

# Fully Automated Cherry Picking Process by using remote data on a Beckman BiomekFX platform

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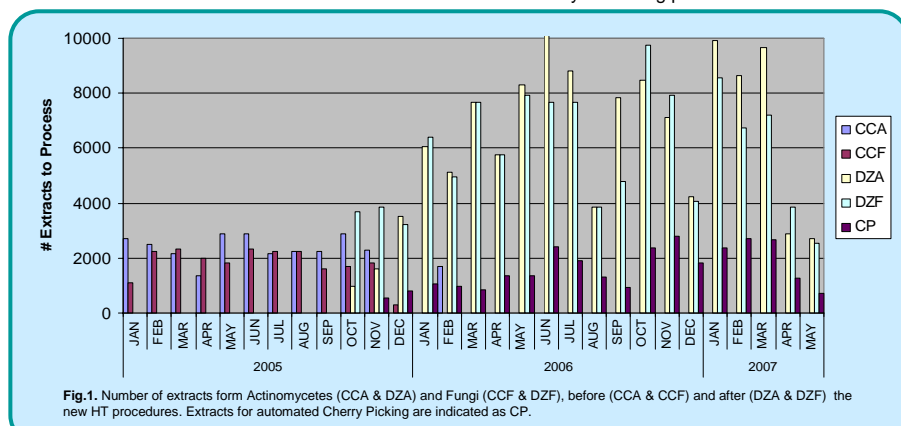
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## Introduction

> The Natural Products effort at CIBE covers the initial steps of the current research program on new Antiinfectives at Merck. Since the introduction in October 2005 of a new High Throughput platform for the preparation and evaluation of extracts from fungi or actinomycetes, the number of extracts processed has increased considerably. Current numbers reach the 20,000 complex extracts evaluated per month.

> After primary screening assays some of the extracts are selected for being confirmed. The unexpected growth in the number of extracts (Fig.1) made necessary an automated way of managing these extracts whose activities needed to be confirmed and tested in our secondary screening platforms.



> In response to this challenge, a new system was proposed for performing a full automated Cherry Picking at CIBE. The initial objectives were to avoid manual procedures and reduce the risks of mistakes by using Barcodes. To decrease the manpower needed per extract for primary screening was a secondary benefit of the system where the active extracts are transferred between positions of 96 Deep Well plates with a robot.

> For this new process the robot selected for the development of the application and Workflow was determined to be a BiomekFX + Cytomat platform due to its availability in the lab and the capability of this equipment to manage high numbers of plates without human interaction (Fig. 2).



Fig.2. Equipment determined to develop the Cherry Picking process due to its specifications: Carrousel, grippers and Vspan® head

> A key obstacle in the implementation of the new automated Cherry Picking resulted to be the impossibility of finding a commercial solution. Requirements of connecting our Oracle databases to determine which where the source and destination positions, and the idea of tracking any plate by barcodes forced us to design a proprietary VB application as a way to create working lists and send 'ready to use data' to the robot.

## Materials & Methods

> The source and destination plates were AB-gene 0765 0.8mL storage blocks. The extracts from natural products came from fungi and actinomycetes fermented in complex media with different amounts of nutrient sources. Acetone extracts were prepared by adding acetone [1:1]. Aliquots were taken and the organic solvent was evaporated to 1x Whole Broth Equivalent (WBE); 650ul of a 0.75xWBE dilution in water were placed in the 80 central positions of the assay blocks. Columns 1<sup>st</sup> and 12<sup>th</sup> were left empty for assay purposes. These plates were bar-coded with a different automated system: a Vcode with BenchCell from



> The robot platform was obtained by the combination of a Beckman Biomek FX with dual arm and a Cytomat carrousel with a capacity of nine racks of seven positions each, reaching in total the capability of handling 63 or 63x2 plates.

> Because of the high volumes required for the Cherry Picking process (about 500ul left of heterogeneous natural products extracts) it was necessary to use large volumes and large opening disposable tips to avoid cross contamination and any tip blocking. A new 1ml Beckman tip design was available and selected as a good solution for the

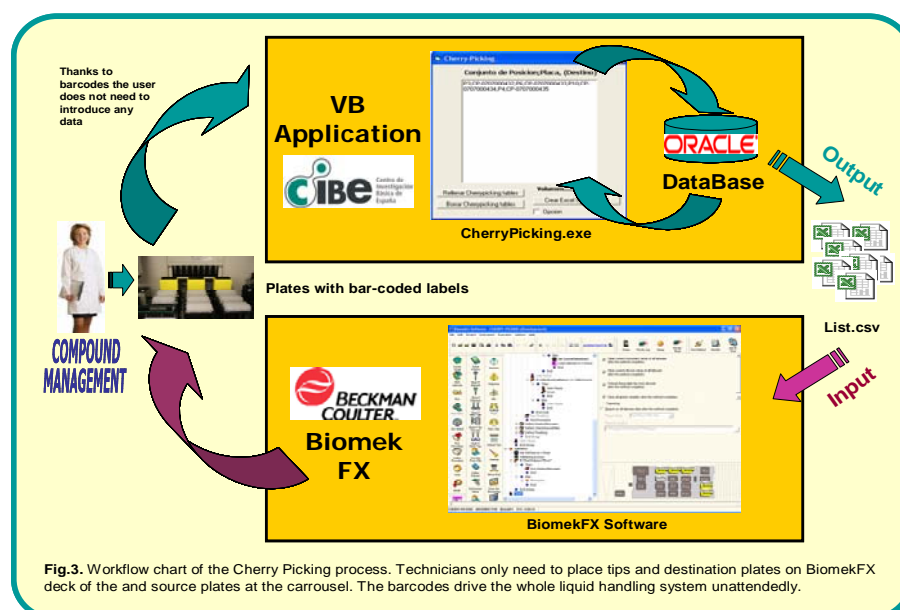
> Two independent barcode readers were implemented in the system: a deck-flight-by BC reader for checking destination plates and a conveyor BC reader to allow tracking of carrousel source plates.

> The different software applications created were written in Visual Basic. MS Excel and 'csv' files were used to transfer data between Oracle and the Beckman application.

> The database that holded the source and destination positions was the same one where primary screening results were stored and processed at CIBE, an remote Oracle db from Merck LIMS.



## Results & Discussion: Automated Cherry Picking



### BIOMEKFX Method Description

> Users do not need to introduce any variable (positions, # or name of source/destination plates, volumes, etc.) nor interact with our Laboratory Information Management System (LIMS) nor the BiomekFX software:

- There are seven position on the deck for destination plates. These positions do not need to be in order because a MS Excel file is created per each source plate needed when the destination barcode is read. Thus, the destination deck position and plate become data in columns of several MS Excel files.
- User can place the source plates in the carrousel, including not needed plates, at convenience. These neither need to be in a given order because the method reads each barcode and checks for the name of the sourcing plate within the names of a set of MS Excel files. When the correct one is loaded the equipment uses it. When all the necessary plates have been used the system finishes the method.

> Variables defined in the method include possible number of source and destination plates, transfer volume, labware definitions (tips, titerplates, etc.), instrument setup and Cytomat carrousel.

> A VB application is needed to process the barcodes of the destination plates at the beginning of the method and create as many MS Excel files as source plates. Each of these worklists defines the positions of the extracts in each source plate and its destination plate on the BiomekFX deck. It is important for this

SourcePlateName	SourcePlatePos	NumSamples	SourcePlateVol	SourcePlatePos	DestinationPlate	Volume
Cur01	Plate 1	1	100µl	CharPicking01	02_00	500
Cur01	Plate 1	1	100µl	CharPicking02	02_00	500
Cur01	Plate 1	1	100µl	CharPicking03	02_00	500
Cur01	Plate 1	1	100µl	CharPicking04	02_00	500
Cur01	Plate 1	1	100µl	CharPicking05	02_00	500
Cur01	Plate 1	1	100µl	CharPicking06	02_00	500
Cur01	Plate 1	1	100µl	CharPicking07	02_00	500

**RIGHT**

SourcePlateName	SourcePlatePos	NumSamples	SourcePlateVol	SourcePlatePos	DestinationPlate	Volume
Cur01	Plate 1	1	100µl	CharPicking01	02_00	500
Cur01	Plate 1	1	100µl	CharPicking02	02_00	500
Cur01	Plate 1	1	100µl	CharPicking03	02_00	500
Cur01	Plate 1	1	100µl	CharPicking04	02_00	500
Cur01	Plate 1	1	100µl	CharPicking05	02_00	500
Cur01	Plate 1	1	100µl	CharPicking06	02_00	500
Cur01	Plate 1	1	100µl	CharPicking07	02_00	500

**WRONG**

Table 1. Right and Wrong formats of the MS Excel files needed to transfer data between the Oracle database and the BiomekFX

> An additional 'Source Plates' csv file indicates the number and plates to process. This additional file defines the number of loops for the method, this number is increased by one within the method each time a source plate without extracts to be cherry picked is received from the carrousel. When all the plates have been used a 'Finish Process' message is displayed and the method stops.

> Within each loop, the system unloads the labware from Cytomat, reads the barcode, checks if the plate has to be used, and if so, then loads the csv file identified by the barcode. With the correct information obtained and by using a Script the values of the variables are charged in order to be further used in a 'Transfer From File' steps with the positions that need to be aspirated or dispensed.

### Future Improvements of the Method

Our current system is in 96 wells plate format. A new system with 384 wells plate format is under development. We are also planning to introduce messages with the HTML code for displaying on run time the name of the plate that is currently being processed. To have non-conductive tips is a possibility we are considering because our samples are from natural products origin and have many different physical properties from batch to batch, so by having transparent 1mL tips we would be able to modify the pipetting techniques easily (have a lump, change gaps, mixing, etc.)

## Conclusions for this Cherry Picking System

- Fully Automated:
  - Data feed and Management of plates
- Faster and more efficient than manually
- High Reduction of mistakes thanks to Barcodes
- Open-Design model for future developments