Cambridge Consultants

COST OF GOODS AND MANUFACTURING ANALYSIS OF GENEXPERT CARTRIDGES

FINAL REPORT

Médecins Sans Frontières

Report: Approval and Disclaimer

This report was produced by Cambridge Consultants Limited for Médecins Sans Frontières under terms specifically limiting the Author's liability. The material in it reflects the Author's judgement in the light of information available to it at the time of preparation. Any use which a third party makes of this report, or any reliance on, or decisions to be made based on it, are the responsibility of such third party. The Author accepts no responsibility for damages, if any, suffered by any third party as a result of decisions made or actions taken based on this report.

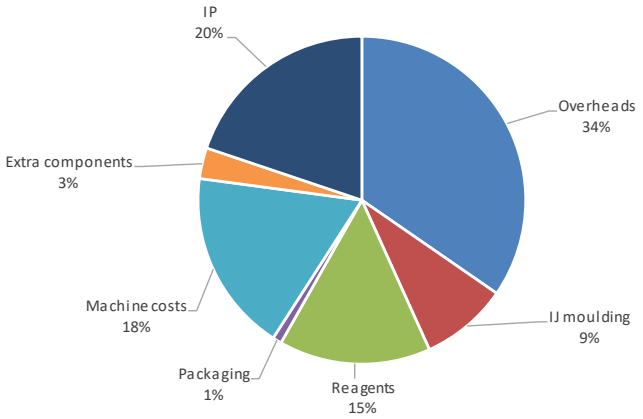
EXECUTIVE SUMMARY

Our high level estimate for the Cost of Goods of the Cepheid GeneXpert MTB/RIF Ultra cartridge is $8.82

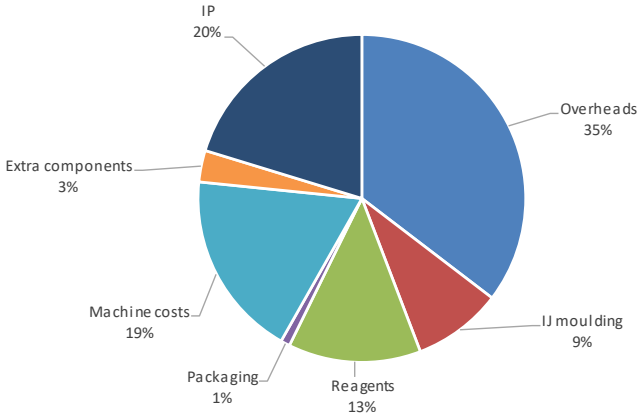
Cartridge analysis – Cepheid GeneXpert MTB/RIF Ultra	
Product Cost of Goods	**US$8.82**
Principal cost parameters	Majority of cost is attributed to Overheads
Manufacturing complexity	High
Additional costs to complete test	None; cartridge comprises of all reagents and packaging required from sample preparation through to test implementation (sample reagent is outside of cartridge)
Transportation requirements	Requires storage at 2-8℃

- Our Cost of Goods estimate for the GeneXpert MTB/RIF cartridge is **$8.63**; the slight reduction in COGS relative to the Ultra cartridge is due to a reduction in cost of reagents
- Based on our high-level analysis, we do not observe significant differences in cartridge manufacturing from an engineering standpoint that justify separate production lines between the TB cartridges (based on MTB/RIF Ultra) and the viral load cartridges (based on HCV-VL)

MTB/RIF Ultra cost breakdown



MTB/RIF cost breakdown

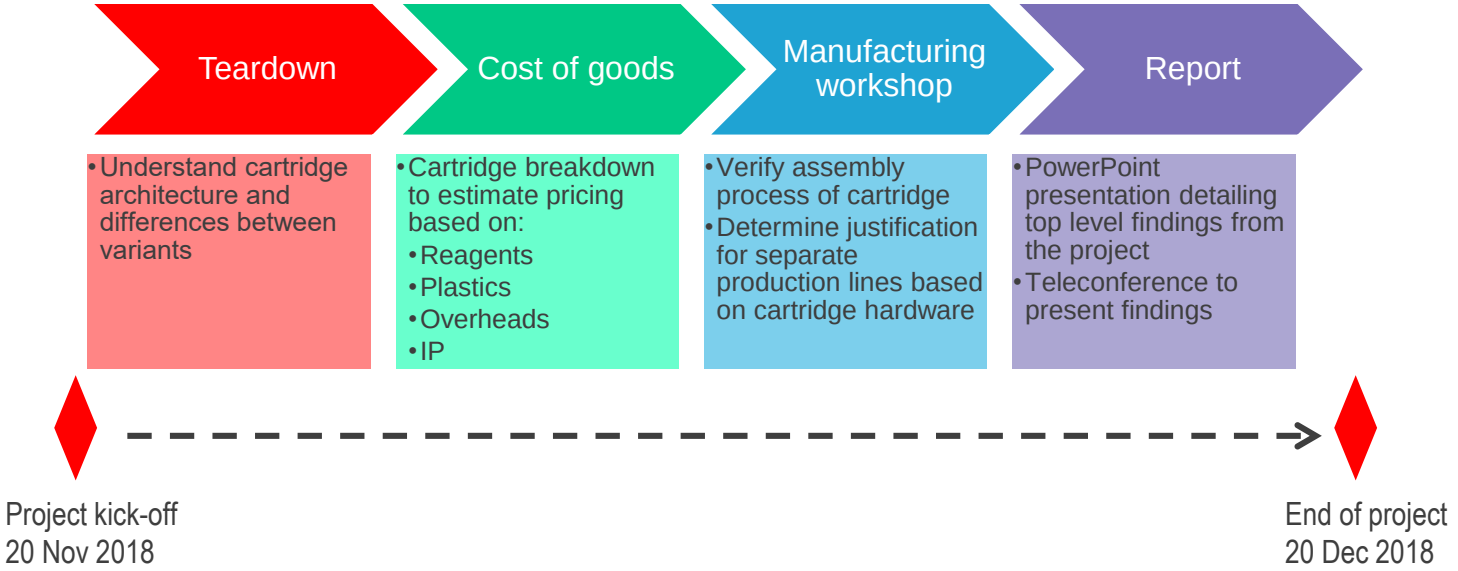


AGENDA

METHODOLOGY

We have taken a systematic approach to evaluating COGS

- By taking costs of the cartridge system we have additionally gained an understanding of the system architecture and the process by which these products are produced
  - Additional cartridge information as a result of the project process is found in the appendix



METHODOLOGY

Top-level project assumptions

Assumption ID	Description
A1	Technical assumptions are based on Cambridge Consultants' expert opinion of point-of-care diagnostics and manufacturing engineering experience
A2	Labour cost and overheads are for European manufacturing ($26.22/hr Labour, $19.67/hr overheads) and 1 working week comprises 40 hours
A3	Our estimate for Cost of Goods is expected to be within +/-20% of the actual cost of the cartridges
A4	Exchange rate £1 = $1.26 (previous assessment was £1 = $1.46)
A5	Average European inflation of 1% per annum since 2014 (updated cost is 104.1% of the estimation from 2014)
A6	Manufacturing rate of 1 million TB cartridges per variant per year
A7	All TB cartridges assembled on one production line, and virology (specifically those available in the HBDC pricing) cartridges on the other

AGENDA

CARTRIDGE TEARDOWN

Teardown of the cartridges was performed in Cambridge Consultants' analytical labs

- This task was performed to:
  - Understand cartridge architecture
  - Provide hardware input for the production engineering workshop
  - Provide basis for COGS estimation

Part ID	Moulding description	Material	Additional parts included
1 – Lid	Single open shut tool and heat-sealed film	Polypropylene + Polyethylene film	N/A
2 – Reagent chamber	Tool with over mould and 1 side action	Polypropylene + over moulded TEP	Polypropylene retention beads, liquid filters, label
3 – Reaction chamber (cuvette)	Single open shut tool and 2 x heat-sealed films	Polycarbonate + Polypropylene film	N/A
4 – Plunger valve	3 part assembly bonded with UV cured glue	Polycarbonate	Cell filter, rubber stopper
5 – Base	Single open shut tool	Polypropylene	N/A

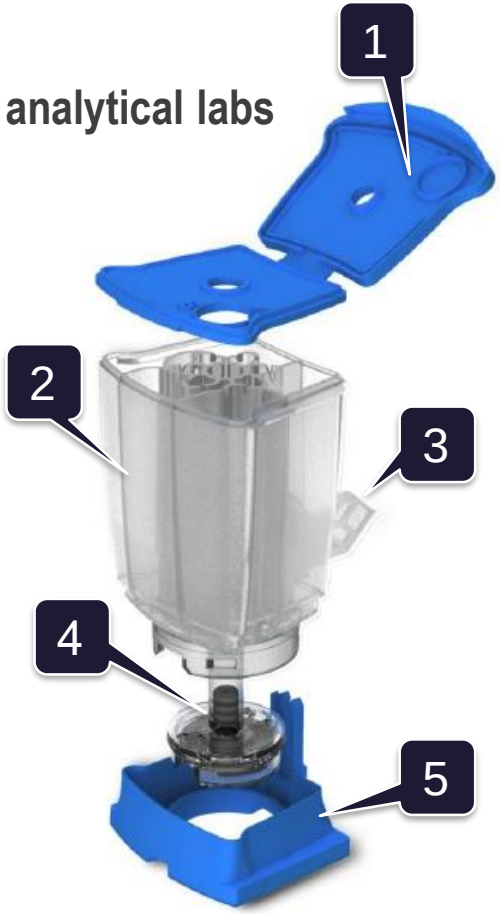


Image taken from http://www.moleculartb.org/gb/pdf/ppt/13_SYMP_ISoundiram_GeneXperttech_2902.pdf

CARTRIDGE TEARDOWN

We have highlighted qualitative component differences between cartridges

Part ID	MTB/RIF Ultra	HCV-VL
1 – Lid	Orientation of heat-sealed film above interface with reagent chamber lumens	
2 – Reagent chamber	3 retaining beads and 2 filters inserted	Only 2 retaining beads and no filters; additional removable polypropylene part is placed in the sample collection lumen
3 – Cuvette	Different geometry of part, same fabrication process	
4 – Plunger valve	3 parts, bottom has ultrasonic coupler geometry, circular filter included within assembly	3 parts, plunger part is identical but other 2 parts have different geometry and no ultrasonic coupler geometry, rectangular filter included within assembly
5 - Base	No difference	

- Additional details and images are found in the appendix

AGENDA

COST OF GOODS ANALYSIS

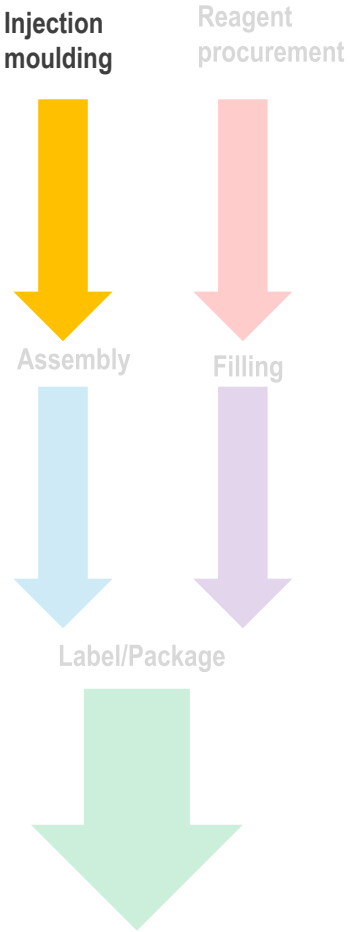
We determined a high-level cost of goods based on a verified systematic process

- There are four main estimation processes
  - Plastics; proprietary manufacturing analysis tool for estimation of costs for injection moulded parts
  - Reagent pricing; analysis of reagent costs based on wholesale batch manufacturing
  - Assembly and filling; use of internal engineering know-how
  - Packaging; estimations based on non-binding quotations
- Additionally we considered IP licensing costs
- We focussed analysis on the MTB/RIF Ultra cartridge and extrapolated values to the MTB/RIF cartridge
  - At this level of discrimination the only difference in cost of goods between the two cartridges is due to the reagents

AGENDA

Plastic part cost estimation is based on proprietary design tools

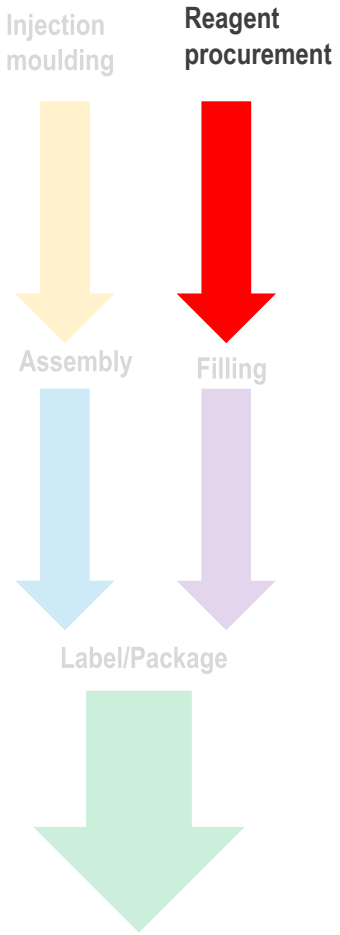
- Our cost estimate is **$2.06** to mould all the plastics required for a single cartridge
- Our manufacturing analysis tool has been developed based on manufacturing experience to estimate part and assembly cost
- Assumptions:
  - Material costs are extrapolated from quotations received in 2014
  - Tool cost is amortized over 3 years
  - A class 10,000 clean room mark-up of 100% is applied to each part cost
- The tool considers:
  - Part material cost (from quotations in 2015)
  - Part thickness and size
  - Part complexity (over moulds, side actions, twist-offs)
  - Throughput (number of cavities)
  - Labour rates
  - Level of automation
  - Mould tool array design
- The tool estimates
  - Cooling (and cycle) times for parts
  - Tool cost
  - Part cost
  - Assembly cost
  - Tool validation and management



AGENDA

Reagent costing was performed using wholesaler batch pricing

- Reagent cost estimate is **$1.32** for the Xpert MTB/RIF Ultra Assay and **$1.13** for the Xpert MTB/RIF Assay
  - This is the only difference in cost between the cartridges in this analysis
- The significant reagent cost contributors are the labelled probes and the polymerase
  - All other reagents only contribute less than $0.10 of the final reagent cost
  - Probe and polymerase price can be highly dependant on supplier and quantity
- Assumptions:
  - Costs were all divided by 4 (as in the previous HIV-VL COGS assessment) to allow for the bulk discount expected if dealing in high volumes directly with a vendor vs the price shown online
  - Volumes were based on the stated contents of the kit:
    8ml Sample Reagent, 4ml Reagent 1, 4ml Reagent
  - 120µl volume was assumed for resuspending the beads based on the teardown
  - Additional assumptions relevant to each reagent are contained within the spreadsheet

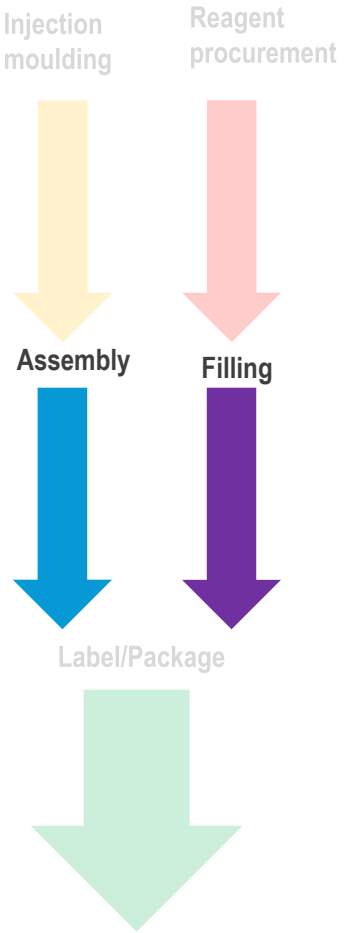


AGENDA

COST OF GOODS ANALYSIS – ASSEMBLY AND FILLING

Parts are assembled and reagents are filled

- Cost estimate is **$2.67** for automated assembly and filling. Additionally, manual labour costs to complement automated costs is estimated at **$0.63.** Additional parts integrated into the cartridge during assembly (filters, barrier films, stopper) are estimated at **$0.20**
- The key drivers for cost are the level of automation and the utilisation of the production line, which varies per country
- Assumptions
  - Fully automated assembly
  - Automated machine running cost is £50/hr
  - Average machine cost is $250k that is amortized over 3 years
  - Machine rental cost – machines are fully utilised over working day hours in the year (8hr/day, 5 day/week, 52 weeks)
  - 12 machines are implemented, each with a separate function for production
    - Plunger valve assembled and formed with glue
    - Heat seal cuvette and lid
    - Cartridge assembly
    - Freeze dry reagents
    - Pick and place reagent
    - Insert retaining sphere
    - Insert desiccant
    - US weld lid
    - Insert buffer
    - Label
    - Foil seal
    - Package



AGENDA

COST OF GOODS ANALYSIS - PACKAGING

Cartridges are individually packaged and boxed in packs of 10

- Our cost estimate is **$0.08** for packaging and labelling. Additional costs for Instructions for Use (CD) and pipettes are estimated at **$0.07**
- Cartridges are foil sealed to mitigate against water ingress
- Assumptions:
  - Price estimates taken from previous analyses and quotations

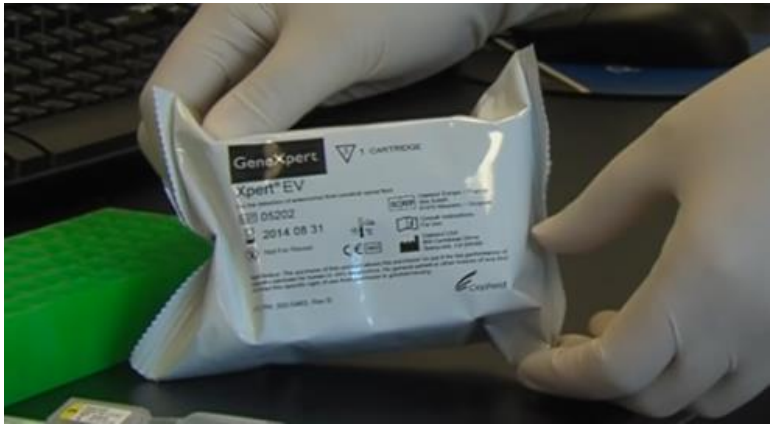
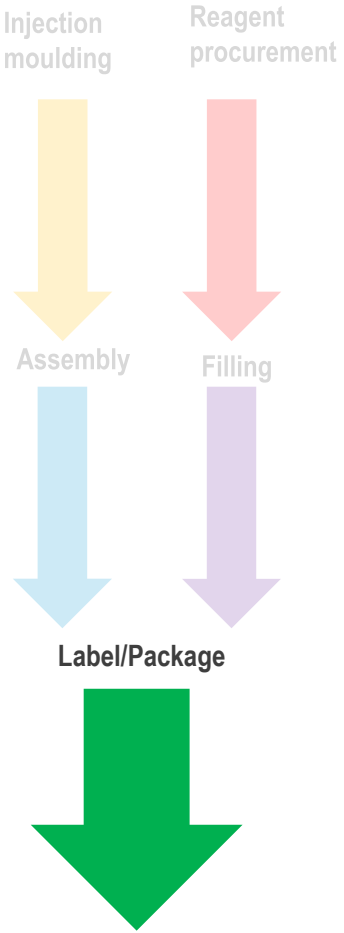


Image taken from https://www.youtube.com/watch?v=wGExfLOTW6Y



AGENDA

COST OF GOODS ANALYSIS - IP

Royalty costs for Intellectual Property Rights (IPR) licensing has been estimated

- Our estimated cost for IPR licensing is **$1.69**
- A nominal royalty rate of up to 10% net price per test may be applied to in vitro diagnostic tests requiring a licence for commercial application of third party technology
  - This rate assumes a non-exclusive licence to a non-core technology
  - Royalty stacking scenarios may also need to be considered
- The cartridge protocol references two third-party technologies:
  - AmpliTaq Gold (ThermoFisher); use of polymerase enzyme for non-research use will incur royalty cost
  - Molecular Beacons (Sigma-Aldrich); use of novel probes will also incur royalties

Assumptions:

- 10% of selling price ($16.86 prior to buy-down) is licensed as royalties
- Price of MTB/RIF Ultra is equivalent to MTB/RIF prior to buy-down agreement

AGENDA

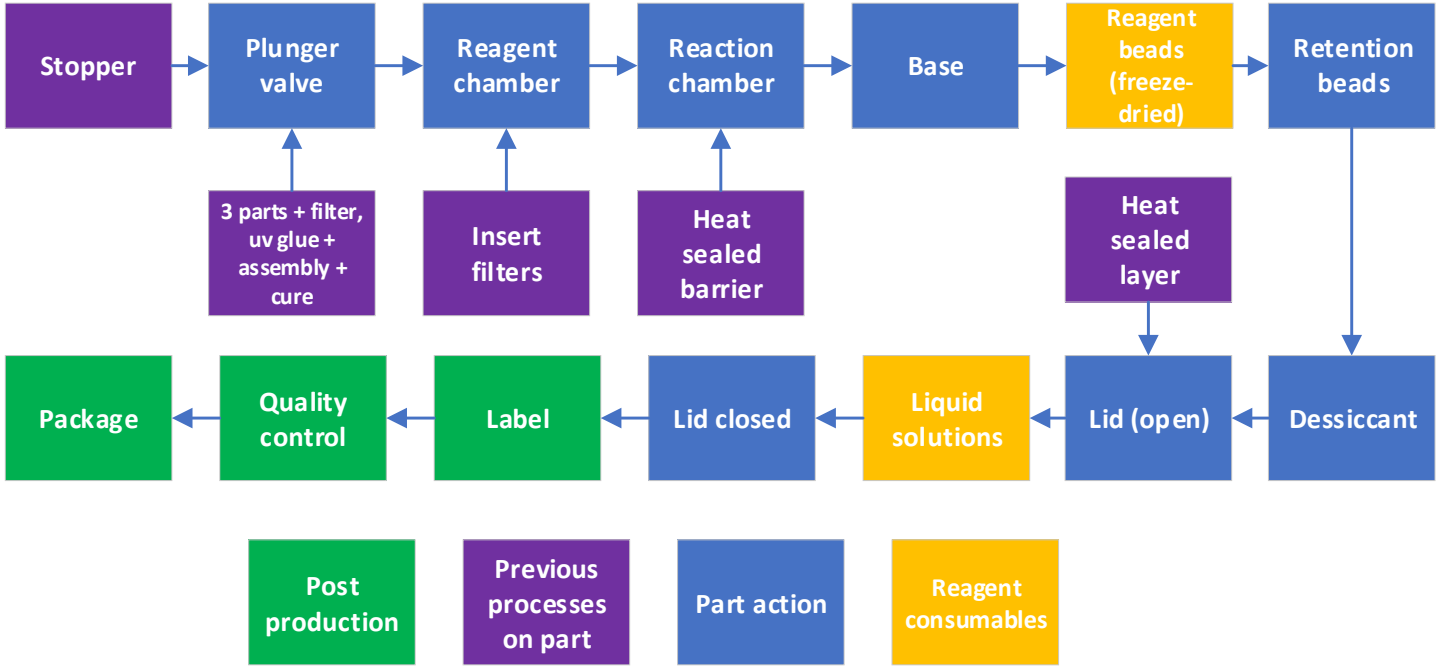
PRODUCTION LINE ANALYSIS

We held a workshop with manufacturing experts to evaluate the rationale for separate production lines for TB and virological tests

- We now have confidence in assembly process and manufacturing tools required, along with the system architecture
- Based on the outputs of a workshop considering the engineering and manufacturing of the plastic parts of the cartridge, we do **not** believe the differences between the cartridges justify the need for separate production lines
  - This is based on an evaluation of the architecture of the plastic parts *out of context* that are assembled to form each cartridge
  - There are several potential reasons why, in practice, the production lines are kept separate

Production line process

- The high level assembly process was discussed in the workshop and we have confidence that this approach is similar to what Cepheid have implemented



PRODUCTION LINE ANALYSIS

Cepheid claims that a separate production line is required for the GeneXpert MTB/RIF assay

Possible rationale for separate production line

1. Current Good Manufacturing Process (cGMP)

Regulations can be managed with reduced burden by defining specific products on each production line; validation of products is streamlined when there are fewer differences between products on a line. From this standpoint, Cepheid may wish to minimise the change between parts; quality control and risk of wrong part assemblies is reduced by using separate lines instead of multiplexing on the same line.

2. Parts are similar in shape and top level architecture and assembly is identical, however there are several separate parts that are distinct and have specific functionality for each assay

The risk of incorrect cartridge assembly by multiplexing production on one line is greater; therefore time-based shifts on assembly machines are not advised if not required; MTB/RIF & MTB/RIF Ultra reagent filling involves one different reagent bead that is placed in the Ultra vs the original and a change in the cuvette, which are both manageable swaps, therefore they would be produced on the same line.

3. Specific storage conditions during filling of reagents

Assays requiring extraction of genetic material from MTB are more hazardous than reagents required to extract material in virology assays.

4. Utilisation is a key driver for volume-based pricing: overhead costs are fixed, maximum utilisation/ throughput through the line

This includes (i) cost of the machine, (ii) labour costs, (iii) machine running costs, (iv) facility costs

Therefore, volume pricing is based on utility of cartridges that are multiplexed on same production line e.g. virology, to utilise the machine more.

The more cartridges put through that production line, the lower the overhead cost per part as the machines are greater utilised.

In the case of TB, if the products are produced in high volumes and the line is fully utilised, therefore there is no incentive to provide bundle price discounts to incentivise greater volumes.

AGENDA

SENSITIVITY ANALYSIS

MSF is interested in how CC's cost estimate varies with independent variables

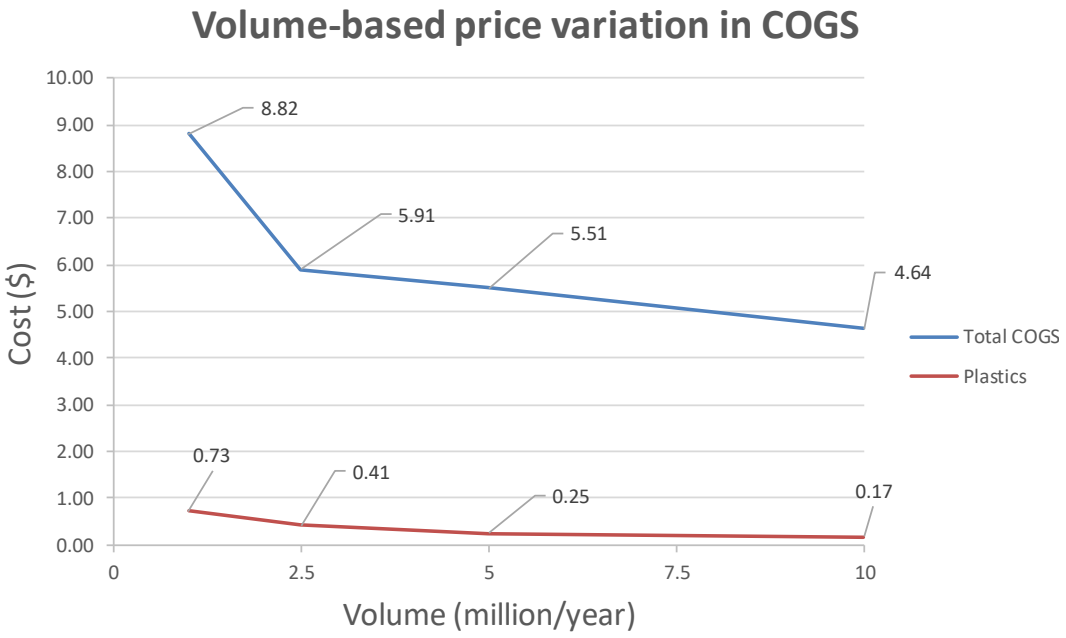
Aim: to perform a brief sensitivity analysis on estimations determine how the MTB/RIF Ultra cartridge COGS varies with:

- Production volumes (1M, 2.5M, 5M, 10M) on plastic part fabrication and assembly
  - We do not believe there is additional value in estimating COGS using the current approach for volumes >10M, as the assumptions used in our analysis are used to determine a bottom-up estimation on a potential manufacturing strategy that is used; any additional estimation of COGS for greater volumes requires further insight to retain the same error level in estimation
- IP license expiration

SENSITIVITY ANALYSIS

Plastic part costs vary significantly with volume

- Total COGS can be reduced to $4.64 at 10M parts/year
- Assumptions
  - Tools amortized over 3 years
  - Prices estimated at 1, 1.5, 5, 10 million parts/year
  - Same exchange rate as used in December 2018 (1.26 USD to 1 GBP)
  - IP licensing remains for 2 patents
  - Production line facility doubles at 5M parts/year
  - European charge-out rates for labour and machine usage



SENSITIVITY ANALYSIS

Eliminating IP licensing further drives down the COGS

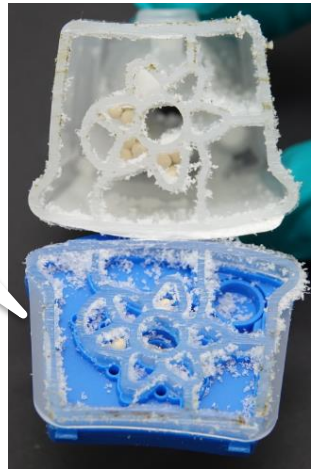
IP expiry matrix	Cost contributor fraction	Cost contributor ($)	Total cost (COGS)
Baseline (2 x IP licenses)	10% of selling price	1.69	8.82
1 x IP licence	5% of selling price	0.85	7.94
No licensing	0% of selling price	0	7.06

AGENDA

Lid

- Material: Polypropylene
- **Both lid designs are identical**
- The heat-sealed film is not positioned concentrically over the circle however it's centre is towards the opening side of the lid in all cartridges
  - The film is oriented as an 'x' for TB and as a '+' for HCV, reasons unknown

Lid sealed to reagent chamber with ultrasonic welding



Heat-sealed film (Polyethylene)

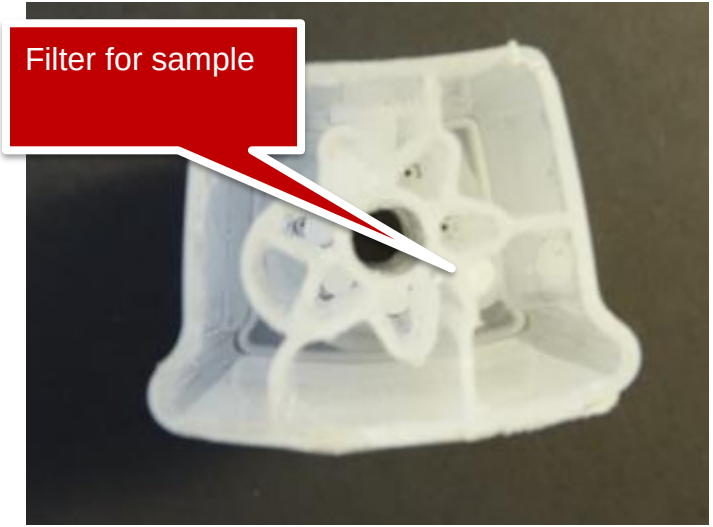
- Orientation-specific placement: circles are not concentric and positioned with intent

HCV

MTB/RIF Ultra

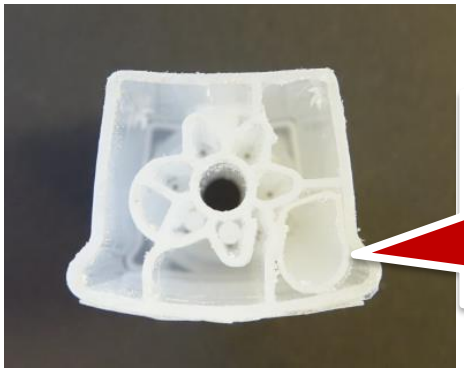
Reagent chamber (1)

- Material: Polypropylene with TEP overmould (1 side action)
  - Overmould is trimmed after tool ejection
- **Both reagent chambers are identical**
  - However the inserts into the chambers are different
- MTB –
  - 2 Filters into 2 lumens
  - 3 lumens filled with reagent beads, retaining spheres and desiccant
- HCV
  - No filters
  - 2 lumens filled with reagent beads, retaining spheres and desiccant
  - Additional part insert into sample lumen for volume reduction



Overmoulded TEP

- Single over mould with a side action, edge of side plastic is trimmed

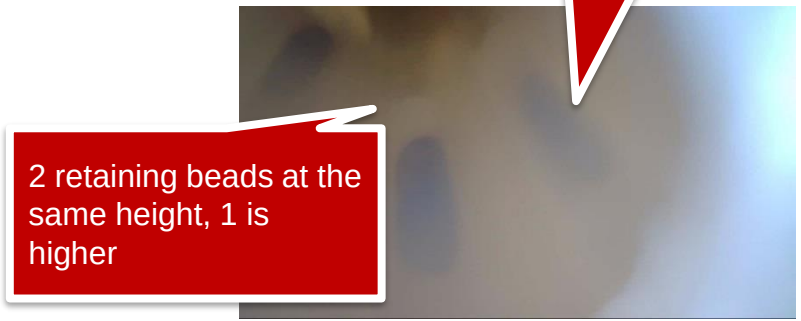


Extra part in sample lumen

Reagent chamber (2)

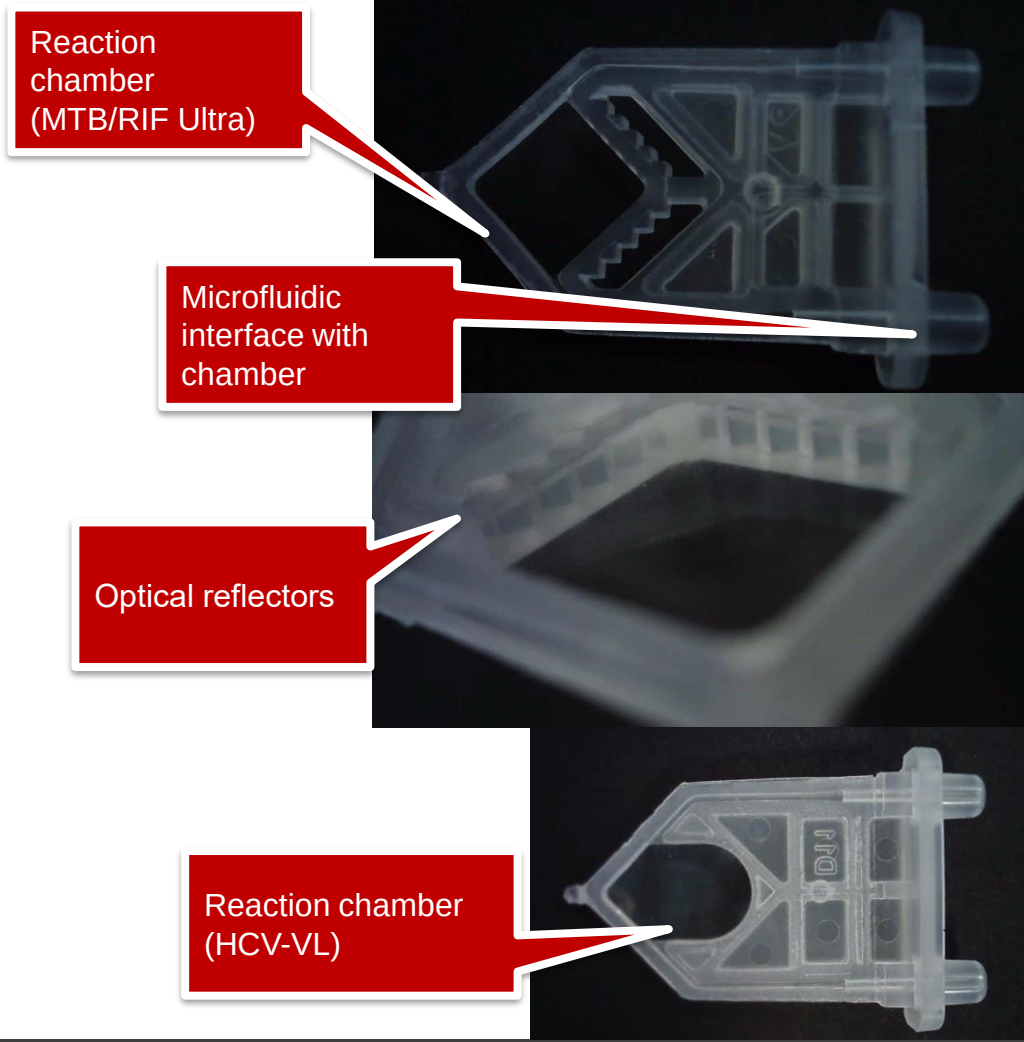
- Retention spheres are inserted to a known height above the base of 3 lumens
  - 2 beads are inserted to a known height (15mm above the base to retain reagent beads in a volume which will form the master mix (i.e. <120uL)
  - 1 bead is placed at a nominal higher position, this lumen is used for the control buffer

Dry beads (left), moist beads and partially wet paper (centre), wet paper (right)



Cuvette

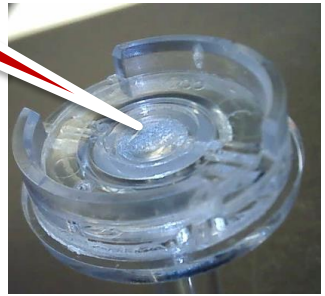
- Material: Polycarbonate
  - Polypropylene heat sealed barrier
- **Reaction chambers are different**
  - Injection moulding action and heat sealing process is the same, tool geometry and finish is different
- MTB/RIF - Ridged structure used to boost signal to noise ratio of optical readout
  - Polished surfaces of prisms (together with a subsequent air gap) act as a total internal reflector to increase the irradiance of excitation light and therefore boost the fluorescence signal
- HCV – no obvious structure to optimise fluorescence signal



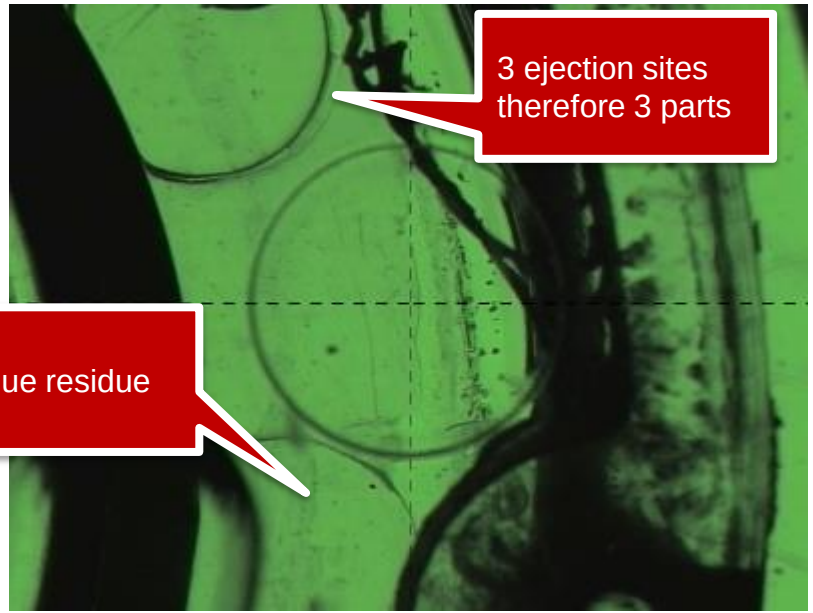
Plunger assembly

- Material: Polycarbonate with rubber stopper insert (most likely Chrlorobutyl)
  - Subassembly made from 3 parts as verified by 3 ejection markings and online resources
- Parts are assembled and bonded with UV-curing glue
- **Plunger assemblies are significantly different**
- It is estimated that the MTB plunger valve would be more expensive to make than the HCV valve

Ultrasonic coupler onto membrane



Lateral flow filter, no apparent ultrasonic coupler

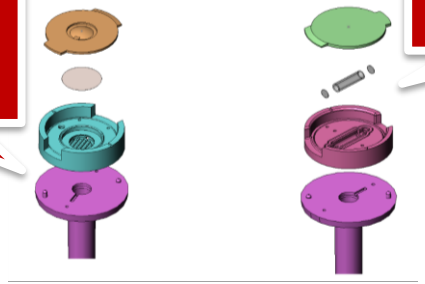


3 ejection sites therefore 3 parts

UV glue residue

TB plunger assembly

HCV-VL plunger assembly



Reagent costs – approach

- Reagent volume and concentration were estimated based on:
  - Cepheid website / IFU / online presentations
  - Published papers referenced in Lawn & Nicol Future Microbiol. 2011 Sep; 6(9): 1067–1082. (Table 1) as being involved in the development of the Xpert MTB/RIF assay
  - Volume measurements from cartridge teardown
- Estimated costs were then found by looking up quotes for maximum quantities available at molecular grade from online vendors eg Sigma, Thermo-Fisher
- The final concentration and final volume of these key reagents will be a driver of cost per cartridge
- We have assumed a volume of 120µl and the primer and probe concentrations found in the literature quoted by Cepheid
  - These are often used in excess in lab applications and so this may be an overestimate
- For the polymerase we have assumed that 1 reaction worth of enzyme is present in the 120µl volume (although only 25µl or 50µl are analysed in the cuvette so this may be an underestimate)
  - If 1 reaction worth of enzyme per 25µl was used, this would significantly increase the reagent cost
- For the primers and probes, sequences were entered into Sigma's custom DNA ordering service and quotes for the maximum available quantity was requested
- The difference between the Xpert MTB/RIF Assay and the Xpert MTB/RIF Ultra Assay from a reagent point of view is minor.
  - Reaction volume is doubled – however the concentration in the 120ul is unlikely to change, since we believe the QPCR reagents are dissolved in the same volume for both tests
  - Different combinations of primers and probes are used. However, primer cost is negligible and probe number only increases from 5 to 6, which is the primary reason for the increased reagent cost

Cambridge Consultants

UK ▪ USA ▪ SINGAPORE ▪ JAPAN

www.CambridgeConsultants.com

Cambridge Consultants is part of the Altran group, a global leader in Innovation. www.Altran.com

Registered no. 01036298 England and Wales