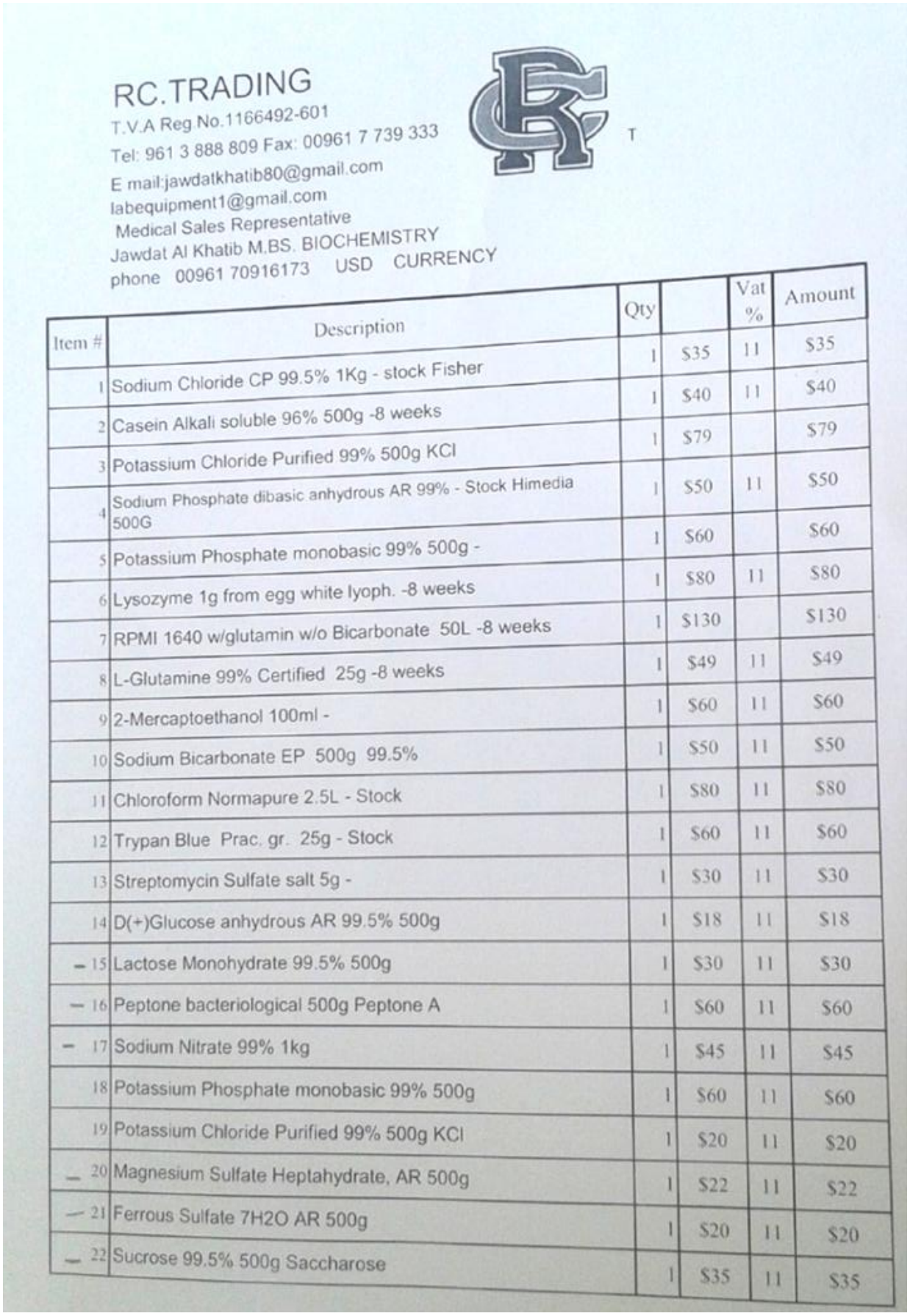
سنويا الانتاج	المنشئة كلفة	
200 t	العاملة اليد كلفة	$248,400
	المواد كلفة+الالات	$806,451.82
	total	$1,054,852

المحطة لتشغيل السنوية الكلفة	
صيانة	150,000
عمال	$248,400
كهرباء	$45,000
total	$443,400


fermenter
materials
lab
طاولة
طاولة

2.9.1.1 Materials

Offer from Jawdat AlKatibe



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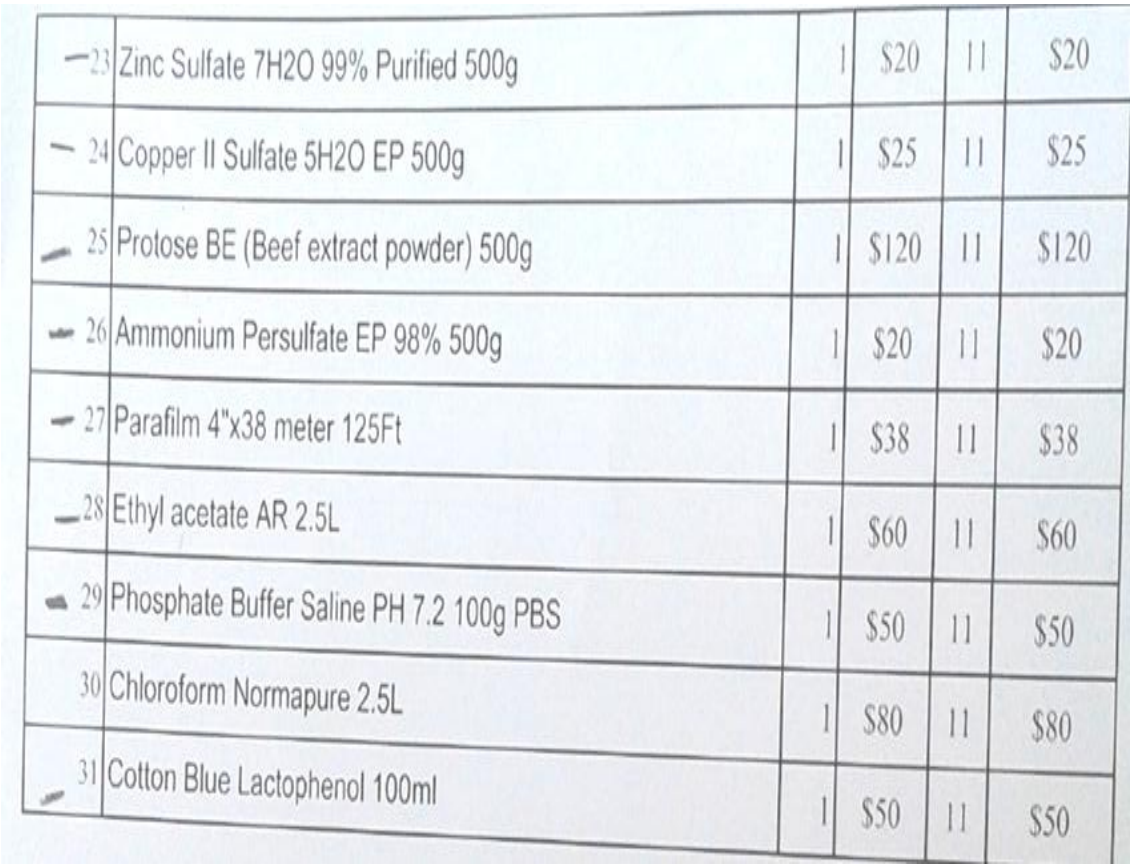
labequipment1@gmail.com
Medical Sales Representative
Jawdat Al Khatib M.BS. BIOCHEMISTRY
phone 00961 70916173 USD CURRENCY

Item #	Description	Qty		Vat %	Amount
1	Sodium Chloride CP 99.5% 1Kg - stock Fisher	1	$35	11	$35
2	Casein Alkali soluble 96% 500g -8 weeks	1	$40	11	$40
3	Potassium Chloride Purified 99% 500g KCl	1	$79		$79
4	Sodium Phosphate dibasic anhydrous AR 99% - Stock Himedia 500G	1	$50	11	$50
5	Potassium Phosphate monobasic 99% 500g -	1	$60		$60
6	Lysozyme 1g from egg white lyoph. -8 weeks	1	$80	11	$80
7	RPMI 1640 w/glutamin w/o Bicarbonate 50L -8 weeks	1	$130		$130
8	L-Glutamine 99% Certified 25g -8 weeks	1	$49	11	$49
9	2-Mercaptoethanol 100ml -	1	$60	11	$60
10	Sodium Bicarbonate EP 500g 99.5%	1	$50	11	$50
11	Chloroform Normapure 2.5L - Stock	1	$80	11	$80
12	Trypan Blue Prac. gr. 25g - Stock	1	$60	11	$60
13	Streptomycin Sulfate salt 5g -	1	$30	11	$30
14	D(+)Glucose anhydrous AR 99.5% 500g	1	$18	11	$18
15	Lactose Monohydrate 99.5% 500g	1	$30	11	$30
16	Peptone bacteriological 500g Peptone A	1	$60	11	$60
17	Sodium Nitrate 99% 1kg	1	$45	11	$45
18	Potassium Phosphate monobasic 99% 500g	1	$60	11	$60
19	Potassium Chloride Purified 99% 500g KCl	1	$20	11	$20
20	Magnesium Sulfate Heptahydrate, AR 500g	1	$22	11	$22
21	Ferrous Sulfate 7H2O AR 500g	1	$20	11	$20
22	Sucrose 99.5% 500g Saccharose	1	$35	11	$35



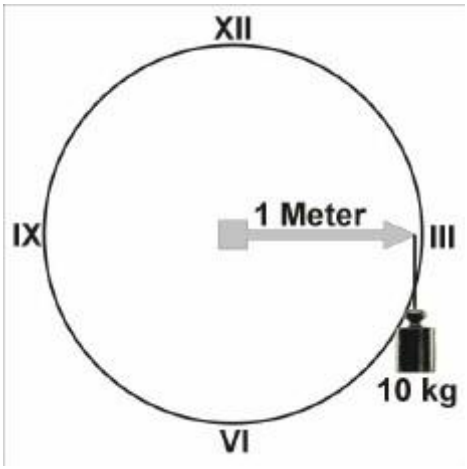
23	Zinc Sulfate 7H2O 99% Purified 500g	1	$20	11	$20
24	Copper II Sulfate 5H2O EP 500g	1	$25	11	$25
25	Protose BE (Beef extract powder) 500g	1	$120	11	$120
26	Ammonium Persulfate EP 98% 500g	1	$20	11	$20
27	Parafilm 4"x38 meter 125Ft	1	$38	11	$38
28	Ethyl acetate AR 2.5L	1	$60	11	$60
29	Phosphate Buffer Saline PH 7.2 100g PBS	1	$50	11	$50
30	Chloroform Normapure 2.5L	1	$80	11	$80
31	Cotton Blue Lactophenol 100ml	1	$50	11	$50

Offer from Bourhan Kabbara

Ampicillin Pilot Plans			
ID			cost$
Glucose		500g	20
Lactose		500g	24
Peptone		500g	56
NaNo3		500g	32
Na2HPO4		500g	25
MgSO47H2O		500g	18
FeSO47H2O		500g	20
Sucrose		500g	18
ZnSO47H2O		500g	20
CuSO45H2O		500g	18
(NH4)2SO4		500g	30
Sodium acetate		500g	22
Ethyl acetate		2.5 L	60
Sodium acetate		500g	22
Chloroform		2.5L	75
Lacto phenol cotton blue stain		100ml	46
Titriplex		250g	25
total			531
K2HPO4 (dibasic)			
yest extract			
CaCO3			
Corn steep liquor			
Beef extract			
Na2SO4			

3.1 Torque at Stepper Motors and Servos

Wenn man an den Zeiger einer Turmuhr in der Stellung auf 3 Uhr ein Gewicht von 10 kg hängt, wirkt auf die Achse ein Drehmoment von 100 Nm (also 10000 Ncm). Ein Getriebemotor mit 100 Ncm könnte beispielsweise bei einem Hebel von 1 cm (an der Achse) noch 10 kg heben.



3.1.1 Product Example (from www.cnclablb.com)

Metal Gear Servo TowerPro MG995 Servo - 9kg

Price : 8$

Serial number : ACT0005

Description:

Modulation: Digital

Torque: 4.8V: 130.54 oz-in (**9.40 kg-cm**) 6.0V: 152.76 oz-in (11.00 kg-cm)

Speed: 4.8V: 0.20 sec/60° 6.0V: 0.16 sec/60°

Weight: 1.94 oz (55.0 g)

Dimensions:Length:1.60 in (40.7 mm)

Width:0.78 in (19.7 mm)

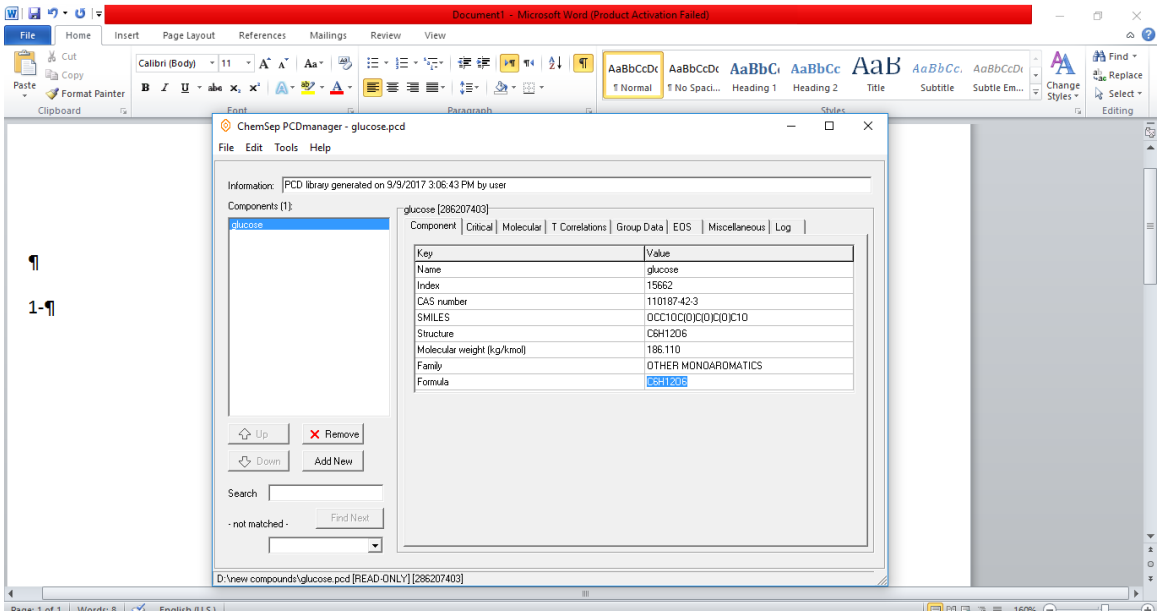
Height:1.69 in (42.9 mm)

3.2 Chemical Process Simulation with COCO[2]

3.2.1 How to add new compounds with COCO

❖ Steps:

1- Open PCD manager



2- Press Add New

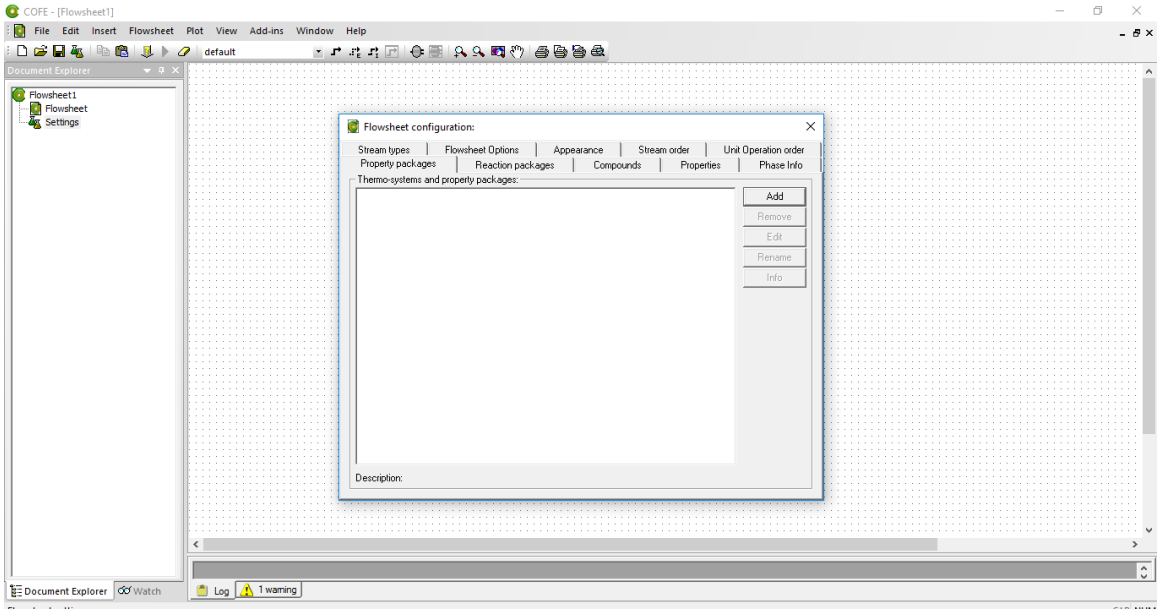
3- Enter compound's information

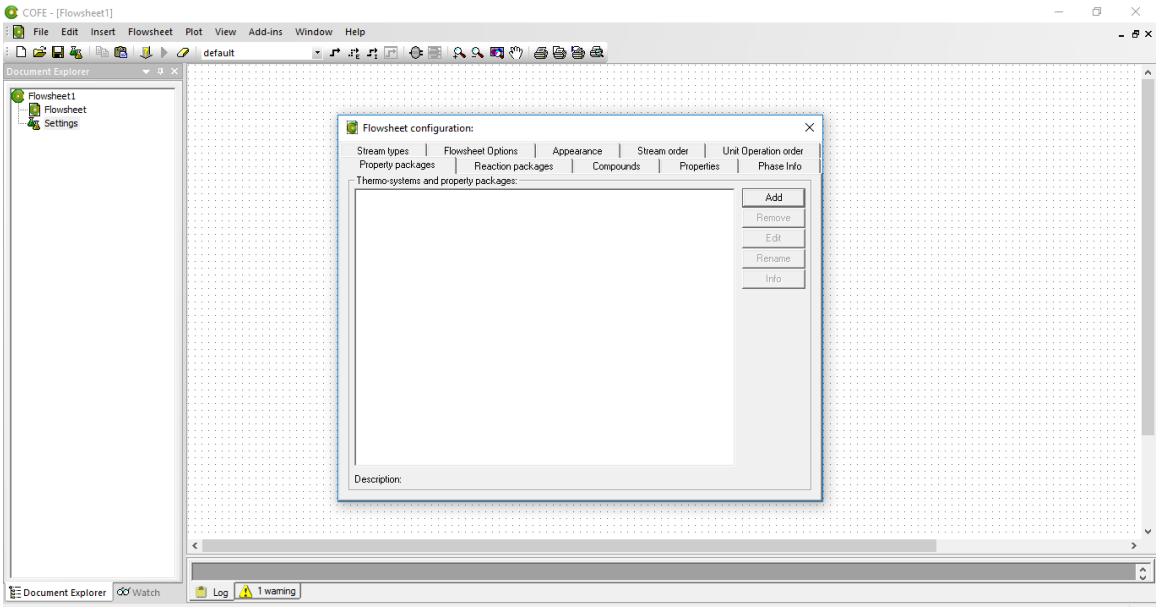
4- Save as in a file in local disk D

5- Open coco program

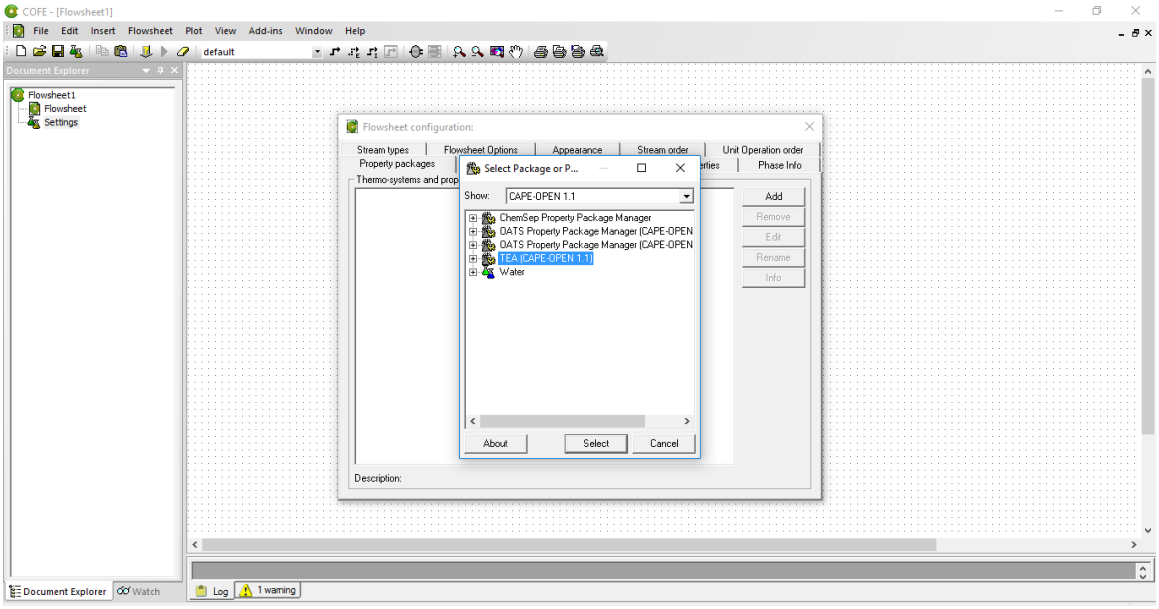
6- Press sittings(left) then press new

[2] Razan Kalawoun

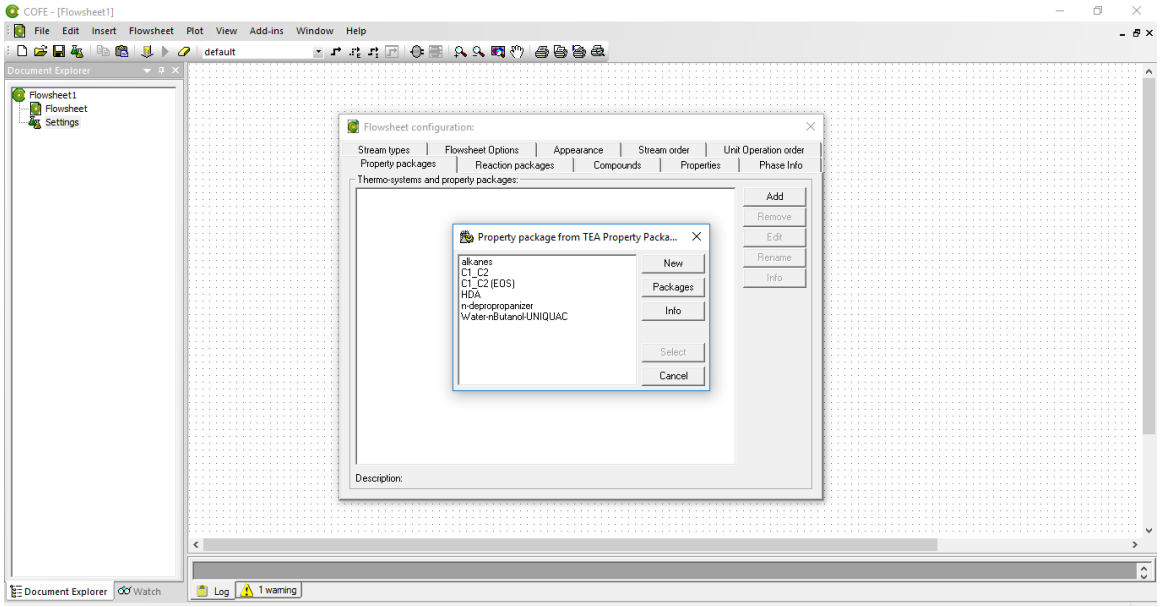




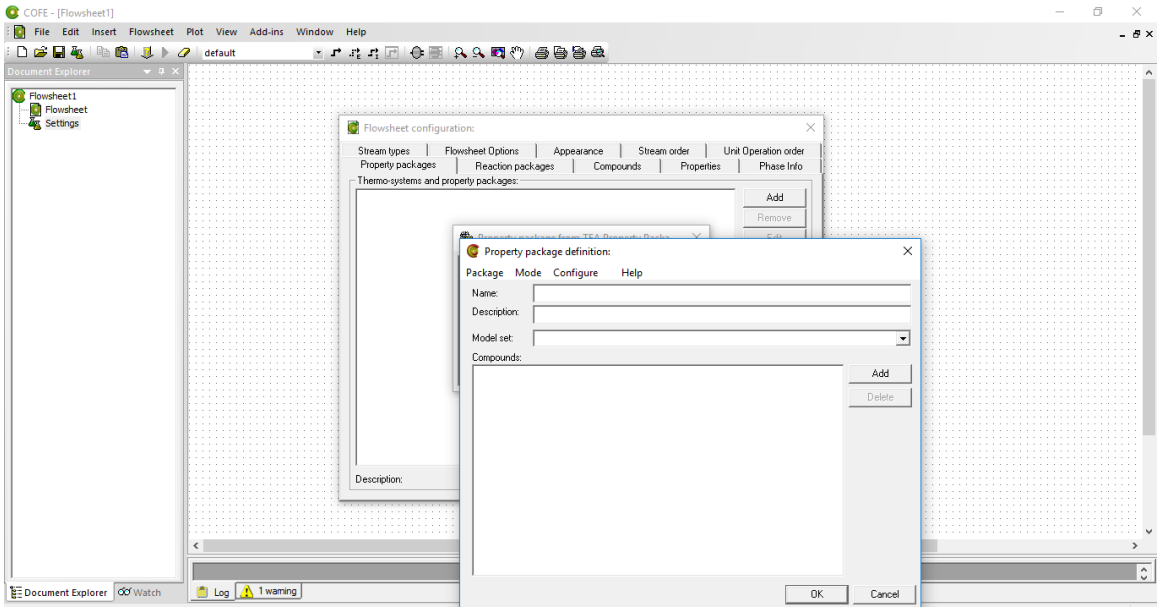
7-Select tea



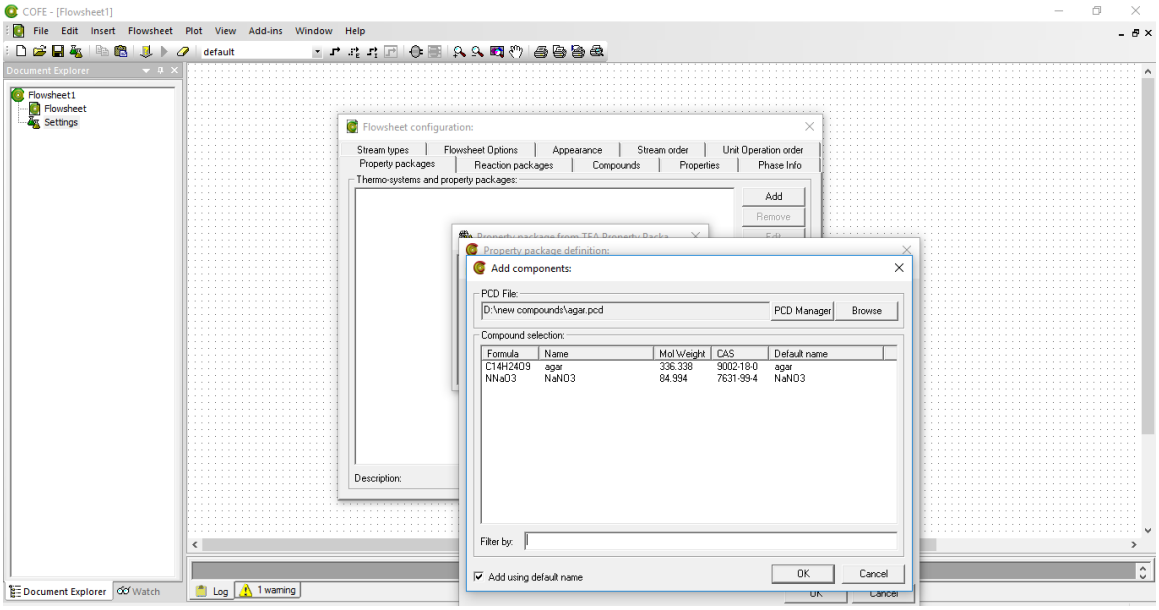
8-Then press new



9-Press add



10-press browse (right)



11-choose the compound you add it

3.3 Detailed Semi-synthetic Penicillin production steps and technologies[3]

3.3.1 General Process of Penicillin Production

15. Culture methods ◎ The fungus can be cultured in two methods ,namely Surface culture method Submerged culture method

16. Surface culture method ◎ In surface culture method ,the fungus is cultured on the surface of a liquid medium without agitation. ◎ After an appropriate incubation period ,the penicillin is extracted from the medium . ◎ This is an old method .

16. سطح ◎ الثقافة طريقة السطحية الثقافة فطر ◎ ثقافة واساليب يمكن المثقفين فى طريقتين, وهى طريقة غمر سطح الثقافة الثقافة طريقة. طريقة فطر هو المثقفين وذو سطح السائل متوسطة دون انفعال ◎ .بعد فترة حضانة مناسبة للنهار البنسلين يستخرج من المتوسطة ◎ .وهذا الاسلوب القديم.

17. Submerged culture method ◎ In submerged culture method ,the fungus is grow in a liquid medium which is vigorously aerated and agitated. ◎ After an appropriate incubation period ,the penicillin is separated from the medium . ◎ Today penicillin is produced by the submerged method .

18. Production process medium fermentation centrifugation filtration Solvent extraction precipitation crystallization

FERMENTATION • It is done in a fed-batch mode as glucose must not be added in high amounts at the beginning of growth (which will result in low yield of penicillin production as excessive glucose inhibit penicillin production). • The fermentation conditions for the Penicillium mold, usually requires temperatures at 20-24°C while pH conditions are kept at 6.5 • The pressure in the bioreactor is much higher than the atmospheric pressure (1.02atm). This is to prevent contamination from occurring as it prevents external contaminants from entering. • It is necessary to mix the culture evenly throughout the culture medium. Fungal cells are able to handle rotation speed of around 200 rpm.

[3] Fatima Antar

19. Media formulation ◎ Ph6.5 ◎ Temperature 20-24c ◎ Oxygen ◎ Nitrogen (corn steep liquor 8.5%) ◎ Glucose 1% (preferred for penicillium notatum) ◎ 80% ethanol ◎ Phenyl acetic acid ◎ Probenecid

20. ◎ Lactose 1% ◎ Calcium carbonate 1% ◎ Sodium hydrogen phosphate 0.4% ◎ Antifoaming agent : Vegetable oil

.17غمر ◎ الثقافة فى غمر طريقة طريقة, فان الثقافة هى تنمو فى السائل aerated الواسطة بقوة واثاروها ◎ .بعد فترة حضانة مناسبة للنهار البنسلين مفصولة عن متوسط ◎ .اليوم البنسلين الذى تنتجه المغمورة.

.18عملية الانتاج التخمر النابذة مذيب تصفية متوسط هطول الامطار بلورة 19

استخراج صياغة ◎ الوسائط ◎ ◎ Ph6.5 الحرارة 20-24ج ◎ الاكسجين والنتروجين (كورن الانحدار ◎ الخمر 8.5% الجلوكوز 1% (يفضل 80% notatum penicillium) ◎ ايثانول Probenecid ◎ ◎

استنتجت بان فرض مراقبة دولية على انهيدريد حمض 20 ◎ .اللاكتوز والغلوتين ◎ كربونات الكالسيوم 1% 1% فوسفات الصوديوم ◎ ◎ الهيدروجين 0.4% Antifoaming عميل: الزيوت النباتي

21. Heat sterilization ◎121 degree celcius at 30 psi (pounds per square inch). ◎For high temperature short time for sterilization is used to minimize the degradation of certain components of media.

22. FERMENTATION ◎ Usually done by fed-batch mode ◎ High amount of glucose result in low yield of Penicillin. ◎ Temperature : 20 to 24 c ◎ pH : 6.0 to 6.5 units ◎ Pressure : 1.02 atmosphere (higher than atmospheric pressure to prevent contamination)

23. Fermentation: • Sparging of air provided for providing sufficient oxygen required for cell viability. IMPELLER: •Rotor used to increase the pressure and flow of fluid. • Used to mix culture throughout the medium • Fungal cells are hardy • Hence handled at rotation speed around 200rpm FERMENTORS

24. SEED CULTURE: o First done in lab by adding penicillium spores to the liquid medium. o After growth , inoculated into the fermentor. o In some cases spores are directly inoculated into the fermentor. Spore: produced during stress condition

.الحرارة درجة مائوية التعقيم 30 121ϖ رطل لكل بوصة مربعة (رطل لكل بوصة مربعة). درجة حرارة عالية Forϖ قصيرة التعقيم لتقليل تدهور عناصر معينة من وسائل الاعلام.

.22تخمير θ المعتاد عبر θ ضاق متقطع بقدر عال من الجلوكوز تؤدى الى تدنى غلة البنسلين. درجة الحرارة: 20 24 θ ج 6.0 :pH θ الى 6.5 وحدات الضغط : 1.02 جو) θ اعلى من الضغط الجوى لمنع تلوث) 23. تخمير * :Sparging قدمت الجوية لتوفير ما يكفى من الاوكسجين اللازم خلية على البقاء. قابض المضخة: * دوار تستخدم لزيادة الضغط تدفق السائل. * استخدام مزيج الثقافة بين متوسطة * الخلايا الفطرية هاردى * ومن ثم معالجتها دوران حوالى 200 لفة فى الدقيقة FERMENTORS 24بذرة الثقافة o :اولا فى المعمل باضافة penicillium

25. FILTERATION: ◎ Rotary vaccum filter is used for large scale production. ◎ To remove biomass such as fungus, other impurities from the medium. ◎Phosphoric acid is added pH become 8.5 ◎This can leads to the loss of penicillin activity. ◎Thus pH is maintained at 6.0 to 6.5. ROTARY VACCUM FILTER

26. Addition of solvents : ◎ AMYL ACETATE or BUTYL ACETATE is added to dissolve penicillin in filtrate. ◎ Now, penicillin is present in the form of solution. ◎ Other solids are considered as wastes.

27. CENTRIFUGAL EXTRACTION: ◎ Tubular bowl or chamber bowl centrifuge is used. ◎ To separate solid waste from liquid component which contains the penicillin. ◎ Supernatent is transferred to downstream process.

28. EXTRACTION PENICILLIN + ACETATE SOLUTION 1.Phosphate buffer 2.Chloroform solution 3.Again phosphate buffer 4.Ether solution Mixed with

29. ◎ Penicillin is present in high concentration in ether solution ETHER SOLUTION CONTAINING PENICILLIN Mixed with SODIUM BICARBONATE Penicillin sodium salt BASKET CENTRIFUGATION ◎Solids are easily removed by basket centrifugation. ◎Penicillin salt is in stable powdered form at room temperature . Basket centrifuge

30. Fluid bed drying: ◎ To remove the moisture present in the penicillin salt. ◎ Hot gas is pumped from the base of the chamber. ◎ Powdered salt is contained in a vaccum chamber. ◎ Results in dried form of penicillin.

31. Storage: ◎Stored in containers in dried environment. ◎Then packaged into ◎Liquid penicillin ◎Penicillin in pills

32. process ◎ Medium (corn steep liquor lactose starter culture Yeast extract (penicillium) pHbuffers minerals) batch fermenter (10 times in 6 days to remove 30% culture add 30% fresh medium)

33. rotating filter filtrate fungal cells Dissolve in butyl acetate animal feed Potassium ions added to Precipitate salt of penicillin Wash, filter and dry 99.55% pure penicillin

25. ◎ FILTERATION: لازالة الكتلة الحيوية مثل ◎ .الدوار يستخدم الكهرباء بهواء معكوس و يعمل عامل تصفية واسعة النطاق تصبح 8.5 يمكن ان يؤدى الى فقدان البنسلين ◎This Phosphoric pH◎ الفطريات وغيرها والشوائب من الوسيط. تتم اضافة حمض خلات ◎ AMYL :على 6.0 الى 6.5. الدوار 26 الكهرباء بهواء معكوس و يعمل عامل تصفية اضافة المذيبات ◎Thus pH .النشاط الان البنسلين فى شكل الحل. ◎ .رصاص ثنائى او استبدل فيها شق بالميثايل خلات رصاص ثنائى الى حل البنسلين فى تسلل فلسطينى بلباس .تعتبر النفايات ◎ المواد الصلبة الاخرى

27. فصل النفايات الصلبة الناتجة عن ◎ .استخراج: الوعاء او وعاء انبوبية قاعة ويستخدم جهاز الطرد المركزى ◎ اجهزة الطرد المركزى .النهر ◎ Supernatent عنصر السائل الذى يحتوى على البنسلين. نقل

28. استخراج البنسلين + حل 1.فوسفات خلات رصاص ثنائى المخزن المؤقت 2.الحل 3.جديد الكلوروفورم الفوسفات

29. ◎ البنسلين فى تركيزات عالية فى حل بالاثير الاثير الحل الذى يتضمن البنسلين ممزوجة بيكربونات الصوديوم البنسلين لملح الصوديوم ◎ شكل المجفف مستقرة عند درجة حرارة الغرفة. 30 الطرد سلة سرير Penicillin◎ سلة النابذة ازالتها بسهولة سلة النابذة. الملح Solids◎ فى الكهرباء ◎ الغازات الساخنة من قاعدة الحجرة. الملح المجفف ◎ السائل: التجفيف لازالة الرطوبة الموجودة فى البنسلين الملح. ويضخ .المجفف شكل البنسلين ◎ بهواء معكوس و يعمل. نتائج

31. التخزين: ◎Stored فى حاويات فى المجفف .◎Liquid ◎Then ◎Penicillin فى حبوب البنسلين فى عملية متوسطة (كورن - 32 ◎ الدفعة) جهاز تخمير المعادن) (10 مرات) pHbuffers مستخلص الخميرة starter penicillium ثقافة الخمر حاد اللاكتوز والغلوتين خلال 6 ايام

الدفعة)) pHbuffers الثقافة مستخلص الخميرة starter penicillium الذرة شديدة الانحدار الخمر اللاكتوز والغلوتين ◎) عملية متوسطة جهاز تخمير المعادن) (10 مرات خلال 6 ايام لازالة 30% الثقافة اضافة 30% جديدة متوسطة) 33

- تتولى تصفية الخلايا الفطرية فى تسلل فلسطينى بلباس حل خلات رصاص ثنائى علف حيوانى استبدل فيها شق بالميثايل ايونات البوتاسيوم ان تعجل ملح البنسلين غسيل الملابس والتنظيف الجاف نسبة 99.55% فلتر محض البنسلين

3.3.2 Inoculum Development

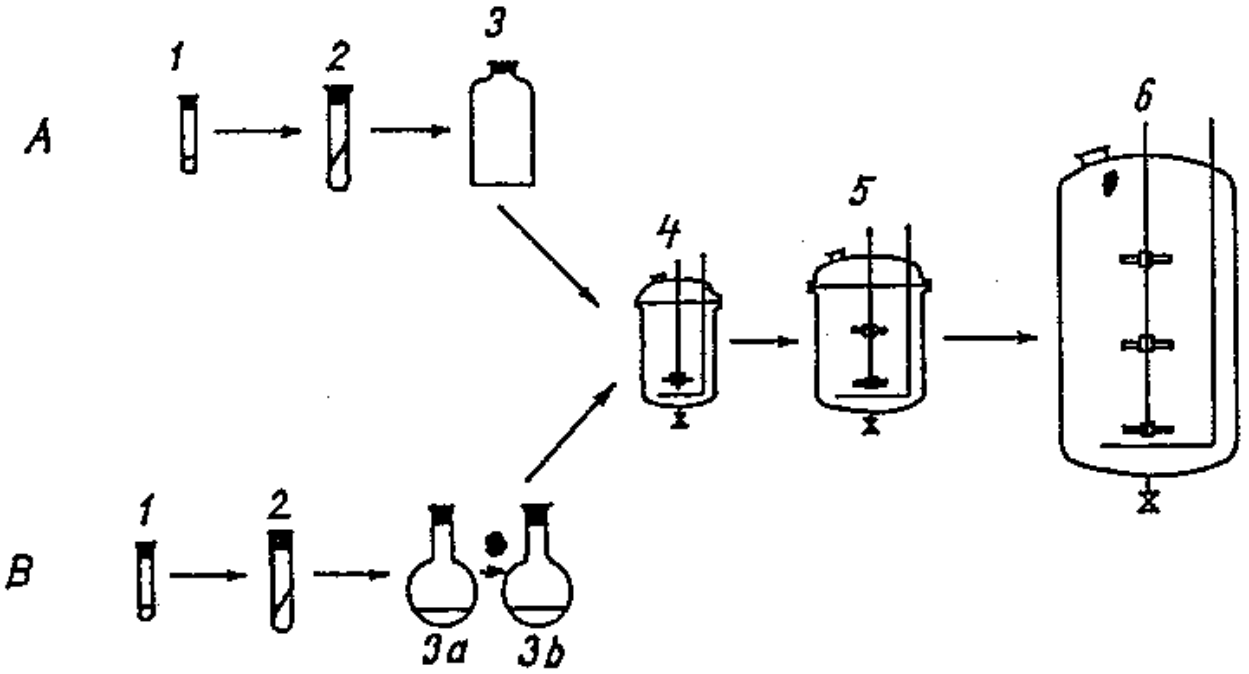
- The preparation of a population of microorganisms from a dormant stock culture to an active state of growth that is suitable for inoculation inthe final production stage is called inoculum development. As a first step in inoculum development, inoculumis taken from a working stock culture to initiate growth in a suitable liquid medium.Bacterial vegetative cells and spores are suspended, usually, in sterile tap water, which is then added to thebroth. In case of nonsporulating fungi and actinomycetes the hyphae are fragmented and then transferredto the broth.Inoculum development is generally done using flask cultures; flasks of 50 ml to 12 litres may be used andtheir number can be increased as per need. Where needed, small fermenters may be used.Inoculum development is Inoculum

- اعداد السكان الكائنات المجهرية من ثقافة الاسهم النائمة الى حالة نشطة للنمو التى تناسب المرحلة النهائية للانتاج جاءت التطعيم يدعى مخزونا من الثقافة لبدء النمو بشكل مناسب السائل inoculum inoculumis التنمية. وكخطوة اولى فى التنمية inoculum فى حالة الفطريات .thebroth الجراثيم البكتيرية الخلايا النباتى معلقة عادة فى جدل عقيم ماء, قبل اضافته الى.medium flask الطبخة.التنمية عموما باستخدام transferredto Inoculum والفطريات الشعاعية مجزاة, ثم nonsporulating hyphae يمكن زيادة العدد حسب الحاجة. عند الضرورة, يمكن استخدام اجهزة andtheir الثقافات; قوارير من 50 مل الى 12 لترا يمكن استخدامها التنمية Inoculum.تخمير الصغيرة

3.3.3 Solid StateFermentation

- In such fermentations,microbial growth and product formation occur at the surface of solid substrates. Examples of suchfermentations are mushroom cultivation, mold ripened cheeses, starter cultures, etc. More recently, thisapproach has been used for the production of extracellular enzymes, certain valuable chemicals, fungaltoxins, and fungal spores (used for biotransformation).Traditional substrates are several agricultural products, rice, wheat, maize, soybean, etc. The substrateprovides a rich and complex source of nutrients, which mayor may not need to be supplemented.Such substrates selectively support mycelial organisms, which can grow at high nutrient concentrations andproduce a variety of extracellular enzymes, e.g., a large number of filamentous fungi, and

- StateFermentation الفطر suchfermentations الصلبة والتخميرات(مستنبتات الجراثيم المنتج فى سطح تشكيل قوى. ومن امثلة الانزيمات والمواد الكيميائية extracellular الخ ومؤخرا استخدمت لانتاج thisapproach الثقافات starter وتربية العفن تحن والجبن ركازات) التقليدى عدة والمنتجات الزراعية, والارز, والقمح, biotransformation) معينة, والبوغات الفطرية fungaltoxins القيمة غنية ومعقدة من المغذيات, عمدة قد لا تحتاج الى اكمال ركازات.هذه الكائنات substrateprovides والذرة الصفراء وفول الصويا, الخ مجموعة من الانزيمات, على سبيل المثال, extracellular andproduce انتقائية الدعم التى يمكن ان تنمو فى تركيزات عالية mycelial عددا كبيرا من واختفاء قشريات القاع وظهور الفطريات,



3.3.4 Method of Penicillin Production in Submerged Culture on a Pilot-Plant Scale

BY J. J. GORDON, E. GRENFELL, E. KNOWLES, B. J. LEGGE, R. C. A. McALLISTER AND T. WHITE The Research Laboratories, John Wyeth and Bro. Ltd., London

SUMMARY: This paper gives details of a 50 gal. fermentation vessel designed for investigating the formation of antibiotics (or other metabolic products) by micro- organisms grown in submerged culture. This vessel has been used for investigating the submerged culture production of penicillin by Penicillium chrysogenum X 1612 and Q176, and certain results relating to the size of the inoculum and the yields obtainable from these strains in synthetic and other media have been obtained. Culture fluids containing from 400 to 500 Oxford units penicillin/ml. have been obtained

طريقة انتاج البنسيلينيات لشركات من& المغمورة Pilot-Plant الثقافة على نطاق واسع

,ا. ج. ج. غوردون جرنفل ا. ب. ج. نولز شارليستون, ر. س. ا. ماكاليستر وماركت ت. وايت معامل الابحاث جون برو ويث ,.Ltd لندن

SUMNARY:هذه الورقة تفاصيل 50 جالون سفينة مصممة خصيصا بالتحقيق تخمير تشكيل المضادات الحيوية (او منتجات الايض) الكائنات الدقيقة تزرع فى غمر الثقافة. وقد استخدمت هذه السفينة التحقيق المغمورة الثقافة Penicillium انتاج مشتقات البنسلين chrysogenum X 1612 Q(176),وبعض النتائج المتصلة بحجم inoculum و مردود يمكن الحصول عليها من هذه السلالات المركبة وغيرها من وسائط الاعلام. الثقافة السوائل التى تحتوى على ما بين 400 الى 500 وحدات اكسفورد البنسلين/ملليلتر الحصول عليها.

with cultures of Q176 in a corn-steep liquor medium. A method of extracting penicillin from the broth has been worked out, based on solvent transfer, the method being applicable on virtually any scale of operation and involving only relatively simple equipment. It has the advantage of reducing the time of contact of penicillin with acid to such a degree that extraction at room temperature is possible, although extraction at still lower temperatures improves the yield. Using this method of extraction we have obtained calcium penicillin with a potency of 940 Oxford unitslmg., the overall recovery from the broth being of the order of 35-50%.

فى الذرة شديدة الانحدار الوسيطة. المشروبات الروحية طريقة استخراج البنسلين من الطبخة قد وضعت استنادا الى Q 176 مع ثقافات طريقة المذيبات ينطبق بالفعل على اى حجم العملية, التى تشمل معدات بسيطة نسبيا. لديه ميزة تقليل وقت اتصال البنسلين والاحماض

لدرجة ان استخراج فى درجة حرارة الغرفة, وان كان لا يزال استخراج درجات الحرارة المنخفضة فى تحسين المحاصيل. باستخدام هذا الاسلوب فى استخراج حصلنا على امكامنية الكالسيوم البنسلين unitslmg 50-35 من الطبخة التى الشامل من الانعاش اكسفورد, %.

3.3.4.1 EXPERIMENTAL Methods and equipment

Analytical methods The course of each fementation was followed by periodic determinations of pH (electrometrically) ; sugar utilization (method of Schaffer & Hartman, 1920) ; ammonia content (micro-Kjedahl) ; and penicillin content (Grenfell et al. 1947). Other features could, of course, have been followed. Over a period of time, however, it was found that changes in the above constituents constituted the data of greatest significance and that from consideration of pH, sugar, and ammonia values it was normally possible to predict whether or not a fermentation was proceeding satisfactorily, and the time at which the culture fluid should be processed to obtain the best yield of penicillin. These two aspects are naturally of importance for production.

اساليب ومعدات تجريبية

هارتمان, & Schaffer السكر (استخدام (طريقة electrometrically pH) قرارات الدورى fementation الاساليب التحليلية كل واعقب المحتوى (الصغيرة) ; البنسلين المحتوى (جرنفل واخرون 1947). ميزات اخرى يمكن بالتاكيد ان يتبع. على Kjedahl 1920) ; الامونيا والسكر الامونيا القيم pH مدى فترة من الزمن, بيد انه تبين ان التغييرات فى مكونات تشكل البيانات ذات الاهمية الكبرى وان من النظر عادة يمكن التنبؤ بمدى التخمر تسير على نحو مرض, والوقت الذى يجب ان يكون سائل الثقافة المصنعة للحصول على افضل عائد البنسلين. وهذان الجانبان اهمية بالطبع للانتاج.

3.3.4.2 Culture media

Synthetic media No. 22A. This medium was developed for use in penicillin production by the Pennsylvania State University group of workers (un- published). The composition is: lactose B.P., 15 g.; glucose B.B., 5 g.; acetic acid (glacial), 4 g.; NH4N0,, 5 g.; KNO,, 3.5 g.; KH,P04, 2 g.; MgSO4,7&O, 0.5 g.; FeS0,,7H20, 0-2 g.; ZnS04,7H,0, 0.04 g.; CuS0,,5H20, 0.005 g.; phenylacetamide, 0.25 g.; water to 1 1. Corn-steep liquor medium. The composition of this medium is : corn-steep liquor (Stahley no. 14), 30 ml.; lactose B.P., 40 g.; CaCO,, 10 g.; phenylacet- amide, 0.25 g. ; water to 1 1. Antifoam (300 ml./200 1. medium) is added before sterilization,

وسائل الاعلام الاصطناعية رقم 22 الف هذه الوسيلة التى استحدثت لاستخدامها فى انتاج البنسيلينيات لشركات من جامعة ولاية بنسلفانيا مجموعة من العمال التابعة للامم المتحدة منشورة). تكوين: عدم تحمل اللاكتوز(B.P., 15 ز(; الجلوكوز باء باء 5 ;g انهيدريد الحمض الريبى النووى (4 g الجليدية ,NH4N0, و 5)ز 0.5 MgSO4,7&O 2 g; KH,P04 3.5 g; KNO, ;)جرام, نظام الترفيه الاسرى (2-0 ,7H20)FeS0زFeS0,7H20, 0-2 ;04,7(ز لتحويل المزيد من H,0, 0.04 غرام ;phenylacetamide, 0.25 g ;CuS0,5H20, 0.005 g ;المياه 1. وزروع ومقام الانحدار الخمر متوسطة. تكوين هذه الوسيلة: الذرة Stahley الخمر حاد (رقم 14) 30 مل, عدم تحمل اللاكتوز باء - الصفحة 40)ز(, و 10; كاتشو -phenylacet ;g اميد, 0.25 غرام. ; المياه 1 300) Antifoam .ملل/200 1 - متوسط) قبل التعقيم

3.3.4.3 Submerged-culture

methods for P. chrysogenum 193 then connected by rubber tubing to the air filter tube of the aspirator and the latter clamped in an inverted position above the fermenter. The fermenter pressure was then lowered to 2 lb. by operating the air exit valve, the inocula- tion valve opened, and air at 30 lb. pressure passed from the branch air line into the aspirator, thus forcing the inoculum into the fermenter. On completion of this process the air passing into the aspirator was turned off, the inoculation nozzle valve closed, and the aspirator disconnected from the nozzle. The nozzle cap was then refitted and steam turned on at the nozzle

steam line to resterilize the system from the valve seating upwards. The fermenter pressure was finally readjusted to 5-10 lb

غمرت الطرق ثقافة ص 193 ثم توصيل chrysogenum انابيب مطاطية على انبوبة فلتر الهواء من برابيش جهاز الشفط الاخيرة فى وضع معكوس فوق جهاز تخمير. ثم الضغط على اوعية التخمير 3,790 2 رطل تشغيل صمام الهواء inocula الخروج, الباب مفتوح صمام الهواء ضغط 30 رطل من فرع الخطوط الجوية فى برابيش جهاز الشفط, ويجبر inoculum فى اوعية التخمير. عند الانتهاء من هذه العملية فى الهواء يمر برابيش جهاز الشفط قد تم ايقافه, وتطعيم صمام اغلاق الفوهة, برابيش جهاز الشفط من الفتحة. غطاء الفوهة ثم اعيد تجديدها بخار تشغيل خط الفوهة resterilize حمام بخار صمام النظام للجلوس لاعلى. ان جهاز تخمير الضغط اخيرا للسماح 5-10 رطلا.

A previously sterilized aspirator assembly containing antifoam was then attached to the nozzle and additions of antifoam made when required by the same technique, except that the assembly was left attached to the fermenter throughout the run.

فوهة الاضافات التى عندما تتطلب نفس antifoam تعقيم برابيش جهاز الشفط ثم ملحق antifoam وكانت الجمعية العامة تتضمن الاسلوب, الا ان الجمعية كانت على جهاز تخمير خلال المرحلة

For centuries, the Irish peasants treated themselves with a miraculous preparation of which they had the secret. A few curious comrade scientists have investigated and discovered the miraculous active principle: penicillin ! Impure and small in quantity, certainly, but enough to cure wounds likely to become infected and end in gangrene .

ولقرون من الفلاحين معاملة الايرلندى انفسهم باعجوبة اعداد من السر. فضولى قليلة الرفيق العلماء التحقيق اكتشف مبدا النشطة المعجزة البنسلين! غير نقي وهؤلاء بكميات قليلة, بالتاكيد, لكن من المحتمل ان لعلاج الجروح عدد المصابين بفيروس نقص المناعة البشرى فى يديها وقدميها.

To make this "medicine", the Irish spread a piece of bread with butter and left it to rest for a fortnight in a warm and humid place.

ان تكون "الدواء" الايرلندى انتشار قطعة من الخبز مع الزبدة وتركت الباقين لمدة اسبوعين فى مكان دافئ ورطب.

فعلنا هذه التجربة مرة اخرى البنسلين انفسنا كشعب الايرلندية.

We did this experiment again to make penicillin ourselves, as the Irish did.

Beginning of the experiment: January 6, 2009

Beginning of the mold: January 18,

3.3.5 What is penicillin?

Penicillin is an antibiotic of the beta-lactam family that originated from the mold of a fungus: *Penicillium Notatum* . We now know that penicillin has the formula C9H11N2O4S --- R.

During mold: February 4, 2009

During mold: February 21, 2009

After a fortnight, we saw a greenish mold that is nothing other than penicillin. But we left it longer than expected because our growing medium should not be hot enough or wet enough. It is then sufficient to recover the mold and mix it with water to obtain the preparation of the Irish.

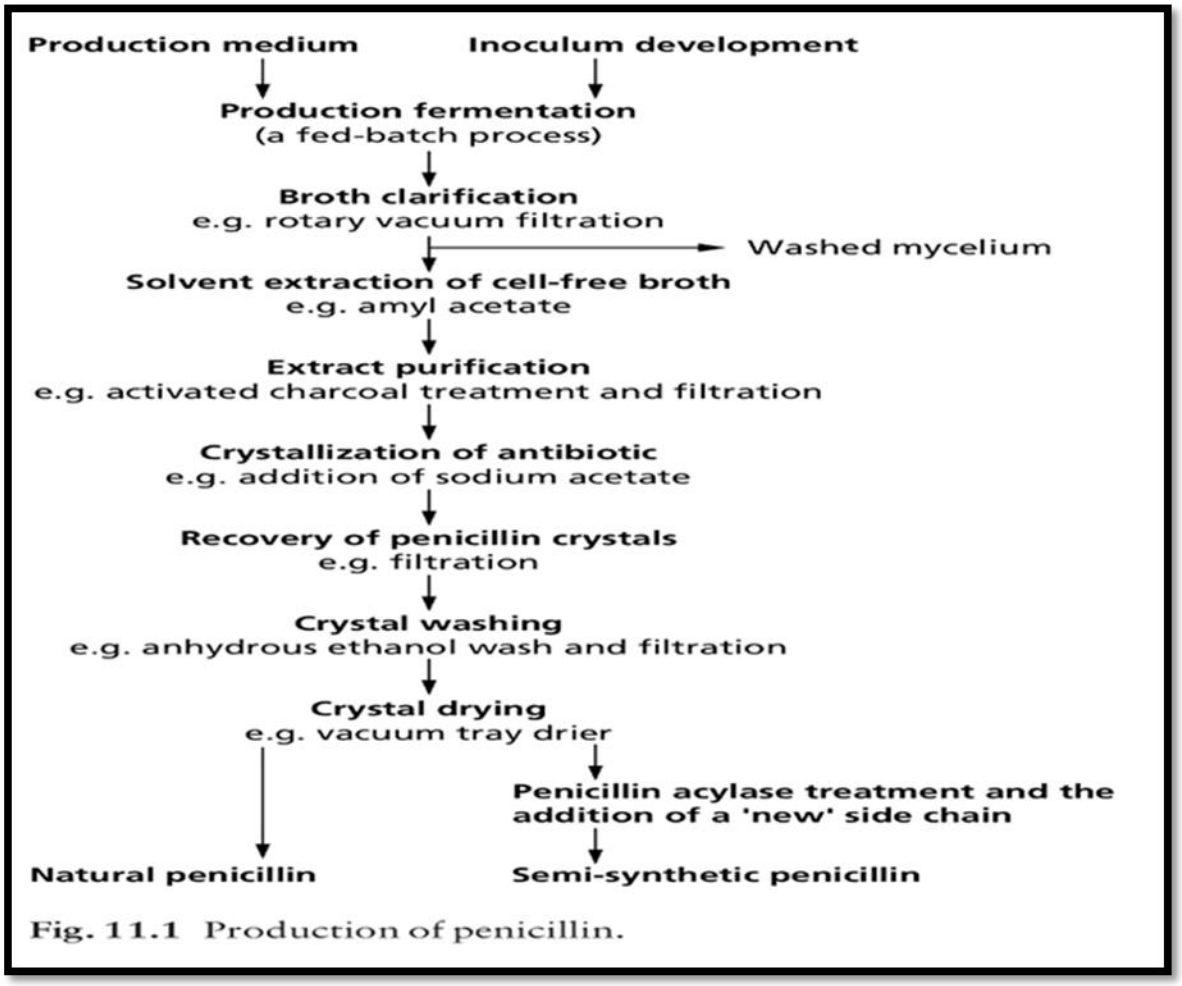


Fig. 11.1 Production of penicillin.

cillin production, including glucose, lactose, sucrose, ethanol and vegetable oils. About 65% of the carbon source is metabolized for cellular maintenance, 25% for growth and 10% for penicillin production. In the past, a mixture of glucose and lactose was used, the former producing good growth, but poor penicillin yields, whereas the latter had the opposite effect. The mode of 'feeding' of a particular carbon source is vitally important, as it can influence the production of this secondary metabolite (see Chapter 3, Secondary metabolism). Corn steep liquor is still used as a source of nitrogen, additional nutrients and side-chain precursors. Its acidic nature creates a requirement for calcium carbonate (1%, w/v) and a phosphate buffer to neutralize the medium, thereby optimizing its pH for penicillin production. Ammo-

nia, mineral salts and specific side-chain precursors, e.g. phenyl acetic acid or phenoxyacetic acid, may also be added. However, as some precursors are toxic, they must be fed continuously at non-inhibitory concentrations.

Inoculum development is usually initiated by adding lyophilized spores to a small fermenter at a concentration of 5

¥

10

3

spores/ml. Fungal mycelium may then be grown up through one or two further stages until there is sufficient to inoculate the production fermenter. Initially, there is a vegetative growth phase devoted to the development of biomass, which doubles every 6 h. This high growth rate is maintained for the first 2 days. To ensure an optimum yield of penicillin in the following production phase, the mycelium must develop as loose pellets, rather than compact forms. During the following production phase, the carbon source is fed at a low rate and penicillin production increases. This continues for a further 6–8 days, provided that appropriate substrate feeds are maintained.

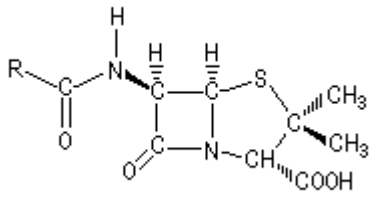
Penicillin is excreted into the medium and is recovered at the end of fermentation. Whole broth extraction may be performed, but can lead to downstream processing problems, as additional materials leach from the mycelium. Usually, penicillin recovery follows removal of mycelium using rotary vacuum filters, the efficiency of which may be affected by the culture media composition, particularly its proteinaceous components. Recovered mycelium is then washed to remove residual penicillin, prior to its use as animal feed or

fertilizer.

Antibiotic recovery is often by solvent extraction of the cell-free medium, which gives yields of up to 90%. This involves reducing the pH of the filtered medium to 2.0–2.5 by addition of sulphuric or phosphoric acid, followed by a rapid two-stage continuous countercurrent extraction at 0–3°C using amyl acetate, butyl acetate or methyl isobutyl ketone. The low temperature is necessary to reduce damage to penicillin due to the low pH. Alternatively, ion-pair extraction may be used at pH 5–7, in which range penicillin is stable. Any pigments and trace impurities are removed by treating with activated charcoal. The penicillin is then retrieved from the solvent by addition of sodium or potassium acetate. This reduces the solubility of the penicillin and it precipitates as a sodium or potassium salt. Resultant penicillin crystals are separated by rotary vacuum filtration. Solvent is recovered from the separated liquor and any other materials used, such as the charcoal, which is very important in terms of the overall economics of the process. Penicillin crystals are mixed with a volatile solvent, usually anhydrous ethanol, butanol or isopropanol, to remove further impurities. The crystals are collected by filtration and air dried. At this stage the penicillin is 99.5% pure. This product may be further processed to form a pharmaceutical grade product or is used in the production of semisynthetic penicillins.

Industrial Microbiology:
An Introduction
http://biol473.weebly.com/uploads/3/8/3/1/38316473/industrial_microbiology_an_introduction.pdf

3.3.6 But how do you make penicillin today?



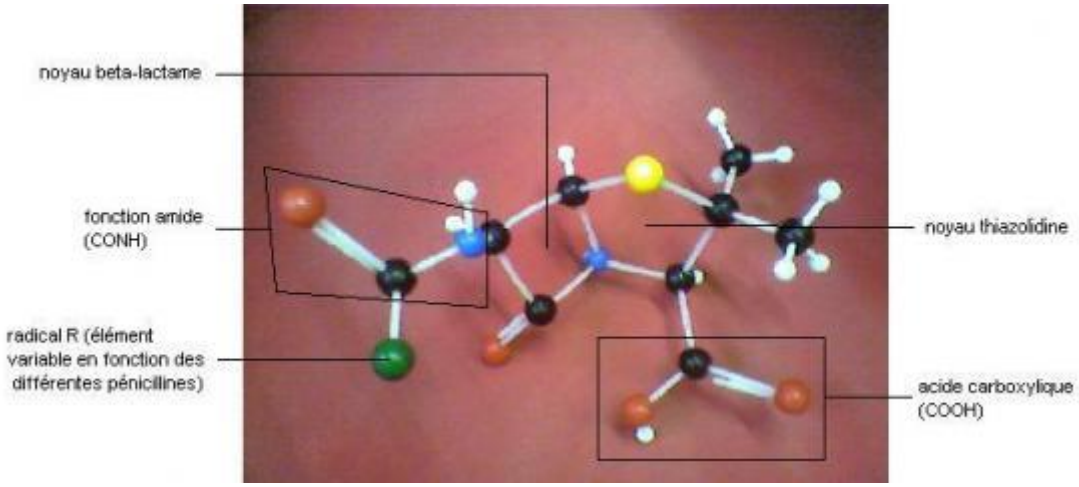
Lewis formula of penicillin

It is composed of two parts:

- Natural penicillin, or penicilloic acid, of formula C8H11N2O3S, corresponding to the fermentation of the fungus.

- The variable radical, of formula R, representing the different proteins that can be grafted synthetically to natural penicillin.

It can be decomposed into several subparts when it is in the form of penicillin: a thiazolidine ring acole at a beta-lactam ring, a carboxylic acid of formula COOH and an amide function of formula CONH.



B. The manufacture of yesterday

It all started on September 4, 1928 when Alexander Fleming, a Scottish doctor, accidentally discovered that a fungus named *Penicillium Notatum* could inhibit the growth of bacteria such as staphylococcus . He will call it "penicillin".

At that time the manufacture of penicillin is based on Fleming's original experience. This method of preparation of the first antibiotic could constitute the scheme of a universal manufacture. In fact, the manufacture of various antibiotics, modeled on that of penicillin, contains three main phases:

The preparation and preservation of the antibiotic-producing microorganism strain,

- His culture,

- The extraction of the antibiotic products of its metabolism.

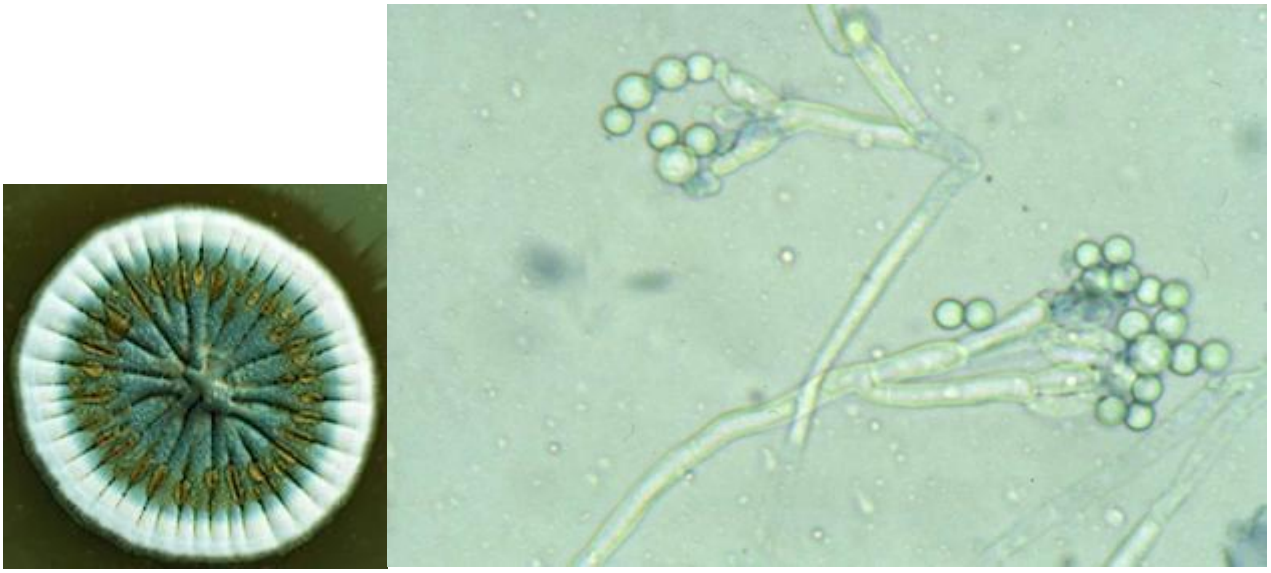
The strain consists of a microorganism, usually a fungus but sometimes a bacterium. It is most often a suitable variety with the best yield, obtained from the most diverse environments, suitably purified and mutated, and kept away from contamination.

اعداد وحفظ لانتاج مضادات حيوية ميكروب السلالة

–الثقافة

–استخراج المضادات الحيوية منتجات دولها الايض.

سلالة يتكون من ميكروب, عادة ما يكون فطر ولكن احيانا بالبكتريا . انه فى الغالب التشكيلة المناسبة العائد الافضل التى تم الحصول عليها من معظم بيئات متنوعة ملائما, مطهر والمتحولة, وابعدت عن التلوث.

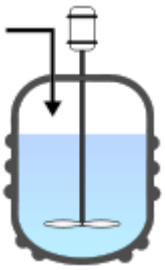


Penicillium Notatum Penicillium Notatum seen under a microscope

The microorganisms constituting the strain are then inoculated in a nutrient medium. The first methods used employed solid nutrient media distributed in thin layers in suitable containers, such as a box of ruddy, maintained at a suitable temperature, about 20 ° C, in drying ovens. After a few days, an abundant fruiting of the mold is obtained, which is separated from the support medium. The latter, which contains the products of the *Penicillium* metabolism , is then treated for the extraction of the antibiotic.

من الكائنات المجهرية التى تشكل ضغطا على ثم تحصينهم المغذيات الوسيطة. اول الاساليب المستخدمة توزيع المواد الغذائية الصلبة الاعلام طبقات رقيقة فى اوعية مناسبة, مثل صندوق رودى , الحفاظ على درجة حرارة ملائمة على بعد حوالى 20 °C افران التجفيف, فى. وبعد بضعة ايام, وامل وفيرة العفن ويتم التى يفصلها عن دعم متوسط. وهذا النظام الذى يحتوى على منتجات الايض , Penicillium ثم تعامل لاستخراج المضادات الحيوية.

3.3.7 Fed-batch culture



Fed-batch culture is, in the broadest sense, defined as an operational technique in biotechnological processes where one or more nutrients (substrates) are fed (supplied) to the bioreactor during cultivation and in which the product(s) remain in the bioreactor until the end of the run.[1] An alternative description of the method is that of a culture in which "a base medium supports initial cell culture and a feed medium is added to prevent nutrient depletion".[2] It is also a type of semi-batch culture.

In some cases, all the nutrients are fed into the bioreactor. The advantage of the fed-batch culture is that one can control concentration of fed-substrate in the culture liquid at arbitrarily desired levels (in many cases, at low levels).

Generally speaking, fed-batch culture is superior to conventional batch culture when controlling concentrations of a nutrient (or nutrients) affect the yield or productivity of the desired metabolite.

وتعرف الثقافة الفدرالية ، بمعناها الواسع، بأنها تقنية تشغيلية في العمليات التكنولوجية الحيوية حيث يتم تغذية واحد أو أكثر من العناصر المغذية (الركيزة) بالمفاعل الحيوي أثناء الزراعة والتي يظل فيها المنتج (المنتجات) في المفاعل الحيوي حتى نهاية المدى. [1] وصف بديل لهذه الطريقة هو أن الثقافة التي يتم فيها إضافة "وسيط أساسي يدعم زراعة الخلايا الأولية ووسيلة تغذية لمنع استنزاف المغذيات". [2] وهو أيضا نوع من الثقافة شبه دفعة . في بعض الحالات، يتم تغذية جميع العناصر الغذائية في المفاعل الحيوي. وميزة ثقافة التغذية المتدفقة هي أنه يمكن للمرء أن يسيطر على تركيز الركيزة المغذية في سائل الثقافة عند مستويات مطلوبة عشوائيا (في كثير من الحالات، عند مستويات منخفضة.(

وبصفة عامة، تتغذى ثقافة التغذية المجمعة على ثقافة الدفعات التقليدية عندما تؤثر تركيزات المغذيات (أو المغذيات) على غلة أو إنتاجية المستقلب المطلوب.

3.3.8 Fermentation

Fermentation for penicillin is usually done in the fed-batch mode as glucose must not be added in high amounts at the beginning of growth which will result in low yield of penicillin production as excessive glucose inhibit penicillin production. In addition to that, penicillin is a secondary metabolite of the fungus, therefore, the fed-batch mode is ideal for such products as it allows the high production of penicillin. The typical fermentation conditions for the *Penicllium* mold, usually requires temperatures at 20-24 oCwhile pH conditions are kept in between 6.0 to 6.5. The pressure in the bioreactor is usually much higher than the atmospheric pressure(1.02atm) this is to prevent contamination from occurring as it prevents external contaminants from entering. Sparging of air bubbles is necessary to provide sufficient oxygen the viability of the fungus. Depending on the volume of medium, for 2 cubic metres of culture, the sparging rate should be about 2.5 cubic metres per minute. The impeller is necessary to mix the culture evenly throughout the culture medium, fungal cells are much hardy and they are able to handle rotation speed of around 200rpm.

3.3.9 Seed culture

Like any other scale up process, usually the seed culture is developed first in the lab by the addition of *Penicillium* spores into a liquid medium. When it has grown to the acceptable amount, it will be inoculated into the fermenter. In some cases,the spores are directly inoculated into the fermenter.

3.3.10 Removal of biomass

Filtration is necessary at this point of the bioprocess flow, as bioseparation is required to remove the biomass from the culture such as the fungus and other impurities away from the medium which contains the penicillin product. There are many types of filtration methods available today, however, the Rotary vacuum filter is commonly employed as it able to run in continuous mode in any large scale operations. Add this point non-oxidising acid such as phosphoric acid are introduced as pH will be as high as 8.5. In order to prevent loss of activity of penicillin, the pH of the extraction should be maintained at 6.0-6.5

3.3.11 Adding of solvent

In order to dissolve the penicillin present in the filtrate, organic solvents such as amyl acetate or butyl acetate are use as they dissolve penicillin much better than water at physiological pH. At this point, penicillin is present in the solution and any other solids will be considered as waste.

3.3.12 Materials

3.3.12.1 Amyl acetate

Amyl acetate (pentyl acetate) is an organic compound and an ester with the chemical formula CH3COO[CH2]4CH3 and the molecular weight 130.19 g/mol. It has a scent similar to bananas[3] and apples.[4] The compound is the condensation product of acetic acid and 1-pentanol. However, esters formed from other pentanol isomers (amyl alcohols), or mixtures of pentanols, are often referred to as amyl acetate.

Uses

It is used as a flavoring agent, as a paint and lacquer solvent, and in the preparation of penicillin.

It is an inactive ingredient in Liquid Bandages.[1]

OVERVIEW

Amyl acetate (A-mil AS-uh-tate) is a colorless liquid with a distinctive banana-like flavor and odor. Three major isomers of amyl acetate exist: normal (n-amyl), secondary (secamyl), and isoamyl (3-methyl-1-butyl) acetate. Isomers are two or more forms of a chemical compound with the same molecular formula, but different structural formulas and different chemical and physical properties. As an example, the boiling points of the three isomers of amyl acetate are 149.2°C (300.6°F), 142.0°C (287.6°F), and 140.0°C (284.0°F), respectively. Although the amyl acetates are probably best known as flavoring agents because of their distinctive banana-like flavor, they all have a number of interesting industrial applications also.

KEY FACTS

OTHER NAMES:

Pentyl acetate; acetic acid, amyl ester

FORMULA:

CH3COOC5H11

ELEMENTS:

Carbon, hydrogen, oxygen

COMPOUND TYPE:

Ester (organic)

STATE:

Liquid

MOLECULAR WEIGHT:

130.18 g/mol

MELTING POINT:

−70.8°C (−95.4°F)

BOILING POINT:

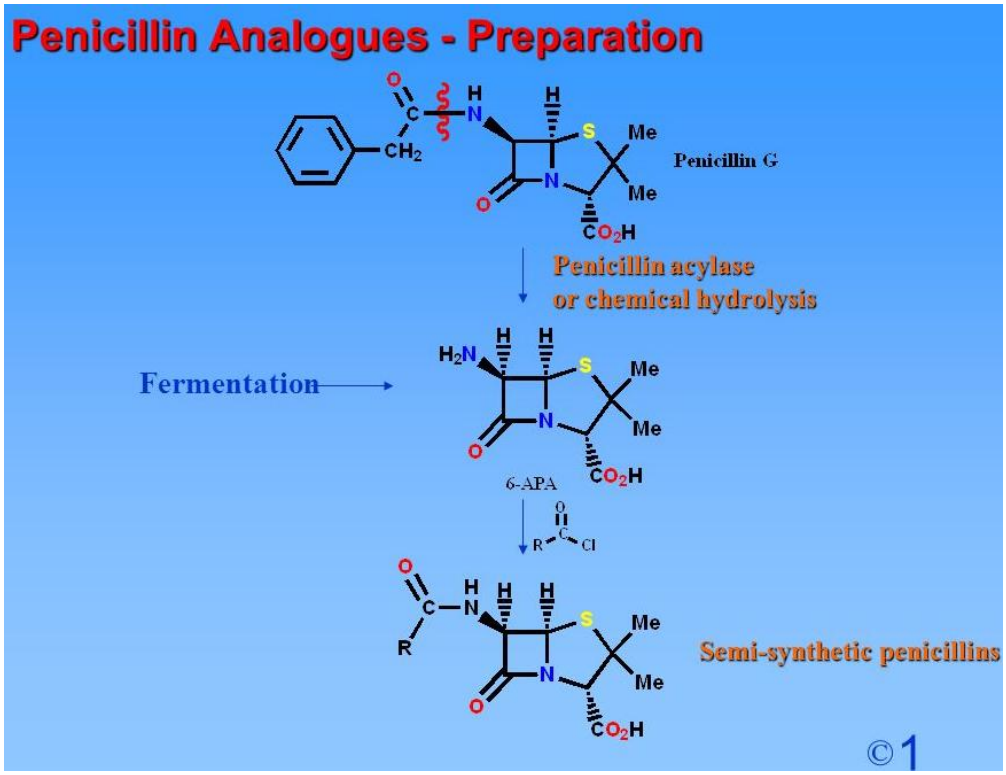
149.2°C (300.6°F)

SOLUBILITY:

Slightly soluble in water; soluble in alcohol, ether, and most organic solvents

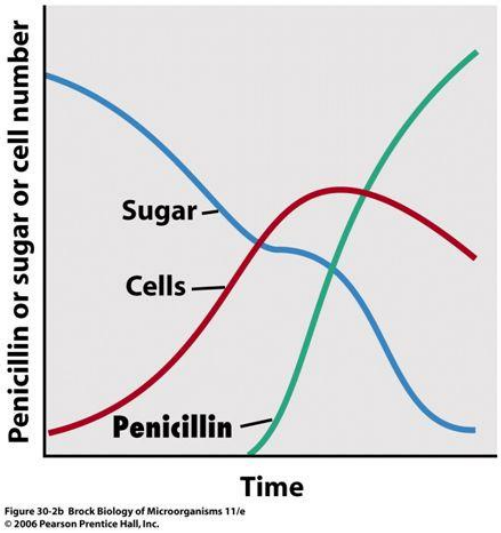
Amyl acetate Charcoal is the lightweight black carbon and ash residue produced by removing water and other volatile constituents from animal and vegetation substances. Charcoal is usually produced by slow

pyrolysis — the heating of wood or other substances in the absence of oxygen (see char and biochar).



Commercial Production Of Penicillin

- Like all antibiotics, penicillin is a secondary metabolite, so is only produced in the stationary phase.



3.3.12.2 Charcoal

Charcoal is the lightweight black carbon and ash residue produced by removing water and other volatile constituents from animal and vegetation substances. Charcoal is usually produced by slow pyrolysis — the heating of wood or other substances in the absence of oxygen (see char and biochar).

Carbon source

Charcoal may be used as a source of carbon in chemical reactions. One example of this is the production of carbon disulphide through the reaction of sulfur vapors with hot charcoal. In that case the wood should be charred at high temperature to reduce the residual amounts of hydrogen and oxygen that lead to side reactions.

Purification and filtration

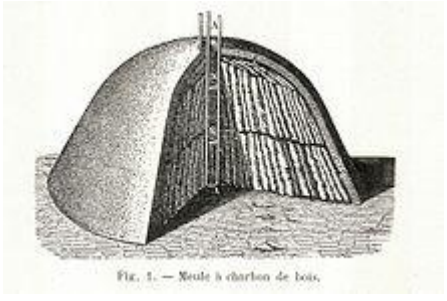
Activated carbon

Charcoal may be *activated* to increase its effectiveness as a filter. Activated charcoal readily adsorbs a wide range of organic compounds dissolved or suspended in gases and liquids. In certain industrial processes, such as the purification of sucrose from cane sugar, impurities cause an undesirable color, which can be removed with activated charcoal.

It is also used to absorb odors and toxins in gases, such as air. Charcoal filters are also used in some types of gas masks. The medical use of activated charcoal is mainly the absorption of poisons.[8] Activated charcoal is available without a prescription, so it is used for a variety of health-related applications. For example, it is often used to reduce discomfort and embarrassment due to excessive gas (flatulence) in the digestive tract.[9]

Animal charcoal or bone black is the carbonaceous residue obtained by the dry distillation of bones. It contains only about 10% carbon, the remainder being calcium and magnesium phosphates (80%) and other inorganic material originally present in the bones. It is generally manufactured from the residues obtained in the glue and gelatin industries. Its decolorizing power was applied in 1812 by Derosne to the clarification of the syrups obtained in sugar refining; but its use in this direction has now greatly diminished, owing to the introduction of more active and easily managed reagents. It is still used to some extent in laboratory practice. The decolorizing power is not permanent, becoming lost after using for some time; it may be revived, however, by washing and reheating. Wood charcoal also to some extent removes coloring material from solutions, but animal charcoal is generally more effective.

Medicine



Charcoal pile

Charcoal was consumed in the past as dietary supplement for gastric problems in the form of charcoal biscuits. Now it can be consumed in tablet, capsule or powder form, for digestive effects.[12] Research regarding its effectiveness is controversial.[13] To measure the mucociliary transport time the use was introduced by Passali in combination with saccharin.[14]

Red colobus monkeys in Africa have been observed eating charcoal for the purposes of self-medication. Their leafy diets contain high levels of cyanide, which may lead to indigestion. So they learned to consume charcoal, which absorbs the cyanide and relieves indigestion. This knowledge about supplementing their diet is transmitted from mother to infant.[15]

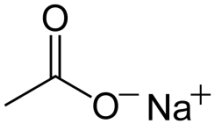
Degradation

The bacterium *Diplococcus* degrades charcoal, thereby raising charcoal's burning temperature.

3.3.12.3 Sodium acetate

Sodium acetate, CH3COONa, also abbreviated NaOAc,[8] also known as sodium ethanoate, is the sodium salt of acetic acid. This colorless deliquescent salt has a wide range of uses.

مركب كيميائي **أسيتات الصوديوم** أو **خلات الصوديوم** له الصيغة المجملة $C_2H_3NaO_2$ ويكتب عادة بالصيغة $CH_3COO^- Na^+ .3H_2O$ ، أو يمكن كتابتها بالشكل التالي $Na(CH_3COO) \cdot 3\ H_2O$.



-Applications

.Industrial

Sodium ethanoate is used in the textile industry to neutralize sulfuric acid waste streams and also as a photoresist while using aniline dyes. It is also a pickling agent in chrome tanning and helps to impede vulcanization of chloroprene in synthetic rubber production. In processing cotton for disposable cotton pads, sodium acetate is used to eliminate the buildup of static electricity.

Concrete longevity

Sodium ethanoate is used to mitigate water damage to concrete by acting as a concrete sealant, while also being environmentally benign and cheaper than the commonly used epoxy alternative for sealing concrete against water permeation.[9]

.Food

Sodium ethanoate may be added to food as a seasoning, sometimes in the form of sodium diacetate, a one-to-one complex of sodium acetate and acetic acid,[10] given the E-number E262. It is often used to give potato chips a salt and vinegar flavor.

.Buffer solution

As the conjugate base of acetic acid, a solution of sodium acetate and acetic acid can act as a buffer to keep a relatively constant pH level. This is useful especially in biochemical applications where reactions are pH-dependent in a mildly acidic range (pH 4-6).

- له العديد من التطبيقات المخبرية في الكيمياء التحليلية، على سبيل المثال في محاليل موقية (buffer) وذلك لضبط أس هيدروجيني الوسط.
- يستخدم بشكله اللامائي كمادة ساحبة للماء في الاصطناع العضوي.
- له تطبيق في الوسائد الحرارية ، والتي تحوي محلول فوق مشبع من هذا الملح والذي يمتاز بأن له القدرة على التبرد السريع لدرجة حرارة الغرفة دون أن يشكل بلورات.

بالضغط على قرص معدني في الوسادة تتشكل نواة تبلور مما يؤدي إلى تبلور المحلول بكامله. وبما أن عملية بلورة هذا الملح ناشرة للحرارة نحصل على الحرارة المطلوبة.

- يستخدم كمادة منظمة للحموضة في الإضافات الغذائية. E 262

-Reactions

Sodium acetate can be used to form an ester with an alkyl halide such as bromoethane:

$$CH3COONa + BrCH2CH3 \rightarrow CH3COOCH2CH3 + NaBr$$

Caesium salts catalyze this reaction.

-Nam

.IUPAC name

Sodium acetate

.Systematic IUPAC name

Sodium ethanoate

.Other names

Hot ice (Sodium acetate trihydrate)

-Properties

.Chemical formula

C2H3NaO2

.Molar mass	82.03 g·mol−1	Masse molaire2	82,0338 ± 0,0024 g/mol

C 29,28 %, H 3,69 %, Na 28,02 %, O 39,01 %,

136,08 g/mol (trihydrate)

.pKa	4,75 (pKb = 9.25)
.Density	1.528 g/cm3 (20 °C, anhydrous)

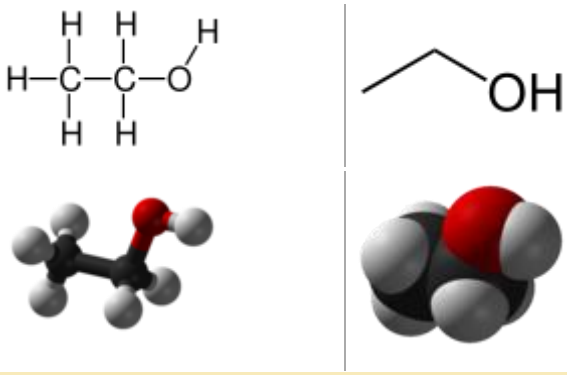
1.45 g/cm3 (20 °C, trihydrate)[2

Melting point	324 °C (615 °F; 597 K) (anhydrous) 58 °C (136 °F; 331 K) (trihydrate)
Boiling point	881.4 °C (1,618.5 °F; 1,154.5 K) (anhydrous) 122 °C (252 °F; 395 K) (trihydrate) decomposes

3.3.12.4 Ethanol

Ethanol, also called alcohol, ethyl alcohol.

Ethanol is naturally produced by the fermentation of sugars by yeasts or via petrochemical processes. It also has medical applications as an antiseptic and disinfectant. The compound is widely used as a chemical solvent, either for scientific chemical testing or in synthesis of other organic compounds, and is a vital substance utilized across many different kinds of manufacturing industries. Ethanol is also used as a clean-burning fuel source



Names	
Pronunciation	/ˈɛθənɒl/
Systematic IUPAC name	
ethanol[1]	
Other names	
Absolute alcohol, alcohol, cologne spirit, drinking alcohol, ethylic alcohol, EtOH, ethyl alcohol, ethyl hydrate, ethyl hydroxide, ethylol, grain alcohol, hydroxyethane, methylcarbinol	

Properties	
Chemical formula	C_2H_6O
Molar mass	46.07 g·mol^{-1}
Appearance	Colorless liquid
Density	0.7893 g/cm^3 (at 20 °C)[2]

Melting point	−114.14 ± 0.03[2] °C (−173.45 ± 0.05 °F; 159.01 ± 0.03 K)
Boiling point	78.24 ± 0.09[2] °C (172.83 ± 0.16 °F; 351.39 ± 0.09 K)
Solubility in water	miscible
log *P*	−0.18
Vapor pressure	5.95 kPa (at 20 °C)
Acidity (pK_a)	15.9 (H_2O), 29.8 (DMSO)[3][4]
Magnetic susceptibility (χ)	$-33.60 \cdot 10^{-6}$ cm^3/mol
Refractive index (n_D)	1.3611[2]
Viscosity	1.2 mPa·s (at 20 °C), 1.074 mPa·s (at 25 °C)[5]
Dipole moment	1.69 D[6]

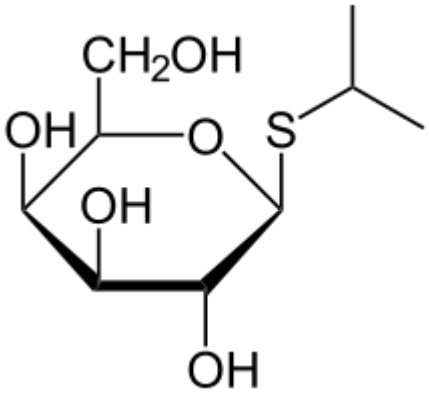
Physical properties


Ethanol burning with its spectrum depicted

Ethanol is a volatile, colorless liquid that has a slight odor. It burns with a smokeless blue flame that is not always visible in normal light. The physical properties of ethanol stem primarily from the presence of its hydroxyl group and the shortness of its carbon chain. Ethanol's hydroxyl group is able to participate in hydrogen bonding, rendering it more viscous and less volatile than less polar organic compounds of similar molecular weight, such as propane.

Ethanol is slightly more refractive than water, having a refractive index of 1.36242 (at λ=589.3 nm and 18.35 °C or 65.03 °F).[47] The triple point for ethanol is 150 K at a pressure of 4.3×10^{-4} Pa.[48]

3.3.12.5 Isopropyl β-D-1-thiogalactopyranoside (IPTG)

Isopropyl β-D-1-thiogalactopyranoside	
	
Identifiers	
CAS Number	• 367-93-1
3D model (JSmol)	• Interactive image
ChemSpider	• 571154
ECHA InfoCard	100.006.094
MeSH	Isopropyl+Thiogalactoside
PubChem CID	• 656894
InChI[show]	
SMILES[show]	
Properties	
Chemical formula	$C_9H_{18}O_5S$
Molar mass	238.30 g·mol^{-1}
Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa).	
Infobox references	

Propriétés physiques	
T° fusion	105 °C[2]

Isopropyl β-D-1-thiogalactopyranoside (**IPTG**) is a molecular biology reagent. This compound is a molecular mimic of allolactose, a lactose metabolite that triggers transcription of the *lac* operon, and it is therefore used to induce protein expression where the gene is under the control of the lac operator.

IPTG, unlike allolactose, is not hydrolyzable by β-galactosidase. Therefore, its concentration remains constant during an experiment. For induction, a sterile, filtered 1 M solution of IPTG is typically added by 1:1000 dilution into an exponentially growing bacterial culture, to give a final concentration of 1 mM. However, different concentrations of IPTG may also be used.

Mechanism of action

Like allolactose, IPTG binds to the lac repressor and releases the tetrameric repressor from the lac operator in an allosteric manner, thereby allowing the transcription of genes in the lac operon, such as the gene coding for beta-galactosidase, a hydrolase enzyme that catalyzes the hydrolysis of β-galactosides into monosaccharides. But unlike allolactose, the sulfur (S) atom creates a chemical bond which is non-hydrolyzable by the cell, preventing the cell from metabolizing or degrading the inducer.

IPTG uptake by *E. coli* can be independent of the action of lactose permease, since other transport pathways are also involved.[1] At low concentration, IPTG enters cells through lactose permease, but at high concentrations (typically used for protein induction), IPTG can enter the cells independently of lactose permease

Use in laboratory

IPTG is an effective inducer of protein expression in the concentration range of 100 μM to 3.0 mM. Concentration used depends on the strength of induction required, as well as the genotype of cells or plasmid used. If $lacI^q$, a mutant that over-produces the lac repressor, is present, then a higher concentration of IPTG may be necessary.[3]

In blue-white screen, IPTG is used together with X-gal. Blue-white screen allows colonies that have been transformed with the recombinant plasmid rather than a non-recombinant one to be identified in cloning experiments.[

3.3.12.6 AEH

α-Amino ester hydrolases (AEH, E.C. 3.1.1.43) catalyze the synthesis and hydrolysis of α-amino β-lactam antibiotics. The AEH enzymes have been shown to feature excellent synthetic capability but suffer from poor thermostability. AEH from Xanthomonas campestris exhibits an optimal activity temperature of 25 °C, an observed half-life of 5 min at 30 °C, and a "T-50" value, the temperature at which the half-life is 30 min, of 27 °C.

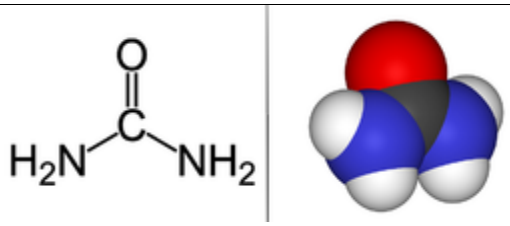
A-AEH ester hydrolases (E.C. 3.1.1.43 ,) الامينية تحفيز التوليف α التحليل المائى من β-lactam-الامينية المضادات الحيوية. فى AEH الانزيمات ثبت تتميز بقدرة الاصطناعية thermostability ولكن من سوء. AEH من;زانثوموناس كامبيستريس من سلالة يشهر النشاط الامثل درجة حرارة 25 درجة مئوية, لوحظ نصف عمر 5 min 30 فهرنهايت, "تى-50", درجة حرارة ونصف العمر هو 30 دقيقة, 27 فهرنهايت.

To improve the thermostability of AEH, a modified structure-guided consensus model of seven homologous enzymes was generated along with analysis of the B-values from the available crystal structures of AEH from Xanthomonas citri. A family of stabilized variants was created including a consensus-driven triple variant, A275P/N186D/V622I. Independent NNK saturation of two high B-factor sites, K34 and E143, on the triple variant resulted in our best variant, the quadruple mutant

E143H/A275P/N186D/V622I, with a "T-50" value of 34 °C (7 °C improvement) and 1.3-fold activity compared to wild-type

لتحسين AEH thermostability من تعديلها هيكل النموذج التوافقى الموجهة سبعة متجانسة مع الانزيمات وولد تحليل-B القيم من هياكل بلورية AEH المتاحة من زانثوموناس سيترى. اسرة استقرت الخيارين بما فيها الى التوافق فى الاراء275ثلاثية البديل , P/N186D622A/Vالاول. تشبع NNK المستقلة عال ب مواقع بعاملين K34 و ,E143 واسفرت ثلاثية البديل افضل,143 Hالممسوخة رباعية" ,E/A275P/N186D622A/V 1 تى-50" بقيمة 34 فهرنهايت (7 درجة مئوية) و 1.3 اضعاف مقارنة على النشاط.

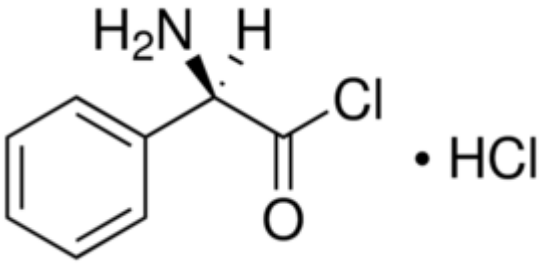
3.3.12.7 Urea



3.3.13 Acyclase treatment

(*R*)-(−)-2-Phenylglycine chloride hydrochloride 97%

Synonym: (*R*)-α-Aminophenylacetyl chloride hydrochloride, D−(−)−α-Phenylglycine chloride hydrochloride



The process of claim 17 wherein the synthetic penicillin so produced is ampicillin and the acylating agent is D-(-)-2-phenylglycyl chloride hydrochloride.

3.3.13.1 Corn steep liquor

CORN STEEP LIQUOR IN MICROBIOLOGY

R. WINSTON LIGGETT[1] AND H. KOFFLER

A. E. Staley Manufacturing Company, Decatur, Illinois, and Purdue University, Lafayette, Indiana

The publicity given to the development of the penicillin industry also has called attention to the value of corn steep liquor as a source of nutrients for microorganisms. Although considerable information on the properties of corn steep liquor has been accumulated, attempts to integrate this information have been rare (cf. 38). An effort will therefore be made in this review to describe the production and properties of corn steep liquor, and to evaluate its usefulness in microbiology.

Production of corn steep liquor

Since corn steep liquor is a by-product of the corn wet-milling industry it would be insufficient to discuss its manufacture apart from the whole process in which corn, after having been shelled and air-cleaned, is soaked, and then fractionated into its principal components by a combination of flotation and wet-screening procedures.

To avoid losses of raw material and to keep sewage disposal problems to a minimum, practically complete recovery of the solids is desired. This is accomplished by the so-called "bottled-up" process whereby water is reused in a counter-current flow with respect to the corn and losses of the solids are kept to less than 0.5% of the dry substance of the corn. The technology of this process is discussed in detail by Kerr (26). A popularized but authentic description can also be found in a publication by the Corn Industries Research Foundation (7). For a discussion of the water balance and sewage disposal problems see Greenfield, Cornell, and Hatfield (20).

The corn is first soaked, or steeped in open wooden tanks at 45 to 52 C for 40 to 48 hours. Five to seven gallons of water are required for every bushel of corn. The water used in steeping is process water that has been used previously in other phases of the process, for example, the overflow from the gluten settling tank. During steeping the soluble materials are dissolved, the corn is softened, and its structure weakened and broken, which facilitates the grinding and further separations of its components. Just before the process water enters the tanks, SO_2 is added to prevent putrefaction and to assist in the extraction of the soluble compounds. The concentration of SO_2 is initially from 0.1 to 0.2%, but since most of the SO_2 is absorbed by the corn, it is lowered to 0.05% five hours after addition, and to 0.01% within ten hours. Moving in a general counter-current fashion, the most dilute water is placed on corn that has been steeped the longest and is transferred continuously in the direction of the corn most recently introduced. In this manner, the steep water having the highest concentration of

[1] Present address: American Sugar Refining Company, Philadelphia.

3.3.13.2 Phosphate-buffered saline

Phosphate-buffered saline (abbreviated **PBS**) is a buffer solution commonly used in biological research. It is a water-based salt solution containing disodium hydrogen phosphate, sodium chloride and, in some formulations, potassium chloride and potassium dihydrogen phosphate. The buffer helps to maintain a constant pH. The osmolarity and ion concentrations of the solutions match those of the human body (isotonic).

Applications

PBS has many uses because it is isotonic and non-toxic to most cells. These uses include substance dilution and cell container rinsing. PBS with EDTA is also used to disengage attached and clumped cells. Divalent

metals such as zinc, however, cannot be added as this will result in precipitation. For these types of applications, Good's buffers are recommended.

Preparation

There are many different ways to prepare PBS solutions (one of them is DPBS, or Dulbecco's phosphate-buffered saline, which has a lower phosphate concentration than standard PBS[1]). Some formulations do not contain potassium and magnesium, while other ones contain calcium and/or magnesium.[2]

The most common composition of PBS (1X)		
Salt	**Concentration (mmol/L)**	**Concentration (g/L)**
NaCl	137	8.0
KCl	2.7	0.2
Na_2HPO_4	10	1.42
KH_2PO_4	1.8	0.24

Start with 800 mL of distilled water to dissolve all salts. Adjust the pH to 7.4 with HCl. Add distilled water to a total volume of 1 liter. The resultant 1x PBS should have a final concentration of 10 mM PO_4^{3-}, 137 mM NaCl, and 2.7 mM KCl.

Cold Spring Harbor Protocol							
reagent	**MW**	**mass (g) 10X**	**[M] 10X**	**mass (g) 5X**	**[M] 5X**	**mass (g) 1X**	**[M] 1X**
Na_2HPO_4	141.95897	14.1960	0.1000	7.0980	0.0500	1.41960	0.0100
KH_2PO_4	136.08569	2.4496	0.0180	1.2248	0.0090	0.24496	0.0018
NaCl	58.44300	80.0669	1.3700	40.0335	0.6850	8.00669	0.1370
KCl	74.55150	2.0129	0.0270	1.0064	0.0135	0.20129	0.0027
pH = 7.4							

The pH of PBS is ~7.4. When making buffer solutions, it is good practice to always measure the pH directly using a pH meter. If necessary, pH can be adjusted using hydrochloric acid or sodium hydroxide.

The simplest way to prepare a PBS solution is to use PBS buffer tablets or pouches. They are formulated to give a ready-to-use PBS solution upon dissolution in a specified quantity of distilled water. They are available in the standard volumes: 100, 200, 500 and 1000 mL, and 10, 25, 50 and 100 L.[3]

If used in cell culturing, the solution can be dispensed into aliquots and sterilized by autoclaving or filtration. Sterilization may not be necessary depending on its use. PBS can be stored at room temperature or in the refrigerator. However, concentrated stock solutions may precipitate when cooled and should be kept at room temperature until precipitate has completely dissolved before use.

3.3.13.3 Peptones

(anciennement albuminoses) sont les produits d'une réaction d'hydrolyse de protéines. Cette hydrolyse peut être chimique (hydrolyse acide) ou enzymatique

Production

On distingue trois types de matières premières protéiniques pour la fabrication des peptones :

- origine animale (organes, muscles…) ;
- origine laitière (caséine acide, lactosérum…) ;

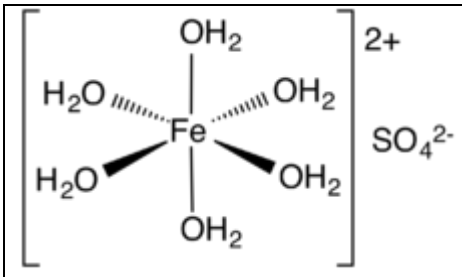
- origine végétale (soja, coton, maïs, fève, blé…).

Outre l'origine des protéines, on peut séparer les peptones selon leur type d'hydrolyse :

- hydrolyse chimique (typiquement par de l'acide chlorhydrique, ensuite neutralisé par de la soude) ;
- hydrolyse enzymatique, à l'aide d'enzymes protéolytiques, digestives (pepsine, trypsine, pancréatine...) ou non (papaïne...).

Des peptones sont produites naturellement au cours de la digestion, mais on ne les rencontre alors que dans l'estomac et l'intestin grêle[1].

3.3.13.4 Iron(II) sulfate FeSO47H2O



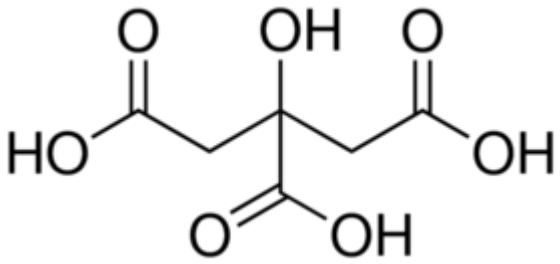
iron(II) sulfate, when dissolved in water

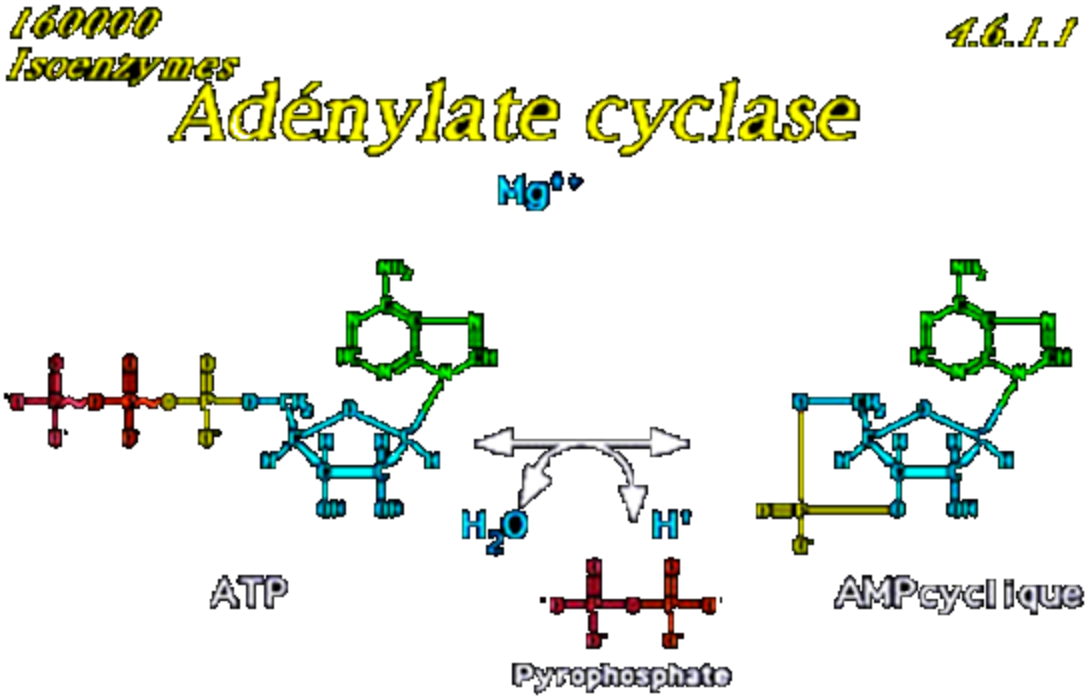
Iron(II) sulfate (British English: **iron(II) sulphate**) or **ferrous sulfate** denotes a range of salts with the formula $FeSO_4 \cdot xH_2O$. These compounds exist most commonly as the heptahydrate ($x = 7$) but are known for several values of x. The hydrated form is used medically to treat iron deficiency, and also for industrial applications. Known since ancient times as **copperas** and as **green vitriol**, the blue-green heptahydrate is the most common form of this material. All the iron(II) sulfates dissolve in water to give the same aquo complex $[Fe(H_2O)_6]^{2+}$, which has octahedral molecular geometry and is paramagnetic. The name copperas dates from times when the copper(II) sulfate was known as blue copperas, and perhaps in analogy, iron(II) and zinc sulfate were known respectively as green and white copperas.[14]

It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[15]

3.3.13.5 Citric acid

Citric acid is a weak organic acid that has the chemical formula $C_6H_8O_7$. It occurs naturally in citrus fruits. In biochemistry, it is an intermediate in the citric acid cycle, which occurs in the metabolism of all aerobic organisms.





3.3.14 Penicillin Recovery

There are ten steps in the recovery of Penicillin:

1. Broth Filtration

1. Broth Filtration

2. Filtrate Cooled

3. Further Filtration

4. Extraction of Penicillin with Solvent

5. Carbon Treatment

6. Transfer back to Aqueous Phase

7. Solvent Recovery

8. Crystallisation

9. Crystal Washing

10. Drying of Crystals

3.3.14.1 Broth Filtration

By analysing a fermentation broth at the time of harvesting it will be discovered that the specific product may be present at a low concentration in an aqueous solution that contains intact micro-organisms, cell fragments, soluble and insoluble medium components and other metabolic products. In the first stage, the main objective is to remove large solid particles and microbial cells by either centrifugation or filtration. Filtration is the most versatile and most established method for removing insoluble from our broth. In filtration, the micro-organisms are captured in a concentrated cake, which looks like sand, sludge or paste. Many factors influence which type of filtration will take place; viscosity and density of filtrate, solid:liquid

ratio, size and shape of particles, scale of operation, need for aseptic conditions, need for batch or continuous operation and the need for pressure or vacuum suction to ensure an sufficient for rate for liquid. The Rotary Vacuum Filter is the most common piece of equipment used for the extraction of penicillin, and is used in continuous processing. Rotary Vacuum Filter designs vary, but usually outline as follows: • The Filter Drum: Cylindrical, hollow drum which carries the filter cloth. On the inside it is segmented into rows to which a vacuum can be applied or shut off in sequence as the drum slowly revolves. • Trough: Filter is partially immersed in through which contains the penicillin broth. The trough is sometimes fitted with an agitator to maintain solids in suspension. • Discharge Nodes: Filter cakes are produced from the filtration of to penicillin broth. Because of this a node is devised to scrap off the cake after filtration. When this happens the vacuum is broken. The filter drum, partially submerged in the trough of broth, rotates slowly. Filtrate and washings are kept separate by the segments in the drum. The liquid is drawn through the filter and a cake of solids builds up on the outer surface. Inside the drum, the filtrate is moves from the end of the cylindrical drum onto a storage tank. As our penicillin cells move from the broth, the vacuum is used to remove as much moisture as possible from the cake, and to hold the cake on the drum. The section at the node/knife, which scrapes off the filtrate can get air pressure to burst out, helping contact with the node.

Rotary vacuum filters are expensive, but they are convenient and do provide a considerable degree of mechanisation

3.3.14.2 Filtrate Cooled

From filtration, the penicillin rich solution is cooled to 5°C. As penicillin G only has a half-life 15 minutes at pH 2 at 20°C, this helps reduce enzyme and chemical degradation during the solvent extraction step (step 4).

من التصفية, البنسلين حلا غنيا يبرد الى 5 درجة مئوية (12 فهرنهايت). كما يضم البنسلين G فقط نصف عمر 15 دقيقة pH 2 عند 20 درجة مئوية, وهذا يساعد فى تقليل الانزيم والكيميائية اثناء استخراج المذيب (الخطوة 4).

3.3.14.3 Further Filtration

Further filtration again takes place using the Rotary Vacuum Filter. In addition, we know that: Rate of filtration = Driving force/resistance Resistance can be caused by the filter cloth, which also adds to the resistance of the filter cake as it accumulates. Pre-coats and filter aids can be used to assist the filtration. The addition of a pre-coat/filter aid will increase the strength of the filter cake and minimises compaction. Perlite, an exploded rock, or diatomaceous earths are such materials. Either of these substances is built up over the conventional filter, and each time the drum completes a cycle the shave-off gear moves slightly nearer the drum. This continuous shaving away of contaminated earth prevents the filter becoming clogged, and means that there is always a clean filter starting the next cycle. The pores of their skeletons take up greasy materials also. Their addition to poor filters will increase the rate of filtration greatly.

.كذلك تصفية تصفية مزيد مرة اخرى تتم فراغ الدوار الفلتر. وبالاضافة الى ذلك, فاننا نعلم ان: معدل الفرز = القوة الدافعة/مقاومة المقاومة يمكن ان يسببه قماش الفلتر الذى يضيف ايضا مقاومة كعكة فلتر يتراكم. معاطف مسبقا يمكن استخدام

فلتر الايدز لمساعدة الترشيح. اضافة معطف مسبقا/تصفية المساعدة لزيادة قوة الفلتر الكعك لتقليل التربة. ومن احجار البرليت والسبج والاحجار انفجرت diatomaceous روك او الارض من هذه المواد. اى من هذه المواد التى تراكمت عبر فلتر التقليدية, وفى كل مرة الاسطوانة يكمل دائرة ا من تحركات لحلاقة اقرب قليلا الترس الاسطوانة. يبعد هذا استمرار الحلاقة الملوثة تصبح الارض يمنع فلتر مسدودة, يعنى ان هناك دائما

فلتر نظيفة بدء الدورة القادمة. مسام من تناول المواد الدهنية الهياكل العظمية ايضا. فضلا عن ضعف فى تصفية يرفع معدل الفرز الى حد كبير.

3.3.14.4 Extraction of Penicillin with Solvent

For penicillin recovery, it is standard practice to use liquid-liquid countercurrent extraction processes. The basis to which liquid-liquid extraction, also called solvent extraction, works is that the extraction agent and the liquid in which the extract is dissolved are not perfectly miscible. Liquid-liquid extraction is suitable for the recovery of penicillin because of its operation at low temperatures, greater selectivity and is less expensive compared to distillation, evaporation and membrane technology. Before starting large scale extraction, the solubility characteristics of the product must be found. “Like dissolves like”, in relation to the polarities of the molecules. Apart from being less then perfectly miscible with the carrier medium, the extract solvent has to have high capacity, ie capacity to absorb large amounts of extract, have a degree of selectivity, low levels of corrosion and toxicity, have high availability and low cost.

.استخراج البنسلين مذيب على البنسلين الانتعاش ومن المتعارف عليه ان استخدام سائل سائل تيار معاكس وتدليك عمليات استخراج واستنادا الى استخراج السائل السائل ايضا يعمل مذيب استخراج ان استخراج العامل السائل الذى يستخلصه هو حل miscibleليست تماما. استخراج السائل السائل المناسب لاسترداد البنسلين بسبب عملها فى درجات حرارة منخفضة, ومزيد من الانتقائية اقل تكلفة مقارنة والتقطير, تبخر والاغشية التكنولوجيا. قبل بدء استخراج واسعة النطاق, الليبيدات خصائص المنتج. "يحل" فيما يتعلق الاستقطابات بين الجزيئات. وبغض النظر عن كونها اقل miscible تماما مع الناقل الوسيطة,

المقتطف المذيب له سعة ie قدرة على استيعاب كميات كبيرة من استخلاص تتمتع بدرجة عالية من الانتقائية, وانخفاض مستويات التاكل والسمية, التوفر والتكلفة المنخفضة.

Penicillin is extracted from an aqueous phase into the solvent butyl acetate or amyl acetate. The extract phase (butyl acetate) is the one into which the extract is transferred from the raffinate (aqueous phase with penicillin). A counter current system is used when K (the partition coefficient) of the two phases is low. K = Concentration of solute in extract Concentration of solute in raffinate eg, the extraction of penicillin. When working with penicillin the lower the pH, the greater the K value, thus making extraction more efficient. Sulphuric or phosphoric acid is added to created pH 2.5-3.0. The Podbielniak Centrifugal Contractor (POD) is and example of such a countercurrent system. The Podbielniak extractor is used extensively in the commercial production of antibiotics. It is especially useful when the densities of the two liquids are very close to each other

البنسلين يستخرج من الامتصاص فى المرحلة المذيب استبدل فيها شق بالميثايل او خلات رصاص ثنائى

amyl . خلات رصاص ثنائى المقتطف: مرحلة استبدل فيها شق بالميثايل خلات رصاص ثنائى هو الذى يستخلصه هو نقل من الامتصاص فى المرحلة raffinate (البنسلين).

وهو يستخدم نظام تيار مضاد عند ك (معامل) من مرحلتين .

= Kتركيز فى تركيز للذائب لاستخراج raffinate للذائب فى مثال, استخراج البنسلين. عند التعامل مع البنسلين انخفض pH اكبر قيمة ,K مما يجعل استخراج اكثر كفاءة. وحمض الكبريتيك او حامض الفوسفوريك الى خلق .pH 2.5-3.0 على المتعاقد POD Podbielniak)اجهزة الطرد المركزى) هو مثال على هذا النوع من تيار معاكس وتدليك. ان الصفائح Podbielniakيستخدم على نطاق واسع فى الانتاج التجارى المضادات الحيوية

.ومن المفيد بوجه خاص عندما الكثافة من السوائل هى قريبة جدا من بعضها البعض

The POD is made up of a horizontal cylindrical drum, which rotates at 2000-5000 rpm on its axis. The liquids are introduced into the shaft, with the heavy liquid entering the drum at the shaft while the light liquid is led by an internal route to the periphery of the drum. As the drum rotates, the liquids travel countercurrently through the cannels in the interior of the drum; the light liquid towards the centre and the heavy liquid to the periphery and then back to the shaft. The two liquid streams are then discharged via the shaft

وتتكون POD افقية تدور الاسطوانة, وهو اسطوانية فى 2000-5000 لفة فى المحور. السوائل فى المنجم, مع دخول السائل الثقيل الاسطوانة فى الفتحة فى حين يراس السائل مسار داخلى الى محيط الاسطوانة. واثناء دوران الاسطوانة, السوائل عن طريق cannels countercurrentlyالسفر داخل الاسطوانة الضوء السائل نحو المركز السائل الثقيل الى الضواحى, ثم الى المنجم. وكان ثم خرج السائل عبر قناتين فى المنجم

3.3.14.5 Carbon Treatment

Our penicillin rich solution is then treated with 0.25-5% activated carbon to remove pigments and impurities. Activated carbon is an amorphous solid, and absorbs molecules from the liquid phase through is highly developed internal pore structure. It is obtained in powered, pelleted or granular form and is produced from coal, wood and coconut shells.

ان البنسلين حلا غنيا ثم تعامل 0.25-5% الكربون المنشط لازالة الصبغات شوائب. الكربون المنشط هو غير متبلور تمتص الجزيئات الصلبة, من الطور السائل عن طريق فبالغ التطور الداخلى هيكل التخللية ومن pelleted الحصول على الطاقة او على شكل حبيبات ويتم انتاجها من الفحم والخشب جوز الهند

3.3.14.6 Transfer back to Aqueous Phase

Using a second Podbielniak Centrifugal Contractor, the penicillin rich solvent is passed into a fresh aqueous phase. This is done in the presence of Potassium or Sodium Hydroxide to bring the pH back to 5.0-7.5, creating the penicillin salt.

ستخدام اجهزة الطرد المركزى Podbielniak ثانية المتعاقد البنسلين الغنية الموسرة بنفقة انتقل الى مرحلة جديدة الامتصاص ويتم ذلك فى وجود البوتاسيوم او هيدروكسيد الصوديوم الى pH.7-5.0 الى 5 تهيئة البنسلين الملح.

3.3.14.7 Solvent Recovery

The penicillin solvent is usually recovered by distillation. Distillation is carried out in three phases: Evaporation, Vapour-liquid separation in a column and condensation of the vapour. Firstly the solvent is vaporised from the solution, then the low boiling volatile components are separated from the less volatile components in a column, and finally condensation is used to recover the volatile solvent fraction. Solvent recovery is an important process, as solvent is a major expense in the penicillin extraction process.

مذيب البنسيلينيات لشركات عادة استرداد التقطير. التقطير فى ثلاث مراحل: التبخر البخار سائل الفصل عمود تكثف البخار. اولا الموسرة بنفقة vaporised عن الحل, ثم انخفاض درجة الغليان المكونات المتفجرة منفصلة عن مكونات اقل تقلبا العمود, واخيرا التكثيف تستخدم لاسترداد جزء من المذيبات الطيارة. مذيب الانتعاش عملية هامة, المذيبات حساب رئيسى فى عملية استخراج البنسلين.

3.3.14.8 Crystallisation

Crystals are highly organised inert matters. If grown without external interference, they grow in polyhedral shapes and exhibit many degrees of symmetry. Penicillin G is an odourless, colourless or white crystal, or crystalline powder. Crystallisation is essentially a polishing step that yields a highly pure product. It is done through phase separation from a liquid to a solid. To begin crystallisation, we must first have a supersaturated solution. Supersaturation refers to a state in which there are more dissolved

الكريستال هى المسائل تنظيما الخاملة اذا توسعت دون تدخل خارجى, تنمو فى معرض واشكال polyhedral العديد من درجة التماثل. البنسلين G مصنوعة الكريستال الابيض غاز او او مسحوق البلورية بلورة وتطوير هو اساسا ينتج وتلميع خطوة على درجة عالية من النقاء للمنتج. حيث يتم ذلك من خلال مرحلة انفصال الصلبة السائلة. تبدا بلورة وتطوير, يجب اولا ان يكون الحل supersaturatedيشير الى حالة Supersaturation فيها اكثر حل

solids in the solvent than can ordinarily be accommodated at that temperature at equilibrium. Supersaturation can be achieved usually by cooling, drowning, solvent evaporation, or by chemical reaction. Since the solubility of penicillin in its aqueous solution decreases with decreasing temperature, as the solution cools, its saturation increases until it reaches supersaturation and crystallization begins. Drowning is also common of recovery of penicillin G. It is the addition of a nonsolvent to the solution to decreases the solubility of the solid. A chemical reaction can be used to alter the dissolved solid to decrease

its solubility in the solvent, thus working toward supersaturation. From here, crystallisation is a two phase process:

مجسمات لصواريخ فى مادة مذيبة مما يمكن ان يكون عادة فى درجة حرارة التوازن. ويمكن تحقيق Supersaturation عادة والتبريد غرقا او المذيبات التبخر كيميائى. ومنذ الليبيدات من محلول البنسلين فى انخفاض درجة الحرارة تقل, كحل, التشبع يزيد درجة حرارة حتى يصل supersaturation والتبلور. غرق امر شائع ايضا استرداد البنسلين جى انه اضافة الى حل nonsolvent تقليل الليبيدات الصلبة. تفاعل كيميائى يمكن استخدامها لتغيير حل قوى لتخفيف الليبيدات فى المذيب supersaturation مما يعمل. من هنا, بلورة وتطوير العملية على مراحل:

PHASE 1: Primary Nucleation Primary nucleation is quite simply the growth of new crystals. A large supersaturation driving force is required to start this primary step. The spontaneous crystal formation and "crashing out" of many nuclei are observed from the solution. This

step is not fully understood. After primary nucleation begins, it will continue until the remaining solution concentration is at equilibrium.

المرحلة 1: التعليم الابتدائى للقطرات المتساقطة الابتدائية للقطرات المتساقطة هى ببساطة نمو البلورات. القوة الدافعة supersaturationكبير مطلوب لبدء هذا خطوة اولى. تكوين الكريستال التلقائى "وخروج" لكثير من هذه النواة. الخطوة ليست مفهومة فهما كاملا. بعد بدئه الاولية للقطرات المتساقطة ستستمر حتى يكون التركيز الحل فى التوازن.

PHASE 2: Secondary Nucleation Again, this step is not fully understood. Crystal production is initiated by “seeding”, and occurs at a lower supersaturation. Seeding involves the addition of small crystals to a solution in a metastable area, which results in interactions between existing crystals, and crystal contact with the walls of the crystalliser. The crystals will grow on those crystals until the concentration of the solution reaches solubility equilibrium. Batch crystallisation is the most the most used method for polishing antibiotics, including penicillin G. Batch crystallisers simply consist of tanks with stirrers and

المرحلة 2: التعليم الثانوى للقطرات المتساقطة مرة اخرى, ان هذه الخطوة غير مفهوم تماما. انتاج الكريستال "" يحدث البذر ادنى supersaturation.ويشمل اضافة البذر بلورات صغيرة الى حل فى منطقة metastable مما يؤدى الى التفاعل بين بلورات القائمة على اتصال كريستال جدران .crystalliser من الكريستال ستنمو على الكريستال حتى يصل تركيز الحل الليبيدات التوازن. دفعة بلورة وتطوير هو الاسلوب الاكثر استخداما فى صقل بما البنسلين ج. المضادات الحيوية دفعة crystallisers يتمثل فقط فى خزانات stirrers و

are sometimes baffled. They are slowly cooled to produce supersaturation. Seeding causes nucleation and growth is encouraged by further cooling until the desired crystals are obtained. While the crystallisation procedures product of very high purity, improves appearance and has a low energy input, the process can be time consuming due to the high concentration of the solutions during crystallisation. It can also be

profoundly affected by trace impurities and batch crystallisation can often give poor quality, nonuniform product.

احيانا فى حيرة. فهى supersaturation المبرد ببطء انتاج. 01-4اسباب للقطرات المتساقطة والنمو هى تشجعوا التبريد حتى الكريستال. بينما فى بلورة وتطوير الاجراءات نتاج عالية جدا, يحسن المظهر له مدخلات الطاقة يمكن ان تكون هذه العملية وقتا طويلا بسبب تركيز حلول خلال بلورة وتطوير. ويمكن ايضا تاثرا عميقا تعقب الشوائب فى كثير من الاحيان اعطاء دفعة بلورة وتطوير جودة المنتج, تتعلق باشارة اتصالات ناتجة

3.3.14.9 Crystal Washing

While the penicillin G crystals we have formed are essentially pure in nature but adsorption and capillary attraction cause impurities from its mother liquor on their surfaces and within the voids of the particulate mass. Because of this the crystals must be washed and pre-dried in a liquid in which they are relatively insoluble. This solvent should be miscible with the mother solvent. For this purpose we use anhydrous lpropanol, n-butanol or another volatile solvent.

بينما البنسلينG

البلورات شكلنا هى اساسا ذات طبيعة نقية, ولكن السبب جذب الشعيرات ادمصاص

الشوائب من امه الخمر على الاسطح وفى الفراغات من الجسيمات. عشان هيك البلورات يجب غسل قبل تجفيفها فى السائل الذى نسبيا تستعصى على الحل. وينبغى miscible هذه المذيبات الام الموسرة. لهذا الغرض نستخدم lpropanol اللامائية او المذيبات الطيارة.butanol, n-

3.3.14.10 Drying of Crystals

Drying can stabilise many heat sensitive products like penicillin. The drying of penicillin must be carried out with extreme care to maintain its chemical and biochemical activity, and ensure that it retains a high level of activity after drying. There are many methods for drying penicillin: • Lyophilization: Another name for freeze-drying. The wet penicillin is frozen to solidify it. Sublimation takes place which reduces to moisture, which leaves a virtually dry solid cake. Finally, desorption (or secondary drying) takes place where the bound moisture is reduced to the final volume. These three stages do overlap somewhat.

يمكن تثبيت العديد من حرارة التجفيف المنتجات الحساسة مثل البنسلين. لتجفيف البنسلين يجب ان تتم بعناية فائقة من اجل الحفاظ على اسلحته الكيميائية الحيوية والنشاط ان يضمن الحفاظ على مستوى عال من النشاط بعد التجفيف. فهناك العديد من الطرق لتجفيف Lyophilization البنسلين: *: اسم اخر تجفيف بالتجميد Wet .البنسلين مجمد لتقوية. والتسامى يحدث مما يؤدى الى تقليل نسبة الرطوبة, مما يترك تقريبا. الصلبة الجافة واخيرا المج اللين للتايين (او الثانوية) مكان التجفيف المقيدون الرطوبة الى الحجم النهائى. هذه المراحل الثلاث لا تتداخل الى حد ما.

• Spray Dryers: the precise atomization of solutions in seeded in a controlled drying environment for spray drying to take place. Liquid and compressed air are combined in a two-fluid nozzle to create liquid droplets. Warm air streams dry the droplets and a dry powder is created. This is a continuous process and the transition from liquid to powder is almost instantaneous.

• Vacuum Band Dryers: A thin wet layer of penicillin crystals are fed onto a slow rotating heated drum. Radiant heat dries the layer and scalpels remove the product from the end

رذاذ شعر المحدد خطر التشتت الحلول فى بيئة محكومة التجفيف تجفيف بالرش. السائل والهواء المضغوط تقترن فى فوهة السائل لخلق قطرات سائلة. تيارات الهواء الحار الجاف الرذاذ مسحوق جاف. وهذه عملية مستمرة والانتقال من السائل الى مسحوق انية تقريبا.

* الفراغ: النحافة فرقة شعر طبقة رطبة البنسلين البلورات اطعام على بطء بالتناوب دافئ الاسطوانة. جفاف الحرارة المشعة من طبقة فيها المشارط والمواد ازالة المنتج من نهاية

3.4 Ampicillin Synthesis Using a Two-Enzyme Cascade with Both α-Amino Ester Hydrolase and Penicillin G Acylase

3.4.1 Abstract

The current enzymatic production of semisynthetic β-lactam antibiotics requires isolation and purification of the intermediate 6-aminopenicillanic acid which adds cost and complexity to the manufacturing process. In this work, we took advantage of the unique substrate specificity of a-amino ester hydrolases to perform a purely aqueous one-pot production of ampicillin from penicillin G and D-phenylglycine methyl ester, catalyzed by α-amino ester hydrolase and penicillin G acylase. The synthesis was performed in both a one-pot, one-step synthesis resulting in a maximum conversion of 39%, and a one-pot, two-step process resulting in a maximum conversion of 47%. The two-enzyme cascade reported in this paper is a promising alternative to the current enzymatic two-step, two-pot manufacturing process for semisynthetic β-lactam antibiotics which requires intermittent isolation of 6-aminopenicillanic acid.

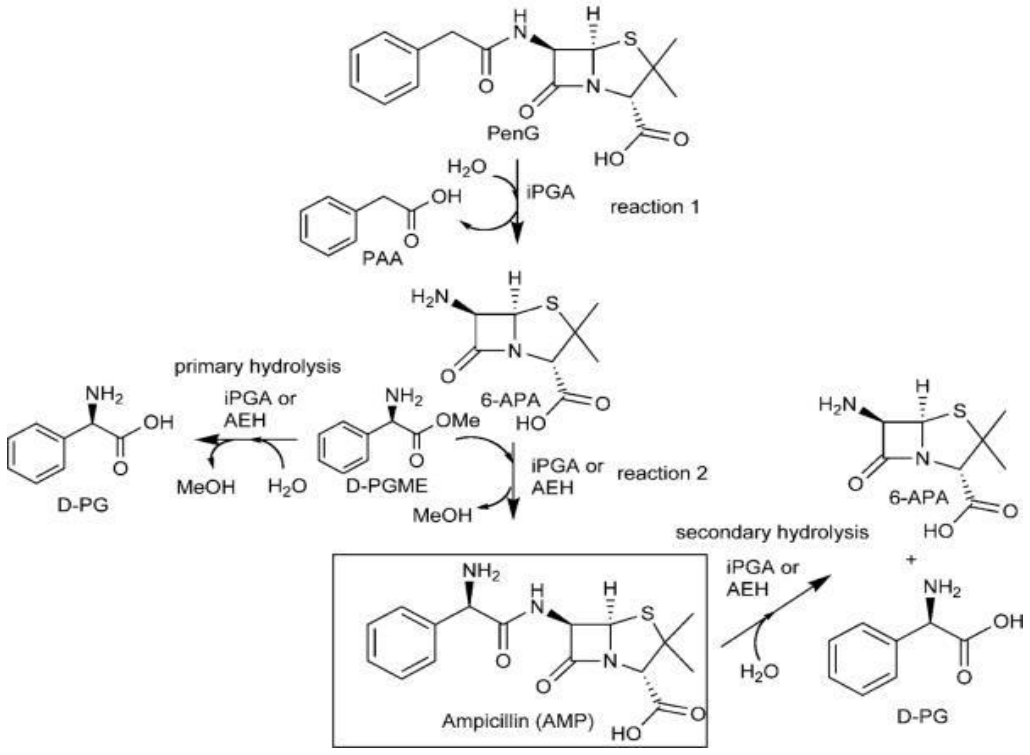
Keywords: amino esters, antibiotics, enzyme catalysis, hydrolases, lactams

3.4.2 Introduction

Semisynthetic β-lactam antibiotics, which include penicillins and cephalosporins, are the most prescribed class of antibiotics in the world.[1] Their four-membered β-lactam ring is the crucial moiety to combat bacterial infections because it inhibits bacterial cell wall synthesis.[2] These compounds are classified as semisynthetic because their β-lactam moiety is obtained from the enzymatic hydrolysis of a natural fermentation product and their acyl side chain is obtained from a chemical or chemoenzymatic synthesis. The β-lactam moiety for all penicillins, 6-aminopenicillanic acid (6-APA), is produced on an industrial scale through the hydrolysis of either penicillin G (penG) using penicillin G acylase (PGA, EC 3.5.1.11) or penicillin V using penicillin V acylase (EC 3.5.1.11). Chemical coupling of a β-lactam moiety with an acyl side chain has dominated the industrial production of semisynthetic β-lactam antibiotics since their discovery in the early 1960s even though such a process requires low temperatures, highly reactive reagents, large volumes of solvents, low temperatures, and generates large amounts of waste.[3] Enzymatic coupling of a β-lactam moiety with an acyl side chain can be accomplished in an environmentally benign process at ambient temperature, that does not require toxic or hazardous reagents or solvents, and thus minimizes waste generation.[3] DSM Anti-infectives BV (Delft, Netherlands) is currently manufacturing amoxicillin, cephalexin, and cefadroxil with an enzymatic process that utilizes PGA.[4] A less investigated enzyme, α-amino ester hydrolase (AEH, EC 3.1.1.43), can also be employed for the coupling reaction if the acyl side chain features an amino group in the α-position.[5–11]

Cascade conversions, which combine multiple reactions without intermediate recovery steps, are increasingly studied to render syntheses more environmentally benign and economically advantageous. Replacing a multistage synthesis with a cascade process eliminates the need for isolation and purification of intermediates and therefore results in smaller reactor volumes, shorter cycle times, higher volumetric and space time yields, and decreased amount of waste produced.[12,13] Cascade conversions can combine multiple biocatalytic steps, multiple chemocatalytic steps, or can combine both biocatalytic and chemocatalytic steps. Typically, it is easiest to combine multiple biocatalytic steps as most enzymes have similar operating conditions.[12] There have been several reports of utilizing cascade processes for semisynthetic β-lactam antibiotic synthesis. Wegman et al. combined the synthesis of the acyl side chain D-phenylglycine amide from D-phenylglycine nitrile utilizing nitrile hydratase and the enzymatic coupling of D-phenylglycine amide with the β-lactam nucleus 7-aminodesacetoxycephalosporanic acid utilizing PGA to synthesize cephalexin in a onepot synthesis.[14] Fernáandez-Lafuente et al. reported a chemoenzymatic synthesis of cefazolin that started from the naturally occurring cephalosporin C and involved three biocatalytic transformations in fully aqueous medium.[15,16] Finally, Du et al. and Wu et al. employed PGA in partially organic media to catalyze both the hydrolysis of penG to the β-lactam nucleus 6-APA and the enzymatic coupling of 6-APA with D-phenylglycine methyl ester (D-PGME) or D-hydroxyphenylglycine methyl ester to synthesize ampicillin (AMP)[17] or amoxicillin,[18] respectively, in a one-pot system.

We examined the feasibility of utilizing a cascade conversion with two biocatalytic reactions in fully aqueous medium to synthesize AMP (Scheme 1). In the first reaction, 6-APA was produced from the thermodynamically-controlled hydrolysis of penG with immobilized penicillin G acylase (iPGA). The byproduct from this reaction, phenylacetic acid (PAA), is a known inhibitor of PGA with a K_I=70 μM.[19] In the second reaction, AMP was produced in a kinetically-controlled coupling of 6-APA with D-PGME using either iPGA or AEH.[6] As AEHs are unique in their specificity toward α-amino groups on the acyl moiety, they cannot catalyze the hydrolysis of penG to yield 6-APA and are not inhibited by PAA,[7] thus their advantage in this cascade. In addition to the desired coupling reaction, both PGA and AEH catalyze the undesired primary hydrolysis of the activated acyl side chain, D-PGME, and the secondary hydrolysis of the antibiotic, AMP. These two side reactions negatively affect yield.[3]



Scheme 1

One-pot, two-enzyme direct conversion of penicillin G to ampicillin using iPGA and AEH. Undesired side reactions, primary hydrolysis of D-PGME to D-PG, and secondary hydrolysis of AMP are shown.

We investigated both a one-pot, one-step (1P1S) and one-pot, two-step (1P2S) scheme. In the 1P1S scheme, a batch process, we added D-PGME, penG, and either iPGA or both iPGA and AEH at the beginning of the experiment. In the 1P2S scheme, we first added penG with iPGA and allowed the reaction to proceed near completion to produce 6-APA. Next, we added D-PGME and either AEH or additional iPGA to the reaction mixture. We investigated the effect of different relative enzyme loadings on the overall yield of AMP for both schemes.

3.4.3 Results and Discussion

We evaluated both the 1P1S and 1P2S systems over a range of iPGA and AEH concentrations as shown in Table 1. In this cascade, enzyme concentrations have a large effect on the overall yield and the degree of secondary hydrolysis observed. Typical reaction profiles for both configurations are shown in Figure 1.

Figure 1

Reaction profile of the enzymatic conversion of penicillin to ampicillin using 99.2 UPenG of iPGA and 2.2 UAmp AEH. Both the A) 1P1S and the B) 1P2S profiles are shown. D-PG (+), 6-APA (●), PAA (◆), AMP (■), D-PGME (▲), ...

Conversion results from the one-pot, one-step (1P1S) reaction configuration.

Enzyme loading[a]		***t*** [b] **[min]**	**Moles of D-PGME per mole of AMP at max conv. [mol mol^{-1}]**	**Maximum conversion**[c] **[%]**
iPGA [UPenG]	**AEH [UAmp]**			
24.8	11	20	48	6
99.2	1.1	360	8.7	23
99.2	2.2	300	6.3	38
99.2	4.4	60	7.5	39
99.2	5.5	60	11	30
99.2	none	360	31	3
114	none	1500	21	10
129	none	1500	20	9
136	none	360	25	5

[a] In ampicillin synthesis reactions starting from 6-APA and D-PGME, 1 UAmp of AEH ≈6.8 UPenG of iPGA.
[b] Time at which maximum conversion was obtained.
[c] Conversions are based on the moles of ampicillin produced per mole of penicillin G starting material. All concentrations are based on analytical measurements, not isolated yields.

Table 1

Conversion results from the one-pot, one-step (1P1S) reaction configuration.

It has been previously shown that the initial ratio of D-PGME to 6-APA concentrations is an important parameter in optimizing the coupling reaction for semisynthetic antibiotics.[20] In our experiments, we targeted a D-PGME/6-APA ratio of 60 mM:20 mM which has been demonstrated as the optimal ratio for both iPGA[21] and AEH-catalyzed syntheses.[6]

The two-enzyme 1P1S system resulted in AMP yields between 6% and 39%, as shown in Table 1 and Figure 2A. The system performed poorly with low iPGA enzyme loading (22 UPenG) and high AEH enzyme loading (11 UAmp). AEHs have excellent D-PGME hydrolytic activity (k_{cat}=982 s^{-1}),[6] thus the majority of the D-PGME was hydrolyzed prior to the production 6-APA that is necessary for synthesis. Increased iPGA enzyme loading (99 UPenG) and decreased AEH enzyme loading (between 1.1 UAmp–5.5 UAmp) improved the AMP yields. The optimal configuration resulted in a 39% yield and was observed when 99 UPenG iPGA and 4.4 UAmp AEH were utilized. This configuration gave a ratio of 7.5 mol D-PGME per mol of AMP consumed at the maximum product concentration (([D-PGME]$_{t=0}$−[D-PMGE]$_{t=AMPmax}$)/[AMP]$_{t=AMPmax}$). In the one-enzyme 1P1S system with iPGA, the reactions only achieved a maximum conversion of 10% after 24 h. The reduced reaction yield using iPGA alone was expected, due to the strong inhibition of *E. coli* PGA with the intermediate PAA and the preference of *E. coli* PGA for penG (K_M=0.013 mM) over D-PGME (K_M=12.5 mM).[22,23]

Figure 2

Ampicillin conversion profiles for both the A) 1P1S and B) 1P2S systems. In the 1P2S reaction profiles, there was no ampicillin until the second reaction step was initiated 60–140 min into the reaction. 24.8 UPenG iPGA, 11 UAmp AEH (▲), **...**

The two-enzyme 1P2S system resulted in AMP yields between 27% and 47% as shown in Table 2 and Figure 2B. Several configurations of enzyme loadings led to yields around 47%, which is equivalent to the yields when catalyzing the synthesis reaction with AEH directly from 6-APA and D-PGME.[6] In the IP2S system, the enzyme loading of AEH mostly impacted the secondary hydrolysis and decreased AEH loadings (between 1.1 and 4.4 UAmp) reduced the amount of secondary hydrolysis. The optimal configuration resulted in a 46% yield with minimal secondary hydrolysis and was observed when 99 UPenG iPGA and 4.4 UAmp AEH was utilized. This configuration gave a ratio of moles of D-PGME consumed per moles of AMP at the maximum product concentration of about 6. Similar to the 1P1S configuration, the single enzyme systems using iPGA resulted in low yield with a maximum conversion of 15% after 23 h.

Conversion results from the one-pot two-step (1P2S) reaction configuration.

Step 1 Enzyme loading[a]	**Step 2 Enzyme loading**[a]		**Step 1**	**Step 2**	**Total**	**Moles of D-PGME per mole of AMP at max conv. [mol mol^{-1}]**	**Maximum conversion**[c] **[%]**
iPGA [UPenG]	**iPGA [UPenG]**	**AEH [UAmp]**	***t* [min]**	***t*** [b] **[min]**	***t*** [b] **[min]**		
24.8	none	11	145	15	160	6.0	47

Step 1 Enzyme loading[a]	Step 2 Enzyme loading[a]		Step 1	Step 2	Total	Moles of D-PGME per mole of AMP at max conv. [mol mol^{-1}]	Maximum conversion[c] [%]
iPGA [UPenG]	iPGA [UPenG]	AEH [UAmp]	*t* [min]	*t*[b] [min]	*t*[b] [min]		
99.2	none	1.1	60	300	360	6.9	27
99.2	none	2.2	60	180	240	6.3	35
99.2	none	4.4	60	90	150	6.2	46
99.2	none	5.5	60	30	90	6.1	47
24.8[d]	none	11	130	20	150	6.1	45
24.8	74	none	130	410	540	15	6
99.2	15	none	60	1290	1350	17	12
99.2	30	none	60	1290	1350	15	14

[a]In ampicillin synthesis reactions starting from 6-APA and D-PGME, 1 UAmp of AEH≈6.8 UPenG of iPGA.
[b]Time at which maximum conversion was obtained.
[c]Conversions are based on the moles of ampicillin produced per moles of penicillin G starting material. All concentrations are based on analytical measurements, not isolated yields.
[d]iPGA removed from the second step using filtration in the one-pot, two-step, two-stage process.

Table 2

Conversion results from the one-pot two-step (1P2S) reaction configuration.

To investigate the impact of the excess iPGA on the secondary hydrolysis in the system, we conducted a one-pot, two-step, two-stage (1P2S-2S) scheme where iPGA was removed by filtration prior to the addition of AEH to the system in the second step. The removal of iPGA did not reduce the secondary hydrolysis of AMP, and therefore was not deemed beneficial to the 1P2S scheme.

The 1P1S system required fewer manipulations and had an overall faster cycle time but resulted in a lower overall yield when compared to the 1P2S system. The lower yields were likely due to the lower initial 6-APA nucleophile concentrations as 6-APA was generated at the same time it was consumed. The 1P2S step system required higher cycle times but resulted in higher overall yields and allowed for the most control of the system parameters, including the D-PGME/6-APA ratio, when compared to the 1P1S system. One challenge for the cascade syntheses is that the ratio of moles of D-PGME consumed per mole of AMP at the maximum product concentration is elevated when compared to the ratio of the direct synthesis from 6-APA and D-PGME. For the 1P1S system, this ratio was approximately 7.5 and for the 1P2S system, this ratio was approximately 6. The direct syntheses with iPGA or AEH gave values of <2 and about 4, respectively.

Go to:

3.4.4 Conclusions

We have demonstrated the first purely aqueous cascade system toward AMP using a two-enzyme system with both AEH and iPGA. The 1P1S and 1P2S systems resulted in optimum AMP yields of 39 and 46%, respectively. At such conditions, the 1P1S configuration required 7.5 moles of D-PGME per mole of AMP at the maximum product concentration, compared to only 6.2 for the 1P2S scheme. Maximum conversions were achieved in one to two hours, significantly reducing the reaction times previously observed in the systems that used iPGA and ethylene glycol.[17,18] In all cases, the two-enzyme system with iPGA and AEH outperformed the systems that used only iPGA, thus demonstrating the clear advantage of using AEH. While the 1P1S system resulted in slightly lower yields, it could be advantageous due to its operational ease

and faster cycle times. In the 1P2S system, higher conversion was achieved and secondary hydrolysis was minimized by adjusting the relative enzyme loadings. These reaction schemes could be scaled up and incorporated with enzyme reuse, which has been previously demonstrated for iPGA.[13,24] However, further optimization is still required to improve yields and reduce ester usage for these processes.

3.4.5 Experimental Section

3.4.5.1 Materials

6-Aminopenicillanic acid, (D)-phenylglycine, ampicillin, (D)-phenylglycine methyl ester hydrochloride, penicillin G, phenylacetic acid, and Eupergit-immobilized penicillin G acylase from *Escherichia coli* were all procured from Sigma Aldrich (St. Louis, MO). Soluble amino ester hydrolase from *Xanthomonas campestris pv. campestris* was prepared in our laboratory as described in Blum et al.[6]

One-Pot, One Step Synthesis: PenG (15 mL of 20 mM) and D-PGME (60 mM in 100 mM phosphate buffer, pH 7) were added to a round bottom flask along with iPGA or iPGA and purified *X. campestris pv. campestris* AEH (Table 1). The reactions were stirred using a magnetic stir plate and carried out at room temperature (22 °C–25°C).

One-Pot, Two-Step Synthesis: PenG (7.5 mL of 40 mM) in phosphate buffer (100 mM, pH 7) was added to a round bottom flask along with iPGA (Table 2; 124 UPenG per gram of carrier), where 1 UPenG is defined as one μmol of penicillin G hydrolyzed per minute. The reactions were stirred using a magnetic stir plate and carried out at room temperature (22 °C–25°C). After the reaction reached near completion, as determined by HPLC, D-PGME (7.5 mL of 120 mM) was added. The pH was adjusted with NaOH from approximately 6.4 to 7.0 and *X. campestris pv. campestris* AEH was added (Table 2; 79 UAmp mg^{-1} protein), where UAmp is defined as one mmol of AMP hydrolyzed per minute under saturation conditions. Additional experiments were conducted in which pH was controlled between 7.0±0.1; the pH control had no effect on the results of the experiment. In reactions where iPGA was used in both steps, we replaced the AEH with equivalent AMP synthesis units of iPGA based on initial synthesis rate data from 6-APA and D-PGME using only AEH[6] and only iPGA[21] where 1 UAmp of AEH≈1 UAmp of iPGA≈6.8 UPenG of iPGA.

One-Pot, Two-Step, Two-Stage Synthesis: These experiments were conducted analogously to the 1P2S schemes, with the exception that after the completion of the first step, the iPGA was removed from the reaction using filtration.

3.4.5.2 HPLC Assay

All analyses were conducted using high performance liquid chromatography complete with a Shimadzu-LC-20AT pump, Beckman Coulter Ultrasphere ODS 4.6 mm×25 cm column, and SPD-M20A prominence diode array detector (PDA) monitored at 215 nm. Samples (100 μL) were diluted 10×into 900 μL of HPLC quench buffer (75% methanol, 25% 0.02 M potassium phosphate, pH 6.0). The sample (2 μL) was loaded onto the column. A step change method was used with a 1 mL min^{-1} flow rate. The initial mobile phase was 20% methanol and 80% 0.02 mM phosphate buffer (pH 7). From 5.5–25 min the methanol was increased to 35%. At 25 min, the methanol was returned back to 20% for the duration of the method of 35 min. All components, D-PG, PAA, 6-APA, D-PGME, AMP and penG were detected using this method. Results were normalized based on the penicillanic ring mass balance.

3.4.6 Acknowledgements

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3.4.7.1 Pénicillines de semisynthèse

Après centrifugation, le filtrat subit une centrifugation pour la production des pénicillines de semi-synthèse. Celle-ci s'effectue en 2étapes :

1-ère étape : hydrolyse

2-èmeétape : modification de la chaine latérale (hémi-synthèse.(

L'hémi-synthèse a pour objectif de développer différentes pénicillines afin de remplacer certains antibiotiques antérieurs devenus inefficaces à la suite de développement de résistances ou d'élargir le spectre d'activité

de certaines pénicillines .

La modification chimique d'un précurseur biologique de la pénicilline a permis la synthèse d'un grand nombre de pénicillines semi- synthétiques.La semi-synthèse des pénicillines comporte 2 étapes:

-Obtention de l'acide 6 amino-pénicillanique

-Acylation de l'acide 6 amino-pénicillanique

◎Exemple de la préparation de l'oxacilline : celle ci est obtenue à partir de

la pénicilline G

◎Obtention de l'acide 6 amino-pénicillanique : l'acide 6amino-pénicillanique est obtenu par une méthode enzymatique:

sous l'action d'une enzyme :Pénicilline amidase, produite par E.coli, la pénicilline G s'hydrolyse pour donner l'acide 6 amino-pénicillanique .

Celui ci subira ensuite une acylation[Fig. 17.[

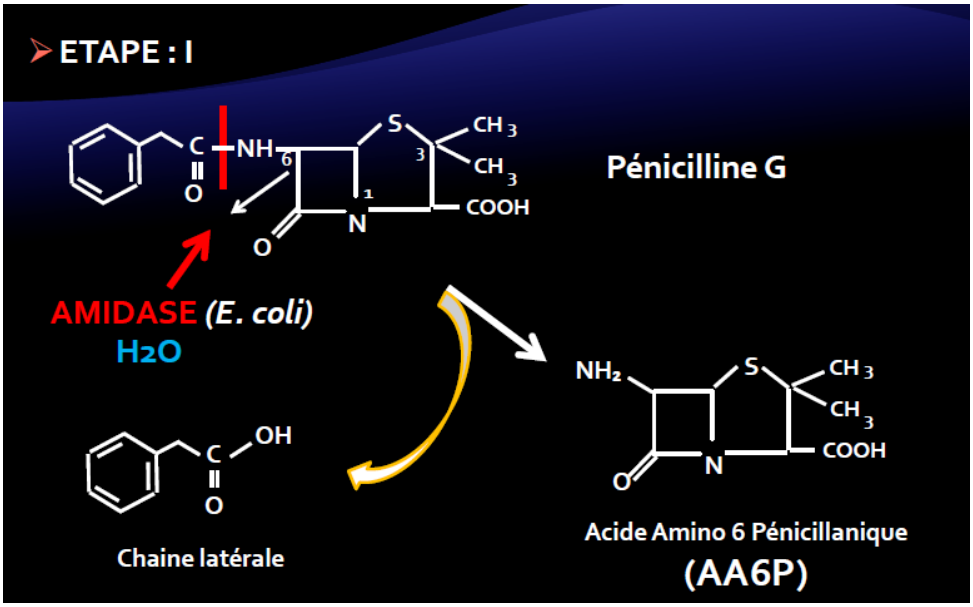
◎L'acylation se réalise avec des anhydrides mixtes, des chlorures

d'acides...etc.

L'oxacilline, par exemple, est obtenu par acylation

de l'acide 6 amino-pénicillanique par l'ajout de chlorure d'acide [Fig.18.[

1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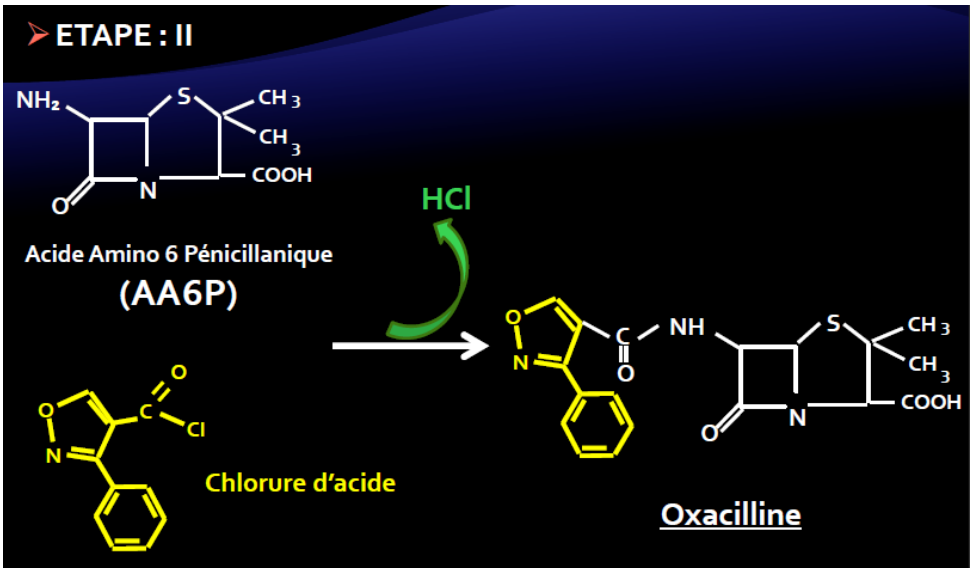
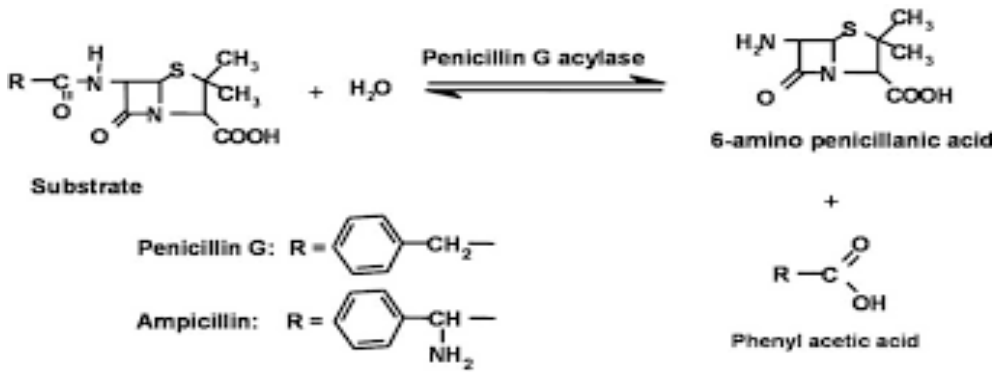
AMIDASE (E. coli)
H2O
Chaine latérale
Acide Amino 6 Pénicillanique
(AA6P)

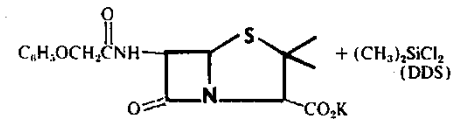

ETAPE : II
Acide Amino 6 Pénicillanique
(AA6P)
HCl
Chlorure d'acide
Oxacilline


Penicillin G acylase
6-amino penicillanic acid
Substrate
Penicillin G: R =
Ampicillin: R =
Phenyl acetic acid

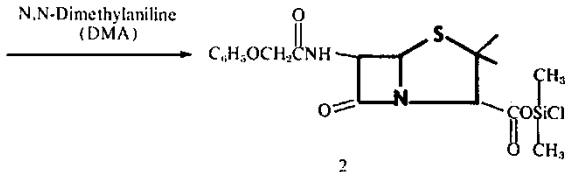
lin by the use of 5-methyl-3-phenyl-4-isoxazole-carbonyl chloride and cloxacillin by the use of 5-methyl-3-(2′-chlorophenyl)-4-isoxazole-carbonyl chloride and dicloxacillin by the use of 5-methyl-3-(2′,6′-dichlorophenyl)-4-isoxazole-carbonyl chloride and flucloxacillin (floxacillin) by the use of 5-methyl-3-(2′-chloro-6′-fluorophenyl)-4-isoxazole-carbonyl chloride and indanyl carbenicillin by the use of 5-indanyl phenylmalonyl chloride and 6-[D-α-(3-guanyl-1-ureido)-phenylacetamido]-penicillanic acid by the use of D-α-(3-guanyl-1-ureido)phenylacetyl chloride hydrochloride and levopropylcillin by the use of (-)-2-phenoxybutyryl chloride and sulfocillin (sulbenicillin; sulfobenzylpenicillin) by the use of α-sulphophenylacetyl chloride and azidocillin by the use of D-(-)-α-azidophenylacetyl chloride and 3,4-dichloro-α-methoxybenzylpenicillin by the use of 3,4-dichloro-α-methoxyphenylacetyl chloride and 6-[D-m-chloro-p-hydroxyphenylacetamido]penicillanic acid (U.S. Pat. No. 3,489,746) by the use of D-(-)-2-m-chloro-p-hydroxyphenylglycyl chloride hydrochloride and 6-[D-α-amino-(2-thienyl)acetamido] penicillanic acid by the use of D-(-)-α-(2-thienyl)-glycyl chloride hydrochloride and 6-[D-α-amino-(3-thienyl)acetamido] penicillanic acid by the use of D-(-)-α-(3-thienyl)glycyl chloride hydrochloride.

The present invention is further illustrated specifically in terms of ampicillin and amoxicillin by Scheme I below and the discussion and results which follow Scheme I.

SCHEME I



I
Potassium Penicillin V



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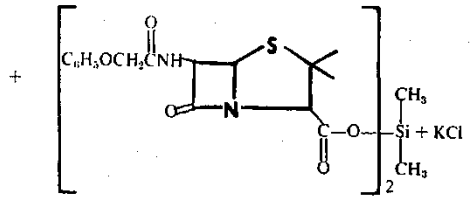

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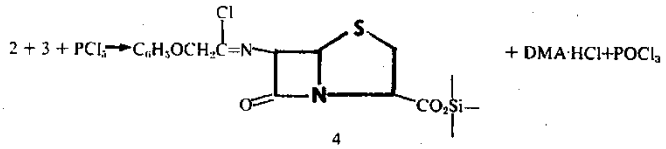

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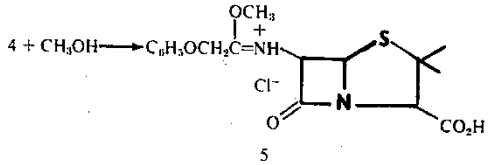
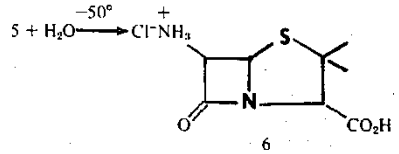


5

+ $(MeO)_2SiMe_2$ + methyl phosphates + HCl



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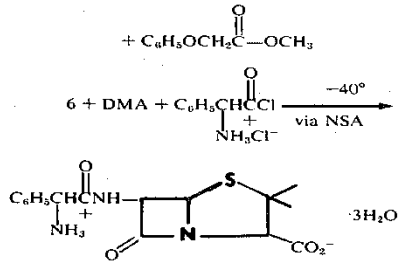
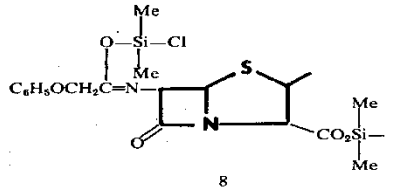


7

The esterification of penicillin V potassium (1) in methylene chloride solution at 25° with dimethyldichlorosilane (DDS) in the presence of N,N-dimethylaniline gives rise to a mixture of monomer ester (2) and dimer ester (3) (Scheme I). Low levels of DDS (0.60 moles/moles pen V) give predominantly dimer ester (3), whereas high levels of DDS (0.9–1.1 moles/mole pen V) give rise to a mixture of both (2) and (3); monomer ester predominating. In either case, the esterification is essentially quantitative. Long term stability studies indicate that the preferred technique for esterification is to add all of the DMA required for the cleavage (2.7–3.0 moles/mole pen V) to the suspension of pen V K salt in methylene chloride, prior to adding the DDS. This esterification mixture shows no tendency to undergo degradation after 16 hours at 25°. An examination of esterification mixtures (0.94 moles DDS + 0.22 moles DMA/mole pen V) after 16 hours showed approximately 9% degradation of the silyl ester to a compound tentatively assigned as the O-silylated amide, (8)



8

The treatment of the silylation mixture with phosphorous pentachloride (1.1–1.2 moles/mole Pen V) at −40° gives rise to the chloroimide (4). After 2 hours chlorination was quantitative and free from undesirable side reactions. No degradation was observed after 8 hours at −40°.

The dropwise addition of precooled (−60°) anhydrous methanol to the chlorination mix (this order of addition is preferred), maintaining the temperature at −50°, produces the imino ether hydrochloride free acid (5) after 1–2 hours reaction time at −50°. The alcoholysis reactions of the chlorimide and the silyl ester are quantitative and also free from any undesirable side reactions; the latter reaction occurring within 10–15 minutes at −50°.

The addition of 2.5–3% water by volume of methylation mix at −50° rapidly (e.g. within 5 minutes) cleaves the imino ether to 6-APA and methy phenoxyacetate. This reaction is nearly quantitative. In addition, there is no evidence to suggest that β-lactam breakage occurs during this step. Empirical data have shown that no loss of 6-APA occurs over 16 hours in this hydrolysis mix if it is stored that long.

The overall conversion of penicillin V to 6-APA in this process approaches 98–99%. Residual penicillin V assays of spent mother liquors are generally under 1%.

The resulting solution of 6-APA is treated with DMA at −50°, followed by the addition of D-(-)-phenylglycyl chloride hydrochloride (PGH) at −40°. After aqueous quench and workup via NSA/MILA, pure ampicillin trihydrate is produced in yields of 68–80% overall from penicillin V K salt.

Further laboratory investigations were then carried out by hydrolyzing methylation mix (prepared by adding chlorimide to methanol) with 6volume percent water at −45°, followed by acylation at this temperature with varying levels of DMA and PGH. Table I summarizes the effects of base and acid chloride on in-solution yields of ampicillin.

It appeared that the best conditions for acylation involved the use of 6–6.2 eq. of DMA and 1.1–1.3 eq. PGH (run numbers 9 and 10) at −45°. These conditions gave rise to 69–72% of ampicillin in solution. Higher mole ratios of PGH (run numbers 4, 8, 12, 16) apparently resulted in over acylation of 6-APA (acylation of ampicillin), whereas lower levels of both DMA and PGH apparently resulted in incomplete acylation of the 6-APA (run numbers 1–4).

A study of the effect of temperature on in solution yields of ampicillin was also carried out using the DMA/PGH levels described in Run No. 10 (Table 1). In these instances, methylation mix was prepared from known potency pen V K salt via esterification with DDS, chlorination with phosphorous pentachloride and by the addition of 25 eq. of methanol to the chlorimide. maintaining the addition temperature below −50°. The single phase methylation mix was hydrolyzed at −50° with 2.6% water based on the volume of the methylation mix, and acylated at the temperatures described in Table II.

TABLE I

The Effect of DMA and PGH Levels on Ampicillin Yields in Solution

TABLE I—Continued

Run No.	Moles of DMA added for Acylation	Moles of PGH added for Acylation	Calculated[1] % Ampi Free Acid in Soln.[2]
1	4.0	1.1	25.4
2	4.2	1.3	21.9
3	4.4	1.5	26.0
4	4.6	1.7	14.7
5	5.0	1.1	38.7
6	5.2	1.3	40.1
7	5.4	1.5	50.0
8	5.6	1.7	40.2
9	6.0	1.1	69.6
10	6.2	1.3	71.6
11	6.4	1.5	67.2
12	6.6	1.7	54.7
13	7.0	1.1	59.4
14	7.2	1.3	63.2
15	7.4	1.5	66.0
16	7.6	1.7	61.1
17	8.0	1.1	61.8
18	8.2	1.3	65.6

[1]A 2.0 ml. aliquot was taken from the acylation mix, stripped in vacuo, diluted to 20 mls. with pH 7.00 phosphate buffer and sent for bioassay. Yields are not corrected for input pen V potency.

[2]% Ampicillin in Solution =

$$\frac{\text{(Bioassay mcg/ml) (20 mls.) (Volume of Acylation mix)}}{\text{(2 mls.) (1000 mcg/mg) (1000 mg/gm) (Theoretical Yld in gms)}} \times 100$$

TABLE II

The Effect of Temperature on Ampicillin Yields in Solution[1]

Run No.	Moles of DMA for Acylation	Moles of PGH for Acylation	Acylation Temperature	% Ampi in Soln.
19	6.2	1.3	−50° C.	81.0
20	6.2	1.3	−40° C.	88.9
21	6.2	1.3	−30° C.	85.5
22	6.2	1.3	−20° C.	85.5
23	6.2	1.3	−10° C.	87.5

[1]Yields are corrected for input pen V potency.

Somewhat higher yields were noted at temperatures above −50° (Run Nos. 20–23). Interestingly, the rate of dissolution of the acid chloride was virtually instantaneous at −10°, whereas it requires 20 minutes at −50°.

Bioassay data tend to indicate that better yields of ampicillin are obtained using the controlled addition of 25 ea. of methanol to chlorimide (compare bio yields in Table I with Table II). Thus, several isolation variations were carried out using this methylation technique, some of which are illustrated in Table III.

TABLE III

Isolation Conditions and Yields of Ampicillin Trihydrate*

Run No.	Chem Assay in mcg/mg	% of Theory	Yield in gms.	% Yld.	Method of Isoln.
24	853;856	98.7	4.17	70	1[a]
25	810;811	93.8	15.8	76	1
26	817;812	94.1	5.4	77	2[b]
27	848;855	98.3	16.6	79	2
28	849;853	98.3	66.6	68	2
29	820	94.7	12.2	50	3[c]

*Yields are not corrected for purity.

[a]DMA removed by vacuum distillation at pH 7 (3.0N NaOH used for pH adjustment); NSA/MILA.

[b]DMA removed by extraction (MIBK) at pH 7 (6N NH_4OH used for pH adjustment); NSA/MILA.

[c]DMA removed by extraction (MIBK) at pH 7 (6N NH_4OH used for pH adjustment) direct crystallization of ampicillin by pH adjustment.

Workup in all cases consisted of aqueous quench of acylation mix at 0–5°. No emulsions were observed at this stage. The organic layer was removed and the aqueous was processed as follows:

Isolation method 1 involved adjustment of the rich aqueous with 3 N sodium hydroxide to pH 7–7.5. In addition to encountering an emulsion, a gummy solid precipitated during this step which was removed with difficulty via diatomaceous earth ("Dicalite") treatment and filtration. The formation of this solid, however, was precluded by continuous pH adjustment at pH 7.5, but pH control was difficult. The two phase mix (DMA and aqueous) was concentrated at 50° in vacuo to complete DMA removal. Slow acidification with aqueous β-naphthalenesulfonic acid (NSA) gave ampicillin NSA salt. The conversion of the wet NSA cake to ampicillin trihydrate using MIBK-LA-1 resin (MILA) gave yields up to 70–75% of good quality product.

Isolation method 2 involved adjustment of the rich aqueous with 6 N ammonium hydroxide to pH 7–7.5 in the presence of MIBK. An amorphous solid was found in addition to an emulsion, but was easily removed by filtration with added "Dicalite". The MIBK layer containing DMA was removed and the clean aqueous processed via NSA/MILA to good quality ampicillin trihydrate.

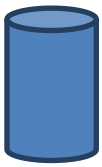
Method 3 consisted of removal of the DMA by solvent extraction (MIBK) at pH 7–7.5 (6 N ammonium hydroxide used for pH adjustment), followed by direct crystallization of the ampicillin by pH adjustment. The yields were considerably lower (Table 3) using this technique.

Either of these three methods is capable of yielding good quality ampicillin trihydrate in reasonably good yields from penicillin V Method 2 has thus far processed most smoothly of the three methods.

The acylation to ampicillin was also investigated using other bases such as triethylamine, imidazole and pyridine. The yields respectively in each case (bioassay of acylation mix) under best conditions were 55% (6.5 eq. TEA, 1.4 eq. PGH), 27.2% (5 eq. imidazole, 1.1 eq. PGH) and 30% (20 eq. pyridine, 1.1 eq. PGH). These yields were all lower than those obtained using DMA.

Using the best conditions thus far obtained, an acylation of the resulting solution of 6-APA with D-(-)-2-(4-hydroxyphenyl)glycyl)chloride hydrochloride PHPGH) was examined at −40° using 6.2 eq. DMA/1.3 eq. PHPGH. Bioassay data indicated yields of amoxicillin in solution approaching 85% average on three occasions.

The silyl esters of the process of the present invention are made, for example, by the use of such agents as are described in U.S. Pat. Nos. 3,499,909, 3,249,622, **3,654,266, 3,678,037, 3,741,959** and 3,694,437, e.g., trimethyl chlorosilane, hexamethyl disilazane, triethyl chlorosilane, methyl trichlorosilane, dimethyl dichlorosilane, triethyl bromosilane, tri-n-propyl chlorosilane, bromomethyl dimethyl chlorosilane, tri-n-butyl chlorosilane, methyl diethyl chlorosilane, dimethyl ethyl chlorosilane, phenyl dimethyl bromosilane, benzyl methyl ethyl chlorosilane, phenyl ethyl methyl chlorosilane, triphenylchlorosilane, triphenyl fluorosilane, tri-o-tolyl chlorosilane, tri-p-dimethylaminophenyl chlorosilane, N-ethyl triethylsilylamine, hexaethyl disilazane, triphenyl silylamine, tri-n-propyl silylamine, tetraethyl dimethyl disilazane, tetramethyl diethyl disilazane, tetramethyl diphenyl disilazane, hexaphenyl

Volume Par Cm3 	hauteur	rayon
Amylacetate=5849.14	34	7.4
AEH=SODIUM ACETAT=PENICILLIN=CHAORECOL TREATMENT=crystal dring=Ethanol=40212.38L	50.5	16
Acyclase treatement=ampicillin=56297.34	70	16

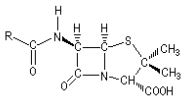
Cm3=ml

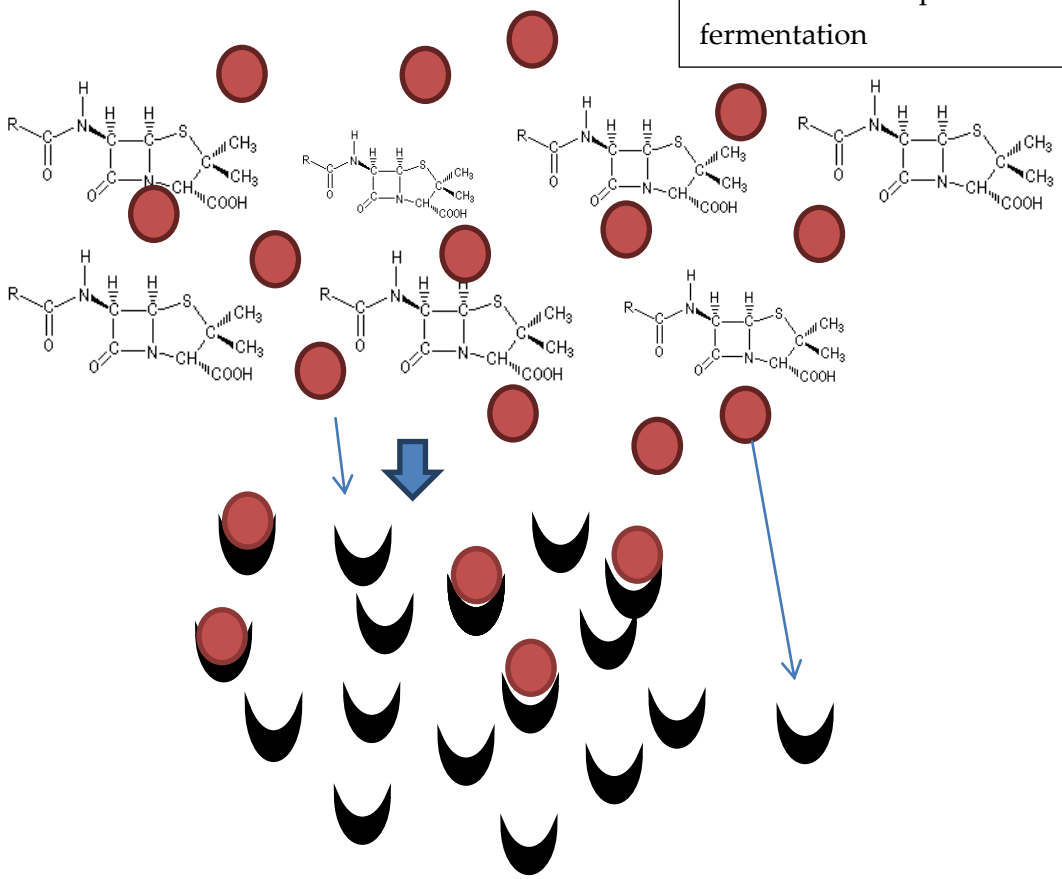
Cm3=10^{-3}l

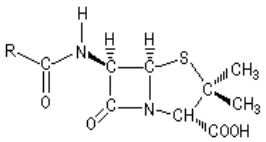
V=3.14*r²*h

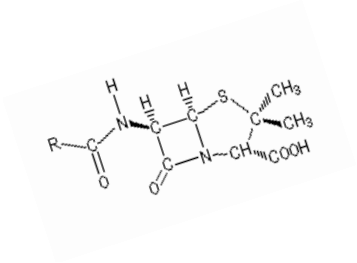
:produit indesirsble

: Charcoal


:penicillin produit par fermentation





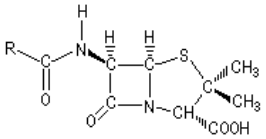


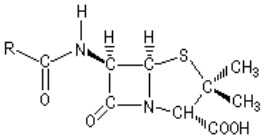
Sodium acetate

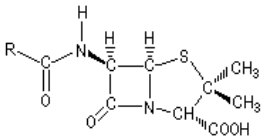
Filtration

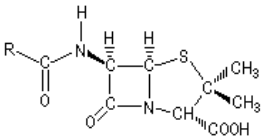
Ethaol

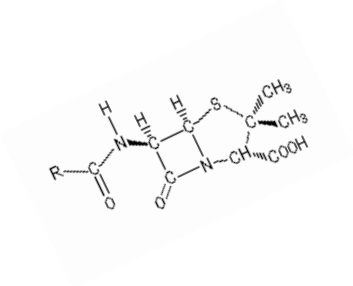
filtration

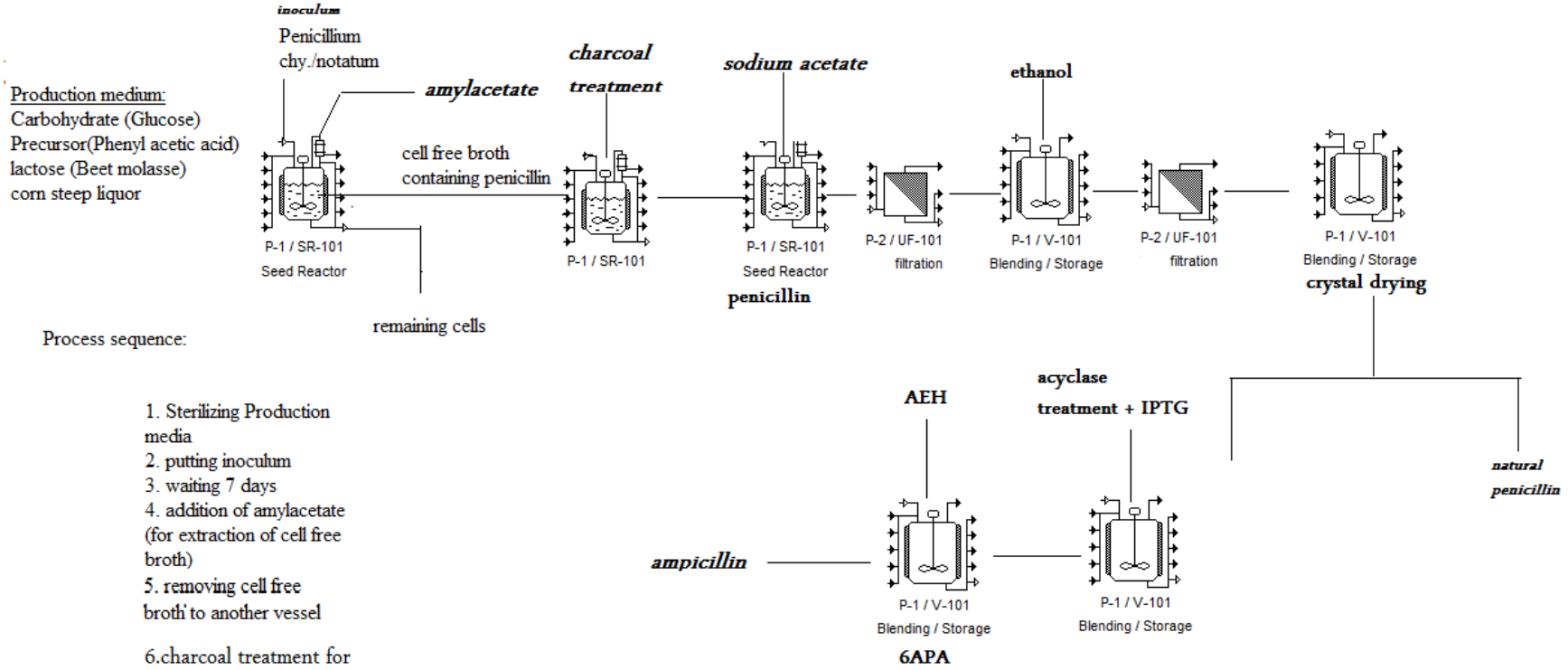






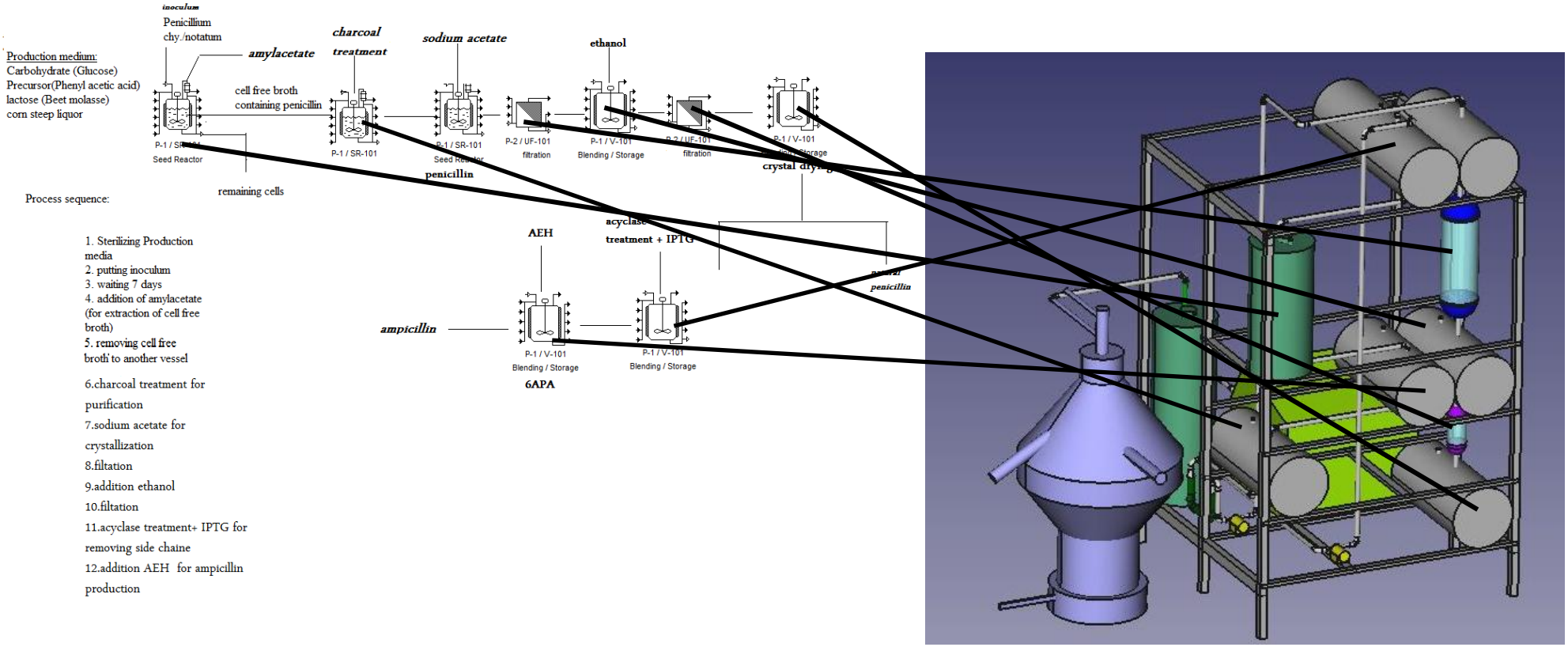






Process sequence:

1. Sterilizing Production media
2. putting inoculum
3. waiting 7 days
4. addition of amylacetate (for extraction of cell free broth)
5. removing cell free broth to another vessel
6. charcoal treatment for purification
7. sodium acetate for crystallization
8. filtation
9. addition ethanol
10. filtation
11. acyclase treatment+ IPTG for removing side chaine
12. addition AEH for ampicillin production



Process sequence:

1. Sterilizing Production media
2. putting inoculum
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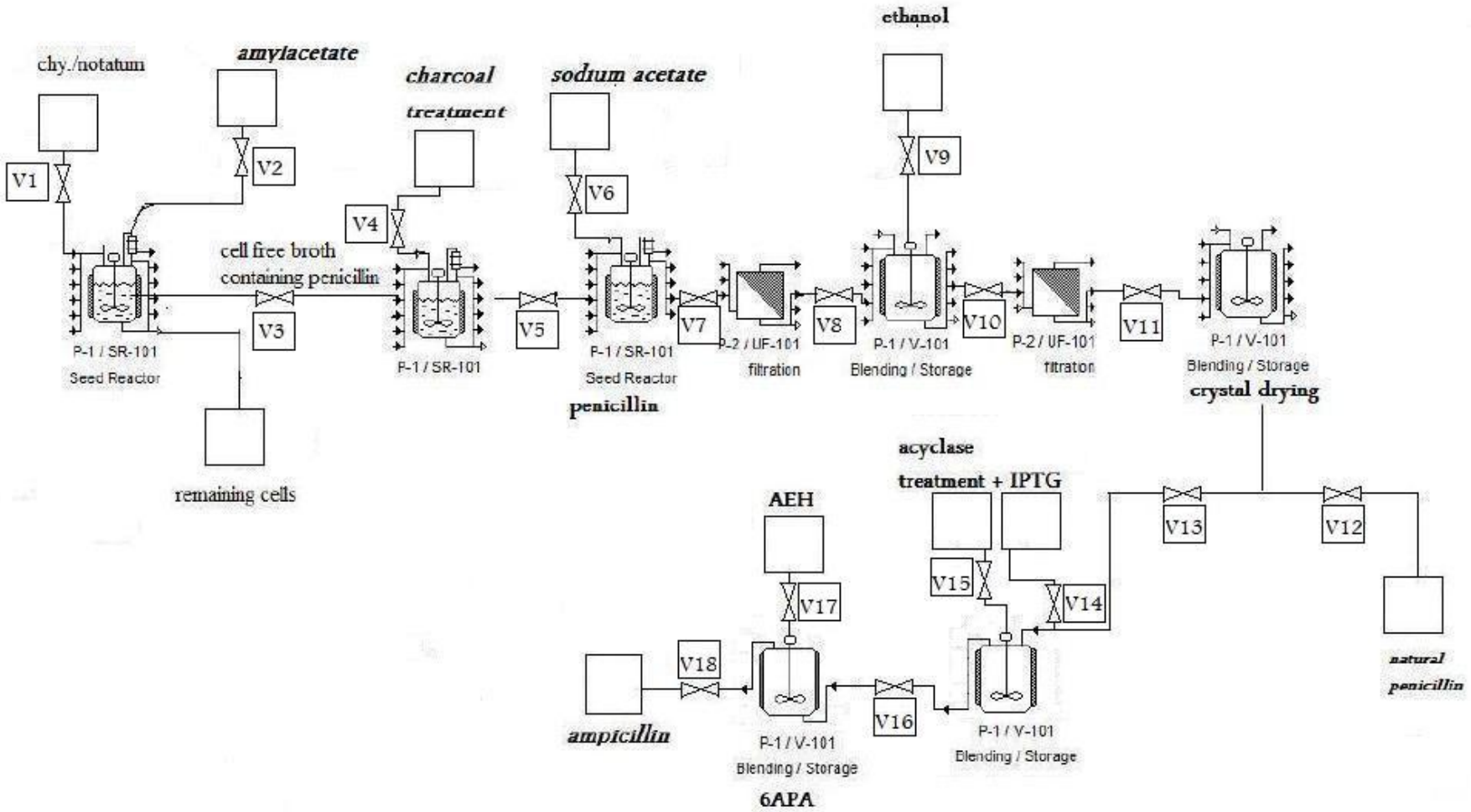
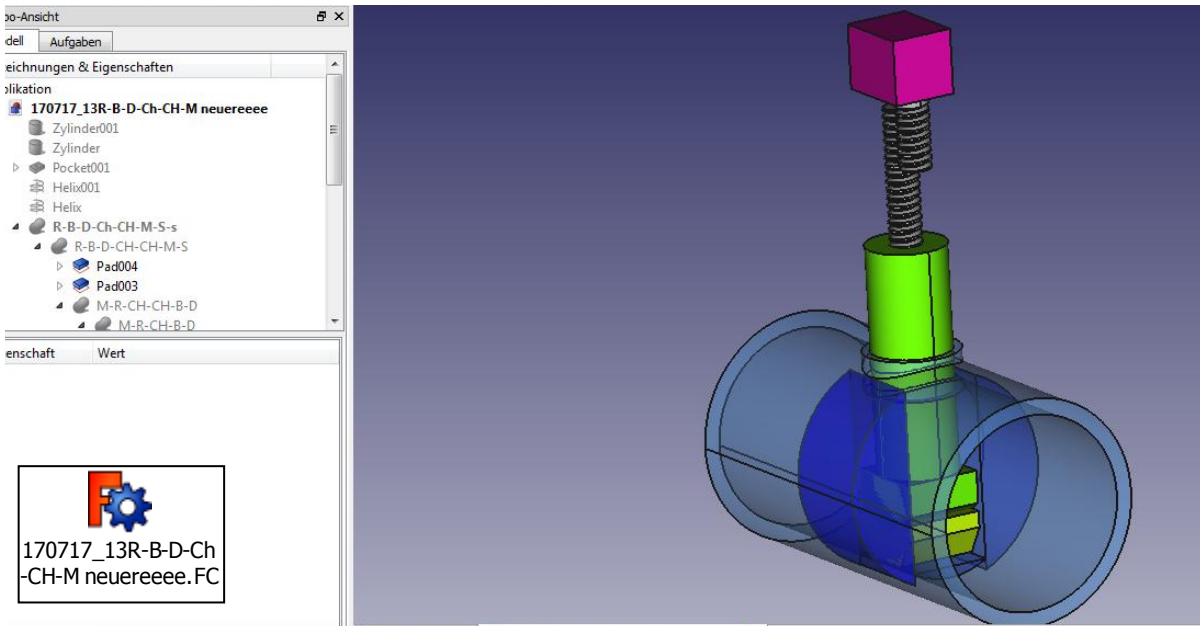
12. addition AEH for ampicillin production


chy./notatum
amylacetate
charcoal
treatment
sodium acetate
ethanol
V1
V2
V4
V6
V9
cell free broth
containing penicillin
V3
V5
V7
V8
V10
V11
P-1 / SR-101
Seed Reactor
P-1 / SR-101
P-1 / SR-101
Seed Reactor
P-2 / UF-101
filtration
P-1 / V-101
Blending / Storage
P-2 / UF-101
filtration
P-1 / V-101
Blending / Storage
penicillin
crystal drying
remaining cells
acyclase
treatment + IPTG
AEH
V13
V12
V15
V14
V17
V18
V16
ampicillin
P-1 / V-101
Blending / Storage
P-1 / V-101
Blending / Storage
6APA
natural
penicillin

5 MEGBI-APP Process Control System

5.1 Automatic Valves: Conception

5.1.1 Preliminary Design of Automatic Control Valve



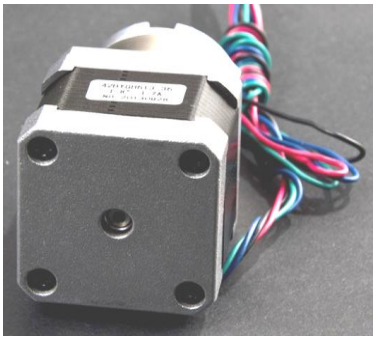
5.1.2 Alternative 1: DC Motor for automatic valves

from www.cnclablb.com: **Metal DC Geared Motor - 12V 50RPM 9kg.cm rated torque,** Price : 15.95$, Serial number : ACT0022

Description: This is a metal DC geared motor, 100% pure copper coils, high-density molecular layer, 100:1 metal reducer, small size, large torque. The maximum torque could arrive 50 kg.cm, stable and durable!

Specification: Rated voltage: 12 V, Gear reduction ratio: 100:1, D output shaft diameter: 6 mm, No-load speed: 50 RPM @ 12 v, No-load current: 0.17 A, Rated speed: 45 RPM @ 12 v, Current rating: 0.68 A, Rated torque: 9 kg.cm, Locked-rotor torque: 50 kg.cm, Locked-rotor current: 2.19 A, Power: 5W, Weight: 210 g, **Shipping List:** Metal DC Geared Motor - 12V 50RPM 50kg.cm x1

5.1.3 Alternative 2: Stepper Motor



From www.cnclablb.com

from www.cnclablb.com: Bipolar Stepper Motor with Planet Gear Box (18kg.cm), Price : 40$, Serial number : ACT0017, **!!!needs additional drive!!!**

5.1.4 Alternative3: Servo

5.1.4.1 Low Cost Servo

	from www.cnclablb.com: Metal Gear Servo TowerPro MG995 Servo - 9kg, Price : 8$ Serial number : ACT0005 **Description:** Modulation: Digital, Torque: 4.8V: 130.54 oz-in (**9.40 kg-cm**) 6.0V: 152.76 oz-in (11.00 kg-cm) Speed: 4.8V: 0.20 sec/60° 6.0V: 0.16 sec/60°, Weight: 1.94 oz (55.0 g), Dimensions:Length:1.60 in (40.7 mm), Width:0.78 in (19.7 mm), Height:1.69 in (42.9 mm)

5.1.4.2 High cost Servo

	DF15MG Tilt/Pan Kit, Price : 47.5$, Mark : DFRobot, Serial number : FIT0046 This is a 2DOF Pan and Tilt Kit assembly for horizontal surface mount. It equipped with a DF15MG servo which offers 15 kg high-torque

5.2 Actual Motorized Valve Implementation

5.2.1 Hardware and Electronics

5.2.1.1 Adopted Motor: Low Cost Servo (Alternative 3 (Low Cost Variante)

The adopted motor is the TowerPro MG995 DC Servo Motor with the following specs:

- Modulation: Digital
- Torque: 4.8V: 9.40 kg-cm 6.0V: 11.00 kg-cm
- Speed: 4.8V: 0.20 sec/60° 6.0V: 0.16 sec/60°
- Weight: 1.94 oz (55.0 g)
- Dimensions:Length:1.60 in (40.7 mm)
- Width:0.78 in (19.7 mm)
- Height:1.69 in (42.9 mm)
- LINK – CNC LAB Shop

Figure 5-1 – TowerPro MG995

The adopted motor provides the required torque to turn the ball valve.

A set of 18 servos are used with a control unit shown in 6.2.2 to allow opening and closing of 18 ball valves.

5.2.1.2 Motor Controller and Interfaces

To accommodate 18 servo motors and ensure best response the Arduino Mega 2560 was chosen for the following reasons:

- Enough PPM capable IO count to control the servos. The Arduino Mega 2560 allows control of 48 Servo motors while most of other Arduino boards allow control of only 12 servos max.
- Availability of an IO shield that makes powering and connecting all the servos much more convenient and much less time consuming.

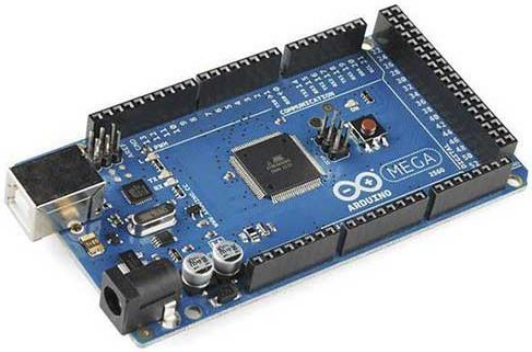


Figure 5-2 – Arduino Mega - LINK

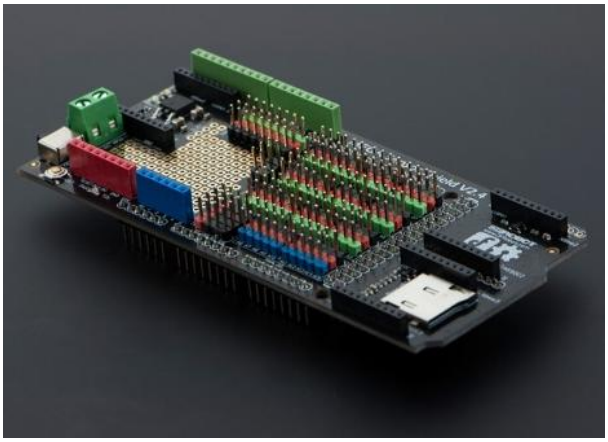


Figure 5-3 – Mega Sensor Shield - LINK

Interfacing between MEGBI python GUI and the servos can be accomplished in two ways:

a. Via Digital input signals on the Arduino Shield.

b. Via Communication through the Arduino USB port.

Digital interface mode and communication mode can be used at the same time if necessary.

The following IO map illustrates the IO allocation for the servos and the digital inputs on the Arduino Shield:

VAVLE ID	COMMAND PIN (ARDUINO INPUT)	SERVO PIN (ARDUINO OUTPUT)
1	DIO 33	DIO 14
2	DIO 34	DIO 15
3	DIO 35	DIO 16
4	DIO 36	DIO 17
5	DIO 37	DIO 18
6	DIO 38	DIO 19
7	DIO 39	DIO 20
8	DIO 40	DIO 21
9	DIO 41	DIO 22
10	DIO 42	DIO 23
11	DIO 43	DIO 24
12	DIO 44	DIO 25
13	DIO 45	DIO 26
14	DIO 46	DIO 27
15	DIO 47	DIO 28
16	DIO 48	DIO 29
17	DIO 49	DIO 30
18	DIO 50	DIO 31

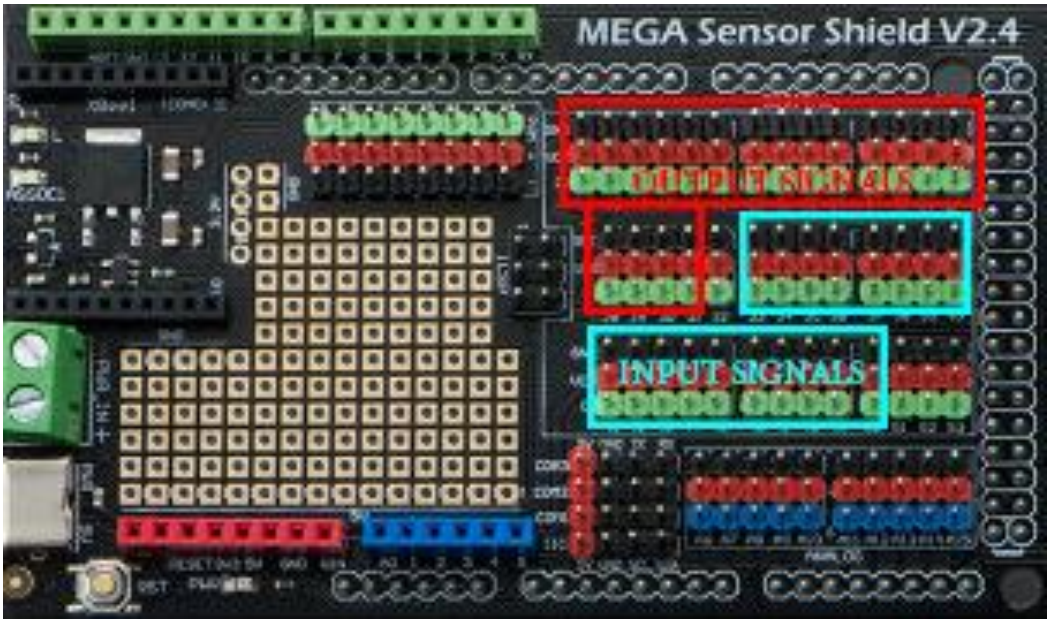


Figure 5-4 – Inputs and Outputs Allocation

The digital input mode of control allows closing and openning the valves by set or clearing the corresponding DIO respectively.

On the other hand, controlling the valves via USB communication with Arduino is implemented in an example Python code using a couple of Python classes discussed in more details in part 6.2.2.

5.2.1.3 Power Management

One of the reasons of choosing Arduino Mega IO shield was powering the motors as mentioned earlier, as 18 Servo motors can consume a hefty amount of power.

Each servo motor can consume up to 1.2 Amps at 5V at certain moments when closing or openning the valves. Thus in terms of power management the following mesures were taken:

- The IO shield allows powering the servos from a separate power connector (Green screw terminal in Fig6-4) thus isolating the limited Arduino regulator from motors consumption and ensuring microcontroller chip performance and functionality.
- Within the Arduino Firmware, precautions were taken so that the servos are only consuming power while opening or closing and for a limited time beyond that. After the time delay of a motor's activity the motor is powered down to cut its consumption to almost zero Amps.

Having mentioned the above points, selecting the motors power supply is highly related to the number of motors that are expected to be active simultaneously. For example, if the automatic mode of the plant requires that 6 motors have to be active at a certain moment; and active means is currently in the process of opening or closing; then the power supply should be a 5 VDC with at least 6 x 1.2A = 7.2 Amps.

The arduino board itself can be powered either by a USB cable connected to PC or by any standard wall adapter with voltage between 7.4V and 12V.

5.2.2 Firmware and Software

5.2.2.1 Arduino Firmware

The Arduino controller is loaded with a firmware featuring the following: • Control of 18 Servo motors with preset positions for closed and opened valve. • Digital Input control for all 18 valves. • Communication protocol class for two way communication with Python GUI on PC. • Power management for all motors. The firmware was developed by CNC LAB. The code is developed with maintenance and scalability in mind.	 ArduinoSourceCode.zip

CommandMessanger.h

```
/*
CmdMessenger - library that provides command based messaging
Permission is hereby granted, free of charge, to any person obtaining
a copy of this software and associated documentation files (the
"Software"), to deal in the Software without restriction, including
without limitation the rights to use, copy, modify, merge, publish,
distribute, sublicense, and/or sell copies of the Software, and to
```

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permit persons to whom the Software is furnished to do so, subject to
the following conditions:
The above copyright notice and this permission notice shall be
included in all copies or substantial portions of the Software.
THE SOFTWARE IS PROVIDED "AS IS", WITHOUT WARRANTY OF ANY KIND,
EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO THE WARRANTIES OF
MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE AND
NONINFRINGEMENT. IN NO EVENT SHALL THE AUTHORS OR COPYRIGHT HOLDERS BE
LIABLE FOR ANY CLAIM, DAMAGES OR OTHER LIABILITY, WHETHER IN AN ACTION
OF CONTRACT, TORT OR OTHERWISE, ARISING FROM, OUT OF OR IN CONNECTION
WITH THE SOFTWARE OR THE USE OR OTHER DEALINGS IN THE SOFTWARE.
*/
#ifndef CmdMessenger_h
#define CmdMessenger_h
#include <inttypes.h>
#if ARDUINO >= 100
#include <Arduino.h>
#else
#include <WProgram.h>
#endif
//#include "Stream.h"
extern "C"
{
// callback functions always follow the signature: void cmd(void);
typedef void(*messengerCallbackFunction) (void);
}
#define MAXCALLBACKS 50 // The maximum number of commands (default: 50)
#define MESSENGERBUFFERSIZE 64 // The length of the commandbuffer (default: 64)
#define MAXSTREAMBUFFERSIZE 512 // The length of the streambuffer (default: 64)
#define DEFAULT_TIMEOUT 5000 // Time out on unanswered messages. (default: 5s)
// Message States
enum
{
kProccesingMessage, // Message is being received, not reached command separator
kEndOfMessage, // Message is fully received, reached command separator
kProcessingArguments, // Message is received, arguments are being read parsed
};
#define white_space(c) ((c) == ' ' || (c) == '\t')
#define valid_digit(c) ((c) >= '0' && (c) <= '9')

class CmdMessenger
{
private:
// **** Private variables ***
bool startCommand; // Indicates if sending of a command is underway
uint8_t lastCommandId; // ID of last received command
uint8_t bufferIndex; // Index where to write data in buffer
uint8_t bufferLength; // Is set to MESSENGERBUFFERSIZE
uint8_t bufferLastIndex; // The last index of the buffer
char ArglastChar; // Bookkeeping of argument escape char
char CmdlastChar; // Bookkeeping of command escape char
bool pauseProcessing; // pauses processing of new commands, during sending
bool print_newlines; // Indicates if \r\n should be added after send command
char commandBuffer[MESSENGERBUFFERSIZE]; // Buffer that holds the data
char streamBuffer[MAXSTREAMBUFFERSIZE]; // Buffer that holds the data
uint8_t messageState; // Current state of message processing
bool dumped; // Indicates if last argument has been externally read
bool ArgOk; // Indicated if last fetched argument could be read
char *current; // Pointer to current buffer position
char *last; // Pointer to previous buffer position
char prevChar; // Previous char (needed for unescaping)
Stream *comms; // Serial data stream
char command_separator; // Character indicating end of command (default: ';')
char field_separator; // Character indicating end of argument (default: ',')
char escape_character; // Character indicating escaping of special chars
messengerCallbackFunction default_callback; // default callback function
messengerCallbackFunction callbackList[MAXCALLBACKS]; // list of attached callback
functions
// **** Initialize ****
```

```
void init(Stream & comms, const char fld_separator, const char cmd_separator, const char
esc_character);
void reset();
// **** Command processing ****
inline uint8_t processLine(char serialChar) __attribute__((always_inline));
inline void handleMessage() __attribute__((always_inline));
inline bool blockedTillReply(unsigned int timeout = DEFAULT_TIMEOUT, byte ackCmdId = 1)
__attribute__((always_inline));
inline bool checkForAck(byte AckCommand) __attribute__((always_inline));
// **** Command sending ****
/**
* Print variable of type T binary in binary format
*/
template < class T >
void writeBin(const T & value)
{
const byte *bytePointer = (const byte *)(const void *)&value;

for (unsigned int i = 0; i < sizeof(value); i++)
{
printEsc(*bytePointer);
bytePointer++;
}
}
// **** Command receiving ****
int findNext(char *str, char delim);
/**
* Read a variable of any type in binary format
*/
template < class T >
T readBin(char *str)
{
T value;
unescape(str);
byte *bytePointer = (byte *)(const void *)&value;
for (unsigned int i = 0; i < sizeof(value); i++)
{
*bytePointer = str[i];
bytePointer++;
}
return value;
}
template < class T >
T empty()
{
T value;
byte *bytePointer = (byte *)(const void *)&value;
for (unsigned int i = 0; i < sizeof(value); i++)
{
*bytePointer = '\0';
bytePointer++;
}
return value;
}
// **** Escaping tools ****
char *split_r(char *str, const char delim, char **nextp);
bool isEscaped(char *currChar, const char escapeChar, char *lastChar);
void printEsc(char *str);
void printEsc(char str);
public:
// ****** Public functions ******
// **** Initialization ****
CmdMessenger(Stream & comms, const char fld_separator = ',',
const char cmd_separator = ';',

const char esc_character = '/');
void printLfCr(bool addNewLine = true);
void attach(messengerCallbackFunction newFunction);
```

```
void attach(byte msgId, messengerCallbackFunction newFunction);
// **** Command processing ****
void feedinSerialData();
bool next();
bool available();
bool isArgOk();
uint8_t commandID();
// **** Command sending ****
/**
* Send a command with a single argument of any type
* Note that the argument is sent as string
*/
template < class T >
bool sendCmd(byte cmdId, T arg, bool reqAc = false, byte ackCmdId = 1,
unsigned int timeout = DEFAULT_TIMEOUT)
{
if (!startCommand) {
sendCmdStart(cmdId);
sendCmdArg(arg);
return sendCmdEnd(reqAc, ackCmdId, timeout);
}
return false;
}
/**
* Send a command with a single argument of any type
* Note that the argument is sent in binary format
*/
template < class T >
bool sendBinCmd(byte cmdId, T arg, bool reqAc = false, byte ackCmdId = 1,
unsigned int timeout = DEFAULT_TIMEOUT)
{
if (!startCommand) {
sendCmdStart(cmdId);
sendCmdBinArg(arg);
return sendCmdEnd(reqAc, ackCmdId, timeout);
}
return false;
}
bool sendCmd(byte cmdId);
bool sendCmd(byte cmdId, bool reqAc, byte ackCmdId);
// **** Command sending with multiple arguments ****
void sendCmdStart(byte cmdId);
void sendCmdEscArg(char *arg);
void sendCmdfArg(char *fmt, ...);
bool sendCmdEnd(bool reqAc = false, byte ackCmdId = 1, unsigned int timeout =
DEFAULT_TIMEOUT);
/**
* Send a single argument as string
* Note that this will only succeed if a sendCmdStart has been issued first
*/
template < class T > void sendCmdArg(T arg)
{
if (startCommand) {
comms->print(field_separator);
comms->print(arg);
}
}
/**
* Send a single argument as string with custom accuracy
* Note that this will only succeed if a sendCmdStart has been issued first
*/
template < class T > void sendCmdArg(T arg, unsigned int n)
{
if (startCommand) {
comms->print(field_separator);
comms->print(arg, n);
}
```

```
}
/**
* Send double argument in scientific format.
* This will overcome the boundary of normal d sending which is limited to abs(f) <=
MAXLONG
*/
void sendCmdSciArg(double arg, unsigned int n = 6);
/**
* Send a single argument in binary format
* Note that this will only succeed if a sendCmdStart has been issued first
*/
template < class T > void sendCmdBinArg(T arg)
{
if (startCommand) {
comms->print(field_separator);
writeBin(arg);
}
}
// **** Command receiving ****
bool readBoolArg();
int16_t readInt16Arg();
int32_t readInt32Arg();
char readCharArg();
float readFloatArg();
double readDoubleArg();
char *readStringArg();
void copyStringArg(char *string, uint8_t size);
uint8_t compareStringArg(char *string);
/**
* Read an argument of any type in binary format
*/
template < class T > T readBinArg()
{
if (next()) {
dumped = true;
return readBin < T >(current);
}
else {
return empty < T >();
}
}
// **** Escaping tools ****
void unescape(char *fromChar);
void printSci(double f, unsigned int digits);
};
#endif
```

CommandMsg.cpp

```
/*
CmdMessenger - library that provides command based messaging
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a copy of this software and associated documentation files (the
"Software"), to deal in the Software without restriction, including
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LIABLE FOR ANY CLAIM, DAMAGES OR OTHER LIABILITY, WHETHER IN AN ACTION
OF CONTRACT, TORT OR OTHERWISE, ARISING FROM, OUT OF OR IN CONNECTION
WITH THE SOFTWARE OR THE USE OR OTHER DEALINGS IN THE SOFTWARE.
Initial Messenger Library - Thomas Ouellet Fredericks.
```

```
CmdMessenger Version 1 - Neil Dudman.
CmdMessenger Version 2 - Dreamcat4.
CmdMessenger Version 3 - Thijs Elenbaas.
3.6 - Fixes
- Better compatibility between platforms
- Unit tests
3.5 - Fixes, speed improvements for Teensy
3.4 - Internal update
3.3 - Fixed warnings
- Some code optimization
3.2 - Small fixes and sending long argument support
3.1 - Added examples
3.0 - Bugfixes on 2.2
- Wait for acknowlegde
- Sending of common type arguments (float, int, char)
- Multi-argument commands
- Escaping of special characters
- Sending of binary data of any type (uses escaping)
*/
extern "C" {
#include <stdlib.h>
#include <stdarg.h>
}
#include <stdio.h>
#include "CmdMessenger.h"
#define _CMDMESSENGER_VERSION 3_6 // software version of this library
// **** Initialization ****
/**
* CmdMessenger constructor
*/

CmdMessenger::CmdMessenger(Stream &ccomms, const char fld_separator, const char
cmd_separator, const char esc_character)
{
init(ccomms, fld_separator, cmd_separator, esc_character);
}
/**
* Enables printing newline after a sent command
*/
void CmdMessenger::init(Stream &ccomms, const char fld_separator, const char cmd_separator,
const char esc_character)
{
default_callback = NULL;
comms = &ccomms;
print_newlines = false;
field_separator = fld_separator;
command_separator = cmd_separator;
escape_character = esc_character;
bufferLength = MESSENGERBUFFERSIZE;
bufferLastIndex = MESSENGERBUFFERSIZE - 1;
reset();
default_callback = NULL;
for (int i = 0; i < MAXCALLBACKS; i++)
callbackList[i] = NULL;
pauseProcessing = false;
}
/**
* Resets the command buffer and message state
*/
void CmdMessenger::reset()
{
bufferIndex = 0;
current = NULL;
last = NULL;
dumped = true;
}
/**
* Enables printing newline after a sent command
*/
```

```
void CmdMessenger::printLfCr(bool addNewLine)
{
print_newlines = addNewLine;
}
/**
* Attaches an default function for commands that are not explicitly attached
*/
void CmdMessenger::attach(messengerCallbackFunction newFunction)
{
default_callback = newFunction;
}
/**
* Attaches a function to a command ID
*/
void CmdMessenger::attach(byte msgId, messengerCallbackFunction newFunction)
{
if (msgId >= 0 && msgId < MAXCALLBACKS)
callbackList[msgId] = newFunction;
}
// **** Command processing ****
/**
* Feeds serial data in CmdMessenger
*/
void CmdMessenger::feedinSerialData()
{
while (!pauseProcessing && comms->available())
{
// The Stream class has a readBytes() function that reads many bytes at once. On
Teensy 2.0 and 3.0, readBytes() is optimized.
// Benchmarks about the incredible difference it makes:
http://www.pjrc.com/teensy/benchmark_usb_serial_receive.html
size_t bytesAvailable = min(comms->available(), MAXSTREAMBUFFERSIZE);
comms->readBytes(streamBuffer, bytesAvailable);
// Process the bytes in the stream buffer, and handles dispatches callbacks, if
commands are received
for (size_t byteNo = 0; byteNo < bytesAvailable; byteNo++)
{
int messageState = processLine(streamBuffer[byteNo]);
// If waiting for acknowledge command
if (messageState == kEndOfMessage)
{
handleMessage();
}
}
}
}
/**
* Processes bytes and determines message state
*/
uint8_t CmdMessenger::processLine(char serialChar)
{
messageState = kProccesingMessage;
//char serialChar = (char)serialByte;
bool escaped = isEscaped(&serialChar, escape_character, &CmdlastChar);
if ((serialChar == command_separator) && !escaped) {
commandBuffer[bufferIndex] = 0;
if (bufferIndex > 0) {
messageState = kEndOfMessage;
current = commandBuffer;
CmdlastChar = '\0';
}
reset();
}
else {
commandBuffer[bufferIndex] = serialChar;
bufferIndex++;
if (bufferIndex >= bufferLastIndex) reset();
```

```
}
return messageState;
}
/**
* Dispatches attached callbacks based on command
*/
void CmdMessenger::handleMessage()
{
lastCommandId = readInt16Arg();
// if command attached, we will call it
if (lastCommandId >= 0 && lastCommandId < MAXCALLBACKS && ArgOk &&
callbackList[lastCommandId] != NULL)
(*callbackList[lastCommandId])();
else // If command not attached, call default callback (if attached)
if (default_callback != NULL) (*default_callback)();
}
/**
* Waits for reply from sender or timeout before continuing
*/
bool CmdMessenger::blockedTillReply(unsigned int timeout,byte ackCmdId)
{
unsigned long time = millis();
unsigned long start = time;
bool receivedAck = false;
while ((time - start) < timeout && !receivedAck) {
time = millis();
receivedAck = checkForAck(ackCmdId);
}
return receivedAck;
}
/**
* Loops as long data is available to determine if acknowledge has come in
*/
bool CmdMessenger::checkForAck(byte ackCommand)
{
while (comms->available()) {
//Processes a byte and determines if an acknowlegde has come in
int messageState = processLine(comms->read());
if (messageState == kEndOfMessage) {
int id = readInt16Arg();
if (ackCommand == id && ArgOk) {
return true;
}
else {
return false;
}
}
return false;
}
return false;

}
/**
* Gets next argument. Returns true if an argument is available
*/
bool CmdMessenger::next()
{
char * temppointer = NULL;
// Currently, cmd messenger only supports 1 char for the field seperator
switch (messageState) {
case kProccesingMessage:
return false;
case kEndOfMessage:
temppointer = commandBuffer;
messageState = kProcessingArguments;
default:
if (dumped)
current = split_r(temppointer, field_separator, &last);
```

```
if (current != NULL) {
dumped = true;
return true;
}
}
return false;
}
/**
* Returns if an argument is available. Alias for next()
*/
bool CmdMessenger::available()
{
return next();
}
/**
* Returns if the latest argument is well formed.
*/
bool CmdMessenger::isArgOk()
{
return ArgOk;
}
/**
* Returns the commandID of the current command
*/
uint8_t CmdMessenger::commandID()
{
return lastCommandId;
}
// **** Command sending ****
/**
* Send start of command. This makes it easy to send multiple arguments per command
*/
void CmdMessenger::sendCmdStart(byte cmdId)
{
if (!startCommand) {
startCommand = true;
pauseProcessing = true;
comms->print(cmdId);
}
}
/**
* Send an escaped command argument
*/
void CmdMessenger::sendCmdEscArg(char* arg)
{
if (startCommand) {
comms->print(field_separator);
printEsc(arg);
}
}
/**
* Send formatted argument.
* Note that floating points are not supported and resulting string is limited to 128 chars
*/
void CmdMessenger::sendCmdfArg(char *fmt, ...)
{
const int maxMessageSize = 128;
if (startCommand) {
char msg[maxMessageSize];
va_list args;
va_start(args, fmt);
vsnprintf(msg, maxMessageSize, fmt, args);
va_end(args);
comms->print(field_separator);
comms->print(msg);
}
}
```

```
/**
* Send double argument in scientific format.
* This will overcome the boundary of normal float sending which is limited to abs(f) <=
MAXLONG
*/
void CmdMessenger::sendCmdSciArg(double arg, unsigned int n)
{
if (startCommand)
{
comms->print(field_separator);
printSci(arg, n);
}
}
/**
* Send end of command
*/
bool CmdMessenger::sendCmdEnd(bool reqAc, byte ackCmdId, unsigned int timeout)
{
bool ackReply = false;

if (startCommand) {
comms->print(command_separator);
if (print_newlines)
comms->println(); // should append BOTH \r\n
if (reqAc) {
ackReply = blockedTillReply(timeout, ackCmdId);
}
}
pauseProcessing = false;
startCommand = false;
return ackReply;
}
/**
* Send a command without arguments, with acknowledge
*/
bool CmdMessenger::sendCmd(byte cmdId, bool reqAc, byte ackCmdId)
{
if (!startCommand) {
sendCmdStart(cmdId);
return sendCmdEnd(reqAc, ackCmdId, DEFAULT_TIMEOUT);
}
return false;
}
/**
* Send a command without arguments, without acknowledge
*/
bool CmdMessenger::sendCmd(byte cmdId)
{
if (!startCommand) {
sendCmdStart(cmdId);
return sendCmdEnd(false, 1, DEFAULT_TIMEOUT);
}
return false;
}
// **** Command receiving ****
/**
* Find next argument in command
*/
int CmdMessenger::findNext(char *str, char delim)
{
int pos = 0;
bool escaped = false;
bool EOL = false;
ArglastChar = '\0';
while (true) {
escaped = isEscaped(str, escape_character, &ArglastChar);
EOL = (*str == '\0' && !escaped);
if (EOL) {
```

```
return pos;
}
if (*str == field_separator && !escaped) {
return pos;
}
else {
str++;
pos++;
}
}
return pos;
}
/**
* Read the next argument as int
*/
int16_t CmdMessenger::readInt16Arg()
{
if (next()) {
dumped = true;
ArgOk = true;
return atoi(current);
}
ArgOk = false;
return 0;
}
/**
* Read the next argument as int
*/
int32_t CmdMessenger::readInt32Arg()
{
if (next()) {
dumped = true;
ArgOk = true;
return atol(current);
}
ArgOk = false;
return 0L;
}
/**
* Read the next argument as bool
*/
bool CmdMessenger::readBoolArg()
{
return (readInt16Arg() != 0) ? true : false;
}
/**
* Read the next argument as char
*/
char CmdMessenger::readCharArg()
{
if (next()) {
dumped = true;
ArgOk = true;
return current[0];
}
ArgOk = false;
return 0;
}
/**
* Read the next argument as float
*/
float CmdMessenger::readFloatArg()
{
if (next()) {
dumped = true;
ArgOk = true;
```

```
//return atof(current);
return strtod(current, NULL);
}
ArgOk = false;
return 0;
}
/**
* Read the next argument as double
*/
double CmdMessenger::readDoubleArg()
{
if (next()) {
dumped = true;
ArgOk = true;
return strtod(current, NULL);
}
ArgOk = false;
return 0;
}
/**
* Read next argument as string.
* Note that the String is valid until the current command is replaced
*/
char* CmdMessenger::readStringArg()
{
if (next()) {
dumped = true;
ArgOk = true;
return current;
}
ArgOk = false;
return '\0';
}
/**
* Return next argument as a new string
* Note that this is useful if the string needs to be persisted
*/
void CmdMessenger::copyStringArg(char *string, uint8_t size)
{
if (next()) {
dumped = true;
ArgOk = true;
strlcpy(string, current, size);
}
else {
ArgOk = false;
if (size) string[0] = '\0';
}
}
/**
* Compare the next argument with a string
*/
uint8_t CmdMessenger::compareStringArg(char *string)
{
if (next()) {
if (strcmp(string, current) == 0) {
dumped = true;
ArgOk = true;
return 1;
}
else {
ArgOk = false;
return 0;
}
}
return 0;
}
```

```
// **** Escaping tools ****
/**
* Unescapes a string
* Note that this is done inline
*/
void CmdMessenger::unescape(char *fromChar)
{
// Move unescaped characters right
char *toChar = fromChar;
while (*fromChar != '\0') {
if (*fromChar == escape_character) {
fromChar++;
}
*toChar++ = *fromChar++;
}
// Pad string with \0 if string was shortened
for (; toChar < fromChar; toChar++) {
*toChar = '\0';
}
}
/**
* Split string in different tokens, based on delimiter
* Note that this is basically strtok_r, but with support for an escape character
*/
char* CmdMessenger::split_r(char *str, const char delim, char **nextp)
{
char *ret;
// if input null, this is not the first call, use the nextp pointer instead
if (str == NULL) {
str = *nextp;
}
// Strip leading delimiters
while (findNext(str, delim) == 0 && *str) {
str++;
}
// If this is a \0 char, return null
if (*str == '\0') {
return NULL;
}
// Set start of return pointer to this position
ret = str;
// Find next delimiter
str += findNext(str, delim);
// and exchange this for a a \0 char. This will terminate the char
if (*str) {
*str++ = '\0';
}
// Set the next pointer to this char
*nextp = str;
// return current pointer
return ret;
}
/**
* Indicates if the current character is escaped
*/
bool CmdMessenger::isEscaped(char *currChar, const char escapeChar, char *lastChar)
{
bool escaped;
escaped = (*lastChar == escapeChar);
*lastChar = *currChar;
// special case: the escape char has been escaped:
if (*lastChar == escape_character && escaped) {
*lastChar = '\0';
}
return escaped;
}
/**
```

```
* Escape and print a string
*/
void CmdMessenger::printEsc(char *str)
{
while (*str != '\0') {
printEsc(*str++);
}
}
/**
* Escape and print a character
*/
void CmdMessenger::printEsc(char str)
{
if (str == field_separator || str == command_separator || str == escape_character || str
== '\0') {
comms->print(escape_character);
}
comms->print(str);
}
/**
* Print float and double in scientific format
*/
void CmdMessenger::printSci(double f, unsigned int digits)
{
// handle sign
if (f < 0.0)
{
Serial.print('-');
f = -f;
}
// handle infinite values
if (isinf(f))
{
Serial.print("INF");
return;
}
// handle Not a Number
if (isnan(f))
{
Serial.print("NaN");
return;
}
// max digits
if (digits > 6) digits = 6;
long multiplier = pow(10, digits); // fix int => long
int exponent;
if (abs(f) < 10.0) {
exponent = 0;
}
else {
exponent = int(log10(f));
}
float g = f / pow(10, exponent);
if ((g < 1.0) && (g != 0.0))
{
g *= 10;
exponent--;
}
long whole = long(g); // single digit
long part = long((g - whole)*multiplier + 0.5); // # digits
// Check for rounding above .99:
if (part == 100) {
whole++;
part = 0;
}
char format[16];
sprintf(format, "%%ld.%%0%dldE%%+d", digits);
```

```
char output[16];
sprintf(output, format, whole, part, exponent);
comms->print(output);
}
```

ValvesControl.ino

```
#include <Servo.h>
#include "CmdMessenger.h"
//#include <MemoryFree.h>
//To control a valve use one of the following option:
// 1- Set the corresponding Valve Input Signal
// Input Pin: 33 -> 50
// Valve index: 0 -> 18
// 2- Send a serial command with the following syntax:
// v<x><y> where
// x is a character {0-9,:,;,<,?,@,A} corresponding the valve index {0-17} respectively
// y is a character {0,1} corresponding to OPEN and CLOSE respectively
//The servos are to be connected as follows:
// Output Pin: 14 -> 31
// Valve index: 0 -> 18
#define OPEN 138
#define CLOSE 35
enum {
cmd_connect,
rep_connected,
cmd_open_valve,
cmd_close_valve,
rep_valve_state,
rep_error,
};
const int BAUD_RATE = 9600;
CmdMessenger c = CmdMessenger(Serial,',',';','/');
/*
char servoCharV[18] ={'0', '1', '2', '3', '4',
'5', '6', '7', '8', '9',
':', ';', '<', '=', '>',
'?', '@', 'A'};
*/
int signalsPins[18] ={33, 34, 35, 36, 37,
38, 39, 40, 41, 42,
43, 44, 45, 46, 47,
48, 49, 50};
int servosPins[18] = {14, 15, 16, 17, 18,
19, 20, 21, 22, 23,
24, 25, 26, 27, 28,
29, 30, 31};
bool virtualSignals[18];
bool preVirtualSignals[18];
bool prevInputSignals[18];
bool servoStates[18];
bool prevServoStates[18];
Servo servos[18];
long servosTimers[18];
long detachInterval = 3000;
bool anyAttached = false;
void setup()
{
pinMode(13,OUTPUT);
Serial.begin(BAUD_RATE);
attach_callbacks();
//Serial.println("Initializing Valves");
InitValves();
digitalWrite(13,HIGH);
//Serial.println("Initialization Complete");
}
```

```
//long fmpm = 0;
void loop()
{
c.feedinSerialData();
//StateMachine();
UpdateValves();
/*if(millis() - fmpm >= 1000)
{
Serial.println(freeMemory());
fmpm = millis();
}*/
}
/* callback */
void on_connect(void)
{
c.sendCmd(rep_connected,"OK");
}
/* callback */
void on_open_valve(void)
{
int value1 = c.readBinArg<int>();
if(value1 >= 0 && value1 < 18)
{
virtualSignals[value1] = true;
c.sendCmdStart (rep_valve_state);
c.sendCmdBinArg<int16_t>((int16_t)value1);
c.sendCmdBinArg<int16_t>((int16_t)1);
c.sendCmdEnd ();
//c.sendBinCmd(rep_valve_state,value1,1);
}
else
c.sendBinCmd(rep_error,"Invalid Valve Index");
}
/* callback */
void on_close_valve(void)
{
int value1 = c.readBinArg<int>();
if(value1 >= 0 && value1 < 18)
{
virtualSignals[value1] = false;
c.sendCmdStart (rep_valve_state);
c.sendCmdBinArg<int16_t>((int16_t)value1);
c.sendCmdBinArg<int16_t>((int16_t)0);

c.sendCmdEnd ();
//c.sendBinCmd(rep_valve_state,value1,0);
}
else
c.sendBinCmd(rep_error,"Invalid Valve Index");
}
/* callback */
void on_unknown_command(void)
{
c.sendCmd(rep_error,"Unknown Command");
}
/* Attach callbacks for CmdMessenger commands */
void attach_callbacks(void)
{
c.attach(cmd_connect,on_connect);
c.attach(cmd_open_valve,on_open_valve);
c.attach(cmd_close_valve,on_close_valve);
c.attach(on_unknown_command);
}
/*int machineState = 0;
int rxVIdx = -1;
void StateMachine()
{
char c;
```

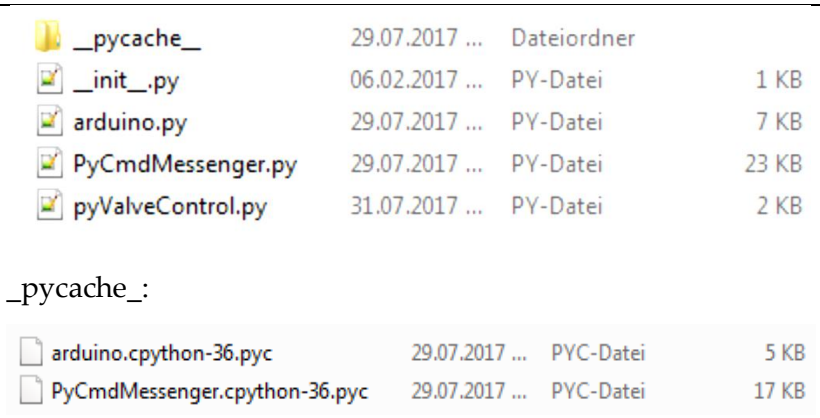
```
if(Serial.available())
{
c = Serial.read();
//Serial.print("Rx: ");
//Serial.print(char(c));
//Serial.print(" - S ");
//Serial.print(machineState);
switch(machineState)
{
case 0:
if(c == 'v') machineState++;
else if(c == 'C') Serial.println("OK");
break;
case 1:
rxVIdx = int(c) - 0x30;
//Serial.print(" - IDX ");
//Serial.print(rxVIdx);
machineState++;
break;
case 2:
if(rxVIdx >= 0 && rxVIdx < 18)
{
if(c == '1') virtualSignals[rxVIdx] = true;
else if(c == '0') virtualSignals[rxVIdx] = false;
//Serial.print(" - OC ");
//Serial.print(virtualSignals[rxVIdx]? "Open":"Close");
}
machineState = 0;
rxVIdx = -1;
break;

default:
machineState = 0;
rxVIdx = -1;
break;
}
//Serial.print(" - NS ");
//Serial.println(machineState);
}
}*/
void UpdateValves()
{
for(int i = 0; i < 18; i++)
{
bool doMove = true;
bool state = !digitalRead(signalsPins[i]);
//Serial.print(!state? "1":"0");
//Serial.print("-");
if(state != prevInputSignals[i])
{
prevInputSignals[i] = state;
}
else if((preVirtualSignals[i] != virtualSignals[i]))
{
state = virtualSignals[i];
preVirtualSignals[i] = virtualSignals[i];
}
else
doMove = false;
//state = state || virtualSignals[i];
if(doMove)
ControlValve(i, state? OPEN:CLOSE, false);
//Serial.print(servoStates[i]? "1":"0");
//Serial.print("-");
}
//Serial.println();
DetachServos();
}
void InitValves()
{
```

```
bool ledState = false;
for(int i = 0; i < 18; i++)
{
pinMode(signalsPins[i], INPUT_PULLUP);
virtualSignals[i] = false;
preVirtualSignals[i] = false;
servoStates[i] = false;
prevServoStates[i] = false;
ControlValve(i, CLOSE, true);
//delay(1000);
delay(100);
DetachServos();
prevInputSignals[i] = !digitalRead(signalsPins[i]);
digitalWrite(13,ledState);
ledState = !ledState;
}

DetachServos();
}
void OpenValve(int idx)
{
ControlValve(idx, OPEN, false);
}
void CloseValve(int idx)
{
ControlValve(idx, CLOSE, false);
}
void ControlValve(int idx, int state, bool force)
{
servoStates[idx] = (state == OPEN);
virtualSignals[idx] = servoStates[idx];
if((servoStates[idx] != prevServoStates[idx]) || force)
{
//Serial.print((state == OPEN)? "Open":"Close");
//Serial.print(" Servo "); Serial.println(idx);
prevServoStates[idx] = servoStates[idx];
if(!servos[idx].attached())
servos[idx].attach(servosPins[idx]);
servos[idx].write(state);
servosTimers[idx] = millis();
anyAttached = true;
}
}
void DetachServos()
{
if(!anyAttached) return;
bool ledState = false;
bool tempAnyAttach = false;
for(int i = 0; i < 18; i++)
{
bool isat = servos[i].attached();
//Serial.print(isat? "1":"0"); Serial.print("-");
if(isat)
{
if(millis() - servosTimers[i] >= detachInterval)
servos[i].detach();
else
tempAnyAttach = true;
}
digitalWrite(13,ledState);
ledState = !ledState;
}
//Serial.println();
anyAttached = tempAnyAttach;
}
```

5.2.2.2 Python Software



Two Python classes are available to allow two communication with Arduino:

- "arduino.py" Class defines and Arduino object with all the communication hardware settings and buffers encapsulated to send and receive general binary data. [Ref [6]] (Harms)
- "PyCmdMessenger.py" Class encapsulates a communication protocol that allows developer to define custom commands and replies and the class instance can manage and parse all communication with Arduino. . [Ref [6]] (Harms)

An additional Python code file is also included:

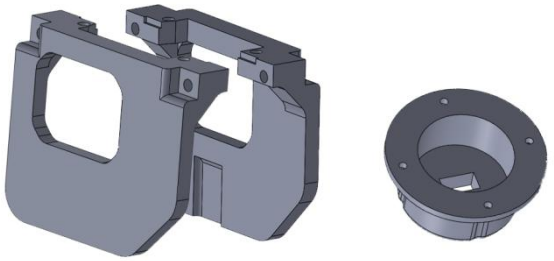
"pyValveControl.py" This code illustrates how to use the above mentioned classes to define the requires commands and replies that are compatible with the Arduino firmware and shows how to control the valves using the USB communication mode. [Developed by CNC LAB]

5.2.3 Retrofit,3D Models and 3D Prints

Retrofitting the ball valve with Servo motor was achieved by designing a functional mechanism that ensures the following:

- Fixating the Motor body to the Valve body to prevent motor body from rotating.
- Coupling the motor shaft with the valve shaft while improving or at least not hindering the motor torque.
- Minimize the scale factor of the mechanism.

The following design was modeled, 3D printed and tested during 3 iterations. Tweaked and optimized with each iteration.



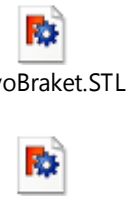


Figure 5-5 – Retrofit 3D Model

The 3D model was printed and test as shown in the following pictures:

Figure 5-6 - Out Of Printer

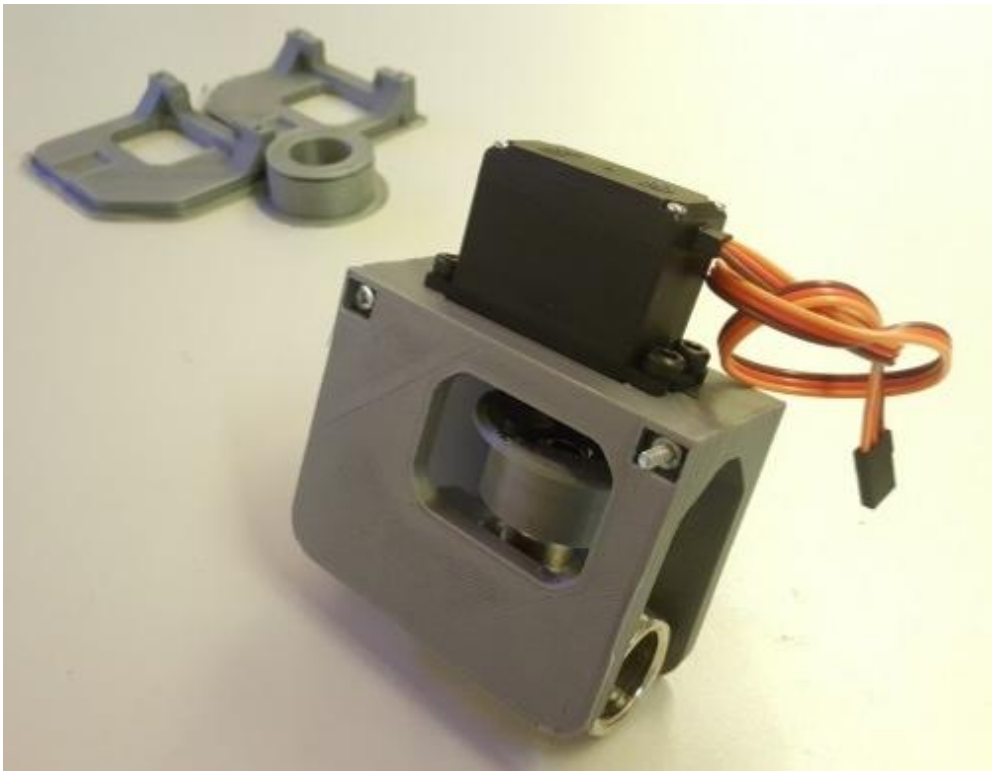


Figure 5-7 - Valve Assembly

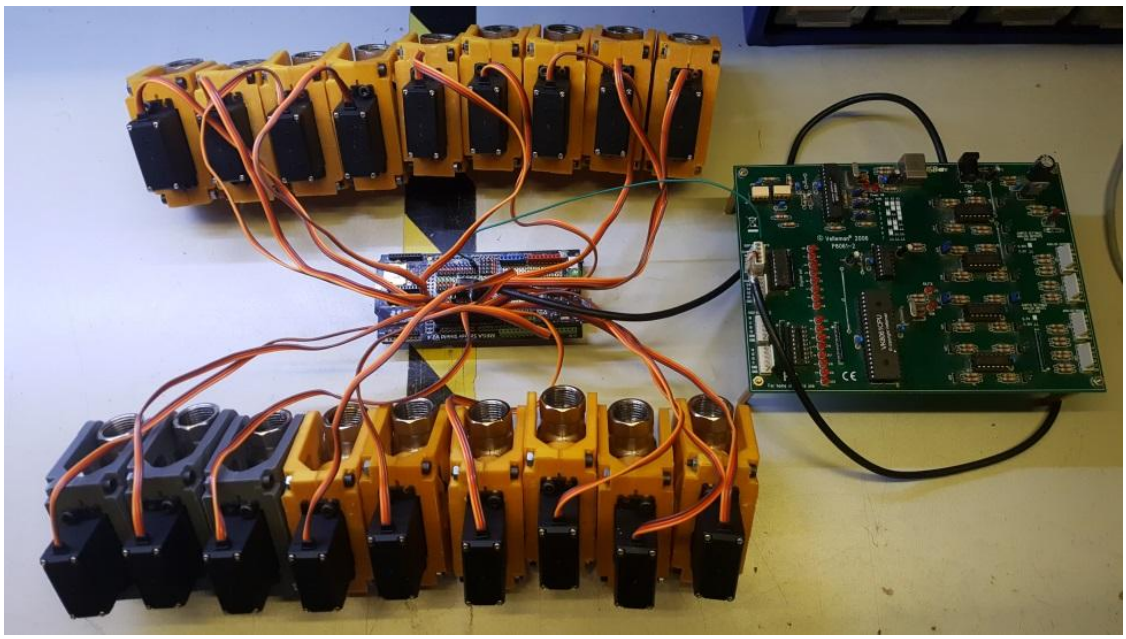
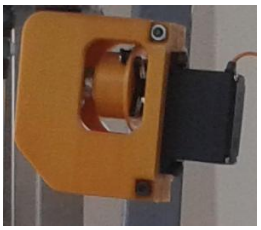


Figure 5-8 - Complete System

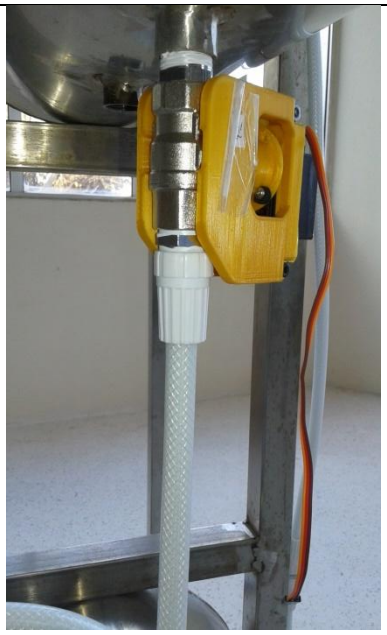
5.3 Integration

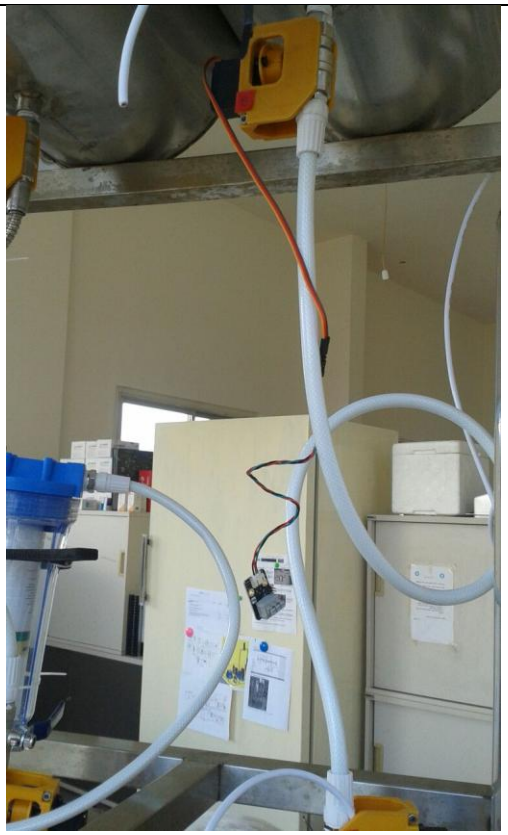
5.3.1 Costs

	#	Cost/#	Total
 Valve	18	$60	$1.080
	36	$2	$72
	36	$1	$36

Stand 29.10.17: Noch offen zur Beendigung des Teststandes: Anschlüsse für 18 Valves

5.3.2 Piping

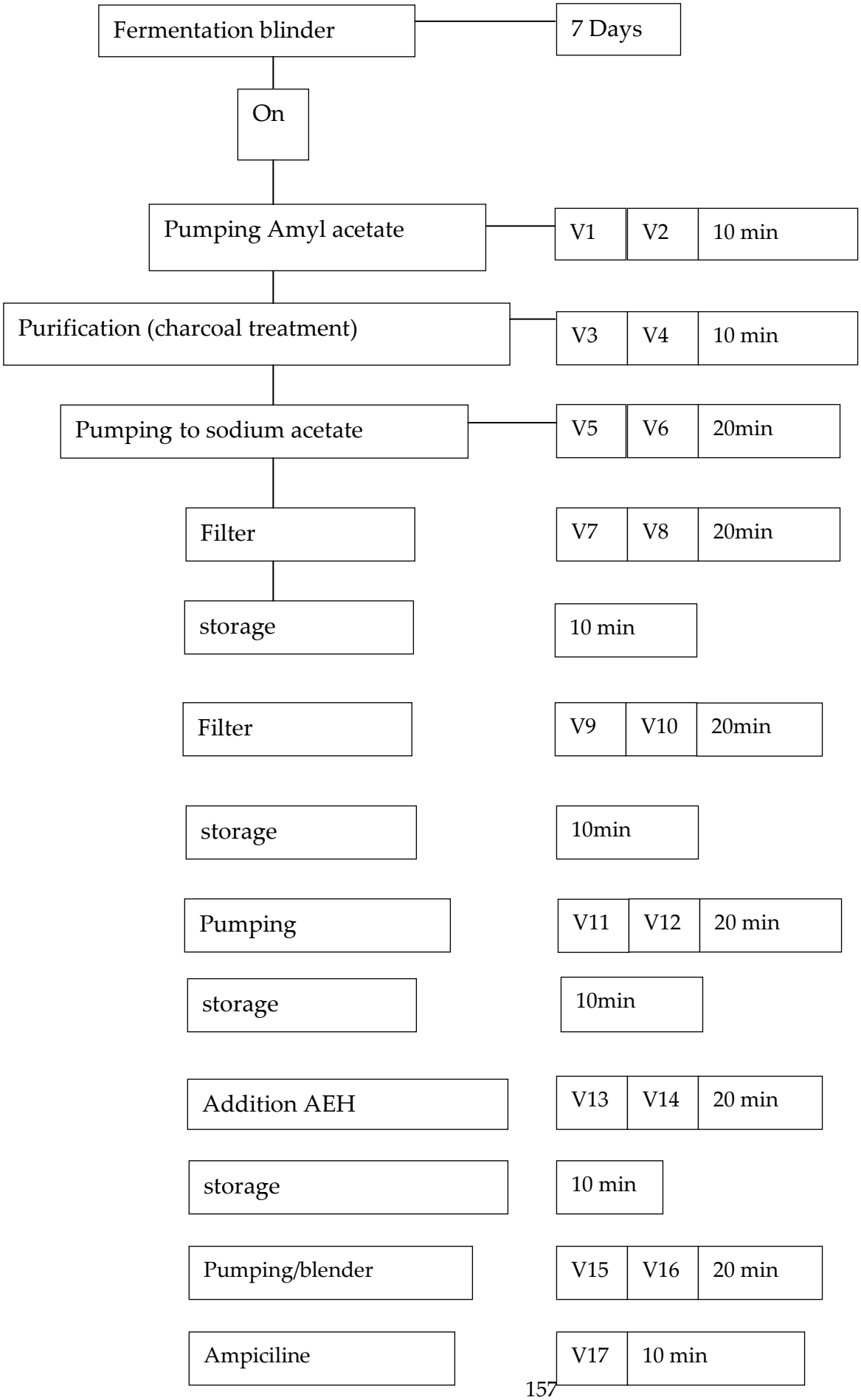




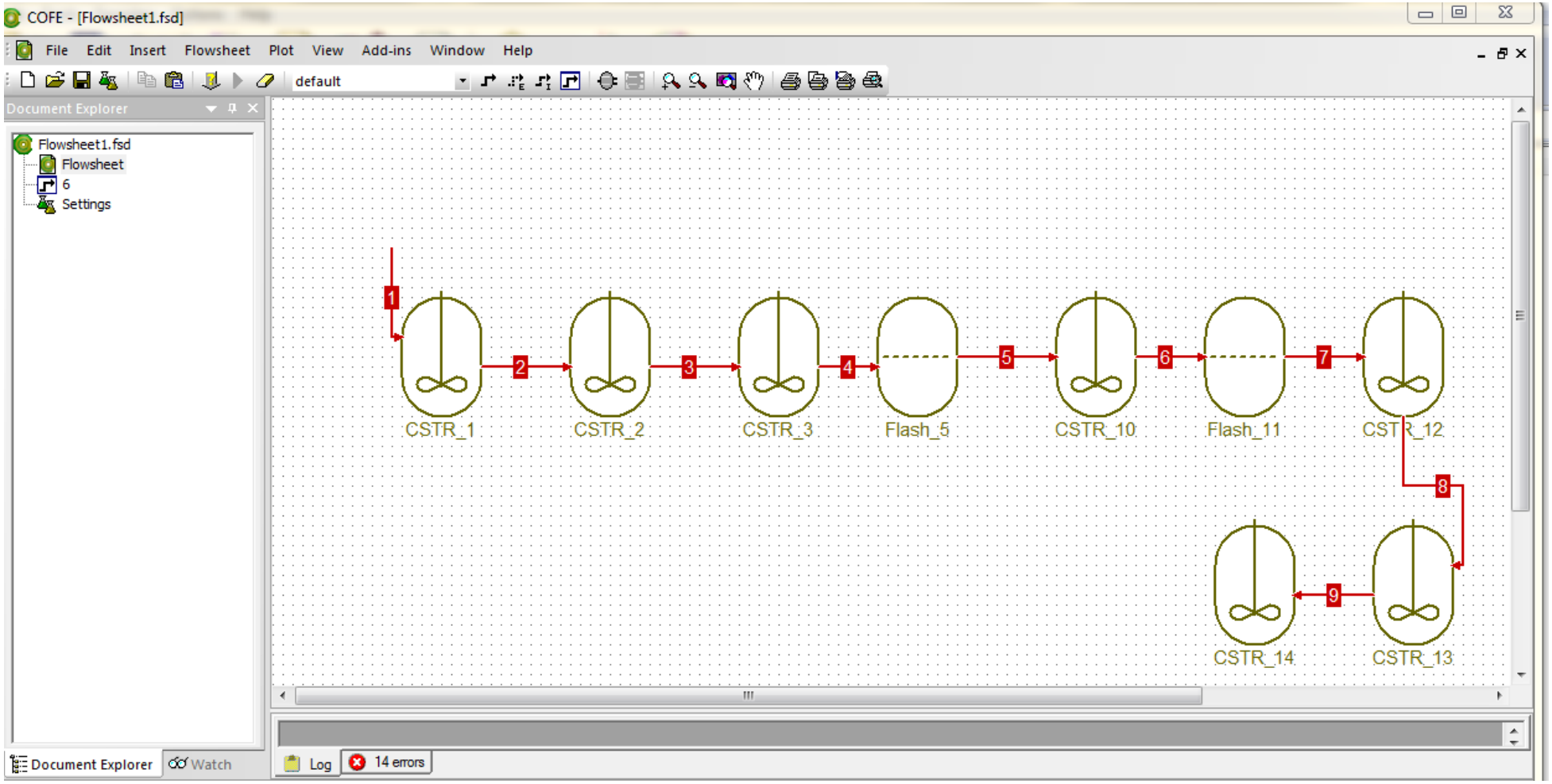
5.3.3 Connecting to automation system

Possibility: Portating GUI to Raspberry

5.4 Process Control Algorithm



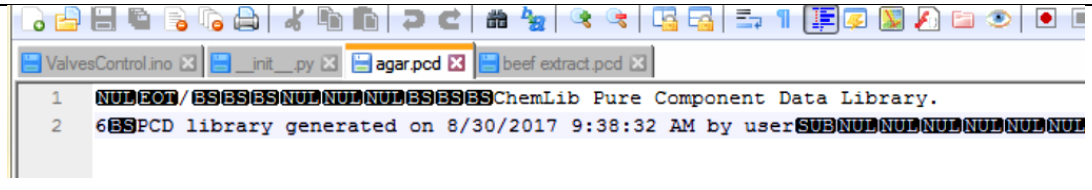
6.1 Flowsheet



6.2 Compounds (pcd files)

all	pcd-Files.zip
Agar Chloroform Corn steep liquor CuSO4 . 5H2O FeSO4 . 7H2O KCl MgSO4 . 7H2O NaNO3 Peptone Phosphate buffer Sucrose Yeast extract ZnSO4 . 7H2O	corn steep liquor.log, corn steep liquor.pcd, CuSO4.5H2O.log, CuSO4.5H2O.pcd, FeSO4.7H2O.log, FeSO4.7H2O.pcd, glucose.log, glucose.pcd, KCl.log, KCl.pcd, metal solution.log, metal solution.pcd, MgSO4·7H2O .log, MgSO4·7H2O .pcd, NaNO3.log, NaNO3.pcd, peptone.log, peptone.pcd, phosphate buffer.log, phosphate buffer.pcd, sucrose.log, sucrose.pcd, yeastextract.log, yeastextract.pcd, ZnSO4·7H2O.log, ZnSO4·7H2O.pcd, agar.log, agar.pcd, amylacetate.log, amylacetate.pcd, beef extract.log, beef extract.pcd, chloroform.log, chloroform.pcd

6.2.1 Example files

agar.log	agar.log	Added component 13097 agar agar; LIX=13097; CAS number[70]; old=; new=9002-18-0; chk=126179476; on 8/30/2017 9:45:08 AM by user agar; CAS=9002-18-0; Molecular weight[13]; old=*; new=336.337; chk=146441160; on 8/30/2017 9:51:53 AM by user agar; CAS=9002-18-0; Structure[3]; old=; new=C14H24O9; chk=177770139; on 8/30/2017 10:08:35 AM by user agar; CAS=9002-18-0; Molecular weight[13]; old=336.337; new=336.3382; chk=180295062; on 8/30/2017 10:08:39 AM by user agar; CAS=9002-18-0; Family[4]; old=0; new=73; chk=185080742; *->other polyfunctional organics on 8/30/2017 10:28:49 AM by user Added component 19599 NaNO3 NaNO3; LIX=19599; CAS number[70]; old=; new=7631-99-4; chk=133951884; on 8/30/2017 10:41:34 AM by user NaNO3; CAS=7631-99-4; Molecular weight[13]; old=*; new= 84.99; chk=180189686; on 8/30/2017 10:42:11 AM by user NaNO3; CAS=7631-99-4; Structure[3]; old=; new=NaNO3; chk=205267212; on 8/30/2017 11:04:42 AM by user NaNO3; CAS=7631-99-4; Structure[3]; old=NaNO3; new=NNaO3; chk=205267193; on 8/30/2017 11:05:16 AM by user NaNO3; CAS=7631-99-4; Molecular weight[13]; old=84.99; new=84.99467; chk=195302116; on 8/30/2017 11:05:18 AM by user NaNO3; CAS=7631-99-4; Molecular weight[13]; old=84.99467; new=84.994; chk=206263521; on 8/30/2017 11:05:34 AM by user NaNO3; CAS=7631-99-4; Family[4]; old=0; new=80; chk=211514386; *->sodium salts on 8/30/2017 11:08:35 AM by user
Agar.pcd	agar.pcd	

7.1 Chemicals from Sigma Aldrich

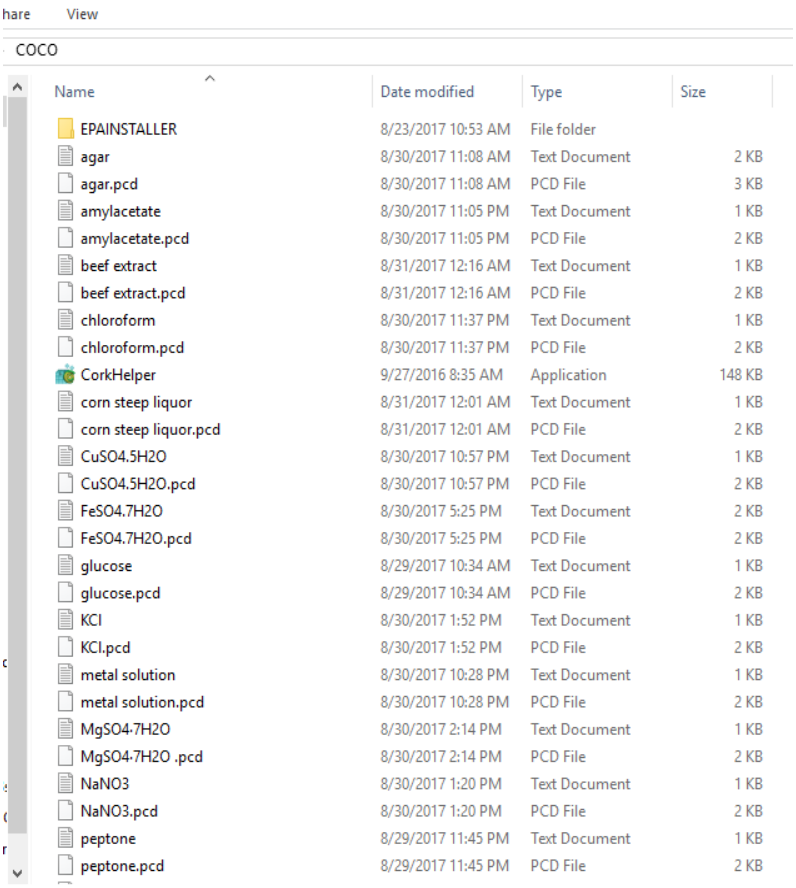
Latvia

SIA LABOCHEMA LATVIJA
Riga, Latvia
Phone: +371 67553688
Fax: +371 67553688
Email: info@labochema.lv
Website: http://www.labochema.lv/

Lebanon

Ibra Hadad Et Fils
Jdeideh-Nahr El Mott
Roumieh Old Road -Near Mazda
Unileb Bldg-2nd Floor
Phone: 96119013245
Fax: 96119013245
Email: ibra@ibrahadad.com
Website: Export Sales and Service

7.1.1 new compounds on coco



hare View

COCO

Name	Date modified	Type	Size
EPAINSTALLER	8/23/2017 10:53 AM	File folder	
agar	8/30/2017 11:08 AM	Text Document	2 KB
agar.pcd	8/30/2017 11:08 AM	PCD File	3 KB
amylacetate	8/30/2017 11:05 PM	Text Document	1 KB
amylacetate.pcd	8/30/2017 11:05 PM	PCD File	2 KB
beef extract	8/31/2017 12:16 AM	Text Document	1 KB
beef extract.pcd	8/31/2017 12:16 AM	PCD File	2 KB
chloroform	8/30/2017 11:37 PM	Text Document	1 KB
chloroform.pcd	8/30/2017 11:37 PM	PCD File	2 KB
CorkHelper	9/27/2016 8:35 AM	Application	148 KB
corn steep liquor	8/31/2017 12:01 AM	Text Document	1 KB
corn steep liquor.pcd	8/31/2017 12:01 AM	PCD File	2 KB
CuSO4.5H2O	8/30/2017 10:57 PM	Text Document	1 KB
CuSO4.5H2O.pcd	8/30/2017 10:57 PM	PCD File	2 KB
FeSO4.7H2O	8/30/2017 5:25 PM	Text Document	2 KB
FeSO4.7H2O.pcd	8/30/2017 5:25 PM	PCD File	2 KB
glucose	8/29/2017 10:34 AM	Text Document	1 KB
glucose.pcd	8/29/2017 10:34 AM	PCD File	2 KB
KCl	8/30/2017 1:52 PM	Text Document	1 KB
KCl.pcd	8/30/2017 1:52 PM	PCD File	2 KB
metal solution	8/30/2017 10:28 PM	Text Document	1 KB
metal solution.pcd	8/30/2017 10:28 PM	PCD File	2 KB
MgSO4·7H2O	8/30/2017 2:14 PM	Text Document	1 KB
MgSO4·7H2O .pcd	8/30/2017 2:14 PM	PCD File	2 KB
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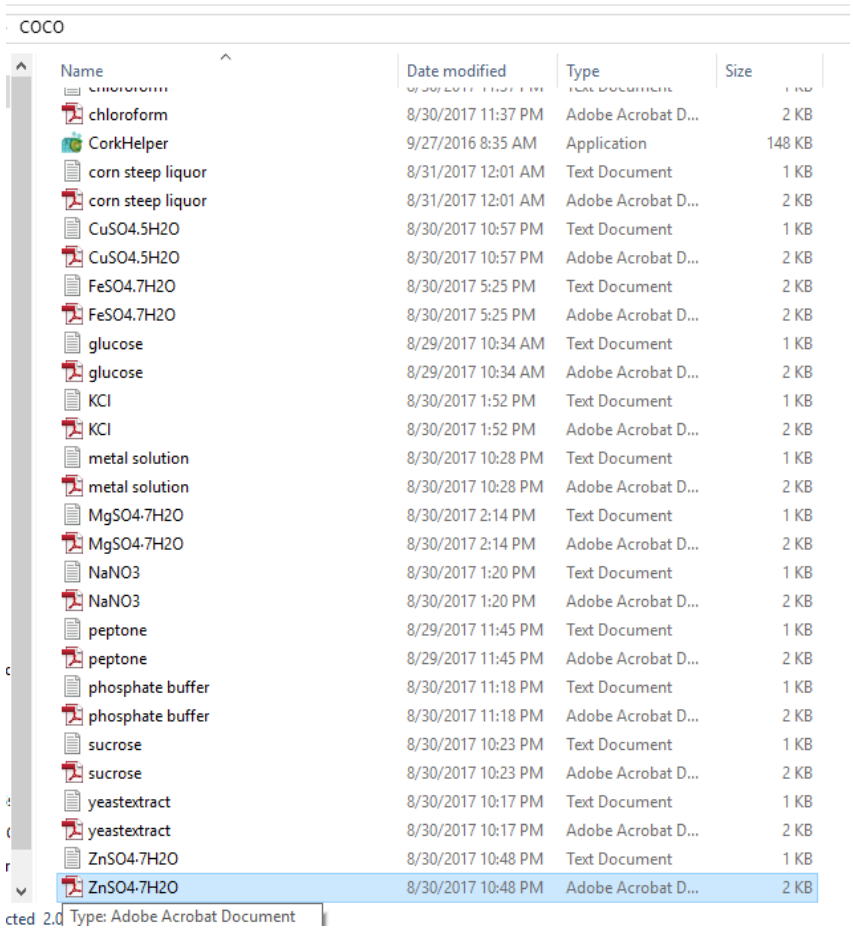
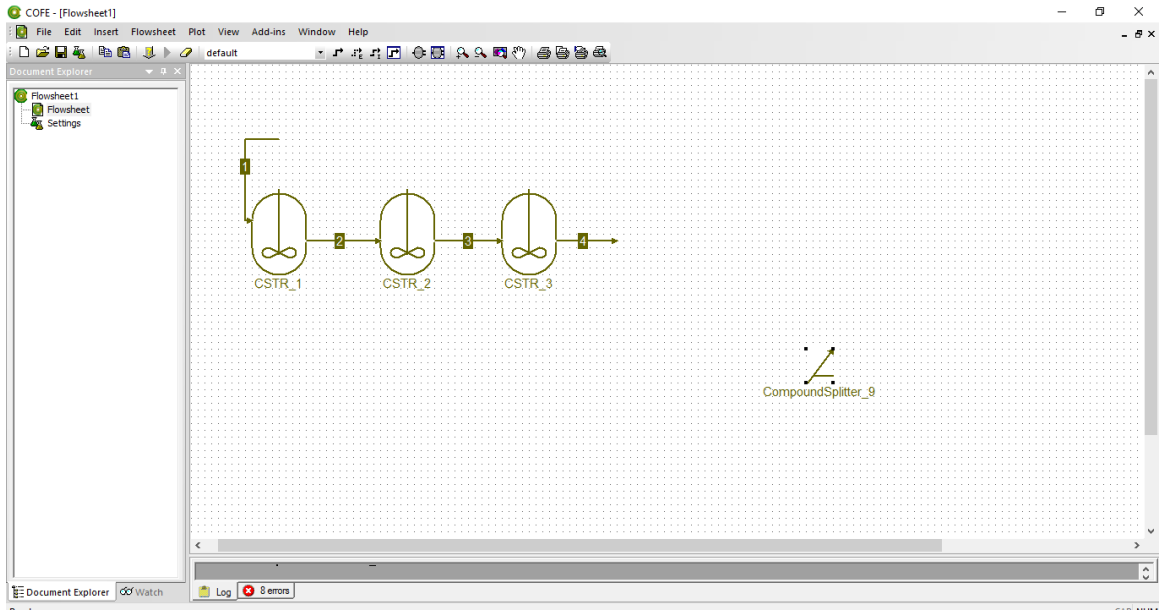
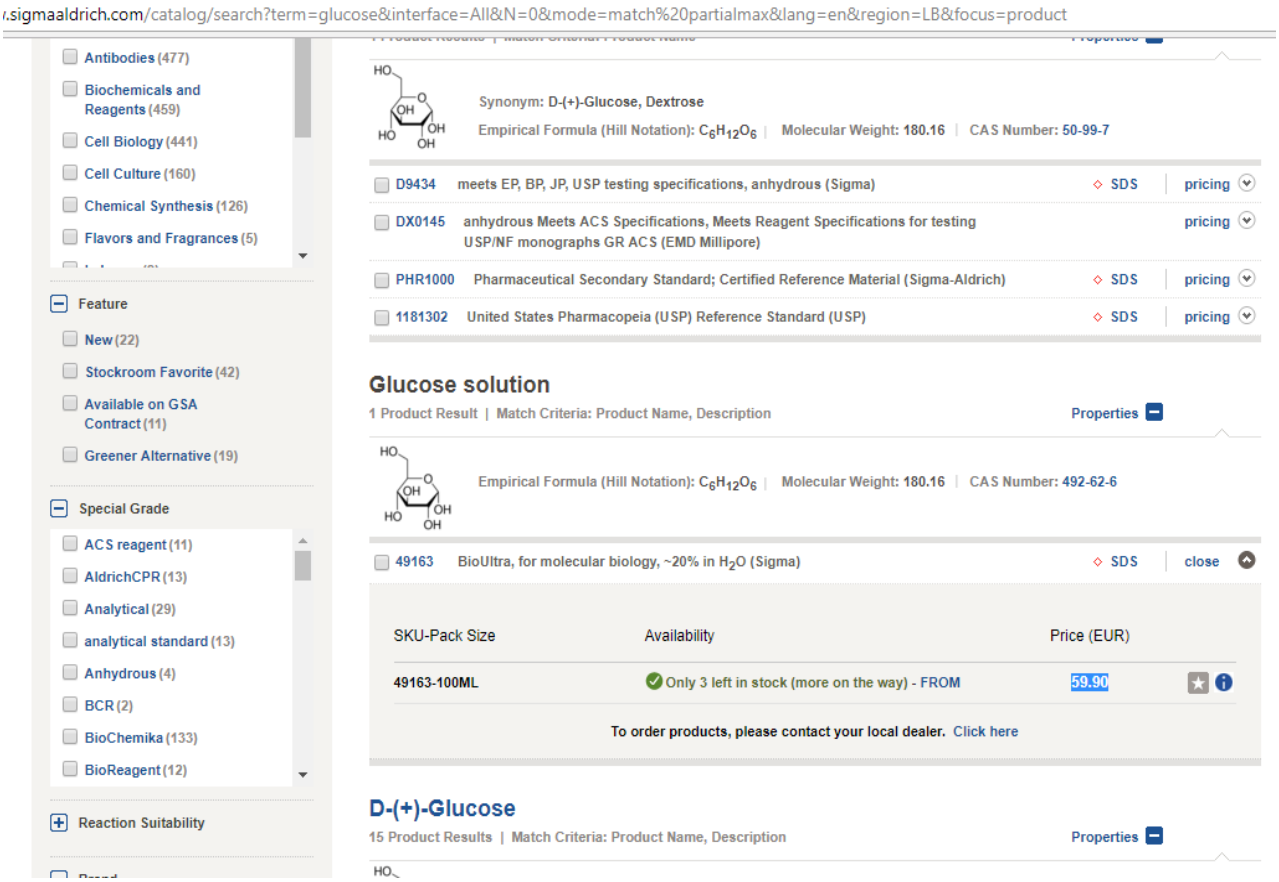
NaNO3.pcd	8/30/2017 1:20 PM	PCD File	2 KB
peptone	8/29/2017 11:45 PM	Text Document	1 KB
peptone.pcd	8/29/2017 11:45 PM	PCD File	2 KB



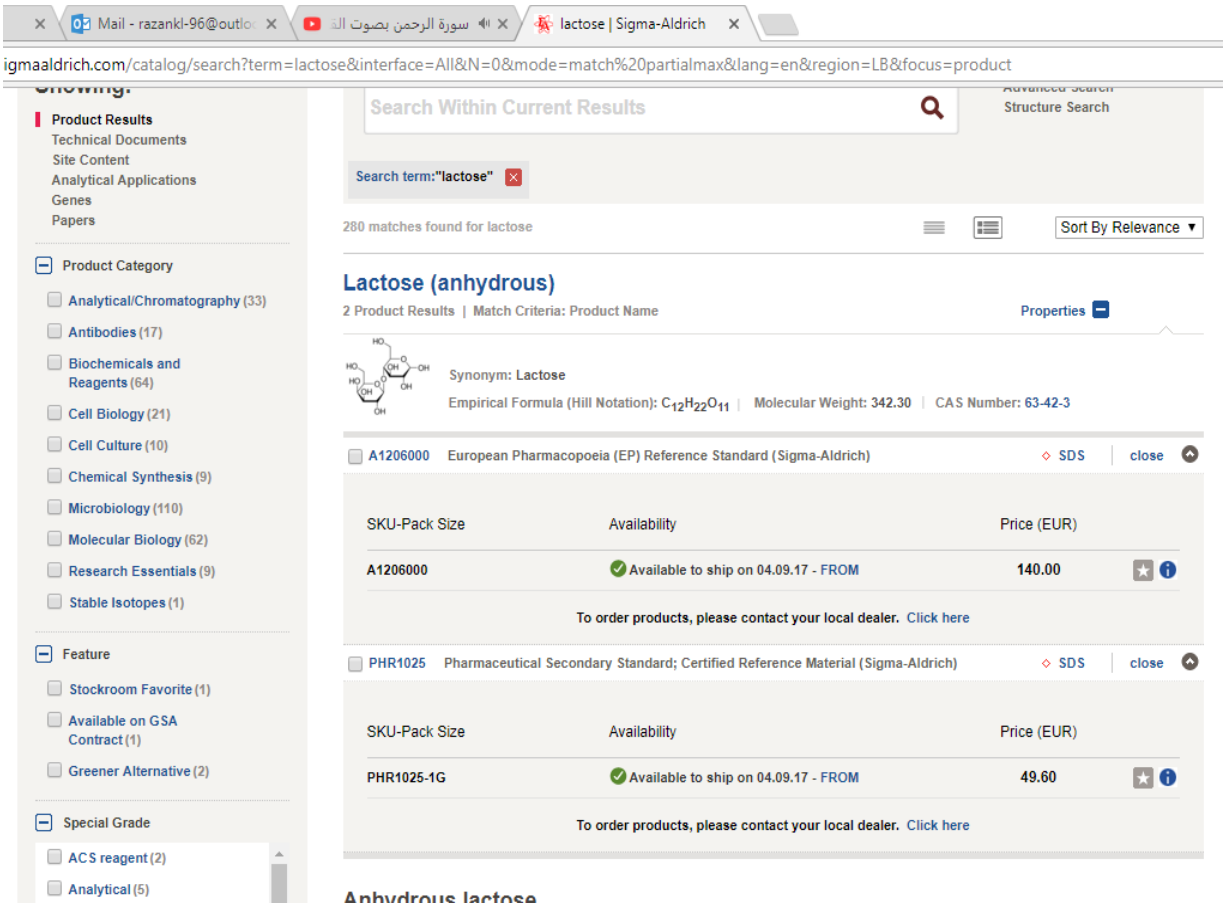
Problem: I can't use these compounds in coco (cofe 64)



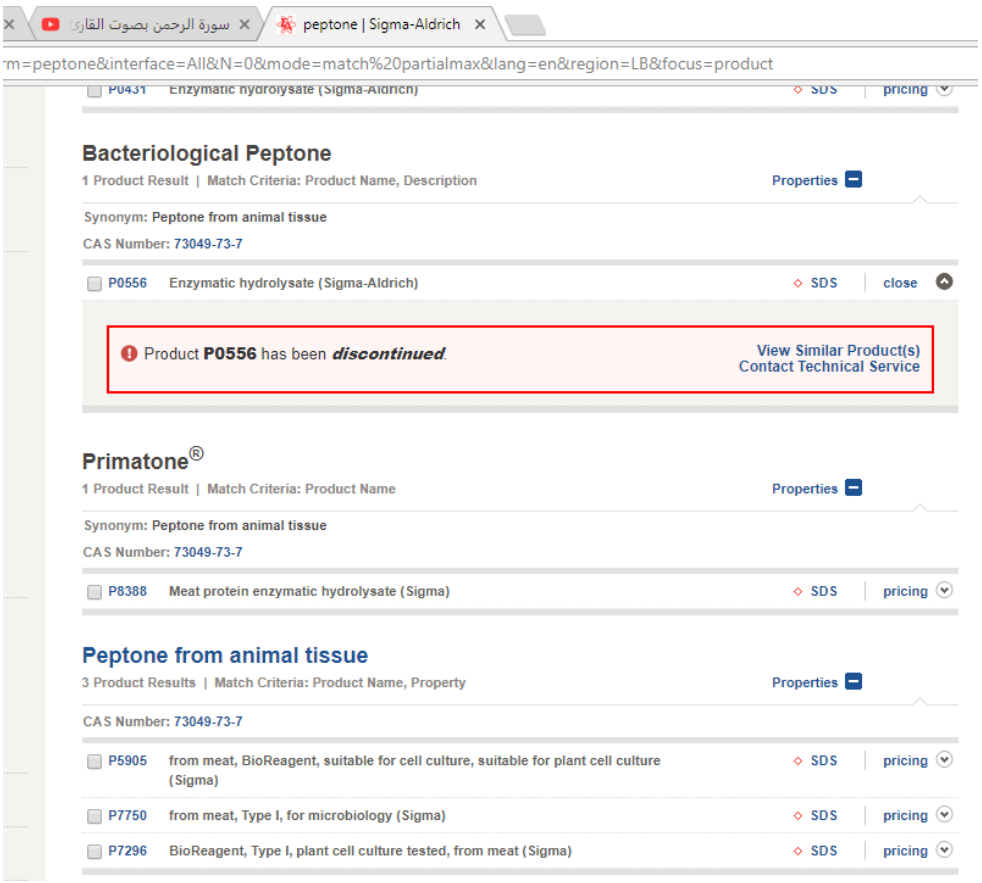
7.1.2 Glucose:



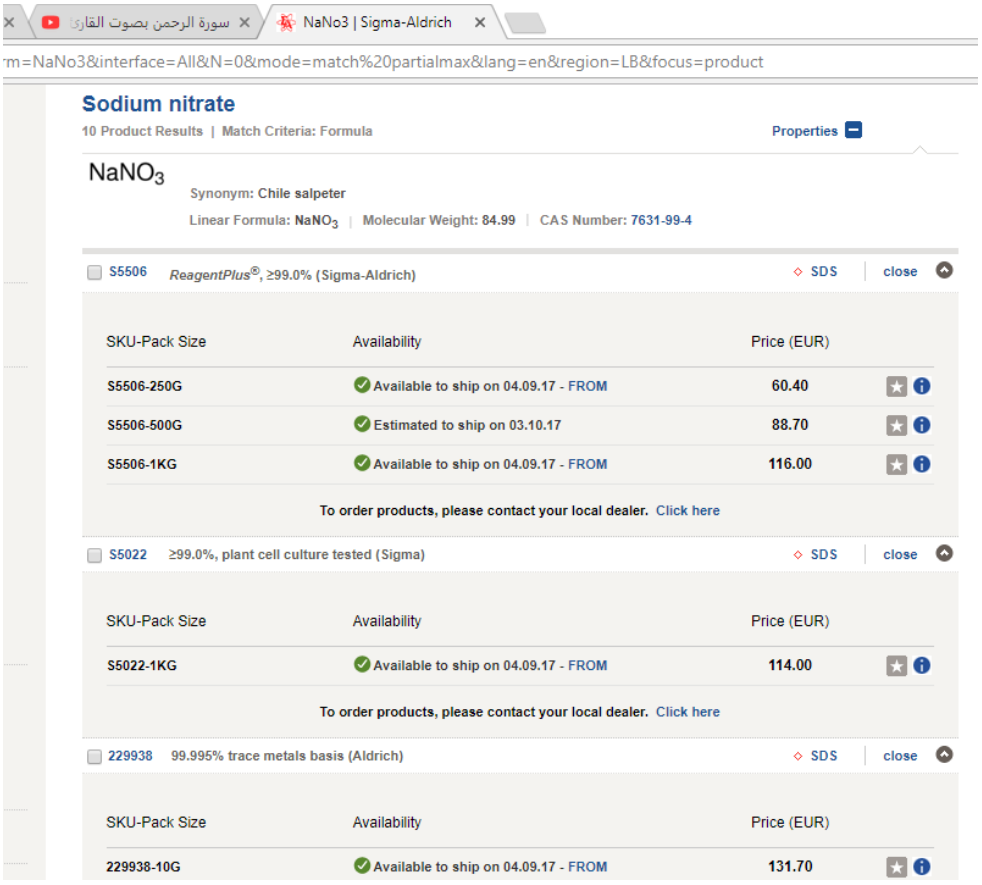
7.1.3 Lactose:

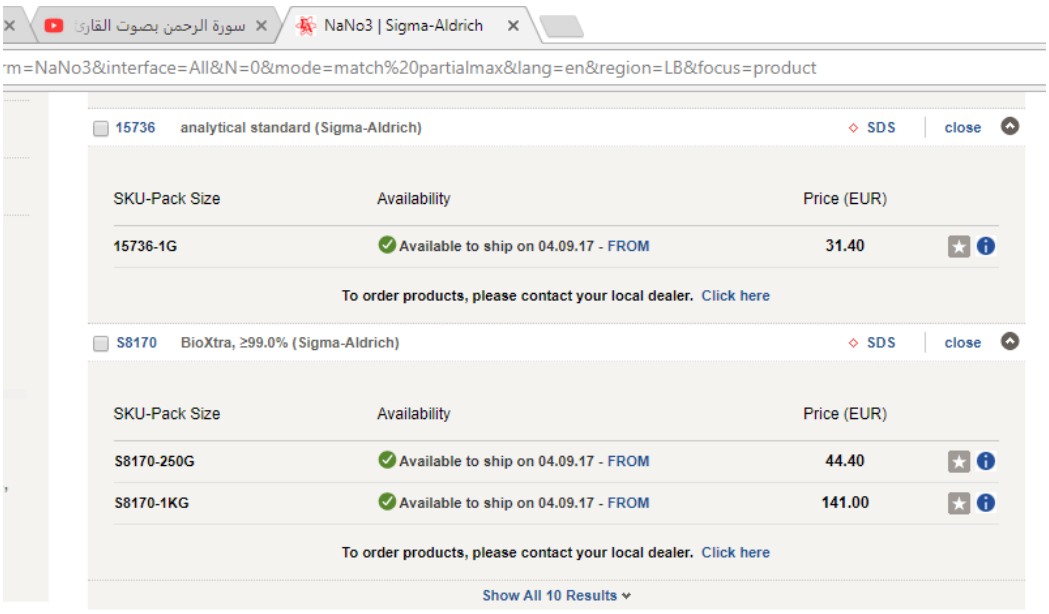


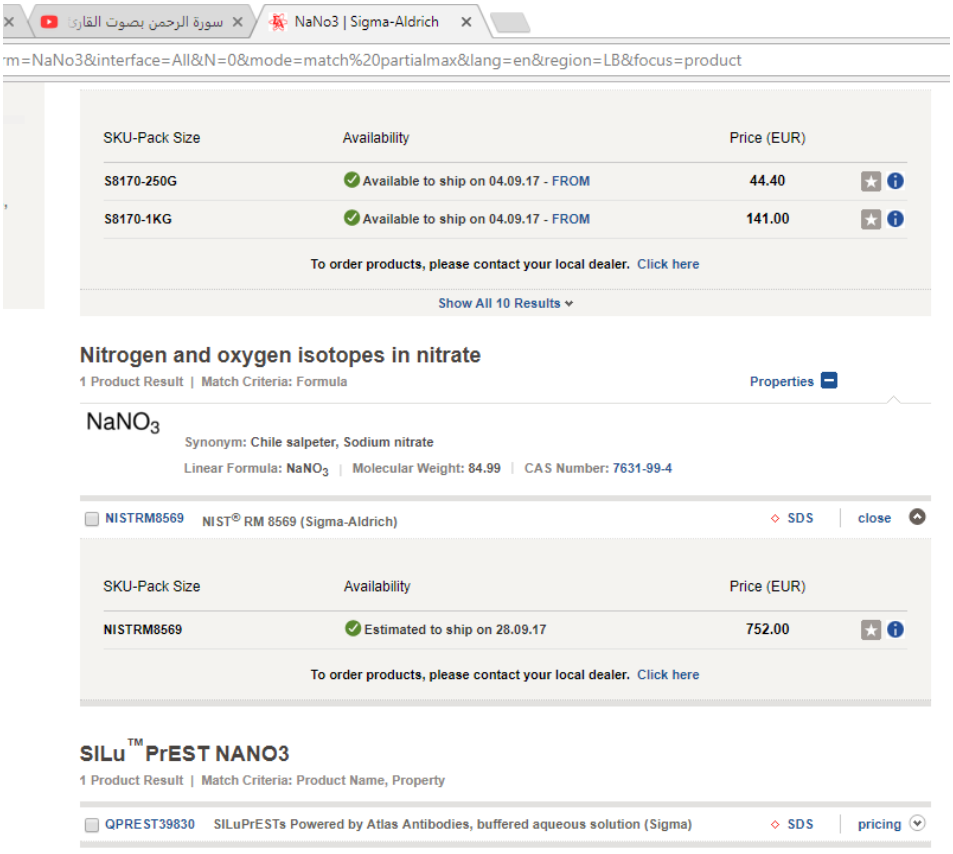
7.1.4 Peptone:



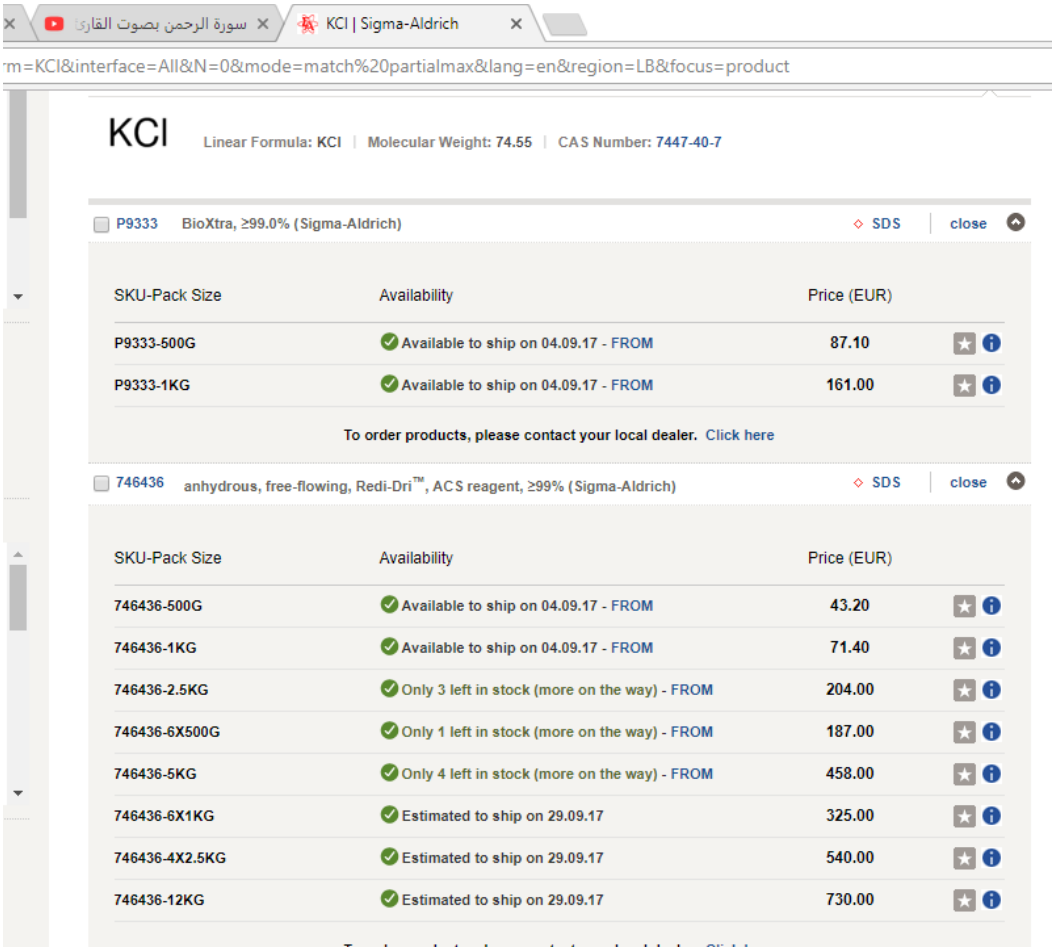
7.1.5 NaNO3:




سورة الرحمن بصوت القارئ
NaNo3 | Sigma-Aldrich
m=NaNo3&interface=All&N=0&mode=match%20partialmax&lang=en&region=LB&focus=product
15736 analytical standard (Sigma-Aldrich)
SDS
close
SKU-Pack Size
Availability
Price (EUR)
15736-1G
Available to ship on 04.09.17 - FROM
31.40
To order products, please contact your local dealer. Click here
S8170 BioXtra, ≥99.0% (Sigma-Aldrich)
SDS
close
SKU-Pack Size
Availability
Price (EUR)
S8170-250G
Available to ship on 04.09.17 - FROM
44.40
S8170-1KG
Available to ship on 04.09.17 - FROM
141.00
To order products, please contact your local dealer. Click here
Show All 10 Results
Nitrogen and oxygen isotopes in nitrate
1 Product Result | Match Criteria: Formula
Properties
NaNO3
Synonym: Chile salpeter, Sodium nitrate
Linear Formula: NaNO3 | Molecular Weight: 84.99 | CAS Number: 7631-99-4
NISTRM8569 NIST® RM 8569 (Sigma-Aldrich)
SDS
close
SKU-Pack Size
Availability
Price (EUR)


سورة الرحمن بصوت القارئ
NaNo3 | Sigma-Aldrich
m=NaNo3&interface=All&N=0&mode=match%20partialmax&lang=en&region=LB&focus=product
SKU-Pack Size
Availability
Price (EUR)
S8170-250G
Available to ship on 04.09.17 - FROM
44.40
S8170-1KG
Available to ship on 04.09.17 - FROM
141.00
To order products, please contact your local dealer. Click here
Show All 10 Results
Nitrogen and oxygen isotopes in nitrate
1 Product Result | Match Criteria: Formula
Properties
NaNO3
Synonym: Chile salpeter, Sodium nitrate
Linear Formula: NaNO3 | Molecular Weight: 84.99 | CAS Number: 7631-99-4
NISTRM8569 NIST® RM 8569 (Sigma-Aldrich)
SDS
close
SKU-Pack Size
Availability
Price (EUR)
NISTRM8569
Estimated to ship on 28.09.17
752.00
To order products, please contact your local dealer. Click here
SILu™ PrEST NANO3
1 Product Result | Match Criteria: Product Name, Property
QPREST39830 SILuPrESTs Powered by Atlas Antibodies, buffered aqueous solution (Sigma)
SDS
pricing

7.1.6 KCl


سورة الرحمن بصوت القارئ
KCl | Sigma-Aldrich
rm=KCl&interface=All&N=0&mode=match%20partialmax&lang=en&region=LB&focus=product
KCl
Linear Formula: KCl | Molecular Weight: 74.55 | CAS Number: 7447-40-7
P9333 BioXtra, ≥99.0% (Sigma-Aldrich)
SDS
close
SKU-Pack Size
Availability
Price (EUR)
P9333-500G
Available to ship on 04.09.17 - FROM
87.10
P9333-1KG
Available to ship on 04.09.17 - FROM
161.00
To order products, please contact your local dealer. Click here
746436 anhydrous, free-flowing, Redi-Dri™, ACS reagent, ≥99% (Sigma-Aldrich)
SDS
close
SKU-Pack Size
Availability
Price (EUR)
746436-500G
Available to ship on 04.09.17 - FROM
43.20
746436-1KG
Available to ship on 04.09.17 - FROM
71.40
746436-2.5KG
Only 3 left in stock (more on the way) - FROM
204.00
746436-6X500G
Only 1 left in stock (more on the way) - FROM
187.00
746436-5KG
Only 4 left in stock (more on the way) - FROM
458.00
746436-6X1KG
Estimated to ship on 29.09.17
325.00
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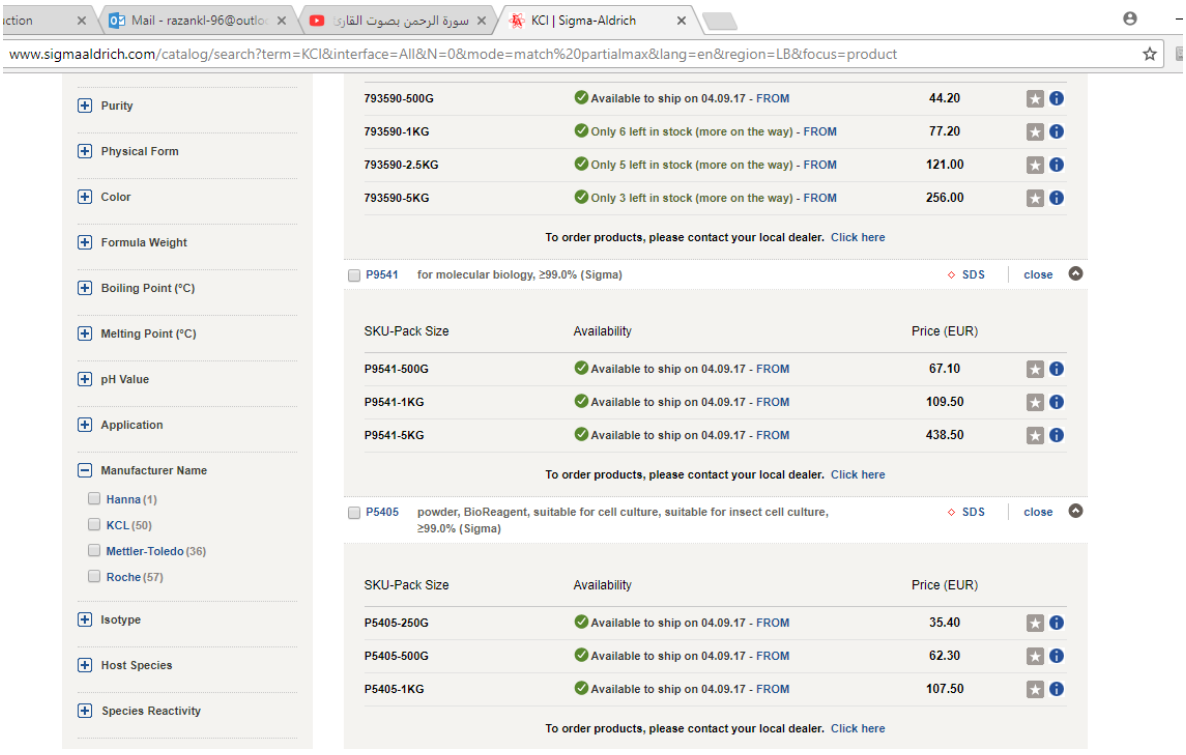
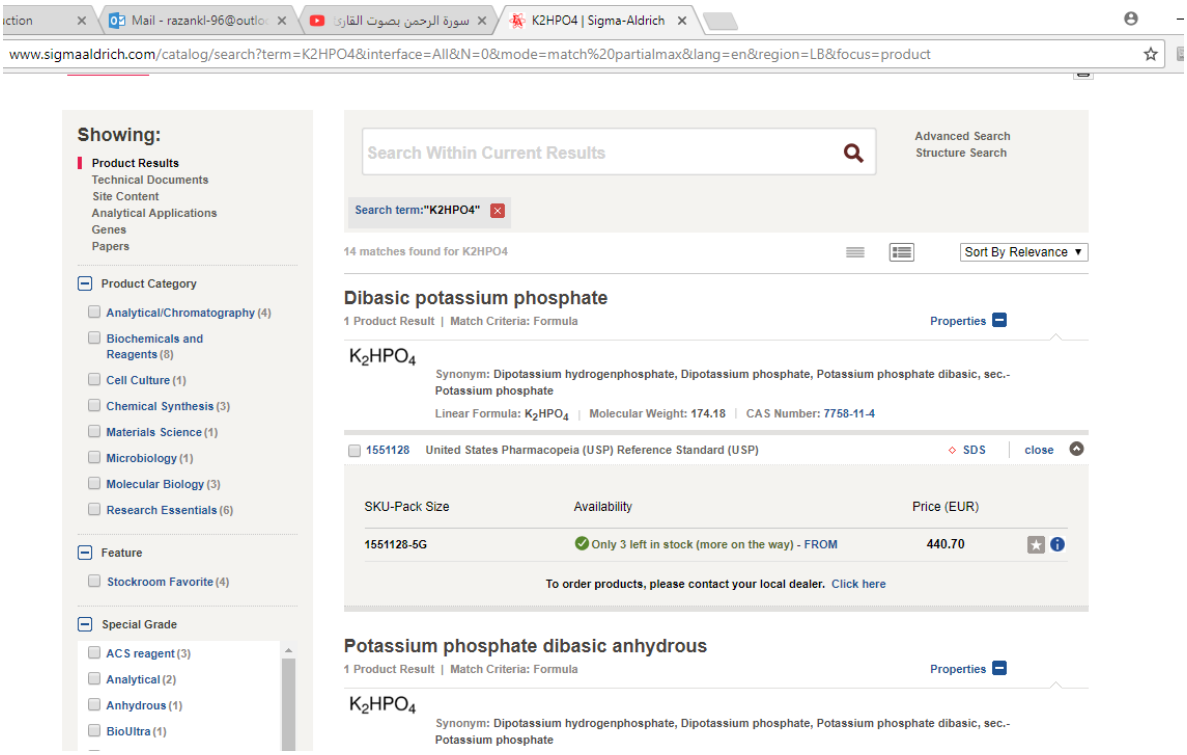
730.00


Mail - razankl-96@outlo
سورة الرحمن بصوت القارئ
KCl | Sigma-Aldrich
www.sigmaaldrich.com/catalog/search?term=KCl&interface=All&N=0&mode=match%20partialmax&lang=en&region=LB&focus=product
Purity
Physical Form
Color
Formula Weight
Boiling Point (°C)
Melting Point (°C)
pH Value
Application
Manufacturer Name
Hanna (1)
KCL (50)
Mettler-Toledo (36)
Roche (57)
Isotype
Host Species
Species Reactivity
793590-500G
Available to ship on 04.09.17 - FROM
44.20
793590-1KG
Only 6 left in stock (more on the way) - FROM
77.20
793590-2.5KG
Only 5 left in stock (more on the way) - FROM
121.00
793590-5KG
Only 3 left in stock (more on the way) - FROM
256.00
To order products, please contact your local dealer. Click here
P9541 for molecular biology, ≥99.0% (Sigma)
SDS
close
SKU-Pack Size
Availability
Price (EUR)
P9541-500G
Available to ship on 04.09.17 - FROM
67.10
P9541-1KG
Available to ship on 04.09.17 - FROM
109.50
P9541-5KG
Available to ship on 04.09.17 - FROM
438.50
To order products, please contact your local dealer. Click here
P5405 powder, BioReagent, suitable for cell culture, suitable for insect cell culture, ≥99.0% (Sigma)
SDS
close
SKU-Pack Size
Availability
Price (EUR)
P5405-250G
Available to ship on 04.09.17 - FROM
35.40
P5405-500G
Available to ship on 04.09.17 - FROM
62.30
P5405-1KG
Available to ship on 04.09.17 - FROM
107.50
To order products, please contact your local dealer. Click here

7.1.7 K2HPO4


K2HPO4 | Sigma-Aldrich
www.sigmaaldrich.com/catalog/search?term=K2HPO4&interface=All&N=0&mode=match%20partialmax&lang=en&region=LB&focus=product
Showing:
Product Results
Technical Documents
Site Content
Analytical Applications
Genes
Papers
Product Category
Analytical/Chromatography (4)
Biochemicals and Reagents (8)
Cell Culture (1)
Chemical Synthesis (3)
Materials Science (1)
Microbiology (1)
Molecular Biology (3)
Research Essentials (6)
Feature
Stockroom Favorite (4)
Special Grade
ACS reagent (3)
Analytical (2)
Anhydrous (1)
BioUltra (1)
Search Within Current Results
Advanced Search
Structure Search
Search term:"K2HPO4"
14 matches found for K2HPO4
Sort By Relevance
Dibasic potassium phosphate
1 Product Result | Match Criteria: Formula
Properties
K2HPO4
Synonym: Dipotassium hydrogenphosphate, Dipotassium phosphate, Potassium phosphate dibasic, sec.-Potassium phosphate
Linear Formula: K2HPO4 | Molecular Weight: 174.18 | CAS Number: 7758-11-4
1551128 United States Pharmacopeia (USP) Reference Standard (USP)
SDS
close
SKU-Pack Size
Availability
Price (EUR)
1551128-5G
Only 3 left in stock (more on the way) - FROM
440.70
To order products, please contact your local dealer. Click here
Potassium phosphate dibasic anhydrous
1 Product Result | Match Criteria: Formula
Properties
K2HPO4
Synonym: Dipotassium hydrogenphosphate, Dipotassium phosphate, Potassium phosphate dibasic, sec.-Potassium phosphate

8 Suppliers

8.1 Chemicals, Devices, Molecular Biology

8.1.1 Burhan Kabbara, Tripoli, Tel. 03/339523

8.1.2 Jaudat al-Khatib, Tel. 70916173

RC.TRADING
Tel :961 3 888 809 Fax:00961 7 739 333
Email:jawdathkatib80@gmail.com

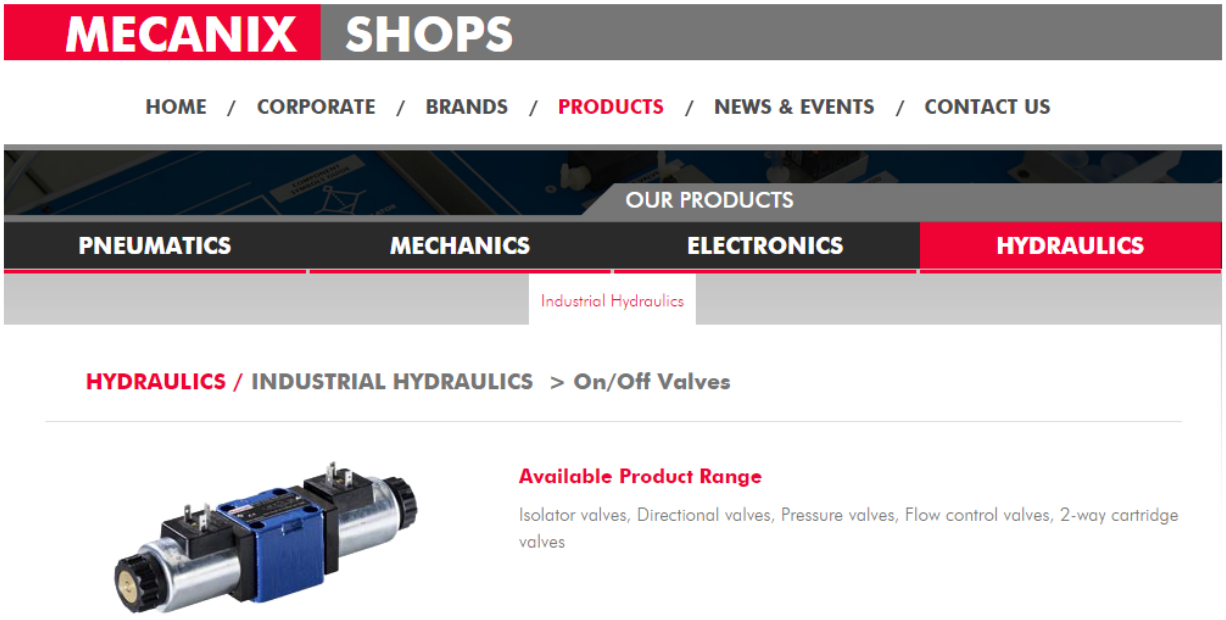
8.2 Mechanical Parts (Valves, Sensors)

Sin El Fil, Horch Tabet
P. : +961-1-486701/2 - +961-1-490754/5
M. : +961-3-783778 / +961-3-763678
F. : +961-1-490929

| +961-76-500880

Mail : P.O. Box 55384 Beirut, Lebanon
Email : sales@mecanixshops.com

8.2.1 Valves



8.2.2 Temperature Sensors

ELECTRONICS / SENSORS > THERMOCOUPLE

Available Product Range

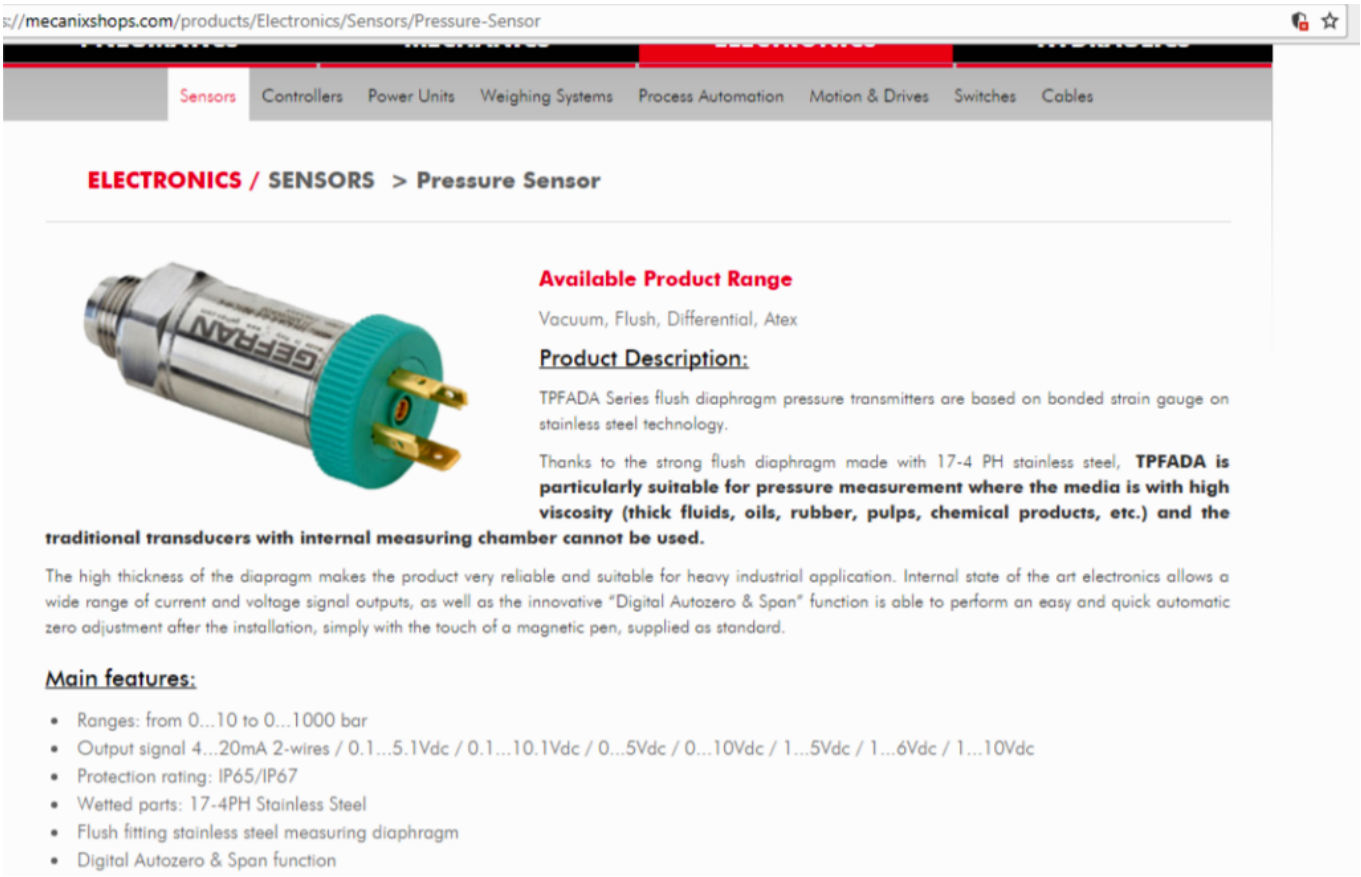
Din Head, Air Probe, MGO, Ceramic, SS316

Product Description:

PT100 EASY-UP

Diameter 6mm, three-wires cable

8.2.3 Pressure Sensors



8.2.4 Flow Meters

https://mecanixshops.com/products/Electronics/Process-Automation/Flow-Meter

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OUR PRODUCTS

PNEUMATICS | MECHANICS | ELECTRONICS

Sensors | Controllers | Power Units | Weighing Systems | Process Automation | Motion & Drives | Switch

ELECTRONICS / PROCESS AUTOMATION > Flow Meter

Available Product Range

Magnetic, Ultrasonic, Rotary, Mass

8.2.5 Visualization Software

s://mecanixshops.com/products/Electronics/Process-Automation/Process-visualization-software

OUR PRODUCTS

PNEUMATICS | MECHANICS | ELECTRONICS | HYDRAULICS

Sensors | Controllers | Power Units | Weighing Systems | Process Automation | Motion & Drives | Switches | Cables

ELECTRONICS / PROCESS AUTOMATION > Process Visualization Software

Available Product Range

-Tank configuration-Transmitter configuration-Tankpark visualization-Displaying of measured values-Displaying of limit values-Trend monitoring-Data logging-Database handling-Archiving-Other log functions(alarm)-Remote connection (LAN or Internet)

Product Description:

- -Tank configuration
- -Transmitter configuration
- -Tankpark visualization
- -Displaying of measured values
- -Displaying of limit values
- -Trend monitoring
- -Data logging
- -Database handling
- -Archiving
- -Other log functions (alarms)
- -Remote connection (LAN or Internet)

9 مراجع (References)

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[6] https://pypi.python.org/pypi/PyCmdMessenger

https://www.google.com/patents/US2488559

https://penicillin.wikispaces.com/General+bioprocess+flow

https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=9&cad=rja&uact=8&ved=0ahUKEwiM4a6bzqXYAhVFIlAKHZzSDOwQFghrMAg&url=https%3A%2F%2Fen.wikipedia.org%2Fwiki%2FAmyl_acetate&usg=AOvVaw2fpr6RAqeyoDOFpf6mBSvz

http://www.encyclopedia.com/science/academic-and-educational-journals/amyl-acetate