Atenolol – 30 Years of Life Cycle Management

Stewart Jolly

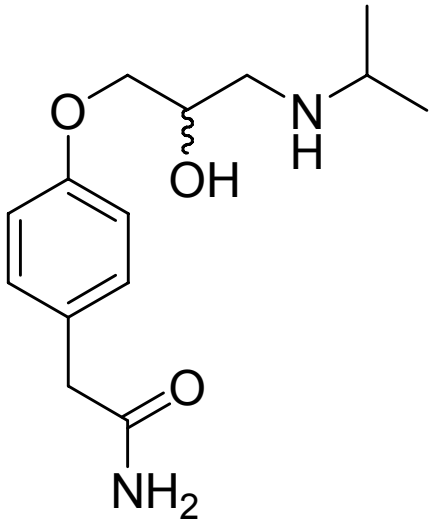
Process Research & Development Department

Avlon Works, Bristol, UK

Global Process R&D

AstraZeneca

Atenolol



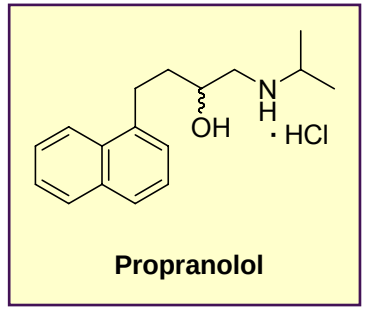
4-[2-hydroxy-3[(1-methylethyl)amino]propoxy]benzeneacetamide

ICI 66082

CAS 29122-68-7

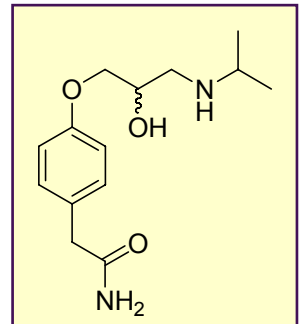
- β1-selective adrenoceptor blocking agent
- Active Pharmaceutical Ingredient in Tenormin®
- Indicated for hypertension, angina and acute heart failure
- Daily dose up to 100 mg
- Racemic mixture – both enantiomers active

Atenolol – brief history



Propranolol

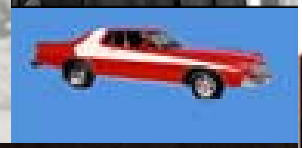
- **1957** - ICI Pharmaceuticals Division created
- **1958** - β blocker research programme started within ICI
- **1965** - Propranolol launched as Inderal®
- **1972** - Atenolol entered development
- **1976** - Atenolol launched as Tenormin®
- **1987** to **1990** - Peak sales / patent expiry in major markets
- **1993** - Zeneca demerged from ICI
- **1999** - Astra and Zeneca merged
- **2007** - Substantial generic manufacture, but Tenormin® still on the AZ product range



Atenolol

Back to the ’70s




Global Process R&D

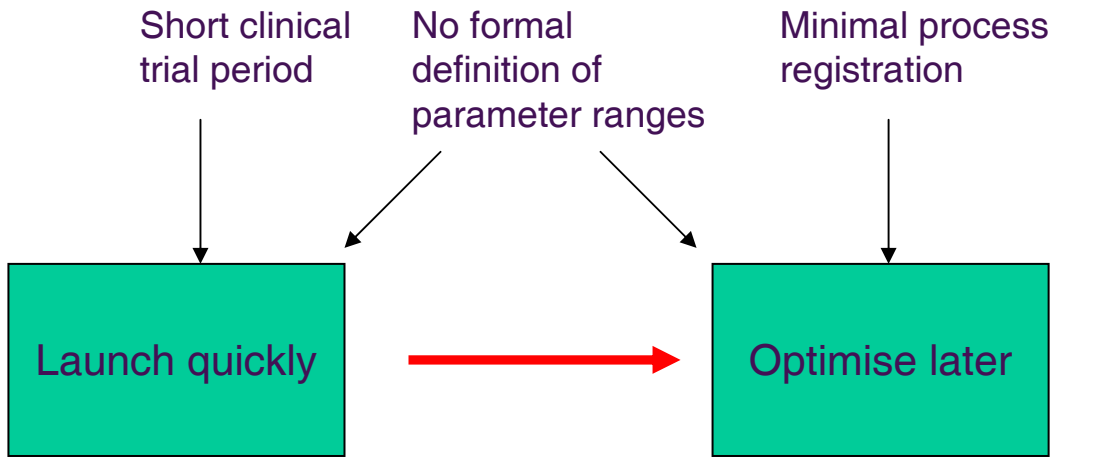
AstraZeneca

Regulation in the ’70s

- Synthetic route required registration, but no guideline re. number of steps / stages / choice of Registered Starting Material
- No specific guidance re the registration of process details
  - Level of detail could be very limited
- Organic impurity specification ≤ 0.5 %w/w acceptable (TLC)
- GMP standards basic and not legally-binding
- No specific requirement for formal process validation / definition of critical parameters
- Clinical trials limited in size and scope

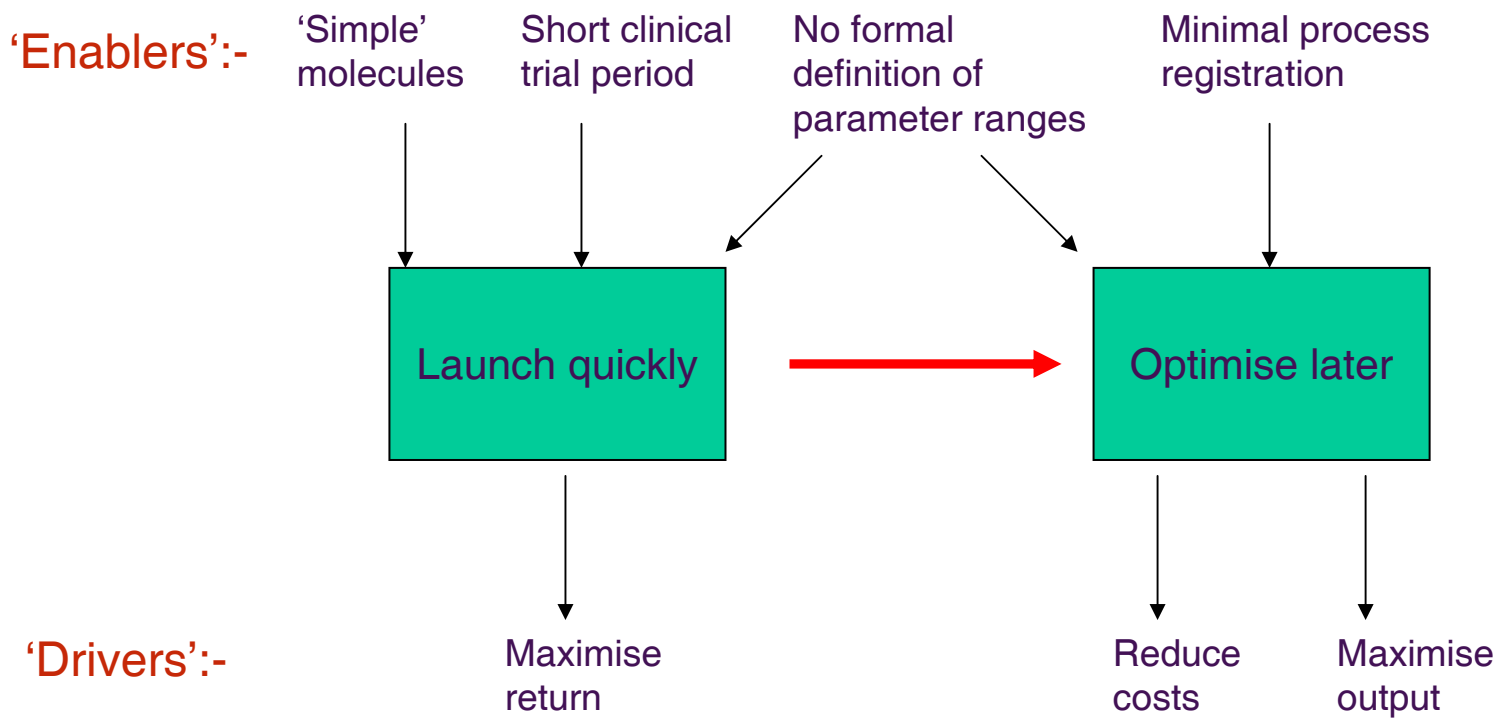
Atenolol Process Development 'Model'

'Enablers':-

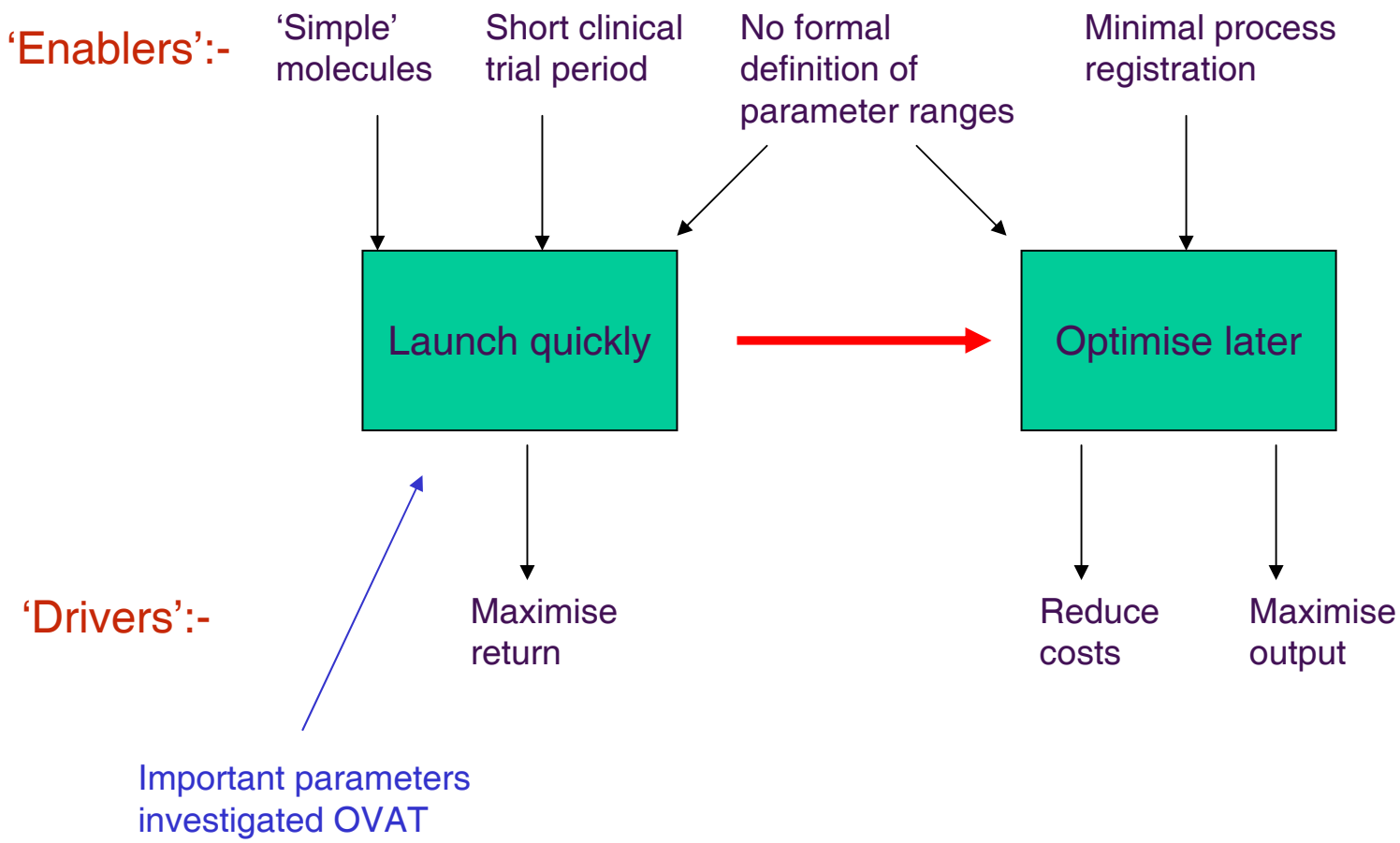


'Drivers':-

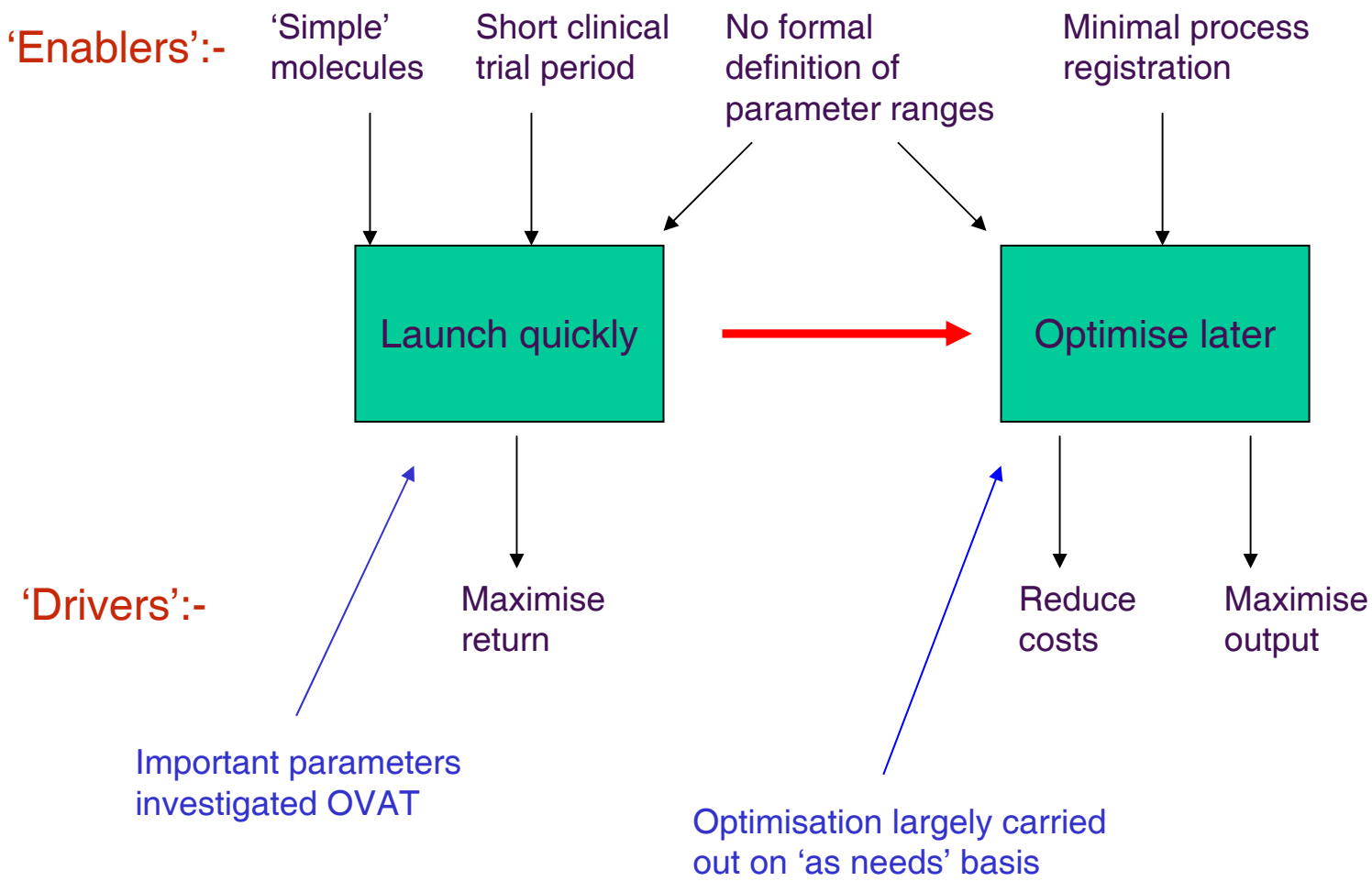
Atenolol Process Development 'Model'



Atenolol Process Development 'Model'



Atenolol Process Development 'Model'



Changing Approach to Process Development

Within ICI/Zeneca Pharmaceuticals & AZ

Late 1980s / early 1990s

- US FDA Guideline on Process Validation
- Concept of Acceptable Parameter Ranges and Critical Parameters
  - Defined at lab scale one variable at a time (OVAT)
  - Included in regulatory submission
- Process change becoming more time-consuming and expensive

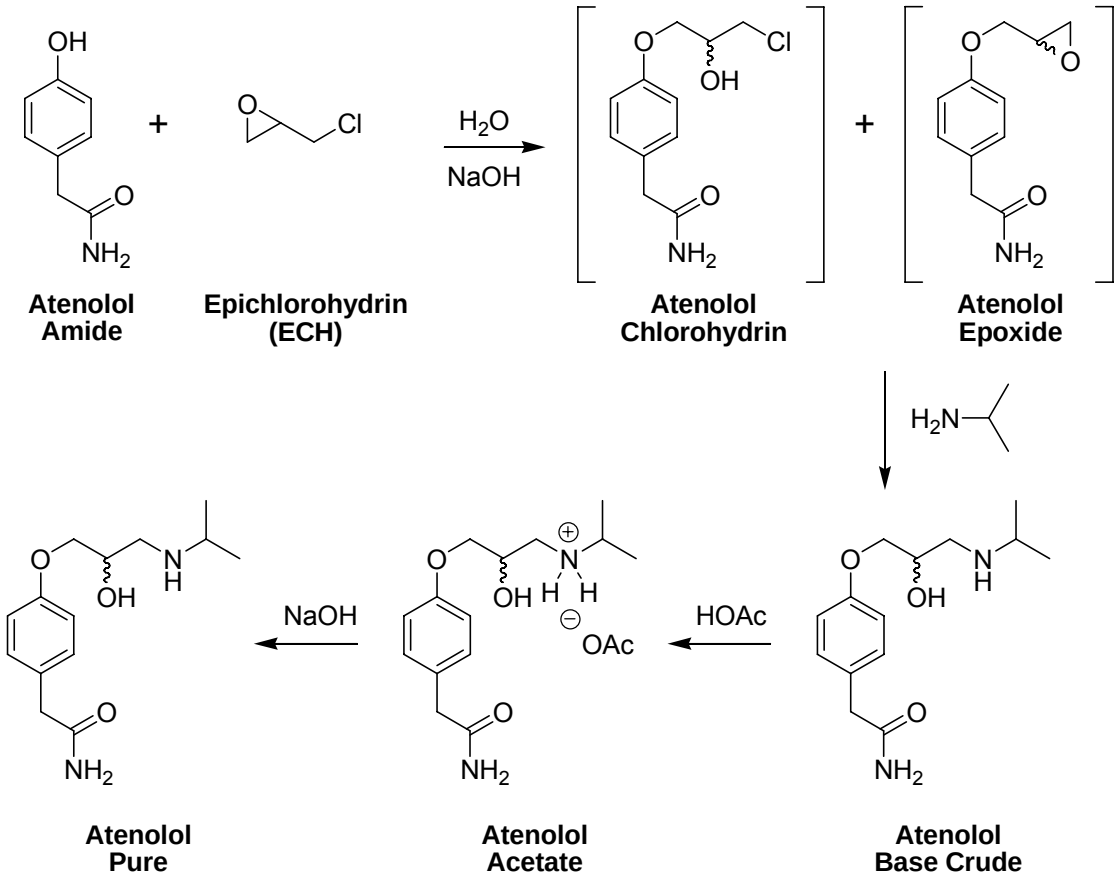
Late 1990s

- Prior understanding of process robustness desirable
- Parameter ranges established by Factorial Experimental Design (FED)
  - Usually highly fractionated robustness test
  - Narrow ranges to ensure 'success'

2005 onwards

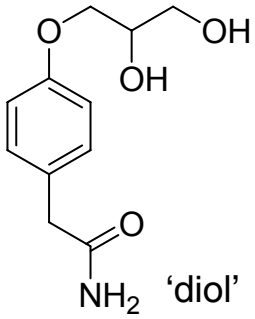
- FED becoming more accepted as basis for API registration
  - US FDA 'Pharmaceutical Quality Assessment System' (PQAS)
    - 'Quality by Design' approach (QbD)
    - Based on science and process understanding
    - Flexibility to operate within 'design space'

Atenolol – Synthetic Route

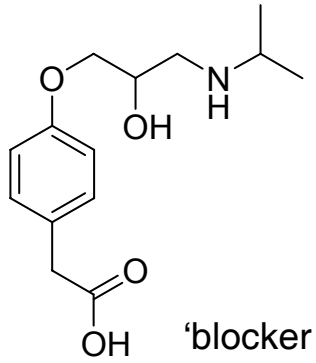


- Chemistry similar to Propranolol
- Other routes were considered
- This route registered by ICI with regulatory authorities worldwide
- Route remained essentially unchanged within ICI / Zeneca / AZ
- Steps to formation of Atenolol amide would require registration nowadays

Atenolol – principal impurities (1)



'diol'



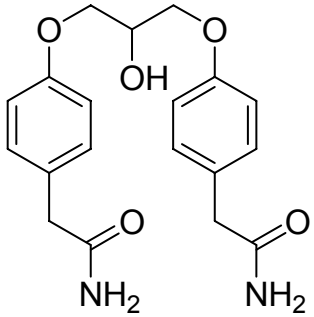
'blocker acid'

Formation:	Hydrolysis of epoxide/chlorhydrin Reaction of amide with glycidol or chloropropane diol	Hydrolysis of amide fuctionality
Control:	Limit batch temperature during epoxide formation and stripping of excess ECH	Limit batch temperature during epoxide formation and stripping of excess ECH and *i*PrNH$_2$

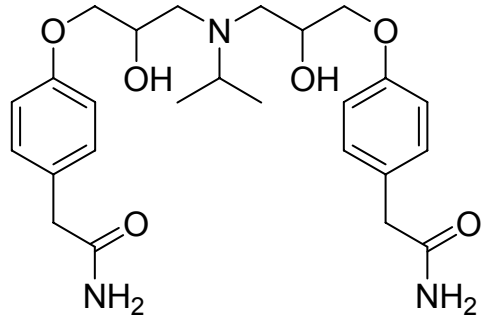
Global Process R&D

AstraZeneca

Atenolol – principal impurities (2)



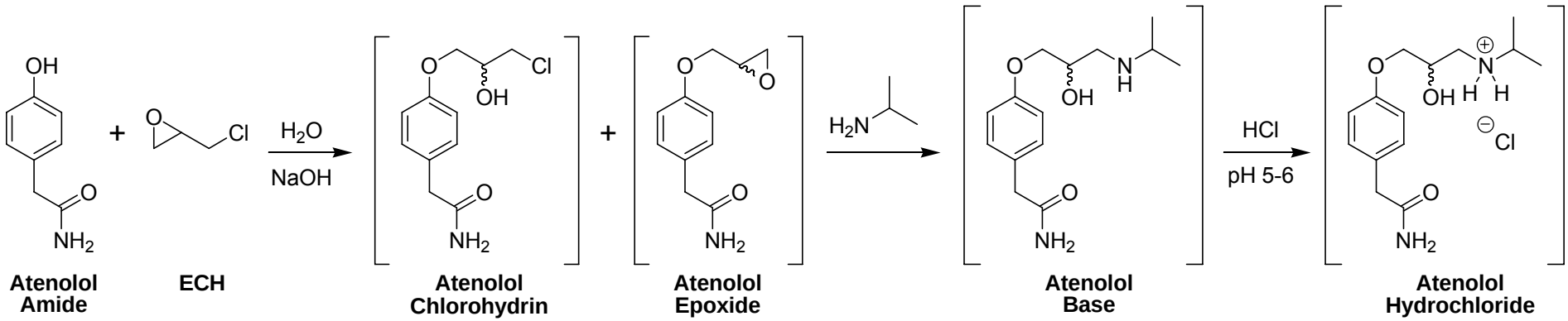
'bis ether'



'tertiary amine'

Formation:	Reaction of epoxide/ chlorhydrin with unreacted amide	Reaction of Atenolol with unreacted epoxide/chlorhydrin
Control:	Use excess ECH	Use excess *i*-PrNH_2

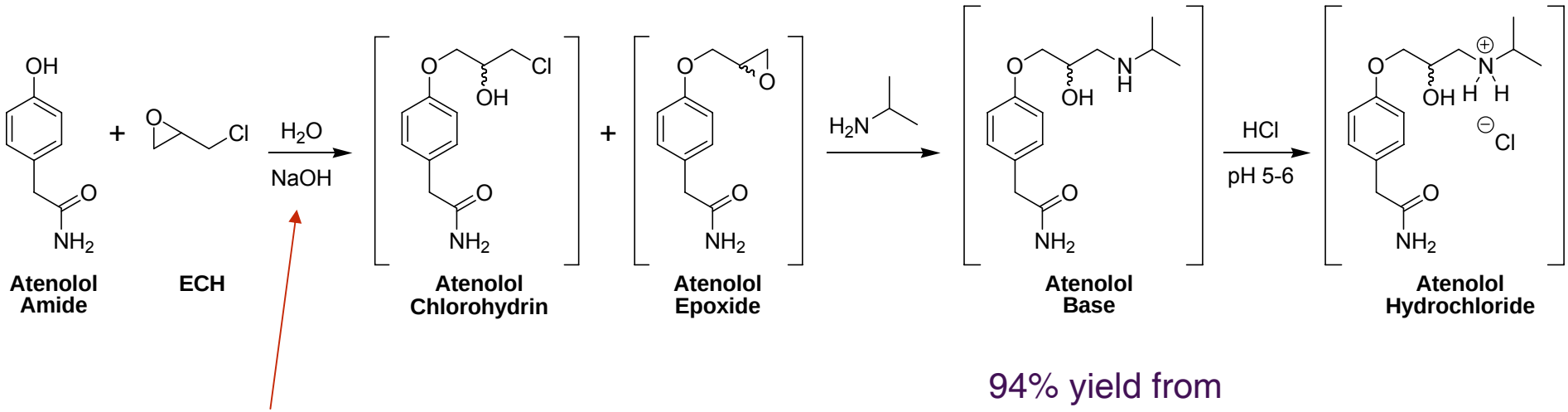
Atenolol – first manufacturing process



Atenolol Amide | **ECH** | **Atenolol Chlorohydrin** | **Atenolol Epoxide** | **Atenolol Base** | **Atenolol Hydrochloride**

94% yield from amide

Atenolol – first manufacturing process



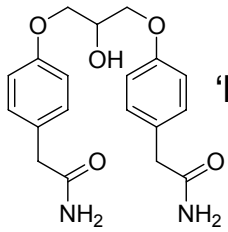
Atenolol Amide + **ECH** → **Atenolol Chlorohydrin** + **Atenolol Epoxide** → **Atenolol Base** → **Atenolol Hydrochloride**

Addition of liquid paraffin to prevent priming during stripping of excess ECH post reaction

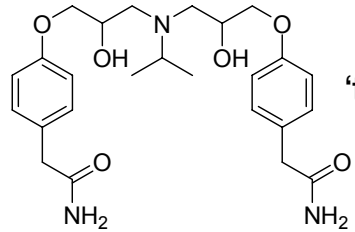
Was this registered??

94% yield from amide

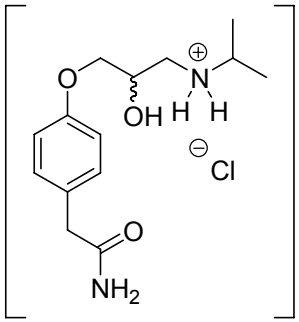
Atenolol – first manufacturing process



'bis ether'



'tertiary amine'

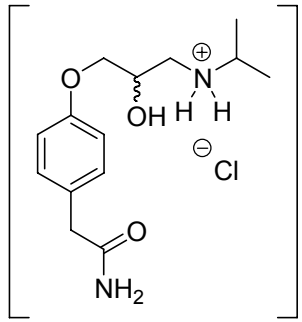


Atenolol Hydrochloride

1) Cool to crystallise '**bis ether**' impurity

2) Remove '**bis ether**' by filtration

3) NaOH to pH 9.00 - 9.05

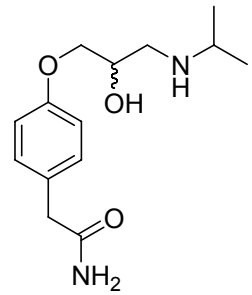


Atenolol Hydrochloride

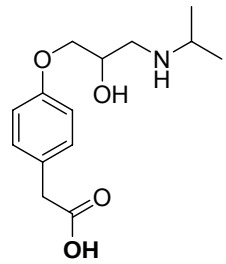
1) Remove '**tertiary amine**' by filtration

2) NaOH to pH 11-12 to crystallise Atenolol base

3) Isolate and water wash



Atenolol Base Crude



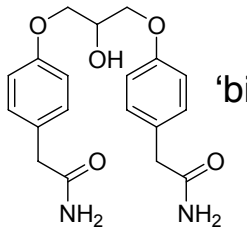
'blocker acid'

Global Process R&D

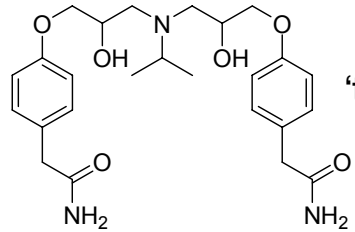
AstraZeneca

Atenolol – first manufacturing process

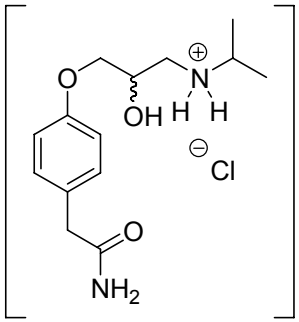
'Bis ether' was removed effectively by precipitation/filtration from Atenolol hydrochloride solution



'bis ether'



'tertiary amine'

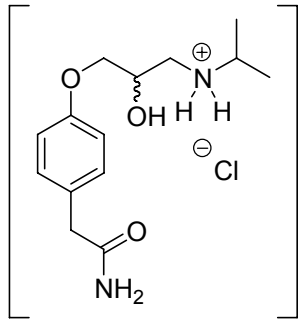


Atenolol Hydrochloride

1) Cool to crystallise '**bis ether**' impurity

2) Remove '**bis ether**' by filtration

3) NaOH to pH 9.00 - 9.05

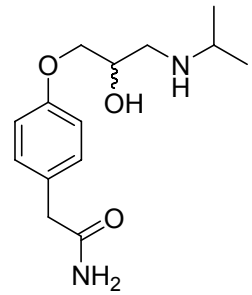


Atenolol Hydrochloride

1) Remove '**tertiary amine**' by filtration

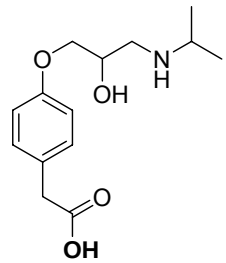
2) NaOH to pH 11-12 to crystallise Atenolol base

3) Isolate and water wash



Atenolol Base Crude

'Blocker acid' was removed effectively via alkaline mother liquor and washes during isolation of the base



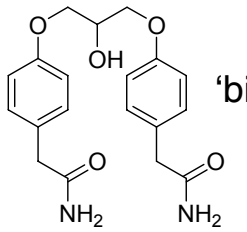
'blocker acid'

Global Process R&D

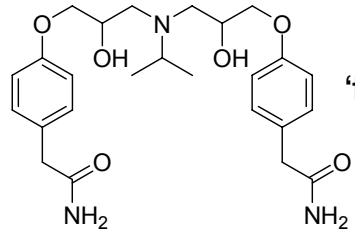
AstraZeneca

Atenolol – first manufacturing process

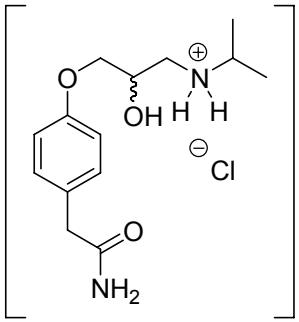
'Bis ether' was removed effectively by precipitation/filtration from Atenolol hydrochloride solution



'bis ether'



'tertiary amine'



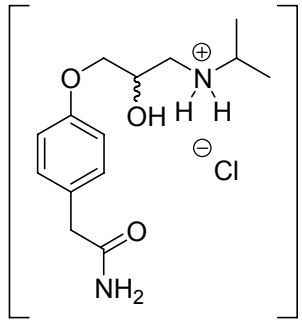
Atenolol Hydrochloride

1) Cool to crystallise '**bis ether**' impurity

2) Remove '**bis ether**' by filtration

3) NaOH to pH 9.00 - 9.05

Impracticable for routine manufacture !



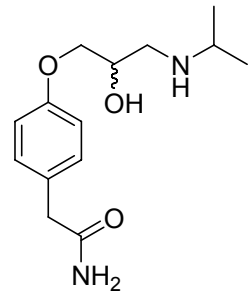
Atenolol Hydrochloride

1) Remove '**tertiary amine**' by filtration

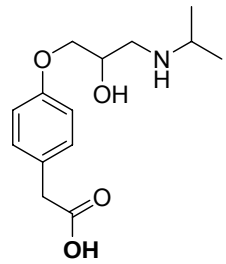
2) NaOH to pH 11-12 to crystallise Atenolol base

3) Isolate and water wash

'Blocker acid' was removed effectively via alkaline mother liquor and washes during isolation of the base



Atenolol Base Crude

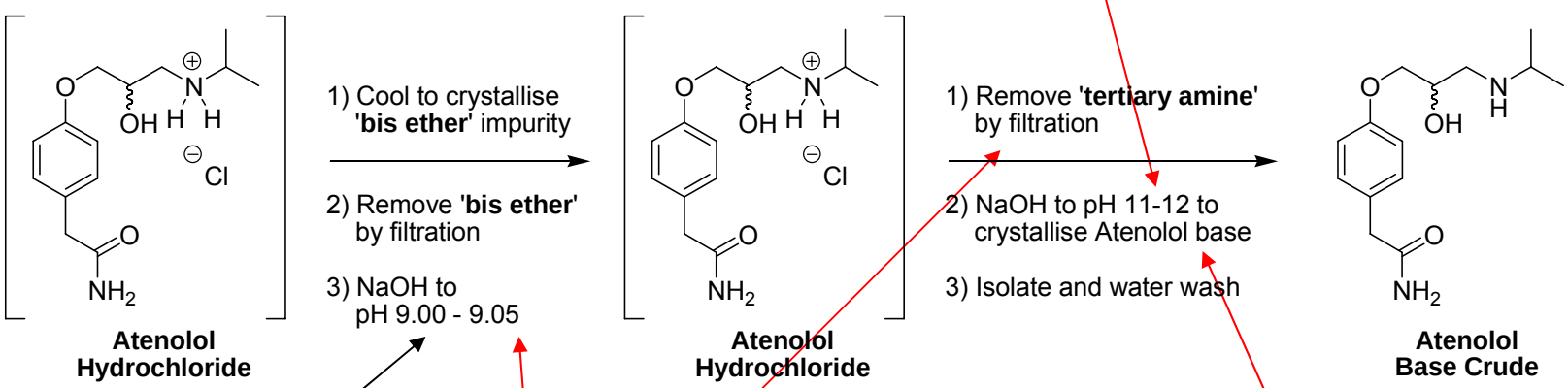


'blocker acid'

Atenolol – first manufacturing process

Final pH after basification lowered from 12.0 to 11.5 without loss of yield

- Washing more effective
- Less hydrolysis of amide during drying



Impracticable for routine manufacture !

Excess of isopropylamine increased from 10 to 15 equivalents

Reaction hold time increased at lower temperature

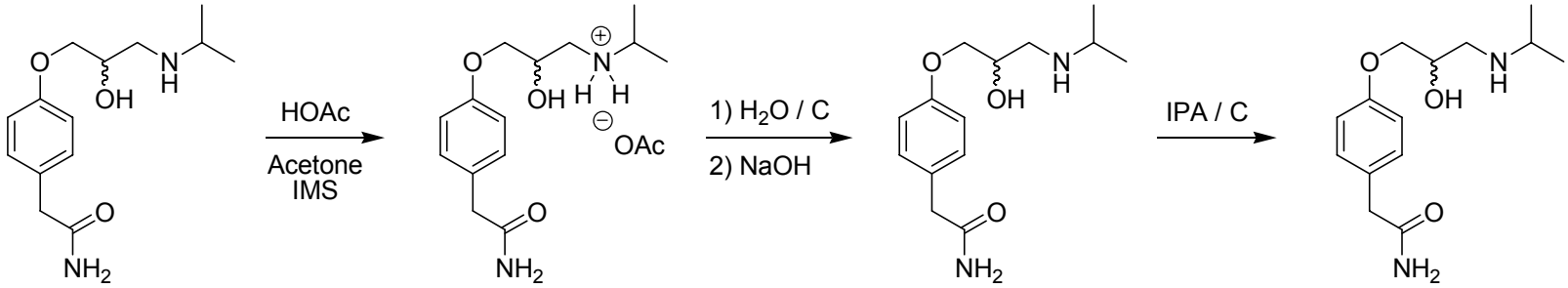
Basification of the crude at 50°C rather than 20°C

- Improved physical form
- Washing even more effective

Global Process R&D

AstraZeneca

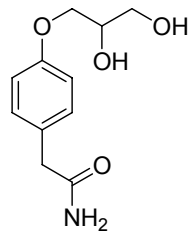
Atenolol – first manufacturing process



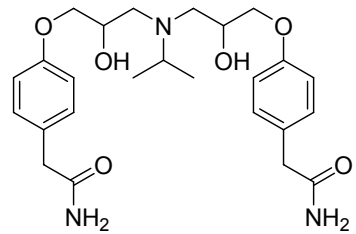
38% Overall yield from amide

Main challenge was control of the 'diol' and 'tertiary amine' impurities

Removal via isolation was inefficient, hence 4 isolation steps were still required



'diol'



'tertiary amine'

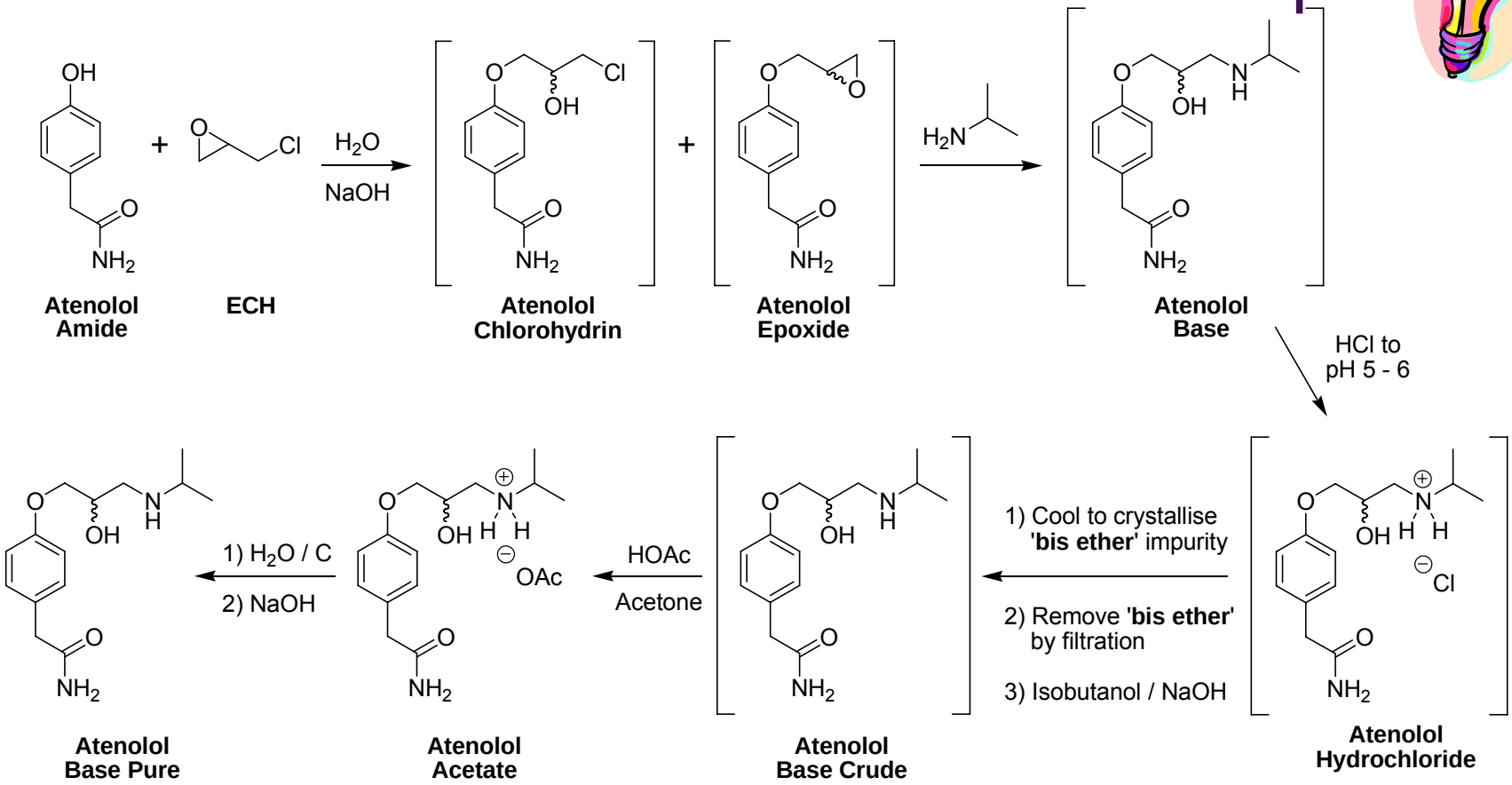
Global Process R&D

AstraZeneca

Atenolol c1980

- Good end-of-reaction yield of Atenolol base
- Process improvements concentrated on operability & robustness
- Market demand satisfied, but…
- Sales of the drug were increasing rapidly
- Manufacturing capacity was becoming constrained by the number of isolation and drying steps

Peak Demand - Atenolol acetate telescope

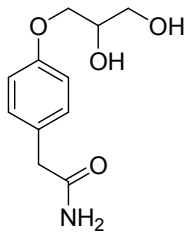


63% Overall yield

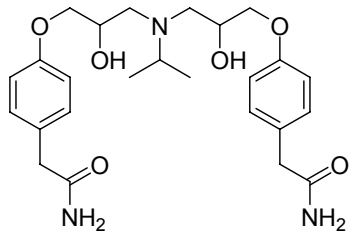
- Process unchanged up to formation of the hydrochloride and removal of the ‘bis ether’
- Base then extracted into isobutanol, concentrated and dried by distillation
- Acetate salt crystallised following addition of acetone at elevated temperature

Atenolol acetate telescope

- Effective removal of ‘diol’ and ‘tertiary amine’ via a single isolation
- Yield from amide to pure increased from 38% to 63%
- Capacity increased by 65%
- Annual cost saving in 1985 £450,000 / 100 te pure API, plus £500,000 stock removed from supply chain by eliminating isolated steps



‘diol’



‘tertiary amine’

Atenolol acetate telescope

- Yield loss minimised by washing with acetone alone – but relied on good displacement wash technique
  - ➢ Robustness compromised
- Holding at isolation temperature for more than a few hours prior to filtration encouraged crystallisation of impurities
  - ➢ Robustness compromised
- Acetone and isobutanol recovered by distillation for re-use within the process
  - ➢ Possible regulatory issue nowadays
- Several percent 'blocker acid' present in acetate, but removed effectively at pure stage
  - ➢ Possible regulatory issue nowadays
- Only 1 isolated stage between registered starting material and final API
  - ➢ Would now be a regulatory issue

Atenolol acetate telescope

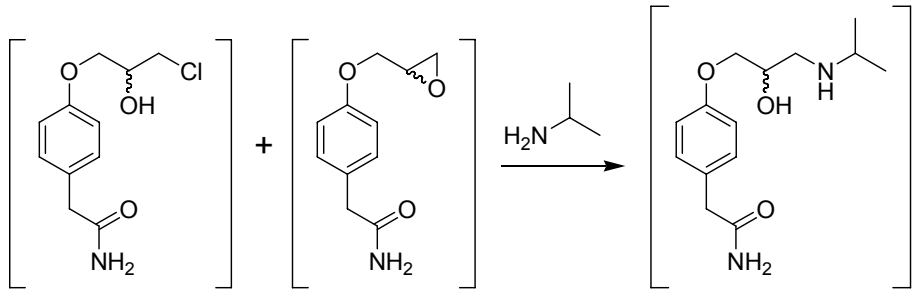
- 1st batch gave very poor physical form at isolation – greatly improved by returning slurry to reflux following acetone addition

- Residual batch water content following removal of excess isobutanol had to be < 0.5 %w/w to avoid yield loss
  - Achieved at lab scale but not on plant - attributed to fractionation on cold glassware in lab
  - Solution adopted was to over-distil on plant then make up to volume with fresh solvent

Further changes to the telescoped process

Driven by demand for product:

- Batch concentration increased by 15%
- 3 hour hold period for completion of amination step removed – cycle time 21 → 18 hr



- Accommodation in alternative plant - reactors at the same level, epoxide slurry difficult to pump
  - ➢ Counter-intuitive ‘reverse addition’ of isopropylamine to epoxide

Driven by external regulatory environment:

- Critical parameters defined retrospectively via paper assessment of lab & plant data
- More detailed regulatory submission made – limit on future changes

Further changes to the telescoped process

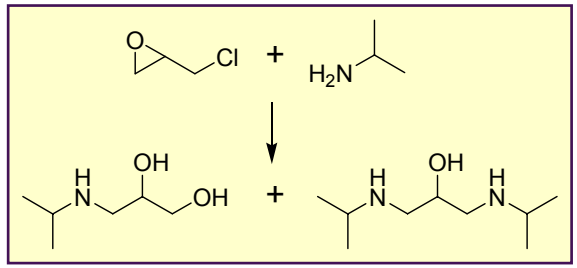
Driven by environmental requirements:

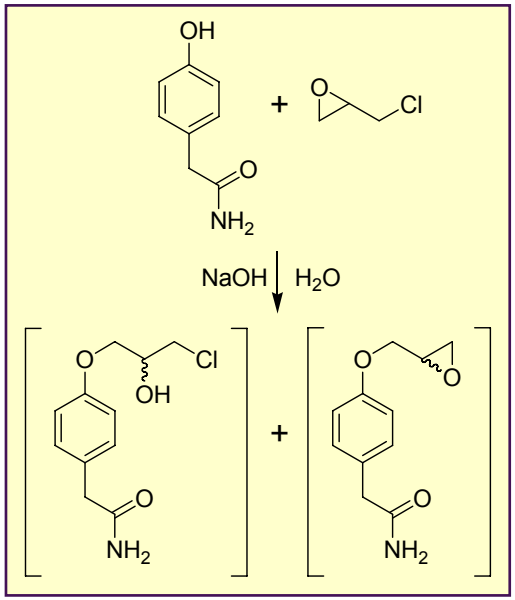
- Solvent abatement required under IPC, but fitted to only one pressure filter due to forecast decline in demand
  - ➢ Decline in demand slower than expected, so ability to deliver was compromised
  - ➢ Lack of robustness at isolation (compromised by 15% concentration increase) became significant
    - Some batches gave very thick slurry – poor ripening / washing, slow filtration
    - Shown in lab that solvent ratio and water content of mother liquor were significant – limits defined
    - Control of distillations improved to achieve solvent composition reproducibly on plant

Further changes to the telescoped process

Driven by safety requirements:

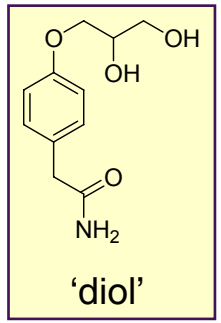
- Perceived high risk of vessel rupture if maloperation caused excess ECH to come into contact with isopropylamine





- Reduction in ECH charge from 6.0 to 3.5 equivalents - available ECH is limited by its miscibility with aqueous phase

- Other process benefits from this change:
  - Shorter recovery distillation step, hence reduced 'diol' formation and greater throughput
  - Improved physical form of the epoxide due to less incorporation of ECH – easier transfer of slurry to amination vessel



Several of the above changes could have been implemented much earlier in the product lifecycle via an FED approach during development

A little serendipity

- Reduced levels of the ‘blocker acid’ impurity in Atenolol acetate correlated with mis-calibration of the measure vessel used for charging NaOH to the epoxide formation step
  - NaOH consistently undercharged for several weeks
  - Charge set point reduced following confirmatory lab work

- Elevated levels of the ‘blocker acid’ impurity in Atenolol acetate, including several batch failures, correlated with a period of low atmospheric pressure in the Bristol area
  - The distillate temperature probe controlling distillation of excess isopropylamine had drifted to the lower limit of its calibration tolerance, hence under low atmospheric pressure the measured temperature never reached the required endpoint.
  - Batches therefore experienced high temperature for prolonged periods under aqueous alkaline conditions

A little serendipity

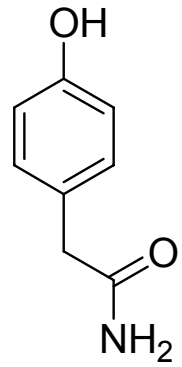
- An increase in the number of acetate batches filtering very slowly during isolation correlated with replacement of the quick-release charge hole on the crystalliser by a sight glass
  - Changed to improve GMP & SHE compliance
    - Process operators required to perform visual check for crystallisation before returning batch to reflux for ripening
    - Difficult to assess via sight glass – batches which were barely out of solution appeared as dense slurry, hence were returned to reflux
    - Crystallisation of the bulk of the batch occurred during final cool-down, omitting the ripening step

Routes to Atenolol Amide

"This molecule is a deceptively simple synthetic target and in spite of the dozens of 'paper' routes which can be generated…..the vast majority of these on detailed examination are very unattractive for tonnage scale operation."

"…although it is not at first sight a complex molecule, it has proved to be one of the most difficult products to make on the large scale that we have ever encountered…"

(ICI internal reports 1974)



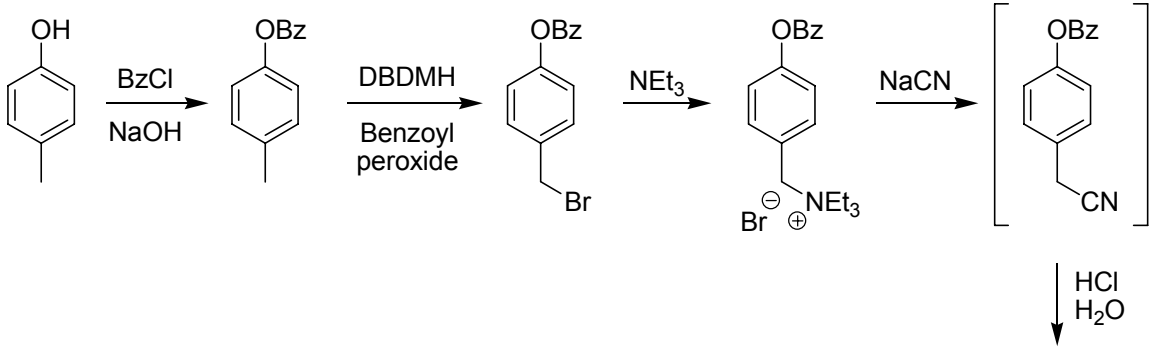
Atenolol Amide

Routes to Atenolol Amide

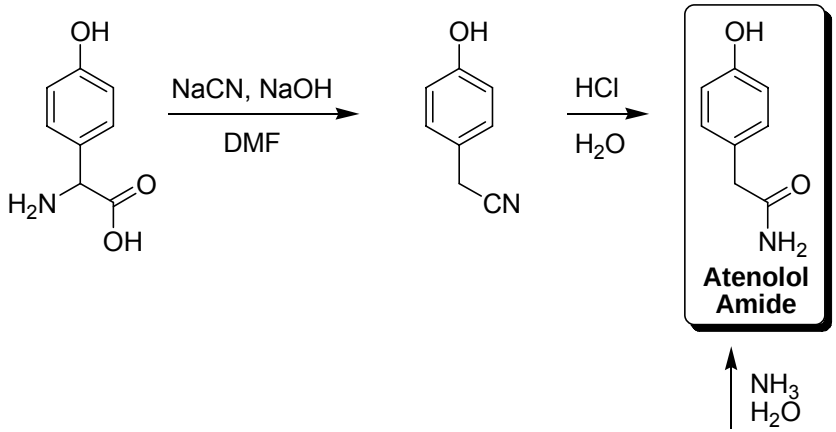
- Many routes investigated at lab scale during development and post-launch
- Possible to launch with unoptimised process because the stage was unregistered
- Route to amide changed approx. 3 years after launch
- Amide became available commercially with generic manufacture of Atenolol
  - Able to source from any available route

Routes to Atenolol Amide

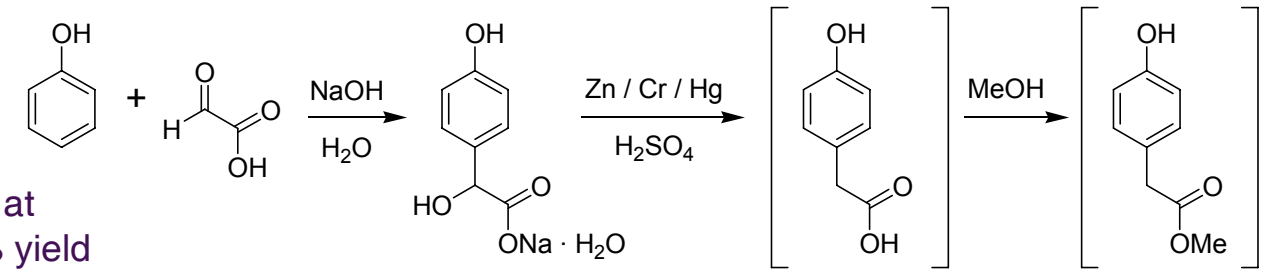
Route 1 - Development
38% yield



Route 2 - First process at commercial scale - 45% yield



Route 3 - Final process at commercial scale - 49% yield



Global Process R&D

AstraZeneca

The Present

- Tenormin® is still part of the AstraZeneca cardiovascular product portfolio
- Substantial worldwide generic market for Atenolol
- Atenolol is on the WHO core list of Essential Medicines
- API no longer manufactured in-house by AZ

If we developed it now…?

- Single enantiomer
- Convergent route to eliminate ‘bis ether’ and ‘tertiary amine’ ?
- More registered steps with (potentially) commercially-available RSM
  - Process conditions registered in detail
  - Optimised by FED prior to establishment at scale
  - Validated prior to launch
- Fewer route / process changes post launch
  - Quality by Design could reverse this trend...?
- Environmental constraints
  - Amide stage unlikely to be environmentally acceptable
- >> 4 years from start of development to product launch !

If we developed it now…?

- Single enantiomer
- Convergent route to eliminate ‘bis ether’ and ‘tertiary amine’ ?
- More registered steps with (potentially) commercially-available RSM
  - Process conditions registered in detail
  - Optimised by FED prior to establishment at scale
  - Validated prior to launch

Would this have delivered a better process? - solution yield very good from outset
- telescope gave most significant improvement

- Fewer route / process changes post launch
  - Quality by Design could reverse this trend...?
- Environmental constraints
  - Amide stage unlikely to be environmentally acceptable
- >> 4 years from start of development to product launch !

If we developed it now…?

- Single enantiomer
- Convergent route to eliminate ‘bis ether’ and ‘tertiary amine’ ?
- More registered steps with (potentially) commercially-available RSM
  - Process conditions registered in detail
  - Optimised by FED prior to establishment at scale
  - Validated prior to launch

Would this have delivered a better process? - solution yield very good from outset
- telescope gave most significant improvement

- Fewer route / process changes post launch
  - Quality by Design could reverse this trend...?
- Environmental constraints
  - Amide stage unlikely to be environmentally acceptable
- >> 4 years from start of development to product launch !

Is the patient <u>really</u> better-served by current ways of working …?

If we developed it now…?

- Single enantiomer
- Convergent route to eliminate ‘bis ether’ and ‘tertiary amine’ ?
- More registered steps with (potentially) commercially-available RSM
  - Process conditions registered in detail
  - Optimised by FED prior to establishment at scale
  - Validated prior to launch

Would this have delivered a better process? - solution yield very good from outset
- telescope gave most significant improvement

- Fewer route / process changes post launch
  - Quality by Design could reverse this trend...?
- Environmental constraints
  - Amide stage unlikely to be environmentally acceptable
- >> 4 years from start of development to product launch !

Is the patient <u>really</u> better-served by current ways of working …?
Has life for the Process Chemist become more or less interesting …?

Acknowledgements

Many chemists within ICI / Zeneca / AstraZeneca Process Development & Process R&D Departments, too numerous to mention individually

AZ Information Science, Libraries & Archives

A G Wylie

R Barton

J A Stott

Global Process R&D

AstraZeneca