

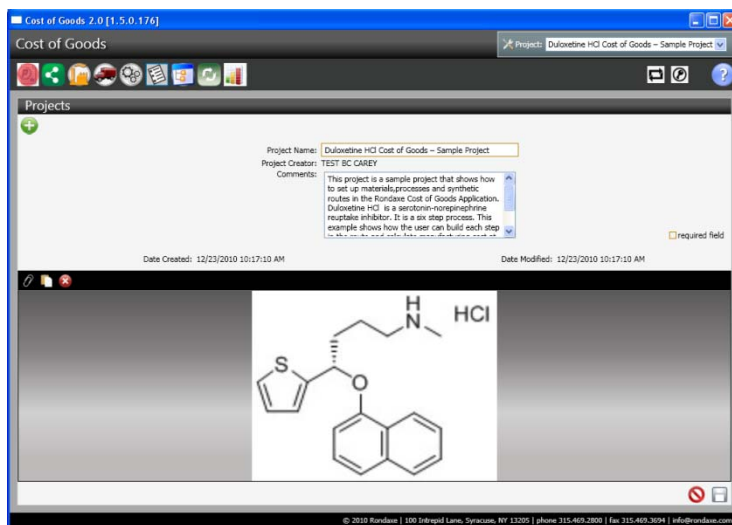


# Rondaxe

## Cost of Goods Version 1.5 - User Guide









Rondaxe Cost of Goods is a software application that allows consistent, secure and integrated cost estimation for professionals in the pharmaceutical industry.

This document is intended to provide an outline of the functionality and user support and reference.





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## General Guideline for Using

In order to populate the Cost of Goods, the following guidelines are useful guide to follow in order to efficiently build the database.

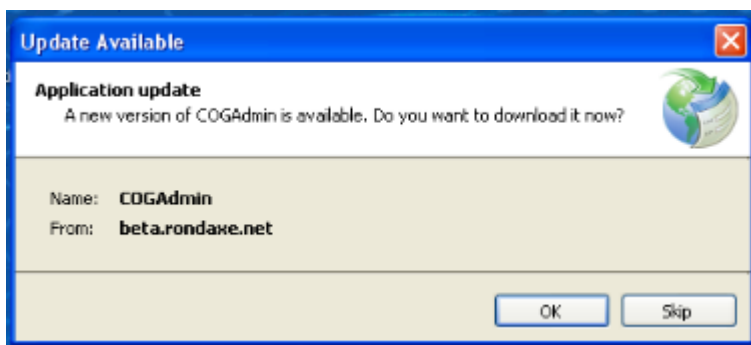
1. Begin by populating the libraries with the basic information for your project: Materials (raw, starting, intermediates, API), Facilities etc.
2. Build Processes.
3. Model Unit Operations
4. Build Worksheets
5. Link Worksheets to form Scenarios and Reports

Remember to **SAVE** your work at regular intervals and when moving between pages/tabs. This will avoid any inadvertent loss of your work.

## Application Updates

Rondaxe is continually updating and improving the software and will push new versions of the software to your computer.

Please note that when you see the following popup informing you that a new version of the software is available, you should ALWAYS choose OK.





## General Navigation

User the Main Menu Bar to move within the application



To Log Out click the button of click the Log Out button.

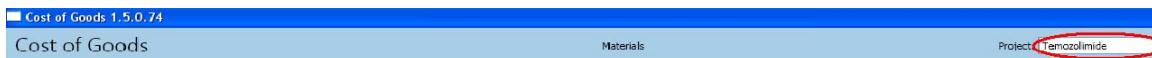


## Icons

The following Icons are common within the application.

Attach	
Add/Remove	
Create New/Add Item	
Delete /Cancel	
Edit	
Exit	
Save	Save As
Add	
Print	
View / Zoom	
Cancel	
Paste item from Clipboard	

At all times the application displays in the upper right side of the top menu the name of the project currently open.





## Logging In

Launch the Cost of Goods application from your All Programs menu. Enter your Client, Name and Password.

A screenshot of a Windows-style login window titled "Login". It has a blue title bar with standard window controls. The window contains three input fields: "Client:" with the text "CLIENTNAME", "Username:", and "Password:". A "Login" button is located at the bottom right of the form area.

A screenshot of the "Cost of Goods 2.0 [1.5.0.176]" application main page. The window title bar shows the application name and version. The interface includes a top navigation bar with icons for various functions. The main content area is titled "Projects" and displays a form for a project named "Duloxetine HCl Cost of Goods - Sample Project". The form fields include "Project Name", "Project Creator" (Brendan Carey), and "Comments" (a text area with a sample comment). Below the form, it shows "Date Created: 12/22/2010 4:27:13 PM" and "Date Modified: 12/22/2010 4:27:13 PM". A large chemical structure of Duloxetine HCl is displayed in the center, showing a thienopyrrolidine core with a thienothiopyran substituent. The footer contains copyright information: "© 2010 Rondaxe | 100 Intrepid Lane, Syracuse, NY 13205 | phone 315.469.2800 | fax 315.469.3694 | info@rondaxe.com".


From this main page the user can navigate through the application creating new projects, worksheets etc.




## ADMINISTRATOR

Administrator will have access to create new projects in the application. To navigate between different projects select from the drop down menu and the application will navigate to the selected project.

### CREATE NEW PROJECT

To create a new Project click on the Create New Project Button . Complete the Project Name, add any Project Description and Image

information and hit .

The new Project will be available in drop down menu.



User can change between Project by selecting desired project from Select Project drop down.




## Project Home Page

The main Project page provides the user with a brief overview of the project.


The screenshot shows the 'Cost of Goods 2.0 [1.5.0.176]' application window. The main area displays project details for 'Duloxetine HCl Cost of Goods - Sample Project'. The project creator is 'Brendan Carey'. A text area contains a comment: 'This project is a sample project that shows how to set up materials, processes and synthetic routes in the Rondaxe Cost of Goods Application. Duloxetine HCl is a serotonin-norepinephrine reuptake inhibitor. It is a six step process. This example shows how the user can build each step in the system and calculate manufacturing cost.' Below the comment, it shows 'Date Created: 12/22/2010 4:27:13 PM' and 'Date Modified: 12/22/2010 4:27:13 PM'. A chemical structure of Duloxetine HCl is displayed in the center, showing a thienopyrrolidine ring system connected to a naphthalene ring system, with a hydrochloride salt (HCl) indicated. The interface includes a toolbar with various icons for project management and a footer with contact information for Rondaxe.

Image files can be uploaded to show chemistry.

Use the Attach icon , select the Browse button to choose the file you want to display (jpeg, bmp format).


Paste Image from Clipboard  - Supports pasting images from Chemdraw

To remove the image, click the Remove icon .


Click the Save icon to save your changes .

The Project Description area is a useful area to record brief project summary information.

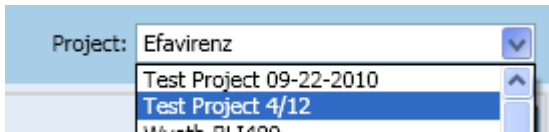


Click the Save icon  to save any changes before moving to a new page.

## Application > Project

From any screen within the application the Project icon  will bring you back to the main project page.

From here, you can switch to other projects using the drop down menu:



## Application > Administration

From any screen within the application the CTRL ALT A will bring you back to the admin page where passwords can be changed, projects can be allocated and organized.

Note this functionality is limited to Admin User.



## Material Library

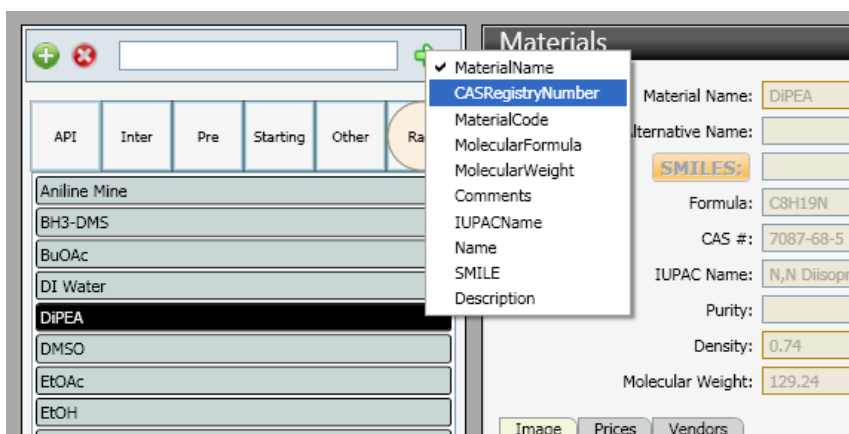



Materials are the basic building block. This is where the user can view and create materials in the software.

As in other libraries, the default view is a list view of all the materials created within the application. The list is displayed by Material type.


Use the type-ahead box to locate the material.

By right clicking on the icon you can search by other criteria such as material code, CAS Registry Number etc.



To add a new material, click the Add icon  and complete the information. Add name, CAS #, molecular wt, density (NOTE: only a required field for non-solids) etc.



When completed, hit SAVE  to update with new entry. Required fields are indicated by a key.  required field

Note IT IS IMPORTANT that the user selects Material Type (Raw, Starting, Intermediate, API, Other, Pre-formulated API). This functionality is important in order to build the Synthetic Route and Processes.

Material Type:  \*

- API \*
- Intermediate \*
- Other
- Pre-formulated API
- Raw
- Starting

User can attach vendors, impurities and any other required documents etc. to a material using the standard attach functionality.

User can add pricing information as they require.




Different pricing can also be added by selecting the add button  to reflect different vendors or tiered pricing. The Size and Comments fields are intended as informational.

Image	Prices	Vendors				
+	Size/Order Description	Comments	Price/UOM	UOM	Price/Kg	Use
	<input type="text"/>	<input type="text"/>	\$400.00	kg	\$400.00	<input type="radio"/>

Select the USE radio button to designate a Default pricing for the material.

The Price/KG field is updated or calculated when you click another area on the screen or Save.

Image	Prices	Vendors				
+	Size/Order Description	Comments	Price/UOM	UOM	Price/Kg	Use
	<input type="text"/>	<input type="text"/>	\$400.00	kg	\$400.00	<input type="radio"/>

The Rondaxe Database pricing is displayed in grey. If user has alternate pricing they wish to use, that can be entered. When the database is updated the Rondaxe pricing will be updated but other pricing entered will not be affected.



The Global check box is used to determine if a material is local to the current project or should be present globally in the database. For example, if the same starting material is used for two different projects the user can save time by saving it as a Global material. Global:



Once all the information available is entered click 

## Facility Library



Facility information is stored in the Facility Library



The user can add a new facility by clicking the Add icon  .

Facility Name:   
 Global:

Enter the facility name and any comments or other information about the facility. Within a facility the user can add Suites with associated Suite, Labor and Waste rates.

Facility Name:  Global:   
 Comments:

required field

					
	Suite Name	\$Rate/Week	\$Dir.Labor/Hour	\$Dir.Prof.Labor/Day/Worker	\$Waste/Drum
	<input type="text"/>	<input type="text" value="0"/>	<input type="text" value="0"/>	<input type="text" value="0"/>	<input type="text" value="0"/>

For each Suite the following information should be included.

- ◆ Rate (\$/week)
- ◆ Direct Labor (\$/hour/worker)
- ◆ Direct Professional Labor (\$/day/worker)
- ◆ Waste (\$/200L drum)

Once all the information has been added click Add Suite and Save .



The new suite is added to the existing facility. As many Suites as required can be added.

Rondaxe supplies a library of facility costs. Currently the library holds estimates for synthetic capacity in a Western country (G7 member) and Developing Country (China/India). These rates are subject to periodic review.

- ✚ “Large” means 5000 L - 8000 L vessels and 500 - 1000 kg output batch size.
- ✚ “Small” means 500 L - 2000 L vessels and 50 - 200 kg output batch size.
- ✚ “Lab” means prep lab scale with glass reactors around 100 L and 10 kg output scale or less
- ✚ “API” means the process areas are specially designed to reduce cross-contamination. Turnaround times are longer and QA oversight is greater and thus these suites are more costly.
- ✚ “cGMP” means the process areas are subject to QA oversight, more maintenance, and cleaning protocols which limits their turnaround speed and flexibility, making them more costly.

## Vendor Library



A library of vendors can be created to hold critical information about suppliers, specifications, contracts and pricing. User can create a Vendor library with information regarding address, documents, comments, audit dates. Contracts, Supply Agreements etc. can be attached. This can be a powerful resource to manage complex sourcing and purchasing functions.

The screenshot shows a software window titled "Vendors". On the left is a search bar and a list of existing vendors: Alfa Aesar, BASF, BASF, Beijing Louston Fine Chemical Co. Ltd., DSM, Lonon AG, Phoenix Chemicals Ltd., and Vendor Test. The main area is a form for adding a new vendor with the following fields:

- Company Name: Alfa Aesar
- Address Line 1: 26 Parkridge Road
- Address Line 2: (empty)
- City: Ward Hill
- State: Massachusetts
- Country: United States Of America
- ZipCode: 01835
- Contact: Christopher Verbitsky
- Contact Email: info@alfa.com
- Contact Phone: 800 343 0560
- Contact Fax: (empty)
- Last Audit Date: 12/23/2010
- Next Audit Date: 12/23/2010

At the bottom, there is a "Material Name" field with "Aniline Mine" selected and a "Comments" field with "less than 100 kg" entered. A "required field" checkbox is visible at the bottom right of the form.

Associate a material with a vendor using the type ahead dialog box, add any comments.

Click Save before exiting



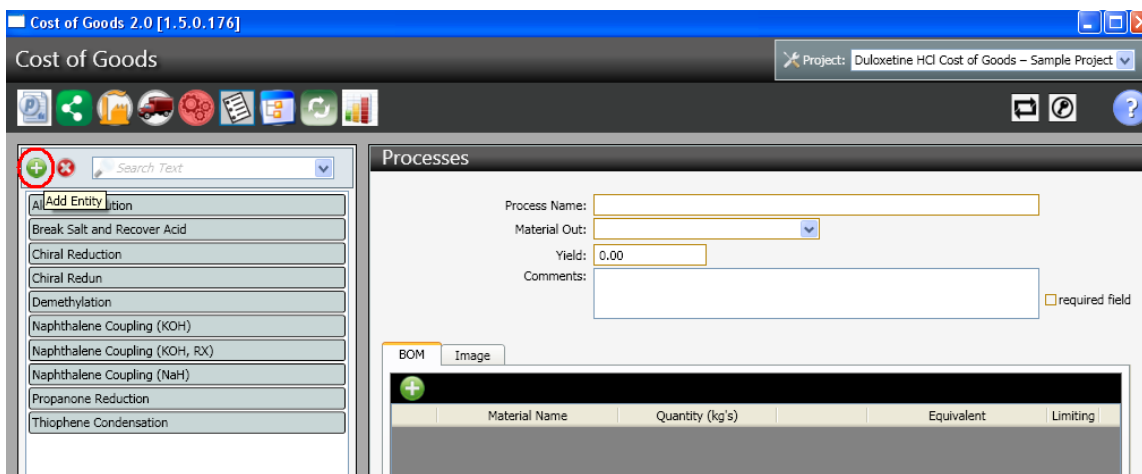


## Processes

The Cost of Goods software allows the user to build the API synthetic route in the system. The user will create each individual process with input and output materials, yield information etc.



Click Add to create a new process and enter Process Name.

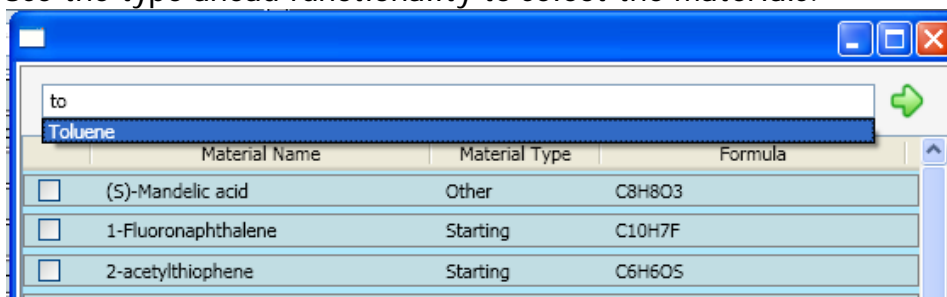


Select Material Out from the drop down.  
Enter Yield information (Molar %).



Build the Bill of Materials from the Process Input Dialog Box

Use the type ahead functionality to select the materials.



Clicking them in the drop down menu checks the box next to that material, when materials are select click OK.

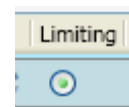
Complete the material and quantity.



<input type="checkbox"/>	DI Water	3.30		kg	<input type="text"/>		<input type="radio"/>
<input type="checkbox"/>	K2CO3	0.17		kg	<input type="text"/>		<input type="radio"/>
<input type="checkbox"/>	Heptane	0.71		kg	<input type="text"/>		<input type="radio"/>
<input type="checkbox"/>	THF	1.66		kg	<input type="text"/>		<input type="radio"/>

	Material Name	Material Type	Formula
<input type="checkbox"/>	10-DAB(III)	Starting	C29H36O10
<input type="checkbox"/>	4 A Sieves	Raw	
<input type="checkbox"/>	Acetic Anhydride	Raw	C4H6O3
<input type="checkbox"/>	Acetone	Raw	C3H6O
<input type="checkbox"/>	Acetone, Tech Grade	Raw	C3H6O
<input type="checkbox"/>	Acetyl Chloride	Raw	CH3COCl
<input type="checkbox"/>	Activated Charcoal	Raw	C
<input type="checkbox"/>	Ammonium formate	Raw	CH5O2N
<input type="checkbox"/>	Aniline	Raw	C6H7N
<input type="checkbox"/>	BH3, 1M THF	Raw	C4H11BO
<input type="checkbox"/>	BHT	Raw	C13H24O
<input type="checkbox"/>	Boc Anhydride	Raw	C10H18O5
<input type="checkbox"/>	Br2	Raw	Br2

Complete the material and quantity.



Identify the limiting material by clicking on the radio button.

### CALCULATING EQUIVALENTS


If required, the application can perform calculations based on the quantity entered of the Limiting Material.

Firstly, the user must enter the Limiting Material, Quantity and check the Limiting Material field in the Bill of Materials.

There are two options:

- (i) For any other material on the BOM, the User can enter a quantity of that material and click the Calculate icon to see how many equivalents that quantity equals. The application will calculate and display the number of molar equivalents (based on the quantity of limiting material).




- (ii) Alternatively the User can enter the desired number of molar Equivalents for a material and click Calculate  and the application will calculate the quantity (KG) of that material (based on the quantity of limiting material)



In this example, 10 equivalents of water would be 180kg.

Complete the Bill of Materials.


Click Save before exiting .



## Worksheets

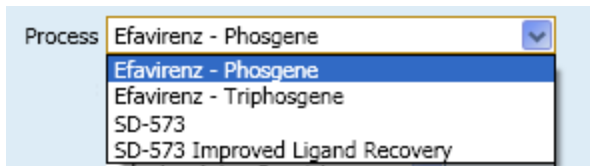


A Worksheet allows the user to scale the operations, associate facility/labor and assign and adjust materials and L&O parameters.

The User creates a new worksheet by selecting the Create New button . User can name the worksheet; select the process and facility to be run.

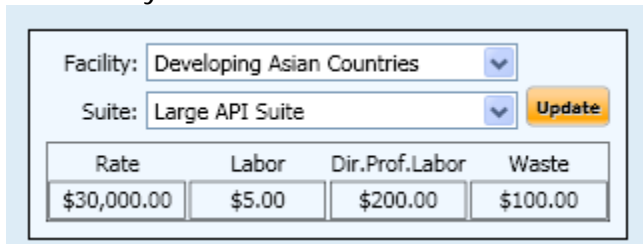
### Process

Select Process from drop down menu.



### Facility

Select a facility and suite of manufacture. Use the drop down menus to select the facility and suite. Associated costs are displayed.



Click Update icon to use those costs associated with that facility.

The Material Costs tab can be used to adjust the batch size and update the output as required. The user can scale the existing process by changing the quantity on the bill of materials of any material. The quantities for the other


materials scale automatically. Click  to update the results.

Material Name	kg/Batch	Kg(i)/Kg(o)	L(est)/Batch	Price/Kg	Cost/Kg Product	Contribut
MtBE Recovered	425.00	1.00	170.00	\$205.87	205.35	% 84.69
DI Water	9800.50	23.00	9800.50	\$0.00	0.00	0
IPA	2103.75	4.94	2679.94	\$1.55	7.65	% 3.16
MtBE	314.50	0.74	425.00	\$2.80	2.07	% 0.85



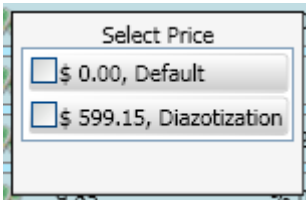
Alternatively the user can select the output KG of product and the input materials will scale automatically also. Click **Calculate** to update the result.

**NOTE: USING PRICES CALCULATED IN OTHER WORKSHEETS**

For material manufactured in a previous step, the user can pull in a cost calculated in a previous worksheet by using the Select Price icon  beside

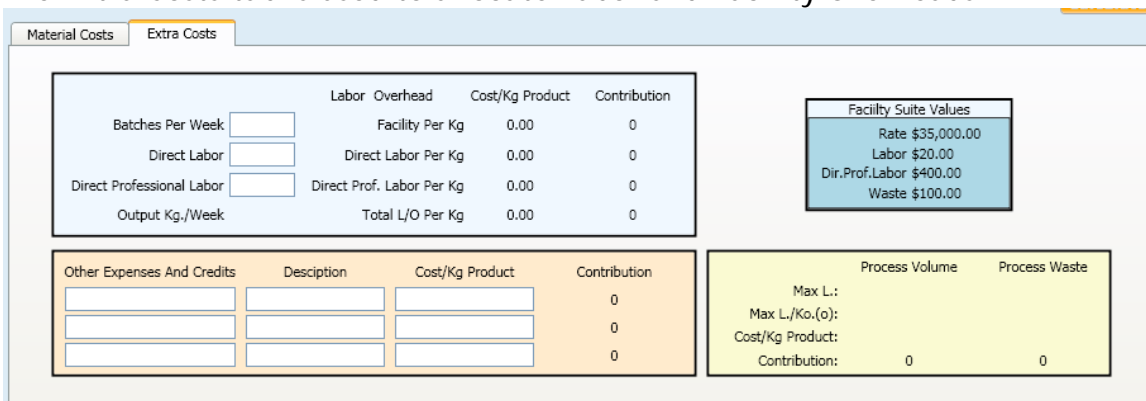


This displays a list of prices for that material as calculated in worksheets or entered in materials library.



User checks the desired price to be used and clicks away from the box for the price to be accepted. This price for that material or intermediate will then be utilized in that worksheet.

The Extra Costs tab is used to allocate Labor and Facility Overheads.




The user can assign (based on knowledge of the process or estimate if at early development stage) labor and overhead requirements. The number of batches per week can be assigned. You will note that the Unit Operations information related to equipment/time is displayed for the selected process on this screen. This information can assist the User to better determine an appropriate throughput number.




Once the information is entered the application automatically updates the worksheets with the costs and calculates the final cost per kg of the output material.

Lastly the Other Costs/Expenses & Credits can be used to assign additional costs/credits to the process (e.g. solvent recovery may reduce some of the solvent costs incurred per kg).

Entering a positive number indicates a Cost to be added per KG of Product (100). Entering a negative number indicates a Credit (-100). This amount per kg will be included in the final calculation.

Once the desired configuration of materials and labor has been assigned the user can save a worksheet .

Alternatively, the user can take an existing worksheet, rename and .

Results are shown in the Cost/Kg Product box broken down into Key Materials, Step Raw Materials, Processing Costs and giving a total Cost/Kg Product for that chosen Process, Facility, Scale etc.

Cost/Kg Product	
Key Materials(\$)	501.69
Step RM(\$)	22.61
Processing(\$)	492.29
Total Cost(\$)	1016.60

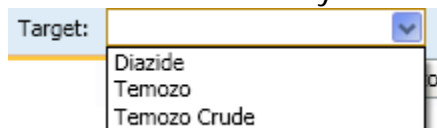


## Synthetic Routes

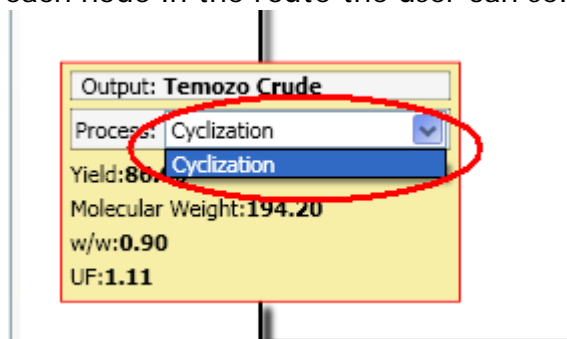


Individual Processes are created first as building block. The user can link the component processes together to build the overall synthetic route from purchased raw/starting materials through to API. The software allows the user to add new processes or completely new synthetic routes as the process is developed or new sources of starting materials are identified. These processes are linked together to form the synthetic route. This is shown in the schematic block diagram.

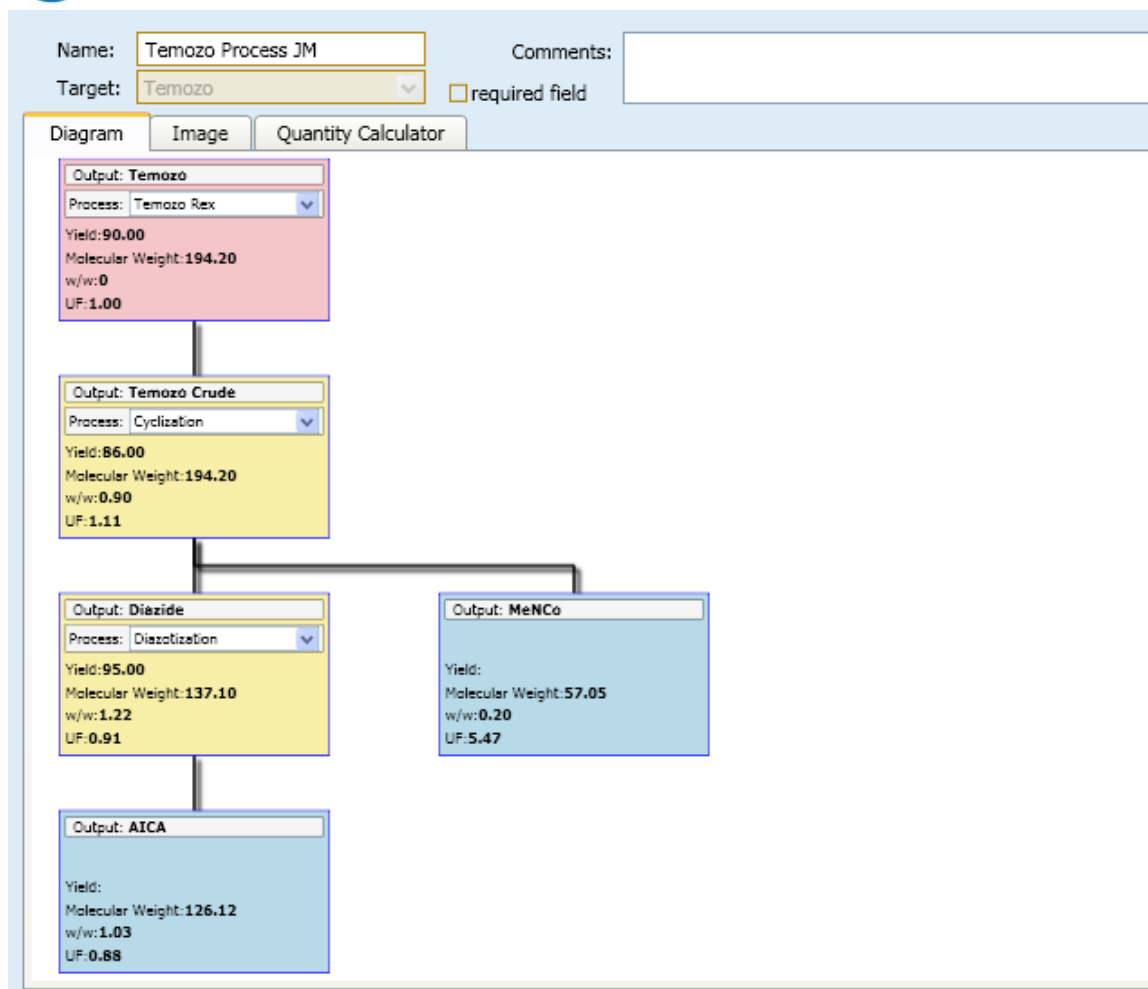
User selects a saved Synthetic Route from the drop down.



The application builds a route based on the relationship of the materials. For each node in the route the user can select from the available Process.



Once the route has been formed the user can assign a name and save. This will be available to pull from the Saved Route list the next time the user returns.



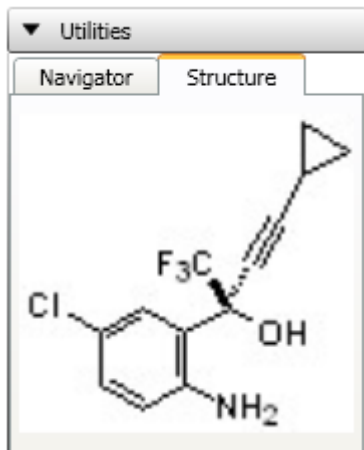
The Synthetic Route diagram displays the name, process name and version, utilization factor (UF) based on 1 kg output of API, molecular weight and the yield information.

#### Display Options

User can zoom into the Synthetic Route or display the structure associated with a material by using the Utilities window.



The Navigator tab allows the user to zoom in on a portion of the route.

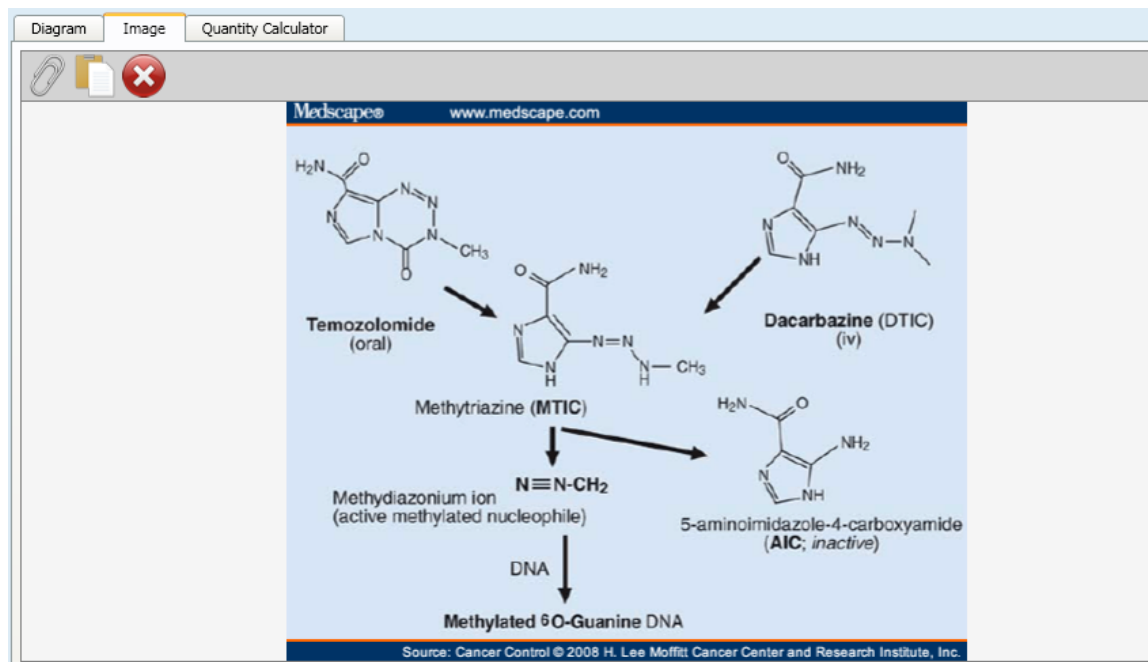
The Structure tab will display the associated image/structure for that material.




## Route Image

Go to the Image tab.

Attach a file by clicking  and browsing to attach the file or by pasting an image directly using the paste  button.




When completed, click  to ensure that the information is saved.



## Quantity Calculator

User can use the application to calculate campaign quantities by using the calculator feature.

Once the user has selected a target or a saved route, click on the calculate quantity button

In the pop up enter the quantity of API and click the calculator  to calculate the quantities of intermediates and starting materials.

Material Name	Material Type	Utilization Factor	Quantity	Quantity
Temozo	API	1.00	5000	0.00
Temozo Crude	Intermediate	1.11	0.00	0.00
Diazide	Intermediate	0.91	0.00	0.00
AICA	Starting	0.88	0.00	0.00
MeNCo	Starting	5.47	0.00	0.00

A second column is provided so a user can do side by side calculations.

Material Name	Material Type	Utilization Factor	Quantity	Quantity
Temozo	API	1.00	5000.00	75000.00
Temozo Crude	Intermediate	1.11	5555.56	83333.33
Diazide	Intermediate	0.91	4560.55	68408.26
AICA	Starting	0.88	4416.11	66241.70
MeNCo	Starting	5.47	27363.30	410449.57

The report can be sent to Excel and saved to your computer by clicking on the

export button  .



## Scenarios



A scenario is a collection of worksheets based on a specific route. For example, one could compare the economics for a route using Site A's costs and Site B's costs by creating a scenario for both sites.

Name:  \* Comments:   
 Route:  \*  Snapshot

To create a new scenario click .

Select the saved route to use from the drop down menu

Route:  \*  
 Temozo Process JM  
 TEST

For each node on that route the user assigns the appropriate worksheet by selecting the node and then clicking the checkbox as shown to assign the worksheet.

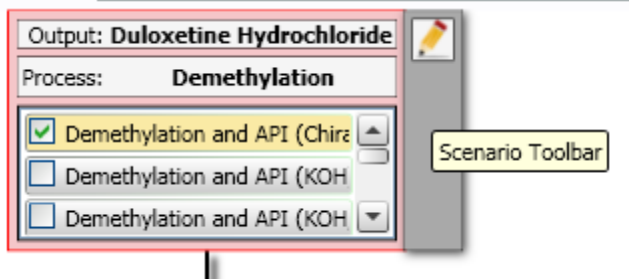
Output: **Temozo Crude**  
 Process: **Cyclization**  
 Cyclization  
 TEST 2  
 TEST 3


User selects a worksheet for each step in the route and to build the Scenario.

User can name and saves the Scenario when completed .

## Scenario Toolbar

The scenario toolbar allows the user to view/edit/save as worksheets directly from the scenario page.



By clicking on the pencil icon  the user can open the checked worksheet  Demethylation in a new window.

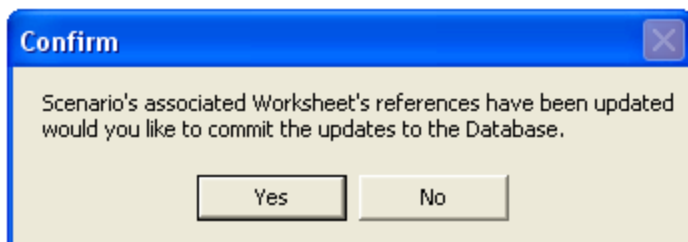
## Snapshot

Snapshot

The Snapshot check box allows users to have the application automatically updated referenced prices throughout a scenario.

If the Snapshot box is checked  Snapshot, no automatic updates will happen. This is the default setting.

If Snapshot is unchecked  Snapshot and a worksheet containing a reference is updated the user will get a pop up box telling him/her that the changes will be updated in the database. This automates what was a manual step in previous version of the software.



## Reports

One of the most powerful functionalities of Rondaxe Cost of Goods is the reporting functionality.

Two reports are currently being produced as standard. Choose the report from the drop down menu.



Choose the Report Select Report

- Select Report
- Cost Report
- Cost Ladder Report

Cost Ladder - The Cost Ladder report shows graphically the contribution of each step in the route by material and processing cost to the overall cost per kg of the API. This report can be displayed as a stacked bar chart or as a pie chart.

Cost Report - Cost report shows a cost sheet for each step in the process with a breakout of all material and labor costs. This is similar to industry standard cost sheets.

The user can select a scenario from the drop down menu. User then clicks on the Scenario listed underneath to generate the report.

Choose the Report Cost Report

Temozo

9/23/2010 8:10:45 PM

**Cost Report**

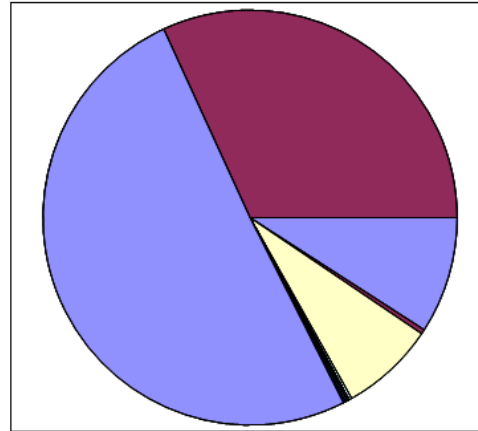
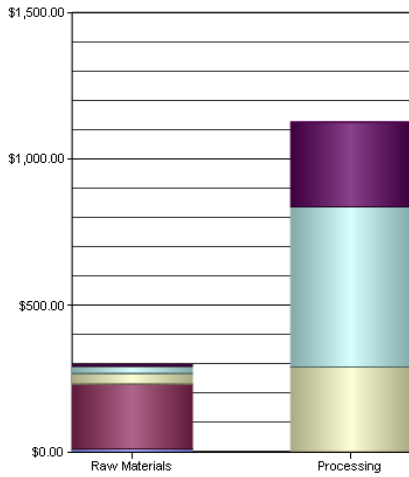
Material	Output kg/Batch	Output kg/Week				
Temozo	90	270.00				
Scenario	Worksheet	Process		Molar Yield		
Temozo	Rex	Temozo Rex		90		
Material Name	Chemical Name	Kg(i)/Kg(o)	Usage per Batch	Price/Kg Input		Cost Kg Output
Acetone	Acetone	4.44	400.00	\$1.03		\$4.58
Activated Charcoal	Darco G60	0.11	10.00	\$4.50		\$0.50
DI Water	Deionized Water	4.44	400.00	\$0.00		\$0.00
Temozo Crude		1.11	100.00	\$1,016.60		\$1,129.55
					<b>Subtotal:</b>	\$1,134.63
Facility	Suite	Hrs/Week	Batches/Week	Cost/Week (\$)		Cost Kg Output
	Small High Potency Suite	168	3	\$50,000.00		\$222.22



User can change the display or scroll through the Cost Report sheets using the standard control buttons

The Cost Ladder can be shown as a Ladder Report or as a Pie Chart.

**View Report As Bar Graph**    **View Report as Pie Graph**



Both reports can be printed or exported as PDF or Excel file by selecting the format and clicking on Export



## Glossary

### Project

A software “workspace” for a group of experts to share information, usually related to the synthesis of a particular API or group of related APIs.

### Route

A collection of processes, leading in a chain, sometimes branched, from starting materials to the target compound.

### Process

The usage relations between raw materials and product for a synthetic step.

### Worksheet

View that allows user to enter the scale of operations and collect the facility, labor, and raw material costs for a process.

### Scenario

A collection of worksheets based on a specific route. For example, one could compare the economics for a route using Site A’s costs and Site B’s costs by creating a scenario for both sites.

### Utilization Factor

UF is defined as the kg quantity of Starting Material or Intermediate required to make 1 kg of API. The UF is based on the Molar Yield assumption for each process step.

## Material Classes

### Active Pharmaceutical Ingredient (API)

The ultimate “target” of a synthetic process

### Pre-formulated API

A material composed of API that has been milled, blended with excipient, or processed in some way to ready the material for drug product formulation. While it is part of the process, and its cost of manufacture needs to be counted, it is not part of the synthesis.

### Intermediate

A compound isolated in the synthesis route to the API

### Raw Material



Purchased or received materials. Generally: reagents, solvents, resins, catalysts, buffer salts, and inexpensive organic compounds

#### Starting Material

SM is not necessarily the same as regulatory starting material. It is a purchased or received material that the user designates (usually because it is more expensive or difficult to source) and is a component of the API. Allows the user to see its cost impact separately from other materials and display it as a node on the route and scenario diagrams.

#### Other

A miscellaneous category available to the user. An example might be Merrifield resin for a solid phase protein synthesis. While it is the limiting reagent, it is not a component of the API. Other examples are expensive catalysts or reagents or other materials that are difficult to source. Allows the user to see its cost impact separately from other materials and display it as a node on the route and scenario diagrams.